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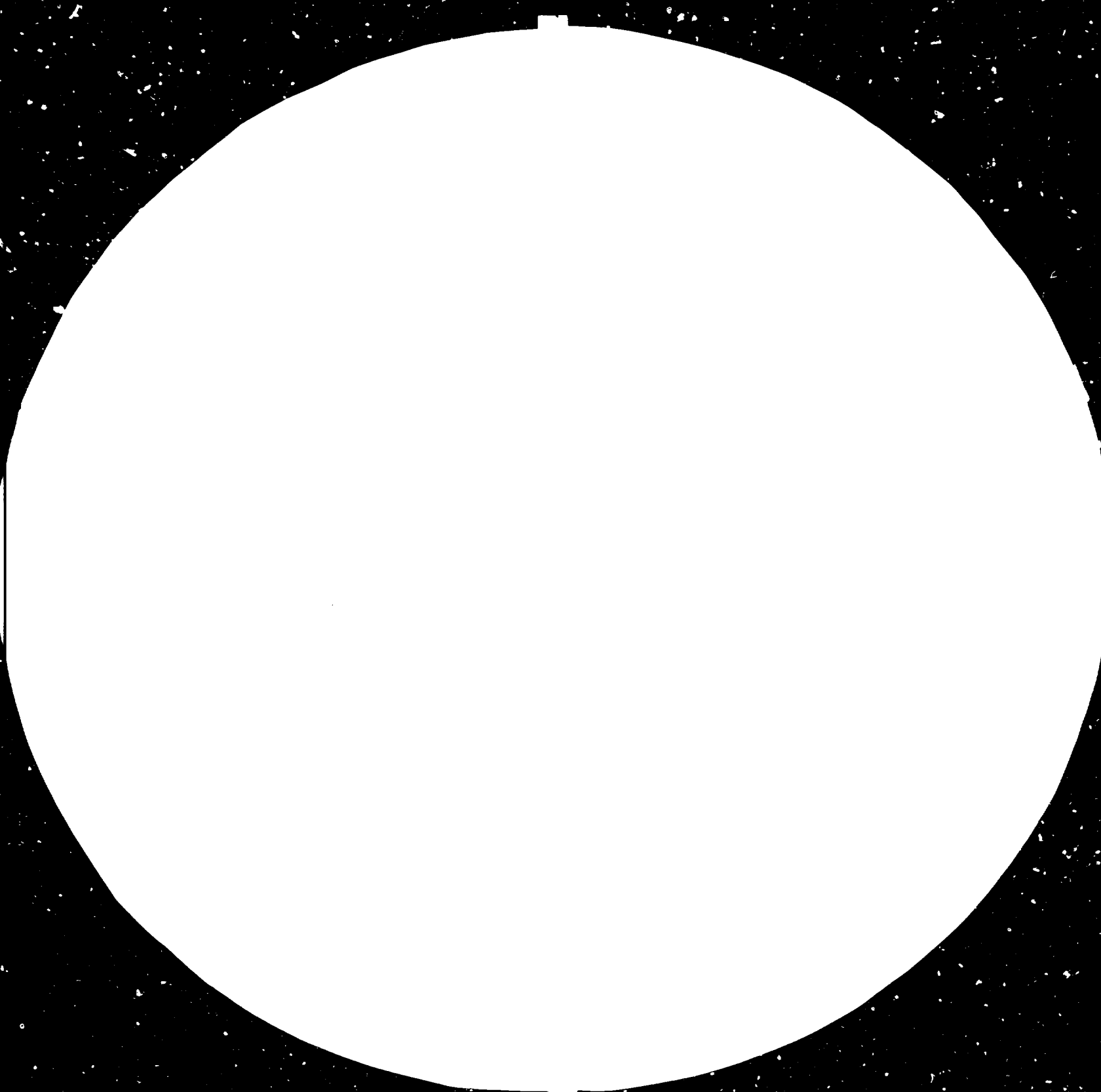

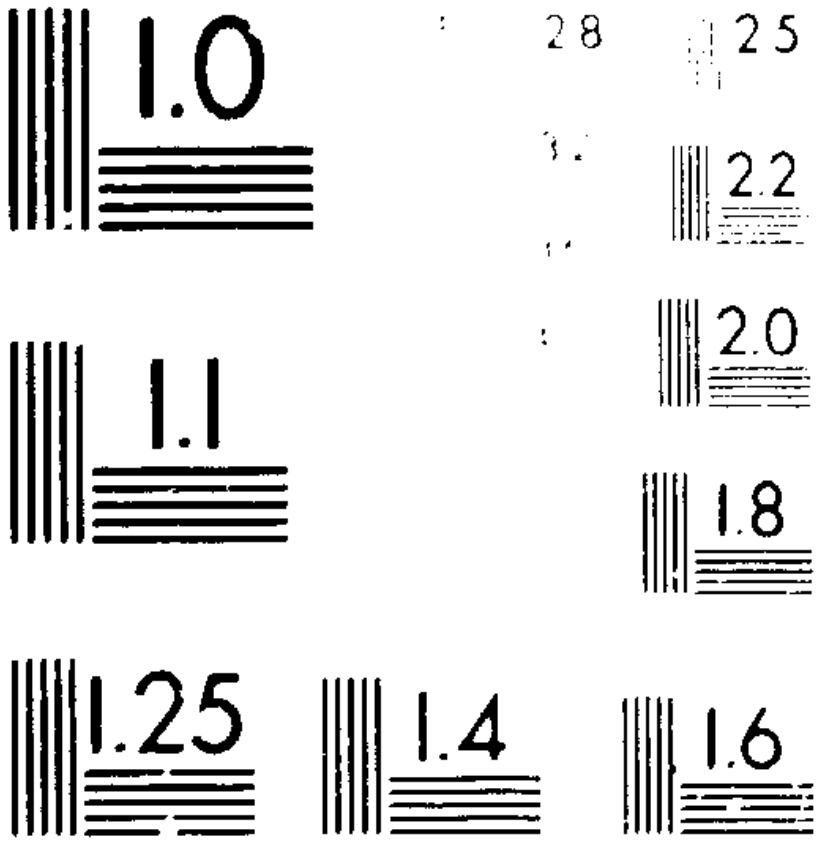

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

Genetic Engineering and Biotechnology Monitor

Issue Number 4 January 1983

Dear Reader,

Readers will be glad to know of the successful outcome of the High-level Meeting on the Establishment of the International Centre for Genetic Engineering and Biotechnology, held at Belgrade from 13 to 17 December 1982. It decided that such a Centre should be established soonest and that a ministerial-level plenipotentiary meeting should be held in July 1983 to subscribe to the act of establishing the Centre. Conclusions and recommendations of the meeting as well as the discussions that took place will be found under the item "News and Events".

For some of us the meeting was an unforgetable experience, being a signal act of international co-operation in an important field with considerable potential for developing countries. As Dr. Abdel-Rahman Khane, Executive Director of UNIDO, mentioned in his address to the meeting, this new technology places at the hands of developing countries an important tool on the basis of which they could move forward in their economic and social development in a manner suited to their own resources and conditions. Dr. Abdus Salam, Nobel Laureate and Director of the International Centre for Theoretical Physics at Trieste (Italy), in his address to the meeting thought that the 21st century will be the century of applied biology, particularly for the developing world.

Another event of significance was the Expert Meeting Preparatory to the International Forum on Technological Advances and Development, which was held at Moscow from 29 November to 3 December 1982. A working group of this meeting went into the question of genetic engineering and biotechnology and made a valuable review of the state-of-the-art. The report of this working group will be summarised in a later issue.

We in the UNIDO Secretariat are now working hard on two major events which will take place in the next six months. From 10 to 15 April 1983 the International Forum on Technological Advances and Development will be held at Tbilisi, USSR, and one of the important areas to be covered in this Forum will be genetic engineering and biotechnology. The Ministerial-level Plenipotentiary Meeting on the Establishment of the International Centre for Genetic Engineering and Biotechnology will be held from 13 to 17 July 1983.

I take this opportunity to wish all the readers a happy and prosperous New Year.

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Director
Division for Industrial Studies

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NEWS AND EVENTS

International Centre for Genetic Engineering and Biotechnology to be established

The September issue of the Monitor announced a meeting in Belgrade, Yugoslavia, which was held from 13 to 17 December 1982 in order to examine and arrive at conclusions on the location of the Centre, the guiding principles of its structure and operations, its work programme and the financial contributions from the participating countries. The meeting was attended by about 200 participants comprised of high-level government officials and policy-makers, scientists and members of international organizations from 28 countries and observers from a further 7 countries.

A general agreement among interested countries has been reached that the UNIDO promoted International Centre for Genetic Engineering and Biotechnology should be established soonest. Offers for hosting the Centre have been received from a number of countries which will be visited by an expert committee. The report of the expert committee and other essential proposals will be considered by a ministerial level plenipotentiary meeting in July 1983 which will take the final decisions concerning the Centre and subscribe to the act of establishing it. A brief account of the meeting held in Belgrade, where these decisions were taken, is given below.

In view of the consensus on the importance of genetic engineering and biotechnology for development, and on the need for international co-operation in assisting developing countries in this area, many countries voiced their support for the idea of establishing an International Centre for Genetic Engineering and Biotechnology. It was felt that such a Centre would be one of the important instruments for the developing countries to enter into the mainstream of technological development in this area, and thereby promote and accelerate the development of many sectors of their economies. The Centre would provide a forum whereby developing countries could strengthen their technological capabilities by having free access to the latest technologies. Small, developed countries could also make use of such a Centre, and the suggestion was made that participation in the Centre should be open to all countries on an equal basis. A note of caution was given by a few participants that the Centre was conceived to be too ambitious and a more modest mechanism, such as an international network, was to be preferred. However, it was emphasized that only a Centre such as envisaged in the documentation produced by UNIDO would provide the critical mass of expertise in order to be effective. The Centre could also be a major force in catalysing national level activities and promoting centres of related specializations in the regions in a manner suitable to the resources and needs of the countries concerned.

As regards the activities of the Centre, it was thought that these should not be confined to research alone, but be directed towards increasing the capability of national centres of developing countries through training facilities which could be most effectively achieved through an active interlinkage. The training component could well be a starting point of action for setting up the Centre. The national centres would therefore be considerably strengthened after the trained scientific and technical manpower returned to their home laboratories. It was also suggested that initially an international network or clearing-house be established as an alternative to the Centre, but many of the participants stated that the Centre should be regarded as a foundation on which to build a network of regional and national institutions rather than the other way around.

Concerning the location of the Centre, it was pointed out that it should be at a place where there was adequate infrastructure and an attractive and stimulating environment in which experienced and creative scientists could work, preferably in a developing country. Definite proposals for hosting the Centre were put forward by Belgium, Canada, Cuba, Pakistan, India and Thailand with possible proposals to be forthcoming from Italy and Spain. Before a definite decision is reached, it was decided to establish a select committee of representatives from seven countries and two UNIDO staff members to visit the several sites offered and then submit their findings to a plenipotentiary ministerial-level meeting to be held in Madrid from 15 to 23 July 1983 for further consideration.

It was generally agreed by the participants that the distinguishing feature of the Centre, its rationale and its success would depend on its programme of work, and it was stressed that apart from avoiding obvious duplication, the work should relate closely to national and regional level priorities and activities, as well as activities promoted by international organizations. These linages were to be stressed more prominently and, in addition, should consider a number of other mechanisms such as the systematic building up of ties with national centres (perhaps even assist in the setting up of such centres), regional centres and networks

either on a geographical basis or on the basis of distinct specializations. The work programme's main focus should be on enabling the Centre to provide a point of open access to advanced technologies, high-level training and serve as a possible source of provision of vectors, restriction enzymes, etc. to national and regional institutions carrying out research work relevant to their own problems and conditions. There should be continuous and systematic efforts to identify the needs of developing countries and their scientific and technological priorities. The important developments in biotechnology such as single cell protein, enzyme engineering, microbial leaching, etc. and those that might occur in future should be kept in mind, indicating that the programme be kept flexible.

The meeting also discussed the guiding principles of the structure of the Centre as had been set out in the document covering the subject. The principles state that participation should be open to members of the United Nations or a specialized agency, or the International Atomic Energy Agency. Three government bodies were proposed comprising a Board of Governors, a Council of Scientific Advisers, the Director and staff. The Board of Governors would consist of representatives of participating nations and would meet once a year in order to determine general policies, decide on financial matters and otherwise take appropriate action to further the objectives of the Centre. A suggestion was made that an executive committee of the Board be set up to meet more often to take decisions as required between Board meetings. The Council of Scientific Advisers would consist of ten eminent scientists and technologists elected by the Board and would hold office for two years. Its members should be chosen from the scientific community outside the Centre and representation should be on the basis of an equitable geographical distribution. It was also suggested that it may be beneficial to have economists or policy-planners sit on the Council. The Council's purpose would be to examine the Centre's work programme twice a year, review its implementation and budget, assist the Director on all scientific and technical matters and made recommendations to the Board as needed. The Director of the Centre would be elected by the Board as needed. The Director of the Centre would be elected by the Board, upon the recommendation of the Council, and serve for a period of five years.

A list of the documents presented at the meeting is entered under "Publications" on page 29 of this issue.

Genetic Manipulation Advisory Group

The Third Report of the Genetic Manipulation Advisory Group published by Her Majesty's Stationery Office, London, concludes that health risks involved in rDNA technology are, and are likely to remain, negligible. The report notes that the Group's advice on the large-scale use of genetically manipulated organisms would be restricted to the biological properties of the organisms in use. It was planned to hold a full meeting of the Group to discuss the future of the Group since many of its members are not in agreement as to what role it should play, whether as a watchdog or advise on the saftey of certain experiments, including the ethics of genetic manipulation in humans.

The terms of reference of the Group will remain the same as when it was established in 1976, except that it will have to present a report on an annual basis rather than ad hoc, as hitherto. There were some fears expressed, as a result of the report, that the Group may have reached the end of its usefulness and a delegation sponsored by the Association of Scientific Technical and Managerial Staffs met with the minister responsible for the Genetic Manipulation Advisory Group in order to put forward a case in its support. They pointed out that GMAG had played an important role in ensuring the safe development of genetic manipulation and in the successful identification of potential health and safety risks as has been shown by contraceptive pills and biological washing powders, but there still remained some areas where knowledge was limited and where careful scrutiny was needed, such as gene replacement therapy which could effect the population as a whole and the decisions for its use ought not to rest with hospital ethical committees alone and large-scale fermentation processes which could leak into the environment. The minister however felt that the GMAG was not the appropriate body to advise on ethical matters, whilst being fully aware of the important impact that biotechnology will have on industry in the next five years. (Extracted from Nature, Vol.299, 30 September 1982, New Scientist, 30 September 1982 and Genetic Technology News, November 1982, address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Regulation of research in California

A bill to regulate research in the state of California on rDNA has not been passed since it was considered that the legislation was unduly restrictive and may be the basis for litigation against firms involved in biotechnology. The bill, had it been passed, would have obliged state agencies, including the university to follow the guidelines set out by US National Institutes of Health and use these as a basis for defence in lawsuits arising from alleged harm from rDNA. (Extracted from Technology Update, 30 October 1982.)

Evironmental protection

The US Environmental Protection Agency has asked one of its advisory committees to consider the applicability of the Toxic Substances Control Act to the field of biotechnology, including the manipulation of genetic material in bacteria, fungi and viruses. The Act could be applied to the production of specific chemicals in fermentors or biochemical systems, safety and the inadvertent or deliberate release of chemicals into the environment. The Agency would also be concerned with any materials released into the environment from a new biotechnology process, especially those microbes injected into oil wells for enhanced oil recovery or spread on oil spills. The application of the Act to biotechnology raised the question of whether a normal bacterial constituent produced through biotechnology should be considered a new chemical requiring a pre-manufacture notification submission. (Extracted from Technology Update, 25 September 1982 and Genetic Technology News, October 1982, address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

A European view on regulation

The European governments who are members of the Council of Europe debated a feasibility study which had been prepared by the secretariat of the Council at the request of the Committee of Ministers, which is the Council's controlling body. The feasibility study concerns the issue of whether international controls on genetic engineering was necessary or not, and if action to be taken is urgent. Many European scientists feel that the dangers of rDNA research have been over-exaggerated, whereas the lawyers on the other hand feel the scientists are too complacent. The main proposal is for a multidisciplinary committee to discuss how to implement the recommendation, whether to limit regulation to a code of conduct or to recommend legislation. (Extracted from New Scientist, 16 December 1982.)

Genetic engineering may raise antibiotic yields

The University of Wisconsin recently described work undertaken in the area of increasing antibiotic yields through genetic engineering. The molecular genetics of biosynthesis of erythromycin A by a strain of Streptomyces erythreus (NRRL 2338) has been studied. In the first stage of biosynthesis, in which simple straight chain compounds, propionate and 2-methylmalonate, are apparently converted into 6-deoxyerythronolide B were of main interest. This compound is the first precursor to erythromycin that contains the big 14-membered ring structure that characterizes the macrolide group of antibiotics, to which erythromycin belongs. The Wisconsin researchers are searching for genes that they believe may code for an enzyme that catalyzes formation of the ring. If they can find these genes and clone them they will gain an understanding of how the organism controls output of the antibiotic. Then they may be able to use rDNA methods to engineer super-producing strains, and to construct hybrid strains that could produce new macrolide antibiotics.

The NRRL 2338 strain of S. erythreus contains plasmids. These have been suspected as the site of genes governing antibiotic production. Other producing strains contain no plasmids, therefore the function of the plasmids is not clear.

Commercial antibiotic producers are not completely secretive. Lilly (Indianapolis, IN) has released some information on genetic engineering of Streptomyces species that produce tylosin. The John Innes Institute (Norwich, UK) has isolated and cloned genes coding for resistance to a number of antibiotics from several species of streptomycetes into Streptomyces lividans: neomycin resistance from S. fradiae; viomycin resistance from S. vinaceus; thiostrepton resistance from S. azureus; and erythromycin resistance from S. erythreus. Now the group is working to develop broad-host-range plasmids containing the resistance genes they have isolated. Introduced into an antibiotic-producing strain they may increase output. (Extracted from Genetic Technology News, October 1982, address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Genetically engineered insulin

Insulin, which is the first product of genetically manipulated bacteria to be marketed for human use is now on sale in the United Kingdom. Two companies have received official approval to market their product - Eli Lilly and Novo Industri. Following considerable clinical tests, the new substance (which is produced from two bacterially produced fragments that are supplied with synthetic genes for either the A or B fragment of insulin), was found to be effective although it had the tendency to be absorbed slightly faster from the site of injection resulting in more insulin being required to obtain the same reduction of blood sugar than through the use of conventional bovine or porcine derived preparations. The slight disadvantages are however considered to be considerably offset by the advantages in that it reduces the incidences of allergic reactions which some sufferers develop towards animal insulin, and that the new insulin is better at hastening the removal of detones from the bloodstream. However, availability and cost will determine the choice of insulin on the market. At present the new insulin costs almost twice as much as bovine insulin, but only 10 per cent more than porcine insulin. (Extracted from Financial Times, 15 June 1982; European Chemical News, August 1982; The Times, 21 September 1982; Nature, Vol. 299, 23 September 1982; Genetic Technology News, October 1982; Technology Update, 30 October 1982; Chemical and Engineering News, 8 November 1982; Nature, Vol. 300, 11 November 1982; Genetic Technology News, December 1982, address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Interferon

A Japanese consortium of companies are conducting research on the mass production of interferon via large-scale culture tanks. Both alpha-type and beta-type interferons have successfully been produced using small-scale tanks. Japan has also developed the first artificial gene for producing gamma interferon.

Israeli scientists have discovered that interferon can prevent the multiplication of viruses in plants. Researchers at the Hebrew University's School of Agriculture at Rehovat discovered that treatment of tobacco plants with interferon inhibited the growth of tobacco mosaic virus. Additional studies will be carried out to see if interferon will combat viral infections in other plants.

The recombinant DNA interferon developed by Biogen, the Geneva-based specialist biotechnololgy company, has been shown to be effective in preventing the common cold.

Results of a limited clinical study show that the recombinant protein is as effective as samples obtained from natural sources in the prevention of infection by the common cold virus.

In the study, 41 patients were infected with a strain of rhinovirus, which causes colds and other respiratory illnesses. None of the 19 patients who received interferon by nose spray before the injection with the virus showed common cold symptoms. However, eight members of the control group of 19. who were not given the interferon treatment, caught colds. Results of tolerance studies on the interferon were also favourable.

Since these results, although significant, are not completely conclusive, further tests will be carried out as to their repeatability and also on the effectiveness of the interferon treatment against other types of cold viruses. The genetically-engineered interferon used in the study was of the alpha 2 human leukocyte type and was produced in genetically altered E. coli by Biogen, in conjunction with Schering-Plough, and purified using the Swiss firm's large-scale chemical purification technology. (Extracted from European Chemical News, 8 March 1982, Technology Update, 16 October 1982, 23 October 1982 and Chemical Week, 10 November 1982.)

Cholera

Critics of genetic engineering, who fear that the ingenious new microbiological techniques could unleash a plague of "superbugs", will doubtless raise questions about an announcement in September that researchers had managed to get the common bacterium E. Coli that lives in the human intestine to produce cholera toxin.

The bacterium that causes cholera does so by colonising the small intestine and secreting a protein - cholera toxin - which penetrates the cells that line the walls of the intestine, causing them to secrete water. Result: diarrhoea, severe dehydration and - if untreated - death.

The protein itself is a complicated structure made up of two types of subunit, called A and B. One A subunit is surrounded by a ring of five B subunits. This ring binds to "receptors" on the surface of the cell, and only the A part of the molecule enters. For the toxin to be active, both subunits are necessary.

Scientists at the London School of Hygiene and Tropical Medicine have exploited this fact, using the basic techniques of genetic engineering. They took the DNA molecule out of the cholera bacterium and cut it up into even smaller pieces. Having identified the section of DNA that codes for cholera toxin, they inserted it into a plasmid, and then introduced this recombinant DNA into the bacterium E. Coli.

There is no danger from such an organism, because the strain of E. Coli used in such experiments is defective and can no longer survive in the human intestine. Moreover, the work is done under "category 3" regulations - rigid containment conditions laid down by the Government's Genetic Manipulation Advisory Group.

The really interesting part of the work comes in the next step: the size of the piece of DNA initially inserted into the plasmid was chosen to maximise the chances of getting the entire toxin molecule made. However, once the group had got a "clone" of cells doing just this, they took out the plasmid and recovered the DNA coding for cholera toxin which they had inserted, and cut it up still further. They then repeated the process of inserting the piece of DNA into a plasmid and growing it in E. Coli. In this way, they got a clone of cells that makes only a part of the cholera molecule. This molecule is still recognised by antibodies that spring into action when the body is attacked by cholera toxin, but it no longer has any toxic activitiy. This suggests that the DNA in this particular clone codes for all the B subunit but only part of the A subunit.

The advantage of such a molecule to medicine could be immense. At present, the only way of acquiring long-lasting immunity to cholera is by natural infection - a rather drastic measure. Existing cholera vaccines give protection for only a few months. Even then, the protection is limited. However, a cholera toxin molecule that no longer has any toxic activity could be used to produce a really effective cholera vaccine. (Extracted from The Economist, 18 September 1982.)

Genetic engineers crack the secrets of the immune system

A union between scientists expert in recombinant-DNA techniques and immunologists has succeeded in perfecting an elaborate package of experiments which could shed much light on the determinants of the body's response to foreign invasion. The protocol holds out promise for accurate intervention in the fight against disease, even cancer, and is exciting in its application to the problems of transplant rejection (Nature, Vol. 298, p. 529).

The predominantly British team, working on mouse genes coding for the major histo-compatibility complex (MHC - a group of molecules sitting on cell surfaces and important in cell-cell interactions, the fight against disease and transplant rejection) isolated a single molecule, mapped its gene on the mouse's genome, and proved that the mere existence of this molecule on a cell surface was sufficient to make the cell a sitting target for the action of a specific attacker.

In the group of experiments the scientists used cosmids containing "bits" of DNA known to include genes coding for cell-surface antigens. Cosmids are hybrids of phages (viruses that infect bacteria) and plasmids (loops of bacterial DNA). They combine the best features of each in picking up pieces of foreign DNA and inserting them into cells. The researchers used them to transform a mouse cell line. When they came to screen the transformed cells, instead of using DNA probes to complement the desired genes, they looked for the molecule the inserted gene expressed - a process that is more efficient and only recently developed. The molecule they located was indistinguishable from a known cell-surface antigen in mice (called H-2K^{b}) and was mapped back to the B gene of the mouse's MHC region. And the mere presence of this molecule on the cell surface made it a target for a specific immune response.

The implication is that any cell surface antigen could be isolated and characterised using the immunological and recombinant-DNA techniques outlined here. They could introduce a new and powerful weapon in the fight against disease. Take the following hypothetical case. It has recently been discovered that many cancerous cells have a specific marker protein (antigen) on their surfaces (New Scientist, Vol. 95, p. 152). If this marker is not identified as foreign then the body will fail to attack and kill the cancerous cells, treating them as "self" rather than "non-self". But can the body be persuaded otherwise? The techniques described above suggest it can.

If the marker is identified and its gene isolated, then the gene could be slightly altered to produce a slightly altered marker. If this changed marker is introduced into the body, maybe it could produce an immune response where the original and very similar cancer antigen did not. Antibodies specifically against one type of antigen may have a similarly destructive effect on a slightly different antigen - in this case the one represented by the cancer cell.

Some of the future applications envisaged for this technique include enhancing the body's immune response to fight against cancer and even fooling the body of a transplant patient that the incoming organ is "self" rather than "other", thereby avoiding the problems of rejection. (Source: New Scientist, 9 September 1982.)

Equipment for biotechnology

According to the conclusions of a market study carried out by Tag Marketing Associates of Erie, Pennsylvania, USA, sales of equipment used for biotechnology research will rise from approximately $90 million in 1981 to at least $140 million by 1985. Specifically, the study analyses the equipment opportunities presented by programmes in rDNA, monoclonal antibodies and interferon and shows that the greatest growth in equipment sales was for protein expression on a pilot plant or production scale. By 1985 it is estimated that the largest categories in annual sales will be fermentors, centrifuges, final isolation and purification appratus, tissue culture devices, filters and membranes, freeze driers, freezers and refrigerators, autoclaves and sterilizers, and last of all water purification equipment. Manufacturers are generally optimistic about their industry's future, predicting an annual growth rate of between 15 and 25 per cent although they realize that some potential buyers may go out of business. The user's main concern is for a better service and support for biotechnology equipment. (Extracted from Chemical and European News, 6 September 1982; Technology Update, 23 October 1982.)

Computer data bases

In order to cope with the growing volume of information on DNA sequence research being carried out at laboratories throughout the world, computer programmes and data bases are being evolved to help researchers obtain information more cheaply and conveniently. Two companies are making available their software at very reasonable prices. The companies are Bolt Beranek and Newman Inc. with their Genetic Sequence Data Bank (GenBank) and IntelliGenetics. (Extracted from Technology Update, 9 October 1982, 30 October 1982 and Genetic Technology News, November 1982, address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Biotechnology impact on food and agriculture

Products from biotechnology in the agriculture, food and beverage industries will be worth some $6.2 billion by 1985, rising to $103 billion by 1995, according to a study just released by Cleveland-based consultants, Predicasts Inc.

With techniques such as recombinant DNA and plant tissue culture set to have a growing impact on agriculture by the end of the century, Predicasts predicts that biotechnology's influence on grains, fruits and vegetables will account for $50 billion in products or 20 per cent of the total major food crop market by the mid-1990s. Application of advanced genetics to livestock breeding, it adds, will account for animals with a projected value of $48 billion in 1995, or 30 per cent of the total market for cattle and calves.

"Biotechnology markets and companies (agricultural, food and beverages)" is available from Predicasts inc., 110011 Cedar Avenue, Cleveland, Ohio 44106, USA; for $995. (Source: European Chemical News, August 1982.)

Biomass as an energy source

Biomass could play an important role in minimizing future oil shortages, according to Jaycor's Advanced Technology Group (Alexandria, Va). Reasons for their finding include that it is the only fuel-based renewable energy source; that biomass can be converted easily to new energy supplies because its technology is not as complicated as conventional energy technology; and that biomass resources are distribued widely throughout the U.S. Since biomass energy source prices are competitive with conventional fuel prices, investments in biomass for an emergency would enlarge domestic energy production capabilities overall. US biomass energy use in 1981 was estimated at 2.4 quads, or 3 per cent plus of total, and could reach 10 per cent by 1985. (Source: Technology Update, 18 September 1982.)

Real biotechnology

Future energy use was considered by Dudley Gibbs of Pollution Prevention (Consultants) Ltd. in his paper, 'Low energy routes by biotechnical processes'. Gibbs indicated areas in which bioprocesses might be used to provide chemicals. However, he also raised the considerable technical and logistical problems which might face a large biotechnical industry.

Industry has to 'address biotechnology with reality', Gibbs says. A quite considerable range of chemicals could be produced utilizing bioprocesses, however, the provision of sufficient feedstock for such routes has to be considered first, and extraction methods have to be substantially improved.

It is technically feasible to produce heavy commodity chemicals such as ethylene, propylene, butylene and butadiene using biotechnical routes. But the provision of sufficient carbohydrate feedstock for any routes that might be developed would involve quite radical changes in the world's economic structures. This may not take place in the foreseeable future. Areas which show greater promise include the production of oxygenated hydrocarbons, carboxylic acids, lipids, sterols, polymeric materials and amino acids.

Autotrophic systems show most promise for the future. Organisms such as Alcalignes eutrophus, which uses carbohydrate as a feedstock, but can, as effectively use hydrogen and carbon dioxide, could open up a whole new range of fermentation possibilities. Alcalignes eutrophus will produce the natural polymer, polyhydroxybutyrate (PHB) from carbohydrate as well as from H_2 and CO_2. Recent research has shown that using a mutant organism, pyruvic acid is secreted into the surrounding medium. It was considered that by further genetic manipulation, pyruvic acid could be channelled into other metabolic routes to produce a wide range of substances. As the understanding of microbial physiology increases, the concept of mixed cultures could be advanced so that two or even three organisms could be fermented together to produce the desired end product.

Europe could be faced with a number of strategic energy options for the future in which biotechnology will play a part. Mainstream feedstock for the chemical industry will be derived from oil and gas for at least the next three decades, and, as less oil and gas is burned, nuclear power must come into its own as an energy source. Coal may be used to some extent to provide energy and chemical feedstock but eventually routes which combine H_2, CO_2 and CO to form more complex molecules will be developed. Such routes could be based either on biotechnical or classical chemical processes depending on the cost effectiveness of each. Biotechnology will initially come into its own in the chemical industry by providing high value added products. (Source: Chemistry and Industry, 7 August 1982.)

Theft of wild plant species

An aspect of biotechnology and genetic engineering that seems to have been somewhat overlooked is the theft of wild plants from Third World countries by scientists employed by multinational firms in order to cross-breed them with less disease resistant varieties of plants used for large-scale food crops. In a publication entitled Wild Genetic Resources (published by Earthscan of London) it is said that many countries receive no recompense for the filching of their plants that eventually result in enormous profits for the huge multinational seed companies and many countries are even totally unaware that their plants are being taken at all. The publication cites several examples of the debt owing to the developing countries: in the 1960's wheat crops in the United States were saved from an epidemic of strip rust thanks to germplasm obtained from wild wheat found in Turkey. It is estimated that the profit gained from this operation resulted in $50 million annually ever since, but Turkey apparently received no payment for its contribuiton. Another case involved obtaining a single gene from Ethiopia to protect the Californian barley from yellow dwarf disease. Picking valuable plants from developing countries is usually quite legal and a few have passed laws banning it, amongst these are Mexico and Ethiopia, but it is difficult to enforce the laws, and allegations of multinational companies ignoring them are widespread. Very often the improved varieties of seeds are re-imported to the countries supplying the genes at a considerable price since the new strains are protected by the breeder's rights and subject to payment of royalties. (Extracted from New Scientist, 28 October 1982.)

Synthetic foot and mouth disease vaccine

Almost simultaneously, a German and an Anglo-American team of scientists have succeeded in developing a synthetic vaccine for foot and mouth disease. The laboratory produced substance, which the scientists are confident can be further improved, uses as its antigens not the usual dead or weakened viruses, but a small albuminous body from the virus membrane which

can be chemically produced by synthesis. The first step in this development was made by scientists at the Max Planck Institute of Biochemistry in Munich, who succeeded in integrating the hereditary material of the foot and mouth disease pathogen in bacteria, thus making it possible to identify the relevant protein molecules. The new generation of vaccines is confidently expected to work more efficiently than conventional vaccine forms. (Extracted from Scila Information No. 10, 1982.)

Chemical synthesis may be cheaper than rDNA for some polypeptides

It has recently been reported that it is more economical to produce certain polypeptides synthetically than by rDNA processes. This was found to be the case with somatostatin, a 14-amino-acid polypeptide hormone used for treating bleeding ulcers. The material used in the initial test programme (which has received the approval from the U.S. Food and Drug Administration for clinical trials) is being supplied by ARES-Serono of Switzerland to its US subsidiary. The synthentic route to polypeptides generally becomes feasible when the polypeptide is small, as somatostatin, and is unlikely to be used for producing insulin, HGH or other polypeptides with several times as many amino acids as somatostatin. The upper limit for economic chemical synthesis of polypeptides is probably about 20 amino acids, although it is possible to make longer molecules. Chemical synthesis is also more feasible if the quantities required are small.

The chemical synthesis of vaccines may provide an easy, cost-effective way to immunize humans aganist viral diseases. The synthetic vaccines are made in laboratories using amino acids linked together to form a chain of a "synthetic peptide" which corresponds exactly to the small part of a whole virus protein that the immune system recognises. Compared to conventional vaccine preparations, artificial vaccines are easy to make and store, and since they contain no virus or viral products, bear no threat of infection. The vaccines have been used successfully to treat foot and mouth disease in livestock by the Scripps Clinic of California and the Animal Virus Clinic in England. The next targets for the vaccines will be such viruses as rabies, hepatitis B, influenza and polio. In addition, cancer R+D has isolated supposed "cancer genes" - DNA that under certain conditions appears to code for proteins involved in tumor development. Researchers hope that the methods for making synthetic peptides will help produce specific anti-cancer monoclonal antibodies. (Extracted from Genetic Technology News, December 1982, address: 158 Linwood Plaze, P.O. Box 1304, Fort Lee, NJ 07027, USA; and Technology Update, 16 October 1982.)

RECENT DEVELOPMENTS

What turns genes on?

The sequence of events that transform an embryo from a shapeless cluster of cells to a recognisable individual - differentiation - is undoubtably the most important biological puzzle still to be solved. Experimental biologists know that this process of cell specialisation is achieved by the ordered switching on (and in some cases off) of different genes which direct the synthesis of specific proteins. American scientists recently uncovered evidence that gene-activation may involve a chemical change in one of the four bases that constitute the alphabet of DNA. The four common bases found in DNA are guanine, cytosine, adenine and thymine, and their arrangement along the linear backbone of the DNA molecule provides the instructions for the cell. Cytosine however is also fequently found in a modified form known as 5-methyl cytosine, in which a methyl (CH_3-) group has been attached to one of its carbon atoms. Methylated cytosines are not spread evenly throughout the DNA molecule and in regions where they are clustered the DNA is silent (inactive). It is now thought that differentiation may involve a process of selective demethylation.

The first clue that this might be so came from studies of the globin gene. Globin - the protein part of haemoglobin - is only made in the red blood cells. In 1979 the National Institutes of Health, Bethesda, Maryland compared the pattern of methylation of the globin gene in red blood cells with cells from other tissues where globin is not made. They found that in red blood cells specific sites in the globin gene were unmethylated. This correlation between the activity of a gene and a reduced level of methylation in its DNA has now been shown for a number of other genes.

The next question is whether the decreased level of methylation is a cause or an effect of gene activation. DNA exists in the cell as a double stranded molecule. When cells divide the two strands separate and each then replicates. Cytosine is incorporated into the new "daughter" strands of DNA and subsequently methylated at positions where it finds itself next to a methylated cytosine in the "parent" strand. This methylation is carried out by an enzyme predictably called methylase. One trivial explanation for the correlation could be that in active genes methylase is physically blocked by other proteins which are known to bind to active DNA.

The alternative and much more exciting possibility is that demethylation is an essential preliminary for the activation of a gene. Two types of experiment favour this explanation.

Pieces of DNA can be introduced into a cell in such a way that the cell will integrate the foreign DNA into its own and accept its instructions. At the Hebrew University, Jerusalem, a piece of DNA was taken and methylated in vitro. It was then inserted into a cell and its expression compared with identical - but unmethylated - DNA. It was found that although both are integrated equally well, only the unmethylated DNA is active.

The second type of experiment is even more convincing. One type of drug previously known to be able to induce differentiation turns out to be an analogue of cytidine which carries a nitrogen atom that specifically prevents cytidine from becoming methylated. Three scientists have looked at the expression of two closely related genes in chicken DNA. Only one of the two genes is expressed, and as expected this is the least methylated. However, if the cells are given the drug 5-azacytidine the silent gene is activated, so that the protein it codes for is now made by the cells. DNA of the previously silent gene turned out to be unmethylated.

Methylation cannot be the only factor regulating expression (since not every gene in the chicken cells was switched on) but it may play a part in the control of differentiation. (Extracted from New Scientist, 28 October 1982.)

Broken genes grow

Research teams working at Sussex University and St. George's Hospital, Tooting, have recently demonstrated that the fragmentation and rejoining of DNA has a vital role in cell differentiation. Up to 300 breaks in a complete genome and from one to five per chromosome occur during cell divisions leading to differentiation, and if the process of fragmentation and rejoining is blocked, then differentiation does not occur. This was demonstrated in at least four very different classes of cells, giving goood reason to suppose that it is a universal phenomenon.

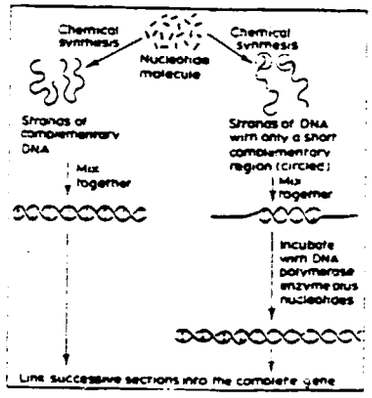
The first observations were made at Sussex University during investigations on the activity of an enzyme, ADP ribosyl transferase (ADPRT) which seemed to be involved in gene expression and cell differentiation. ADPRT is required for the fragmentation and repair of DNA because it regulates the activities of other DNA-cutting and repair enzymes such as DNA ligase. It was discovered the levels of ADPRT at the time of cell differentiation are three times higher than normal. If a specific inhibitor of ADPRT activity is introduced into the culture, then differentiation does not take place, with the obvious conclusion that ADPRT and DNA break-up and rejoining is vital to differentiation. Differentiation was only studied in myoblasts (embryonic muscle cells that differentiate to form myotubules) and lymphocytes, which effectively differentiate when they come into contact with an antigen to which they respond by producing antibodies or by cell mediated immunity. This form of differentiation is also blcoked by inhibitors of ADPRT activity.

At St. George's, Tooting, work has been undertaken on the single-celled parasite Trypanosome cruzi which causes a common tropical disease (Chagas) and it has been discovered that the morphological differentiation of T. cruzi is completely blocked by ADPRT inhibitors. Similar work being untertaken at the Nigerian National Institute for Medical Research at Lagos has shown that mice infected with malaria and treated by an ADPRT blocker show a significant reduction in their rate of infection, apparently because the blocker inhibits a step in the differentiation of the malarial parasite from one state in its life cycle to another.

Precisely how ADPRT and the fragmentation and rejoining that it mediates are involved in differentiation remains to be seen, but the theoretical implications of this work are certainly interesting and the practical implications in medicine are even more so. It may be possible to develop new drugs to treat Chagas' disease, malaria and maybe others, based on ADPRT blockers which effectively hinder the parasites' life cycles by blocking differentiation. Drugs based on ADPRT blockers, which stop lymphocytes responding to new antigents, could be used to prevent transplants being rejected while leaving intact existing immune responses against disease organisms. An important advantage of existing immuno-suppressive drugs is the cheapness of ADPRT inhibitors - i.e., approximately £12 per 100 grammes. (Extracted from New Scientist, 9 December 1982.)

Bacterial enzyme makes genes for humans

A group of American scientists has recently devised a new method of making genes, which, the scientists, claim, is faster, simpler and more efficient than the methods currently in use.



The conventional techniques for gene synthesis were developed in the 1970s. Individual nucleotide molecules are first chemically linked together in the desired sequence to form a short single strand of DNA (see figure). Genes are composed of two complementary DNA strands, held together by weak links called hydrogen bonds, so the next task is to make the DNA strand that is complementary to the first. The two strands are then mixed to give a short section of double-stranded DNA.

The length of double-stranded DNA that can be made in this way is rather limited; so many short sections must be made separately, and then linked together to produce the completed gene.

The problem with making DNA with this method is that the entire length of both DNA strands must be assembled synthetically. Although much has been automated the process is still complex and time-consuming. A new technique devised at the City of Hope Research Institute in California employs a bacterial enzyme to do most of the chemical synthesis, which begins in the convential way by making a piece of DNA corresponding to a portion of one of the strands of the desired gene. Next a piece of the opposite strand is made, but beginning with a short section that is complementary to the end of the first strand (see figure). When these two are mixed, there is only a small region of overlap.

The partially double-stranded complex is then added to a preparation of an enzyme called DNA polymerase I (isolated from the bacterium Escherichia coli), along with a supply of nucleotides. The enzyme recognises single-stranded regions of the synthetic DNA as in need of "repair", and so it links together the proper sequence of nucleotides to produce a long section of double-stranded DNA. These can then be linked as before to construct the whole gene.

This technique reduces by more than 40 per cent the amount of chemical synthesis required, because large portions of the gene are made by the bacterial enzyme. (Source. New Scientist, 11 November 1982.)

Genetic engineering research

A molecule that binds to and cleaves double-helical DNA has been designed by chemists at the California Institute of Technology, who have used the compound to study how certain drugs bind to DNA. The researchers tied together 2 molecules, each with a property gleaned from bleomycin as important in that molecule's activity. To bind DNA, methidium bromide, a molecule with planar portion that intercalates DNA, was chosen. To furnish a complex ferrous ion, ethylenediaminetetraacetic acid (EDTA), a well-known iron chelator was chosen. The researchers linked the two with a short hydrocarbon chain. The result was methidiumpropyl-EDTA of MPE. MPE's activity and relationship to DNA is examined. Similar, independent DNA-drug binding studies are discussed. (Source: Technology Update, 30 October 1982.)

Enzymes that make tryptophan

One of the approaches Genex (Gaithersburg, MD) is taking to scale up its recombinant DNA process for making tryptophan, rather than trying to maximize production of the amino acid by using gentically modified microorganisms in the fermenter, is to maximize output of key enzymes responsible for tryptophan synthesis. Separated enzymes can then be used as biocatalysts to synthesize tryptophan outside the fermenter without the microorganisms.

One of their procedures involves work with genes for the enzyme tryptophan synthase from Escherichia coli. Two of the gene products catalyze conversion of indoleglycerol-P (or indole) and serine (also an amino acid) to tryptophan and glyceraldehyde-3 phosphate. The genes, trpA and trpB, encode two subunits, α and β, which combine to form very stable $\alpha 2 \beta 2$ complex. The $\alpha 2$ portion of the complex catalyzes conversion of indoleglycerol-P to indole. The $\beta 2$ part combines serine with indole bound to the enzyme and catalyzes synthesis of tryptophan.

The first task was to splice the trpAB genes, together with hybrid trp/lac promoter, into a plasmid. By adding compunds that induce higher production, output of the enzymes was increased 230-fold. The enzymes made u approximately 20 per cent of total cell proteins. While initial work was with enzymes from E. coli, the final production organism will probably be a strain of nonpathogenic Salmonella typhimurium LT2 or Klebsiella aerogenes, both of which the Genex researchers have been able to transform with the same plasmids used in E. coli. The next step was to use extracted enzyme preparation to synthesize tryptophan. Indole and serine were added to the enzyme extract and 97 to 100 per cent of the indole was converted into tryptophan at concentrations up to 78.2 g/L, so high that part of the tryptophan precipitated out.

To lower production costs, Genex is also working on a process to make one of the starting materials, serine, cheaply. Techniques similar to those used for tryptophan synthase can be used to produce the enzyme serine hydroxymethyltransferase (SHMT). Normally SHMT converts serine to glycine; however, the reaction can be reversed to produce serine from glycine and formaldehyde.

Genex is actively developing production processes for both serine and tryptophan. The final result may be a process for each amino acid or a combined process. One efficient method for final production of tryptophan is to use immobilized cells in a multi-column packed bed reactor system. The goals is to lower production costs so that the price of tryptophan can be dropped to a level where it will be economical to use the amino acid to supplement corn and soybean feeds for poultry and swine. The two most limiting amino acids in these feeds are lysine and methionine, which are already sold as supplements. The next most limiting amino acid is tryptophan. (Extracted from Genetic Technology News, October 1982, address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

New enzymes helps wineries in a colour bind

A new enzyme called anthocyanase gives wineries an alternative to the ion exchange and activated charcoal methods of changing red wine into white. Added just before the yeast, the enzyme, called Pectinol DL, decolourizes the product and then is removed along with other residual particles from the fermentation process. The process could be used to convert excess red wine into a white wine capable of being blended with inexpensive whites, such as chablis. It could also aid in the production of light-coloured premium wines, where yields

from the red grapes now are limited by the need to keep the colour light. With the enzyme, presses could be used to increase yields, yet maintain the desired light colour. The enzyme is extracted from the commonly occurring Aspergillus niger fungus. (Source: Industry Week, 19 April 1982.)

Basics of protein secretion by yeast become clearer

Latest advances in understanding how yeast cells process their proteins drew a lot of attention at the 11th International Conference on Yeast Genetics and Molecular Biology at Montpelier, France, in September 1982.

When yeast cells using messenger RNA with the proper genetic code first combine amino acids to synthesize an organellear or secretory protein, the protein may not be in its final form. (Soluble proteins that float freely inside the cell, not attached to organelles, follow a different pattern.) The first product is often a larger precursor protein that will eventually be cleaved to form a smaller protein. Many of these proteins are also modified by glycosylation-acquisition of saccharide side chains. Scientists at the University of California, Berkeley, have developed a number of mutant yeast strains with blocks at various stages of protein modification in order to get a better idea of where some of the modifications of the original protein molecule are made within the cell.

It was found that the protein carboxypeptidase Y (CPY) is first synthesized as a proenzyme - or precursor protein, designated P1. Original synthesis takes place at the endoplasmic reticulum tubules. P1 is only partially glycosylated at this stage. Final glycosylation of CPY takes place in another organelle (small cellular structure), the Golgi apparatus. There P1 is converted into fully glycosylated P2. The P2 protein then moves into a vacuole. There an amino acid sequence with a molecular weight of about 8,000 is cleaved off to leave the protein end product. Final molecular weight of CPY is about 61,000, including saccharide side chains with molecular weights totalling about 10,000.

The Berkeley group is now trying to get a better understanding of just what goes on at the Golgi apparatus. This seems to be the point at which paths of proteins to be retained within the cell diverge from those that will be secreted.

Scientists at McGill University have been using mutants developed at Berkeley to study a different protein which the yeast probably secretes to kill competing yeast strains.

Primary product for the toxin is an amino acid sequence with a molecular weight of about 36,000. This is then glycosylated to a 43,000-molecular weight protoxin (precursor protein). From the Golgi apparatus the protoxin does not go into a vacuole the way CPY does but into small secretory vesicles. Yeasts and animal cells package proteins to be secreted in these vesicles, which then fuse with the cell membrane. After fusion the vesicles open to the outside of the cell and release the proteins. Protoxin is not cleaved to its final until it is inside the secretory vesicles, probably after the vesicle contacts the outer cell membrane.

Secretion of proteins in yeasts is much more complicated than it is in bacteria. Working out the basic mechanisms of protein processing should enable the genetic engineer using yeast to produce a recombinant DNA product a number of alternatives to choose from. Yeast could be controlled so that it would either retain or secrete the product, whichever makes purification easier. (Extracted from Genetic Technology News, November 1982, address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Mitochondrial DNA could have advantages as a vector

It was reported at the 11th International Conference on Yeast Genetics and Molecular Biology at Monpellier, France, last September that mitochondrial DNA may become an efficient alternative to conventional plasmids in constructing vectors for genetic engineering. Apart from yeasts, few eukaryotes have plasmids that can be used as vectors for transforming cells with foreign DNA. Plasmids (small circles of DNA) function outside the nucleus, but replicate when the cell does. However, eukaryotic cells do have DNA outside their nuclei in small organelles called mitochondria, which are small bodies within the cell composed chiefly of proteins and which play a key part in the cell's metabolism. They contain enzymes for transferring energy from food taken up by the cell into a form in which the cell can use it. Although mitochondria contain their own DNA, most of their proteins are encoded by DNA in the cell's nucleus. Earlier work indicates that nuclear DNA is first translated into larger percursor proteins which are then taken up by mitochondria. An agent that blocks uptake of percusor proteins in living cells causes protein to accumulate outside the mitochondria.

Removing the blocking agent allows accumulated percursor to be imported and processed into mature protein by the mitochondria. Research with mitochondria separated from whole cells suggests that a protein exposed on the mitochondrial surface is essential to recognise a percursor protein. Once recognised, the percursor is attached and imported into the organelle for processing into final form. Work in this area is being undertaken at the Ruhr University at Bochum in the Federal Republic of Germany. (Extracted from Genetic Technology News, November 1982, address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Transposons act as vectors to transfer DNA into fruit flies

Vectors that transfer DNA into the chromosomes of the fruit fly, Drosophila melanogaster greatly improve the outlook for genetic engineering in higher animals. Using transposons, segments of DNA that can move around among chromosomes, plasmids and viruses, scientists at the Carnegie Institution of Washington (Baltimore, MD) have been able to transfer DNA into embryos of fruit flies, where it becomes integrated into the chromosomes and reappears in the flies' offspring.

Transforming cells of higher animals with DNA from outside the cell is much more complicated than transforming bacteria or yeast as existing methods have low efficiencies and may disrupt chromosomal DNA. They also cannot be controlled to any degree. Transposons have been used in bacteria, but until now have not worked with complex higher organisms.

The Carnegie researchers first constructed a plasmid by inserting a 3-kilobase pair (kb) segment of DNA from the fruit fly genome along with 1.8 kb of flanking DNA sequences into the common Escherichia coli plasmid, pBR322. The 3-kb segment selected was the transposable P element, believed to be responsible for genetic defects in certain strains of fruit flies. The plasmid was cloned in E. coli and then injected into fruit fly early embryos. When the embryos matured they were found to contain the 3-kb segment. Some of their offspring also carried this DNA in their chromosomes. The next step was to insert DNA coding for a marker enzyme, xanthine dehydrogenase, into the plasmid and repeat the procedure. About 8 per cent of the injected embryos grew to maturity. Of these, 39 per cent gave offspring containing the transposon.

Apparently the gene was transferred without having its DNA sequences rearranged. In other methods genes frequently rearrange themselves and sometimes are repeated. The transposons insert themselves into the chromosome at any of about 50 sites.

Fruit fly mutants that lack the gene coding for xanthine dehydrogenase have darker than normal eye colour. Mutants lacking the gene but which had been transformed with the transposons containing the gene showed the normal red eye colour.

Being able to transform a complete higher organism in this way rather than only transforming cells that grow in tissue culture has some big advantages. One of them is that it may give a better look at how genes are expressed in various cells in the organisms so that different tissues and organs develop as the individual grows from the embryonic stage to maturity.

This technique should make it possible to transfer very large segments of DNA into the fruit fly, an organism that has been studied extensively from a genetic viewpoint. The method is efficient, stable and can be controlled. (Source: Genetic Technology News, November 1982, address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Transferring DNA into mammalian cells

At present, the most efficient means of transferring DNA into mammalian cells is through the use of very fine glass tubes to inject DNA into the nuclei of cells one at a time - a very time-consuming task. The method of transfection (the passage of DNA through the membranes of cells in suspension) has been compared with the micro-injection technique with very favourable results - it can transform up to 70 per cent of treated cells.

DNA, in the form of genes for simian virus 40A or herpes simplex virus thymidine kinase spliced into plasmids, was placed in contact with mammalian cells that had been treated with polyethylene glycol. The most important variable in transfection efficiency is the type of mammalian cell line. The most efficient cell line is one derived from baby hamster kidney cells deficient in thymidine kinase and temperature sensitive. The efficiency of micro-injection does not depend upon the type of cell line, but the real barrier to expression of genes introduced by transfection into mammalian cells appears to be the nuclear membrane. (Source: Genetic Technology News, November 1982, address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Human genes inserted into mouse eggs

Human beta-globin genes inserted into mouse eggs can function fully in the adult mouse and be passed on to offspring in classical Mendelian proportions. Although the acceptance rate of their foreign DNA is not great, the results support the expectation that foreign DNA may be introduced into mammals early in their development and used to study genetic diseases and malignancy. This work is being done at the Fox Chase Cancer Centre. (Source: Technology Update, 18 September 1982.)

Japan - Hepatitis-B vaccine

Japan: A method of mass producing a new vaccine against type-B hepatitis by using yeast has been developed at Osaka University. The method involves replacing part of one of the genes of a given yeast with a cut-off chip of the virus and letting the yeast produce a replica of the protein of the antigen concerned found in the patient's blood. When the replica is used as a vaccine, it stimulates an antibody to resist the invading virus. It was discovered that the yeast produces 500,000 molecules of the replica/fungus unit, half or more of the best know interferon yield of yeast/fungus unit. How much more in that yield that can be attained is the key to the clinical applicability of the vaccine, especially because yeast is several hundred times larger than the colon bacillus. (Source: Technology Update, 9 October 1982.)

Emphysema

More human proteins are becoming available through recombinant DNA processes then are commonly known. Alpha-1 antitryspin (AAT), for example, is a protein produced in the human liver and then enters into the blood stream. Researchers at Zymos have just produced AAT in yeast in which they cloned the human gene coding for protein. Cooper Laboratories, which funded the research and has rights to the discovery, believes AAT may be useful for treating some types of emphysema, which is a condition in which small air sacs in the lungs are damaged and cause respiratory difficulties. In some cases, emphysema is a result of a congenital deficiency of AAT. In a normal individual, AAT counteracts surplus quantities of certain enzymes the body produces to destroy bacteria, air pollutants or cigarette smoke in the lungs. If not counteracted, surplus enzymes attack lung tissue itself, causing death by emphysema eventually. Cooper Laboratories believe AAT produced in yeast might also have broader applications in treating other types of emphysema, but a great deal of laboratory and clinical work must be done first. AAT is unlikely to reverse emphysema, but may prevent further deterioration. (Extracted from Genetic Technology News, 29 September 1982, address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

A possible cure for haemophilia

Thanks to the work of scientists at a small British biotechnology firm, haemophiliacs may soon be able to look forward to a normal life. Speywood Laboratories claim to be the first in purifying human "factor VIIIC", one of the blood-clotting factors that prevents uncontrolled bleeding. Children will benefit most because with large amounts of pure product available doctors will be able to begin treatment early in life. Speywood recently signed an agreement with Genentech, who will clone the gene for factor VIII, enabling them to manufacture the product on a large scale within three years.

Factor VIIIC is one of two active components of Factor VIII. Classic haemophiliacs have little or no Factor VIIIC in their blood, while a lack of Factor VIIIRAg causes a variant of haemophilia called von Willebrand's disease. Most of the Factor VIIIC used in treatment at present is derived from human blood and whilst there is no shortage of human plasma, the extraction process is costly. Most of the supplies are used in developed countries, leaving those in the developing countries virtually untreated as a result. After further research is carried out, it is hoped that the new product will not only be cheaper, but safer through being uncontaminated by the hepatitis B virus which is often carried in the material presently supplied, mostly from the United States. (Extracted from New Scientist, 2 December 1982.)

Vaccine to prevent herpes simplex

American Cyanamid will be working with Molecular Genetics in order to commercialise a herpes simplex vaccine based on the latter's laboratory success in cloning herpes virus protein with a corresponding virus gene in Escherichia coli. Injection of the protein into a human should cause the body to respond with an antibody giving immunity but not a cure. The herpes virus is large - its DNA contains about 150,000 nucleotide base pairs (about 20 times

as many as in, for example, foot and mouth disease virus and for which a rDNA vaccine has been prepared. Each herpes virus particle contains not only DNA surrounded by protein, but an outer lipid layer through which only part of th protein protrudes at scattered points. Researchers at Molecular Genetics chose one of the four types of protein that protrude which appears to be similar in both herpes-1 (which causes cold sores in the mouth and around the lips) and herpes-2 (which causes a venereal disease that has been rapidly increasing and for which there is no known cure). The next step towards a vaccine is to test the protein in animals for efficacy and side effects and to choose the best formulation. Data collected in these tests can be supplied to the US Food and Drug Administration when Molecular Genetics applies for permission for clinical testing in humans, hopefully within two years. A rDNA vaccine such as this prevents the possibility of infection from a live virus particle - always a danger in conventional vaccines made from killed or weakened viruses. Molecular Genetics' orientation is towards animal vaccines which happened to lead to the human herpes work, and towards other agricultural applications of genetic technology. (Extracted from Genetic Technology News, October and November 1982, address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Faster testing of foetal lungs

A nine-minute clinical immunodiagnostic kit, called Aminostat-FLM, allows a physician to decide whether the lungs of a human foetus have matured enough to support normal breathing. The test kit, developed by Hana Biologics, a biotechnology company in Berkeley, California, detects the presences of phosphatidyl glycerol in the mother's amniotic fluid, an indication that the foetus' lungs are not yet fully developed. That condition, known as hyaline membrane disease, is responsible for 50-70 per cent of the deaths of premature infants. The kit, which will be sold to clinical laboratories for $300 each in lots of 12, will be available next month, pending approval by the US Food and Drug Administration. (Extracted from Chemical Week, 3 November 1982.)

Monoclonal antibodies for two purposes

Monoclonal antibodies, perhaps the most promising product of the new biotechnology firms, are valuable tools for detecting cancer and other abnormalities, and may hold the key to effective treatment. The process of culturing immortal monoclonal antibodies consists of immunizing mice with target antigens and removing their spleens, which contain large amounts of lymphocytes, the antibody producing white blood cells. When comined with myeloma cells and polyethylene glycol (PEG), which binds the outer membranes of some of the cells, they begin to fuse. Later the clones of individual fused cells are checked for antibody secretion. This hybridoma technique has been adopted by many independent ventures as well as large chemical and pharmaceutical firms.

The most successful application of monoclonals has been in kits to diagnose allergies, prostate cancer, pregnancy and anemia. Long-range research is aimed at developing monoclonal antibodies that attack cancer causing agents. Currently, the effectiveness of monoclonals as anticancer agents has been demonstrated in lymphoma and bone-marrow transplants on victims of leukemia. According to research being done at the Johns Hopkins University, monoclonals linked with iodine-131 have the potential of extending the lives of patients with inoperable liver cancer by delivering radiation doses directly to the tumors, a concept improved with the use of indium-111 by the University of California (San Diego). (Source: Technology Update, 16 October 1982.)

Monoclonal test kits for VD

As the incidence of venereal diseases increases, the need for quick and inexpensive diagnostic tests intensifies. To capitalize on this market, Genetic Systems, a young biotechnology firm in Seattle, has developed test kits based on monoclonal antibodies for detecting chlamydia, gonnorhoea, and two forms of herpes simplex. The company is awaiting Food and Drug Administration clearance for the chlamydia test, and plans to request FDA approval for its herpes and gonnorhoea tests soon. The tests have already received scientific praise.

The assay kits are all built around monoclonal antibodies that have been tagged with flourescent dyes, and each one requires a different monoclonal antibody. Monoclonals are pure in that they recognize and react to only one specific microorganism. Using monclonals means that their tests make very few mistakes in identifying the presence or absence of a particular organism.

The assay kit closest to the market is the test for chlamydia which will appear on the market in February 1983. The U.S. Center for Disease Control in Atlanta estimates that there are 10 million cases a year, compared with 3 million new gonnorhoea cases a year.

Chlamydia is the most prevalent of sexually transmitted diseases in the US and is a disease that can cause sterility in women. It may be the major factor in urinary tract infections. It is effectively treated with antibiotics. However, while current tests take six days to perform, the monoclonal antibody test takes a mere 20 minutes, allowing the patient to begin taking medication soon and to reduce the risk of complications from the infection. (Extracted from Chemical Week, 20 October 1982.)

Possible new treatement for sickle-cell disease and beta thalassaemia using gene therapy

In a completely new approach to the treatment of genetic disease, clinicians in America have used a drug that can activiate normally inactive genes to bring about a significant improvement in patients with two of the most important hereditary blood diseases: sickle-cell anaemia and beta thalassaemia.

Despite having been tested on patients, the therapy is still at an experimental stage. But it has generated great excitement in America as an example of how an understanding of fundamental genetic mechanisms can make a direct contribution to clinical medicine.

Two separate groups of scientists and clinicians have been involved in the experimental trials, from the National Heart, Lung and Blood Institute at Bethesda, the West Side Veterans Administration Hospital, the University of Illinois in Chicago, and the Johns Hopkins University reported successful results of treating three beta thalassaemia patients and three sickle-cell sufferers with the drug 5-azacytidine.

Both sickle-cell disease and beta thalassaemia are caused by genetic defects in one of the two types of protein chain, alpha and beta globin, that make up the red blood cell protein haemoglobin: the defects are in the beta chain and in severe cases of beta thalassaemia, no beta chains are produced at all. Both diseases are incurable and individuals inheriting the defect from both parents die in childhood unless treated with frequent transfusions. Both also cause secondary defects in blood cells that result in considerable pain and distress.

The 5-azacytidine treatment was aimed at a special property of the genes that encode beta globin. There are four kinds of beta globin gene, only two of which are normally active in adults. The other two genes are active only in the unborn baby, when they produce embryonic and foetal beta globin molecules, which differ slightly from the adult versions in ways that are specially adapted to foetal life. The embryonic gene is usually switched off before birth and the foetal gene soon after. Because the foetal beta globin gene is free from the genetic fects in the adult sickle-cell and thalassaemic beta globin genes, these diseases only become detectable clinically as the newborn baby matures. In a few kinds of nereditary aenaemia, the defect in the adult gene by a happy chance also prevents the switch from the foetal gene, which continues to produce normal beta chains throughout adult life and saves the individual from the effects of the damaged gene. It was the hope of switching on the foetal gene in other anaemic patients that inspired the use of 5-azacytidine on patients in America.

The rationale for the treatment derives directly from fundamental research on the regulation of gene expression. It is known from experiments on a number of different genes in various species of animal that one important determinant of gene activity is a chemical modification of the DNA known as methylation. In general, heavily methylated genes are inactive, and active genes tend to have few methyl groups on them. The American haematologists thus reasoned that if they could prevent the foetal beta globin genes from being methylated in the cells of their anaemic patients, it might be possible to replace the defective or absent adult beta chains with normal foetal ones. 5-azacytidine is very commonly used to prevent DNA methylation in laboratory experiemtns on gene regulation; and indeed, has already been used in a preliminary experiment on baboons and found to stimulate the produciton of the foetal protein.

Some very important and difficult questions have to be answered before treatment can be considered suitable for long-term administration on a wide scale. First of all, the drug is known to be toxic, particularly affecting the bone-marrow cells that give rise not only to red blood cells but the white blood cells of the immune system. Furthermore its effects cannot be expected to be confined to the bone-marrow, and may entail a risk of cancer. Finally, there is a possibility that the drug does not switch on the foetal gene but simply selects cells already expressing it. This would be a very great disappointment, since otherwise the exciting prospect this treatment offers is gene manipulation, without the complication of manipulating embryos. (Extracted from New Scientist, 16 December 1982 and International Herald Tribune, 10 December 1982.)

Hormone deficiency

A genetic hormone deficiency that inhibits sexual development may be treated with brain grafts in recent research involving mice. At the Mount Sinai Medical Center (New York, NY), brain graphs on female hpg mice were performed. In order for the changes of puberty to take place, hormones are released from the pituitary gland at the base of the brain. In order for this to occur, the pituitary needs another hormone, gonadotropin (realising hormone GnRH) that is released by nerve cells in the hypothalamus. Mutant hpg mice do not produce enough GnRH, resulting in undeveloped reporductive organs. Although brain grafts will probably never be used to treat human patients, the results of the studies can help clinicians to plan courses of hormone treatment. (Source: Technology Update, 30 October 1982.)

Genetic engineers find many ways to maximize output

At a recent meeting of the Society for Industrial Microbiology at St. Paul, Minnesota, an excellent update on some of the tools genetic engineers regularly use to maximize output of recombinant DNA products was given, and is briefly described as follows:

Transcription synthesis of messenger RNA using the DNA of the gene as a template is made to take place at high frequency. In the transcription process RNA polymerase, the enzyme that catalyzes synthesis of messenger RNA, must first recognize and then bind to a specific promoter site on the DNA, upstream of the gene to be transcribed. Once bound, the enzyme travels quickly along the DNA strand, synthesizing RNA as it goes. Some promoter sequences are much better than others. Genetic engineers routinely splice good promoters into plasmids containing DNA sequences they want to convert into proteins. The lac promoter (which governs genes producing enzymes for lactose metabolism) has been spliced into plasmids to increase production of human growth hormone and beta-endorphin in Escherichia coli. The trp promoter (involved in tryptophane production) has been used to increase human growth hormone, interferon and foot-and-mouth disease vaccine yields. These promoters raised human insulin and foot-and-mouth disease vaccine production in E. coli to a level of 20 per cent of total cellular protein.

Sometimes one can splice multiple copies of a promoter into a plasmid and increase transcription efficiency. Two lac promoters improved production of human growth hormone. Three worked with fibroblast interferon. Up to five copies have been tried for other products.

Mutation of the promoter (altering the DNA sequence slightly) may also be used. Another technique is to use chemical synthesis to make a DNA sequence that will act as a good promoter.

Translation synthesis of protein product from amino acids as directed by messenger RNA can be made more efficient by modifying the ribosome binding site. The site is an RNA sequence lying between the promoter and the gene portions of the RNA strand. The binding site on the RNA attaches to ribosomes. Adding just four extra nucleotide pairs between the binding site and the initiation site increased human growth hormone yield by 60 per cent in E. coli. Altering a number of nucleotides in this region increased interferon yields up to 100 times. Moving the promoter varying distances from the gene increased productivity up to 2,000-fold. Varying the length of the sequence between the promoter and gene sites increased human leukocyte interferon five-fold in yeast.

Using host cells with a large number of plasmids (up to 50 in E. coli) increased human insulin and foot-and-mouth disease vaccine output many-fold.

Adding an inducer, a chemical that inactivates the repressor protein that binds to the operator site on the DNA, can be a potent technique. Repressor proteins normally bind to operator sites to control the cell's protein output. Adding isopropylthiogalactoside (IPTG) as an inducer to E. coli modified to produce human growth hormone increased yield 5,000-fold. IPTG has also been used to increase beta endorphin output. (Source: Genetic Technology News, October 1982, address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Preservation of living organisms

One problem slowing the commercialisation of biotechnology is the lack of a handy means for preserving living organisms until they are needed. The two methods currently used - "cryopreservation" and "freeze-drying" - both have drawbacks. Fortunately, scientists believe they are getting close to understanding why such preservation techniques can mash up cells so badly.

Cryopreservation depends on the fact that chemical reactions slow down as the surroundings get colder. Biological material kept really cold can remain unchanged almost indefinitely. In theory, it ought then to be possible to restart their activity simply by thawing. Or, in the case of freeze-dried organisms, by adding water.

The problem with both freezing and drying is how this may be done without damaging the organism, or killing such a large proportion of the cells that the resuscitated sample is too weak to be of use. Clearly, the freezing cycle alters the complex structure of the living material in some way. Exactly how is still not known, despite detailed study since the 1950s. However, it is now becoming possible to probe the molecular level of the frozen micro-organism. So far it has been discovered that if a suspension of cells is frozen in a so-called "isotonic" solution (i.e., a salt solution of the same strength as the weak solution found inside living cells), ice crystals form and take pure water out of the solution. The remaining solution therefore becomes stronger. Unfortunately, the process does not stop there. By a phenomenon known as "osmotic pressure", the stronger solution starts to suck the weaker solution out of the cells, causing them to shrink. This can be particularly damaging to the delicate membranes that act as cell overcoats. It can either kill the cells outright, or at least cripple them seriously. (The problem can be overcome to some extent by adding "cryoprotectants" such as glycerol.)

The damage done to cell membranes is not the only problem. The freezing process can also damage the genetic material inside the cell and render some of its enzymes inactive. In both cases, the cell may still function when thawed out, but it may have lost its power to do things which make it industrially important. A bug that has been specially engineered genetically, for instance, may cease expressing the gene which has been inserted into it to produce a particular metabolite. Enzymes may simply stop producing, and a penicillium species may cease to turn out penicillin.

The most encouraging news comes from scientists working at Dow Chemical (one of the few companies spending money on preservation research). Researchers there have shown that the viability of yeast cells seems to depend on chemicals in the cell membrane. They have also found that the damage done to the cell by freezing is not always irreversible. Badly-mauled cells can sometimes be reactivated if the preservation technique has not harmed the cell's own inbuilt repair mechanisms.

In freeze-drying, the cells are desiccated at low temperature and then stored at room temperature. The process has many of the drawbacks of cryopreservation. In some bacteria, scientists have found that freeze-drying increases the concentration of salts in the cells. So when they are rehydrated (ie, have water added), osmotic pressure then causes the cells to absorb too much water and burst.

Another problem is that the energy required to freeze-dry cells is just about the same as that required to disrupt the special hydrogen bonds which endow a cell's protein and DNA hereditary molecules with the precise shape that allows them to do their job.

Chemists studying cell membranes believe that, with a modest push in the right direction, they could overcome most of the outstanding problems associated with living organisms. The results would provide an enormous benefit to industry. Some, however, fear that it would also lead to possibly unpatentable laboratory techniques which would then benefit their competitors. Few biotechnology firms are therefore enthusiastic about investing in much research. This is precisely the sort of work that needs to attract industrial (or even international) support. The British Government is investigating a possible project with the Federal Republic of Germany. (Source: The Economist, 9 October 1982.)

Protein recovery and scale-up

The best genetically engineered microorganism is useless for commercial production unless its product (usually a protein) is economically extracted on a large scale.

Unless work involves 10-litre quantities, US National Institutes of Health guidelines dictate that rDNA organisms must be killed before the extraction process begins. Acid, phenol, peroxide, detergents or organic solvents may be used to kill Escherichia coli cells, but care must be taken that these additives do not reduce bio-activity or make the protein more difficult to purify.

Unless the microorganism used, secretes the product, the protein will have to be extracted from the dead cells. This may be done by using a common homogenizer, such as a Manton-Gaulin unit operating at about 7,000 lb/in2. Two or three passes through the homogenizer usually break up the cells adequately and also reduce viscosity caused by extracted DNA. Part of the energy for breaking up cells is converted into heat. This must be removed by passing the process stream through a heat exchanger. Cells may also be broken chemically.

Centrifugation or filtration removes cell debris from the mixture. Removal is helped by first adding polyethylene imine or some other flocculant.

Immunoadsorbent chromatography is a powerful method for separating a protein from a mixture. A purified antibody to the protein wanted, preferably a monoclonal antibody, is used on a non-adsorbent support, such as agarose. However, preparation of monoclonal antibodies is not a trivial undertaking. It may take four to six months to establish a stable hybridoma which produces antibodies. Then they must be harvested, purified and chemically coupled to the support. Since antibodies are very expensive it is essential that they can be used over and over again in the extraction process. (Extracted from Genetic Technology News, October 1982, address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Fragrances

Fragrance or aroma chemicals form a product area of great commercial significance in biotechnology. These compounds (not including flavour enhancers such as monosodium glutamate) command an annual market of $2,000 million and are mainly, though not exclusively, used in the cosmetics, toiletry and detergent industries. Recently the Biotechnology Department at Henke GaA, Duesseldorf, have provided a brief and fascinating overview of the literature on fragrance production by microorganisms, together with a survey of some enzymatic transformations, including racemate resolution, of odoriferous terpenoid compounds.

In many cases, the chemical structures of the volatile organoleptics produced in the microbial cultures have been established, and the table below gives a selected listing of the variety of fragrances that may be emitted by microbial cultures; where more than one fragrance is listed, the proportions of the various chemicals depend rather finely on the cultural conditions.

Often, agricultural or synthetic chemical production of particular fragrances may be more suitable than 'biotechnological' production, but the former is subject to seasonal fluctuations and the latter has the great disadvantage that it usually lacks stereoselectivity. For instance, the world demand for L-menthol (much used in confectionery and tobacco products) is approximately 3,000 tonnes per annum, and a variety of immobilized yeasts, or enzymes derived from them, have been used to effect the resolution of synthetic DL-menthol by stereospecific esterification or de-esterification reactions. Optical purities of 100 per cent may be obtained, and methods have been described which include reactions on the 800 kg scale.

Owing to both the complexity of the synthetic pathways involved and the polynuclear structure of many of the organisms capable of producing fragrant chemicals, the more novel biotechnologies have so far made relatively little impact in this area; it is clear that 'microorganisms provide an interesting opportunity to improve on existing technologies of fragrance production'.

TABLE I

Some microbially produced fragrances of known chemical structure

Microorganism	Fragrance	Chemical structures (some)
Ascoidea hylacoeti	Rose, fruity	β-Phenylethanol, furan-2-carboxylate
Ceratocystis moniliformis	Banana, peach, pear, rose	3-Methylbutylacetate, geraniol, citronellol, linalool, α-terpineol
Ceratocystis variospora	Geranium	Citronellol, geranial, geraniol
Inocybe corydalina	Jasmine, fruity	Cinnamic acid methylester
Penicillium decumbens	Pine, rose, apple, mushroom	3-Octanone, 1-octen-3-ol, β-phenylethanol
Sporobolomyces odorus	Peach	γ-Decalactone
Trametes odorata	Honey, rose, fruity, anise	Trans-1, 10-dimethyl-trans-9-decalol 2-exohydroxy-2-methylbornane
Trichoderma viride	Coconut	6-Pentyl-2-pyrone

(Source: Trends in Biochemical Sciences, December 1982.)

Bacteria to produce petroleum and hydrocarbons

Genetic engineers are developing strains of bacateria to produce petroleum and hydrocarbons. At the University of Illinois, Dr. A.M. Chakrabarty is working under a contract with Petrogen Inc. (Arlington Hts. Ill.) to develop bacteria that eat waxes and paraffins from heavy oil to produce liquid energy. Chakrabarty has already developed bacteria that can digest petroleum to clean up oil spills and eat Agent Orange and other toxic chemicals.

Dr. T.G. Tornabene of Georgia Institute of Technology, believes that archaebacteria, which are widely distributed in nature and have remarkable resistance to harsh environments in some strains, could have been the primary agents responsible for the conversion of plant and animal matter in oil. He is developing single 'bacterial weeds' to provide a workable substitute for petroleum-based chemicals such as those used for paints, lubricants, emulsifiers, antibiotics and other valuable products. So far strains have been isolated that generate 0.5 - 14 per cent of their respective body weight in hydrocarbons. The idea would be to engineer a strain that can produce 80 per cent of its body weight in usable 'fat'. (Source: Technology Update, 16 October 1982.)

Organisms for refining tar sands

Omni Biotechnology has developed a method of refining tar sands by using mutated organisms. Organisms such as Pseudomonas and Micrococcus are mutated with high-energy radiation and placed in an aerated, rotating vessel to which tar sands are added. The organisms act upon the tar to produce hydroxyl groups that loosen the tar from the sand. As much as 93 per cent of the contained tar can be recovered with the organisms and Omni's vortex-generating vessel. Full commercialization will be delayed until the Canadian tar sands industry revives. (Source: Technolgy Update, 30 October 1982.)

Plant herbicide resistance

A team at Calgene is close to cloning a herbicide resistance gene in Escherichia coli, to be followed by transfering the gene into a higher plant and cause it to express. If a crop plant can be made resistant to a herbicide, farmers could use the herbicide to kill weeds without damaging the crop plant. Unlike most higher plant characteristics which are controlled by sets of genes herbicide resistance is probably coded for by a single gene. Calgene has worked only with glyphosphate or N-(Phosphonomethyl) glycine. A gene coding for resistance to this herbicide is found in strains of Salmonella bacteria. The workers at Calgene have transferred the gene from Salmonella into Escherichia coli with three alternative approaches to trying to make the gene express in a higher plant: using the Ti plasmid, a virus vector or micro-injection. Although Calgene has so far worked only with Monsanto's herbicide, (Roundup), the latter is not involved in the Calgene research, who have selected cotton, with its many weed problems, as the first plant to try to modify with herbicide resistance genes. The alternative to a genetically engineered gene for herbicide resistance would be the development of new broad-spectrum herbicides, which are costly to bring to market. (Extracted from Genetic Technology News, October 1982; address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07 024, USA; and Technology Update, 9 October 1982.)

Chemical pesticides

Genetic engineering could play a big part in developing better chemicals herbicides and insecticides and a strong argument can be made for protecting the environment by designing pesticides and matching pesticide removal technology simultaneously.

A complete pesticide technology (both application and removal) would make it possible to control residence time of the pesticide in the field. A properly designed micro-organism would destroy any pesticide remaining a short time after the pesticide had time to act. Removal of residual pesticide would not only protect the environment, it should also, in the case of insecticides, deter development of resistant strains. Engineered micro-organisms might be applied directly to the soil or plants, or the micro-organisms might be used to produce enzymes that could be applied to destroy pesticides.

Many pesticides, such as DDT, are very resistant to microbial degradation, but there is no reason to believe that rDNA research may not produce micro-organisms to degrade many chemicals. Plasmids, such as those that contain genes governing microbial degradation of halogen compounds, might be modified or entirely new plasmids might be found. Plasmids responsible for degrading compounds not found in nature are generally larger and more complex than those for antibiotic resistance. Antibiotics exist in nature and many organisms have plasmids to resist them.

Another way genetically engineered micro-organisms might be used in developing chemical pesticides is somewhat similar to techniques being tried for antibiotics. New antibiotics might be produced by mutating an antibiotic-producing micro-organism and feeding the mutant a modified precursor to obtain a modified antibiotic. Metabolic intermediates that occur when a micro-organism degrades a pesticide sometimes have pesticide activity of their own. When such metabolites are found the micro-organism producing them might be fed an altered precursor that would produce a new metabolite with pesticidal properties. Mutants could then be constructed to overproduce interesting metabolites.

Genetic engineering also has a big potential in producing purely biological pesticides, such as toxins from Bacillus thuringiensis. Natural compounds produced by insects, such as pheromones (sex attractants) and juvenile hormones have possibilities for insect control and are also good candidates for production by rDNA processes. However, biological pesticides are not necessarily superior to chemical pesticides. Carefully controlled use of both types may be the best solution. (Source: Genetic Technology News, November 1982; address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07 024, USA.)

Insecticidal protein

The insecticidal properties of Bacillus thuringiensis (BT), whose dried cells are commonly used to control gypsy moths and other insects, is due to a protein. A team of French researchers, at the Institut Pasteur (Paris, France) has cloned a B. thuringiensis gene coding for the toxic protein and caused it to express in Escherichia coli and B. subtilis. The protein is apparently tied in with spore formation by the bacterium. It is expressed in B. subtilis only during the sporulating stage, not during normal vegetative growth. Depending upon the strain of B. thuringiensis, the gene may be found on a plasmid, the bacterial chromosome or both. (Extracted from Genetic Technology News, December 1982; address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07 024, USA.)

Nitrogen fixation

Little by little the basic mechanism of the complex symbiotic nitrogen fixation process that takes place in nodules on roots of legumes infected with Rhizobia bacteria is becoming known. Latest advance is the cloning and identification, of a Rhizobium meliloti gene that codes for the enzyme that synthesizes δ-aminolevulinic acid. This compound is an important precursor to heme, which in turn, is a component of leghemoglobin (a hemoprotein similar to the protein responsible for carrying oxygen by red cells in human blood). Leghemoglobin regulates oxygen concentration in the nodules to protect the nitrogen-fixing enzymes, nitrogenase, which is sensitive to oxygen.

Mutations of R. meliloti without the gene do not nodulate alfalfa (the bacterium's normal host), but when plasmids containing the gene were introduced into the mutant the bacterium nodulated almost as well as the wild type. (Source: Genetic Technology News, October 1982; address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07 024, USA.)

Pollen may be a potential vector for inserting foreign DNA into plants

Inserting foreign DNA into higher plants is not easy. Common vectors that work in bacteria or yeasts do not work in higher plants. Vectors such as the Ti plasmid can integrate their DNA into the chromosomes of higher plant cells, but are not really satisfactory for expressing foreign DNA in plant cells. Research at Cornell University is trying to use pollen as a vector.

Pollen cells are the male sex cells of plants. Each cell contains only half the number of chromosomes that non-sex cells do. Normally a pollen grain falls onto the female reproductive organ of a flower and then extends itself to join an egg cell inside. The egg cell also contains half a set of chromosomes. The fertilized egg cell then contains a complete set of chromosomes and develops into an embryo plant, contained within a seed.

It hoped to introduce plasmids from Escherichia coli or yeast into pollen cells from tobacco and tomato plants by incubating plasmids and pollen together. If enough cells are treated in this way, some of the plasmids may pass through the cell walls. The walls of pollen cells cannot be removed, as they can in ordinary cells, to make protoplasts which are easier for plasmids to penetrate. Once inside the cells, the plasmids are unlikely to replicate themselves separately as they do in bacterial cells. If they replicate at all, it will probably be after they are integrated into the DNA of the plant chromosomes.

The gene that it is hoped to be introduced is one that codes for resistance to the antibiotic, kanomycin. The gene should have no significant effect on the plant, but it can serve as a marker to determine whether the technique works. guidelines of the Recominant DNA Advisory Committee (RAC) of the National Institutes of Health prohibit introducing plants or other organisms modified by recombinant DNA into the environment. It is felt that this rule was not adopted to apply to harmless modifications, such as those being attempted, so permission has been applied to field test the plants out of doors. Even so, approving any work involving introduction of recombinant DNA modified plants into the environment will mean a big policy decision by RAC. In the meantime a limited number of experiments under P1 containment conditions inside a greenhouse are being carried out. (Source: Genetic Technology News, November 1982; address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07 024, USA.)

Frost damage

Researchers at International Plant Research Institute (IPRI), a biotechnology firm at San Carlos, California, and the University of California at Berkeley have isolated a gene that may ultimately provide a way to protect cerain food crops from frost damage. The gene, found in several species of bacteria (Pseudomonas syringae and Erwinia herbicola) encodes a cell product that causes water to form ice crystals at temperatures only slightly below freezing (43°F). (Source: G.V. Olsen Associates, August 1982.)

Healthy plant stock

A research team at the American Type Culture Collection (ATCC) has produced monoclonal antibodies to several plant viruses. Monoclonals are expected to be a big improvement over the conventional polyclonal antisera ATCC now supplied to US state experimental stations which use them to ensure that young plants sent to nurseries are virus-free. Trees planted in orchards are expected to last for 20 to 40 years, therefore it is important they should be virus-free.

The ATCC group has made hybridoma cells by fusing myeloma cells (that continue to reproduce indefinitely) with immune cells (that produce antibodies) from rabbits immunized against plant viruses. Each resulting hybridoma cell line produces antibodies that are very specific. Conventional antisera contain a mixture of antibodies to a number of substances. So far monoclonal antibodies have been made to prunus nectotic ring spot virus (infecting plants such as apricots, cherries, peaches and plums), apple mosaic virus, tobacco streak virus and alfalfa mosaic virus.

First application will be to mix several monoclonals to form a reconstituted polyclonal. The reconstituted polyclonals can be made with known proportions of each antibody. Hybridoma cells can be frozen and stored for long periods of time, thawed and made to produce identical monoclonal antibodies. This wil make it possible to produce uniform polyclonals whenever needed. Conventional polyclonal antisera may vary somewhat from batch to batch.

The most important potential of this technique in the long run may be the ability of monoclonals to pinpoint differences among virus strains. Today's polyclonal antisera can do this to some extent, but monoclonals would make it possible to finely tune the differentiation. (Source: Genetic Technology News, November 1982, address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07 024, USA.)

Crop improvement

Recombinant DNA techniques have spawned improved varieties of plants and provided clues to understanding diseases in animals. The prospects of being able to modify the genetic make-up of plants and animals prompts mixed reactions of hope and concern. On one hand, the possibilities of 'gene therapy' for incurable diseases and the development of pest-resistant crops hold great allure for improving life on earth. In contrast, the doubts surrounding the implications of human genetic manipulation abound. However, current research is aimed at understanding the way in which genes are controlled. Making any desired gene in large quantities has been improved by gene synthesis, chemically lining the nucleotide building blocks of DNA in a desired sequence. This technique offers the prospect of manufacturing completely new genes that are not found naturally. Gene control hinges on getting the new genes to perform in sensibly in a foreign environment to produce a desired result. (Extracted from Technology Update, 25 September 1982.)

Plant tissue culture

The genetic manipulation of plant tissue cultures will produce improved strains and new capabilities for drug production. The goals of current research are to isolate plant cells responsible for secreting compounds vital to pharmaceutical preparations, grow vast quantities of the cells with low-cost processes and extract their valuable components in commercial quantities. While tissue culturing techniques may produce big-priced but low-volume products, the prospect of breeding specialized strains from cultured cells will open agricultural research opportunities. Protoplast fusion may improve crops by mixing genes for high yields in one plant variety with genes for disease-, drought-, or pest resistance in another variety. In addition, desirable traits may be transposed from one plant cell into another by recombinant DNA techniques. (Source: Technology Update, 18 September 1982.)

COUNTRY NEWS

Australia

Rapid advances in biotechnology have led to continual questioning on who should create policy on the techniques. Usually the responsibility rests with a remote committee of experts, often viewed as inaccessible and faceless to the public. In order to give the public some redress on the issues, the Australian Law Reform Commission (ALRC) has been established to give the government and parliament advice on the form, modernization and simplification of federal laws. With the expertise of consultants, scientists, theologians and philosophers, the committee assembles information as the basis for recommending changes in laws about science and technology. (Source: Technology Update, 25 September 1982.)

China

China's first institute of agrobiological genetics and physiology opened on 21 September at Nanjing, the capital of Jiangsu province. The new institute, which falls under the jurisdiction of the Jiangsu provincial Academy of Agricultural Sciences, is one of China's key projects for agricultural scientific research and was constructed from funds donated from the Ministry of Agriculture, Animal Husbandry and Forestry and from the Province of Jiangsu. The institute has three research sections - genetics, physiology and biochemistry and is well equipped with laboratories and equipment. The director of the institute, Professor Xi Yuanling, explained that the aim of the institute was to improve the material and technical conditions for the country's agricultural scientific research and strengthen applied and basic research in agro-genetics, physiology and biochemistry, and will concentrate on working out new approaches and methods for providing nfew materials for the development of new cultivation techniques and crop strains. The institute presently has a staff of 43 research workers and will also train scientists specialising in agro-genetics, physiology and biochemistry. Since preparations for the institute began in 1979, scientists have completed seven major research projects, including the technology of regeneration of the rape plant from tissue culture through embryos and the technology for photosynthetic breeding of rice.

France

The French Ministry of Industry and Research has agreed with the Japanese Ministry of International Trade and Industry (MITI) to establish an R&D team to investigate the production of industrially important products from cellulosic biomass and algae species, as well as the production of acetone and butanol. Both ministries will conduct a number of joint feasibility studies and exchange technical information. (Extracted from European Chemical News, August 1982.)

Japan

A method of gene recombination on hay bacillus which ends the problem of losing the recombinant gene during culture has been developed at the University of Tokyo's Insitute of Applied Microbiology. It has been confirmed that the plasmid and the chromosome gene share a common amino acid - histidine. By marking the plasmid of the bacillus cell with a scratch to distinguish it from other genes, and then sending it into the cell, the plasmid was discovered to enter the gene of the chromosome through a natural process of gene recombination. An advantage of the research result is stability without loss of the recombinant gene once it is carried into the chromosome gene.

Japan has revised its guidelines for rDNA experiments so that they very nearly resemble those of France, but are far stricter than those applied in the United States. Escherichia coli K-12, Saccharomyces cerevisiae and Bacillus subtilis Marburg 168 are the only hosts permitted, and cultivation tank capacity is limited to 20 litres. However, at the end of August 1982, the Government eased its genetic engineering research guidelines for university and corporate research. The Japanese Science and Technology Agency predicted that the amendment will enable many new firms to take up biotechnolgical development since readily available research facilities are adequate for undertaking experiments.

An hepatitis-B vaccine based on yeast used for making bread and beer has been mass produced using rDNA technology by the University of Osaka and the Chemical-Seropherapeutic Research Institute. A virus gene was extracted from infected blood and incorporated into the yeast by means of plasmid vector of the gene and thereby enabling the mass culture of antigen protein against the virus and forming the substance of the vaccine. It is estimated that approximately 2 million people in Japan suffer from the B type of hepatitis virus, which in many cases develops into cancer of the liver. Using the rDNA technology, only the antigen protein can be produced without infection from the virus.

As a result of work over many years on the movement of cytoplasm in plant cells and the molecular mechanism of muscle contraction, Professor H. Shimizu of the University of Tokyo synthesized a molecular motor powered by muscle proteins and the energy carrying chemical adenosine triphosphate (ATP). Following this work, the Japanese Government has initiated a five-year project in the area of "biomolonics" (the science of self-organising life phenomena) and has allocated 1.8 million yen to the project. Its object is to develop motors powered by biochemistry, and even a biochemical computer. Details of the research are not as yet available, but they seem to involve storing in nerve membranes the "ones" and "zeros" that constitute the information normally found in computer memories. The data would be coded as electrical signals that register either "on" or "off". (Extracted from Technology Update, 24 July 1982, 14 August 1982, 25 September 1982, 23 October 1982 and New Scientist, 11 November 1982.)

United Kingdom

The British Government will be funding a three year programme involving biotechnology in industry for an estimated sum of £16 million. The work will cover consultancy, feasibility studies, demonstration plants and industrial research projects at British universities and research insitutes. Companies in the United Kingdom that are involved in biotechnology may expect financial help of up to 50 per cent for strategic studies and up to 75 per cent for feasibility studies. Small and medium-sized companies may also obtain 100 per cent financing for consulting costs. The Government's commitment for biotechnology research is £20 million which should assist the apparent lack of progress in turning biotechnological substances into commercial products. One of the reasons given for this rather slow development is that there is a lack of biochemical engineers arising from the education system which separates biology from engineering, that there is a lack of qualified teachers in certain fields and a lack of Government strategy for developing process engineers. However, some advances have been made - notably that the Science and Engineering Research Council has established a new Directorate, giving the field a higher priority and a link between the Biotechnology Directorate and the Department of Industry to foster links between the Government, industry and the research institutions.

At the end of November 1982, the British Government launched a new programme in support of biotechnology. Namely, the Department of Industry intents to spend £16 million over the next three years on consultancies, research and demonstration projects. This sum is in addition to the £14 million spent on commercial projects through the British Technology Group. The bulk of the money will be to support collaborative projects with the Department's own research establishments at Harwell and Warren Spring and the newly established Biotechnology Institute and Studies Centre. Some capital will be to develop the pilot plant facilities at the Centre for Applied Microbiology Research at Porton Down and to establish a new national collection of animal cells and hybridomas. Further funds will be given to the high technology consultancy, Patscentre and for Imperial Chemicals who intend to develop a process for making microbial plastics from microbes. Paticular focus is to be given to a research programme on bio-sensors and elements of process engineering such as fermenter design and large-scale growth of mammalian cells.

At a recent panel meeting of the OECD and British scientists, it was said that biotechnology should be universally defined as the "application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services". Materials would encompass all organic and inorganic substances, and the panel

suggested that more emphasis be placed on basic plant science, plant physiology and plant genetics, as well as microbial biology. Future studies should included typical organisms such as anaerobic, photosynthetic and thermophilic bacteria, filamentous fungi and yeasts. It was pointed out that the future of biotechnology depended on the availability of raw materials. Policy makers were cautioned to assess biotechnology in connection with other developing technologies and attempt to determine those areas where biotechnology may replace more traditional technologies. Other issues discussed included biotechnology's effect on trade patterns, safety and environmental protection and the international patent situation.

(A report, recently published by the OECD and entitled "Biotechnology - International Trends and Perspectives" (No. ISBN 92-64-12363-8) contains details of study and is obtainable from the OECD Press Division, 2 rue André Pascal, 75775 Paris Cedex 16, France.)

The British Insitute of Manpower Studies has been asked to make a survey of the rate of emigration amongst qualified British biotechnologists, following the departure of some of Britain's eminent scientists in this area to work for large concerns abroad. The Institute said in October that the amount of people leaving the country would certainly amount to several hundred, graduate students included. The demand for scientists with the right kind of expertise and background is considerable, and for once, the emphasis is on the well-qualified post-graduate, but local industry has been slow to recognise the talent and compared with US salaries, these are uncompetitive and investment venture capital all too cautious for the good of local industry. Nonetheless, the intention of the survey seems partly to be a means by which British research councils may keep in touch with departed biotechnologists through a register of names and addresses.

In an interim report on its continuing inquiry into British biotechnology, the Education, Science and Arts Committee of the House of Commons said that it is opposed to exclusivity in patent rights arising from research council work, and urged that the Government should review the issue before the Agricultural Research Council gives similar arrangements to that given to the British company Celltech by the Medical Research Council. The Committee seems to fear that some good ideas might not be pursued effectively in these circumstances. It also consistently advocates that the British Technology Group be deprived of its monopoly right of first refusal of patent rights developed in research council laboratories, a matter which has long been overdue for consideration. The report says that the Department of Industry should have a formal channel of communication with the University Grants Committee (UGC) so as to be able to make its opinion felt that a greater share of the universities' budget be spent on science and technology. The UGC should conversely be represented on the department's biotechnology committee (which might raise constitutional difficulties) and should set up a "more specific decision-making structure" for "strategic decisions about biotechnology". The report pleads for a "more coherent science policy" and in particular for the restoration of support for research "within the dual support system", it also asks that there be a study of tax incentives as a means of stimulating industrial links with the universities and more deliberate study by the British research councils of the earmarking of student training places for intending biotechnologists. (Extracted from Nature, Vol. 298, 5 August 1982, Chemistry and Industry, 7 August 1982, OECD Press Release, 27 September 1982; the Economist, 2 October 1982; Nature, Vol. 299, 7 October 1982; Daily Telegraph, 11 October 1982; Technology Update, 30 October 1982; New Scientist, 25 November 1982; Technology Update, 4, 11 and 18 December 1982.)

United States of America

After two years of study, the Presidential Commission for the Study of Ethical Problems in Medicine and Biomedical Behavioral Research is recommending that a permanent group be established to monitor rDNA technology, which would include representatives from the Government, scientific, business and religious communities as well as the general public. At a time when the National Institutes of Health Recombinant RNA Advisory Group is easing restrictions set by its guidelines, the Presidential Commission seems to be more concerned by the ethical problems such as the possibility of genetically modifying humans, and is of the opinion that whilst rDNA may lead to great progress in dealing with inherited diseases, ageing and other human problems, in the hands of unscrupulous individuals its potential may be abused. (Extracted from: New Scientist, 25 November 1982; Technology Update, 4 December 1982, 11 December 1982; and Genetic Technology News, December 1982; address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07 024, USA.)

PATENTS

Gene machine patented

Recently a patent has been issued to Bio Logicals Inc. for a polynucleotide synthesizer (U.S. Patent No. 4,353,989), although it is still not back on the market after having withdrawn it from sale owing to a number of problems. Several of the 'gene machines' are being used by the company, but after some modifications the machines should be available.

Canada changes its patenting policy

The Canadian Commissioner of Patents has recently decided to change the policy and permit the patenting of life forms following an application from Abitibi Co. of Toronto for a patent on a process that uses a mixed culture of five micro-organisms that degrade sulphite pulp waste liquor. The decision, which will have broad implications for rDNA and other organisms for biotechnological processes, brings Canadian practice into line with that already established in the United States, United Kingdom, Japan and many other countries. The decision indicates that in future patentability should extend to "all micro-organisms, yeasts, moulds, fungi, bacteria, actinomycetes, unicellular algae, cell lines, viruses or protozoa". The decision implied that a life form as complex as an insect might be patentable if it otherwise contained the attributes of patentability - a new insect, for example, may be developed as a predator against a harmful one. (Extracted from Technology Update, 11 December 1982 and Genetic Technology News, December 1982; address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07 024, USA.)

Plant tissue culture patent

The firm of Agrigenetics has been awarded a major biotechnology patent covering the application of genetic engineering to food crops. The patent includes the use of plant tissue culture and breeding to produce hybrid plants enabling their more rapid production and reducing the cost of producing new vegetable seeds. The patent is already being licensed and is being field tested on several plants including tomatoes and cabbages. (Extracted from Technology Update, 7 August 1982.)

Cohen-Boyer patent

The convolutions of the case on the Cohen-Boyer patent covering genetically engineered plasmids are increasing with the formal claim of co-inventorship by a professor at the University of Michigan who had worked with Dr. Boyer during 1972-73 and co-authored the 1973 paper in Proceedings of the National Academy of Sciences that forms the basis of the patents. The University of Stanford claims that the professor in question has so far ignored several requests to prove his case and has asked the US Patent Office to close the files until final judgement has been recieved. The US Patent Office had already approved the first of the two-part patent application - on the basic techniques of gene-splicing - but the second part on products is still pending while the Patent Office investigates a number of objections. Meanwhile the patent is in limbo. (Extracted from Technology Update, 24 July 1982, 7 August 1982; International Herald Tribune, 31 August 1982; New Scientist, 4 November 1982; Nature, Vol. 300, 11 November 1982, 25 November 1982; New Scientist, 16 December 1982 and Genetic Technology News, December 1982; address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07 024, USA.)

Other recombinant DNA patents

4,338,397, Walter Gilbert and Karen Talmadge, assigned to Harvard University: A nucleotide sequence coding for the signal sequence attached to the gene coding for the wanted protein product in the plasmid used to transform a bacterium. It might be very useful in a second wave of improved recombinant processes. Secreting the protein product into the medium rather than retaining it inside the bacterial cells could make purification much simpler. Harvard has granted Biogen an exclusive license.

4,322,499 and 4,350,764, John Baxter et al., assigned to University of California. These two patents cover production of beta-endorphin by microorganisms genetically modified with vectors containing the human gene coding for the hormone.

4,343,832, David V. Goeddel and Herbert L. Heyneker; 4,356,270, Keichi Itakura, both patents assigned to Genentech. Goeddel's patent covers trimming back a DNA sequence to be placed in a plasmid so that no excess polypeptide is attached to the product expressed. The sequence is trimmed back so far that some of the DNA of the gene is lost, making sure that

extraneous ploypeptides are eliminated in the product. Any DNA needed to make the gene complete again is chemically synthesized and attached to the gene fragment. The second patent covers production of a functional polypeptide from a gene of chemically synthesized DNA. This was first done by Itakura at City of Hope Medical Center (Duarte, CA) in 1977.

4,332,900, 4,338,400, 4,340,674, Jack J. Manis and Sarah K. Highlander, assigned to Upjohn. Taken at face value, these patents cover some very specific plasmids derived from pBR322. The plasmids can be transferred back and forth between Escherichia coli and Streptomyces espinosus. Upjohn is obviously interested in improving Streptomyces, the group of microorganisms that are the source of a large number of important antibiotics. But eventual interpretation of the patents might be broad enough to include plasmids from other bacteria and other species fo Streptomyces.

In any new technology, inventors who get in early often gain a commanding patent position. But key patents often don't stand up in court. Litigation in genetic engineering patents will not resolve this for a long time.

Apparently a great many genetic engineering patent applications are now in the works at the Patent Office. The Patent Office has improved its expertise in this new area. Alvin E. Tannenholtz, Patent Office's primary examiner for nearly all patents issued so far in genetic technology, has also recently acquired more staff to help cope with the growing volume of applications in this field. (Extracted from Genetic Technology News, December 1982; address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07 024, USA.)

MEETINGS

Date	Title
12-14 January 1983	Chemistry and Biology of Alpha-2-Macroglobulin, New York, Academy of Sciences Conference, New York, NY, USA. (The Conference Dept., The New York Academy of Sciences, 2 East 63rd Street, New York, NY 10021, USA)
17-21 January 1983	15th Miami Winter Symposium, 'Advances in Gene Technology': Molecular Genetics of Plants and Animals', Miami, FL, USA (Miami Winter Symposium, P.O. Box 016129, Miami, FL 33101, USA)
24-28 January 1983	8th International Specialized Symposium on Yeasts, Bombay, India. (Dr. T.V. Subbaiah, Convener, VIIIth ISSY, c/o Foundation for Medical Research, 84-A.R.G. Thadani Marg, Worli Seaface, Bombay 400 018, India)
24-28 January 1983	Seventh Annual Symposium on Energy from Biomass and Wastes. Lake Buena Vista, Florida. Contact: Maryann Manrot, Institute of Gas Technology, 3424 South State St., IIT Centre, Chicago, IL 60616
6-10 February 1983	"Third Annual Congress of DNA Research". Philadelphia, PA. For information, contact: DNA, c/o Scherago Associates, Inc., 1515 Broadway, New York, NY 10036, 212-730-1050
6-11 March 1983	ASM Annual Meeting (83rd). New Orleans, Louisiana. Contact: Richard R. Clark, Meetings Dept., ASM, 1913 I St, N.W., Washington, DC 20006
7-28 March 1983	"COGENE Course on Recombinant DNA Techniques". Hong Kong. Contact: A.M. Skalka, Roche Institute of Molecular Biology, Nutley, NJ 07110
9-10 March 1983	Phytochrome: Properties and Functions, London, UK (Miss C.A. Johnson, The Royal Society, 6 Carlton House Terrace, London SW1Y 5AG, UK)

Date	Title
16-19 March 1983	7th Annual Meeting of the Cell Kinetics Society, Baltimore, MD, USA (Dr. F. Kimler, Secretary, Cell Kinetics Society, Dept. of Radiation Therapy, University of Kansas Medical Center, Rainbow Boulevard at 39th Street, Kansas City, KS 66103, USA)
17-18 March 1983	Swiss Union of the Societies for Experimental Biology, 15th Annual Meeting, General subject: 'The nervous system: molecular, structural and functional aspects', Fribourg, Switzerland. (USGEB-Sekretariat, Biochemisches Institut, Vesalgasse 1, CH-4051 Basel, Switzerland)
21-22 March 1983	The Biological Council's Annual Symposium 'Actions and Interactions of GABA and Benzodiazepines', London, UK (Mrs. J. Kruger, c/o Dept. of Pharmacology, University College, Gower Street, London WC1E 6BT, UK)
23-25 March 1983	1st International Meeting for Cell Biochemistry and Function. Guildford, UK (Prof. J.W. Bridges, Secretary, 1st International Meeting on Cell Biochemistry and Function, Scientific Committee, Institute of Industrial and Environmental Health and Safety, University of Surrey, Guildford, Surrey GU2 5XH, UK)

Corrigenda: In our last issue we inadvertently scheduled the VIIth International Biotechnology Symposium (New Delhi) as 19-25 February 1983 - this should of course be 1984. Our apologies for the slip.

PUBLICATIONS

Aide-Mémoire for High-Level Meeting on the Establishment of the International Centre for Genetic Engineering and Biotechnology. Belgrade, Yugoslavia, 13-17 December 1982.

UNIDO/IS.254	The Establishment of an International Centre for Genetic Engineering and Biotechnology (ICGEB)
ID/WG.382/1	Draft Memorandum of Understanding and Guiding Principles of the International Centre for Genetic Engineering and Biotechnology prepared by the UNIDO Secretariat
ID/WG.382/2 and Corr.1	Five-Year Work Programme of the International Centre for Genetic Engineering and Biotechnology prepared by the UNIDO Secretariat
ID/WG.382/2/ Add.1	Selective Application of Advanced Biotechnology for Developing Countries prepared by Carl-Göran Hedén
ID/WG.382/2/ Add.2	Application of Genetic Engineering for Energy and Fertilizer Production from Biomass prepared by Ray Wu
ID/WG.382/2/ Add.3	Hydrocarbon Microbiology with Special Reference to Tertiary Oil Recovery from Petroleum Wells prepared by Ananda Chakrabarty
ID/WG.382/2/ Add.4	Application of Genetic Engineering and Biotechnology for the Production of Improved Human and Animal Vaccines with Particular Reference to Tropical Diseases prepared by Ahmad Bukhari and Ulf Pettersson
ID/WG.382/2/ Add.5	Improved Agricultural and Food Products through Genetic Engineering and Biotechnology prepared by David McConnell
ID/WG.382/2/ Add.6	Bio-Informatics prepared by Carl-Göran Hedén
ID/WG.382/3	Proposed Budget of the International Centre for Genetic Engineering and Biotechnology prepared by the UNIDO Secretariat. Provisional List of Participants.

Genetic engineering and biotechnology firms USA - 1981/82

A new directory which gives the basic information on American genetic engineering and biotechnology firms has been published by the firm of Sittig and Noyes. It describes some 250 firms in the United States, indicating research activities, equity interests, laboratory locations etc. (Extracted from Chemical Week, 6 October 1982.)

Investment guide

A guide for prospective investors in biotechnology has been written by two scientists at Queen Mary's College, London and published by the Economist Intelligence Unit, (Biotechnology: a guide for investors, by Vivian Moses and Bob Rabin). It is strictly a guide to the science of biotechnology rather than a guide to the technology of the subject. The price at £50 for 115 pages works out at £2.30 per page! (Extracted from Financial Times, 15 June 1982.)

Newsletters relating to genetic engineering and biotechnology

Title	Issues per annum	Annual subscription rate	Publisher
NEWSLETTERS			
Agricultural Genetics Report	6	$90 U.S.A. $106 Elsewhere	Mary Ann Liebert Inc., 500 East 85th Street, New York, NY 10028, U.S.A.
Applied Genetics News	12	$250	Business Communications Co Inc., PO Box 2070C, Stamford, CT 06906, U.S.A.
Biomass Bulletin	4	£48, $96	Multi-Science Publishing Co. Ltd, 42/45 New Broad Street, London EC2M 1QY, U.K.
Biomass Digest	12	$120 N. America $144 Elsewhere	Technical Insights Inc., 158 Linwood Plaza, PO Box 1304, Fort Lee, NJ 07024, U.S.A.
Biotech News	12	£65 U.K. £70 Elsewhere	Microinfo Ltd, PO Box 3, Newtown Lane, Alton, Hants GU34 2PG, U.K.
Biotech Quarterly	4	£12	Science and Technology Letters, 12 Clarence Road, Kew, Surrey TW9 3NL, U.K.
Biotech-Update	10	$95 N. America $105 Elsewhere	Scientific Newsletters Inc., PO Box 4546, Anaheim, CA 92803, U.S.A.
Biotechnology Bulletin	12	£80	Scientific and Technical Studies, Bath House (3rd Floor), 56 Holborn Viaduct, London EC1A 2EX, U.K.
Biotechnology Bulletin Reports	12	£48	Scientific and Technical Studies, Bath House (3rd Floor), 56 Holborn Viaduct, London EC1A 2EX, U.K.
Biotechnology Information	12	Free	Paul Mayer, Library Services, Teesside Polytechnic, Middlesbrough, Cleveland TS1 3BA, U.K.
Biotechnology Investment Opportunities	12	$125 U.S.A. $155 Elsewhere	High Tech Publishing Company, PO Box 266, Brattleboro, VT 05301, U.S.A.
Biotechnology Law Report	12	$275 N. America $323 Elsewhere	Mary Ann Liebert Inc., 500 East 85th Street, New York, NY 10028, U.S.A.
Biotechnology News	26	$185 U.S.A. $210 Elsewhere	CTB International Publishing Co., PO Box 579, Summit, NJ 07901, U.S.A.
Biotechnology Newswatch	24	$377	McGraw-Hill Inc., 1221 Avenue of the Americas, New York, NY 10020, U.S.A.
Biotechnology Patent Digest	26	$235 N. America $265 Elsewhere	OMEC Publishing Company, PO Box 546, Great Falls, VA 22066-0546, U.S.A.
Biotechnology Press Digest	12	$185 U.S.A. $217 Elsewhere	Mary Ann Liebert Inc., 500 East 85th Street, New York, NY 10028, U.S.A.
D-I-M Enzyme Report		$165 U.S.A. $177 Elsewhere	Deborah J. Mysiewicz Publishers Inc., 109 Minna St, Suite 516, San Francisco, CA 94105, U.S.A.
Genetic Engineering and Biotechnology Monitor	4	Free	Technology Programme of UNIDO, PO Box 300, A-1400 Vienna, Austria
Genetic Engineering Letter	24	$295	Environews Inc., 1077 National Press Building, Washington, DC 20045, U.S.A.
Genetic Engineering News	6	$90 U.S.A. $106 Elsewhere	Mary Ann Liebert Inc., 500 East 85th Street, New York, NY 10028, U.S.A.
Genetic Technology News	12	$180 N. America $204 Elsewhere	Technical Insights Inc., 158 Linwood Plaza, PO Box 1304, Fort Lee, NJ 07024, U.S.A.
Industrial Biotechnology	12	£115 U.K. £130 Elsewhere	Industrial Biotechnology, 5th Floor, 31-33 High Holborn, London WC1V 6BD, U.K.
Practical Biotechnology	6	£90 U.K. $200 U.S.A.	Practical Biotechnology, 4 Woodlands, Harpenden, Herts, U.K.
Recombinant DNA Techniques	3/4	$20	University of Michigan, Dept of Biological Chemistry, Univ. of Michigan Med. School, Ann Arbor, MI 48109, U.S.A.
Scrip	104	£195 U.K. £235 Europe, Middle East, N. Africa £249 Elsewhere	PJB Publications Ltd, 18/20 Hill Rise, Richmond, Surrey TW10 6UA, U.K.
ABSTRACTING SERVICES			
Abstracts in BioCommerce	24	£60 U.K. $120 U.S.A. (plus £10/$20 for microfiche)	IRL Press, PO Box 1, Eynsham, Oxford OX8 1JJ, U.K.
Derwent Biotechnology Abstracts	24	£275	Derwent Publications Ltd, Rochdale House, 128 Theobalds Road, London WC1X 8RP, U.K.
Telegen Reporter	12	$1200 (inc. Telegen Reporter Review + access to Document Delivery System)	Environment Information Center Inc., 48 West 38th Street, New York, NY 10018, U.S.A.
MAGAZINES			
Biofutur	11	FF315 France FF355 U.K. and U.S.A.	Biofutur, 12 bis, rue Jean-Jaures, 92807 Puteaux, France

Readers should check with publishers for changes in prices and publication frequencies before subscribing.

(Source: Trends in Biomedical Sciences, December 1982.)

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