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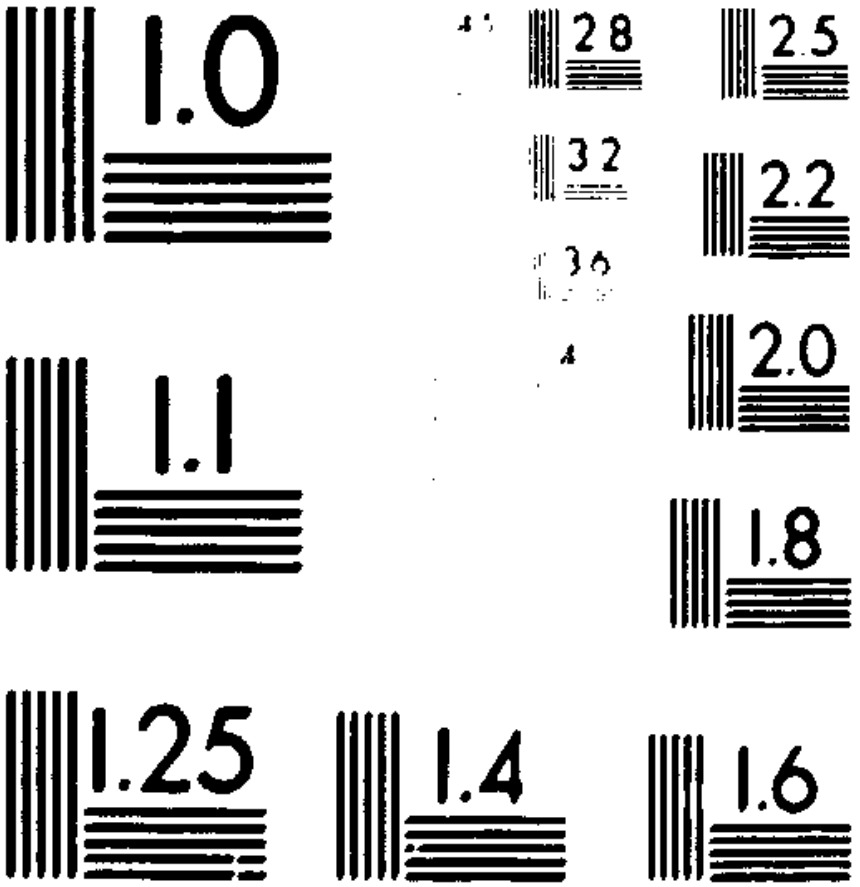

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

Genetic Engineering and Biotechnology Monitor

Issue Number 9 July/August 1984

Dear Reader,

The world is confronted with a glaring paradox. In spite of the remarkable, even startling technological advances, fundamental human rights to the essential needs of life of the majority of the people remain unfulfilled. Even worse, the number of persons for whom the right to "a standard of living adequate for their health and well-being" and other basic rights set forth in the Universal Declaration of Human Rights, are beyond reach, and appear to be increasing. Reflecting a growing concern that science and technology are being increasingly used toward destructive ends, the United Nations General Assembly (in its resolution 38/113, December 1983) called on the international community to take necessary steps to ensure that "the results of scientific and technological progress are used exclusively in the interests of international peace, for the benefit of mankind and for promoting and encouraging universal respect for human rights and fundamental freedoms."

It is in the above context, that a new form of international co-operation was conceived at the International Forum on Technological Advances and Development held at Tbilisi in April 1983. It is a call to the international community to launch a broad frontal attack instead of engaging in occasional and unrelated skirmishes with the application of emerging technologies for development. For this purpose, a limited number of technologies to meet particular needs of a clear urgency to the human community are to be identified and designated as "Technologies for Humanity" (TH). The forum asked UNIDO to work further on this concept of TH and present it to the UNIDO IV Conference in August 1984.

These technologies are those modern technologies, including technological advances which in their application would bring benefit to a large number of people in greatest need and more particularly to the poorest of the poor. They are unlikely to be developed in the normal course of the present structure of technology development where technologies are developed mostly in industrialized countries. TH is a call for the international community to launch a major, conscious, co-ordinated world-wide movement with a critical mass for mobilizing and directing those technological advances that offer great promise for the benefit of the poor. It will draw upon what exists, but the effort required is dimensionally much larger than at present.

The initial area from which TH may be selected would include food and nutrition, water and sanitation, basic health protection, pollution control and rural energy. An example of TH is the improvement of cassava-based traditionally fermented food, particularly in Africa through the use of advances in biotechnology and genetic engineering.

(Continued)

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TH at the moment requires the commitment of political leaders, the dedication of scientists and mobilization of resources. All nations are encouraged to contribute to this endeavour, both in the private and public sectors. UNIDO will act as the promoter of the movement with the support of eminent scientists and leaders of society who will constitute a consultative body to UNIDO in this field. Projects for problem-oriented technology development and application will be identified and elaborated with the help of experts and substantive and financial participation secured from all interested institutions. Once a technology is developed, it will be disseminated, freely if in the public domain, and under moderate costs if in the private sector. A suitable technology field delivery system will be devised to demonstrate TH to the people.

UNIDO will co-operate with other interested agencies to promote this concept. Resources will be drawn essentially from the existing global pool of resources available for technology development; funding/development agencies will be encouraged to fund TH bilaterally and multilaterally, and an International Roster of Scientists and Technologists in selected Technological Advances is being developed to mobilize the co-operation of high-level scientists in the development and application of technologies unique to developing country conditions and in particular the development of Technologies for Humanity.

Genetic engineering and biotechnology has a particular role to play in the TH movement, and we will keep you informed of its progress.

G. S. Gouri
Director
Division for Industrial Studies

A. POLICY, NEWS AND OTHER EVENTS

UNIDO News

Capability building in biotechnology and genetic engineering by developing countries

Under the sponsorship of the AAAS Office of International Science, a UNIDO staff member (Dr. R. A. Zilinskas) and Prof. David McConnel of Trinity College, Dublin arranged a seminar on the above topic, held on 26 May 1984 in New York. Abstracts of papers presented by the four speakers are re-printed in this issue of the Monitor. The following is taken from the introductory notes to the seminar.

While it is obvious that recent advances in biotechnology such as genetic engineering hold great promise for the developing countries (DCs) to help solve their pressing needs related to health, food, and energy, the question remains how best to make certain these advances, all realized through R & D in developed countries, will benefit them. This can partially be done by focusing applied R & D being performed in the developed countries to finding answers to specific problems in the DCs and partially, though be it long term, by strengthening the capability of Third World researchers to perform advanced biotechnology R & D and for industries in the DCs to capitalize on its results. Important vehicles for mobilizing the resources of the science community to make certain the promises of biotechnology are realized by the DCs include intergovernmental organizations. The United Nations Industrial Development Organization (UNIDO) has been active in this endeavour since early 1981, taking four general approaches: (i) promoting and establishing an International Centre for Genetic Engineering and Biotechnology (ICGEB) wherein R & D of pertinence to the DCs will be performed by world-class scientists and where researchers from the DCs will be trained in the advanced techniques; (ii) providing expert advisory services to the governments that are formulating national policies and programmes vis-à-vis biotechnology; (iii) acting as a "technology scout" by catalyzing joint, co-operative projects between R & D units in developed countries and DCs, likewise by promoting joint commercial ventures; and (iv) seeking the co-operation and involvement of scientists and technologists of all countries in the tasks of boosting national capabilities. Here, UNIDO assembled one of its officials and four working scientists (two from DCs) who have served as scientific experts. All have been, and are, involved in building biotechnology capability in DCs. This group attemped to do the following during the seminar: (i) to review the past efforts of UNIDO in the area of biotechnology for the purpose of drawing useful lessons to suggest and/or enhance future activities both by UNIDO and other organizations; (ii) to stimulate an exchange between symposium participants and the audience in order to generate further ideas about DC prospects and problems; (iii) to introduce the ICGEB to a wider sector of the science community and to discuss its role as a vehicle for capability building in new biotechnology; and (iv) to compile a roster of scientists and technologists active in new biotechnology who wish to lend their assistance for advancing capabilities in the Third World.

Proposed centre of biotechnology in Lorena SP, Brazil

A panel of scientists, at the invitation of UNIDO and FTI (Fundaçao de Tecnologia Industrial), met in November 1984 to discuss the proposed establishment of the Centre of Biotechnology in Lorena SP, Brazil. They reviewed the detailed plan of work proposed by FTI, the personnel resources, and the existing research and development facilities. Site visits were made to laboratories and pilot plants.

The panel addressed itself to the questions and issues related to why the Centre of Biotechnology is needed, its proposed programmes, how it is planned to execute them, and the funding required.

Brazil, with its abundant, renewable resources (including biomass and certain derivatives such as starch and sugar) and land space is without sufficient liquid fuel or other petrochemically derived resources, but has during the past decade successfully developed the fuel alcohol programme (PROALCOOL) using biotechnological approaches. Therefore, in view of the internationally recognized leadership of Brazil in the alcohol programme it was felt advisable to sustain and further broaden the endeavour by engaging the proposed Centre of Biotechnology in activities requiring the utilisation of new scientific and technological advances.

The proposed Centre of Biotechnology is expected to enhance the advancement of renewable resources based on biotechnology that would be of significant benefit to many countries throughout the world, and to the Brazilian economy as a whole. The Centre's objectives will be devoted:

(1) to research and development in renewable resources based on biotechnology;

(2) to train and educate scientists and technologists, as well as promote international and regional co-operation between countries;

(3) to develop process technology for ethanol-based biomass; and

(4) to broaden future activities to encompass a long-range programme in sucro-chemicals, fine chemicals and agro-chemicals based on renewable resources.

Finally, the panel recognized this Centre of Biotechnology to be an institution for regional as well as for international collaboration with the International Centre for Genetic Engineering and Biotechnology promoted by UNIDO.

UN and other organizations' news

Third world nations vote change in system to conserve germplasm over objections of industrialized countries

At the general meeting of the UN Food and Agriculture Organization (FAO) in Rome last November, Third World countries won approval of a proposal designed to give them more influence in a system in which the industrialized countries exercise major control. The effect of the action remains unclear because the willingness of the donor nations to continue to participate is uncertain.

The intent of the proposal is to replace the relatively informal organization now in place with a legal structure that would give the less-developed countries (LDC's) a greater voice. Specifically, the meeting voted to replace the present working agreement with a formal international undertaking whose participants would collaborate in operating a network for the collection, preservation, and exchange of plant genetic material. In another action, a Third World majority successfully pushed the establishment of an FAO Commission on Plant Genetic Resources that would monitor the programme. The assumption is that the new commission would have review power over policy for the germ plasm system.

Such changes would diminish the status of the International Board for Plant Genetic Resources (IBPGR), which promotes the activities of existing international plant research centres that are also concerned with collecting and preserving plant germ plasm. IBPGR is one of 13 institutions operating under the aegis of the Consultative Group on International Agricultural Research (CGIAR), familiarly known as CG, which administers the network of international research and plant breeding centres identified with the Green Revolution. The CG is a consortium of government, international, and private organizations whose policy has been dominated by the industrial countries which have been major donors of operating funds. The CG has functioned without a charter and with an unusual independence of action for an international agency.

The international effort to preserve plant genetic resources developed in the 1960's and early 1970's because of a growing recognition that the world genetic base for food plants was being narrowed. Heavy pressure on original native plant varieties was being exerted by a widespread trend in agriculture toward use of high-yielding varieties of food plants which are genetically similar.

IBPGR was established in 1974 in response to the concern. By the mid-1970's, criticism was building from the LDC's about their lack of influence in the germ plasm system. At the same time, seed companies were pressing for enactment of a model law conferring virtual patent status on commercially developed plant varieties propagated by seeds. Action by industrial countries to strengthen so-called plant breeders rights (PBR) had a polarizing effect on Third World attitudes.

Third World sentiment surfaced at the 1981 general meeting of FAO with a demand for establishment of an international convention to provide a legal framework for the preservation and exchange of plant germ plasm and for creation of an international gene bank. A resolution embodying these demands was passed and Third World and donor nations then began fencing over how to proceed.

In the discussion, the LDC's invoke the formula familiar in the ongoing North-South dialogue in the United Nations that natural resources such as plant germ plasm are part of a "common heritage" of mankind and that benefits from them should be shared on a more equal basis. The argument has been applied, for example, in the Law of the Sea Conference and the debate over international allocation of radio frequencies.

In respect to germ plasm resources, the United States, Japan, and the countries of Western Europe are decided have-nots. Because of the ice ages, a preponderance of the present major food crop plants originated in regions of Latin America, Africa, and Asia. Northern countries, however, have larger gene bank holdings than the South. As a result, Third World countries accuse the industrial countries of creating a system under which they claim free access worldwide to germ plasm material, but assert proprietary rights to commercial plant varieties developed from that germ plasm.

Exponents of the Third World case blame trends in the seed industry for exacerbating the situation. Large American and European chemical, pharmaceutical, and energy companies which produce fertilizer, herbicides, and pesticides have moved strongly into the seed trade in the last decade or so by buying existing seed companies. The critics say that the multinationals have successfully promoted plant breeders rights legislation with their governments and they accuse the companies of using PBR to control the market and raise the costs of seed in the Third World. The United States and other donor countries have also been charged with limiting LDC access to germ plasm holdings, but such charges do not appear to be clearly documented.

The issue of plant breeders rights attracted moderate attention when the U.S. Plant Variety Protection Act was amended in 1980 and the seed company position was bolstered. The implications of biotechnology for the seed industry, however, has piqued the interest of Congress, and the action taken at the FAO meeting is likely to result in a broadening of the focus to include international issues.

Donor country attitudes toward the international germ plasm system continue to be influenced by the views that led originally to the establishment of IBPGR. Although such views are not aired it is evident from FAO debates that the donor countries feel the U.N. machinery is ill adapted to running a programme such as the plant germ plasm network. Donor countries argue that high-yielding crop varieties have revolutionized agriculture in the LDC's by dramatically increasing production and that only PBR protection offers the incentives necessary to develop and distribute the new plant varieties required to maintain and increase production. The proponents of the present system argue that it is not plant breeders in the Third World but politicians who insist on change.

The issue, however, is now thoroughly politicized. A worst case scenario would have industrial countries reject the undertaking and withdraw support and

the LDC's prohibit collection of germ plasm in their countries by those outside the scheme. Such an outcome should not be inevitable since all sides agree that genetic erosion is proceeding at an alarming rate, the present level of effort is inadequate, and effective action is necessary to forestall irreparable losses. But far from settling the issue, the FAO vote revealed something very like a deadlock. It should also dramatize the urgency of reaching an accommodation. (Source: Science, Vol. 223, 13 January 1984)

Social issues

Approval on Shigella dysenteriae gene clone

The U.S. recombinant-DNA Advisory Committee has approved the cloning of a gene for a powerful toxin, despite opposition. The toxin has the same properties as those produced by Shigella dysenteriae, a bacillus found in a strain of E. coli that produces a kind of dysentery that kills many children in the Third World. Author-activist, J. Rifkin believes the cloning could bring the world closer to biological warfare, but microbiologists from the Uniformed Services Union of the Health Sciences, claim they are only conducting research into basic microbiology. They say that once the gene cloning for the Shiga-like toxin is isolated and removed, a vaccine could be produced from E. coli. The Uniformed Services Union is not part of the military establishment dealing with chemical and biological warfare, however Rifkin challenged the government before a RAC meeting in Bethesda, MD, to prove that it has no intention of developing biological weapons before beginning the experiments.

RAC officials maintain that the gene for the toxin is not in itself dangerous, and is found naturally in several types of bacteria. The RAC was nevertheless split 9-5 in its vote on the gene cloning issue. There were four abstentions. Rifkin and several scientists during the meeting complained that the RAC has no ecologists for judging proposals for releasing micro-organisms outside the laboratory. Some Congressional observers believe the RAC should hand the job of judging experiments outside laboratories over to a special panel of government experts. (Extracted from New Scientist, 16 February 1984).

Low risks at a premium

The Sun Alliance insurance group and Reed Stenhouse UK Ltd. are planning to launch "Biotech Protection" - claimed to be the first insurance package geared specifically to the needs of biotechnology laboratories. The policy includes all-risks cover on assets and earnings against cross-infection of cultures, contamination of premises and seizure or closure of premises by safety authorities. Legal liabilities to third parties for environmental pollution and innocent or fraudulent breach of confidential information can also be insured.

According to Reed Stenhouse, market research has shown that many biotechnology laboratories are not adequately insured against the risks peculiar to their work. Celltech Ltd., the UK biotechnology company, refuses even to discuss its insurance protection. Others in the industry are surprised that seizure by civil authorities is an insurable risk. And there is some scepticism about whether the risk of breach of confidential information could be assessed or a claim proved. Reed Stenhouse is undeterred by such questions. The company will provide full advice to its clients on safety and security issues, and the company's "loss engineers" will be able to assess the value of cell lines and evaluate dangerous practices. (Extracted from Nature, 12 April 1984).

Regulatory issues

Regulation on genetically engineered products

The responsibilities of the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health are being re-evaluated. Since 1974 the RAC has monitored laboratory research on DNA, but the board is now being called on to review field tests of recombinant DNA organisms. The Foundation on Economic Trends (FET) charges that the RAC is not capable of such review, and has brought suit in the federal court to force the RAC to file environmental impact statements and add

ecologists to the staff. The NIH is considering questions of whether the RAC should monitor non-laboratory experiments and whether it should review corporate research proposals. The Environment Protection Agency's Office of Toxic Substances feels that it must assume part of the responsibility for reviewing genetically engineered organisms, but the RAC's activities should not be curtailed until a clear delineation of responsibility has been established. Industry observers say that if the RAC curtails its activity, there will be no regulation at all of someDNA research, possibly leading to a government-imposed moratorium on research not subject to NIH review. An interagency panel representing NIH, EPA and the US Development Agency is needed to review environmental release of genetically engineered organisms, according to Representative A. Gore Jr. Representative Gore urged the heads of several federal departments to study a new Congressional biotechnology report prepared by the House Science and Technology Subcommittee on Investigations and Oversight, which he chairs. The document raises questions about the rule-making roles of the Environmental Protection Agency (EPA), the National Institutes of Health, and the Department of Agriculture. Besides listing detailed recommendations for each agency, it calls for forming a new federal interagency regulatory panel on biotechnology, which would review corporate proposals for environmental release of genetically engineered substances to ensure that each product is "adequately evaluated according to a uniform set of guidelines." Gore asserts his report shows that "the current regulatory framework does not guarantee adequate consideration of the potential environmental effects of a deliberate release."

The Reagan administration is not convinced that the Congressman's assessments and recommendations are correct, and is particularly concerned about over-regulation of a promising new field. In fact, it was the EPA's heightened interest in regulating gene splicing that prompted interest at the Office of Management and Budget (OMB). The EPA has for the past couple of years been working on plans to monitor biotechnology products under the Toxic Substances Control Act (TSCA) and the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). The EPA offices that administer these laws are expected to publish in the Federal Register a notice of intent to regulate biotechnology products covered by TSCA and FIFRA in August. (Source: Chemical Week, 29 February 1984 and McGraw-Hill's Biotechnology Newswatch, 2 April 1984)

Biological ethics

The first international conference on life sciences and mankind ended in Tokyo on 22 March with a set of conclusions to be presented to the heads of the Western industrial nations countries at the London summit in July.

The conference grew out of the proposal made by Japan's Prime Minister, Yasuhiro Nakasone, at last year's Williamsburg summit that problems presented by the rapid advance of the life sciences should be examined by an international committee. Nineteen scientists, theologians and philosophers were chosen to represent the seven summit countries and invited to visit Japan. In opening the conference, Mr. Nakasone spoke of the growing public concern over in vitro fertilization, artificial determination of the sex of embryos, euthanasia ... and the treatment of those in a persistent vegetative state. The conference did not, however, succeed in solving the problem on the spot. Indeed, given that only a week earlier Pope John Paul II, speaking at a conference on Gregor Mendel at the Vatican, had warned genetic engineers against the "moral misuse" of their abilities and reinforced Roman Catholic opposition to techniques that allow fetal abnormalities to be detected, it would have been hard for universally acceptable ethical principles to be spelled out. All the conference could do was to acknowledge that the "more the life sciences are applied, the more they would bear on ethics, customs, politics and law" and that "critical problems might arise in the future" but "no agreement on specific (ethical) norms could be attempted at present". Emphasis was, however, given to the need for scientists to make their discoveries much more "understandable to the public" and to encourage discussion through education and the media.

Conference participants saw their main contribution in setting a precedent for a group of independent scholars, not representing their individual governments, to discuss major scientific issues and directly to advise heads of state. Deliberations are to continue next year, this time with the sponsorship of the French Government. The exact format has yet to be decided but it is hoped that attention will shift to specific problem areas and that representatives from outside the summit countries - particularly from the developing countries - will be permitted to attend. (Source: Nature, 29 March 1984)

Looser rules urged for DNA research

A commission appointed by the Swedish government has recommended that there be no special regulations or agencies for workers or environmental protection at recombinant-DNA facilities. The commission reports that existing agencies and regulations that cover occupational health and safety and the environment are sufficient to handle DNA-related activities. The commission adds that there are no more risks involved with recombinant-DNA activities than there are with ordinary cells or microorganisms, and that chances of any of these organisms escaping into the environment and harming human, animal or plant life are nonexistent. (Source: Chemical Engineering, 14 May 1984)

Biotech firms win approval for more open-air tests

Two biotechnology companies in the U.S., the Cetus Corporation of Wisconsin and Advanced Genetic Sciences (AGS) of Connecticut have won preliminary approval to release genetically engineered organisms into the environment.

The RAC decision allows Cetus to go ahead with an experiment involving a novel strain of tobacco that is resistant to disease, but has not decided whether to proceed. AGS has also made no decision on its experiment, which involves the same bacterium Pseudomonas Syringae, which retards the formation of frost on plants. (Extracted from New Scientist, 7 June 1984).

General (miscellaneous information)

New biotechnology centre at Duke University

A new R & D centre for work on biotechnology is being organized at Duke University's school of engineering. The Center for Biochemical Engineering is affiliated with the departments of biomedical engineering and mechanical engineering and materials science and will focus on engineering problems in molecular biology, such as designing techniques and equipment for large-scale production of monoclonal antibodies. Other work will involve production andpurification of human and animal vaccines and new reagents for chemical analysis. (Source: Chemical and Engineering News, 26 March 1984)

New U.S. genetic engineering research centre to be established

A new facility to be built in Rockville, Md., called the Center for Advanced Research in Biotechnology (CARB), is being jointly sponsored by the National Bureau of Standards and the University of Maryland; completion is planned for late 1985. CARB will offer collaborative research opportunities and resources to companies interested in making newer and more refined biotechnology products. The new centre will be particularly helpful to corporate scientists who want to go beyond the development of first-generation products - naturally occurring biochemicals that have been modified to improve their efficiency. Ultimately, CARB sponsors say, researchers may succeed in developing synthetic biochemistry for producing novel substances not found in nature, the manufacture of which will require tools and techniques that allow scientists to study and manipulate genetically engineered or natural macromolecules. CARB will do much of the expensive work needed to advance the new science. Specifically, it will develop computer capability for modeling and theoretical analysis of biological systems. This, says the centre's charter, will allow studies of the structure, function and design of biomolecules. The centre will also develop the biophysical tools and techniques for molecular manipulation, using the resources of NBS and the University of Maryland.

NBS scientists will serve as research advisors to CARB-affiliated graduate students and industrial researchers in what should prove to be easy co-operation. The new centre is being built less than five miles from the main NBS campus, which has a staff of 2,800 specialists in virtually all areas of science and engineering.

Of particular interest to CARB co-ordinators are the NBS centres of chemical physics and analytical chemistry. The former is interested in the use of enzymes in catalysts.

The University of Maryland will contribute a strong background in plant genetics, biology, animal science, vaccine development, marine biotechnology and molecular biology. The school's veterinaries are able to test poultry for contagious diseases in only one-tenth the time it took a couple of years ago, and at the university's medical school in Baltimore, vaccine researchers are involved in studies of cholera, typhoid fever, influenza and other diseases. They have developed an oral vaccine for cholera by using genetic engineering techniques. (Extracted from Chemical Engineering, 16 April 1984).

Europe's biggest cell bank planned

The largest store in Europe for animal cells is being constructed on Salisbury Plain. The UK government's Centre for Applied Microbiology Research at Porton Down has received £500,000 from the Department of Trade and Industry to design, build and run a national collection of animal cell cultures. This bank will keep valuable lines of animal cells alive in cold storage for as long as 30 years. Such cells are proving more suitable than bacteria for many applications in biotechnology, and there is a rush to protect them.

The types of cells for which no adequate facilities exist in Europe include monoclonal antibodies, a mainstay of the biotechnology industry, as well as cells that can be used for manufacturing scarce natural proteins, such as interferon. Also stored will be other valuable substances which could boost the body's own natural defences against disease.

The new cell bank at Porton Down will eventually provide rented accommodation for 20,000 samples. The centre is applying to the World Intellectual Property Organisation in Geneva for registration as a recognized depository of patented cells.

To patent new processes in biotechnology it is often necessary to store a sample of the cells used in the process for later examination by the authorities. At the moment the only European bank for cultures of mouse and human tissue is a small, unofficial repository in a corridor at the Pasteur Institute in Paris.

Most biotechnologists prefer to send their samples to the much larger and better organised bank in the American Type Culture Collection (ATCC) in Washington, DC. However, the ATCC is very choosy about the samples it will accept from Europe, no matter how pure, for fear of importing foot-and-mouth disease.

The centre's director, Dr. Peter Sutton, envisages offering both a cheap banking service for cells, which would aim to become a national collection open to all, and a more expensive "safe deposit" which would keep samples confidential. This latter service is aimed at industrial and academic researchers who are anxious to keep secret a particularly valuable cell line. (Extracted from New Scientist, 17 May 1984).

A look at a few of the biotechnology companies

There are some 200 biotechnology companies throughout the world and their number is still growing. Fierce competition has not yet led to the sort of shake-out that thins out the players in most fast-growing fledgling industries. During the past five years, biotechnology companies have been through three forms of finance. First, seed corn was provided by venture-capital firms. Typically, handouts of about $1 million were used to help academics with bright ideas set up firms, but when research got more costly and companies began to talk about

production on a large scale, biotechnology firms opted for equity capital, the second stage and the biotechnology companies have not been immune from stockmarkets' recent general decline.

Firms have become more reliant on a third source of finance - R & D limited parternships. Sums of up to $75 million have been advanced by rich private investors in America keen to exploit the tax breaks they can get from such investments. The general disenchantment with high-technology stocks and the realisation that it will be five years or so before biotechnology products come to market in a big way has caused investors to lose their enthusiasm for R & D partnerships. Those few products already on the market have not sold well. It is predicted that companies specialising in biotechnology will find the going even harder as big drug companies enter the industry.

After a slow start, bioengineering products seem to be heading for profitable markets. Despite investments in R & D exceeding $2 billion, only a handful of marketable products have emerged from the laboratories. A number of new products are working their way through the arduous testing process, some of the most promising substances of which researchers hope will soon reach the market. These are the human growth hormone, a protein that may stop heart attacks in progress, substances that diagnose sexually transmitted diseases like herpes, drugs for treating AIDS, and a form of interferon that can be used on several types of cancer. To remain solvent until the products pay off, many firms are seeking fresh capital infusions and alliances with big chemical and drug manufacturers.

Cytogen (Princeton, NJ) has developed a kit for diagnosing gonorrhea, but has sold the technology to Health Care Manufacturing, Becton Dickinson (Paramus, NJ), which will actually make the product. Eli Lilly has assembled its own team of scientists and is developing a hormone that stimulates milk production in cows. Molecular Genetics has limited entangling alliances by searching for products it can develop itself and has introduced in the U.S. a treatment four scours, an often fatal diarrheal infection in newborn calves. (Extracted from Time, 27 February 1984 and Technology Update, 31 March 1984, and The Economist, 2 June 1984).

Courses

A graduate course in "Management and operation of alcohol production plants for liquid fuels", organized by the Faculty of Chemical Engineering of Lorena, Sao Paulo, Brazil, will be held from 7 January 1985 till 26 October 1985. The course, which is sponsored by the Ministry of Industry and Commerce, will be conducted in Spanish. Course fee including food and accommodation is US$4,000. For further information, please apply to Dr. José Antonio Nunes Romeiro, Faculty of Chemical Engineering of Lorena, P. O. Box 116, Lorena, Sao Paulo, Brazil.

Course offered at Valencia, Spain, in food processing

The Polytechnic University of Valencia will be holding a masters course in science and food processing from 1 October 1984. The purpose of the course, which will cover two years, is to train specialists in the field of food processing in areas such as management, manufacturing processes, quality control, maintenance, design and building of industrial machinery, analyses, inspection, etc. Theoretical training will be complemented by laboratory and pilot plant activities and visits to various industrial installations. The first part of the course covers food chemistry and biochemistry, processes of food conservation, instrumental analysis and quality control and industrial applications. The second part encompasses food microbiology, nutrition and toxicology and chemical analysis.

As there is only limited space available, participants are restricted to those holding degrees in engineering, chemistry, biology, pharmacology and veterinary medicine. The course will be held in Spanish. The two-year course fee is 300,000 pesetas. For further information, please write to Secretaría Permanente, Cátedra de Operaciones Básicas, Escuela Técnica Superior de Ingenieros Agrónomos, Universidad Politécnica de Valencia, Apartado de Correos 22012, Valencia, Spain.

B. COUNTRY NEWS

Canada

New research centre

Two Canadian universities are promoting food, fuel and chemical production for the Third World. The Microbiological Research Centre, being established by the Universities of Guelph and Waterloo in Ontario, will research fermentation and biomass conversion. This will aid biotechnology applications in underdeveloped countries. Biomass describes anything that is alive or that once lived, and that can be converted by fermentation and other methods to food, fuel and chemicals. Biomass materials include a large number of waste products of agriculture, forestry and the paper-making and food-processing industries. The centre will also train scientists from Thirld World countries. (Canada, Vol. 12, No. 19, 9 May 1984)

China

Preliminary report on preparation of monoclonal antibody against E receptor

Studies on the E-rosette receptor have gained interest among immunologists recently, as it represents a unique parameter of human T cells which is readily isolated and identified. Hitherto, little work has been done on the monoclonal antibody against porcine E-rosette, but we have now obtained two antibodies which can combine with these receptor-carrying lymphocytes, as shown by an indirect immuno-fluorescence test as well as the inhibition of E-rosette formation of ovine red blood cells. From two successful fusion experiments, two clones were found which possessed apparently specific characteristics as anti-E receptors. These demand further study. (Source: Beijing ZHONGGUO YIXUE KEXUEYUAN XUEBAO [ACTA ACADEMIAE MEDICINAE SINICAE] No. 1, 15 February 1984)

Analysis of Human leucocyte interferon

Plasmid p8218 is obtained by cloning human umbilical leucocyte interferon gene into vector pBR322 at PstI site. Analysis with restriction endonucleases indicates that the number and site of restriction endonucleases at IFN gene in p8218 are the same as IFN- D. Partial DNA sequencing also indicates that the sequence of one fragment of IFN gene in p8218 is the same as the sequence of a corresponding fragment of IFN- D. So the human leucocyte interferon gene in p8218 belongs to the D subtype. According to the restriction endonuclease map, the interferon gene and the ampicillin-resistant gene in p8218 are transcribed in the same direction. (Source: Beijing ZHONGGUO YIXUE KEXUEYUAN XUEBAO [ACTA ACADEMIAE MEDICINAE SINICAE] No. 1, 15 February 1984)

Genetic engineering breakthrough

Chinese scientists have separated 40 milligrams of proinsulin protein from one litre of bacterial culture, four times more than the existing international standards, according to the Shanghai Institute of Cell Biology of the Chinese Academy of Sciences at Shanghai, representing a major breakthrough in China's production of insulin. The success was made by assistant research fellow Guo Lihe and three other scientists. Foreign scientists had been trying to separate proinsulin protein from bacterial culture for a long time, but so far, they can only obtain 10 milligrams from one litre of bacterial culture. Guo Lihe has also developed two fast-analyzing methods to determine DNA molecular structure and the sequences of nucleotides. (Extracted from Xinhua, 8 March 1984).

Italy

Report on Italian biotechnology projects

In February the Federation of Scientific and Technical Associations (FAST) reported on the status of biotechnology in Italy, the first complete presentation of resources used in this area, including a list of research teams and their results achieved. The research, co-ordinated by Professor Gabriele Milanesi of the

CNP Genetics Institute of Pavia and supported by the Banca Popolare of Milan, Caboto, Montedison, Pierrel, and the Chimica Fine e Secondaria project team of the CNR [National Research Council], included interviews concerning work at research centres and industrial laboratories throughout Italy. The analysis focused on six specific research branches of advanced biotechnology not yet applied to productive processes in Italy, but where recent technical headway makes it possible to anticipate a wide range of applications. In short, they concern the most promising fields of biotechnology, those of fundamental strategic importance for industry; and not only in the pharmaceutical fields. The six research fields have to do with genetics engineering, or the technology of the rearrangement of the DNA, hybrids, the cultivation and distribution of vegetal cells, the immobilization and compartimentalization of biomolecules, the chemistry of proteins, and the chemistry of the oligonucleotides. (Extracted from Il Mondo, 20 February 1984).

Japan

Guidelines for organism innoculation and plant genetic engineering

The Japanese Ministry of Education will allow organism innoculation and plant genetic engineering. Guidelines covering both types of biotechnology research have been issued by the Science Council, which will regulate the insertion of E. coli capable of vaccine or hormone production into experimental animals. No innoculation of genetically engineered substances into humans or the fertilized eggs of primates will be allowed. The guidelines for plant engineering cover the isolation of seeds and pollen. Researchers will have to obtain Ministry approval before transferring experimental plants and animals. Research is expected to eventually result in the development of a new organism, such as a plant that requires no fertilizer. (Extracted from The Japan Economic Journal, 21 February 1984).

Biochemistry in Japan

Japan's reputation for industrial invincibility has run so far ahead of it that its rivals start trembling before it sets foot in the ring. The west is now afraid of what Japan might do to it in biotechnology: a report by the American government's Office of Technology Assessment said earlier this year that the Japanese pose a big threat. The Japanese are in fact catching up fast. But they are not yet as threatening as westerners like to think. The Japanese were characteristically out of sight when the biotechnology industry got going in the west in the 1970s. Now that the industry's earliest days are past, however, the virtues of large-scale production and mass-marketing will start to tell. The challenge from Japanese biotechnology should prove different from that of Japanese electronics.

One reason is that the role of the Japanese government is trivial in biotechnology. The Ministry of Trade and Industry (Miti) has plans to funnel $43 million into research on genetic engineering over the next decade, but it already finds its budget trimmed. Venture capital is scarce, and there is a dearth of biologists in Japanese universities to provide any new entrepreneurs. All of the 30 or so firms that are trying gene-splicing are from other industries such as chemicals (Sumitomo Chemical), synthetic fibres (Toray), pharmaceuticals (Takeda) or food processing (Ajinomoto). None of these had an existing biotech research team before it got into the business. To help make up for that, many have opted for ties with American and European concerns.

The most important fact about the biotechnology industry, though, is that its big products at this stage are drugs; and Japanese firms are ill-equipped to take on western companies in pharmaceuticals. An interesting test of Japanese abilities in biotechnology will come with interferons.

Bio-engineered interferons are the first fruit of biotechnology that offers a new product rather than just a new way of making an old product (such as insulin). The Japanese have a special interest in interferons as cancer is the leading cause of death in Japan, and sales of anticancer drugs are more than $500 million a year. Japanese bio-engineered interferon is already undergoing clinical trials.

There are problems - engineered bugs are notoriously unstable, and purification is tricky - but the firm of Toray, like other biotechnology companies, has discovered that beta-interferon is effective against certain rare cancers such as brain tumours. There is, however, little commercial potential here.

Another problem is that beta-interferon, produced by splicing genes into bacteria, is less potent than natural interferon. Firms are experimenting with yeasts and using mammalian cells to yield a better drug, but as yet with no success.

As a result, Japanese firms are planning to produce interferon first by mass culture of human cells. It is in things like this, not in gene-splicing, that the Japanese firms' strength in fermentation technology comes in handy. Some people at Miti think Japanese firms should stick to mass-culture technologies instead of trying gene-splicing.

The firm of Suntory is now working on gamma-interferon, in a joint venture with Schering Plough of America. Gamma-interferon is far less ready than beta-interferon to be put on the market, but it may have the potential, which the beta strain lacks, of being useful against a broad range of cancers; and in the long run it could prove a more profitable drug.

Japanese biotechnology firms think they have narrowed the gap with the west, which is true, but they ignore a huge obstacle - Western drug companies are experienced in getting government approvals for their products in a lot of different countries, the Japanese are not. This will put the Japanese at a substantial disadvantage when worldwide competition in the pharmaceutical products of biotechnology gets under way.

American and European biotech firms such as Genentech, Biogen and Hoffmann-La Roche have been keen to strike up joint ventures with the Japanese and to share knowhow. They want to use these contacts to get into the Japanese market. Lacking overseas sales and marketing teams, the Japanese drug firms have yet to break into the large export markets.

In another report, this time to Prime Minister Yasuhiro Nakasone by Japan's top science policy-making body, the Council for Science and Technology, increased support for fundamental research in the life sciences is planned.

Concern about the long lead of the United States in basic research in molecular biology and the effect this will have on the commerical exploitation of genetic engineering lies behind the report, and swift action is expected on its main recommendations - increasing the numbers and mobility of young researchers and strengthening the technical back-up for biotechnology. University researchers are likely to be disappointed, for although the report is entirely concerned with "fundamental" research, the government sees this as "essential research fundamental to planned applications". Expansion of truly fundamental research in the universities is unlikely.

To prepare the report, the council, which includes the heads of the science and finance-related ministries and agencies as well as industrial leaders, took special advice from both a life sciences group drawn from government, universities and industry and from a special committee comprising 22 of Japan's leading molecular biologists. The financial implications should be included in ministry draft budgets by the end of the year.

The most important point made by the report is the need to give more young people a training in biotechnology, perhaps by means of special fellowships which would allow young scientists to carry out original research - a possibility already under consideration by the Ministry of Education, Culture and Science (MESC).

The report particularly emphasizes that all three of Japan's research groupings - the universities, government research laboratories and industry - must be encouraged to work together more closely. The idea of a special research institute, supported jointly by government and business, where young people could be trained, is floated, but the university side shows little enthusiasm for that project, and the chances are that it will proceed no further.

A more promising proposal is the removal of restrictions that hamper original research. Increased flexibility is, for example, to be encouraged in the research system so that research proposals not fitting into the conventional "project" funding can find support.

University workers may gain from the recognition in the report that the pace at which biotechnology is advancing means that scientists can stay on top only if they can circulate around top laboratories - increased exchange of researchers is called for, both within Japan and between Japan and foreign countries, including more visits from foreign scientists.

The report also calls for the government to step up efforts to secure the basic resources of biotechnology. Calls are made for the creation of a larger collection of microorganisms, including those with special characteristics and from unique environments, as well as increasing stocks of cell lines, particularly those useful for the creation of hybridomas.

More rapid and thorough dissemination of data, particularly DNA and protein sequences but also data on the special characteristics of organisms and their life cycles, is seen to be important. A new computerized database to complement those exisisting elsewhere may result. Finally the report argues for the provision of more sophisticated tools for molecular biology - automatic DNA and protein synthesizers and analysers, and microinjection and laser techniques. (Extracted from The Economist, 19 May 1984 and Nature, Vol. 309, 17 May 1984).

United Kingdom

A new immobilized enzyme for corn syrup

An immobilized enzyme could save U.S. corn-syrup manufacturers millions of dollars annually and significantly reduce capital costs of new production plants. British Charcoals and Macdonalds (Greenock), a Scottish biotechnology company that is part of the Tate & Lyle sugar group have developed the new enzyme, called immobilized AG. It replaces the soluble enzyme glucoamylase that converts dextrins in corn syrup to glucose. Soluble glucoamylase needs up to two days to complete the syrup-production cycle and must be replaced after each cycle. The enzyme is said to complete the process in under 10 minutes and is reusable. (Source: Chemical Week, 21 March 1984)

UK community seeks access

British molecular biologists, frustrated by inadequate computing facilities, are attempting to persuade research councils and cancer charities to finance a new national computer link-up and software support scheme for protein and DNA sequencing. Their concern arose from a feeling in the research community that scientists have to waste too much time in writing or modifying programmes that are system-dependent. It was also felt there was scope for an improvement in access to databases. Enthusiasts in the research community, however, are already talking of a network of "may be 6 or 8" VAX machines at national centres, providing regular updates for databases and allowing the transfer of the latest software. These might in turn be connected to microcomputers for local analysis once the letter crunching had been done by the large machines. One estimate puts a price of "one or two million" pounds on the scheme.

The three research councils involved, the Medical Research Council, the Agricultural and Food Research Council (AFRC) and the Science and Engineering Research Council, all have their own budgetary problems, but, all of these bodies give a high priority to the new biology, and the cancer charities are thought likely to look favourably on the idea. One of the difficulties is that the subject falls between the concerns of several research councils; however, the existence of the inter-research committee has allowed a quick response. It is also argued that the advantages of a computer link-up have already been demonstrated by the "Starlink" network used by astronomers. (Extracted from Nature, 17 May 1984).

C. RESEARCH

Research on human genes

Herpes on the rise in newborns

A herpes infection for most adults is more nuisance than health threat, but the virus can be deadly in newborns. Though the incidence in infants is still quite small, one report hints that those numbers could be climbing.

From 1966 to 1969, doctors in King County, Wash. recorded 2.6 incidences of neonatal herpes for every 100,000 babies born. That figure had jumped to 11.9 by 1981, paralleling a suspected increase in genital herpes in adults. Although the total number of infants born with the disease is still small, the increase underscores the need for a fast, accurate method of diagnosing herpes in pregnant women.

One-third of the newborns afflicted with equally dangerous Herpes I or Herpes II virus die from the illness, and another one-fourth suffer brain damage. The vast majority acquire the disease at birth as they pass through an infected mother's birth canal. Most women with herpes deliver healthy babies through vaginal delivery; only an active herpes episode within the few days preceding delivery could be dangerous for the infant. At least 85 per cent of these episodes are accompanied by easily detected lesions, and an obstetrician alerted to the danger can deliver the baby by cesarean section if the need arises. But occasionally the episodes are not accompanied by obvious symptoms, and are probably the source for most cases of neonatal herpes, the scientists say. (Source: Science News, December 1983)

Collaborative Research seeks FDA Approval of Thyroid Test

Collaborative Research Inc. has applied for US Food and Drug Administration approval of a new test for thyroid disorders, based on its Enzyme Membrane Immuno Assay (EMIA) technology. This highly sensitive technology is based on the use of liposomes. Antigens or antibodies are attached to the external surfaces of liposomes containing enzymes. The antibody-antigen reaction in the presence of complement (a set of serum proteins activated by antibody-antigen complexes) causes a puncture of the liposome, which in turn releases an enzyme - which is then measured by a spectrophotometer. Collaborative expects to market the thyroid test by the end of the year. (Extracted from Biotechnology Bulletin, Vol. 3, No. 1, February 1984).

Fertility hormones cloned

A group of researchers at Integrated Genetics, a biotechnology firm in Framingham, Massachusetts, has succeeded using recombinant DNA technology to produce two human fertility hormones, human chorionic gonadotropin (hCG) and human luteinizing hormone (hLH). This is one of the first reports of investigators using recombinant DNA technology to produce molecules that are a combination of proteins and carbohydrates in mammalian cells, according to molecular biologist Leroy Hood of the California Institute of Technology.

The two fertility hormones have similar structures, each consisting of two polypeptide chains that are put together inside cells and "processed". A section at one end of each chain is a marker that guides the chain to the cell's secretory apparatus and is cleaved once the chain gets there. Before the hormones are secreted from the cell, sugar molecules are added to them. The hormone hCG, for example, is 30 per cent sugar by mass. If sugars are not added to these hormones, the hormones are biologically inactive.

Bacteria, which molecular biologists usually use as protein factories, cannot carry out this type of processing. Although they can express added mammalian genes, they do not add sugars to the molecules and do not excrete them. Thus molecular biologists believe the only way to produce molecules as complex as the fertility hormones is to make them in mammalian cells, using standard methods of

genetic engineering. David Housman, a founder of Integrated Genetics and a faculty member at Massachusetts Institute of Technology, used mouse cells to make hCG and hLH, infecting them with a bovine papilloma virus, which inserts itself in the chromosomes of the cells. To the virus, he and his associates added the fertility hormone genes and a mouse metallothionein gene containing control regions that promote gene transcription. These are well-known methods, although, says Housman, to actually make the methods work was a "nontrivial achievement".

The major problem with this method is that the engineered DNA is unstable - the genes tend to rearrange themselves. If this happens, the hormone genes may not be expressed.

Judith Vaitukaitis, an endocrinologist and fertility specialist at Boston City Hospital, has tested the biological activity of the fertility hormones produced by the Integrated Genetics group. She thinks that these hormones will be clinically useful in the treatment of infertility because they can induce both ovulation and sperm production. Although hCG and hLH are now available for infertility treatment, the hormones are extracted from pituitaries, urine, or placentas and so are not completely pure. Vaitukaitis estimates that there is between 1 and 5 per cent cross-contamination with other hormones, which can complicate treatment and clinical research. (Extracted from Science, 24 February 1984).

Celltech's human growth hormone may be safer than Genentech's

Genentech's synthetic hGH may not be the first on the market. The American company is still struggling to resolve some of the serious side effects which have arisen in the clinical trials, resulting in delays in obtaining approval from the US Food and Drug Administration. The UK company Celltech is understood to have developed a version of hGH which is identical to that found in the human pituitary gland. Celltech, which has been collaborating with the Swiss company Serono Laboratories, hopes that its product will be free of the side effects associated with the Genentech one, which, has the 'wrong' final protein. Some research results indicate that hGH could help heal wounds, opening up a significant post-operative market worth perhaps £70 million worldwide. (Extracted from Biotechnology Bulletin, Vol. 3, No. 1, February 1984).

Virus may produce anti-hepatitis vaccine

Vaccinia virus combined with genetic material from hepatitis B virus produces a vaccine against hepatitis, according to researchers at the National Institute of Allergy & Infectious Diseases (NIAID). The hybrid virus contains the gene for hepititis B surface antigen. This stimulates protective antibodies when injected into animals. The foreign DNA is inserted into the vaccina virus genome at specific sites that do not affect the infectivity of the virus. Genes for antigens of various disease-causing agents could be used to make a number of different live vaccines. The hybrid virus produces a local reaction to vaccinia virus and stimulates significant amounts of antibody to hepatitis antigen when injected into rabbits. Further animal studies are needed to determine the vaccine's safety and effectiveness. Human studies can then be planned. (Extracted from Life Sciences, February 1984).

A genetically engineered "orphan drug"

The first product of genetic engineering to be granted "orphan drug" status by the Food and Drug Administration has been produced by Cooperbiomedical (Palo Alto, Calif.). The drug, alpha-1 antitrypsin (AAT), has potential value in treating an unusual form of emphysema. Under the Orphan Drug Act of 1983, which was enacted to encourage development of drugs for rare diseases, companies get tax breaks on money that they spend researching drugs with a limited market. They are also permitted to sell such drugs exclusively for seven years. Clinical trials of AAT are expected to begin in October. If these tests are favourable, AAT could be available to treat patients by the end of 1985. An estimated 50,000 people in the US suffer from the rare form of emphysema. (Extracted from Chemical Week, 29 February 1984).

Human-human hybridomas

A method to produce human-human hybridomas has been patented by R. E. Ritts, Jr. of the Mayo Clinic. Most hybridomas are a fusion of human and mouse cells, but the human-human hybridomas could provide additional benefits. The hybridomas are produced from a line of human cancer cells that can be cultured continuously and that do not secrete antibodies. They are fused with healthy cells from the immune system to make the desired antibodies. (Extracted from Chemical Market Report, 5 April 1984).

New proteins

The history of organic synthesis promises to repeat itself in genetic engineering. For their first decade in practice, biotechnologists were largely limited to the synthesis of products made by plants and animals. Now they are trying to improve on nature by producing new proteins that are stronger than the ones nature makes, are more active as catalysts, and are better at fighting and warding off diseases.

The procedures and techniques are already available to do just that, but a fundamental understanding of how to apply these techniques to the modification of the structure of the protein in order to improve its function is missing. Biotechnologists are now obtaining some of the needed understanding and have already taken the first steps toward developing the art of protein engineering via two different approaches to tailoring proteins. One involves borrowing techniques and know-how from organic chemists; the second involves reworking a protein's DNA, so that it instructs the cell to make a novel protein the cell would not ordinarily produce. Using the first approach, biotechnologists have already produced human insulin.

Genetic engineers have yet to succeed commercially with the second approach to engineering proteins - reworking the DNA coding for the protein - but they have scored some laboratory successes, such as the modified human enzyme dihydrofolate reductase (DHFR) which helps bring carbon atoms together to build amino acids and other molecules in the body, and altering the ability of a human enzyme, tyrosyl transfer ribonucleic acid synthetase, to bind with its substrate, adenosine triphosphate. The binding is a key step in the manufacture of all human proteins.

Reworking the DNA coding for a protein presents genetic engineers with a dual challenge. Proteins are generally complex molecules made up of long chains of amino acid building blocks folded in a convoluted, three-dimensional structure. Both the amino acid sequence and the three-dimensional structure are crucial to a protein's ability to do its job.

The genetic engineer's first problem in trying to improve on natural proteins is mapping the protein's structure. The job is so time-consuming that, thus far, researchers have deciphered the amino acid sequence of only about a hundred of the thousands of proteins found in nature. (Extracted from Chemical Week, 21 March 1984).

Human interleukin-2 by recombinant DNA

Human interleukin-2 (IL-2), a protein that enhances the effect of many natural immune functions can now be made in large amounts by recombinant DNA technology. Steven A. Rosenberg and Elizabeth A. Grimm of the National Cancer Institute, and Michael McGrogan, Michael Doyle, Ernest Kawasaki, Kirston Koths, and David F. Mark of Cetus Corp. have engineered the expression of the protein in Escherichia coli using complementary DNA derived from a human leukemia cell line. This material is found by the researchers to make a protein product that is identical to that made by normal human blood cells. Their purified recombinant material supports the growth of mouse and human cell lines that are dependent on IL-2 and generates IL-2 activated killer cells from mouse and human lymphocytes. In the mouse, it has a half-life of two to three minutes - about the same as natural IL-2 - and stimulates the same immune system response the natural protein does. (Source: Chemical and Engineering News, 26 March 1984)

Gene therapy may become feasible soon

Scientists predict that it will be only a few years before it will be technically feasible to treat patients with certain rare inherited diseases by using viruses to transfer genes into cells.

The idea of using viruses for gene therapy is not new but, until recently, investigators could see no way to overcome what looked like insurmountable problems with it. The viruses they wanted to use are retroviruses - RNA tumor viruses that are highly unusual because they do not kill cells like most other viruses do. Instead, they enter cells during periods of division and insert their viral genes into the cells' chromosomes. The goal, now close to attainment, is to use these viruses as a vehicle for carrying certain therapeutically valuable genes into a patient's defective cells.

The challenge has been to find a way to make a noninfectious virus that carries particular genes to be transferred but that can essentially do nothing but enter a cell and insert the genes. Researchers knew how to engineer such a virus and realized that they would have to produce it in a cell along with a "helper virus" that would supply it with a coat which it would need to enter cells. But they were baffled by the problem of separating the infectious helper from the uninfectious virus to be used for gene transfer. If both the helper and the uninfectious virus were released from the same cell and if they both were wrapped up in coats supplied by the helper, the two viruses should look identical.

About a year ago, researchers at MIT found a way to avoid this helper virus problem. The key was their discovery that a particular segment of the viral RNA is essential for packaging an infectious virus in a protein coat. If that segment is missing, the virus can never leave the cell. The MIT group engineered a helper virus that was missing in the piece of RNA. In this way, the helper could supply a coat for the recombinant virus but would not itself be wrapped in a coat and so would not be able to leave the cell or enter others. Although the recombinant virus can get into another cell and insert its genes into that cell's chromosomes, it cannot be transmitted any further because it lacks the necessary viral genes.

The recombinant retroviruses theoretically should be capable of inserting their genes into a wide variety of dividing cells that are exposed to them.

In human terms, transfer into stem cells eventually may be important in the treatment of certain hemolytic diseases, such as sickle cell anemia and thalassemia, in which there is a fundamental disorder in blood cell production. However, technical problems with controlling the regulation of transferred genes so far preclude attempting such therapy. Other diseases, such as certain immune deficiency diseases, may, however, be treated by gene transfer into bone marrow stem cells. These diseases are not diseases of blood cells but they may be cured by genes that are expressed in bone marrow stem cells, even though the genes are normally expressed elsewhere.

Despite the promise that the retrovirus method offers, most genetic diseases are not likely to be amenable to treatment by it. The vast majority of genetic diseases are caused by too much genetic material rather than the lack of a gene. For example, Down's syndrome is caused by an extra chromosome 21. No one has any idea how to selectively remove genes and chromosomes. And even those diseases that are caused by missing or non-functional genes may not yet be suitable for retrovirus treatment. The problem is that, so far, molecular biologists have no way of controlling where a transferred gene inserts itself or - in most cases - in which cells it is expressed.

Lesch-Nyhan syndrome and adenosine deaminase deficiency might be ideal test cases for gene therapy for two other reasons as well. In both diseases, for reasons that are not clear, cells that carry the missing gene have a competitive advantage over cells that do not. And, in both diseases, there is reason to believe that even a little bit of the missing gene product can alleviate the disease. (Extracted from Science, Vol. 223, 30 March 1984).

Advances in interferor types from alpha to epsilon

A new type of human interferon has been isolated by Damon Biotech, Inc., as revealed by a recent European patent disclosure. Dubbed e, or epsilon, to indicate its ephithelial origins, not its order of discovery, the antiviral protein is produced by cultured human epidermal, conjunctival, vaginal, and esophageal epithelial cells in response to viral infection. Inventors Allan Jarvis and David I. Kosowsky claim in the patent application that the natural protein "has increased anti-viral and anti-tumor potency in the treatment of epithelial tissue ... as compared to its efficacy with ... other cell types".

Damon hopes the new interferon will be useful in treating epithelial-cell-specific tumors and viral infections, but also suspects it may have broader potency. INF-e has so far been studied only in vitro, the next step will be tests on laboratory animals. (Extracted from McGraw-Hill's Biotechnology Newswatch, 2 April 1984).

Clues to immune system function

Recently reported research provides the first detailed structural information on T-lymphocyte antigen receptors, the nature of which has been one of immunology's most important and controversial issues for the past 10 years. Instead of trying to isolate the receptor proteins themselves - a strategy followed by a number of other researchers - two independent research groups used recombinant-DNA techniques to isolate T-lymphocyte-specific genes that appear to code for the proteins. Tak W. Mak and co-workers at the Ontario Cancer Institute and the University of Toronto isolated genes from human T-cells and showed that they code for a protein similar to the light chain of immunoglobulins. Mark M. Davis, Stephen M. Hedrick, and co-workers at Stanford University's school of medicine and the National Institutes of Health isolated analogous genes from mouse T-cells, which also code for an immunoglobulin-like molecule. Davis' group showed that the genes rearrange in a pattern strikingly similar to that of genes that code for the immunoglobulin light chain.

According to Davis, the findings provide a basis for research on T-cells along the same lines that have proven successful for understanding B-cells. Of the two major immune cell types - B-lymphocytes and T-lymphocytes - the former are much better understood. B-cells, which mature in the bone marrow, bind antigen and give rise to cells that produce antibodies against it. The B-cell antigen receptors are immunoglobulins bound to the cell surface. The structure of these immunoglobulins is well known: They consist of a tetramer of two identical heavy peptide chains and two identical light peptide chains. (Heavy and light refer to the molecular weight of the respective chains.)

The chains are characterized by regions of amino acid sequence that are constant among immunoglobulins of the same type (constant or C regions) and regions that are highly variable (variable or V regions) joined by short amino acid sequences (joining or J regions). Different genes code for each region. Hence the vast diversity of B-cell antigen receptors is generated, in the case of the light chain, by recombination of a C-region gene, one of several J-region genes, and one of the large number of V-region genes. The same pattern applies to the heavy chain except that the C-region, which accounts for the additional molecular weight, requires a total of three gene segments to code for it.

Researchers have long suspected that a similar mechanism must be involved in generating T-cell receptors because a similar level of diversity is required. However, it has been shown that T-cells do not express immunoglobulin genes. An additional complexity arises because T-cells do not respond to free antigen; the antigen must be presented to the T-cell on the surface of another cell. The T-cell responds to the antigen and to molecules coded for by the organism's own major histocompatibility complex (MHC). So a major question has been whether the T-cell receptor has separate binding sites for antigen and MHC or one site that binds both.

According to Stanford's Davis, who is an assistant professor of medical microbiology, the research that led to the current findings began as an effort to study the genetics of lymphocytes.

The researchers essentially work backwards from the messenger RNA (mRNA) of a mouse T-cell hybridoma. Using the enzyme reverse transcriptase, they synthesize what is called cDNA from membrane-bound, T-cell mRNA. These single-stranded molecules are then repeatedly hybridized with B-cell mRNA and fractionated on a hydroxyapatite chromatography column that separates double-stranded molecules - those that hybridize - from single-stranded molecules - those that do not hybridize and are, hence, unique to the T-cells. The procedure eliminates all but about 30 to 70 different mRNA molecules from the total of about 13,000 mRNA molecules that another experiment shows exist in the cells. In the search for the genes for the T-cell receptor protein, the researchers carry out a further selection. The 200 cDNA molecules are used as a probe to screen a library of cDNA clones that was itself constructed by an analogous screening process. That library of about 5,000 clones was enriched about 20-fold for T-cell-specific sequences.

These subtraction screening processes isolated 35 clones. Of those, five were eliminated because they reacted with B-cell mRNA in yet another screening process. The remaining 30 represented 10 distinct patterns of mRNA size and expression.

The series of experiments that isolated those 10 clones was similar in its overall strategy to the work of Mak's group. The Canadian researchers then showed that the protein sequence inferred from one of the T-cell-specific genes they isolated exhibited significant homology, or similarity in amino acid sequence, with a B-cell immunoglobulin.

The Stanford researchers, however, also screened the clones for possible genetic rearrangements. The experiments showed that the DNA in one of the clones, designated TM86, had rearranged in T-cells but not in nonlymphatic cells or in B-cells. They also demonstrated that the gene segments are rearranged differently in T-cells of different antigen specificities, which would be expected because different specificities require different receptors.

The protein inferred from TM86 exhibits about 30 per cent sequence homology with the mouse immunoglobulin light chain. The protein also contains clearly defined C-, V-, and J-regions, the sizes and structures of which are similar to those of immunoglobulins.

Further evidence that the gene encodes one chain of the T-cell receptor is that antisera raised against synthetic peptide fragments of a TM86 clone inhibited antigen-dependent function of T-cells.

Work in other laboratories has shown that the T-cell receptor is probably a dimer of two distinct proteins of about the same molecular weight in contrast to the immunoglobulin tetramer of two light chains and two heavy chains. TM86 was the only clone that exhibited genetic rearrangement, so the gene for the other T-cell receptor protein very likely was not isolated. Davis' group is using the same screening process to obtain additional clones in an attempt to isolate the gene for the other chain. He says about a dozen new clones have been isolated and are being screened for genetic rearrangements.

With the structure of the T-cell antigen receptor eventually in hand, Davis says, investigations of how T-cells mature and function can proceed on a more rational basis. (Extracted from Chemical and Engineering News, 16 April 1984).

Ras binds to cell receptors

Clues to the connection between oncogenes and cell growth come from the work of molecular biologists Toren Finkel and Geoffrey M. Cooper of Harvard's Dana-Farber Cancer Institute, Boston. They study the ras oncogenes, originally identified in mouse sarcoma viruses but now thought to be present in all human cells and activated (by mutation) in about 20 per cent of human tumors of a variety of types. The research workers have identified these genes' protein production, a 21,000-dalton polypeptide called p21, in human cells and have analyzed the role it plays there. They find that the protein complexes with the transferrin receptor on the cell surface. Transferrin, the protein that transports iron into cells, is critical for cell growth, and transferrin receptors are found in high concentration

in both tumor cells and rapidly growing normal cells. The exact effect of p21 on transferrin receptors remains to be established, but the findings "suggest that ras proteins function in conjunction with transferrin receptor in the regulation of cell growth". (Source: Chemical & Engineering News, 23 April 1984)

Evidence mounts for erb B role

Meanwhile, evidence mounts linking a different oncogene, erb B, with a different cell membrane receptor important in cell growth, the human epidermal growth factor (EGF) receptor. Glenn T. Merlino, Ira Pastan, and co-workers at the National Cancer Institute, along with Tadashi Yamamoto and colleagues at the University of Tokyo, find that in epidermal carcinoma cells, which have an unusually high number of EGF receptors, the DNA sequence responsible for EGF receptor production is magnified 30-fold. Furthermore, comparison of this DNA sequence with that from normal cells shows that rearrangements have occurred in this receptor gene region. Earlier this year, Michael D. Waterfield of the Imperial Cancer Research Fund Laboratories, London, and co-workers showed that the protein product of this oncogene resembled that of six distinct peptides from the EGF receptor. (Source: Chemical & Engineering News, 23 April 1984)

Cause of AIDS probably identified

Researchers recently announced the isolation and characterization of a previously unknown virus that they believe, with near certainty, is the cause of acquired immune deficiency syndrome (AIDS). They also announced discovery of a technique for continuous production of large quantities of the virus in cell cultures, a major step toward better understanding of the disease and development of a vaccine against it.

The research was described at a press conference by Robert C. Gallo of the National Cancer Institute, Bethesda, Md.

Gallo heads a research group at NCI which, in collaboration with researchers from a number of other institutions, developed several complementary lines of evidence that strongly suggest that a type of human T-cell lymphotropic virus (HTLV) causes AIDS. The research demonstrates that the new virus, dubbed HTLV-III, shares many characteristics with two previously described members of the viral family, HTLV-I and HTLV-II, but also that it is a distinct new subclass of that family.

HTLV-I and HTLV-II are retroviruses that preferentially infect helper T-lymphocytes. They have been associated with human leukemias, which are essentially cancers of T-cells. T-cells are one of the two major types of immune system cells. In AIDS victims, helper T-cells are severely depressed causing susceptibility to numerous opportunistic infections.

One of the major obstacles overcome by the researchers was development of the technique whereby large quantities of HTLV-III can be grown in cell culture. In early work, they detected HTLV variants in cultures of normal T-cells grown with T-cells or blood plasma from AIDS patients. They detected the variants for only a short time, however, because, unlike HTLV-I and HTLV-II, the variants presumably killed the T-cells that were infected. The researchers discovered and cloned a cancerous T-cell line which HTLV-III can infect and which grows continuously after such infection.

That new "immortal" T-cell line is important for two reasons. For one, it allowed development of immunological reagents to characterize the virus and detect it in humans, essentially forming the basis for the remainder of the research that has been reported. It also holds the promise of assays to screen people at risk of developing AIDS, to screen blood and blood products used in transfusions and in controlling hemophilia, and for a vaccine against the disease.

Using immunological probes coupled with other criteria, the researchers discovered HTLV-III in 18 out of 21 samples from patients with what is now called pre-AIDS (previously called lymphadenopathy syndrome), three of four normal mothers

of children with AIDS, three of eight children with AIDS, and 23 of 64 AIDS patients. HTLV-III was found in none of 115 healthy heterosexuals.

Although the incidence of HTLV-III in AIDS patients appears low, the researchers point out that tissue samples from late-stage AIDS patients contain very few living helper T-cells. In-vitro studies of infected T-cells show that the cells produce virus for only two to three weeks after infection.

The researchers also demonstrated that blood sera from patients with AIDS or pre-AIDS reacted with a number of antigens associated with cells infected with HTLV-III. Characterization of these antigens shows that HTLV-III contains proteins similar to those of HTLV-I and -II as well as proteins that distinguish it as a distinct subclass of the HTLV family.

Further strengthening the case for HTLV-III being the cause of AIDS, the researchers found that 88 per cent of clinically diagnosed AIDS patients and 79 per cent of pre-AIDS patients possessed antibodies to HTLV-III antigens. By contrast, only one of 186 control subjects showed antibodies for HTLV-III.

The research findings open up a number of lines of research both into understanding AIDS and controlling it. (Extracted from Chemical & Engineering News, 30 April 1984).

Research on plant genes

Chromosome position predicts gene expression

Based on the position of chromosomes within the nucleus of hybrid plants, it is possible to predict which genes are most likely to be expressed and which chromosomes are likely to be lost from the cross. Michael D. Bennett, whose paper was a highlight of the 16th Stadler Genetics Symposium, Gene Manipulation in Plant Improvement, presented his work done at the Plant Breeding Institute, Cambridge, England, showing that chromosomes that line up along the outside edges of the metaphase plate during cell division are more likely to have their genes expressed than those on interior chromosomes, but that the peripheral ones are most easily lost from the cross in succeeding generations.

Bennett uses serial-thin-section electron microscopy combined with three-dimensional computer reconstruction to identify unequivocally each of the chromosomes of the plant cross, and to plot the position of the centromeres on the metaphase plate. So far, his team has reconstructed some 300 root-tip cells from 20 cereal hybrids - especially those arising from haploid crosses of various barley and rye species. He found that in many of the karyotypes he examined the haploid genomes had separated.

He explains the dominance of outer-ring chromosomes this way: After cell division, the chromosomes retain their positions as the nuclear envelope reforms. Genes located on chromosomes near the envelope are transcribed more often. (Extracted from McGraw-Hill's Biotechnology Newswatch, 2 April 1984).

Plants that produce their own herbicide

Allelopathy, the harmful influence on plant life by the toxic secretions of other plants and micro-organisms, is moving closer to commercial exploitation. The American Chemical Society symposium in St. Louis, last April focused attention on this area of research. The interest in allelochemicals is not suprising, for there is much at stake. In the US alone, crop losses caused by weeds and the cost of their control total about $14.1 billion annually.

However, some precautions are necessary because allelopathy is known to have profound effects on both land and water ecosystems, including effects on plant succession, patterning of plants, inhibition of nitrogen fixation and the inhibition of seed germination and decay. Thus the major challenges to researchers studying allelopathy are two-fold: To minimize the negative impacts of allelopathy on crop growth and yield and to exploit the positive aspects of allelopathy on weed control and crop growth regulation.

At the ACS meeting, a number of researchers reported on the work they are now doing in allelopathy. Prof. Frank Einhellig of the University of South Dakota, for example, is studying the effects of ferulic acid, para-coumaric acid and extracts from several allelopathic weeds on the water balance in grain sorghum and soybeans. He found that under greenhouse conditions, concentrations as low as 0.25 millimole of weed-generated ferulic acid and p-coumaric acid disrupt the water balance of both soybeans and grain sorghum by reducing the osmotic potential and turgor (fluid) pressure of the plants. He said that research in the field of allelopathy could lead to new agricultural management practices. Farmers may plant a field in autumn with a cover crop, such as rye or clover, let winter's freezing temperatures kill off the crop and then, without tilling the soil, plant a crop in spring that could benefit from the allelopathic effects of the cover crop. The cover crop would decrease wind and water erosion of the soil and would improve the soil's organic content. The problem would be in matching an autumn cover crop with a spring crop so the allelopathic secretions of the cover crop are beneficial instead of detrimental.

Another researcher who believes allelopathy research could change agricultural management practices is Judith M. Bradow, a plant physiologist at the Agriculture Department's Southern Regional Research Center (New Orleans) who is studying the ability of the Palmer amaranth and ragweed to inhibit the germination of different crop and weed seeds. She found that crude extracts of Palmer amaranth inhibit the germination of carrot, onion and apple seeds and that ragweed extract inhibits lettuce, tomato and carrot seed germination.

Prof. Robert van Aller of the University of Southern Mississippi (Hattiesburg) is working on the aquatic effects of allelochemicals released from a species of spikerush on the population of blue-green algae in ponds. At concentrations as low as 0.5 ppm, van Aller found that certain spikerush fatty acids from 18 to 20 carbon atoms in length inhibit the growth of blue-green algae but do not affect other species of algae. The fatty acids could be useful algal regulators, he says, because blue-green algae often reduce the oxygen supply in ponds whereas other species of algae increase the oxygen supply. Also working on the aquatic effects of allelochemicals is Prof. Dean F. Martin, of the University of South Florida. By studying ponds surrounded by cypress trees, he found that the growth of hydrilla is inhibited by a chemical that micro-organisms release when breaking down cypress tree residue. (Extracted from Chemical Week, 2 May 1984).

Research on yeast and fungus genes

Enzyme successfully isolated

High-purity cytochrome B enzyme and adenosine triphosphate have successfully been isolated by a research team at Tokyo University. Cytochrome helps bacteria in E. coli to breathe, and a weak acidic surfactant was used to recover it. Ordinary neutral surfactants destroy its active components. Purification was accomplished via centrifuge separation. Both substances are sandwiched by membranes and are hard to separate into pure forms. E. coli has a tendency to retain the substances it helps produce, and this research will help make recovery easier. (Extracted from The Japan Economic Journal, 28 February 1984).

Gene engineers upgrade brewers yeast

By introducing a new gene-delivery system and a new antibody-resistance selection marker, a major Canadian brewer reports taking two major steps toward genetically altering yeast to make beer more efficiently, at less cost and with fewer calories. Chandra J. Panchal of Labatt Brewing Co. Ltd., London, Ontario, told a workshop at the New Delhi Symposium that traditional Saccharomyces cerevisiae brewing yeasts could do a better job if they had genes from a starch-digesting yeast, Schwanniomyces castelli, to metabolize the calorie-adding starches, dextrins, lactose and cellobiose in beer ferment. Panchal developed a liposome transfer method to introduce a gene for "killer" toxin into brewing strains. Adding the microbial toxin factor cuts down on contamination of brewery strains by wild yeast and other microbes that might cause off-flavours.

Some Saccharomyces strains do act as "killers" by secreting a toxin synthesized by two double-stranded RNA molecules, "L" and "M". The latter, codes for the toxin and also for immunity against it. To transfer this M gene from a killer strain into a non-killer, toxin-sensitive, L-strand-only brewing strain of yeast, Panchal and his associates in Labatt's production research department encapsulated M sequences of RNA into liposomes which were then taken up by the much larger real spheroplasts of brewing yeast strains. Use of liposomes greatly enhanced the nucleic acid uptake by the cells. The resulting transformed colonies expressed killer toxin, but most lacked stability.

Another development that will make engineering brewers yeast an easier task is a new antibiotic resistance gene the group has discovered: starch-digesting Schwanniomyces is resistant to a broad-spectrum antibiotic, geneticin G418. Labatt's brewing strains of S. cerevisiae and S. uvarum lack the resistance gene. (Extracted from McGraw-Hill's Biotechnology Newswatch, 19 March 1984).

Research on viral genes

A virus to control gypsy moths

Despite massive dosings of chemical pesticides, such as carbaryl, diflubenzuron, trichlorfon and acephate, marauding bands of gypsy moths have caused record defoliations in the last three years, spreading from the hardwoods of the American Northeast to forests in the South and the West, and even to urban centres. Pesticide manufacturers have been striving to develop new pesticides - particularly biological ones - that not only are effective against the moth, but are nontoxic to humans, animals or other insects. So far, the micro-organism Bacillus thuringiensis (Bt) has been the leader of the new entries, but now a small biological pesticides firm in Gainesville, Va., Reuter Laboratories, says that by 1985 it will make available commercial quantities of a moth-killing virus. "The virus is said to be a better control because it is endemic to the gypsy moth."

The firm's nucleopolyhedrosis virus (NPV) comes as a wettable powder that is mixed with water and sprayed on leaves. When foraging larvae ingest the leaves, the virus causes them to swell until they rupture, spewing NPV onto foliage where other larvae feed.

NPV is not a product of Reuter. In fact, the Forest Service of the USDA was the first to isolate NPV, and in 1978 registered it with the Environmental Protection Agency under the name Gypchek. Although the technology was available to corporations for commercialization, an economical method to mass-produce the virus remained elusive for years. In 1982 Reuter contracted with Otis Methods Development Center (Boston) to streamline the USDA protocol and is now building a plant that has quarantined chambers for each step.

The virus is likely to be expensive. Unlike Bt, which is made by fermentation or genetic engineering, NPV must be cultivated in vivo but it is hoped the virus will eventually be made by bioengineering techniques. (Extracted from Chemical Week, 25 April 1984).

Research instrumentation

Electricity may alter shape of sickle cells

There might be a way of electrically "shocking" the distorted red blood cells of sufferers from sickle cell anaemia back into shape. Shiro Takashima and Toshio Asakura at the University of Pennsylvania in Philadelphia adapted an electric-shock treatment which some German scientists are enthusiastically developing. They placed sickled cells in solution between two electrodes, and charged them with 5 millisecond pulses of alternating current at radio frequencies of between 10 kHz and 1 MHz. With each fresh pulse the voltage was increased until at a critical threshold the deformed cells turned into normal shapes within a few minutes. This bizarre effect had nothing to do with heating, because the pauses between each burst of current allowed any heat to be dissipated. Instead, the electricity itself seemed the answer, perhaps provoking the red cell membranes into

opening up pores wide enough to let water molecules in, so pumping up the cell. However, Takashima and Asakura also felt that alternating currents could crack up the haemoglobin rods, and break the rigid mould that creates the sickle shape.

A great deal more research will need to be done before experimental trials of this technique can be carried out on patients with sickle-cell anaemia. (Extracted from New Scientist, 26 April 1984).

Computers aid genetic design

Scientists at Battelle Pacific Northwest Laboratories in Washington, are applying the principles of computer aided design (CAD) to designing new genes, and presented a software package, at Biotech 84, an international biotechnology conference held in May in London.

Everything the experimenter could do before in his head, or on paper can be done on a VDU, taking advantage of six-colour graphics. There is no need to constantly dip into and out of a number of computer files, or to print out information before going on to the next step.

The Battelle system is based on graphics. It offers the editorial freedom of a word processor, while other programmes can be compared to an electronic typewriter.

The scientist can do the usual things, such as call up stored information on the genetic profiles of certain molecules, and count the number of DNA building blocks in a particular chunk of genetic material. It is then possible to find areas of similarity between molecules. Also DNA restriction sites can be mapped. The programme can also be instructed to display on the VDU a whole plasmid - a circular piece of DNA from a bacterium.

The special trick of the Battelle package is to zoom in from a global view of a plasmid, that could consist of 4,000 bases, to focus on a minute section, a mere 8 units long.

However, the real novelty in the system lies in its ability to design any genetic engineering experiment that the scientist desires, without resorting to other computer files or to printouts. Pieces of DNA can be inserted or deleted at certain spots, and chuncks inverted - all at any level of magnification.

The software, which should be available by September, will cost between $20,000 and $40,000 and runs on the larger VAX computers made by Digital Equipment Corporation, but will be equally suited to the newer range of digital miniVAX computers.

Biotech 84 had other things to show that reveal how biotechnology is moving out of the laboratory and into the industrial world. A small Swedish biotechnology company plans to challenge the hold the Japanese have on the lucrative market for animal feed additives, with a new process for making amino acids. AC Biotechnics, based near Malmo, claims to have the technology to manufacture large quantities of tryptophan and phenylalanine using genetically engineered microbes.

Tryptophan is already used in manufacturing pharmaceuticals and food, but the company sees a potential market of thousands of tonnes for animal feed-stuffs. Phenylalanine already has an assured future as the building block for the synthetic sweetener aspartame.

Commercial production of amino acids is currently done in large vats with conventional, if heavily inbred, bacteria. Biotechnics' genetically engineered microbes are more productive, cheaper to grow, and can operate over longer periods of time than the conventional bacteria.

In the area of health care Enzo Biochem revealed its scientists are working on a test for oncogenes. Everyone carries these cancer-causing pieces of DNA. The assay uses a strip of DNA, called a probe, to fish out the oncogene or its product

from a library of genetic fragments prepared from the patient's own DNA. The test is very sensitive, is extremely accurate, and can pick up 400 molecules of oncogene product per cell. (Extracted from New Scientist, 31 May 1984).

General

Cancer and the developing countries

More than half of the 6 million people who die from cancer each year are in developing countries making it one of the main killers of people over five years of age in the third world. The main reason is that the poor live longer than they used to. For example, in China, life expectancy at birth is 61 compared with 40 in the 1950s. As infectious diseases such as smallpox and typhoid are progressively contained, the poor die instead from illnesses associated with middle- and old-age.

The pattern of cancers among the world's poorest people is still very different from that of the rich. In industrialised countries people die from lung, intestinal and prostate cancers as a consequence of smoking, alcohol abuse and high fat diets. In the third world the most prevalent forms of cancer are those of the liver, mouth, oesophagus and cervix, each of which claims 100,000-300,000 victims a year. These cancers are associated with poor living conditions and undernourishment.

Liver cancer in Africa, south-east Asia and the western Pacific is mostly the result of infections from hepatitis B, which causes jaundice. Yet about 80 per cent of liver cancers could now be prevented by immunisation with a new hepatitis B vaccine. In some parts of Africa and Asia there are as many as 30 new cases of liver cancer annually per 100,000 people, compared with three new cases per 100,000 in North America, and China accounts for over 40 per cent of liver cancers in the world.

Mouth cancer is the commonest form in south-east Asia where there are some 100,000 new cases yearly. Betel nut and tobacco chewing, which has been practised for thousands of years, is thought to be the main cause.

However, in this instance, extra vitamin A could help to protect the millions of Asians who chew betel quids every day from getting mouth cancer. Researchers at the British Columbia Cancer Research Center in Vancouver and the Medical Ambassadors of the Philippines in Manila, discovered that giving regular quid chewers capsules of Vitamin A and pro-vitamin A can reduce the number of abnormal cheek cells by more than 75 per cent.

Claims that vitamins, particularly vitamins A, C and E, can aid the body to inhibit the initiation and growth of tumours have been around for many years. Other micro-nutrients including selenium have also been attributed with anti-cancer properties, particularly by proponents of "complementary medicine". The rationale for this belief lies in the fact that both vitamins A and E are efficient scavengers of free radicals and other excited and highly reactive molecular species. Free radicals, left to their own devices, react with the first thing they come into contact with, and can be the cause of widespread damage to cell components, most importantly to nucleic acid. The researchers were attempting to investigate the protective effects of retinol (vitamin A) and carotene (pro-vitamin A) on oral cancer in Philippino quid chewers. The quids usually consisted of one-quarter of an areca nut, part of a betel leaf, lime made from heated and crushed snail shells and dried tobacco leaves. The idea of the study was to see whether the two vitamins had any effect on the development of cells (scraped from the inside of the cheeks) with micronuclei.

The proportion of micronucleated cells in 11 quid chewers was much higher, 4.3 per cent at the beginning of the study and 4.8 per cent at the end. But in 40 regular quid chewers who were given 50,000 units of retinol and 150,000 units of carotene twice weekly for three months, micronucleated cells fell from 4.2 per cent to 1.4 per cent.

In Latin America and the Caribbean, cancer of the cervix, associated with promiscuity and lack of personal hygiene, is the most common: some 32 new cases

per 100,000 of the population occur every year. In Egypt the big scourge is bladder cancer, stemming from bilharzia.

The World Health Organization (WHO) estimates that the third world problem will worsen as the poor adopt the lifestyles of the rich and become subject to western-type cancers. For example, between 1963 and 1975 the incidence of lung cancer doubled in Shanghai. Tobacco consumption, while declining in industrialised countries, is increasing in the third world, and cigarettes marketed in some countries, such as India, contain more tar and nicotine than those sold in industrialised countries. The incidence of breast and prostate cancers, linked with high fat and low fibre diets, has long been higher in western countries; now it is on the increase in China and Japan.

A third of all cancers are preventable and a third are curable if detected early enough. WHO is proposing a worldwide campaign on the link between smoking and cancer, which has only recently been acknowledged in chain-smoking China, for example; it will also press for reducing the tar content of cigarettes. An anti-smoking campaign, however, is bound to meet resistance both from governments which raise big revenues from tobacco (63 per cent of the world's tobacco is produced in developing countries) and from western cigarette manufacturers for whom developing countries are an increasingly important market. (Extracted from The Economist, 28 April 1984 and New Scientist, 7 June 1984).

D. APPLICATIONS

Pharmaceutical and medical applications

Dentistry and genetic engineering

Human tooth enamel could be cloned to replace conventional tooth fillings, according to researchers at the School of Dentistry at the University of Southern California and the College of Medicine at Baylor College. The researchers cloned a gene that codes for one of four proteins that make up tooth enamel. If the other three genes could be cloned and if the resultant proteins could be mixed to generate tooth enamel, fillings of silver amalgam, silicate, plastics or gold would become a thing of the past. The researchers used two-day old mice that were producing four enamel proteins. Tissues actually producing the proteins were isolated and mRNA was extracted from the cells. The mRNA was then used to construct a DNA sequence that coded for the largest of the amelogenin proteins. (Extracted from New Scientist, 29 December 1983).

More reliable test for hepatitis

A new diagnostic kit for the detection of hepatitis B (serum hepatitis) has been shown in tests conducted by Massachusetts General Hospital to be significantly more sensitive in detecting infectious blood units than laboratory screens now commonly used. When 6,175 blood donors were screened, the kit, produced by Centocor (Malvern, Pa.), detected 60 per-cent more positive samples than another commercially available immunoassay. The kit is of medical importance in the testing of human blood's ability to transmit viral hepatitis B and in aiding the diagnosis of patients with the disease. The Massachusetts General study showed that the hepatitis B surface antigen is present in the blood far longer than had previously been thought. (Source: Chemical Week, 21 March 1984)

Test for detecting genetic diseases

A test developed by scientists at City of Hope (Duarte, California) that can detect certain genetic diseases by "reading" an individual's DNA is expected to become available worldwide for the diagnosis of those diseases by the end of the year. City of Hope, which has applied for a patent on the technique, has awarded exclusive rights to develop the test in kit form to Molecular Diagnostics (West Haven, Conn.), an affiliate of West German chemical and pharmaceutical firm Bayer AG. Test kits will be produced first for common diseases, such as sickle cell anaemia and thalassemia, but eventually, tests might be made to order

for unusual genetic abnormalities. Sickle cell anaemia afflicts millions throughout the world, and thalassemia, said to be the most common of all genetic diseases, is a serious problem for those living in a geographic band from the Mediterranean to Southeast Asia. In the future, gene sequencing will be accomplished for two wide-spread genetic disorders - cystic fibrosis and schizophrenia.

Researchers have developed a genetic test that can detect sickle-cell anaemia prenatally. Researchers have been able to decipher the DNA cryptogram and precisely detect the errors in nucleotide lettering that cause diseases, and can read the code by removing DNA from cells and using restriction enzymes to cut the strands into pieces. They then expose the pieces to different chemicals that break the strands at various nucleotides. The exact order of nucleotides in the original DNA can then be read by comparing the lengths of the chemically broken fragments.

One way to test for sickle-cell anaemia is to take DNA from cells obtained during amniocentesis and treat it with a restriction enzyme. If the DNA is normal, the enzyme will cut the strand at a specific nucleotide and if the strand contains the wrong nucleotide, the enzyme won't be able to cut it there and the resulting longer strand of DNA will reveal the presence of the sickle-cell gene. Diseases can also be detected by DNA probes using part of the sickle-cell DNA sequence, CCTGTGGAG. Using a DNA synthesizer, researchers put together a complementary sequence of nucelotides that includes GGACACCTC and lable it with a radioactive isotope. If the same of DNA from a patient contains the aberrant sequence, the radioactive probes will bind to it and be detected. If the test DNA is normal the probes won't attach to it. (Source: Newsweek, 5 March 1984 and Chemical Week, 21 March 1984)

Monoclonals scale up for industry

As the flow of biotechnology products begins to reach the marketplace, monoclonal antibodies clearly lead the advance. The antibodies can do everything from detect and fight disease to purify medicinal and industrial products. Already, the USA Food and Drug Administration (FDA) has approved 60 diagnostic kits based on monoclonals and will probably approve another 20 kits this year. In addition, more than 100 companies are currently working on products based on the antibodies.

To meet this ever-growing demand for monoclonals, two U.S. firms - Damon Biotech (Needham Heights, Mass.) and Bio-Response (Hayward, Calif.) - are bringing on line facilities that will produce kilogramme quantities of the antibodies. Conventionally, monoclonals are made in gramme and microgramme quantities by growing the antibody-producing cells in culture or in the abdominal cavities of mice. Kilogramme quantities of monoclonals will be needed for the industrial-scale purification of protein products and for use in therapeutic applications, while only nanogramme quantities of monoclonals are needed for diagnostic uses.

The beauty of a monoclonal - and its commercial allure - is its specificity. It can seek out and isolate almost any protein in existence - but only that protein. The antibodies are made by fusing a mouse or human myeloma cell - a cancer cell that grows forever in culture and thus is "immortal" - with an antibody-producing B lymphocyte, a white blood cell made in the spleen. A lymphocyte makes antibodies against only one protein and, once committed, produces that one antibody for the rest of its life. The cell resulting from the fusion of the myeloma and lymphocyte is called a hybridoma. The hybridoma has the capabilities of both its parent cells: it is immortal and churns out antibodies against only one protein. Thus the hybridoma produces a line of almost unlimited - and specific - antibodies.

Damon Biotech is scaling up its production of monoclonal antibodies through a patented process called Encapcel. In the process, hybridomas are enclosed in a gelatin microcapsule coated with polymers. The capsule forms a tough but porous membrane around the hybridomas, protecting them from contamination or disruption, while at the same time allowing them access to nutrients and oxygen through the membrane pores. These nutrients are contained in the culture medium in which the capsules are bathed.

Once the hybridomas have filled the capsules about 50 per cent full of antibodies, the capsules are broken open to release the antibodies. The broken capsules and the hybridomas are then separated from the antibodies, leaving the antibodies as a 99 per cent pure product. The Encapcel process can also enclose other living cells, such as recombinant bacteria, insulin-producing cells from the pancreas and other mammalian cells.

The National Cancer Institute also has entered a joint development agreement with Damon to test a new treatment for B-cell lymphoma. For the treatment, Damon makes a "customized" antibody against the tumor cells of each B-cell lymphoma patient. The antibody, injected into the patient, acts as a drug targeted to destroy the cancer cells without damaging healthy cells. Damon hopes to be able to produce 2 kilogrammes of antibody a year.

The Bio-Response process for making kilogramme quantities of monoclonal antibodies is entirely difference from Damon's Encapcel process. Called the Mass Culturing Technique system, the Bio-Response process uses live cows in its on-line facility. Lymph is removed from the cow and then passed through a filter system, which removes bovine cells and other components that could interfere with hybridoma cell growth or contaminate the monoclonals.

The lymph filtrate is then supplemented with amino acids, vitamins, oxygen and carbon dioxide before it enters the growth chambers containing the hybridomas. The lymph enters and leaves the chambers through semipermeable membranes, hollow fibres that physically separate the hybridomas from the bulk of the circulating bovine lymph. Spent lymph is then returned to the cow. Fluid from the growth chambers - a single cow can support 10 such chambers - can be removed whenever harvesting of the hybridomas or monoclonal antibodies is necessary. The harvesting can be done continuously, in a chemostat manner, or in batches. The Mass Culturing Technique system can also support the growth of cells producing biological products other than monoclonal antibodies.

The Bio-Response antibody-producing facility, on line since late last year, has 18 cows and can produce up to 2 kilogrammes of monoclonals a month. (Extracted from Chemical Week, 28 March 1984).

Clearance given to begin clinical trials of IL-2

Cetus (Emeryville, Calif.) received clearance from the Food and Drug Administration (FDA) to begin clinical trials of interleukin-2 (IL-2), human T-cell growth factor made by recombinant-DNA techniques. Initial tests will be performed on cancer patients and those suffering from acquired immune deficiency syndrome (AIDS).

For the past several months, Cetus has been supplying over 60 investigators with highly purified samples of its IL-2 for preclinical testing and research at NIH, NCI, Stanford University and the University of California at San Francisco, among others. The investigations have shown that, in laboratory experiments, Cetus' IL-2 will reduce certain tumor growths and prevent the spread of tumors in mice. Besides promoting the growth of T cells, a type of white blood cells, IL-2 stimulates them to kill infected and cancerous cells.

The preclinical testing also has shown Cetus' IL-2 to be effective in reversing the immune-system deficiencies that characterize AIDS. In AIDS patients, the number of T cells is greatly reduced, leaving the victim unprotected against bacteria and viruses, or subject to the proliferation of abnormal cells. Cetus has begun Phase I clinical trials with AIDS patients at San Francisco General Hospital. Cetus also has started trials with cancer patients at NCL.

Market Potential. Should IL-2 prove effective in treating a broad spectrum of cancers, it could be marketed in as little as three years after the drug's safety and efficacy is proved in clinical trials. (Extracted from Chemical Week, 18 April 1984).

Hepatitis B peptide as vaccine

A small synthetic peptide reacts strongly with human hepatitis B virus antibodies and holds promise for a safe and inexpensive vaccine against the disease, according to researchers at the New York Blood Center and California Institute of Technology. Virologist A. Robert Neurath and Nathan Strick of the blood centre and the biochemist Stephen B. H. Kent of Caltech studied nearly identical proteins, P33 and P36, which are minor constituents of the virus surface coat. However, the proteins react strongly with human antibodies for the virus. The researchers found that a synthetic peptide, representing only 26 amino acids of the intact protein, produced a strong immune response in rabbits with production of a high level of antibodies. These antibodies react strongly with the virus in blood samples from humans carrying the disease. Thus, the peptide forms the basis for an improved diagnostic test for the disease, the researchers say. Animal studies are under way to test the peptide as a vaccine against the disease. Although a vaccine for hepatitis B does exist, it is scarce and expensive because it is derived from blood of human hepatitis B carriers. (Source: Chemical and Engineering News, 23 April 1984)

Monsanto's work on bone regeneration

A collaborative research agreement to develop biological materials that direct the regeneration of damaged or missing bone has been signed by Monsanto and Collagen (Palo Alto, Calif.). Research will focus on the production of growth factors, which are naturally occurring proteins that direct cells to synthesize new bone tissue. The two firms will collaborate on the development and application of recombinant-DNA techniques for the manufacture of the proteins. (Extracted from Chemical Week, 25 April 1984).

AIDS test available from Cellular Products, Inc.

Dr. Bernard Poiesz confirms that evidence of prior exposure to Human T-Cell Leukemia Virus (HTLV) has been detected in 80-90 percent of AIDS and lymphadenopathy syndrome (a suspected pre-AIDS condition) patients. His findings support data reported by the National Cancer Institute, the Centers for Disease Control and the Pasteur Institute, Paris. Dr. Poiesz of the Upstate Medical Center and the V.A. Hospital in Syracuse, New York and a member of the team that first identified HTLV in Dr. Robert C. Gallo's laboratory at the N.C.I. stated that "blood shown to be HTLV-positive should not be used for transfusion purposes because of the possible link with AIDS and the well-documented link with certain forms of leukemia."

Dr. Poiesz believes that a test procedure which detects the presence of an HTLV membrane antigen (HTLV-MA) is currently the most sensitive and cost effective method for the detection of HTLV. "The suspected relationship between HTLV and AIDS warrants such testing," asserts Dr. Poiesz.

Northern Clinical Diagnostics, a wholly-owned subsidiary of Cellular Products, Inc., Buffalo, New York has been performing the HTLV-MA test since the beginning of 1984. "We are observing a high correlation between the presence of HTLV-MA and suspected AIDS patients," states Dr. Richard Montagna, President and Scientific Director of Cellular Products. "These tests are being performed at our facilities and we believe that the significance of this test merits the development of a test kit which will permit the rapid screening of blood in blood banks and physicians offices."

"Response from physicians to the idea of a test kit has been very promising," said Mr. Jeffry Meshulam, the Company's Chief Executive Officer, and "getting the test kit to market within 90 days is a high priority."

Cellular Products was licensed by the Research Foundation of the University of New York to perform the test on an exclusive basis for ten years. Cellular Products, a publicly traded (NASDQ symbol CELP) company was incorporated in June 1982 and provides products to the biomedical research community and performs diagnostic testing through its wholly-owned subsidiary, Northern Clinical Diagnostics. (Source: CPI News Release, 24 April 1984)

An ovulation test on the market

The first ovulation test based on monoclonal antibodies will be marketed by Monoclonal Antibodies (Mountain View, Calif.), reports McGraw-Hill's Biotechnology Newswatch. The self diagnostic test is a dipstick that changes colour in response to the luteinizing hormone that is released into a women's urine upon ovulation. The test is claimed to be the first reliable way (other than the use of radio-immunoassays) to determine when a woman releases an ovum. (Extracted from Chemical Week, 25 April 1984).

Human growth hormone and Olympic drug testing

Scientists at the University of California, Los Angeles, are in training for an Olympian event. During the course of the 1984 summer games, the UCLA/LAOOC Olympic Analytical Laboratory will check urine samples from the top four finishers in each event - as well as a random sampling from other athletes - for five classes of banned drugs. The truly awe-inspiring technical feat will take place at the analytical laboratory, where the huge number of samples must be analyzed for trace amounts of drugs with the highest accuracy in a very short period of time.

Last November, the medical commission of the International Olympic Committee (IOC) tested the UCLA laboratory's ability to detect banned drugs in urine and meet other criteria for accreditation. The laboratory was given 10 samples from people who actually had taken drugs, as opposed to normal urine spiked with the drugs of interest. That's an important difference, Catlin says, because rather than just looking for the drug, in working with real biological solutions the analysts look for patterns of the main drug and its metabolites.

The test is difficult, because the list of drugs that one must be able to find is quite long and includes drugs which are not available in the USA. The task is made even more complicated by the fact that the IOC list of forbidden drugs is deliberately open-ended to prevent athletes from using recently developed analogs.

As testing for anabolic steroids gets harder and harder to beat, some athletes are turning to another substance: human growth hormone (hGH). Because hGH occurs naturally in the body, analytical chemists have not yet devised a foolproof way to detect exogenous hormone. Therefore, it's not on IOC's list of banned drugs. Currently the supply of hGH is limited and expensive because the only source is cadavers, but a much larger supply of growth hormone may be available from recombinant DNA technology soon. Genentech's application to market synthetic growth hormone is now being reviewed by the Food & Drug Administration. The company is hoping to get approval sometime this year.

Athletes who use hGH are working in the dark, for the effects of giving hGH to normal adults are almost completely unknown. Even if there are no comprehensive studies, sports medicine specialists are beginning to see individual athletes who have obtained hGH on the black market.

The normal concentration of hGH varies throughout the day, with a big increase shortly after falling asleep. The levels also are affected by nutrition and stress. Certain drugs such as L-dopa and β-blockers can stimulate release of stored hGH. Growth hormone has a very short lifetime in the body and seems to exert its stimulating effect on the growth of bone and cartilage through other peptides called somatomedins, which are produced by the liver.

Growth hormone is attractive to athletes because it stimulates protein synthesis through a number of interconnecting mechanisms. It also accelerates the breakdown of fat while decreasing the amount of carbohydrate burned by the body.

The risks of large amounts of hGH over extended periods of time are clear from the experiences of people with pituitary tumors that overproduce the hormone. Children whose bones are still growing can become giants, sometimes reaching heights of 8 feet. After adolescence, however, the bones are fused and can't grow any longer. Too much hGH in an adult results in a condition known as acromegaly.

There is concern over possible misuse of hGH as it becomes more readily available, not only by athletes, but also by physicians who may be pressured to prescribe hGH to children whose parents want them to be taller. Already there are studies showing that some children who are not deficient in hGH but are nonetheless short respond to treatment with the hormone by growing faster. Just what the effects of freely available hGH will be on athletes remains to be seen. (Extracted from a special report by Chemical and Engineering News, 30 April 1984. Reprints of this C and EN special report will be available at $3.00 per copy. For 10 or more copies, $1.75 per copy. Send requests to: Distribution, Room 210, American Chemical Society, 1155-16th St. N.W., Washington, D.C. 20036. On orders of $20 or less, please send check or money order with request.)

Genentech claims factor VIII

Genentech Inc., the San Francisco-based biotechnology company, working in collaboration with the Haemophilia Centre at the Royal Free Hospital Medical School, London, and Speywood Laboratories in Wales, announced that the human blood protein known as factor VIII, which is lacking in haemophiliacs and essential for their treatment, has been cloned and expressed in biologically active form in a mammalian cell culture. The availability of a completely sequenced cDNA clone for factor VIII, the largest protein ever produced through recombinant DNA technology, is an essential first step towards a source of the factor that is independent of supplies of human blood plasma and not susceptible to contamination by viruses.

The Haemophilia Centre in London developed a method of obtaining factor VIII in high purity using monoclonal antibodies to the protein and established the gross structure. At Genentech, a genetic probe derived from a factor VIII subunit was used to test genomic libraries until a clone was identified that matched one possible predicted DNA sequence. The factor VIII gene turns out, as expected, to be located on the X chromosome. Eventually a clone of the complete gene was obtained (190 kilobases long) and a cDNA clone of factor VIII produced. After transfection of the clone into a mammalian cell line, human factor VIII was detected in the culture medium and measured by a purified enzyme system. The activity of the material is quenched by monoclonal antibodies to human factor VIII - further evidence that factor VIII is being produced.

There are several years' more work ahead before factor VIII will be produced by genetic engineering on a commercial scale, though it is hoped to produce enough factor VIII for clinical trials of the product (probably around 100 mg) within two years. The aim now will be to obtain a cell line able to sustain high output of the protein and which can also be cultured on a relatively large scale. (Extracted from Nature, 3 May 1984).

Factor VIII

In April Genentech became the first research and development firm to isolate, clone and express the entire gene that codes for human factor VIII. So far, Genentech has not said whether it plans to manufacture and market its genetically engineered factor VIII on its own or whether it will collaborate with a pharmaceutical firm. The company does say that it hopes to have the product in a clinical trial in two years and on the market in four or five years.

A safer, purer and more abundant supply of factor VIII would be a boon to haemophiliacs. In the USA alone, each haemophiliac may spend an average of $10,000 a year for blood plasma concentrates, and the worldwide market may be worth more than $250 million/year. However because factor VIII is currently extracted from the plasma of donated human blood, recipients may face the risk of hepatitis or acquired immune deficiency syndrome (AIDS).

Producing a relatively risk-free factor VIII is also the aim of other bio-technology R & D firms, such as Genetics Institute (Boston), who reported that they had taken an important step forward by isolating a portion of the human factor VIII gene; Chiron (Emeryville, Calif.) has isolated substantial parts of human factor VIII gene and is collaborating in the field with a Swedish partner, Nordisk;

Biogen, headquartered in Geneva, together with Sweden's KabiVitrum (Stockholm) and Teijin (Tokyo) is to produce factor VIII at their Cambridge, Mass., facility. However, a biotechnology analyst for Robertson, Coleman and Stephens (San Francisco) suggests that companies that already supply factor VIII purified from human blood plasma could have an edge on the future market for genetically engineered factor VIII. Genetics Institute, for example, is collaborating on its factor VIII work with Baxter Travenol (Deerfield, Ill.), a major supplier of factor VIII purified from blood plasma.

The biggest obstacle has been factor VIII's exceptionally large size. The most complex protein ever produced by recombinant-DNA technology, factor VIII is four times larger than human serum albumin, a blood protein first expressed by Genentech in 1981. Factor VIII has more than 2,300 amino acids, the building blocks of proteins, compared with 585 amino acids in human serum albumin. Alpha interferon, also produced by recombinant-DNA technology, has only 166 amino acids.

Genetech says that until its factor VIII is on the market, researchers can benefit from the production of the recombinant-DNA molecule to further their studies of haemophilia's molecular basis. One research goal is the development of techniques for prenatal diagnosis of the disease. (Extracted from Chemical Week, 9 May 1984).

Commercializing a genetically engineered hormone

A 50-50 joint venture corporation has been formed by the Kirin Brewery of Japan and Amgen (Thousand Oaks, Calif.) for the world-wide manufacturing and marketing of erythropoietin (EPO), which is responsible for controlling production of red blood cells. The hormone is expected to find wide application in the treatment of kidney dialysis patients, who typically have low red blood cell counts. Human clinical trials of the hormone are expected to begin next year, leading to government approvals of the use of EPO by most of the 250,000 people throughout the world who suffer from chronic kidney disease. (Extracted from Chemical Week, 23 May 1984).

New drugs versus malaria

Malaria is the most severe health problem in the world today and it is rapidly reaching crisis point in the Third World. There are an estimated 150 million new cases reported annually and approaching 800 million people are now suspected to be suffering from the disease. In 1956 the WHO implemented a programme to eradicate plasmodium, the unicellular organism which causes malaria, and extirpate anopholine mosquitoes, the insect vectors which transmit the disease-causing parasite. The programme showed initial success, but in recent years there has been a resurgence of the disease due to the ability of both the parasite and the mosquito to develop resistance to chemical control agents.

The Special Programme for Research and Training in Tropical Diseases organized by UNDP/World Bank/WHO is currently pursuing the development of two anti-malarial preparations which do offer some hope for the future.

The first of these, mefloquine, is a drug which is chemically very similar to chloroquine. It is not yet available and WHO will restrict its use in order to retard any resistance that may be developed by the parasite. It will not be pushed as a sole treatment but it has been shown to be effective against chloroquine-resistant and chloroquine-susceptible organisms. Its use will not be permitted in areas where there is no chloroquine-resistance and it will only be administered in a "cocktail" with sulphadoxine and pyrimethamine, once again to postpone the onset of resistance. Therapeutic field trials are under way in Brazil, Zambia and the US, sponsored by industry, government and chemical companies. Clinical trials have proved that, in adult males, the drug is effective and is well tolerated and safe. It is envisaged that mefloquine may be successful in a curative and suppressive capacity.

A second line of research is looking into the efficacy of a traditional herbal remedy from China. An extract from Artemisia annua contains the active principle

Qing Hao-su, or artemisinine. WHO is currently developing analogues together with the Chinese Institute of Materia Medica at Shanghai. The important factor in this line of research is the novel structure of Qing Hao-su which is totally different from any other known anti-malarial.

Results have shown the analogues to be at least as effective as quinine and better tolerated. It is certainly active against chloroquine-resistant parasites and is expected to be effective against mefloquine-resistant organisms when they occur. This agent has drawbacks, however. The analogues are rapidly eliminated from the body if taken orally. Optimum results are achieved by administering Qing Hao-su by oily intra-muscular injection and so it should only be looked upon as a possible solution that needs a lot of research work. At present, question marks hang over its possible mutagenic qualities and the high crudescence rate which follows its use.

Malaria vaccines developed by a team of researchers from the Walter and Eliza Hall Institute in Melbourne will be tested on monkeys within two or three months. Dr. Graham Brown of the Institute told the ANZAAS congress last May that so far the team had isolated between 30 and 40 antigens from the blood state, or merozite, of the Plasmodium falciparum malaria strain. The most hopeful of these antigens will be used to develop trial vaccines for testing on monkeys at the Center for Disease Control in Atlanta in the United States. The tests could begin in July or August and would involve testing cocktails of three different antigens on two sets of monkeys with a third set used as a control.

The work at the Institute is being carried out in cooperation with the Papua New Guinea Institute of Medical Research at Mandang which has provided carefully selected blood samples containing antibodies to the malaria parasite from people resistant as well as victims of the disease. Using these antibodies it has been possible to identify the appropriate malaria antigens that induce the resistance.

If the monkey tests are successful the work will be scaled up and a prototype vaccine developed for clinical trials on humans. This could take a further two to three years and the trials would need to be carried out in a malarial area, such as Papua New Guinea. (Extracted from Development Forum, May 1984 and New Scientist, 24 May 1984).

Livestock applications

Embryo transplants will speed genetic improvement of animals

Egypt is the first country to order a batch of mammalian embryos from International Embryos Ltd., in this case the 500-embryo nucleus of a pedigree Friesian dairy herd. Whereas the overall weight of 500 young heifers would have been about 175 tons, these Friesians travelled to Egypt late last year as seven-day-old frozen embryos in a flask of liquid nitrogen, weighing in as 45 kilos of excess baggage.

International Embryos Ltd. (IEL) received initial support from Technical Development Capital Ltd. and from the British Government, in the form of a Small Business Loan. Marketing visits took place to some 20 countries during 1982, and the company issued 750,000 Ordinary Shares last July to help finance the execution of the Egyptian contract and raise money for further R & D work.

The techniques of embryo transfer are well known. High-quality female livestock are superovulated and inseminated by male animals of similar quality, after which the fertilised eggs (already known as embryos) are collected from the females. These embryos are then frozen in insulated flasks of liquid nitrogen at a temperature of minus 197 degrees Centigrade, in which state they are easy to transport by air - a thousand or more viable embryos weigh no more than 50 kilos. Transferred to local females and born in the environment in which they are to be reared, the transferred animals are spared the shock of adapting to a new climate and unfamiliar diet. The young also obtain antibodies from the foster mother and from the milk suckled directly after birth, protecting them against local diseases.

The frozen embryos may be stored almost indefinitely and the average selling price for a pedigree embryo transfer is of the order of £250. In UK conditions, a 58 per cent conception rate has been achieved, and IEL is expecting a 50 per cent rate in the more difficult climates likely to be experienced overseas.

Many more embryos may be collected from one periodic ovulation of a single animal than would be possible under normal conditions. In ordinary breeding circumstances, exceptional females have a limited breeding life and may produce no more than three or four progeny in a full breeding lifetime, whereas with embryo transfers a single female may produce as many as twenty progeny a year, speeding up the process of herd improvement. Another advantage is that embryos collected from pedigree stock may be transferred to non-pedigree foster mothers and, in most countries, the resultant progeny are acceptable for entry into pedigree stud registers.

IEL has also been working on microsurgical techniques which permit the cloning of embryos, thereby producing identical offspring. In the longer term, IEL also hopes to be able to offer sex determination and a service permitting the removal or introduction of genetic material into the embryo. (Source: Biotechnology Bulletin, Vol. 3 No. 1, February 1984)

New firm claims innovation allowing pig embryo freezing

Two brothers, Dr. David and Richard Vanderford, who founded Trans World Genetics (Burlingame, Calif.) two years ago, drew on their experience in international consulting and marketing, and saw an opportunity for embryo transfer abroad, particularly in developing countries.

The firm may offer its most significant contribution in the development of embryo transfer as applied to pigs. In fact, if its research is borne out in field tests, TWG may have solved an extremely important problem in swine embryo handling: the company's scientists say they have found a way to freeze and thaw pig embryos while maintaining their viability. Cryopreservation is a standard technique for storage and transportation of cattle embryos for transfer, but swine embryos have not heretofore been successfully brought to term after cryopreservation.

Trans World Genetics has made its first international contacts with China, a country with more than 300 million pigs and therefore a big potential market for swine embryos. Meanwhile the company has also established contacts in Singapore, the Philippines, Argentina and Denmark. About a dozen "couriers" will soon work for TWG, collecting cattle or swine embryos from high quality breeding herds under contract in the U.S., accompanying the shipments to their destination, and performing the surgical implantations. To reduce its overhead, the company plans to delegate some responsibilities to regional centres staff mainly with locally trained support personnel.

Handling bovine embryos is easy because they can be frozen in liquid nitrogen and stored for implantation at the desired time. Swine embryos must be shipped in a sustaining medium, which allows survival for 36 hours. This presents logistic problems, for the heat cycles of donor and recipient must be closely synchronized to ensure successful transplantation. Southeast Asia has been the major market for swine embryos, and these destinations rarely present transportation problems.

Embryologists previously have tried to prevent freeze damage to swine embryos by altering the freezing schedule - without much success. Trans World Genetics focuses instead on the repair of freeze-damage to cellular membranes once the embryos are thawed. The company's researchers believe calcium fluxes are responsible for the failure of pig embryos to survive cryopreservation and are attempting to control free calcium throughout the freezing and thawing process.

Trans World Genetics established two subsidiaries, the wholly owned Tradcon, which is headed by David Vanderford and handles ancillary trade agreements, and the 50-percent-owned Trans Asian Genetics in Hong Kong, which is led by Richard Vanderford and covers the Chinese market. (Extracted from Genetic Engineering News, April 1984).

Agricultural applications

Diagnostic kits for plant and agricultural diseases

Koppers will form a joint venture to develop and commercialize kits to diagnose plant and agriculture diseases with DNA Plant Technology. The joint venture will develop a portfolio of diagnostic kits to permit rapid and inexpensive diagnoses of plant and agricultural diseases at earlier stages than is now possible. The venture will initially focus on citrus crops and turf grass. The kits will be sold domestically and internationally through major fertilizer and agricultural product manufacturers, lawn care specialists, food and seed processors and owners of major crop farms. Eventually marketing may reach the retail consumer for home, lawn and garden use. The venture will use DNA Products' Cinnaminson, NJ, headquarters for greenhouse and field testing by 1985. (Extracted from Chemical Market Report, 13 February 1984).

Algae could halve the cost of nitrogen fertilizer

An algae-infused fertilizer said to have the potential of reducing the cost of nitrogen fertilizer by 50% will be marketed next year by Pace National (Kirkland, Wash.). When the algae-infused fertilizer becomes commercially available, it may be the least expensive form of slow-release nitrogen fertilizer available. The fertilizer is described as natural, organic, nontoxic and, therefore, of particular interest to food producers. Cyanotech, Wash. developed the technique for growing the nitrogen-fixing algae. After being dried by a proprietary technique developed by Cyanotech and mixed into fertilizer, the algae transfer nitrogen from the air to the soil. Cyanotech has applied for a patent on a culture method for growing the algae by the ton and has also developed a proprietary technique for drying it. (Source: Chemical Week, 11 April 1984)

Guayule makes progress towards commercialization

A pilot plant contracted by the U.S. Department of Agriculture, as well as another by the Firestone Tire & Rubber Co. will soon begin turning out small quantities of guayule rubber from the three-foot-tall shrub, native to northern Mexico and the southwestern U.S. In 1986, Firestone and the Gila River Indian Community will begin construction of a prototype plant on the Indians' land near Phoenix to demonstrate the commercial feasibility of guayule processing. Both projects are almost entirely supported by government funds. USDA is convinced that work done in the last few years in agronomics and process technology will lead to a guayule industry by the end of this decade, when many government and industry officials predict a natural-rubber shortage.

Guayule research that isn't federally funded is being completed by scientists at General Motors Corporation's research centre in Warren, Mich. GM researchers will present a paper at the 5th International Guayule Conference in Washington, D.C., to be held in June. With the exception of Firestone, most of the major tyre and rubber companies have no guayule projects in the works. Goodyear Tire & Rubber Co. (Akron), for example, still considers guayule processing costs too high. Indeed, on the free market, Hevea rubber is selling for about 60 cents/lb; guayule's price is about twice that amount.

Many experts believe that there is no substitute for natural rubber. The chemical industry has been trying for 40 years to copy the material's chemical and physical properties and it hasn't succeeded yet. Natural rubber can withstand more extreme temperature and pressure changes than synthetics; and it has higher tensile strength.

Process technology will play a significant part in determining whether guayule can be competitive with Hevea. Firestone says that it is now researching a number of extraction processes, including a water-based method used by the Mexicans at a 1-m.t./d pilot plant at Saltillo from 1976 to 1982, when the plant was shut down because of the country's economic crisis. USDA has decided against the water

extraction method because of the dryness in areas where guayule grows. Instead, they are experimenting with two approaches to chemical extraction. The first simultaneously extracts the rubber and resins (volatile essential oils including alpha-pinene, dipentene, and cadinene; and nonvolatiles including carotenoids, palmitic acid, stearic acid, and hard wax) from the shrub, using a nonpolar solvent such as hexane or benzene. Then a polar solvent - acetone, an alcohol or a ketone - is added to precipitate the rubber.

The second method first extracts the resins by using a polar solvent. The deresinated shrub is then cleaned of solvent and immersed in hexane, which removes the rubber. The hexane solution is sent to a series of stripping columns where the rubber is coagulated and collected.

USDA researchers allow the shrubs to dry in the field because the rubber will degrade if allowed to stand in a moist and warm condition. Dried shrubs are ground to 3/16-in. fibres and supplied to the batch-type plant, which can process about 1 ton/d of guayule semicontinuously.

Another way to make guayule more competitive with Hevea is to increase, through the use of bioregulators, the guayule plant's rubber output. A recent discovery is that dichlorophenoxy-triethylamine (DCPTA) doubles guayule's rubber production from 2-2.5 per cent dry weight to 5.7 per cent. A single, untreated guayule plant yields about three ounces of rubber, which does not differ significantly in structure from Hevea rubber. DCPTA, which is not commercially available, is inexpensive and easily synthesized. It is sprayed on the young guayule plants just once shortly after they germinate. Only 20 grams is needed for an acre of guayule. (Extracted from Chemical Engineering, 30 April 1984).

Calgene Inc. and Rhone-Poulenc Agrochimie S.A. sign contract on herbicide-resistant oil seed crop development

Calgene Inc. recently announced its agreement to develop new, herbicide-tolerant varieties of sunflower for Rhone-Poulenc Agrochimie, S.A. of France, a leading international agrichemical company.

The new varieties are expected to be tolerant to Bromoxynil, a post-emergent selective herbicide manufactured and marketed by Rhone-Poulenc. Use of the weed-killer with engineered sunflower crops will enable farmers to improve weed control and farm productivity. Leading seed industry analysts recently predicted that the market for herbicide-tolerant oilseed will increase to $2.1 billion by the year 2000.

Calgene researchers have already cloned the first gene genetically engineered to be useful in crop plants. This was accomplished with a leading herbicide called glyphosate. The company's research programme is rapidly expanding into other major herbicides and crops.

The agreement with Rhone-Poulenc marks the third R & D contract signed by Calgene with a major European agrichemical manufacturer in the past nine months. Last November, Calgene agreed to develop herbicide-resistant varieties of turnip rape for Kemira Oy, a leading chemical company based in Finland. In April, the company also entered a joint research programme with Nestec, the research and development affiliate of Nestle, S.A., to develop herbicide-tolerant varieties of soybeans.

In a related move, Rhone-Poulenc Agrochimie and SeedTec International Inc. of Woodland, California, recently announced the formation of a jointly-owned research corporation to be named Agra Seed Research International. According to Rhone-Poulenc the new firm will initially concentrate on developing new high-oil sunflower hybrids. SeedTec is a leading U.S. developer and supplier of sunflower planting seed. (Source: Calgene News Release, 5 June 1984)

Food production and processing

Gum arabic alternate

IGI Biotechnology, of Columbia, Md., claims it has developed a new low-cost compound to replace gum arabic in food and pharmaceutical applications which will compete with the 20-22 million lb/year market for gum arabic from the Sudan, now said to be an unreliable source because of the country's political and economical volatility. Suggested uses are as a fat emulsifier in confections and preserves, as a fixative for flavours, as a foam stabilizer in beer and as a humectant and emulsion stabilizer in dairy, bakery and cosmetic products. The water-soluble, partially branched polymer, named Poly-LevuLan, is produced at a plant in Hawaii or Puerto Rico, by fermenting raw cane or beet sugar. The new process utilizes a genetically mutated (but not through gene splicing) species, Zymomonas mobilis. The bacterium is fermented in conventional reactors, and the new polysaccharide, tradenamed Poly-LevuLan, is secreted in an extracellular fashion. Ultrafiltration and centrifugation finally lead to an off-white, spray-dried powder. The polysaccharide is a homopolymer of D-fructose, and has the right combination of solubility, stability, viscosity and other properties to replace gum arabic. Pilot-plant quantities are now being test-marketed, and the company is capable of producing "several million pounds" now. (Source: Chemical Weekly, 4 April 1984 and Chemical Engineering, 16 April 1984)

Energy and environmental applications

Micro-organisms that eat toxic chemicals

Fourteen strains of yeast and bacteria have been "trained" to absorb nutrition and energy from chemicals that are environmentally hazardous, such as poly-chlorinated biphenols, polychlorinated phenols, polycyclic aromatic hydrocarbons, creosols, and a range of pesticides containing organo- phosphates. A researcher at Louisiana State University (Baton Rouge), developed the mutant micro-organisms by making a series of laboratory models of the Louisiana wetlands. To these models Ralph Portier added one, or a combination, of the toxic chemicals. He noted which micro-organisms in the natural systems survived the addition and began removing elements from the miniature environments until all that remained were the pollutant and the micro-organism able to feed on it. (Extracted from Chemical Week, 28 March 1984).

Enzymes may be used for testing wastewater

Bioluminescent enzymes may form a useful toxicity test for industrial waste-waters, according to Professor Thomas Baldwin, at Texas A & M University (College Station). He has developed a cloning technique to produce large quantities of the luminescent enzyme luciferase in common bacteria such as Escherichia coli. The enzyme, when added to water contaminated with some toxic chemicals, decreases in luminescence. A photomultiplier cell monitoring the light intensity can then be calibrated to measure this decrease as a function of toxicity. (The exact mechanism of this declining luminescence is not understood, but it may be that the toxic chemical alters the enzyme's electron-transport chain.) This test could replace the "fish kill" assay stipulated by some U.S. Environmental Protection Agency regulations, which require that a sample of fish be exposed to the waste-water for several days. Cost and test time are dramatically reduced with the enzyme.

Baldwin observes that other testing procedures might be replaced with the enzyme, including the Ames test for mutagenicity and various radioimmunoassays used in clinical laboratories and hospitals. (Source: Chemical Engineering, 2 April 1984)

Another source of fuel

Scrubby trees and brush found in chaparral areas could be processed into high-quality diesel fuel, according to J. L. Kuester of Arizona State University, E. A. Davis of USFS and M. O. Bagby of US Development Authority. Indirect lique-

faction involves converting the feedstock to synthesis gas that is then exposed to a catalyst to form a product similar to diesel fuel. The process yields liquid fuel at 40-50 gal/ton of feedstock. The cost of biomass conversion is sensitive to how far the feedstocks have to be moved. Conversion units large enough to be economical are too large to move around. Many industries could convert trash like coconut shells, fir bark and cotton wastes to fuel. (Extracted from Science News, 24 March 1984).

Treating wastewater by polymerizing pollutants

A combination of hydrogen peroxide and the enzyme horseradish peroxidase will precipitate phenols and aromatic amines from industrial wastewater, according to Alexander Klibanov of the Massachusetts Institute of Technology. The enzymatic treatment causes pollutants to polymerize into large molecules that precipitate from the water. The process, it is said, removes more than 99 per cent of many toxic phenols and amines within three hours. The treatment does not form hazardous by-products and is potentially less expensive and more efficient than the removal methods most industrial plants use today. To cut costs further, Klibanov is now experimenting with microbial peroxidases as a substitute for the horseradish peroxidase. (Source: Chemical Week, 2 May 1984)

Industrial microbiology

Micro-organisms boost the production of threonine

A pair of micro-organisms that already produce threonine on an industrial scale are now producing even greater quantities of the amino acid. Researchers at Kyowa Hakko Kogyo, Japan, have increased threonine yields in fermentations using the micro-organisms Corynebacterium glutamicum and Brevi-bacterium flavum, to 21 grammes per litre from a previously obtained high of 18 grammes per litre. This development could be encouraging to industrial chemists attempting to improve amino-acid yields by genetically engineering micro-organisms. Instead of having to change production methods to accommodate the workhorse organisms of genetic engineering, such as Escherichia coli and Bacillus subtitlis, the chemists can work with traditional micro-organisms and, therefore, traditional producton methods. U.S. chemists at the Massachusetts Institute of Technology, are also working to genetically engineer Corynebacterium species. (Source: Chemical Week, 11 March 1984)

French biomass conversion

French plans to replace 10 per cent of their petrol by 1990 have pushed companies into exploring technology to make gasoline substitutes economically viable. One team is from Institut Français du Pétrole and its engineering subsidiary, Technip. The companies are planning a plant they claim will be a world first in biomass conversion.

Among the difficulties of substituting ethanol or methanol for petrol in cars is the need for a solvent to avoid the components separating in the presence of water (frequently encountered in petrol tanks). One of the best solvents is an acetone-butanol mixture; it is this solvent that the new plant will produce. If a small amount of the mixture is added to the tank it eliminates the problem.

Work will start on the plant this year at Soustons in south-west France, and will open in 1986. It will, says Technip, be big enough to allow a proper evaluation of its industrial potential as a producer of solvent for gasoline substitute fuels. The raw material will be mainly corn stover, and the aim is to produce 1 tonne of solvent from 6 tonnes of raw material. Estimates from Technip suggest that the French will consume 600,000 to 800,000 tonnes of solvent per year.

Such solvents can be made by traditional methods of fermentation but this has always been prohibitively expensive, partly due to the cost of enzymes necessary to accelerate the process.

The new approach developed by IFP and Technip is claimed to be economically viable. The key parts of the new unit are a steam cracking technique that splits lignocellulosic input (corn stover, for example) into hemicellulose, lignin and cellulose, and an enzymatic hydrolysis unit which contains genetically improved enzyme strains and new fermentation technology.

In steam cracking, the raw materials are subjected to temperatures between 180 and 240° C by the introduction of pressurised steam. This process separates them into three types of substance, hemicellulose, lignin and cellulose. Taking out the hemicellulose is easy; the five carbon sugars produced are soluble in water. Lignin is then removed using an alkali solvent. That leaves cellulose to be converted into sugars by enzymatic hydrolysis. Experts at IFP say that enzymatic hydrolysis is better than the alternative, acid hydrolysis, because it is more specific and a fermentable sugar solution is obtained immediately. Acid hydrolysis has a number of other disadvantages. It makes it necessary to concentrate the solution and produces less suitable sugars. On the other hand, enzymes have been slow and expensive in the past, but new enzyme strains mean an improvement by a factor of two over the best previous results, which were achieved by the US navy. Once the sugars are obtained, they are fermented to produce acetone and butonal. These are formed in a very dilute solution, and the final stage of the process is to distil them.

If the plant is as successful as Technip expects, it could realise the dreams of many a proponent of biomass conversion. Not only solvent for gasoline substitute, but also a number of other chemicals could be produced economically. It would be possible to produce furfural from hemicellulose for the oil extraction process. Another area of big potential is the derivation of viscose from cellulose. Viscose and rayon have been slowly replaced by polyester for clothing and car tyres because of high production costs. But if the IFP/Technip approach can reduce these costs, there may be a future once more for viscose.

A search is also on to find applications for the lignin, which forms 15 to 30 per cent of the raw material. The lignin separated out in the new process is the only known variety that is not "condensed". This makes it a good candidate for sulphonation. Here too there is an oil connection. Sulphur derivatives can be used for the secondary recovery of oil. (Extracted from New Scientist, 26 April 1984).

Industrial equipment

Separation technologies and the biotechnology industry

Separation technologies may be the key to long-term growth for the bio-technology industry. Selection, isolation and growing (cloning and amplification) of genes are separation-intensive processes well-suited to biotechnology's macro-molecular nature. Industry profitability may be improved via large-scale production using membranes and filters (especially ultrafiltration). Separation sales to the biotechnology market may reach $100 million per year by 1990, primarily involving ultrafiltration, microfiltration and high performance liquid chromatography (HPLC).

Electronics will provide an attractive market for membrane separation processes to improve the industry's low (20 per cent) yield rate resulting from contamination of chips by water and chemicals for rinsing. Ion exchange, ultrafiltration and reverse osmosis separation demand will rise due to the trend towards smaller size and greater density for next-generation chips.

Separation processes will also play a key role in the future availability of drinking water. Though the US holds only 33 per cent of the world desalination market, nearly 75 per cent of brackish water desalination is US-based. (Source: International Resource Development news release, 15 March 1984)

Biocatalysts for acrylamide

A biocatalyst will help to run an acrylamide plant in Japan. Nitto Chemical Industry (Japan) plans to start up a 4,000-tons/year plant in April 1985 that would use a catalyst based on micro-organisms. Nitto has obtained patents on catalysts

using three genuses of micro-organisms: Nocardia, Microbacterium and Corynebacterium. Nitto also is evaluating a Pseudomonas genus developed by Kyoto University to determine whether it can secrete the necessary enzyme to make the reaction go. The ordinary method of making acrylamide is by hydrating acrylo-nitrile with a catalyst, either sulfuric acid or copper. Nitto phased out a sulfuric acid hydration process at Yokohama in 1975 because of environmental concerns and high production costs. The new process is designed to operate at room temperature and atmospheric pressure. Nitto predicts that the quality of the acrylamide from the new process will be good enough to compete for jobs as a flocculant, and in papermaking and enhanced oil recovery. (Source: Chemical Week, 11 April 1984)

Automated cell culture system

A high-growth fermenter for animal or plant tissue cultures is being introduced by KC Biologicals (Lenexa, Kan.), a subsidiary of Corning Glass Works (Corning, N.Y.). The manufacturer claims that it is three to five times more productive than the conventional route of growing such cultures on the surfaces of plastic bottles that are continuously rotated. The heart of the new device, called the Opticell 5300, is a ceramic matrix honeycombed with continuous channels. Once the matrix has been seeded with cells, the nutrients, oxygen and other compounds needed for cell growth can be continuously supplied, and the cells have room to multiply. Electronic controls monitor feed levels, temperature and other quantities such as pH inside the sealed growth-chamber, allowing one person to monitor data from four such units. By contrast, 20 persons might be needed to manage the equivalent number of roller bottles. Risk of contamination in the enclosed core is 10 to 30 per cent less than in the equivalent number of roller bottles. The Opticell 5300 is a pilotscale unit, with a surface area of 42,500 cm^2, and a base cost of $110,000. A production unit, with a surface area of 720,000 cm^2, will be available by the end of the year. (Extracted from Chemical Engineering, 14 May 1984 and Chemical and Engineering News, 7 May 1984).

E. PATENTS AND INTELLECTUAL PROPERTY ISSUES

Novel way to licence patents to biotechnology companies proposed

Two administrators at Stanford and the University of California have proposed a novel plan that would dramatically change the way patents important to genetic engineering are licensed by universities to the burgeoning biotechnology industry. The proposal is designed to cut administrative fuss and legal fees for companies and universities during licensing negotiations and to speed laboratory findings into commercial use.

The outline of the plan is basically that universities pool their patents that cover biotechnology techniques or "tools" and license them to a newly created foundation. The foundation would act as a clearinghouse and sublicense the patents, providing one-stop shopping for biotechnology companies needing a variety of patents. Royalties would be paid to the foundation although most of the revenues would be funneled back to the schools. Though the exact details of the pool proposal have yet to be worked out, the administrators floated a rough form of the plan before executives and patent attorneys from companies at a conference held in March by the Industrial Biotechnology Association.

The concept raised more questions than it answered but nevertheless, companies and universities initially have taken a fairly high interest in the proposal though none committed itself to participate in such an agreement.

It was suggested that a clearinghouse for university patents could address several problems that they think industry and schools now face in licensing agreement. Companies currently need a variety of patented gene splicing techniques to produce a potential product. Under the present system, companies have to go from campus to campus to negotiate numerous licensing agreements. Universities spend valuable time and money to reach a contract with each company for the same patent. Given this cumbersome system, companies are not inclined to license and

may go ahead and use the technique because the patent is difficult to enforce. The universities lose potential royalties. Companies that have taken out a plethora of patents may end up paying high transaction costs.

To simplify this process, a clearinghouse called the University Licensing Association for Biotechnology (ULAB) would be created. The foundation, either nonprofit would handle the licensing agreements after the schools are issued the patents. (Filing costs would be paid by the universities.) ULAB would offer a blanket license to all patent rights and a company could pick and choose which patents it wanted.

In return, ULAB would charge a royalty of perhaps $25,000 or 1 per cent of net sales, whichever is greater. It would keep one-quarter of the revenues to cover its administrative expenses and also to fund fellowships. A formula for dividing the royalties among the schools is being worked out, but there are some potential problems. For example, a major university might contribute many patents of minor importance, but a smaller school may offer one of major significance.

In response to questions about potential antitrust violations, the university administrators said that the plan contains a special provision created to avoid a monopoly. The provision gives companies the option to license a single patent, rather than the entire pool. (Extracted from Science, Vol. 219, 18 March 1984).

Japanese patent guidelines

The Japanese Patent Agency is developing guidelines for biotechnology patents for recombinant DNA and cell fusion techniques essential to avoid conflict between biotechnology related patents. Some determination must be made on whether a patent covering introduction of DNA into a microorganism to produce a specific cellular function would be infringed by creating the same cellular function in some other way. (Extracted from Japan Chemicals, 16 February 1984).

Selection of recent patents

Applicant; Country Inventors	Purpose, use, or process	Application System/No. Date filed; Priority date
Bayer AG, Bayerwerk, Federal Republic of Germany	Microbial breakdown of substituted aromatic compounds	EPO 099,029 28 June 1983 10 July 1982
Genex Co., Rockville, Md, U.S.A.	Microbial production of chymosin and prochymosin	GB 2,123,005 30 June 1983 1 July 1982
Mitsui Toatsu Chemicals Inc. Tokyo, Japan	Plasminogen activator	EPO 099,126 14 July 1983 16 July 1982
F. Hoffmann-La Roche & Co., Basel, Switzerland	Microbial production using phage λ vector	EPO 099,084 8 July 1983 12 July 1982
International Paper Co., New York, N.Y. U.S.A.	Transforming cells with tumour-inducing plasmids	EPO 099,255 8 July 1983 12 July 1982

Philip C. Fitz-James, London, Ontario, Canada	Non-spore-forming mutants OFBTI	EPO 099,301 8 July 1983 9 July 1982
Institut Pasteur Paris, France	Bacterial production of endo- -1,4-glucanase	EPO 100,254 4 July 1983 2 July 1982
Behringwerke Aktiengesel-schaft, Marburg, Federal Republic of Germany	Production of antigens	EPO 100,521 27 July 1983 30 July 1982
ANVAR (Agence Nationale de la Recherche), Paris, France	Antibodies to separate somniferous	EPO 100,734 29 July 1983 30 July 1982
The Salk Institute for Biological Studies, La Jolla, Calif., U.S.A.	Gonadotropin antagonists	EPO 100,218 22 July 1983 26 July 1982
Damon Biotech, Inc., Needham Heights, Mass., U.S.A.	New "epsilon" type from epithelial cells	GB 2,123,835 11 July 1983 12 July 1982

Applicant; Country Inventors	Purpose, use, or process	Application System/No. Date filed Priority date
Genentech, Inc., South San Francisco Calif., U.S.A.	Preparation of homogeneous human lymphotoxin	EPO 100,641 26 July 1983 30 July 1982
Rhône-Poulenc SA, Courbevoie, France	Increasing mycorrhizal infection of roots	EPO 100,691 16 June 1983 16 June 1982

Applicant; Country	Other noteworthy disclosures this month	Application System/No.
Takeda Chemical Industries Ltd., Osaka, Japan	Bacterial production of inosine and guanosine	GB 2,124,225
Vyzkumny Ustav Vodohospodarsky, Prague, Czechoslovakia	Chromatographic identification	GB 2,121,434
U.S. Department of Commerce, Springfield, Va., U.S.A.	Antibodies to treat graft-versus-host disease	WO 84/00382
Carlton Medical Products Ltd., London, United Kingdom	Antibodies to detect cancer cells	GB 2,121,417

F. BIO-INFORMATICS

Microcomputer communication in support of international agricultural networks

Widespread availability of relatively inexpensive microcomputers is facilitating exchange of technical information and comment among scientists who are widely dispersed geographically. Computer conferencing is increasingly lauded as ideally suited for continuing information exchange on a global scale. In this regard, NifTAL became equipped, and gained experience, in microcomputer communications because of its isolated location on the Island of Maui and the immediate local need for a link with facilities and individuals at the University of Hawaii's main campus in Honolulu. More recently NifTAL became interested in the potential of microcomputer communications and computer conferencing to further its international development goals.

NifTAL seeks to provide farmers in less-developed countries with an inexpensive alternative to purchased nitrogen fertilizer by offering comprehensive development support in the form of research, technical and material services, and multi-tier training in all aspects of agrotechnologies based on biological sources of nitrogen.

The quality of legume innoculants available to farmers in developing countries is of concern to NifTAL. Their strategy is to ensure that innoculant quality includes research into improved production processes, and training producers how to manufacture high quality products. A new approach has been added called the Innoculant Quality Incentive Programme (IQIP). This involves formation of a Board on Standards, a definition of uniform standards for innoculant products, the award of "seals of approval" to be carried only by products of companies subscribing to the Board's standards, and the creation of an awareness among users and retailers that the seal is a sign of quality they can trust.

During 1984 NifTAL proposes to determine whether microcomputer communications are accessible to LDC scientists who have a role to play in design and implementation of the IQIP, and will be organizing a computer conference on the theme of legume innoculant production and quality control. The conference will begin on 1 September and culminate in an interactive question and answer session from 1 to 20 December. This latter session is possible due to the presence at NifTAL, Maui, at that time of some of the world's leading authorities on commercial scale innoculant production. They will be serving as instructors at a training course on innoculant production.

NifTAL intends to use the period from now to September to actively arrange for participation of key LDC scientists and the participation of any agency is invited which may wish to use this NifTAL initiative as a test case for appraising the utility of microcomputer communications for the maintenance of international agricultural research networks involving scientists in Third World countries. Contact: Dr. Jake Halliday, NifTAL Project and MIRCEN, P.O. Box 0, Paia, Hawaii 96779, U.S.A.

Computer graphics

Certain white blood cells that combat cancer are repelled by advanced cancer cell secretions, according to P. Noble, University of McGill (Montreal, Que.). This observation was made using an Electro-Optical Information Systems' (Santa Monica, CA) microcomputer, in which a frame grabbing technique determines cell movement. With FORTRAN programmes developed by an electrical engineer at McGill, the system transforms pictures into graphics data and has the added features of standalone capability and user friendliness that allows any biology student or professional to employ the system for research projects and as a healthcare tool. (Extracted from Computer World, 5 March 1984).

Biotech bank - (1)

An international science organization is seeking extra funds and computer facilities to expand a biotechnology data bank into Europe - without resorting to cash from industry. CODATA, a scientific committee of the International Council of Scientific Unions, together with the International Union of Immunological Societies wants to set up new centres in Europe and Japan for a computer bank of information on monoclonal antibodies. The bank is based at the American Type Culture Collections, in Maryland.

The data bank was established last May with a budget of $175,000 a year for the next three years, by the two organizations. It will not be open for inquiries before next spring.

The Department of Trade and Industry (DTI) in Britain is considering supporting a small two-person secretariat to ensure that the information on British research is as comprehensive as possible. Dr. Alan Coleman, a member of the DTI's biotechnology unit, says that this is not a separate initiative but instead "will run alongside CODATA", which would have access to the information.

Biotechnology data bank - (2)

As part of long-term biotechnological research, the British Ministry for Trade and Industry is considering setting up an on-line data bank in which records and information of the nine national culture collections and some private cultures would be combined. Plans have been made for data-bank services to be based on the already computerized system of the National Collection of Yeast Cultures (NCYC), which is located at the Food Research Institute (FRI) of the Agricultural Research Council (ARC). In addition to almost 2,000 authenticated yeast cultures, data on about 100 characteristics is electronically stored at the NCYC. The search fee, with corresponding specific yeast application combinations, is £20 for industry and £10 for non-profit making organizations. Plans have also been made to incorporate the collected data into the Ministry's data system.

The nine-government culture collections store cultures for microbiological and biotechnological research and also have information available in this connection. They offer identification and advisory services. In addition, possibilities are available for storing micro-organisms which form the basis for patents. Five of the collections, the Culture Centre for Algae and Protozoa (CCAP), the National Collection of Fungus Cultures (NCFC), the National Collection of Industrial and Marine Bacteria (NCIMB Ltd.), the National Collection of Cultures for Bacteria in the interest of Human and Veterinary Medicine (NCTC) and the NCYC, are covered by the 1977 Budapest agreement on international recognition of storage of micro-organisms for patent purposes.

The other culture collections include the National Collection of Dairy Organisms (NCDO), the National Collection of Pathogenic Fungi (NCPF), the National Collection of Pathogenic Plant Bacteria (NCPPB) and the National Collection of Wood-Rotting Fungi (NCWRF). There are a total of nearly 30,000 cultures in the nine collections. (Extracted from Chemische Rundschau, 12 October 1983).

"Molecular Electronics Beyond the Silicon Chip"

Vast changes are foreseen in the electronic and chemical industries brought on by developments in molecular electronics, likely to changes and affect companies and their product lines.

A new report, "Molecular Electronics Beyond the Silicon Chip", published by Technical Insights Inc., P.O. Box 1304, 158 Linewood Plaza, Fort Lee, New Jersey 07024, U.S.A. at $267 a copy, with additional charge of $20 for overseas postage describes the pending technological revolution and the opportunities and threats it represents.

Molecular electronics involves construction of electronic chips from organic molecules whose elements will be 50 nanometers long, the size of an individual

molecule. A molecular-electronic chip, the so-called-biochip, will carry thousands - perhaps even millions - more information bits than today's silicon-based micro-chips. This will mean new computer systems. Molecular-scale electronic chips will revolutionize concepts of computer design. Mass production methods for new molecular electronic circuits will lower production costs of a unit of given computing power, and reliability of such systems will increase because it will become economically feasible to include back-up elements for each primary element.

This in turn will lead to truly archival memories and personal computers with ultra-large memories. The latter, for example, might carry full science, engineering, or business records while being no larger than a pocket calculator.

Molecular-scale electronic chips will also show up in more powerful advanced intelligence systems. These systems have many promising applications in medical diagnosis, drug design, and chemical synthesis. Molecular electronics may well bring about the day of the bionic person. Molecular-scale electronic chips will be embedded in artificial limbs to direct their motion. The same chips may be used to construct implantable mini-computers that might help the blind see, the deaf hear and improve memory for all of us. And the same chips will find their way into a new generation of robots with enhanced computer control capacities.

A modified Delphi survey, conducted specially for this report, polled the experts on molecular electronics development. The experts say the first working molecular-scale electronic chip may be 10 to 20 years away, but demonstration of chip components - switches, memory elements - may come within five years.

The Delphi survey also revealed that a majority of the experts polled felt molecular electronics would revolutionize the electronics industry. One expert also suggests that the chemical and drug firms may become the electronic companies of the future since they may find it easier to take advantage of bio-electronics than the traditional semiconductor manufacturers.

Along the road to this new technology, many difficult technical problems must be solved. Chief among these are selection of materials and design of chip elements. One group of experts thinks biological polymers, especially proteins, will be the building blocks for molecular-scale chips. But how will these proteins be designed for this use? How will individual molecules be hooked together in a matrix? Several approaches to these problems are detailed in the study. One possibility: genetically engineered microbes may actually synthesize tailored-to-order chip elements or even entire chips.

G. MEETINGS

Date	Title
29 July - 4 August	8th International Biophysics Congress, Bristol, UK. (Contact: Congress Secretariat, 8th International Biophysics Congress, Meon Conference Services, Petersfield, Hampshire.)
30 July - 2 August	5th International Meeting on Methods in Protein Sequence Analysis, Cambridge, UK. (Contact: Dr. J. E. Walker, MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH.)
5-8 August	EMBO Workshop on Protein Folding, Cambridge, UK. (Contact: T. E. Creighton, MRC Laboratory of Molecular Biology, Hills Road, Cambridge, CB2 2QH.)
11-12 August	Plasmids in Biotechnology: Isolation and Applications (Workshop) Colorado, USA. (Contact: Ann Kulback, Society for Industrial Microbiology, c/o AIBS, 1401 Wilson Blvd., Arlington, VA 22209, USA.)

12-17 August	Society for Industrial Microbiology, Annual Meeting. Colorado State University, Ft. Collins, CO. (Contact: Ann Kulback, SIM, c/o AIBS, 1401 Wilson Blvd., Arlington, VA 22209, 703-256-0337.)
10-12 September	Biotech 84, International Conference and Exhibition. Washington, DC. Call for papers - deadline January 31. (Contact: Biotech 1984, London Online Inc., suite 1190, 2 Penn Plaza, New York, NY 10121, 212-279-8890.)
18-20 September 1984	Biochemical Genetics of Microbial Energy Generating Systems, Sheffield, UK. (R.W.C. Berkeley, University of Bristol, Dept. of Microbiology. The Medical School, University Walk, Bristol BS8 ITD, UK.)
18-19 October	1st European Seminar on Computer-aided Molecular Design, London, UK. (Contact: Fiona Splindlove, Oyez Scientific & Technical Services, Bath House, 56 Holborn Viaduct, London ECIA 2EX or on 01-236 4080.)
21-24 October 1984	The Role of Biochemistry in Food and Energy Production, Manila, Philippines. (The Secretariat, Fourth FOAB Symposium, Dept. of Biochemistry and Molecular Biology, UP College of Medicine, P.O. Box 593, Manila, Philippines.)
1-2 November 1984	International Conference on Investment in Biotechnology, London, UK. (Contact: Miss Helen Raquet, Oyez Scientific and Technical Services Ltd., Bath House (3rd Floor), 56 Holborn Viaduct, London ECI. Tel. 01-236 4080. Telex 888870.)

Date	Title
12-14 November	First Arab Gulf Conference on Biotechnology and Applied Microbiology (single-cell protein, biomass conversion, microbial production of chemicals, bioproduction of fuel). Conference Organizing Committee, Arab Bureau of Education for the Gulf States, Science Dept., P.O. Box 390A, Riyadh-11481, Kingdom of Saudi Arabia.
19-24 November 1984	Expoquimica '84 and Congresses, Barcelona, Spain. (Secretaria de Congresos, Av.R.M. Christina Palacio, Barcelona 4, Spain.)
25 November - 1 December 1984	5th International Congress of Culture Collections, Bangkok, Thailand. (Dr. Robert E. Stevenson, Chairman, ICCC-V, American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD 20852, USA.)
26-30 November 1984	International Resources for Biotechnology, Bangkok, Thailand. (Dr. P. Atthasampunna, Thailand Institute of Scientific and Technological Research, Bangkhen, Bangkok 9, Thailand.)

H. REPRINTED ARTICLES

The following is a reprint of the conclusions and recommendations taken from the Law of the Seed, Another Development and Plant Genetic Resources by Pat Roy Mooney. The Law of the Seed appeared in Development Dialogue 1983: 1-2, a journal of international development co-operation published by the Dag Hammarskjöld Foundation. The journal is published in two issues per year and copies may be obtained from the Dag Hammarskjöld Foundation, Övre Slottsgatan 2, S-752 20 Uppsala, Sweden.

The conservation of plant genetic resources

... and this is where there is need for a vision because I always believe that where a vision is limited, action is equally circumscribed. Dr. M. S. Swaminathan, Chairman of the FAO Council, 16 June 1983.

The world now spends about US$55 million on plant genetic resources conservation. Of this figure, however, only 30 to 40 per cent passes through international channels and is even ostensibly for the benefit of Third World countries. IBPGR presently has a budget of about US$3.8 million. The IARCs spend close to another US$10 million on their own germplasm programmes. There is a drastic need to increase this figure of US$14 million to US$100 million through to at least the middle of the next decade. IBPGR and most scientists believe that such financial increases are impossible and have confined their thinking to the abysmal funding and token budget increases that have constrained conservation efforts over the past decade. Earlier this year, the Directors of the IARCs responded to a request from FAO's Director-General to identify shortcomings in the present conservation system. Their first point was the need to create an awareness of the issue. We believe that public awareness will lead to the kind of financial support that is needed.

The shortage of funds has confined the vision of IBPGR in many ways. Little time has been devoted to biosphere reserves or to co-operation with the international network of botanical gardens, for example. Botanical gardens offer a large body of trained personnel able to assist in plant identification, collection and even conservation. Likewise, inadequate use has been made of the NGO community - especially the International Union for the Conservation of Nature and Natural Resources and the Environmental Liaison Centre. These groups tap important networks that can promote public awareness, increase funding and assist in the technical tasks of conservation.

Most unfortunately, however, the scientific community has been unable to reach farmers and gardeners - those closest to the seeds. FAO's Chairman, Dr. Swaminathan, referred to this in his address to the FAO Council in June 1982. Farmers care about their seed. They can help identify and conserve important land-races and weeds. In many villages in the Third World, it is still possible to find small plots of the old seeds growing in the woods preserved by families not wishing to entirely trust their fate to the HYVs. Very tiny plots of land and very little money would be required to work with villages and individual farmers to turn them into farmer/curators protecting local landraces. The costs could be a small fraction of the costs of transporting and preserving seed overseas and then shipping the seed back to be rejuventated every few years.

Of course, there is no scientific logic to this proposal. Within the space of one or two growing seasons, the genetic variability of the farmer/curator plot would decline dramatically. Some farmers would not be true to their commitment. A host of problems could result in the loss of some plots.

We do not propose the farmer/curator system as an alternative to gene banks for landraces - but as an addition. Governments are not good at saving for eternity. It may just be that one or two centuries from now, what remains of our plant genetic diversity will have to be sought from these dedicated 'amateurs'.

The need for facilities

1. Biosphere reserves: international support for the formation and long-term financial support for natural biosphere reserves within the Vavilov Centres and in other areas is a crucially high priority to safeguard unexplored plant species and the wild relatives of our cultivated crops;

2. Farmer/curators: international support is needed to develop and finance a wide system of village-level landrace custodians whose purpose would be to continue to grow (on small plots) an admittedly limited sample of endangered landraces native to the region. Although this course does not preserve the variability of the landrace, it may finally prove to be the world's best protection against the extinction of landraces;

3. International gene bank system: as an immediately achievable priority in the context of the Mexican proposal, the international community should develop (or, in some cases, adopt existing facilities where they can be surrendered to FAO control) what must eventually become a series of international gene banks in each of the Vavilov regions. These banks would, as a first priority, collect and preserve endangered landraces and modern varieties and then safeguard threatened wild material;

4. National conservation centres: the international community - perhaps in the context of the proposals related to an International Convention - must support national conservation centres which may include nationally important, bio-sphere reserves, farmer-curator initiatives, living collections in botanical gardens, and gene banks. Support for personnel-training, physical facilities, equipment, and collection work are all part of such national centres.

The need for new structures

5. International Convention: of paramount importance is the early agreement to a strong International Convention open to all countries and under the control of FAO;

6. Conservation and development fund: within the framework of the Convention, a fund must be established to support national and international conservation of germplasm and the development and utilization of germplasm resources at the national level;

7. Restructuring IBPGR: the old IBPGR should be brought directly under the control of FAO and the International Convention as the operational arm of genetic conservation. The various scientific committees and the Board itself could become technical advisory groups to FAO, while policy decisions would remain in the hands of governments through FAO;

8. FAO inter-governmental commitee: following the adoption of the Convention, FAO should establish a representative inter-governmental committee to oversee the Convention and supervise all aspects of the international conservation strategy including the international fund and the operational arm (IBPGR);

9. Wider co-operation: despite the concentration of these initiatives in one inter-governmental body - FAO - provision should be made within the new committee for the active participation of other specialized agencies and members of the UN System such as UNEP and UNESCO and for the involvement, in advisory roles, of relevant international non-governmental organizations.

Elements of the International Convention:

10. Categories of germplasm: all categories of material from wild relatives to advanced breeding lines should be included in the Convention;

11. Private collections: the Convention should require national legislation intended to ensure that privately-held germplasm collections are safely stored, publicly documented and freely available;

12. National botanical heritage: The Convention must recognize that plant genetic resources form a part of the national heritage of countries and that the storage of these resources must be assured within the country. Where samples are not in the country but are in other gene banks, duplicates must be repatriated.

The related issues

In ancient times, species were collected and utilized; there was a mythology about 'God farmers' who could test and identify a multitude of grasses to be used as food and medicine for humans. Jiang Chaoyu, Director of Germplasm Conservation, Chinese Academy of Agricultural Sciences, 1982.

The ancient Greeks have a story about a robber named Procrusteus who kidnapped wayfarers and forced them to lie in a bed. If they were too long, he cut them to

fit the size of the bed. It seems we have turned our approach to technology into a modern Procrusteus. Every idea is laid against a series of 'givens' of how agriculture is supposed to progress. If these 'givens' are not met, then the idea is cut off. Increasingly, what the world is 'cutting off' are its farmers.

Research into the seeds issue leads inevitably to the conclusion that the women and men doing our plant breeding at the IARCs and often even in private companies are dedicated, honourable and tremendously hard-working scientists. In talking with those people from CIMMYT to Uppsala it is impossible not to admire them greatly.

At the same time, there is the distinct feeling that the technical approach to plant breeding is not entirely correct. After all, the basic elements of breeding are not so complicated. A great deal has been and is being accomplished by keen observation and by crossing superior plants. In fact, as Vavilov noted more than once, we once had a world of plant breeders - very successful ones - who led us to our present crops. In many ways, the last four-score years of scientific plant breeding, with all their obvious progress, have also been years when the number of plant breeders, or keen observers of their fields, has declined from several million to a few hundred. All the genius of the hill farmers of Austria, the maize and bean planters of Mexico, and the sorghum growers of the Sudan is being lost to a scattering of highly sophisticated institutes.

We need the 'God farmers'. We do not need a return to the last century but, if people are to retain control of world food security and not lose it to a handful of corporations or even a handful of international institutes, we must banish Procrusteus and adapt our agricultural technology to train farmers to continue their own plant selection and adaptation work. We will still need the scientists and the institutes and all the new machinery, but we must re-involve the world's farmers and gardeners. We can take another road that avoids Procrusteus - a road that leads to the demystification of agricultural technology and, eventually, to greater plant diversity.

International agricultural research

13. Continuing the work: the IARCs must be supported in their continuing efforts to develop improved germplasm for national adaptation and equal efforts must be made to resist the pressures of international companies to turn the IARCs into basic research centres for their purposes;

14. International control: the time has come for the IARCs to come under inter-governmental control under the auspices of FAO. This will help to safeguard their scientific objectives against the pressures of companies from the industrialized countries.

The genetics supply industry

15. Monitoring the industry: a full study of the state of the genetic supply industry is urgently needed. The leadership for such an investigation might come from FAO or the World Food Council, and both UNCTAD and the UN Centre on Transnational Corporations should be invited to contribute;

16. TCDC: the very considerable potential for co-operation within the South on the convention and utilization of plant genetic resources for traditional plant breeding and for the genetics supply industry should be pursued with the support of the appropriate specialized agencies in the UN system;

17. Commerciogenic erosion: both public and private institutions should be required to provide national governments with environmental impact studies indicating the effect upon genetic resources of the introduction of new varieties. Notification of significant changes in varieties and crops should also be made to FAO in the event that an emergency collection is required;

18. Separating seeds and pesticides: national legislation should be introduced in every country guaranteeing that manufacturers of pesticide products do not become breeders or traders in the seeds industry. Where such situations already exist, the company should be obliged to divest either its seeds or its pesticides activities.

Plant breeders' 'rights'

19. Evaluation: an evaluation of the impact of exclusive monopoly PBR is sorely needed and should be undertaken in depth by UNCTAD. Information from the UNCTAD study should form the basis for a consultation on PBR prepared by FAO and WIPO with the support of UNCTAD;

20. Legislation: any governments contemplating any form of proprietary plant legislation should reconsider this step and at least delay action until international evaluations are available. Governments considering amendments to their existing legislation to bring laws into line with UPOV should also delay until a full evalulation of their own experience and the international experience is possible;

21. Non-PBR restrictive practices: UNCTAD and national governments should also evaluate the various regulatory measures that have been used by companies to give them de facto PBR. Such regulatory measures should be altered to eliminate this practice;

22. Public breeding: governments must substantially increase their financial commitment to public plant breeding (including both basic research and varietal release work) as the best means of maintaining control of the food system.

* * * * *

The following article is reprinted with kind permission of Genetic Engineering News of the Mary Ann Liebert, Inc. publishing house of New York:

Genetic engineering will bring economic dislocations to global agricultural markets

By Martin Kenney, Ph.D., Frederick H. Buttel, Ph.D., and Jack Kloppenburg, Jr.

Agriculture is increasingly international in scope. There are global markets in virtually all major agricultural commodities, and the firms that sell inputs such as fertilizers, pesticides and veterinary pharmaceuticals market their products on every continent. Foreign multinationals such as Sandoz, Hoechst, Imperial Chemical, Ciba-Geigy and Shell are very active in biotechnology R & D and appear poised to challenge U.S. firms in every corner of the globe - including North America.

Some of these firms have been major agrochemical input suppliers for decades while others have recently entered the competition in agroinput markets. Thus, the roughly 20 multinational firms that have become dominant in manufacturing and marketing petrochemical inputs (which along with plant breeding advances have revolutionized world agriculture over the past 35 years) are positioning themselves to be at the forefront of the next agricultural revolution - the Biorevoltuion.

During the last 10 years a merger movement has begun to transform the world seed industry, especially in Europe and North America. Acquisitions have tended to be undertaken by large transnational petrochemical and pharmaceutical companies. In most cases these acquisitions have had a transnational character, involving purchases of seed companies in a number of countries, generally on more than one continent. The seed industry has thereby become much more concentrated, although this increased concentration is not adquately reflected in the statistical measures (e.g., the percentage of sales in a country accounted for by the four or five largest firms) normally used by industrial organization economists.

There are several reasons for the acquisition of seed companies by large agroinput firms, including increasing world food demand due to population growth, the establishment of plant breeder's rights which are being generalized interna-

tionally, and the synergies that will come from combining agricultural chemical and seed production and R & D. Monsanto's agricultural chemical division was its only division to gain in sales and profits in 1982. Roundup, the broad spectrum of herbicide, had sales approaching $500 million. Hybrid seed profits can also be high; for example, Pioneer's return on equity over the last 10 years has been an average of 20 per cent. Finally, many companies have invested in seed company subsidiaries to acquire marketing networks and in-house research laboratories that dovetail with the R & D investments made in other branches of the company.

Seed genetic engineering

The enormous and growing stakes in the agricultural input industry are convincing the large petrochemical companies not only to buy seed companies, but also to make major investments in biotechnology firms in general and agricultural biotechnology firms in particular. For example, the International Plant Research Institute has had financial links to Davy-McKee, Eli Lilly and Trans KB, a venture firm. Recently Zoecon, which was a subsidiary of Occidental Petroleum, was sold to Sandoz. Similar linkages are evident for nearly all of the other biotechnology firms. Many of these companies have corporate sponsors which also have important agrichemical interests.

Calgene, a California biotechnology company, already claims to have engineered resistance to Monsanto's Roundup into a bacterial cell, and other companies have engineered other genes into plants. The stakes are extremely high, and the large companies have responded by rapidly expanding their biotechnology involvement beyond investments in small biotechnology venture capital firms.

In particular, large pharmaceutical and chemical companies have also founded life science and plant physiology labs to conduct in-house biotechnology research. ARCO, Pfizer, Chevron and Monsanto have established well financed laboratories dedicated to agricultural research. The rapid expansion of multinational investments in seed and biotechnology firms portends more concentration of the agricultural input industry. This may place farmers in a more vulnerable position with regard to the concentrated input suppliers. Will this vulnerability be exercised to extract oligopolistic rents, thereby worsening the position of the farmer, especially the small farmer?

Due to the saturation of seed markets in developed countries, most large companies are paying growing attention to the development of seed export sales, with much of this attention focused on expansion of markets in developing countries. As these companies expand their sales of improved, reproductively unstable seeds in developing countries, there will be profound socioeconomic and ecological consequences. On the positive side, substantial productivity increases will become possible. However, socioeconomic dislocations - similar to those of the Green Revolution, but on a far greater scale - are likely to occur. Increased productivity will tend to result in rising land values, which will marginalize subsistence-oriented peasant producers and lead to further rural-urban migration to already overcrowded cities.

The bulk of the world's genetic diversity lies in the tropical developing countries. Seed companies ultimately depend upon these genetic resources to improve the crop varieties they offer on the market. However, the imperative for seed companies to maintain or enhance their competitive position forces each company to expand its sales volume and market share globally, including zones of genetic diversity. In the aggregate, this competitive process leads to the supplanting of traditional varieties and their genetic resources, and to the long-term erosion of world genetic diversity.

The tendency of seed company competition to lead to a "genetic tragedy of the commons" has created an obvious need for an over-arching international body to ameliorate genetic erosion. Accordingly, organizations such as the International Board for Plant Genetic Resources have been formed. But the ability of these organizations to stem the erosion of genetic resources now and in the future is not bright because of the heightened competition in the seed/agroinputs industry.

The international flow of genetic resources, which since World War II has played a pivotal role in agriculture, has increasingly raised the question to whom the world's genetic resources belong. It is widely recognized that the northern temperate climates are notoriously genetically homogeneous. Nearly all of the important Vavilov centres are in Third World countries, as is much of the nonfood plant diversity. These loci of genetic diversity are increasingly coming to be viewed as natural - and national - resources. Laws are even being developed by some LDCs to forbid the export of germplasm.

Countries are arguing that this genetic information, when incorporated into seeds, is then resold to them at excessive prices. In essence, these countries are repurchasing their genetic information after it is reworked overseas - a classic case of dependency. The Third World is coming to view this relationship as an unwarranted subsidy to the developed countries. It thus seems increasingly likely that genetic information will become a commercial commodity - subject not only to interfirm competition among seed companies, but also to competition among countries and between countries and seed firms.

Animal applications

The animal Biorevolution is, if anything, even more advanced than the crop Biorevolution. Embryology has made it possible to sex cattle embryos six days after fertilization, allowing dairy producers to choose females and cattle producers to choose males. Twinning is being perfected, allowing one embryo to be split and creating a number of twins. Cryogenic techniques allow fertilized embryos to be frozen and shipped anywhere for implantation in host mothers. These embryos need not be quarantined at borders, nor are they nearly as bulky and problematic to ship as a live cow. An added benefit is that the embryos acquire the host mother's environmental immunities, which would not be the case with a live animal. Developments in embryo engineering offer opportunities for the world's farmers to upgrade both beef and dairy herds much more quickly and inexpensively.

Other important developments in the cattle industry include recombinant animal vaccines, the most important of which is a hoof-and-mouth disease vaccine. Finally, the refinement of growth hormones for cattle and chickens, which will be produced by genetically modified bacteria, offers significant potentials to increase milk yields in dairy cows and speed turnover in broiler chickens.

But unanticipated side effects are possible. For example, hoof-and-mouth disease vaccine may enable the production of beef cattle for export from many countries currently under quarantine. This increased demand for cattle due to the export market could easily make cattle ranching more profitable and allow cattle raisers to outbid peasants for land.

Thus, peasant-controlled lands producing staple food crops could be encroached upon by cattle raisers who produce a luxury commodity on a land extensive basis. The relatively advanced state of the animal Biorevolution vis-à-vis the crop Biorevolution makes this scenario all the more likely. Nevertheless, the contradictory aspects of biotechnology are highlighted in this example - the possibility of producing enough meat for everyone, and simultaneously increasing the likelihood that millions who will likely never be able to afford meat will lose what little food they can grow from their peasant plots.

Industrial tissue culture

Industrial tissue culture has the potential to produce nearly any botanical substance through fermentation. Opium, digitalis, ginseng and tobacco are among those actively being examined for potential commercial production. The countries and agriculturalists that have traditionally produced these products will experience dislocations of their economies. In the case of cocoa, the trees require 10 years of cultivation before they bear fruit, but then can continue to produce for 40 to 50 years. If current cocoa tissue culture research is successful any time in the next 20 years, the entire economics of the industry would be transformed to the detriment of Brazil, Ghana, and the thousands who would lose their jobs.

Tissue culture has several potential advantages over extraction and synthesis of chemical substances. Tissue culture raises the possibility of producing substances for which extraction and synthesis are economically prohibitive. It enables the production of purer products, with more reliable quality control. Tissue culture production processes are not limited by season or climate and can operate continuously. A fermenter can be dedicated to one process or can be switched from one product to another, thereby increasing the flexibility of capital equipment. Less labor is required, and labor demand can be made more continuous throughout the year. Tissue culture will enable manufacturers to be free of potentially monopolistic suppliers (either companies or countries). The "natural products" of tissue culture will likely be subject to limited government regulation, and the waste stream from industrial tissue culture is organic and biodegradable.

However, tissue culture remains a very expensive process and most probably will be confined to high value products such as drugs, flavorings, and other rare organic compounds. It is also quite possible that "engineering" the genetic information for the desired compounds into microorganisms may ultimately be a more efficient production method than tissue culture. The relative expense of tissue culture will thus limit its applicability in chemical production and make it vulnerable to the commercialization of other biotechnological processes rooted in recombinant DNA and industrial microbiology.

Other agricultural products

Some commodities produced through biotechnological processes (e.g., high fructose corn syrup, utilizing immobilized enzyme technology) involve one agricultural commodity (corn, for which the U.S. is the predominant residual supplier in world markets) supplanting another (sugar cane, which is a leading export commodity for many tropical LDCs). On the other hand, the future application of genetically modified bacteria to ethanol production would involve the substitution of agricultural commodities (especially sugar cane and cassava) for fossil fuels.

The perfection of single cell protein (SCP) production may become one of the most significant applications of biotechnology to the production of agricultural commodities. Imperial Chemical Industries (ICI) has constructed an SCP factory that may become competitive with soybeans for animal feed. ICI claims that for the same quantity of protein, SCP requires only one-tenth of the labor involved in producing soybeans for animal feed. The promise of SCP is illustrated by the fact that the USSR, with its enormous natural gas reserves, expects to be able to produce all of its animal feed protein in the form of SCP by 1990.

The development of SCP technology thus portends a dramatic reorganization of soybean production and markets across the globe, perhaps to the point of undermining the important role of soybeans in U.S. agricultural exports. A comparable impact on sugar production is already in progress as inexpensively high fructose corn syrup (HFCS) expands its share of sweetener markets in industrial societies. The superimposition of HFCS technical breakthroughs on global recession has resulted in a virtual depression in the world sugar cane industry, which has crippled the export economies of several LDCs.

University-industry ties

The rush to commercialize biotechnology is forging unprecedented links between American universities and companies from around the world in both biomedical and agricultural research. Cornell recently received $2.5 million each from three companies spread over six years to fund a biotechnology institute. Monsanto has committed itself to over $50 million in expenditures at various universities.

The issue of possible conflicts between public and private interests has been very dramatically elevated in the recent case regarding the potential development of a malaria vaccine by researchers at New York University. Genentech, a major biotechnology firm that was initially a collaborator with the New York University

scientists, later withdrew from this World Health Organization (WHO) sponsored attempt to produce the malaria vaccine, arguing that without an exclusive license from WHO they could not be assured sufficient profits to proceed with development. Further, since malaria primarily affects the poor, there is little possibility of directly selling the vaccine to the victims of the disease.

In the case of malaria vaccine, it is likely that one of the large foundations will step in to provide the necessary funds, but will this incident in health be repeated in Third World agriculture? Similar questions can be raised regarding plant breeding goals: Will plants be bred to function efficiently only with specific chemical inputs, or will plants be engineered to minimize chemical inputs?

In response to these problems, United Nations Industrial Development Organization (UNIDO) is in the process of organizing an international center to gather scientists to do biotechnological research of interest to Third World countries. But ultimate success of this center, with a working budget of merely $8.6 million annually, is in doubt. Cetus' or Genentech's annual research and development expenditures each are in the neighborhood of $20 million. In addition, the governments of the U.S. and Japan, the two leading biotechnology powers, chose not to participate at all in the planning of the proposed center, sending a message to UNIDO and the world that the U.S. and Japan stand ready to withhold R & D assistance if it threatens to undermine their international competitive position in biotechnology.

Biotechnologically-related commodity sales in the agricultural and food sectors could reach $50-100 billion by 2000. This Biorevolution is virtually inevitable, given the commercial successes registered thus far and the massive R & D investments that have been made.

The fact that biotechnology will make possible major productivity improvements in the agricultural and food sectors means that significant human benefits will result from the development and deployment of this technology. Yet these benefits will entail social costs, the most significant aspect of which is that the benefits and costs will almost certainly be unequally distributed across countries and social groups.

Our research suggests that there are significant threats of the world's poor receiving meager benefits from biotechnology while absorbing disproportionate shares of the social costs of dislocation, technological obsolescence, and displacement of labor. We are quite frankly shocked at the lack of long-term investment in analyzing the social, economic, and political effects of biotechnologically-induced change on the world agricultural system.

What will be the distributional consequences of the deployment of biotechnology inputs among farmers in developed and developing countries? Will the small, heavily subsidized farms of Western Europe be able to adapt to the new economic conditions and remain competitive? If biotechnology cheapens and increases agricultural production to the degree anticipated, will the Western European and North American governments be able to subsidize ever larger floods of surplus commodities? Will biotechnology result in the attenuation or the sharpening of economic disparities among developed and developing nations?

These questions are admittedly difficult to answer at present. Yet the fact that no one is asking these questions and venturing plausible answers suggests that biotechnology, which will no doubt rival all previous technological "revolutions" in its impact on economic and political institutions, will be developed and commercialized with little understanding of its benefits and costs. The opportunity to establish creative institutions and plans to ameliorate adverse social impacts will again be tragically foregone.

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Capability building in biotechnology and genetic engineering by developing countries. (Abstracts of papers presented at the AAAS on 26 May 1984).

Basic ingredients required for capability building in biotechnology
Dr. David McConnell (Trinity College, Dublin).

In 1981 six molecular biologists met in Vienna under the auspices of UNIDO to consider the likely extent of the impact of genetic engineering and biotechnology on developing countries (LDCs). They found this impact could be significant and that the LDCs should take steps to ensure they would share the benefits of new biotechnology without becoming controlled from abroad or overly dependent on products or processes conceived from these technologies. The group noted the complexity of genetic engineering techniques and suspected that few LDCs had relevant resources or knowledge. They suggested than an International Centre for Genetic Engineering and Biotechnology (ICGEB) be established to undertake training and research in these fields and to provide untrammelled advice to LDCs which planned to invest in these areas. While serving as a UNIDO scientific consultant, I visited many LDCs and developed countries and chaired a Selected Committee which reported to the International Meeting in Madrid in 1983 on the proposals for the location and financing of the ICGEB. I will discuss the needs and difficulties associated with the establishment of high-complexity science and technology. Opportunities will be described for individual scientists, institutions, nations and intergovernmental organizations to collaborate in the development and application of genetic engineering and biotechnology for the benefit of the third world.

Capability building for scale-up and bioscience-based industry
Dr. Raymond Zilinskas (UNIDO, Vienna, Austria).

On the international level, UNIDO has since early 1981 been instrumental in assisting DCs to develop and build advanced capabilities in biotechnology for the purpose of establishing a bioscience-based industry. Attention has been given to mechanisms of both vertical and horizontal transfers of bioscience and bio-technology. The vertical transfer of technology in its simplest form refers to concept development, i.e. the transformation of ideas or findings from basic research into a technology or a product. The horizontal transfer of technology refers here to the dissemination of research findings, concepts and technologies between nations, particularly from developed to developing countries. UNIDO can positively affect both types of technology transfer by a variety of actions and through the ICGEB. To elaborate a best approach for establishing bioscience-based industries, a four-step procedure is followed. First, concept development in developed countries and the mechanisms that have evolved for the international transfer of technology are considered. Next, the present-day biotechnology-based industry in developed countries is characterized. Third, relevant findings from the first two sections are used to formulate suggestions for capability building in developing countries. Last, tentative conclusions are reached as to steps which could be taken by DCs to accomplish capability building in biotechnology R & D as a basis for establishing a bioscience-based industry.

Building biotechnology R & D capability in developing countries
Professor Ray Wu (Cornell University, Ithaca, New York).

For building biotechnology R & D capacity in developing countries, it is essential to first train a group of highly competent biotechnologists (scientists and engineers). The biotechnologists must have a solid grounding in the basic sciences at the undergraduate level and advanced training at the graduate level. Additional laboratory experience through postdoctoral research is desirable for scientists, and practical experience is invaluable for biochemical engineers. Beyond this, a healthy environment for research or development and adequate financial support are necessary for the biotechnologists to realize their potential. Frequent interaction with other biotechnologists is indispensible to a productive career. Any research institute or biotechnology company must possess a critical mass of well-trained scientists within one's specified field, as well as workers in other fields. The minimum requirements for a successful team of workers in genetic engineering and biotechnology must include at least several independent scientists in each of the following disciplines: biochemistry, genetics, micro-biology, immunology, cell biology, and biochemical and chemical engineering.

A healthy environment which fosters success and productivity must include: adequate financial support, a critical mass of scientists and engineers, a skilled technical support staff, a far-sighted director, and a sound national policy on biotechnology.

Building a biotechnology R & D capability in developing countries: An inside perspective

Dr. Sheikh Riazuddin (Nuclear Institute for Agriculture and Biology, Faisalabad, Pakistan).

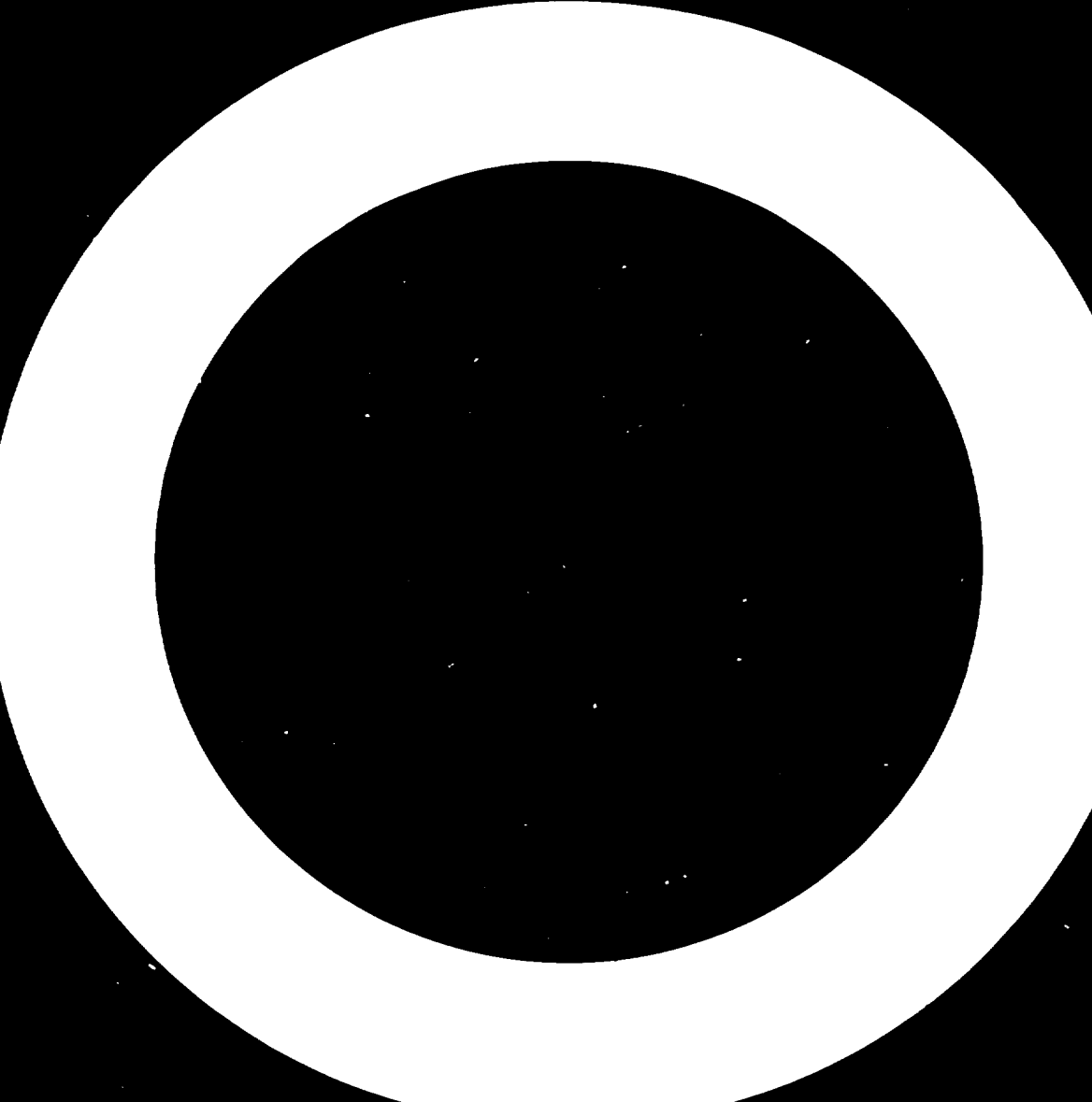
The new biotechnology offers tremendous opportunities to solve specific problems of the developing countries thereby contributing directly to their economic up-lift. Nevertheless, the expertise and infrastructure presently available in these countries to reap the harvest of new technology is almost non-existent. Several measures must be taken to develop and advance their capabilities. First and foremost efforts must begin with creating awareness, willingness and desire among the scientists as well as policy makers to adopt the new technology. Biology courses in secondary schools, colleges and universities will have to be improved, accommodating recent developments in genetics and molecular biology; specialist training courses will have to be arranged for teachers and young researchers; library facilities improved; and interactions with the developed world will have to be strengthened. Basic research must be strengthened so that new initiatives and techniques are developed locally and those devised elsewhere can be easily modified. Perhaps the most important factor will be a willingness to get involved in an area of R & D which requires relatively high expenditure to which developing countries are not accustomed. Efforts must concentrate on the ready availability of needed, rather expensive materials as well as efficient repair and maintenance of equipment. This presentation will discuss measures to be adopted by developing countries at the national level and the role international agencies must play to develop biotechnology capabilities.

Function of a national policy and a national biotechnology centre to develop indigenous capability in biotechnology

Dr. Diogenes Santiago Santos.

A DC by definition can mobilize only limited resources. Therefore, only a limited number of projects a country's decision-makers perceive as having national importance can be undertaken at any one time. A number of DCs have found it effective to first, determine national priorities; second, formulate a national policy for achieving top priorities; and third, mobilizing available resources and focussing them on action to realize those priorities. Severl DCs have perceived that biotechnology offers promises for development and have decided to give this field top priority. One such country is Brazil which is now following up on its successful PROALCOOL Programme with a national biotechnology plan. An integral part of the plan is the establishment of a national biotechnology centre.

The author will discuss the decision-making process which in Brazil led to the formulation of a national plan; will describe the plan and its goals; and will explain the role of a national biotechnology centre to development. The relevance of Brazil's experience to other DCs will be pointed out. The assistance UNIDO and other intergovernmental organizations may render in the realization of goals will be explored. The advantages that may accrue to a national centre from association or affiliation with the ICGEB will also be discussed.



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