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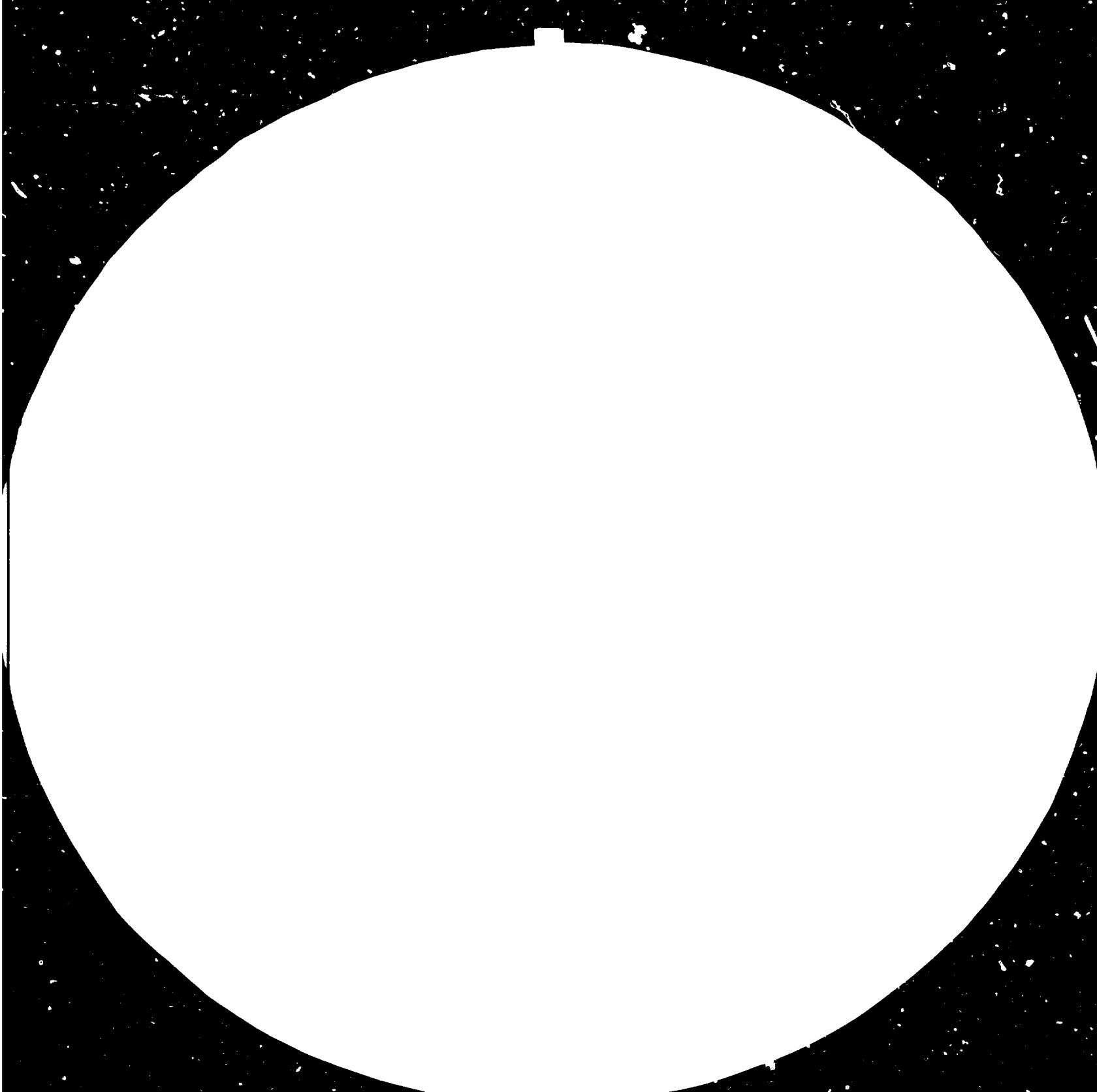

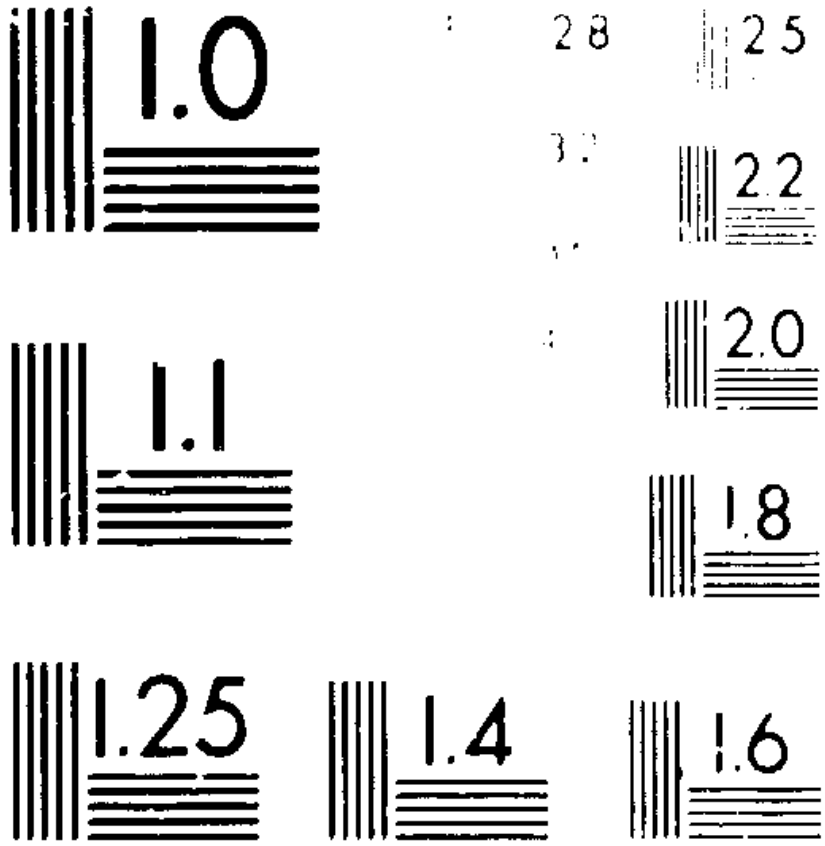

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

Genetic Engineering and Biotechnology Monitor

Issue Number 6 August 1983

13217

Dear Reader,

The major event we are looking forward to is the Ministerial Level Plenipotentiary Meeting for the Establishment of the International Centre for Genetic Engineering and Biotechnology which is to take place from 7 to 13 September 1983 in Madrid, Spain. Preparations for the Meeting have been completed: the Select Committee of Experts has tendered its advice on the question of location; the proposed Statutes of the Centre have been elaborated; and proposals for financing the Centre have been prepared. Representatives from some 50 countries are expected to participate - a number substantially larger than the countries which attended the Belgrade meeting and shows the growing interest and enthusiasm for the Centre. We are hoping that the meeting will take all necessary decisions to establish the Centre since this is an urgent task and the opportunity for international co-operation in this field cannot be lost. The meeting is indeed an important stage for international co-operation in the field of emerging technologies.

Other activities in the Secretariat on genetic engineering and biotechnology are proceeding apace. In the coming months we will be assisting national level meetings in Brazil and the Republic of Korea, and in December the International Genetics Congress in New Delhi, India.

Readers may be interested to know that a study for UNIDO has recently been completed on the microbial leaching of copper, with particular reference to the experience in the Andean Pact countries. What the study shows is that there is a viable technology available for the recovery through microbial leaching of copper from dumps of processed copper ore. Something like 25 developing countries would appear to be involved in the mining and processing of copper and many of them may stand to benefit if they adopt microbial leaching technologies and thereby recover the copper which is now being treated as waste. We shall be addressing the developing countries concerned by furnishing them with a copy of the report and request them to examine to what extent such technologies could be usefully carried out in their countries. In the meantime, readers from developing countries may also provide us with information, if they can, of possible applications of microbial leaching in their respective countries.

Readers will find that a new feature has been included in the Monitor concerning information and assistance sought by a reader from a developing country in the area of tissue culture. If readers would come forward with more requests for information and also what offers for assistance they can give, we could have a useful feature on "Assistance required: Assistance available" in the field of genetic engineering and biotechnology. Readers may note that the recent expert workshop held by the UNIDO Secretariat in Dubrovnik recommended that the UNIDO Secretariat should prepare for the benefit of developing countries an international roster of scientists and technologists in selected technological advances who are willing to assist developing countries through communication, training, field visits or a period of stay in these countries. The workshop recommended that a computerised and up-dated roster of this kind be developed by UNIDO. The roster could contain information on the name, qualifications and affiliations of the scientist and technologist, his field of interest and competence, the countries he is prepared to assist, the period of availability, financial remuneration required, etc. We are working further on this idea.

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NEWS AND EVENTS

Experts' report on the siting of the International Centre for Genetic Engineering and Biotechnology

In the last issue of the Monitor we mentioned that the expert team who inspected the various sites offered were preparing a report on their findings for presentation at the Ministerial Level Plenipotentiary Meeting to be held at Madrid from 7 to 13 September 1983. The report is now available and reviews the offers made by Belgium, Cuba, India, Italy, Pakistan and Thailand, as well as offers received from Bulgaria and Tunisia which were received after the Selected Committee of experts had left Vienna on 20 March 1983 on its mission. We are reprinting hereunder the summary and conclusions. For those of our readers who would like to read the whole report, it is available from us under the symbol ID/WG.397/1.

Summary and conclusions

135. The Selected Committee has fully examined proposals from six countries offering to locate and support the ICGEB. Eight locations have been visited including three in Belgium.

136. There are three countries which have sufficient merits to offer good prospects for the foundation of the ICGEB. These have different strengths. The strengths of Belgium lies in its outstanding and concentrated scientific infrastructure which would guarantee adequate support from the international scientific community. The strength of Italy lies in the profound commitment of the people of the city of Trieste and of the region Friuli-Venezia Giulia as evident in the financial and other details of the proposal and in the record of support for the International Centre for Theoretical Physics. The strength of Thailand is that it has a good quality but limited scientific infrastructure in the relevant sciences, and a gathering momentum. It has the capacity to assimilate an international scientific teaching institution, vide the Asian Institute of Technology.

137. The Selected Committee advises, the ICGEB could be established in Belgium, Italy or Thailand. In Belgium the best location would be Meylermeerson, Brussels, adjacent to the new Hospital of the Free University Brussels (ULB). In Italy there are a number of good sites in Trieste. In Thailand the new Salaya Campus of Mahidol University is a good site.

138. The two major factors which are essential for the foundation of the ICGEB as a centre of high excellence are:

(a) The support it will receive from the international scientific community in genetic engineering and biotechnology;

(b) The financial and political support it will receive from the host and member countries.

Additionally it must be located in an environment which is conducive to the transfer of the science and technology of GEB to the developing countries. Without these three qualities the ICGEB will not become established as a useful institute to serve the needs of developing countries.

139. The Selected Committee advises that the ICGEB could not be established in the other three countries essentially because of the insufficient scientific infrastructure related to the fundamental sciences underlying GEB and the judgement that it would not be possible to attract a sufficient number of good scientists to these places.

New biotechnology institute

Union Carbide, Eastman Kodak, Corning Glass Works and Cornell University will launch a new Biotechnology Institute at Cornell University's Ithaca, NY, campus. The partners will each provide $2.5 million over 6 years for the institute. Corporate scientists will work with the Cornell faculty in an open, basic research programme, with findings available to the public. Over 400 scientists and faculty will participate in the institute. Some biotechnology breakthroughs that have occurred in the past 25 years include development of microorganisms that can produce insulin, development of interferon and a vaccine to protect cattle from hoof-and-mouth disease. Some major future applications include decomposition of wastes, increasing the resistance of plants and animals to insects, and research into disease and environmental stress, new food processing methods and obtaining industrial chemicals from common materials such as trees and plants to replace the current reliance on petroleum. (Source: Technology Update, 30 April 1983.)

European Economic Community research and development: slow progress in the FAST lane

According to the final report of the Commission's five-year research and development study programme, 'one might use the word "despair" to describe the present situation.' It adds: 'We are still in search of what policy measures could possibly bring us out of this web of intertwined problems denoted by the crisis.' The study programme undertook to examine what measures the European Community could take to harness the Community's R&D resources, in order to meet the serious industrial and social problems which the next thirty years will bring. The bleak message is itself an explanation of why such a study was felt necessary, even back in 1979.

The FAST Programme - which stands for 'Forecasting and Assessment in Science and Technology' - was given a budget of 4,4 million ECUs and a team of six researchers, who then brought together experts from all over the Community. Together they produced 36 separate studies, out of which a final report was drawn up outlining an overall research strategy. In it, the FAST group concentrated on three major issues: work and employment; information technology; and the more distant issues related to the development of biotechnology. Each of these themes are closely interlinked with one another, but all relate to the rapid introduction of new technologies which are already beginning to influence trade, industry and the way we live.

The report begins by contemplating the present outlook for Europe. It is poor. Unemployment at 11 per cent is still rising. To achieve an unemployment level of 2 per cent by 1995 would require the net creation of a million new jobs a year from now on. This is clearly an impossible dream. Even during the Sixties, no more than 260,000 new jobs were created annually. The situation is all the worse because of the feeble health of Europe's primary industries. The traditional basic industries - cars, chemicals, textiles, steel, etc. - are having to retrench heavily, while the new sunrise industries created out of the advances in information technology are falling behind in the race with the Japanese and Americans.

The questions to which the FAST team addressed themselves to were not, however, the immediate industrial or employment problems facing Europe. They dealt with the strategic questions concerned with how Europe's R&D policy can in the long term contribute towards improving the competitiveness of European industry. This means both by stimulating innovation in tracitional industries and enabling new industries to grow as quickly as possible.

Two approaches were taken to each of the three areas examined, firstly, to analyse what was at stake; and secondly, to propose the directions that the EEC's research policy should in future take.

Biotechnology is, by comparison, at a far earlier stage of development and the issues and recommendations in the report differ accordingly. The FAST report believes that it is essential for Europe to field an expertise in so wide a range of scientific disciplines and technologies that it is beyond the capacity of any one member state to master. One option would therefore be the creation of multi-disciplinary research centres bringing together the best scientists that Europe has to offer. Beyond this, the report stresses the need for greater mobility and contact among European scientists: a greater exchange of information and more frequent discussions between the administrators of the national research programmes. Related supporting measures which are recommended by the report include data banks, data network services and the collection of biotic materials. In short, the primary role of the EEC would be to foster a practical framework for the development of biotechnology sciences and applications at a European level. The consequences of the growth in the application of biotechnology are also treated. Biotechnology, the report predicts, will have a revolutionary impact on the way natural resources are managed, and more specifically on the agricultural and food processing industries and possibly on the chemical and energy sectors too. The strategic requirement here is to develop a more coherent overall view of the use of land and the integrated management of our renewable natural resource system.

The application of biotechnology could mean being able to use agricultural wastes to provide energy: switching parts of agricultural production in Europe towards energy crops; developing new plant breeds that require fewer inputs of fertilisers; or reducing the use of oil and substituting indigenous raw materials as a feedstock for the chemical industry. The potential for change is enormous. Ultimately, the Community's agricultural policies, its trading relations with the Third World, as well as the structure of the Third World's own economies, will all be shaken..

The report sketches out the various options open, and at the same time defines the areas requiring further scientific research. Although the findings are often too detailed and specific to summarise briefly, some broad conclusions are also reached. (Extracted from Europe '83, April 1983.)

Europe's biotech slated

The European Commission is pessimistic about Europe's chances of competing with the US in biotechnology. A Commission report says Europe spends $160 million on biotechnology research compared to $200 million spent by the United States. "We are not managing to cut down the initial lead taken by the Americans."

The Americans themselves are even more dismissive of Europe. The draft of a report by the US Office of Technology Assessment on competitiveness in biotechnology says the only real competition will come from Japan. Although, it adds, there are some notable exceptions in European companies like ICI, Hoechst and Poulenc.

Dudley Gibbs of Bioprocessing Consultants believes Europe's weakness is due in part to a lack of open and straightforward cooperation between industry and academics. (Source: New Scientist, 30 June 1983.)

Culture collections - their services to biotechnology

The need to recruit qualified and experienced employees is a major concern of many organizations engaged in biotechnology. Universities and industry are scoured to find the right people, but where are we to find promising new candidates for the most numerous, and arguably most talented section of the biotechnological workforce - microorganisms and other types of cells? The international network of culture collections offers the best answer, and a proper understanding of their roles and capabilities can save biotechnologists an immense amount of time and money.

Among the millions of microbial, plant and animal cells stored in the world's culture collections it is often possible to find one that exactly suits a biotechnologist's particular requirements or one that can be developed to perform a specific task. An article which appeared in Trends in Biotechnology, Vol. 1, No. 1, 1983 outlines the services offered by culture collections, generally using the UK collections as examples of the main activities throughout the world, and from which we reprint the following.

The positive use of microorganisms for the production of industrially important substances cannot succeed without a supply to reliable, authenticated cultures and there is now a growing awareness that culture collections provide essential resources and services. The collection, maintenance and characterization of microorganisms form part of the infrastructure of microbiology and together with advisory, identification, preservation and patent services make an important contribution to the development of biotechnology.

The World Data Center on Microorganisms lists 566 culture collections in its directory. While many of these collections provide cultures only by special arrangement and do not publish catalogues, others not only provide cultures, advice and ancillary services on demand to researchers in industry and elsewhere but also publish catalogues. The number of these 'service collections' is small, but many countries are now seeking to establish national microbiological resource centres. In addition, a global network of eleven Microbiological Resource Centres (MIRCENS) has been set up by the International Cell Research Organization. Each is concerned with developing collections of microorganisms, providing training and advisory centres and promoting regional collaboration.

Service collections have developed and are administered in several different ways. The US and the FRG, for example, have single collections which maintain all types of microorganism; other countries, such as the UK and Czechoslovakia, have a decentralized system whereby each type of microorganism is housed in a separate institute and the individual collections are coordinated to form a national network. The United Kingdom supports eleven service collections (Table 1) housed in separate institutes and maintaining bacteria, fungi (including yeasts), algae, protozoa and animal cells. Some have specialist interests in medical, veterinary, industrial or genetical strains; others maintain taxonomic collections of more general interest. The services of these collections are available to scientists throughout the world. Table 2 lists some of the major culture collections in other countries which are particularly useful to biotechnologists.

Table 1. United Kingdom national collections

Culture collection	*Parent institution*	*Type of culture*	*Holding*
NC of Type Cultures (NCTC)	Central Public Health Laboratory, Colindale Avenue, London NW9 5HT, UK	Bacteria (medical, veterinary)	4 000
NCs of Industrial and Marine Bacteria (NCIMB)	Torry Research Institute, 135 Abbey Road, PO Box 31, Aberdeen AB9 8DG, UK	Bacteria (general, industrial, marine)	5 000
Collection of the Commonwealth Mycological Institute (CMI)	Commonwealth Mycological Institute, Ferry Lane, Kew TW9 3AF, Surrey, UK	Fungi	10 000
Culture Centre Algae and Protozoa (CCAP)	Institute of Terrestrial Ecology, Storey's Way, Cambridge CB3 0DT, UK	Algae, protozoa	2 000
NC of Yeast Cultures (NCYC)	Food Research Institute, Colney Lane, Norwich NR4 7UA, Norfolk, UK	Yeasts, other than known pathogens	2 000
NC of Dairy Organisms (NCDO)	National Institute for Research in Dairying, Shinfield, Reading, UK	Bacteria (general, dairying)	2 000
NC of Pathogenic Fungi (NCPF)	Mycological Reference Laboratory, London School of Hygiene & Tropical Medicine, Keppel St, London WC1E 7HT, UK	Fungi pathogenic to man and animals	830
NC of Plant Pathogenic Bacteria (NCPPB)	Plant Pathology Laboratory, Ministry of Agriculture Fisheries & Food, Hatching Green, Harpenden, Herts, UK	Bacteria (plant pathogens) and associated phages	3 000
NC of Wood Rotting Fungi (NCWRF)	Princes Risborough Laboratory, Building Research Establishment, Forest Products Research Laboratory, Princes Risborough, Aylesbury, Bucks, UK	Wood rotting basidiomycetes	620
National Animal Cells Culture Collection (NACCC)	PHLS Centre for Microbiology and Applied Research, Porton Down, Salisbury SP4 0JG, UK	Animal cells	200*
		Total	29 650

*Anticipated holding.

Table 2. Some major international culture collections useful to biotechnologists

Culture collection	*Address*
American Type Culture Collection	12301 Parklawn Drive, Rockville, Maryland 20852, USA
Deutsche Sammlung von Mikroorganismen	Grisebachstrasse 8, Göttingen 3400, FRG
Centraalbureau voor Schimmelcultures	Oosterstraat 1, PO Box 273, 3740 AG Baarn, The Netherlands
Czechoslovak Collection of Microorganisms	J. E. Purkyne University, 662 43 Brno, Czechoslovakia
Collection Nationale de Cultures de Microorganismes	Institut Pasteur, 25 Rue du Docteur Roux, 75724 Paris Cedex 15, France
Culture Collection of the Institute for Fermentation	Institute for Fermentation, 17-85 Jugo-Hohnmachi 2-chome, Yodogawa-ku, Osaka, Japan
USSR All-Union Collection of Microorganisms	Institute of Microbiology, USSR Academy of Sciences, Profsoiuznaia 7, Moscow B-133, USSR

Gene manipulation - clergy against germ changes

A resolution calling for an immediate ban on human genetic engineering that alters germ cells was released in June over the signatures of 21 Catholic bishops, a broad spectrum of Protestant and Jewish religious leaders and three scientists - George Wald and Ruth Hubbard of Harvard University and Ethan Signer of Massachusetts Institute of Technology.

The resolution cites "new advances in genetic engineering technology" that "raise the possibility of altering the human species", and concludes that humans have no right to decide which genetic traits should be introduced and which eliminated from the human gene pool.

The statement appeared to take a much harder line than that espoused by religious leaders and theologians who testified before the President's Commission on Bioethics, which last year produced a report on human genetic engineering called Splicing Life, The Social and Ethical Issues of Genetic Engineering with Human Beings. Hearings on the report called in November by Representative Al Gore (Democrat, Tennessee) elicited strong support for the commission's approach of increased scrutiny together with no a priori bans on human genetic engineering. Several clergymen who testified before Gore's subcommittee also signed the resolution.

Morris Abram, chairman of the now defunct President's Commission, expressed puzzlement at the resolution. "These techniques have already demonstrated a great potential for relief of suffering and possible diagnosis and treatment of diseases", he said. He added that human genetic engineering does indeed raise ethical problems, but that other medical procedures, such as artificial insemination and even cancer chemotherapy, raise similar problems. Alex

Capron, former staff director for the commission, was more outspoken. Calling the resolution "knuckleheaded", he complained that it swept aside difficult ethical issues in favour of a "broadside attack".

Several of the signers were quick to explain that they did not fully agree with the resolution nor with a supporting letter that attempted to explain its philosophical basis. Both were written by Jeremy Rifkin, an author of popular books on social issues. His latest book, Algeny, was recently published, and this has prompted critics to question the timing of the resolution.

According to Rifkin and some of the resolution's signers, the danger is that no line can be drawn between eliminating a genetic defect from the human gene pool and eliminating merely undesirable traits. "Indeed, what is to preclude society from deciding that a certain skin colour is a disorder?" Rifkin writes in the letter accompanying the resolution.

A counter argument says that the "supreme irony" in Rifkin's resolution is that by calling for government regulation in deciding what is acceptable in human genetic engineering and what is not, the very danger that Rifkin is warning of - eugenics - is made all the more likely. The government, would then be left with the responsibility of deciding which diseases gene therapy could be applied to. (Extracted from Nature, 16 June 1983.)

United Kingdom calls for careful monitoring of products

Careful monitoring must be conducted to ensure that microbes and their products do not escape into the workplace, even if they are not genetically engineered. If companies take shortcuts when building new units or refurbishing old ones, workers may be exposed to infectious, allergenic or toxic hazards. Special problems could arise if small companies without adequate resources introduce processes based on genetically manipulated organisms. Companies are not now required to notify the Health & Safety Executive (HSE) when they scale up to commercial production.

In addition to the problem of pathogens escaping from the lab or commercial lab, the possibility exists that workers could be affected by foreign proteins or lipopolysaccharides. Proteins similar to some existing in humans could trigger autoimmune responses, causing antibodies to attack the body's own proteins. ICI's Pruteen single-cell protein caused allergic reactions in workers when commercial production started, although improved ventilation has eliminated the problem. Dista has found no allergic reactions at sites manufacturing human insulin. HSE says that the use of genetically engineered organisms should be no more hazardous than other biotechnology industries such as vaccine or antibiotic production using large vats of microbes. HSE will study the hazards of microbiology. HSE. (Source: Technology Update, 30 April 1983.)

US recombinant DNA - green light for plant field-trials

In April, the Recombinant DNA Advisory Committee (RAC) relaxed its restrictions on field testing of genetically-engineered plants in anticipation of a flood of individual requests to approve such tests. Researchers will no longer need to apply for a formal exemption from the committee's rules against deliberate release of recombinant organisms; instead they may proceed with the approval of the local Institutional Biosafety Committee (IBC) and a small "plant working group" made up of RAC members.

The new rule still forbids the deliberate release of other organisms containing recombinant DNA, and sets general guidelines for the sorts of plant field tests that will be permitted. The plants must be cultivated crops and belong to a genus that contains no known noxious weeds; the inserted DNA must be well-characterized and contain no harmful genes; and the test field must be physically isolated from other stands of the same crop.

Because virtually nothing is known about the risks of such tests, the committee also ordered that field tests should include procedures for assessing alterations in and spread of the plant genes, and that results should be supplied to the committee's risk assessment programme. The original proposal, as published in the Federal Register, would have permitted field tests solely on the authority of the local IBCs. A majority of the committee voted to retain at least some supervision on the federal level, hence the requirement for review by the RAC working group.

The committee also agreed to drop a proposed restriction on the use of antibiotic resistance genes as selectable markers in the genetically-engineered plants.

As well as removing the burden from RAC of having to review and vote on each request separately, the new rule may actually also cut down the number of requests. Agrigenetics Corporation, in a comment filed with RAC, noted that at least one earlier proposal agreed by RAC had never been followed by field testing, and suggested that the new rules should discourage applications filed for "publicity or political purposes". Hitherto, the automatic publication of requests in the Federal Register under the previous system guaranteed a measure of free publicity. (Source: Nature, 21 April 1983.)

More US Government agencies eye regulation of recombinant DNA

The National Institutes of Health (NIH) Recombinant DNA Advisory Committee (RAC) seems to be trying hard to make sure that its recommendations do not place unreasonable barriers in the way of development of recombinant DNA technology. A more immediate possibility is that Environmental Protection Agency (EPA) may become involved. The EPA's Office of Toxic Substances (OTS) seems to believe existing NIH guidelines do not protect the environment from contamination by genetically engineered microorganisms. EPA may attempt to classify recombinant organisms as chemical substances subject to regulation under the Toxic Substances Control ACT (TSCA). This will raise some fine legal points - but EPA may be able to regulate rDNA work under this act.

If this takes place EPA could require premanufacturing notification review, manufacturing regulations, monitoring of health of workers and other regulatory actions. If EPA policies are poorly drawn up or administered the regulatory actions could delay progress in rDNA without improving the safety of the environment or the public. Harvey Price of Industrial Biotechnology Association (IBA), a trade association of companies working with recombinant DNA, has urged EPA to use his organization as an information vehicle between industry and EPA, and to proceed deliberately, taking into account information industry can provide. (Source: Genetic Technology News, May 1983. Address: 155 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Genetic manipulation

The British Government is proposing that its Genetic Manipulation Advisory Committee (GMAC), responsible for licensing experiments in genetic manipulation, should have a less active role but that investigators should continue to disclose experiments they carry out. This proposal is one of four for the future of GMAC contained in a consultative document issued on 5 April and circulated for comment (by 31 May).

The document says that the need to review GMAC's function arises because of "growing indications that early fears about the risks involved in genetic manipulation were exaggerated" (which will seem to many an injudicious phrase), because such concerns as remain about safety centre on large-scale production and because of the reorganization of arrangements for regulating work with dangerous pathogens.

The government is obviously also bothered by the anomalous constitution of GMAC, which by an historical accident has been sponsored since 1976 by the Department of Education and Science under the nose of the then infant Health and Safety Executive and of its supervisory commission, which have direct responsibility for occupational health. The consultative document says that the government departments needing advice no longer include education and science but those responsible for agriculture, environment and industry.

The proposed reorganization, said to have been discussed by GMAC itself, is the favourite among four alternatives - leaving GMAC alone, splitting it into two with responsibility for advising government departments and the health and safety establishments separately, turning it into a joint committee and, finally, transferring it into a dependant of the Health and Safety Executive as recommended. Presumably the first two options are intended derisorily. Abolition is not considered.

Under the proposed reorganization, the committee would be renamed the Health and Safety Commission Advisory Committee on Genetic Manipulation. It would advise the commission and executive on general questions, and give advice to government departments when asked.

The legal requirement that experiments should be notified to the executive would continue, as would the present voluntary undertaking by manufacturers that commercial-scale production plans would be notified. Such data would, however, be adjudicated by officials; only exceptional proposals would go to the committee.

Many researchers will ruefully reflect that the upshot of the proposed reorganization will be that a field of research whose hypothetical hazards are now said to have been "exaggerated" is nevertheless to remain perpetually under regulation. Although for most research laboratories, an annual retrospective report is now sufficient, the principle may stick in some throats.

The government also proposes that the four lay members of the present GMAC should be dispensed with. (Source: Nature, 7 April 1983.)

Genetically engineered plants face US government agencies

Now that modification of plants via recombinant DNA is close to reality, a big question is whether the US government will allow them to be grown outside a greenhouse. At its meeting, on 11 April, National Institutes of Health's Recombinant DNA Advisory Committee (RAC) considered a request from Cetus-Madison (Middleton, WI) to field test plants grown from seeds containing recombinant DNA. Cetus-Madison proposes to test half-acre plots of wheat, cotton, soybean, corn, tobacco and potatoes in Wisconsin and cotton, rice and tomatoes in several southern U.S. states. If the experiments are successful, Cetus-Madison is also requesting permission to test plants in approximately fifty fields of less than 5 acres each in many U.S. locations.

The genes in the plants are not "marker" genes, but genes that, in the greenhouse, at least, give the results sought after. Not all the plant species involved have been transformed and regenerated, but Cetus-Madison is working on them.

In October 1982, RAC approved a request by John Sanford of Cornell University Agricultural Experiment Station (Geneva, New York) (GTN, 11/82, p.1) to field test plants grown from seeds of plants produced with pollen modified by recombinant DNA. However, US Department of Agriculture's (USDA) Recombinant DNA Advisory Committee has only recently decided to approve the release of modified plants into the environment. In the meantime he has been continuing greenhouse experiments to see whether the technique of transforming pollen works. Field testing won't be needed for a couple of months.

RAC rejected a request by Nickolas Panopoulos and Steven Lindow of the University of California (Berkeley, CA) to construct and release genetically modified bacteria of type involved in ice nucleation, which causes frost damage. The California researchers proposed to apply the bacteria, from which genes responsible for ice nucleation had been deleted, to plants in a field test. Some RAC members objected on the grounds that the host range of the constructed organisms was not defined. Another questioned possible effects on rainfall in the area. Lindow tells GTN that he believes the objections have been met and he is optimistic of getting approval this time.

This time USDA will consider these requests in advance of the RAC meeting, according to Susan Tolin, who represents USDA in recombinant DNA affairs. She notes that USDA is well aware that recent successes in plant genetic engineering will probably release a flood of requests for field testing of genetically modified plants. Each case will have to be considered individually. (Source: Genetic Technology News, April 1983. Address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Gene transfer - for adults only

A Copenhagen schoolteacher and his students have transferred the genetic code from one bacteria to another in a classroom experiment. The expriment, carried out a few months ago, was reported this week and drew comments ranging from praise to warnings that such activities should be banned at school level. (Source: The Guardian, 6 June 1983.)

FRG drug authority approves beta interferon for herpes zoster treatment

Interferon has received its first approval for use as a human drug. This country's pharmaceutical licensing authority, the Bundesgesundheitsamt, has cleared a beta-interferon product for treating herpes zoster, a painful and sometimes life-threatening viral disease.

The company making this first claim is Bioferon, a small subsidiary of the Rentschler pharmaceutical company and established in 1974 to scale up human tissue culture. Bioferon's method for producing the product just approved, which is trademarked Fiblaferon, is based on conventional stacked-plate technology for growing human fibroblasts. These cells, when attacked by a virus, secrete beta (or fibroblast) interferon. To induce its cultured cells to overproduce interferon, Bioferon uses a synthetic oligonucleotide, poly I: poly C. A little actinomycin and cycloneximide added to the nutrient broth prevent the breakdown of messenger RNA, thus enhancing output.

This method yields 30 to 50 international units of interferon per milliliter of culture, says Dr. Hans Joachim Obert, director of clinical research at Bioferon. About 55 per cent is lost during purification, a figure that compares very favorably with most bacterial cloning processes. Obert grants that genetically engineered products have much higher specific activity, but tissue-culture systems, he notes, score in two major ways:

- The product is a "natural molecule" and glycosylated, unlike bacteria-made r-DNA proteins. This may be important to patients taking large doses of interferon over a long period of time.

- The anchored fibroblast cells secrete their beta interferon into the culture medium, where purification by established methods is a relatively easy matter. In bacterial producer cells, proteolytic enzymes break down interferon, so much of it is denatured before extraction..

The randomized "sequential analysis" clinical trials on which the regulatory agency's approval is based took place over the past two years at the University of Tübingen Hospital under Dr. Else Haedemann. Thirty patients with severe disseminated herpes zoster (also known as "shingles") and impaired immune resistance to infection, received drip infusions of 500,000 units per kg body weight per day, over three to five days, of Fiblaferon. All 30 patients who responded promptly showed identical results: the characteristic agonizing pain was reduced after 12 hours and completely relieved in two days; the painful red skin rash disappeared after nine days; and the drastic postherpeutic neuralgia that follows in 30 per cent of such patients - and may last for five to 10 years - did not occur. Six patients who did not respond promptly were considered "controls", but later received interferon as well.

Bioferon developed a semiautomated method for growing human diploid fibroblasts on piles of plates: it is elegant but expensive. Microcarrier technology was tried but proved 20 per cent costlier and so was abandoned.

Now the firm is getting ready to test new mammalian cell lines in its pilot plant developed by scientists of the government-sponsored Gesellschaft für Biotechnologische Forschung (GBF), who believe the cells could vastly improve the tissue-culture process's productivity. The most interesting involves inseting the structural gene for human beta interferon, along with a thymidine kinase promoter, into mouse cells that now produce interferon continuously without induction. These "constitutive" cell lines yield 100,000 units of glycosylated interferon per milliliter. (Extracted from: Newswatch, 18 April 1983).

r-DNA E. coli: how safe down the drain, under the skin?

Suppose a researcher accidentally flushes a large quantity of genetically engineered microorganisms down the drain. What are the changes of recombinant plasmids escaping their primary hosts and showing up in indeginous sewage organisms? "Nil" is the preliminary answer from microbiologist William D. Watkins of the U.S. Environmental Protection Agency and adjunct professor at the University of Rhode Island.

What if a researcher cuts himself? Is it liekly that recombinant bacteria will grow under his skin? "Maybe" says Dr. Youji Ikawa of Tokyo's Cancer Research Institute in a paper presented earlier this year at a meeting in that city on genetic engineering.

Watkins introduced Escherichia coli strain K-12, containing a marker recombinant-DNA plasmic, into a model sewage treatment plant. For weeks, he followed the survival of the organism and the frequency with which it passed the gene-spliced vector to other bacteria. Watkins chose K-12 for his safety study, because it was the E. coli strain approved for r-DNA experiments that most closely resembles the wild type. Next, he employed a unique set of temperature- and antibiotic-resistance markers that permitted him to pick out this strain - or its pBF328 plasmid - from all other bacteria in sewage.

In some laboratory experiments, Watkins added a mobilizing plasmid to increase the likelihood of vector transfer via conjugation. The result: fewer than one cell in 100,000 transferred its marker plasmid via conjugation to another E. coli strain, and fewer than one in 10 million lost a plasmic to Aeromonas bacteria.

"So far, we get nothing from the nonconjugative plasmid alone," says Watkins, "no transfer, no escape to other E. coli in the laboratory. Given these low frequencies", he adds, "a large number of cells would have to be released before there was any problem."

In monitoring the addition of non-mobilized E. coli into his model sewage system, Watkins has seen no detectable transfer of the r-DNA marker plasmid to such divers bacteri as Klebsiella, Pseudomonas, Aeromonas, Bifidobacterium, and Clostridium species, as well as E. coli, enterococci, and other coliforms normally present in sewage. He will add mobilized E. coli to the model plant in coming months.

But Watkins points out that "there is another way a plasmid can find its way into a bacterium - by transformation - whereby the cell takes up naked DNA and incorporates it into the genome." He released extracted purified plasmid DNA, including the marker sequences, into static batch cultures of E. coli and into the model plant. "We looked for any organism that expressed the plasmid resistance marker," he states. "We found none."

A subcutaneous threat?

Professor Ikawa, who heads the tumor virology division of the Cancer Research Institute in Tokyo, created a stir at the genetic engineering meeting when he reported the survival in vivo of r-DNA E. coli X1776. This is an auxotrophic strain designed to self-destruct outside the culture flask and is therefore considered safe at the P2 containment level.

He injected 20 to 50 billion of the bacterial cells subcutaneously into germ-free mice. They formed abscesses after two weeks; strain survival was 100,000 cells - a 100,000-fold reduction from the injection dose.

Ikawa inserted a spleen focus forming virus (SFFV) marker on plasmid pBR322 and preinjected the mice with Friend virus, a murine leukemia virus, which helps SFFV to replicate. The animals injected with the r-DNA E. coli did not produce SFFV infection. This showed that although the bacteria could survive in vivo, in this case, they could not transform the mouse cells. Control mice, which received the plasmid-containing bacteria without SFFV, also formed abscesses.

This experiment raises the issue that E. coli X1776 was not reduced a millionfold within 24 hours, as required by Japan's strict r-DNA guidelines. Normally, strain X1776 is killed by ultraviolet light or digestive acids and requires diaminopimelic acid or thymine to survive. These are components of the E. coli cell membrane and do not exist freely in nature. However, Ikawa warns, the danger of high-dose subcutaneous infection is that surviving bacteria can utilize these nutrients released from dead ones and, under the skin, are shielded from killing acid and light. (Source: Newswatch, 2 May 1983.)

$29.3 million for biomass R&D voted by House panel

For the fiscal year 1984, $29.3 million was authorized for the US Department of Energy's biomass research and development programmes by the House Committee on Science and Technology on 27 April. The money will be included in an authorization bill for Department of Energy R&D programmes that may be brought before the House.

The Reagan Administration budget provides only $17.3 million for biomass R&D in 1984. Last year the research was funded for about $21 million.

The breakdown on the committee's authorization is as follows:

- $9 million for feedstock development, including $4 million for short rotation woody crops, $3 million for herbaceous crops, and $2 million for aquatic plants;

- $15.3 million for conversion technology, with $9.1 million for biochemical and $6.2 for thermochemical;

- $5 million for a regional biomass programme to set up centres in the Northeast, Southeast, Midwest, Northwest, and Southwest.

The Administration's proposed breakdown is:

- $1 million for feedstock development;

- $16.3 million for conversion technology, with $12.1 for biochemical and $4.2 for thermochemical.

The Biomass Energy Research Association (BERA) recommended Congress to authorize $20.5 million, not including alcohol fuel R&D, for biomass R&D. BERA is a non-profit education and scientific organization made up of university, business, and utility representatives. (Extracted from Newswatch, 2 May 1983.)

New mutual funds signal healthy state of high technology stocks

Biotechnology stocks are, in the main, thriving, and further proof of healthy market interest in science and technology stocks was provided at the beginning of the month by the launching of twin mutual funds which intend to invest in science and technology companies around the world. The funds, Sci/Tech Holdings Inc. and Sci/Tech SA are notable for two reasons: the vast size of their operations and a novel plan to recruit leading scientists to an international scientific advisory council.

The funds started operating on 1 April with total net assets of $835 million, the biggest sum of money ever in an initial public offering for the mutual fund industry. Sci/Tech Holdings Inc. will be open to investors in the United States and Canada, Sci/Tech SA to investors elsewhere. Both funds will be managed jointly by Merrill Lynch in New York, Lombard Odier in London and Nomura Capital Management in Tokyo.

A nine-member scientific advisory council, headed by Dr. Harry Woolf, director of the Institute for Advanced Study in Princeton, will consult periodically with the investment managers and advise on trends in science. Members of the council include Bruce Hanay, former research vice president at the Bell Laboratories; Reimar Lust, president of Max Planck Gesellschaft; Frank Rauscher Jr, senior research vice president of the American Cancer Society; Heinrich Ursprung, president of the Swiss Federal Institute of Technology; Itaru Watanabe, professor emeritus at the faculty of medicine at Keio University; Chen Ning Yang, Nobel laureate and Albert Einstein professor of physics at the State University of New York, Stony Brook; Horton Stever, former director of the National Science Foundation and president of Carnegie Mellon University and Hideo Itokawa, president of the Systematic Engineering Research Institute.

Each member will receive $2,500 a year in fees plus a similar amount for each meeting they attend formally, with an upper limit of $7,500 a year. Dr. Woolf will be paid an additional $5,000. But these earnings will in fact be doubled since they are offered separately by each of the twin funds.

An initial statement by the funds' investement advisers include biotechnology and health care as areas with "superior" investment potential. Other areas included computers, communications, consumer electronics, electronic components and instruments, robotics and office and factory automation. (Source: Nature, 14 April 1983.)

Biogen's annual report

Among biotechnology companies, Biogen NV is the most like a bank. In its annual report for 1982, Biogen says that its financial assets amounted to $57.5 million, much more than its long-term debt of $5.8 million at the end of the year. Since then it has raised a further $54 million by its public sale of stock in March this year.

Part of the explanation of the company's cash position is that it has been able to finance the construction of its laboratory in Cambridge, Massachusetts, with the help of two low interest bonds arranged by the Massachusetts Industrial Finance Agency in 1981, which provided $4.5 million. During 1982, interest on the company's financial assets amounted to $8.5 million, two thirds of what it earned by means of payments for research and development carried out.

Paradoxically, Biogen's cash mountain may explain why the share price has drifted downwards from the issue price of $23 ten weeks ago. While a large proportion of Biogen's income is investment income, investors may think it preferable to put their money with an institution specialized in investment rather than in biotechnology.

Research and development remains the largest item of expenditure (amounting to $18.4 million in 1982) and spending under this heading will continue to increase for the foreseeable future. The pattern of Biogen's programme remains concentrated on the exploitation of microbially engineered interferons (which are being tested clinically for use in multiple sclerosis, genital herpes and various forms of cancer, not to mention the common cold), vaccines and blood factors. An agreement to produce interleukin-2 in conjunction with a Japanese company was announced earlier this year.

The spread of the company's research contracts remains somewhat narrow. In 1982, 44 per cent of research income came from the Schering Corporation and 37 per cent from the Japanese company Shionogi Ltd. The annual report emphasizes that research income is inherently unpredictable and that 75 per cent of its income in 1982 came from research projects already completed so that further income (from royalties) will not arise until clinical testing is complete.

Biogen's latest project, announced last week, is a partnership to develop a process for making human tumour necrosis factor in conjunction with Suntory Ltd, the Japanese whisky and pharmaceutical manufacturer. This project will be based on a new laboratory called BIOGENT, at Ghent in Belgium, under the direction of Professor Walter C. Fiers, professor of molecular biology at the University of Ghent and a member of the scientific board of Biogen. (Extracted from: Nature, 9 June 1983.)

Biodegradable polymer

ICI's biodegradable polymer, made via biotechnology, may be put into production by 1984. Polyhydroxybutyrate (PHB) is made from Alcaligenes eutrophus in a fermentation process giving properties similar to polypropylene and PET. PHB breaks down slowly into an innocuous effluent and may help rid sewage systems of indestructible mandrels from feminine hygiene products. Strips of PHB lose 60 per cent of volume in 60 days under sewage treatment conditions. (Source: Technology Update, 19 March 1983.)

Schering-Plough - catching a cold

Schering-Plough is one of the few drug companies to wager its future on biotechnology, and it may soon be down on its money. The American firm's first genetically engineered drug, interferon, is expected on the market by the end of 1984. Recent clinical trials suggest that the new drug may not be the money-spinner the company had hoped.

Schering-Plough decided to move into biotechnology three years ago, when most pharmaceutical firms were not prepared to take the risk. The company bought a 12 per cent stake in the Swiss firm Biogen (diluted to 10 per cent when Biogen went public in March) and got the right to three Biogen products. Two were for different types of interferon, the third for a drug against anaemia.

In 1982, Schering-Plough bought the California company DNAX for $30 million and opened its own research laboratory in France. Biotechnology now swallows almost a third of Schering-Plough's research and development spending. In February, the company announced plans to build a plant in Ireland to manufacture interferon for sale next year. (Extracted from The Economist, 9 April 1983.)

Seed companies will take plant genetic engineering to market

Breakthroughs in developing systems of genetic engineering of higher plants are coming through at a rapid rate. The seed companies are at the centre of the new plant biotechnology area, between laboratory research and commercial exploitation. Multinational companies have been quick to realize this. Many have begun research in plant genetic engineering or cell culture techniques, either in their own laboratories or through contract research and/or equity participation in new genetic technology firms. In addition many of them have acquired seed companies. Conventional plant breeding, which brought enormous yield increases during the past fifty years, has by no means reached its upper limit. Plant cell culture methods will be a tool to augment conventional plant breeding programmes, but conventional plant breeding may require ten to 15 years to develop and release a new seed variety. Typically it takes about eight years to develop and test the new variety. Then it takes three years to grow enough of the new variety to supply seed in sufficient quantity to enter the market. After that, it may require five more years to penetrate the market. Plant cell culture makes it possible to screen millions of single cells, which in some cases is the equivalent of screening whole plants. Cell culture screening will lower costs and shorten time needed for development and testing. Cell culture will also speed up multiplication of the new variety to produce large numbers of seed-bearing plants. Recombinant DNA will become a standard tool in the seed industry shortly after year 2000, and this technique opens up ways of improving plants not considered possible with the older plant technology. (Source: Genetic Technology News, June 1983. Address: 158 Linwood Plaza, P.O. Box 1304. Fort Lee, NJ 07024, USA.)

Genentech plots careful course towards a product line of its own

Like most genetic engineering companies Genentech (South San Francisco, CA) has made no secret of the fact that its long-term goal is to develop, manufacture and market its own products, but the company is hemmed in by some stringent limitations. Many promising product areas are off-limits because of earlier R&D contracts. Money is another limitation. Genentech's comfortable $101 million assets could be quickly eaten up by the huge costs of commercializing new recombinant DNA products. To get past these obstacles Genentech is relying initially on commercializing three recombinant pharmaceutical products:

- Human growth hormone (HGH) is expected to be the first product Genentech will market under its own label. Clinical trials in children suffering from hypopituitary dwarfism are well advanced. Genentech is submitting a New Drug Application for HGH to U.S. Food & Drug Administration this year. Funds for clinical testing and marketing are coming from Genentech Clinical Partners, a limited partnership, which raised $55.6 million to fund this work and similar work on gamma interferon.

- Human gamma-interferon is expected to go into clinical trials shortly for testing against cancer and later in the year against viral infections. In addition to the funding it will get from Genentech Clinical Partners this product will benefit from clinical testing by overseas companies to whom Genentech has granted licenses. Boehringer Ingelheim (West Germany) will test and market gamma-interferon in Europe and two Japanese companies, Daiichi Seiyaku and Toray Industries, both in Tokyo, will do the same in Japan and other far eastern markets. Genentech retains rights in the United States and Canada.

- Tissue plasminogen activator (TPA) for treating blood clots may be ready for clinical testing against heart attacks and cardiovascular diseases in 1985. Genentech is setting up another limited partnership to fund development of this product. Private placement should bring in about $32 million for this. Genentech has also licensed Kyowa Hakko and Mitsubishi, also both in Tokyo, to clinically test and market this product in Japan. (Source: Genetic Technology News, June 1983. Address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Southern Biotech in financial trouble

Employees of Southern Biotech got the bad news without much warning on 30 April. Instead of receiving paychecks for the month they had just worked, they were given a memo informing them that the Tampa-based company had run out of cash and could not meet its payroll. In less than a year, Southern Biotech has thus slipped from being potentially one of the largest contenders in the race to commercialize biotechnology, to the brink of bankruptcy. It is being sued by several creditors and former employees, it is in trouble with the IRS, several of its directors have resigned, and it is facing a mountain of bills with scant prospects of generating enough income to pay them off.

If Southern Biotech's financial ills prove to be terminal - which seems likely - the company's demise could signal the start of a long-expected shakeout in the fledgling biotechnology industry. Several other companies which, like Southern Biotech, have raised capital in the past few years on the basis of little more than grand promises, are facing cash-flow problems and finding investors much less willing to open up their chequebooks. Southern Biotech's troubles have some unique features, however.

A year ago, everything looked rosy for the young company. It had just started producing leukocyte (or alpha) interferon from white blood cells and its directors were predicting that the product would be a big money-spinner. William Stewart, a respected interferon specialist at the Sloan-Kettering Institute for Cancer Research, had agreed to join the company as research director. Shearson Loeb Rhoades (now Shearson American Express), one of Wall Street's best known underwriters, had agreed to take the company public with a stock offering of some $25 million. A team of young scientists was being recruited, and prospective investors were told about a broad array of technologies that the company hoped to develop.

Southern Biotech's fortunes soured very quickly. Its troubles began last summer when the stock market became increasingly skeptical of the promises touted by biotechnology companies, and Southern Biotech's stock offering raised far less cash than originally anticipated. This setback was compounded by a series of disastrous policy decisions, a large financial transaction, personnel problems, and regulatory tangles. The company was virtually out of cash and desperately looking for new investors by the end of last year; almost none of its principal product, interferon, has been sold; and its new research facilities have never been in full operation.

Southern Biotech is thus faced with mounting bills, it has a promissory note to Key Energy Enterprises for nearly $1 million due in August, most of its scientific staff has left, and it still has no market for its stockpile of interferon.

Its extraordinarily swift rise and fall says a lot about the financial climate surrounding biotechnology in the past few years. Its impending collapse is likely to make the climate more hostile, however. Other companies now seeking capital will not find their task made any easier by Southern Biotech's performance. Potential investors in biotechnology should now be looking for something more than overblown promises when they decide where to put their money. (Extracted from Science, 4 June 1983.)

73rd licensee signs up for Cohen-Boyer patent

Creative Molecules, Inc., of South San Francisco has become the 73rd entity to take out a license for Stanford University's Cohen-Boyer patent. The company produces a fully linked synthetic gene for human pancreatic growth hormone. Quality control of this 44-amino-acid chain involves technology covered by the patent. The synthetic peptide is extremely expensive, so pharmaceutical companies and university research groups alike are potential customers for the gene sequence. (Extracted from Newswatch, 18 April 1983.)

A biotechnology stock offering

Biotechnology General (New York City) plans to raise $20 million in a public offering of stock this summer. Proceeds from the offering will be used to double the size of the company's research facilities at Kiryat Weizmann (Rehovot, Israel) and to finance the development of a nitrogen-fixing fertilizer, animal growth hormones, and human health products. Biotechnology General and Pfizer Dekalb have agreed to joint development of the fertilizer product for the North American market. Preliminary results from studies conducted by the firms last year on Biotechnology Generals Azospirillum fertilizer were encouraging, and the companies are now continuing research at 25 U.S. sites. Biotechnology General is aiming at putting the fertilizer on the market by 1985. (Source: Chemical Week, 15 June 1983.)

Standard Oil patents probe potentially more selective than radioisotope tracers

A nonradioactive DNA probe that uses light-emitting molecules to tag its targeted nucleic acid sequence and is potentially as sensitive as radioactive tracers has been patented in Europe by Standard Oil Co. The probe does not require the DNA segment it is targeting to be immobilized and washing steps are not necessary to check for hybridization with its targeted DNA segment. Standard Oil hopes to develop a demonstration probe for laboratory use against a bacterial antibiotic resistance gene within a year.

There is a definite need in clinical diagnostics for a simple, rapid way to identify nucleotide sequences. Many so-called 'slow infection' diseases of humans and animals, where symptoms appear long after the infectious process is initiated, are caused by viruses or virus-like agents. These usually cannot be detected by immunodiagnostic techniques because no viral antigens are present. Hybridization assays can directly detect the viral genome.

Radioactive phosphorous is now the most common marker used to tag DNA probes, and sale of this isotope to researchers and medical labs approaches $100 million a year. Such probes require many steps to assay for target-tracer hybridization, and their use is complicated by a short half life and strong beta emissions.

In principle, this is how the non-radioactive probe works: the DNA strand complementary to the nucleic acid sequence being targeted is taken and cleaved in two with a restriction endonuclease. These two pieces of DNA - which can range from 10 to 100,000 nucleotides in length - are now the probe molecules, and at their cleavage site are attached to marker compounds. To one end of the break is coupled a chemiluminescent catalyst, such as peroxidase or luciferase, which facilitates light emission through a chemical reaction. To the other end of the break is attached a fluorescent molecule, such as a porphyrin or polynuclear aromatic, which absorbs light at one wavelength and gives it off at another. When the two DNA probe molecules hybridize to the target strand of nucleic acid, the chemiluminescent and fluorescent markers are side by side, within several angstroms of each other. If the chemiluminescent molecule is giving off light at a wavelength of 400 nanometers - blue light, then the fluorescent molecule will pick this up and convert it to 500 nm - green light. The test tube containing the targeted and probe DNA using a photomultiplier device is assayed and if a light at 500 nm is picked up, then hybridization has been achieved. If the only wavelength picked up is 400 nm, then there is no hybridization. It is a simple one-step assay without immobilization or washing steps, and could be more selective than any method presently available.

Enzo Biochem, Inc., of New York City last year marketed to researchers a nonradioactive DNA probe that uses a polyclonal antibody tagged with an enzymatic dye to assay for probe-target DNA hybridization but their targeted DNA strand must be immobilized for the probe to work. (Extracted from Newswatch, 18 April 1983.)

Diamond Shamrock, SIBIA form joint vaccine firm

A new joint venture to develop animal vaccines has been formed here by SIBIA - the Salk Institute Biotechnology/Industrial Associates - and Diamond Shamrock Ventures, Inc. The latter is a subsidiary of Dallas-based Diamond Shamrock Corp., a domestic oil and gas company with 1982 revenues of $3.2 billion.

Results of biotechnology advances made by the new firm, Animal Vaccine Research Corp. (AVR), will be channeled to Diamond Shamrock's Animal Health Division, which last year had sales of $70 million. But a spokesman for Diamond Shamrock confirms that his firm is studying the idea of selling off its animal medicine component. (Extracted from Newswatch, 18 April 1983.)

Damon joins parade of biofirms going public

Latest to join the parade of biobusinesses going public, Damon Biotech, Inc., of this Boston suburb will put 2.4 million shares of common stock on the market this month through an underwriting group headed by Blyth Eastman Paine Webber. The issue, 12 per cent of the firm's outstanding stock, is expected to return $12 to $14 per share.

Damon will be the fifth New England biotechnology firm to seek an infusion of public investment capital in as many months. In February, Biogen, Inc., of Cambridge, Mass., netted $52.7 million on a 2.5-million share offering, 13.5 per cent of its total common stock. Cambridge BioScience received $5.5 million from the sale of one million shares, 25 per cent of outstanding stock. BioTechnica International, Inc., of Cambridge sold 800,000 shares, 21 per cent of total stock, to raise $7 million. Genetics Institute, Boston, floated two bond issues totaling $9 million. (Extracted from Newswatch, 2 May 1983.)

Monoclonal antibody

Molecular Genetics of Minnetonka, Minn., has received approval from Agriculture Canada to sell its oral monoclonal antibody product in Canada. Genecol 99 is designed to prevent fatal diarrhoea in newborn calves. Molecular Genetics says its product is the first monoclonal antibody licensed for commercial use for disease prevention in animals. Genecol 99 will be distributed in Canada through Vetrepharm of London, Ontario. (Source: Chemical Week, 30 March 1983.)

Monoclonals carry therapeutic agents to body targets

So far, the main medical use for monoclonal antibodies is diagnosis, but their potential for actual disease treatment is considerable. One treatment approach chemically combines the antibody protein (immunoglobulin) - or a fragment - with a toxin, chemotherapeutic agent or a radioactive isotope. The monoclonal antibody protein portion of the conjugate will then combine specifically with the target protein - in a virus, microorganism or tumor - where the therapeutic portion can do its work. Several researchers reported progress in this area at the Second Annual Congress for Hybridoma Research held concurrently with the DNA Congress at Philadelphia, 6-9 February 1983.

- Ricin, a toxic polypeptide derived from the castor bean plant, has been attached to a monoclonal antibody protein that binds to cells involved in leukemia. Combination is being studied by Jonathan W. Uhr and his collaborators at Texas Southwestern Medical School (Dallas, TX). Ricin is composed of two polypeptide chains. One is toxic. The other effects entry of the toxic protein into cells. Uhr combines only the toxic chain with an antibody protein. Object is to eliminate harmful cells in bone marrow. Current work is with mice.

- Radioactive isotopes, such as iodine-131, have been attached to immunoglobulins. These are being investigated by M. Strand at Johns Hopkins University (Baltimore, MD). The immunoglobulins are specific to certain coat proteins of cancer cells.

- Ricin and also diphtheria toxin have been attached to a monoclonal antibody. These combinations have been tested by C.L. Villemez and co-workers at University of Wyoming (Laramie, WY). The target is not a cancer cell but a parasitic protozoan, Acanthamoeba castellanii. A fragment of diphtheria toxin combined with a fragment of immunoprotein specific for the cell membrane protein of the parasite prevents protein synthesis. (Source: Genetic Technology News, March 1983.)

Monoclonal antibodies are valuable tools to study vitamin B_6

Monoclonal antibodies that are specific for nonprotein materials can be made. A group at University of Vermont College of Medicine (Burlington, VT) is using monoclonal antibodies they have developed against vitamin B_6 to study some of the many functions of the vitamin in the body.

They followed the usual procedure of fusing spleen cells from immunized mice with myeloma cells to form hybridomas. Once a hybridoma producing a monoclonal antibody against the studied material is identified, it can be cultured to produce the monoclonal in quantity. The antigen used to immunize the mice in these experiments was a mixture of placental proteins to which a form of vitamin B_6 (the 5'-phosphopyridoxyl-group) was attached chemically. The most promising application is the detection of cellular proteins that bind with vitamin B_6 which are important in cell growth, differentiation and carcinogenesis. (Source: Genetic Technology News, April 1983. Address: 158 Linwood Plaza, P.O. Box 1307, Fort Lee, NJ 07024, USA.)

Quadromas

If you double a hybridoma, you get a "quadroma", a patent controversy, a commercial resurrection - and a potential therapeutic and diagnostic agent. In a European Patent Office application disclosed in January, Dr. Christopher L. Reading revealed his techniques for fusing three or four "parent" cells into a hybrid that makes what he calls "recombinant" monoclonal antibodies with twice the potential: they bind to two predetermined antigens. Reading, who is assistant professor of tumor biology at the University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute in Houston, said that these bifunctional antibodies will be the basis for a new anticancer drug delivery system and for novel biomedical assays.

Within the next three to four months, a Detroit entrepreneur, Eugene Schuster, will be trying to put Reading's research into practice by raising funds via a private placement and public offering to reinstate the now-defunct Quadroma, Inc., formerly of San Marcos, Calif.

By fusing one hybridoma that makes antibodies to a tumor with a second hybridoma, whose antibodies bind to a drug or radioactive marker, Reading's resulting quadromas produce a hybrid monoclonal antibody that carries the drug or tracer on the same molecule that binds to the target tumor cell. "Triomas", the fusing of a hybridoma and a lymphocyte, also produce these dual-binding-site monoclonals. So far the Texas oncologist has worked only with mice.

Hybritech, Inc., of San Diego has also produced a mouse monoclonal antibody with "dual specificity" - to both hepatitis B surface antigen and human prostatic acid phosphatase. For practical and scientific reasons, Reading favors working with quadromas, while Hybritech researcher Joanne Martinis and co-workers use a three-parent cell, a hybridoma fused to mouse-immunized spleen cell, for production of their dual antibodies. (Extracted f Newswatch, 4 April 1983.)

Monoclonal antibody column purifies urokinase

The prohibitive cost of urokinase is retarding scale-up of a purification process developed at Purification Engineering. The process isolates urokinase on a small scale from a variety of impure mixtures and should work with urokinase produced by genetically engineered microorganisms. However, testing a pilot operation to produce 200 grammes of urokinase would require millions of dollars worth of the enzyme. At the present level of development, the process uses a monoclonal antibody specific for urokinase coupled to 2 ml of supporting medium in a 10-ml column. The column absorbs urokinase from an impure commercial preparation, fresh urine, spent tissue culture media or an Escherichia coli broth (to which urokinase was added to simulate a mixture produced in a fermenter with a genetically engineered process). After impurities are washed out of the column, a dilute acid solution removes the urokinase that was attached to the monoclonal antibody in the column. Purity is high and yields range from 60 per cent to close to 100 per cent.

The monoclonal antibody is produced by one of over 40 hybridomas prepared at Purification Engineering. It recognizes a 20-22,000-molecular-weight polypeptide known as the light chain, which is part of the high-molecular-weight form of urokinase. Commercial preparations of urokinase generally contain two forms of the enzyme, one with a molecular weight of 50-55,000 and the other with a molecular weight of 30-33,000. Hybridoma cells were grown in mice - an expensive way to produce them.

Using the company's proprietary support system, the process could probably be scaled up to the 5-litre-column level. This size would produce 200 grammes of urokinase, enough to treat about 8,000 patients suffering from stroke. The columns should be reusable a hundred times or more, a key requirement because of the expense of producing monoclonal antibody. Purification Engineering has also developed a purification process for tissue plasminogen activator (see above). The company is offering the processes for license. (Source: Genetic Technology News, April 1983. Address: 158, Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Monoclonal purification of urokinase set for scale-up

With an immobilized monoclonal antibody, 60 per cent to 100 per cent of an enzyme - urokinase - that dissolves blood clots has been purified from commercial preparations and other sources. Dr. Gary J. Calton, president of Purification Engineering, Inc., in Columbia, Md., reported on his process at a session on scale-up and product development through biotechnology at the American Society for Microbiology meeting in New Orleans last April.

Urokinase has been approved by the Food and Drug Administration for treatment of thrombophlebitis, but is obtained commercially from human urine and tissue-cultured kidney cells where it is present at low concentrations - one to 50 nanograms a millilliter. Calton made a murine monoclonal against high-molecular-weight urokinase, the enzyme form he described as "more active" than its lower molecular-weight counterpart. He coupled the antibody to cyanogen-bromide-activated Sepharose 4B in a bench-scale chromatographic column and isolated urokinase without preliminary concentration steps from commercial preparations, urine, kidney-tissue culture medium, and Escherichia coli broth. When one commercial preparation, Sterling-Winthrop "Winkinase," was chromatographed, 98 per cent of the enzyme was retained after elution with acetic acid. (Extracted from Newswatch, 4 April 1983.)

Microencapsulation could make human monoclonal antibodies feasible

Damon Biotech is using its microencapsulation technique to cultivate human hybridomas so that they produce 30 to 100 times the concentration of monoclonal antibodies possible with conventional methods. This technique could overcome one big problem that has prevented wide use of human monoclonal antibodies. Most monoclonals today are from mice, which are easier to produce but are not always effective in humans and sometimes cause allergic reactions. In Damon's process hybridoma cells grow inside porous carbohydrate microcapsules in a liquid medium. Nutrients and waste products can pass through the microcapsule membrane. Cells and higher molecular weight products, such as monoclonal antibodies, remain inside the capsules. After a growth period, microcapsules can be separated from the growth medium, washed and broken up to yield a fluid with a high concentration of monoclonal antibodies.

The company is carrying out this work for George Eisenbarth of Joslin Diabetes Center, using a human hybridoma developed at Joslin and Wistar Institute (Philadelphia, PA). The hybridoma produces a monoclonal antibody against a factor in the blood of children suffering from a particular type of diabetes. Eisenbarth is investigating the possibility that the factor may be detected in children currently showing no symptoms of the disease, but who risk developing the disorder. Work is being done with test-tube-scale vessels which produce about a tenth of a gramme of monoclonal antibody. This is generally the amount of antibody needed for a therapeutic dose. (Source: Genetic Technology News, April 1983. Address: 158 Linwood Plaza, P.O. Box 1307, Fort Lee, NJ 07024, USA.)

Physical fusion of human cells

Gene transfer and the production of monoclonal antibodies will be made more efficient by a new process that physically fuses human cells. The patented process invented by Ulrich Zimmermann, a scientist with the Nuclear Research Center (Juelich, West Germany) uses electricity to fuse like cells into giant cells or unrelated cells called hybrids. It also encapsulates substances within cell walls more easily than current chemical or biological methods. In electrofusion, cells are exposed to a low-level, nonhomogeneous electric field that orients the cells into a pearl-necklace-like configuration. A short, direct-current pulse is then applied, which opens micropores in adjoining cell walls, allowing mixing of cellular contents and resulting in their fusion. This same process can also change the permeability of a cell's outer wall, allowing substances the size of genes to be encapsulated. Electrofusion is claimed to be up to 10,000 times more efficient than current methods, and depending on the cell type, up to 100 per cent of the cells can be fused. (Source: Chemical Week, 11 May 1983.)

Electrofusion equipment

Genentech and the City of Hope Medical Center (Los Angeles, California), have produced monoclonal antibodies via genetic engineering techniques. Monoclonal antibodies are synthetic versions of the antibodies produced in the body to fight off infections. Previously monoclonal antibodies were produced in vitro from animal cells, but Genentech researchers found a way to induce bacteria to produce the antibodies by employing gene splicing technology. The process could make large-scale production of the antibodies possible at low cost, since the bacteria could be fermented in massive volumes. The 2-step process involves removing antibody genes from mice and placing them in a common intestinal bacteria (probably E. coli). Fragments of antibodies are then removed and used to construct a functional monoclonal antibody in the laboratory. Scientists hope to eventually construct a monoclonal antibody in one step.

Genentech California/Precision Scientific Group has obtained a license from the Nuclear Research Center (FRG) to develop and market a new biotechnology product that physically fuses cells for high-efficiency gene transfer and monoclonal antibody production. Genentech California has the right to produce and market Electrofusion equipment in the US, Japan and Western Europe, excluding FRG. The FRG market will be served by Kruess. (Source: Technology Update, 21 May 1983.)

A new way to make human antibodies

A joint venture to make and market B-cell growth factor (BCGF), a derivative of human white blood cells that permits prolonged growth of human B-cells outside the body, has been undertaken by Biotech Research Laboratories (Rockville, Md.) and Cellular Products (Buffalo, N.Y.). B-cells produce antibodies that protect humans against infectious agents. BCGF enables laboratory production of human monoclonal antibodies directly from normal B-cells, a process that normally requires hybridoma technology, a cellular-fusion process yielding a less desirable product. (Source: Chemical Week, 25 May 1983.)

Agriculture, fishing & forestry - US possible markets lost to new biotechnology products ($ milllion)

	1983	1987	1992
New bioengineered products			
Seeds	2	20	436
Fertilizers	-	219	319
Crop protection chemicals	-	134	231
Total	2	373	986
Markets lost			
Fertilizers	-	145	360
Crop protection chemicals	-	67	231
Total	-	212	591

(Source: Technology Update, 14 May 1983.)

US biotechnology firms' financial data, 1982 ($ million)

	sales	% 82/81	earnings	% 82/81
Novo Industri	324.2	6	56.7	22
Tech America Group	37.4	23	0.1	.94
Genentech	28.8	90	0.6	108
Cetus	16.0	62	3.0	408
Collagen	7.4	275	0.7	-
Collaborative Research	6.5	90	-0.8	-
Hybritech	4.8	158	-7.3	-
Southern Biotech	1.5	54	-2.9	-
Molecular Genetics	1.1	146	-3.8	-
Cytox	1.1	-2	-1.4	-
Enzo Biochem	0.9	42	-1.3	-
Genetic Engineering	0.5	191	-1.1	-
Ribi Immunochem	0.3	78	-0.3	-
Monoclonal Antibodies	0.1	88	-1.1	-
Bio Response	-	-	-1.6	-

(Source: Technology Update, 14 May 1983.)

World: Biological chemical products output, 200 (\$ million)

Viral antigens	200
Enzymes	500
Peptide hormones	1260
Antibiotics	2000
Commodity chemical products	25000

(Source: Technology Update, 19 March 1983.)

Separations for bioprocesses

Separation and purification are among the most important determinants of the technical and economic success of bioprocesses.

To assist companies using and developing bioprocesses and those developing separation technologies, a group study is being proposed by Battelle-Columbus and Battelle-Geneva.

During the study - which is still open for membership - researchers will address the unique separation needs of processes using microbial, mammalian, and plant-cell culture. Researchers also will identify features of available and developing separation technologies that make them appropriate for specific bioprocess applications. For further information please write to: Battelle Memorial Institute, Office of Corporate Communications, Attention Harry R. Templeton, 505, King Avenue, Columbus, OH 43201, USA. (Source: Battelle Today, April 1983.)

RECENT DEVELOPMENTS

Probing the role of DNA repair in cancer

The DNA repair capabilities of members of cancer-prone families will be studied by Brookhaven National Laboratory (Upton, N.Y.) in a project sponsored by the National Cancer Institute and the U.S. Energy Department. In earlier studies, Brookhaven scientists discovered a "big variation" among apparently normal individuals in their ability to remove O^6-methylguanine from their blood cells. O^6-methylguanine is an alteration in DNA, and could be responsible for the carcinogenic activity of alkylating agents such as nitrosamines. The new project will try to determine how DNA repair is distributed among apparently normal individuals, and if differences in repair abilities reflect any enhanced susceptibility to disease. (Source: Chemical Week, 13 April 1983.)

Cetus-Shell venture launches clinical trials of 2-cysteine interferon

Using site-specific mutagenesis techniques, scientists at Cetus Corporation of Emeryville, Calif., have produced beta interferon in Escherichia coli with greater stability and about 10 times the specific activity than their earlier clones had shown. The feat was reported in April to the International Congress on the Biology of Interferon, Rotterdam, by David Mark, manager of Cetus' lymphokines programme. Based on encouraging results from preliminary testing of their new genetically engineered interferon, the company applied to the U.S. Food and Drug Administration in mid-April for Investigational New Drug (IND) permission to test the product clinically. Prior animal and in vitro testing of the modified interferon indicates that it is very similar to the native molecule in its antiviral and immunological activity. It also appears to be nontoxic to animals.

Phase I trials for safety and dosage levels will be carried out by Drs. Ernest Borden at the Wisconsin Clinical Cancer Center in Madison and Thomas Merigan, a Cetus consultant at Stanford University School of Medicine. Then, after more dose-response tests, Phase II studies will measure the interferon's efficacy in treating a variety of conditions. They should start early in 1984, barring unexpected delays, and will take place at university hospitals around the U.S. Target diseases, will most likely include viral infections such as hepatitis, herpes, and influenza and a broad spectrum of cancers, notably of the breast, colon, and prostate. (Extracted from Newswatch, 6 June 1983.)

Gambling on Interferon

The interferon boom erupted 4 years ago when the American Cancer Society (ACS) announced at a press conference in New York that it was making available $2 million to buy interferon for use in clinical trials with cancer patients. At that time, one of the major barriers to research was the sheer scarcity of interferon. Extracting it from human blood was costly and time-consuming. There was only one major supplier: the inventor of the extraction technique, Kari Cantell of Finland. A single course of therapy using his interferon cost around $15,000.

With the advent of gene splicing, in which segments of human DNA are inserted into Escherichia coli bacteria and made to produce interferon, the price has dropped by a factor of 10 to 100, according to a pioneer user of the substance, Thomas Merigan of Stanford. At the same time, the purity of injectable solutions has increased from around 1 to 99 per cent.

These dramatic achievements have been a cause of distress as well as joy in the interferon business. Companies unable to keep up with the frenetic pace of innovation are having trouble.

Interferon, a protein molecule, was recognized in 1957 as a substance that helps the body's natural defenses attack tumors and viruses. Interest in it revived in the late 1960's after Cantell found a way to extract if from human blood. A few experimenters reported good results using this extract in treating cancer. Researchers also hoped to combat viral diseases such as herpes, hepatitis, and perhaps even the common flu with interferon. But antiviral testing has been carried out on a smaller scale than the cancer trials.

Jordan Gutterman of the University of Texas' M.D. Anderson Hospital asked the ACS in 1978 to buy the new Cantell interferon for his cancer patients. The ACS agreed and recruited several other clinics, including Merigan's, to carry out the first major trials. This triggered an explosion of media coverage, with Time magazine, for example, suggesting in a flashy cover story that interferon might be a cure for cancer. Speculation like this generated more than media hype: many investors and researchers leaped into the interferon gamble.

When the importance of interferon was first understood, little was known about its origin or about the mechanism by which it works. Although much remains obscure today, more is known about the sources and types of interferon found in the human body.

There are essentially three types: alpha, beta, and gamma (or immune) interferon. Alpha is produced by white blood cells (leukocytes) in a defensive reflex when they are exposed to a virus. Researchers have identified at least a dozen different genetic variations of alpha, all of which are found in the "soup" of natural interferon in the body. The beta type is produced by the cells of the connective tissues (fibroblasts) in response to a virus. It is more difficult to grow and purify than alpha, and it comes in two genetic varieties. Gamma is produced when cells of the lymph system (T cells) are exposed to virus antibodies. Only one variety of gamma has been found.

The Cantell process, the only one available until recently, and the one used by Southern Biotech, produced alpha interferon exclusively. In addition to being low in purity, Cantell's extract contained all 12 genetic varieties, making it impossible for researchers to determine just which one was producing the effects.

The gene splicers have changed all this. By programming bacteria to make the precise genetic type of interferon desired, they have been able to get large quantities of nearly 100 percent pure alpha, beta, and - last October - gamma interferon. There is a slight difference between a bacterial and a natural interferon, in that the former lacks the carbohydrate fraction found in the latter. However, research completed this year at the National Cancer Institute shows that the gene-spliced alphas have essentially the same effects and potency as the natural alphas. (The bacterial versions used in these trials were produced by the first American biotechnology company, Genentech, in partnership with its large co-venturer, Hoffmann-La Roche Inc.)

Merigan, Gutterman, and Robert Oldham, coordinator of federally sponsored trials at the National Cancer Institute, say that the basic work with Cantell material is now complete. The research that began with the ACS press conference in 1978 has now shown that Cantell's soup had a noticeable effect on tumors in some patients with advanced cancer. Because the same effect has been obtained with gene-spliced interferon, there is little interest in using Cantell's extract any longer.

What are the business prospects of a company like Southern Biotech whose only product, perhaps its only asset, is Cantell interferon? They cannot be bright, unless the interferon can be unloaded on a specialized market outside the mainstream of research.

In the United States, it is not legal to charge patients for any interferon shipped across state lines because the Food and Drug Administration (FDA) considers it an unproven, experimental biologic. The only legitimate sales are between laboratories, with the clinical researcher usually spending grant money to buy the interferon and giving it free of charge to patients. Southern Biotech, to its detriment, has not been able to persuade the FDA that its alpha interferon is fit for human use - even on an experimental basis - in U.S. cancer clinics. Thus, Southern Biotech appears to have sought other markets.

According to the FDA, the government of Jamaica last year requested a formal exemption to allow Southern Biotech to bypass the FDA's approval process for exports of drugs and biologics. The FDA has the request under review and has asked for more supporting data. It has not granted permission.

Southern Biotech opened offices on the Grand Cayman Island and formed a partnership with a company in Jamaica in order to sell interferon on the international market. Neither Southern Biotech nor its Jamaican partner, Federated Pharmaceuticals, would respond to questions about a report that interferon has been shipped from Florida to Jamaica without FDA approval.

However, Southern Biotech's attorney, Marc Bozeman of Bozeman and Geller of Los Angeles, did say that he thought shipments of this sort would be legal, contrary to what the FDA asserts. In his view, a company could escape FDA jurisdiction simply by labeling its interferon an "unprocessed biological product". He said he considered this a defensible policy in spite of the fact that the FDA requires a license to export human blood cells.

According to Genetic Engineering News, there are about 30 interferon companies in the United States. Nearly all are aiming to produce a variety of interferons, both by natural and synthetic means. Southern Biotech mentioned in its prospectus last August that it intended to produce all three types of interferon. The company noted that it had already "contracted to supply a major United States cancer research center" with about $500,000 worth of gamma interferon beginning September 1981, a month after the stock sale. This agreement was made with Gutterman's clinic at the M.D. Anderson Hospital.

However, in September the company fired its chief scientist, William Stewart, and failed to get its gamma production line going. Gutterman says the agreement had been "based on Dr. Stewart's past reputation as a scientist". When Stewart left, "the contract was simply terminated". Gutterman's clinic, which began the first FDA-approved trial of gamma interferon on 9 February, found a new supplier: Meloy Laboratories of Springfield, Virginia, a co-venturer with a much larger company, Revlon Industries.

The pattern of the small, specialized laboratory combining with the large marketer may now be firmly established in the genetic engineering business. This kind of partnership may become more important as the interest in gene splicing grows. Companies with large financial resources will be better able to keep up with the pace of innovation and the demands of this volatile market. Although researchers like Gutterman and Merigan say that much work with natural interferons remains to be done, it is clear that the important competition in the future will be over the gene-splicing methods of production.

At the annual meeting of the American Society of Clinical Oncology in St. Louis in April, the National Cancer Institute released a list of current interferon trials. The only ones using natural substances employ the relatively untested beta and gamma types. Advanced tests (phase II trials) using alpha interferon will rely on the products of gene splicing.

As the trials progress, the FDA will require that the interferons meet higher standards of purity. This will favour manufacturers who have mastered the techniques of gene splicing. So will the growing competition to cut costs. (Source: Article by Eliot Marshall in Science, 4 June 1982.)

Interferon blocks virus entry

American scientists have uncovered a previously unrecognised aspect of the anti-viral effect of interferon, to be added to the already wide range of mechanisms by which it fights viral infections. Researchers at Pittsburgh University have shown that interferon can prevent viruses from getting inside animal cells, and they believe that this might be the first line of defence set up by the interferon system in response to viral attack.

Intensive research has identified several ways in which interferon-treated cells can interfere with the viral life-cycle, particularly by preventing the genetic information stored in the viral genes from being converted into viral proteins. Until now it has been thought that interferon can do little to prevent the initial entry of viruses into a cell.

The Pittsburgh group incorporated a radioactive "label" into the coat proteins of vesicular stomatitis virus (a virus that causes a mild disease in livestock and is much used in interferon research). By adding the virus to cultured animal cells (mouse, chicken and human) they were able to determine the extent of virus entry by later purifying the cells and measuring their radioactivity. Prior to this measurement they used an enzyme to remove viruses that were bound to the outside of the cells. This allowed them to distinguish between the two separate processes of adsorption of viruses onto cells, and actual entry into the cells. In cells that had been treated with interferon the entry of the virus was strongly inhibited, although in agreement with previous findings, the adsorption of viruses onto the cells was unaffected. A clue to the possible mechanism of this effect of interferon is the observation that interferon treatment also inhibits a cellular activity known as endocytosis. Endocytosis is a process by which external material is taken into cells. Dose-responses of inhibition by interferon of viral entry and endocytosis are similar, suggesting that the effect of endocytosis is inhibited. (Source: New Scientist, 5 May 1983.)

Carcinogens awaken sleeping genes

Cancer cells are almost by definition cells that have escaped from the controls that govern the behaviour of the individual cells in a multicellular organism. Recent research has dramatically shown that one way for them to make the break is through the activation of cellular oncogenes - genes that are more or less inactive in normal cells but seem to be altered or activated in tumour cells. Two Americans, Vincent Wilson and Peter Jones at the University of Southern California, have evidence that one of the actions of cancer-causing chemicals may be to jam the mechanism that normally keeps these genes - as well as other cellular genes - under control.

The mechanism they were looking at is a chemical modification of the DNA known as methylation. Methylation is now generally recognised as one way of switching genes off, and is a particularly interesting one because it helps to explain a crucial but mystifying fact of multicellular life - the differentiation of the genetically identical cells of an embryo into the many different tissues of the mature organism. To achieve that, different sets of genes must be shut off in different cells, and shut off heritably - so that, for example, a dividing liver cell produces another liver cell and a dividing skin cell another skin cell, despite having all the genes at its disposal to produce any kind of cell it fancies.

The great appeal of methylation as a means of shutting genes off is that it has a known mechanism for perpetuating itself during cell division and thus ensuring its own inheritance. That mechanism is an enzyme known as a maintenance methylase, and it is the activities of the methylase that chemical carcinogens disrupt.

Wilson and Jones, in their investigations of this effect, did not test the carcinogens on cells, but on DNA extracted from cells and treated so as to make it mimic the methylated DNA of a dividing cell. When DNA replicates itself before cell division, the old strand remains methylated but the freshly replicated strand is unmethylated. The maintenance methylase detects the discrepancy and methylates the new strand in just those positions where the old one is methylated.

Wilson and Jones used preparations of half-methylated DNA to test the effects of a battery of carcinogens on the ability of the maintenance methylase to methylate the unmethylated strand. They found that many of the chemicals substantially reduced the amount of methylation that took place - either by altering the DNA so that the enzyme no longer recognised it, or by inhibiting the enzyme itself in its action.

The actions of carcinogens on methylase activity in a test-tube may not reflect what happens in tissues exposed to those chemicals, but it has recently been shown quite independently by Andrew Feinberg and Bert Vogelstein at Johns Hopkins University that the DNA of tumour cells is much less methylated than that of normal cells from the same tissue, all of which lends circumstantial weight to the idea that oncogenes may be activated by stripping them of their methyl groups - and also explains the common observation that tumour cells may sometimes express inappropriately characteristics of other tissue cells. (Source: New Scientist, 17 March 1983.)

Possible new anti-cancer drug

A platinum compound may become a powerful new anticancer drug, cis-diamminedichloroplatinum (DDP), which acts at the site where cancer begins - the DNA. Cis-DDP chemically bonds to guanine bases in DNA to disrupt the replication of DNA in actively dividing cells. It is a square planar complex. The platinum binds to the nitrogen atom in guanine's smaller ring. When two guanine bases are side by side in the DNA chain, both can attach to the same platinum atom, forming a stable complex. When the drug was reacted with a self-complementary two-stranded, six-base DNA chain, the hydrogen bonding which holds the two strands together cannot compete with the bonding of the platinum complex to adjacent guanine groups. This disruption of the hydrogen bonds which normally hold the two strands of the DNA molecule together could block the replication of DNA chains during normal cell division. (Source: Technology Update, 19 March 1983.)

Gene for interleukin-2 isolated

Ajinomoto and The Cancer Institute of Tokyo have isolated the gene for interleukin-2, a growth factor for human T cell lymphocytes. T cells play an important role in the body's immune system. The gene has been made to function in nonhuman cells in vitro. The interleukin gene has been cloned and the peptide products are being made in sufficient quantities, enabling researchers to grow T cells in vitro to study their properties. (Source: Technology Update, 26 February 1983.)

Gene-splicing brings hope of malaria vaccine

Collaboration between scientists in Australia and Papua New Guinea has resulted in a crucial breakthrough in the search for a vaccine against malaria. It could open the way to controlling many other parasitic diseases in the tropics.

Scientists from the Walter and Eliza Hall Institute of Medical Research in Melbourne and the Papua New Guinea Institute of Medical Research, at Goroka and Mandang, have developed a new technique which allows them to isolate human malaria antigens - the proteins that identify the parasite responsible for the disease and provoke the immune system to produce antibodies against the parasite.

Several groups around the world are working on a malaria vaccine, but only one other has reported the isolation of antigens - and that was for the form of the disease affecting monkeys. The antipodeans devised a new application of recombinant-DNA technology in order to isolate all antigens in the blood stage of the malaria parasite, Plasmodium falciparum. This parasite is transmitted by mosquito bite and causes the potentially deadly falciparum variety of malaria. In this, red blood cells are invaded and destroyed, producing symptoms of severe chills, fever, sweating, anaemia and spleen enlargement. It may develop into respiratory failure, coma and death.

The new technique, published in the Proceedings of the US National Academy of Science, involves inserting fragments of DNA from P. falciparum parasites into E. coli bacteria. Culturing the bacteria resulted in a library of protein antigens, many of which have been tested against blood sera from people living in malaria-prone areas of Papua New Guinea.

The researchers believe the key to development of an effective vaccine lies with those sera which inhibit growth of the P. falciparum organisms and which come from people who are apparently resistant to malaria. The Hall Institute's head of immunoparasitology, Dr. Graham Mitchell, explains that these sera enable scientists to identify the specific bacteria that are producing the antigens capable of stimulating useful immune responses and thus protection against malaria.

During the next six months, the most promising of the 100,000 bacterial clones that have been produced will be grown in large vats by the Melbourne arm of the team. The resulting antigens will be tested by the World Health Organisation in monkeys (the only animal model of the human infection that is available).

Dr. Mitchell says this should indicate whether malaria vaccines that would work around the world will need to contain "a cocktail of antigens". Dr. Mitchell adds: "The malaria parasite is particularly devious, with many trump cards to play in the fight against efforts to control it. And so it may be that the composition of the malaria vaccine will have to be altered every few years to cope with the subtle changes of the parasite."

While a vaccine will help control malaria and reduce its toll of death and illness among children in particular, Dr. Mitchell doubts that malaria will ever be eradicated.

The implications of the latest advance go beyond malaria control. "Similar approaches to the identification of relevant antigens should be possible with other parasite systems such as schistosomiasis and trypanosomiasis which afflict hundreds of millions of people in tropical areas", says Dr. Mitchell. "Until now, the single most important impediment to the development of parasite vaccines has been the scarcity of parasite protein antigens available for testing." (Source: New Scientist, 16 June 1983.)

Genentech bows out of malaria vaccine project as NYU inventors seek new scale-up partner

Until last month, Genentech, Inc., of San Francisco was New York University's chosen partner in the malarial vaccine project. Genentech, which had no formal contract with the university, expected to obtain an exclusive license to commercialize the vaccine, developed by NYU parasitologists Ruth and Victor Nussenzweig. They applied for patents on 12 February 1981, along with Nigel Godson who chairs the biochemistry department at NYU. However, the World Health Organization (WHO) and the U.S. Agency for International Development (AID) both fund the research, and each of these agencies insists on its rights to grant nonexclusive licenses to the fruits of its funding. WHO pays for research to benefit the third world and fears that big pharmaceutical firms with the capital and technical resources to supply the vaccines to a quarter billion Third-World people might not find the operation profitable, and so would sit on an exclusive worldwide license. Last November, NYU, WHO, AID, and Genentech consulted on how to square their conflicting interests.

Genentech formally withdrew last month after reviewing the products on their drawing board and the financial implications. (Source: Newswatch, 18 April 1983.)

Human-human hybridoma in Damon microcapsule breaks yield barrier

A human-human hybridoma grown in a microcapsule is to be targeted against an antigen associated with the onset of diabetes mellitus. The encapsulated monoclonal antibody will be a component of a radio-immunoassay to identify people at high risk of becoming diabetic, says endocrinologist George S. Eisenbarth of the Joslin Diabetes Center at Boston.

Eisenbarth developed the all-human fused cell jointly with Dr. Carlo Croce of the Wistar Institute in Philadelphia. His latest move, culturing the hybridoma in a gel microsphere, aims at producing enough of the antibody so that it can be used clinically rather than as a laboratory curiosity.

Specifically, says Dr. Nigel Webb, general manager of Damon Biotech, Inc., in Needham Heights, Mass., that company's patented "Encapsel" system yields 30 mg to 100 mg of antibody per milliliter of medium, compared with only one or two mg/ml obtained by conventional tissue or ascites culture. In this process, the Croce-Eisenbarth human-human hybridoma, suspended in a solution based on alginate, is pumped through a microjet orifice to form spherical droplets that solidify in a chemical bath into gel microspheres up to half a millimeter in diameter. These, containing the monoclonal-producing cells in suspension, are then coated with a tough, porous, protein polymer membrane. A chelating agent flushes the spheres clean of all their contents except the larger-than-pore-size monoclonal antibodies. (Extracted from Newswatch, 4 April 1983.)

Human growth hormone and somatomammotropin vectors patented

A patent on vectors containing codons for human growth hormone (HGH) and human chorionic somatomammotropin (HCS) has finally been issued by the U.S. Patent Office. The technique used starts with extraction of messenger RNA (mRNA) from cells likely to be synthesizing the peptides sought. Benign tumors of the pituitary gland were the source of mRNA for HGH. Cells from human placentas were used as a source of mRNA for HCS. HCS plays a part in development of the foetus. In both cases, many different mRNAs are present - one for each protein being synthesized by the cell at that particular moment. However, the quantity of the desired mRNA is high because of the specialized function of the cells. The mixture of mRNAs is treated with reverse transcriptase, an enzyme that makes DNA corresponding to the RNA template. The resulting mixture of DNAs is treated with restriction enzymes which have been selected to cut DNA coding for all or part of the wanted protein at two specific sites. This results in fragments of DNA containing all or part of the wanted gene. If the amino acid sequence of the protein coded for by the gene is known, the exact length of these fragments can be predetermined. A band of these fragments shows up on an electrophoresis gel on which fragments of DNA are classified according to their lengths. The wanted fragments can be identified and isolated. Fragments may be several hundred nucleotides long. In some cases they will include the entire gene for the protein. (Source: Genetic Technology News, April 1983. Address: 158 Linwood Plaza, P.O. Box 1307, Fort Lee, NJ 07024, USA.)

Embryo genes take one day to switch on

The idea that fertilisation marks the stage at which the "baby's" genes become active and express characteristics of a new individual may no longer be tenable, according to a research group led by Martin Johnson in the Department of Anatomy at Cambridge University. Johnson and his colleagues have shown that in the mouse embryo at least, genes are not "switched on" until about 20-24 hours after fertilisation, by which time the embryo has already developed to the two-cell stage.

The events leading to the formation of a two-cell embryo appear to be very simple; about 5-10 hours after fertilisation in the mouse, the two nuclei containing genetic material from the sperm and the egg join together, and the first cleavage division takes place 10-15 hours later. However, the apparent simplicity of these morphological events conceals an underlying molecular activity of extraordinary complexity, as described by Hester Pratt at a recent conference of the Ciba Foundation (Ciba Symposium, vol 98, in press). This activity includes both DNA replication (when genetic material is duplicated prior to cell division for distribution to the daughter cells) and the synthesis of many proteins. Although the pattern of synthesis of the majority of these proteins stays the same until the mid-two-cell stage, there are some complex changes, which include the activation of new protein synthesis as well as post-synthetic modifications of proteins.

Two particularly interesting observations regarding these changes have been made by the Cambridge group. First, many of the changes in patterns of protein synthesis which occur after fertilisation also take place in ageing unfertilised eggs, indicating that fertilisation is not the trigger which activates these changes. Second, embryos undergo all the normal morphological and molecular changes through division to the two-cell stage apparently independently of active expression of the embryo's genes. Thus, in the presence of a drug which blocks gene expression, it has been shown that embryos not only undergo the first cleavage division, but they also replicate their DNA, and undergo all the normal changes in patterns of protein synthesis. In fact, not until about nine hours after division to two-cells is there any major activity of embryonic genes, which means that development up to this time needs no contribution from the paternal genome.

From these results, Johnson's group concludes that all the events which take place during the first 24 hours or so of development do so entirely under the influence of components that are already present in the cytoplasm of the egg. Furthermore, while fertilisation certainly activates elements of these cytoplasmic components (for example those governing cell division) many of them are activated irrespective of whether fertilisation takes place or not. Clearly then, fertilisation represents neither the trigger for activation of all the events which take place during the first 24 hours of development of an embryo, nor the time at which the embryo's genes start to be expressed.

This work has particular significance for the ethical debates concerning in vitro fertilisation, the use of human eggs for experimentation, and the use of certain contraceptives such as the "morning after Pill". To date, such debates have centred around the question "when does life begin?" If the mouse embryo proves to be analogous to the human, then perhaps we are a step closer to answering that question, because the equivalent time at which the genes of a human embryo are expressed would be 35-48 hours after fertilisation. (Source: New Scientist, 26 May 1983.)

Gene probes may spot genes missing from embryos

Anyone who has been following the AIDS story (and it has been pretty difficult to avoid) will know that haemophiliacs suffer from an inherited deficiency in blood clotting that can be corrected by extracts from other people's blood. Yet this replacement therapy does not always work: in rare cases, the haemophiliac produces antibodies against the blood-clotting factor he needs, and is forced to resort to less satisfactory forms of treatment. The reason for this rare complication, according to some recent research in Oxford, is almost certainly that the patients in question completely lack the gene for the clotting factor. Since their immune systems have thus never seen it, they identify it as non-self and proceed to attack it.

This conclusion was based on an analysis of six patients with a form of haemophilia known as Christmas disease, or haemophilia B. Christmas disease is actually a very uncommon form of haemophilia, due to a deficiency in clotting factor IX: the more usual form is haemophilia A, which is due to deficiency factor VIII. The reason for choosing the rarer form to study was simple expedience: nobody has yet cloned the gene encoding factor VIII, but George Brownlee and his colleagues at the Dunn School of Pathology in Oxford have very recently succeeded in cloning the gene for factor IX.

The Oxford scientists used a series of radiolabelled DNA probes corresponding to different parts of the factor IX gene to search the chromosomes of the six patients in the UK known to have antibodies to factor IX, to see if any part of the gene was missing. Four of the six proved indeed to have gross deletions in the gene, and in two of those the Oxford researchres could find no factor IX DNA at all.

What about the other two? Their genes may contain mutations that distort their factor IX so much that it is not only useless but unrecognisable to the immune system as the same molecule as normal factor IX.

This research will probably not help patients with antibodies. But it may help potential parents of haemophiliacs with the difficult decision they have to face about having children. It is already possible to diagnose haemophilia before birth, but not until quite late in pregnancy when abortion is relatively traumatic and dangerous. Diagnosis with DNA probes is possible much earlier and much more safe, because doctors do not have to wait until the embryo is producing enough clotting factor to be reliably tested; and there is no need to remove blood from the embryo. All his cells will have the same defective gene and they can be sampled harmlessly from the amniotic fluid. In these circumstances, parents at risk of producing a child with the more severe forms of haemophilia, particularly if they are likely to be antibody-producers, might well prefer the option of an early abortion.

Eventually, of course, the cloning of clotting factor genes is aimed at the possibility of getting genetically engineered bacteria to produce the factors instead of blood donors. And although it seems likely that the danger of AIDS has been grotesquely exaggerated, it could well be that, given the choice, many haematologists would sooner give their patients clotting factors from a nice clean bacterium. (Source: New Scientist, 16 June 1983.)

Detection and diagnosis

A method to detect sickle cell anemia, and possibly other genetic diseases, is being developed at the City of Hope National Medical Center & Research Institutes. According to researchers, the new diagnostic technique examines defective strands of DNA rather than substances produced by defective DNA. One advantage is that diagnosis does not required knowledge of the patient's family history or medical background to determine genetic disorders. The precise sequence of DNA's chemical building blocks in the genes can be detected with specialized probes for a few diseases. With an explosion in the number of genes to be sequenced in the near future, diagnoses by this technique should increase correspondingly. (Source: Technology Update, 21 May 1983.)

Smallpox/hepatitits B combination vaccine could be made cheaply

At National Institutes of Health (NIH) research is being done on vaccina virus recombinants. The first target for applying vaccina virus recombinants is a hepatitis B vaccine that could be made cheaply and administered easily to children in the third world, where 200 million people are chronically infected with hepatitis, but the technique might also be used to develop vaccines against other deseases, and perhaps even a vaccine against several diseases. The idea behind vaccina virus recombinants is to take advantage of the low cost of producing vaccina virus, which was used to vaccinate against smallpox, and the fact that it is stable and easily administered by people with no medical training. These properties of smallpox vaccine made it possible recently for the World Health Organization to completely eradicate smallpox worldwide, with a vaccine that has been around for nearly 200 years.

Vaccina virus causes cowpox. It is similar to small pox but when scratched onto the skin of humans it causes only a small localized infection, which produces antibodies that protect against smallpox.

The NIH team combined live vaccina virus with a gene for a hepatitis B virus protein that acts as an antigen (induces immunity against hepatitis B when injected into humans). They first combined the hepatitis antigen gene with a portion of vaccina DNA in a plasmid. Then they infected cells with both plasmids and whole vaccina virus. In some cases plasmid and virus recombined within the cell to form a hybrid virus. Identified, isolated and injected into rabbits, the hybrid virus produced the characteristic local reaction to vaccina and also stimulated production of antibody against hepatitis B. More animal work is needed before human testing starts.

Vaccina virus recombinants have some drawbacks. They would probably not be effective in people already immune to smallpox, which nearly all adults are. This limits use to children. Also, if a new recombinant for protection against a different disease is developed it would not be effective in people already immunized by vaccina/hepatitis B recombinant. Nor is vaccination 100 per cent safe. It sometimes causes encephalitis. (Source: Genetic Technology News, June 1983. Address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Toxic shock syndrome

Toxic shock syndrome (TSS) may be caused by a virus which implants its genetic material into the bacterium Staphylococcus aureus, rather than by the bacterium's own toxins. TSS is characterized by rashes, vomiting, diarrhea and fever. Researchers at Rockefeller University collected 12 strains of S. aureus from TSS victims and 18 strains from other persons. A virus was found in 11 of the 12 TSS strains but in only one of the 18 non-TSS strains. The virus was then induced to transmit its genetic material to a previously harmless strain. Tests will now be made to see if the infected bacterium can cause TSS symptoms in laboratory animals. Other diseases caused by a viral infection of a bacterium include scarlet fever, which has symptoms similar to toxic shock, and diphtheria. (Source: Technology Update, 30 April 983.)

Reading problems linked to gene

Genetic analysis of nine different families strongly suggests that there is a gene associated with an inability to read. The gene is apparently located on chromosome 15. (Science, vol 219, p. 1345).

A team led by Shelley Smith, of the Boys Town Institute for Communicative Disorders in Omaha, Nebraska, investigated people who had specific reading disability. This is a bit of a rag-bag of disorders, but can be characterised as severe reading and spelling problems with no evidence of any problems of a neurological, intellectual, emotional or environmental nature. In other words, a person cannot read or spell well, but for no obvious reason.

Specific reading disability often runs in families, so there may be a genetic component to it. Smith's study was something of a fishing expedition, to see whether there is a genetic factor and if there is, attempt to narrow it down. They ended up with nine families, or pedigrees, for study. In each, there was evidence of specific reading disability in at least three generations. Results from a battery of 21 routine genetic markers, coupled with a direct look at the chromosomes, were fed into a computer programme designed to look for a link between the disorder under study and one particular chromosome. Specific reading disability is linked to chromosome 15.

Because the disorder is so complicated, and the importance of any possible genetic link, the authors are cautious, and will continue the study with further families until the results are statistically even clearer. (Source: New Scientist, 19 May 1983.)

Leukemia virus linked to AIDS

Researchers have yet another clue in the race to uncover the cause of acquired immune deficiency syndrome (AIDS), but the cause of the disease remains unknown.

Several research groups this week reported findings that link AIDS with a leukemia virus known as HTLV (human T-cell leukemia virus). Doctors have isolated the virus from one patient with AIDS and from another showing early signs of the syndrome. Viral DNA has been found in cells of the immune systems of two other victims. And in another study, the AIDS group displayed a much higher occurence of antibodies to HTLV than did the healthy controls (25 per cent against 1 per cent).

HTLV, as its name implies, infects the human T-lymphocytes, which play a vital role in immune response. People with AIDS have T-cell abnormalities which leave their immune systems undefended, inviting a host of infections and a rare cancer called Kaposi's sarcoma. Like AIDS, HTLV is thought to be transmitted by sexual contact and the prevalence of HTLV in the Carribean area and Africa mirrors a similar occurrence of AIDS among Haitian immigrants to the US, thought to possibly be connected to a new strain of African swine fever infecting pigs in Haiti.

However, there are also major differences between HTLV and AIDS. The former can take a decade or more to develop. AIDS, however, takes at most a couple of years. Furthermore, inhabitants of southern Japan, another area where HTLV is prevalent, have not developed AIDS.

Researchers concede that HTLV may be just another infection that finds easy entry after AIDS has weakened the body's defences, but they also argue that if this were true, there should be less discrepancy between the incidence of antibodies to HTLV in AIDS victims and healthy controls. (Source: New Scientist, 19 May 1983.)

Recombinant DNA products may help fight AIDS

Acquired immune deficiency syndrome (AIDS) seems to be moving from very small population groups (U.S. male homosexuals, intravenous drug users, Haitians, and hemophiliacs) into the general population. Fatality rate for AIDS is very high. Cause has not been pinned down yet - although some tantalizing clues have been found. Eventually recombinant DNA products may help:

- Susan E. Krown and a group of investigators at Memorial Sloan-Kettering Cancer Center (New York, NY) in collaboration with Hoffmann-La Roche (Nutley, NJ) have had partial success with recombinant leukocyte A interferon in treating Koposi's sarcoma in AIDS patients. Kaposi's sarcoma, a rare tumor that starts in cells of blood vessel walls, is not rare in AIDS patients. AIDS causes the immune system to malfunction and the body has no way to fight Kaposi's sarcoma or any number of infections. Of 12 Kaposi's sarcoma patients treated with interferon, three remained free of all signs of the disease after 10 months of therapy. Five showed some response and four none. Five patients in the last two groups died. Although interferon did not seem to improve immune function significantly, it may be useful in treating AIDS-related Kaposi's sarcoma.

- Protein A, found in the cell wall of Staphylococcus aureus bacteria, binds one of the major immunoglobulins in the blood. The protein might be used to remove excess immunoglobulins from the blood of AIDS patients. Excess immunoglobulins resulting from an imbalance in the immune system may be responsible for some of the symptoms of AIDS. Charles Brown of Heriot-Watt University in Scotland has developed a method for producing protein A continuously, but he needs further funding to scale up the process. Speywood (Nottinghamshire, UK) supported the original work but has been forced by its British government backers to cut back on sponsored research.

- Researchers from Harvard, National Cancer Institute, Institut Pasteur and other organizations have recently turned up evidence that AIDS may be associated with human T-cell leukemia virus (HTLV). Antibodies to cell membrane antigens associated with HTLV have appeared in some members of a group of AIDS patients - but not all of them. HTLV has also been isolated in AIDS patients. While the evidence is strong it is not clear-cut. HLTV may only be one of the many diseases that AIDS patients become more susceptible to. However, the fact that HLTV does infect T-cells, which play key roles in the functioning of the immune system, is another indication that it might be the cause. (Source: Genetic Technology News, June 1983. Address; 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Danish firm offers runaway cloning vector giveaway

In a patent-license marketing twist, a pharmaceutical company in Copenhagen, A/S Alfred Benzon, is selling its runaway-plasmid technology on a free-for-a-year trial basis instead of asking for up-front fees. Runaway plasmids (RAP) are novel Escherichia coli cloning vectors and production vehicles whose replication is "turned on" by increasing the temperature. This results in high copy numbers and high levels of cloned protein synthesis. Since Shering-Plough signed the novel non-exclusive licensing agreement in October, some 24 international pharmaceutical and petroleum companies have approached the Danish firm to discuss RAP technology agreements. (Extracted from Newswatch, 6 June 1983.)

Chlorophyll

Increasing the amount of chlorophyll in plants could increase their efficiency as photosynthesizers, according to a recent report from the University of California (Berkeley). A 62 per cent increase in the chlorophyll present in plants results in a 36 per cent increase in the rate of photosynthesis. Previously, plant scientists thought that the elimiting factor in a plant's ability to convert solar energy into chemical energy was not the initial 'light reaction' in which solar energy is captured by chlorophyll and stored in chemical bonds in ATP and NADPH molecules, but the subsequent 'dark reaction' in which that energy is used to form carbohydrates. (Source: Technology Update, 21 May 1983.)

Science tackles the muck mountain

Today's factory farms, which dispense with straw for bedding and have little use for natural manure, turn out thousands of litres of slurry - dung and urine mixed with water - every day. Far from being a resource, most farmers see slurry as just another form of industrial waste. It is also a health hazard.

The UK Ministry of Agriculture, Fisheries and Food estimates that a dairy cow weighing 500 kilogrammes produces 41 litres of slurry every day. A 100-kg sow will produce 8 litres, more if it is feeding a litter. There is no way the farmer can deal with the output of hundreds of animals simply by spreading it on the fields. So the slurry goes into large storage tanks or lagoons where the troubles really start. Slurry stored for any length of time undergoes anaerobic fermentation - and becomes very unpleasant when disturbed. Unlike the aerobic reaction that produces farmyard manure, anaerobic fermentation gives off little heat, so disease organisms thrive. The combination of more slurry being produced, and more townspeople moving to the countryside, increases the risk of disease being transmitted by farm waste.

Scientists at the ARC's Institute for research on animal diseases near Newbury, have been working on ways of reducing the risk of spreading diseases with slurry. The list of diseases that slurry could spread is a formidable one, including anthrax and tetanus, but the one that receives most attention is salmonellosis. The institute reports that 10 per cent of cattle slurries and 23 per cent of pig slurries are contaminated with salmonellas - even if the animals themselves are healthy. Fortunately, salmonellas die rapidly in storage although they can survive if the temperature stays below 10°C, and if the slurry contains more than 5 per cent solids. After a month of storage in a tank or lagoon, the slurry should be safe enough for spreading - although cattle should not graze on it for a month. Separating the solid matter for aerobic fermentation into manure also cuts the risk.

Even when the slurry finally goes onto the land, it is not immediately of much use as a fertiliser. Scientists at the National Institute for Research in Dairying at the University of Reading have found that only part of the nitrogen, phosphorous and potassium in slurry is in a form that plants can immediately take up. For example, much of the nitrogen is locked up in organic materials which plant organisms break down slowly into "plant-available" nitrates. Experiments at Reading have shown that only 15 per cent of the nitrogen in cattle slurry is available to spring crops after spreading in the winter - previous estimates put the figure at 50 per cent. So even if farmers have the equipment and knowledge to use slurry safely as a fertiliser, it still needs added nitrates.

The most attractive way of dealing with slurry is simply to let it ferment in sealed vessels into safe fertiliser and useful biogas (a mixture of methane and CO_2). Biogas plants are already a familiar sight in China and India, although they have had some unforseen side-effects, such as depriving the very poorest people of a source of cow dung.

There are still many problems. Solid matter takes between 10 and 20 days to digest (cattle waste takes longer than waste from pigs), and the size of the plant has to match exactly the input of slurry, which varies according to the season.

Most importantly, farmers are unlikely to go to the expense of installing anaerobic fermenters unless the gas saves them money. (Extracted from New Scientist, 5 May 1983.)

Yeast learns two-step

A team of researchers at the National Research Council of Canada in Ottawa has come up with a process in which a yeast produces alcohol directly from starch. In the current technology of alcohol production, the starch must first be digested into simple sugars by the addition of enzymes called amylases, which come from other organisms, before fermentation of the sugars by brewer's yeast into alcohol can occur. This pretreatment step with amylases is costly and time-consuming. The novel NRC process uses only one yeast, isolated from soil some 20 years ago by a team of researchers and very similar to brewer's yeast, to accomplish both steps. The new yeast, called Schwanniomyces alluvius, produces sufficient amounts of amylase enzymes to break down the starch into simple sugars, which it then ferments into alcohol.

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

starch as the starting material, the versatile yeast can convert other carbohydrates, such as inulin, a large sugar from the Jerusalem artichoke, a plant easily grown in Canada and yielding more than one crop per year. Certain small sugars from wood wastes can also provide useful fodder. Further studies are underway to make the conversion of starch to alcohol with this yeast commercially feasible. The researchers also look to other uses for S. alluvius, such as the conversion of waste starch material to single-cell protein, and the commercial production of amylases. (Source: Science Dimension, 1983/1.)

Collaborative expresses prorennin in yeast

A precursor of an enzyme used in making cheese has been expressed for the first time in yeast by Collaborative Research, Inc., of Lexington, Mass. Collaborative senior research scientist, Dr. Donald T. Moir, reported the work last April at a meeting of the American Society for Microbiology. He told a session on cloning that in Saccharomyces cervisiae he had achieved an expression level for prorennin of 0.1 per cent of the cell's total protein. Prorennin is a forerunner of rennin, the milk-curdling enzyme secreted in the fourth stomach of unweaned calves.

Last year Collaborative, which has filed for patents on its work worldwide, expressed prorennin in Escherichia coli; Celltech Ltd. of Britain and researchers at the University of Tokyo have cloned prorennin in this prokaryotic host.

Dow Chemical Co. of Midland, Mich., supporters of Collaborative's work and 5 per cent owners of the R&D firm, is licensed to manufacture the enzyme. To construct the prorennin gene, Moir's group put an ATG codon (which once transcribed signals a cell to begin protein translation) on the prorennin gene Collaborative already cloned in E. coli. They then attached a strong yeast promoter and terminator to the gene and spliced the entire sequence into a yeast/E. coli shuttle vector, pCGS168, which expressed prorennin in yeast. The precursor was converted to rennin by an acid-catalyzed activation procedure. (Extracted from Newswatch, 4 April 1983.)

Process developed by Chiron Corporation exports recombinant products from yeast cells

If a genetically engineered microorganism secretes product rather than accumulates it inside the cell, purification problems may be simplified. Genetic engineers at Chiron have developed a process that induces genetically modified cells to excrete their products. They have used the process to produce a number of human hormones in yeast cells that export the products into the surrounding liquid. The process uses a yeast plasmid construct that includes, among other things, the leader DNA sequence of the yeast gene coding for alpha sex factor, a polypeptide produced and secreted by certain yeast cells. The gene for the foreign product is inserted into the plasmid after the leader sequence. Yeast cells containing the plasmid produce the foreign peptides in high yields and secrete them effectively, virtually 100 per cent. While a secreted protein product may end up in a more diluted form in the liquid of the culture medium, the medium generally contains fewer proteins from which it must be separated. If the product remains inside the cells, the cells must be broken down and the product separated from a mixture of a large number of proteins.

Some of the peptides Chiron researchers have produced with the process so far are:

- Human insulin, using a plasmid containing a gene derived from a natural human source.

- Epidermal Growth Factor (EGF), using a synthetic gene. EGF stimulated regeneration of growth of epithelial cells found in most internal organs and the skin. It has potential for healing wounds or burns, treating hyaline membrane disease in infants and inhibiting gastric acid secretion in ulcer patients.

- Somatomedins I and II (also called Insulin-like Growth Factors I and II - IGF I and II). These were also coded for by synthesized genes. IGF I and II are normally produced in the liver and are found in the blood. They act as intermediates in control of tissue growth by pituitary gland growth hormone. They may be useful in treating dwarfism and other growth abnormalities. (Source: Genetic Technology News, June 1983. Address: 150 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Danish firm to market Genencor's cloned rennin

Worldwide marketing of genetically engineered rennin, an enzyme essential in making cheese hinges only on FDA approval according to Genencor, Inc. The company has already produced its cloned rennin in pilot scale-up quantities at its laboratory in South San Francisco. Genencor has announced an agreement with the world's largest supplier of rennet, Chr. Hansen's Laboratorium A/S of Copenhagen, Denmark, to sell its enzyme on the world market.

Approval of the recombinant-DNA-made rennin by the Food and Drug Administration may take nine to 18 months, and clearance by regulatory agencies in other countries is not expected any sooner. Genencor has three patents pending in the U.S. covering its process, use of the product in cheese-making, and presumably the product itself. What host microorganism is being used by Genencor is a proprietary secret.

A Chr. Hansen representative in the U.S. estimates the world market for rennin at between $50 to $100 million. He believes that eventually, say in five years, after all regulatory approvals, the cloned form could take 50 per cent of the market. The agreement gives Genecor an option to subscribe up to 25 per cent of Hansen's common stock in the coming five years. (Extracted from Newswatch, 2 May 1983.)

Brewer's yeast, interferon, insulin or HGH

Brewer's yeast's mating factor may aid the production of interferon, insulin, or human growth hormones, according to I. Herskowitz and J. Kurjan of the University of California (San Francisco). Brewer's yeast alpha factor, a pheromone protein composed of 13 amino acids can be manipulated so that yeast cells will secrete useful protein compounds just as they secrete alcohol. It was suggested that by attaching a gene coding for a protein like interferon or insulin to the alpha factor gene, separated from it by the 6 amino acid 'spacer' chain between the alpha factor segments, the yeast cell could produce a precursor containing this protein as well as the 4 copies of alpha factor. During the secretion process, the precursor would be broken into its components and the desired protein then separated from the alpha factor. (Source: Technology Update, 23 April 1983.)

Charge, chromatography snare proteins selectively

To separate proteins from solution, two researchers for the first time are using a type of chromatography that relies on electrical charge to pinpoint selection. Dr. Anthony R. Torres, now an assistant director of clinical microbiology at Yale University School of Medicine here and co-designer of the method along with Dr. Elbert A. Peterson of the National Cancer Institute, say their bench-scale displacement-chromatography technique has high resolution, high capacity, and the cost of scaling it up should be economical. Their work will be published later this summer in analytical Biochemistry.

What the researchers have done to make their system work is selectively add negatively charged compounds, carboxyl groups, to low-molecular-weight dextran molecules. This gives the resulting carboxymethyldextrans (CM-Ds) a more specific binding range in a positively charged chromatographic column. Before, CM-Ds were heterogenous mixtures with wide, rather than narrow, column-affinity ranges.

After pouring a complex protein mixture down an anionic chromatographic column, CM-Ds with low affinities for the column are added. These displace the proteins bound least tightly, thereby separating some of them from the solution. From there, a series of displacers are added with increasing affinities for the column, which separate out more and more protein in a concentrated form. The system has the advantage, that one can analyze the fraction coming out of the column directly by gel electrophoresis without first getting rid of the salts, as sometimes has to be done in other types of chromatography.

To show their system's high resolution, the researchers used a seven-milliliter column to separate - with at least a 90 per cent recovery rate - the A and B forms of β-lactoglobulin, which have isoelectric points that differ by only about 0.1 pH units. To exemplify its high capacity, the two loaded their column with up to 400 milligrams of human serum protein to purify from it a minor component.

There should be no problem scaling up the process as the column and displacers can be used again. The cost should be reasonable, probably cheaper than using monoclonal antibodies, except that the displacement method will not be as selective as one using monoclonals. If a solution has two proteins with the same charge, the dextran molecules would not be able to separate them, whereas a monoclonal would. (Extracted from Newswatch, 2 May 1983.)

Scientist asks sea snail: 'How far is human behavior genetically programmed?'

In higher organism behavior, the animal's genetic makeup seems to provide the substrate that experience acts upon. So concluded Dr. Richard Axel, a biochemist at Columbia University's Institute of Cancer Research and Center for Neurobiology and Behavior, after his talk last month at Columbia's University Lecture Series on the role genes play in regulating behavior.

This deduction is based on his study of the egg-laying behavior of the mollusc, Aplysia. This sea snail acts out a stereotyped sequence that starts with cessation of walking and feeding, followed by head waving, then egg laying. The pattern results from activation of neural circuits, triggered by the coordinated release of a number of small neuroactive peptides.

The Columbia biochemist sequenced two genes coding for the A and B peptides thought to initiate egg laying, as well as a third gene for egg-laying hormone (ELH), which directly controls the process. The mollusc's atrial gland, a secretory organ of its reproductive tract, releases the A and B peptides. These proteins, may - directly or indirectly - excite a collection of neurons, the bag cells, which, once activated, release a battery of peptides, including ELH.

In A, B, and ELH genes, 90 per cent of the sequences are homologous, and all three are representatives of a small multigene family. Each of the peptides they code for are initially synthesized as polyproteins that are then processed into a collection of smaller peptides. "It is tempting to assume," Axel says, "that the egg-laying behavior is mediated by a small set of neuropeptides," all encoded by a single gene, expressed in a single polyprotein, cleaved and stored together, facilitating their coordinate release. Thus a single genetic unit may encode the information dictating a single fixed-action pattern."

A noted molecular geneticist noted that almost all nonlearned lower animal behavior is genetically controlled, the question is: How much learned behavior is genetically controlled? Axel's work is interesting scientifically, but it doesn't clear up at all the issue of how much human behavior is genetically programmed. (Source: Newswatch, 21 March 1983.)

Embryo recovery rates slowly improve

Before embryo transfer can have wide commercial use, the average success rate of embryo freezing must be greatly improved, the necessary training must be made readily available, and the overall cost must be lowered. Nevertheless, some achievements have been reported, and where even with the limitations of current technology, embryo transfer is an alternative that must be considered by any beef producer who wants to develop and maintain a top-quality herd.

Several new developments in embryo freezing which result in greater than the normal 25-50 per cent success rate have been reported:

- A freezing and one-step thawing technique which yielded 80 per cent as many progenies as the non-frozen control group. Using the standard 1.5 molar glycerol solution with the embryo contained within a straw, with an added 25 molar solution, the liquids separated with a tiny air bubble. Upon thawing, the air bubble is shifted to mix the two solutions.

- Fertilization rates, collection rates, and embryo numbers vary inversely with the number of superovulations in Holsteins. In addition, the number of ova which can be recovered when follicle stimulating hormone (FSH) is injected depends upon phase of estrus cycle during injection day, daily milk yields, age of cow, time since calving, and season.

An additional important application of embryo transfer is the preservation of endangered species by using donor mothers of abundant species. Preliminary work is being done to prepare the way for the use of elands as recipients for the embryos of rare antelopes. In this type of trans-specific work, eland embryos are now being transferred to domestic cows (Holsteins). Researchers are also attempting to transfer tiger embryos into lions and to implant wild cat embryos into domestic cats. (Extracted from Bio/Technology, March 1983.)

Canine heartworm test on market, vaccine on horizon, treatment on trial

A diagnostic approach developed by parasitologist Robert Grieve at the University of Pennsylvania School of Veterinary Medicine in Philadelphia may point the way to a vaccine against canine filariasis - heartworm.

Meanwhile, a heartworm detection kit, based on Dr. Grieve's technique and trademarked Dyrotect, was brought to market early last month by Mallinckrodt, Inc., of St. Louis. It involves an enzyme-linked immunosorbent assay (ELISA) using purified adult worm antigen to detect circulating antibodies in the dog. As this is a go/no-go colorimetric test, time-consuming serum dilutions are unnecessary. The advantage of the test lies in its ability to detect occult infections. From 20 per cent to 30 per cent of dogs that carry the parasite, Dirofilaria immitis, don't have microfilaria in their blood, so they show up as false negatives upon visual inspection of a blood smear. The test would distinguish these infections beginning three months into the worm's life cycle.

What encourages Grieve in his search for a vaccine is the dog's ability to manufacture antibody to worm antigens. He is now isolating and identifying a variety of D. immitis proteins and raising monoclonal antibodies to their determinants. Armed with these antigen-specific probes it is hoped to generate a defined vaccine, using either a synthetic antigen on the worms, or perhaps recombinant-DNA methods. Biotechnology may not provide the best weapon against the parasitic infection. Merck & Co., Inc., of Rahway, N.J., is developing a toxin from Streptomyces avermitilis that would be injected once a month into dogs at risk. Already tested for antiparasite treatment of horses, cattle, and sheep, the drug - which has just won FDA approval for horses as "Eqvalan" - is still being field-tested for use against canine heartworm.

Meanwhile, dog owners are left with the current practice of dosing their pets daily with oral diethylcarbamazine. (Extracted from Newswatch, 21 March 1983.)

Genentech gets back rights to foot & mouth disease vaccine

International Minerals & Chemical's (IMC) (Northbrook, IL) decision not to continue joint development with Genentech of a recombinant DNA vaccine for foot and mouth disease (FMD) in cattle gives Genentech another opportunity to commercialize a product on its own. IMC apparently had second thoughts about development of a new product for a market in which it has no direct experience - the company is not in the vaccine business. IMC is continuing genetic engineering research at Terre Haute, Indiana. It also has a contract with Biogen (Cambridge, MA) to develop animal growth hormones - products that would be more in line with IMC's established markets. IMC will retain a right to a share of profits from some of the vaccine products Genentech may commercialize, but Genentech will have full manufacturing and marketing rights. Genentech does not expect a commercial vaccine for several years.

U.S. cattle have been free of FMD for many years, but disease is a major problem in other parts of the world. Existing conventional vaccines are effective, but have also been blamed for some disease outbreaks.

Biogen is also working on a genetically engineered FMD vaccine. Company researchers have cloned antigens for the six major European and South American strains and isolated genes from three other South American strains. But so far Biogen has developed no effective FMD vaccine. Last year workers at Scripps (La Jolla, CA) and Animal Virus Research Institute (Pirbright, Surrey, England) found that a chemically synthesized 20-amino acid segment of one of the FMD virus antigens effectively immunized laboratory animals. (Source: Genetic Technology News, May 1983. Address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Chicken growth hormone

Applied Molecular Genetics will sell a chicken growth hormone made via recombinant-DNA technology that could give the company several cents profit from each of the 4.5 billion chickens per year consumed in the US. The company will use the hormone, a natural substance that determines the rate at which the birds grow and governs their ultimate size, can cut a few days from a broiler's short 8-12 weeks life. Presently, the company has succeeded in implanting into bacteria the gene that produces chicken growth hormone and has produced quantities of the cloned hormone suitable for testing. Early tests with the substance indicate that it can speed the growth of chickens by 15 per cent. The company is building a $10 million plant in Chicago, IL. AMGen has sought USDA testing of the hormone, which must also be cleared by the FDA. (Source: Technology Update, 28 April 1983.)

Gene transfer into intact mammals may be on the way

Transferring a foreign gene into cultured mammalian cells is nothing new. But the system developed by Steve N. Shilaty and H. Vasken Aposhian at the University of Arizona offers the possibility of transferring genes into a living animal. Eventually this might open the way to replace defective genes in humans.

The Arizona group started with empty capsids (protein coats) of polyoma virus particles and combined them with a fragment of DNA from the virus. The result was polyoma-like particles (PLP). The combination was done in the test tube, with no cells present. PLP infected rat embryo cells growing in a culture medium. Changes in the cultured cells indicated the PLP DNA had transformed the cells, in other words had entered the cells and was expressing proteins it codes for.

This summer the Arizona team will combine efforts with researchers from Massachusetts General Hospital (Boston, MA) and Jackson Laboratories (Bar Harbor, ME) to test the system on intact mice. They will attach the gene for mouse growth hormone to the virus DNA in PLP. Then they will administer PLP to mice that lack growth hormone gene. Normally mice with this genetic defect die shortly after birth. If successful the work may point the way to a therapy for genetic defects in humans.

Recent tranformation of mice with rat growth hormone was not carried out on complete animals, but on newly fertilized egg cells. Foreign DNA was injected into male pronuclei of these cells mechanically. (Source: Genetic Technology News, June 1983. Address: 158, Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

New plant cloning vehicle cuts out tumor transmission

Creation of a non-tumor-forming vector for cloning in agricultural crop plants was reported last month by Dr. David Anderson, vice president for research of Phytogen, an R&D firm in Pasadena, Calif. He unveiled the vector at the Plant Molecular Biology Symposium at Keystone, Colorado.

Anderson is using the traditional Ti-plasmid route to infect cells with new genetic information - but with the tumorigenic segments of the DNA deleted. His new vector delivered to tobacco protoplasts alien genetic sequences that confer resistance to the antibiotic kanamycin and to a related compound, G418. In a simple test to confirm that the genetic material had been taken up by the plant genome and was being expressed, the altered cells were exposed to the antibiotic. Those that kept on growing after exposure to these normally lethal agents had acquired resistance from the vector. Phytogen applied for a patent on the technique late last year.

The process started with the bacterial plasmid pBR322 and identified the regions of the Ti plasmid - from Agrobacterium tumefaciens - that was wanted. These were clipped out with restriction enzymes to get rid of tumorigenic material, then isolated and ligated into the pBR322 plasmid.

The Phytogen scientists next began isolating a kanamycin resistance factor from bacterial Tn5 transposable elements to stich into the vector. As this work proceeded, his researchers found that the construction had already been done at the California Institute of Technology, which supplied the Tn5 kanamycin-resistance gene.

Because the new vector's antibiotic-resistance marker gene had been derived from bacteria, it could not be expressed in higher organisms, such as tobacco plants, cotton, or potatoes. So the Phytogen team introduced a promoter sequence for thymidine kinase from a mammalian virus to ensure expression of the resistance gene in the host plant cells. Finally, they introduced into the vector an origin-of-replication segment from the cauliflower mosaic virus, which causes multiple copies of the vehicle to be made in the host cell.

Phytogen's transformed tobacco protoplasts have by now regenerated into plants that stand about six inches tall, but have not flowered yet. It will not be known for a few more months whether the altered plants' inserted genetic message is passed on through their seeds.

As Anderson and his associates wait for their cloned tobacco plantlets to go to seed, they are trying their novel vector on other crops - potatoes and cotton. For potatoes, they are seeking to introduce genes for soybean protein to improve the tuber's food value. (Extracted from Newswatch, 2 May 1983.)

Genes that give antibiotic resistance to plant cells

Bacterial genes which confer antibiotic resistance to plant cells also will function in whole plants, according to researchers at Monsanto's Molecular Biology Group. In 1983, the scientists successfully transferred the genetic trait for antibiotic resistance from a bacterium to a plant cell. A key question that remained unanswered was whether the foreign DNA would still be present and function in whole plants regenerated from the genetically engineered plant cells. The scientists have obtained normal, whole petunia plants which produce the foreign proteins for antibiotic resistance. Using special tissue culture techniques, several independent petunia plants were produced which were completely normal in appearance. Since pieces of the plants' leaves will grow on media containing levels of antibiotic which normally would kill them, the scientists have evidence that the foreign gene is functioning in the intact plant tissue, demonstrating that they have moved closer to the ultimate goal of genetic engineering crop plants for improved productivity. Research into the stability and regulation of gene expression in plant tissues will be required before valuable traits such as resitance to diseases, herbicides and insects can be introduced into crop plants. Antibiotic resistance is not a commercially attractive trait, but it will provide scientists with a research tool for introducing other important genes into plants and for identification plants or plant cells which contain foreign genes. (Source: Technology Update, 14 May 1985.)

Phytogen cotton somaclone to speed up trait selection of pest-resistant strains

A way to produce commercial cotton plants in massive quantity from somatic - not germ - cells has been successfully demonstrated here by Phytogen. The agricultural genetic engineering firm's vice president for research, Dr. David Anderson, announced this regeneration of Gossypium plants via somatic embryogenesis from callus cell clusters on the last day of February.

The work itself was carried out under Dr. Thirumale S. Rangan, director of the cotton regeneration project under contract from J.G. Boswell Co., a leading cotton producer in California's San Joaquin Valley. This vast plain is a major center of the U.S.$4-billion-a-year-cotton industry. Boswell is a leading shareholder in Phytogen.

None of the adult cotton plants that Rangan and his group managed to regenerate from somatic callus in Phytogen's leased laboratory space at California State University, Los Angeles, have yet flowered, Anderson reports. Tissue samples have been regenerated from three commercial strains of cotton: SJ2, SJ4, and SJ5. The SJ5, Anderson explains, is most important to California producers because it is resistant to verticillium wilt, a major problem for Western growers. The number of rgenerated plantlets achieved to date "can be counted in the tens", says Anderson. They are about six cm tall and will soon be transplanted from their special growth medium to normal soil. Phytogen remains intentionally vague on details of the method they used to regenerate cotton, as they are still deciding whether or not to apply for patent protection. (Source: Newswatch, 4 April 1983.)

Progress in the transfer of genes

For the first time, full expression of a gene product has been achieved following transfer of a gene from one plant species to another by recombinant DNA techniques. Researchers at Agrigenetics (Keystone, Colo.) and the University of Wisconsin have "turned on" a foreign gene in both sunflower and tobacco tissues and obtained a bean protein. An especially significant aspect of the work is that the bean gene was expressed under its own regulatory code as well as that of the vector used to move the DNA from one plant species to another. Following isolation and characterization of the gene to be transferred, the researchers used a bacterial plasmid from a soil microbe called Agrobacterium tumefaciens as a vector. While this gene transfer was reported two years ago, the new research shows that it is possible to make the gene direct protein synthesis in the cells of the recipient plant. The results were reported during a University of California at Los Angeles symposium on plant molecular biology held at Keystone. Others also have been working with the Agrobacterium vector system. (Extracted from Chemical Week, 4 May 1983.)

Agrigenetics expresses bean gene in sunflower, but sees protein instability

For the first time, molecular biologists at Agrigenetics Corporation's Advanced Research Laboratory here and at the University of Wisconsin have not only transferred but expressed a gene from one plant, the French bean, into the cells of other plants - sunflower and tobacco. This feat is the latest development in the much touted gene-spliced "sunbean" hybrid of two years ago, which achieved only plant-to-plant, bean-to-sunflower gene transfer. However,

the bean-seed-storage protein, phaseolin, is rapidly degraded by proteases - either in vivo by the host cells or in vitro during the extraction process. This problem will impede the eventual goal of commercializing genetically engineered plants. (Source: Newswatch, 6 June 1983.)

Genetic engineering technique makes plant cells produce foreign proteins

A genetic engineering technique to make plant cells produce foreign proteins has been developed by researchers of Monsanto's Molecular Biology Group (St. Louis, MO). While the technique has been used successfully in other fields such as animal cell transformation and bacterial transformation, this is the first such application to successfully use plants.

In the process, genes that normally make a bacterium resistant to a specific antibiotic were isolated and joined to a piece of DNA, which insured those genes would function in the plant cells. The combination of the 2 pieces of DNA, called a chimeric gene, was then inserted into a unique soil bacterium that introduces its DNA into plant cells. When mixed with the soil bacteria, the normal plant cells incorporated the chimeric gene and were able to grow on a medium that contained enough antibiotics to kill normal plant cells. In this way, the genetic trait of antibiotic resistance had been transferred from the bacterium to the plant cell, indicating that genes from one organism could be transferred to a completely different organism where they would function normally. This technique makes it possible to introduce virtually any gene into plant cells with the ultimate goal of improving crop productivity. (Source: Technology Update, 23 April 1983.)

Peanut hulls 'cracked' to yield cattle fodder

"It's a tough nut to crack!" That's how a leading microbiologist anonymously describes work on turning peanut shells into fodder, reported to a session on biodegradation last month at the American Society for Microbiology. Dr. Thomas J. Kerr, a microbiologist and director of laboratories at the University of Georgia in Athens announced that he has potentially turned an economic loss for peanut shellers (450,000 tons of the waste are produced annually in the U.S. alone) into a fodder supplement for cattle, pigs, and chickens. Worldwide patents have been applied for on the bench-scale process and the microorganism that makes it occur. The Southeastern Peanut Association of Albany, Ga., has supported the work with $20,000 over the last three years.

The hulls are pretreated with nitric acid, which must loosen the hemicellulose and cellulose away from the lignin. The mixture is then incubated for 24 hours with a microorganism tentatively identified as Arthrobacter sp. KB-1. Isolated from a decaying peanut-shell pile in Alabama, the organism uses lignin as its sole carbon source and, together with the acid, increases the digestibility of the hulls to 63.22 per cent. Previously, researchers using solely chemical means had obtained only 25 per cent to 40 per cent hull digestibility.

Saccharomyces cerevisiae is added to the mixture for another 24 hours, thereby increasing its protein content from 10.5 per cent to 13.6 per cent, a level, where no other protein supplement would have to be added to make the material comparable to commercial animal feeds. The material then is ready for potential shipment or storage.

A pilot plant needs to be built so enough material can be produced to conduct extensive feeding trials. The fodder supplement is estimated to cost about $50 a ton. (Extracted from Newswatch, 18 April 1983.)

Genetic engineering may make hydrocarbons from algae

Algae have great potential for making large-volume, low-cost materials like chemical feedstocks, food proteins or fuels because they make their own carbohydrate nutrient by photosynthesis. Even a modest success in improving algae by genetic engineering could make algae culture much more attractive economically.

At the moment, researchers at the Standard Oil Company (Indiana) are doing basic genetic engineering research with three types of photosynthetic organisms. Chlamydomonas reinhardii, a eukaryotic green alga whose cells have nuclei, as do those of all eukaryotes (yeasts and all higher plants and animals). The two other species are prokaryotes (bacteria): Anacystis nidulans, a blue-green algae or cyanobacterium, and Rhodopseudomonas sphaeroides, a photosynthetic bacterium.

Efforts to genetically engineer eukaryotic algae are still at a very early stage. Researchers are developing suitable vector systems for routine cloning. However, scientists at the University of Geneva (Switzerland) have been able to introduce a yeast gene into C. reinhardii, where it became integrated into the algae's chromosomal DNA.

Several plasmids are already available for cloning in Anacystis nidulans, which is not only photosynthetic but also fixes nitrogen. Goal of the work with R. sphaeroides is to find a vector for moving genes from one strain of the species to another. Problems prevent expression of photosynthetic genes from the organism in Escherichia coli.

As a potential hydrocarbon source the eukaryotic alga Botryococcus braunii is of great interest to Standard of Indiana. At times this organism produces heavy "blooms" in Australian lakes. Crude oil content may run over 50 per cent of dry cell weight. The crude oil contains a lipid (fatty acid ester) fraction and a hydrocarbon fraction. Hydrocarbons are C_{25} to C_{31} linear di- and tri-alpha-olefins - potentially valuable as chemical feedstocks. They can also be easily cracked to high quality fuel materials. Protein content, which could be a significant co-product, may run as high as 35 per cent.

Cost of culturing algae is very high. Heller estimates a food-grade algal protein product would cost about $2 per pound if produced in an agitated outdoor pond system. Probably the costliest factor is collection of algae from dilute culture medium. Even slight success in incorporating traits to improve flotation or aggregation of the organisms could reduce collection costs for algae significantly. (Source: Genetic Technology News, April 1983. Address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

DIY algae

Blue-green algae are common as muck in Asia. They do for rice paddies what cheap manure and expensive nitrogen fertilisers do for western grain fields. Scientists in America now reckon that algae, with a little genetic manipulation, could be taught to serve western farmers as well as Asian ones - by providing up to one third of their nitrogen fertiliser requirements.

The lure of growing algae as fertiliser is twofold: Asian algae are cheap, and they grow all by themselves. Producing nitrogen fertiliser, by contrast, is expensive, and requires the energy equivalent of 100 million barrels of oil a year in the United States alone. But development of algae for use in ordinary fields instead of watery paddies is still in its early days. Much remains to be done before researchers can realistically gauge the economics, or the practicality, of their scheme.

The secret of the humble algae lies in their ability to fix nitrogen - that is, to transform the gas from the air into compounds which are useful to plants. Their commercial potential derives from the fact that they are easy to grow, and can reproduce very fast: researchers at the Battelle laboratories in Washington state found that, in laboratory soil at least, algae multiplied 10,000-fold over three weeks. A small amount of algae could, in theory, multiply quickly to cover a whole field, fertilising it as they grow.

In some ways, algae are a better source of fertiliser than industrially-produced nitrates. Commercial fertilisers are ploughed into the soil in one load, which usually has to last the whole growing season. As time passes, a lot seeps down through the soil, out of the reach of plants. Growing algae would release nitrates into the soil slowly and continuously, and so avoid this problem.

In India, algae fertilise around 2 million hectares of paddy fields, the nitrates they produce diffusing through the water of the paddies into the soil. Centres are springing up all over the country to provide farmers with algae in areas where they do not grow naturally. According to people in the Indian government's national algae programme, nitrates produced by algae are much cheaper than those contained in manufactured fertilisers. Nitrates from algae cost (in 1979) around $3.65 for 25 kilograms, compared to $12.20 for the same amount of the artificial stuff. If half India's paddy-fields were fertilised with algae, that would save around $200 million a year.

Before western farmers can reap similar benefits, however, three principal problems must be overcome. One concerns the use of algae on soil instead of water; the second arises from the high levels of nitrogen required by high-yielding crop strains; the third has to do with the adaptability of the algae themselves. Dr. Blaine Metting of R&A Plant Soil, an American company in Pasco, Washington, keen to exploit algae, says the problems now look crackable.

Although algae can grow fast on soil - as the Battelle researchers demonstrated - they do not grow consistently. Sometimes they reproduce at dramatic speeds, sometimes slowly. That is no good for farmers who cannot afford to risk leaving their crops short of fertiliser.

Two approaches to this problem have been adopted. Algae are being screened for types which grow consistently fast. Researchers are also trying to determine how algae respond to the different constituents of soil. It may be that different types of algae reproduce faster in different types of soil. So choosing the right algae for each type of soil might be a way of getting consistent growth.

The second difficulty with algae is that they simply never will be able to produce all of the nitrates demanded by high-yielding western crops. Some crops require up to 300 kg per hectare per year - far more than low-yielding rice in Asia. But algae-men reckon their product could establish high background levels of nitrogen, and so allow farmers to use less commercial fertiliser.

The third problem is the adaptability of algae: when nitrogen is added to their habitat, they stop fixing their own. Researchers at the University of Chicago have identified the genes in algae responsible for the complex nitrogen-fixing process: at least 17 are involved. Now they need to find out which ones turn the process on and off. If that switch can be found and manipulated, scientists would be well on their way to providing farmers with living fertiliser factories. (Source: The Economist, 2 July 1983.)

Plant cells for specialty chemicals

Many specialty chemicals used as pharmaceuticals, flavours, food ingredients, costmetic raw materials and pesticides are extracted from parts of whole plants. Growing plant cells, genetically engineered or not, to produce the chemical wanted in a fermenter is an intriguing possibility. But the same methods for growing plant cells for large-scale production of microorganisms cannot be used. Slow growth, genetic instability and low product yields are big problems in growing plant cells. For experimental purposes researchers at Cornell University cultured tobacco cells. They considered the phenolic compounds they produce as the product analogous to a chemical product. Designing a fermenter - or bioreactor - for plant cells is complicated by the fact that conditions ideal for rapid growth of cells are different from those required for the cells to produce the product. Rapid cell growth is possible only with dedifferentiated cells - as opposed to specialized cells growing in tissues, but conditions for high growth usually suppress expression of genes associated with formation of the product wanted. Therefore the Cornell team used a two-stage system, with the first stage optimized for cell growth, the second for product output.

Plant cells break up quickly if they are subjected to the strong agitation used routinely in some fermenter configurations for growing bacteria or yeasts. When plant cells do grow suspended in liquid they tend to aggregate into large clumps that cause growth to slow down. The slow growth rate of plant cells in a fermenter makes contamination more of a problem than it is with microorganisms. Typical doubling times for plant cells are between 20 and 60 hours - contrasted with a half an hour for many bacteria. So any bacterial contaminant can easily outgrow the plant cells.

Ultimately it may be more commercially attractive to use cells immobilized by entrapment between two membranes. Because plant cells are much larger than bacteria a wider variety of membranes could be used. (Source: Genetic Technology News, April 1983. Address: 158, Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Jumping genes - vectors for corn genetic engineering?

Breakthroughs in using T-DNA to introduce functioning foreign genes into higher plants are of no use to you if the aim is to genetically engineer maize, other cereals, grasses, bananas, pineapples, or palms, which are all monocots. T-DNA works only with dicots, a group that includes most broadleafed plants. At The Fifteenth Miami Winter Symposium, Miami, Florida, 17 to 21 January, a different approach that may work with monocots was heard from W.J. Peacock of Australia's Commonwealth Scientific and Industrial Research Organization, who believes it may be possible to make use of a "jumping gene" DNA sequence - a group of genes that sometimes moves from one part of a plant cell's DNA to another. Jumping genes - or transposons - can be isolated, cloned and injected into a plant cell nucleus, where they become integrated into the cell's chromosomal DNA. If a desired gene, e.g. for resistance to rust disease, is inserted into the transposon it should also become integrated into the plant chromosome.

The transposons Peacock and his group have isolated, cloned and characterized are DNA segments from the maize chromosome. They contain the gene for an enzyme, alcohol dehydrogenase (Adh). The Adh gene is a very useful marker to identify cells that have been successfully transformed with the transposons. Mutant cells that do not retain the Adh enzyme will not grow without oxygen, therefore if these mutant cells are injected with transposons containing the Adh gene and then cultured in the absence of oxygen, only those cells into which the transposons have become integrated will grow. (Source: Genetic Technology News, March 1983. Address: 158, Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

DNA probe throws light on control of amylase in barley

Grains of barley undergo many complex internal changes during the germination process that converts barley into malt for making beer or other beverages. Now plant hormones control one of these changes - formation of the starch-dissolving enzyme, alpha-amylase - has been the object of research by workers at Kansas State University (Manhattan, KS), U.S. Department of Agriculture (Beltsville, MD) and National Institutes of Health (Bethesda, MD). This very basic research is important to understanding the processes all seeds undergo when they germinate.

Key to this research was the cloning of DNA forming barley alpha-amylase gene in Escherichia coli. The DNA, made available in quantity by cloning, can be used to detect messenger RNA coding for alpha-amylase.

One finding of the research is that the plant hormone, gibberellic acid, which induces production of alpha-amylase in barley seeds, acts by stimulating production of messenger RNA for the enzyme. This had been suspected previously, but the possibility that the hormone only activated stored messenger RNA has now been ruled out.

A surprising finding is that a family of genes apparently codes for a number of related alpha-amylases. Multiple genes for storage proteins in plant seeds are common, but a family of enzymes is not. (Source: Genetic Technology News, April 1983. Address: 158, Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Betting on bugs

After gambling and losing £100 million over the past 20 years on a project to make single-cell protein (scp) for animal food-stuffs by feeding methanol to bacteria, Britain's ICI is having a go at bug-produced polymers. It has joined Marlborough Teesside Management, a marketing and management consultancy, to set up a subsidiary called Marlborough Biopolymers Limited. MBL is to market ICI's future lines of bug-produced polymers, starting with polyhydroxybutyrate, or phb for short.

On the face of it, the decision is odd. ICI's petrochemicals and plastics division ran up a trading loss of £139 million ($243 million) last year, thanks to acute overcapacity in the plastics industry. And phb (to be sold as Biopol), a polyester made by genetically engineered bacteria, is broadly similar to oil-based plastics like polypropylene. Worse, it costs two to three times as much to produce. So why bother?

ICI has two answers. First, phb has biological and electrical properties that could win it a market niche as a high-value specialty plastic. For instance, it is biodegradable and biocompatible (that is, it can be used in the human body without being rejected as a "foreign" substance). At the moment it is being test-marketed for use in, e.g., surgical stitching and pins, but other materials are already well rooted in most of the specialty niches phb hopes to occupy. American Cyanamid, for one, produces a polyglycolic acid that has been sold as a biodegradable stitching material since 1970.

Second, the phb-producing bugs could be grown on a variety of renewable feedstocks, like starch and sugar, although at present the bacteria are being fed on methanol. That should make phb's economics more flexible than those of methanol-based scp. Eventually ICI hopes that phb will compete in price with oil-based plastics. When? Perhaps in 20 years.

In short, phb is a long-term gamble, a product in search of a market. As one senior ICI planner put it, the decision to plump for phb was "technology-pulled rather than market-driven". ICI believes that it has a five-year lead in the sterile fermentation-vat technology needed for such bug-produced materials as scp and phb and wants to "keep the snow on the road".

The gamble on phb is on a much smaller scale than the big investment wagered by the company on scp. Unlike most competitors, ICI did not pull out when the price of its methanol feedstocks soared on the back of oil prices in 1973 and 1979. It is now making 50,000 tonnes a year, at a loss.

Single-cell protein now costs twice as much as soya meal, which was meant to be its main competitor. Luckily, there is still some demand for scp as a high-protein food additive for young livestock. While ICI hopes to cut its losses by licensing the technology to methanol-rich, protein-poor countries such as Russia and the Gulf states, negotiations are going slowly and the company's sterile engineering technique is probably not yet ready for export.

Depending on initial orders for phb, ICI hopes to reactivate its 1,000-tonne-a-year scp pilot plant, mothballed since 1979, to churn out its new phb. Britain's department of industry (now the enlarged trade and industry department), which subsidised up to 33 per cent of the research and development costs of scp, is now doing the same for phb. (Source: The Economist, 18 June 1983.)

An enzyme with many faces

Thermodynamically speaking, organisms are improbable. They are only made possible by enzymes - biological catalysts that speed up their chemical reactions to a respectable level. Enzymes are remarkably discriminating. Each catalyses a single reaction of a particular chemical, which is recognised by its shape. This "lock and key" relationship has led to the view that the enzymes' own structure must of necessity be unique and unchanging, and so it is - usually. The notion that an enzymne might exist in a number of forms decided purely on probability is anathema to many scientists. Yet this is exactly what has recently been proposed by Professor David de Rosier and his co-workers at Brandeis University, in Massachusetts.

The enzyme in question is the alpha-keto glutarate dehydrogenase complex (KGDC for short). It is one of the several enzymes involved in the central process of a cell's metabolism known as the citric acid or Krebs cycle. Like all enzymes it is a protein and like some it is made up of a number of polypeptide subunits (so forming a "complex"). But like no other yet characterised it seems able to exist and function in a large number of structural permutations. Therefore no unique structural formula describes all molecules of KGDC.

The complex is made up of three different types of subunit each with its own enzymic activity. The first type forms a core in the shape of a cube. The two remaining types bind to the surface of the cube. There are four binding sites symetrically arranged on each of its six faces. The distribution of sites has the same symmetry as the cubic core, but the occupancy of sites by the two subunits is fairly haphazard. Combinatorial analysis has shown that there are no fewer than 124 896 structural isomers possible for KGDC.

Enzymatic catalysis involves the breaking and making of different chemical bonds. The received wisdom of biochemistry is that active sites in complex enzymes are close to one another, so as to facilitate the movement of intermediate structures among the active sites, rather like a production line in a factory. The de Rosier team argue that this need not be true if an active site on one part of the molecule can affect other sites on the complex in such a way as to facilitate movement of intermediates between sites.

Any advantage bestowed on KGDC by its peculiar structure remains a mystery - but one possiblity is that a molecule with 24 separate binding sites will be much more effective at picking up very small quantities of substrate. (Source: New Scientist, 28 April 1983.)

Better plant regeneration - key to plant genetic engineering?

A new technique for regenerating normal plants from plant cells containing foreign genes may play a key role in genetically engineering higher plants. Two teams have co-operated on the research. One is headed by Mary-Dell Chilton at Washington University, the other by Andrew N. Binns of the University of Pennsylvania.

Breakthroughs just made now enable molecular biologists not only to introduce foreign genes into higher plant cells but also to cause the genes to express - that is, to produce proteins coded for by the foreign genes. But this technique must now be linked to a method that will permit transformed plant cells to grow into complete, fertile plants if genetic engineering of higher plants is to become a reality. Jeff Schell, Marc van Montagu and others at the Free University of Brussels in Belgium have already reported a method of

regenerating transformed plant cells, but Binns tells GTN that the new regeneration procedure consistently works with nearly all cells containing foreign DNA, in contrast to the other method in which some of the cells develop into shoots, of which a fraction develops into complete plants.

Plants regenerated by the procedure Binns and Chilton have developed retain the full length of T-DNA that inserts itself into the plant cell's chromosomal DNA. Normally, T-DNA, which is a portion of the Ti plasmid in Agrobacterium tumefaciens (a microorganism producing crown gall tumors in plants) will cause plant cells containing it to develop into tumors, not complete plants. Binns and Chilton overcame this difficulty by inserting an antibiotic resistance gene into the T-DNA sequence at a point at which the insert inactivates a key gene in T-DNA and hinders tumor formation. Schell and van Montagu prevented tumor formation by eliminating large fragments of T-DNA. In all cases, the ultimate aim is to insert a foreign gene into T-DNA, integrate both into the chromosome of a plant cell and regenerate the cell into a complete plant with the foreign DNA gene in every cell, where it may be expressed and passed on to the progeny.

Chilton - whom Monsanto researchers have given credit for making their recently acquired ability to make higher plant cells express a foreign gene possible - was responsible for preparing plasmids for transforming plants. Binns and his group at University of Pennsylvania did the infection and plant regeneration work. Chilton plans to move from Washington University to the U.S. subsidiary of Ciba-Geigy (Greensboro, NC), where she will head up a research group for molecular biology in higher plants.

A number of other research groups are also working on genetic engineering of higher plants. For example Cetus Madison has propagated three generations of tobacco plants retaining foreign genes introduced through genetic engineering. One of the key scientists in this programme is Kenneth A. Barton, who was until recently a member of Chilton's group at Washington University. Cetus plans to have its first genetically engineered crop plants in commercial use within three to five years.

Instead of introducing the Ti plasmid into plants by infecting them with A. tumefaciens, Kunihiko Syono's group at the University of Tokyo has converted the bacterium's cells into spheroplast by removing their cell walls enzymatically. Spheroplasts can then be fused into plant protoplast cells (which have had their cell walls removed the same way). Polyethylene glycol or polyvinyl alcohol promote fusion. Other bacteria, such as Escherichia coli and Rhizobium leguminosarum, have also been introduced into plant protoplasts the same way. (Source: Genetic Technology News, March 1983.)

Membrane systems

The use of synthetic polymer membranes offer a range of advantages in cell recovery and manipulation in biotechnology. Membrane systems allow the uninterrupted processing of very different quantities of liquid. Membrane systems are closed and produce no aerosols, which is very important in work with vulnerable organisms. Once the system is working, the process runs through automatically to completion. Membrane systems are very quick to set up, versus centrifuges. Membrane processes can be built up from laboratory models to full production sizes. The range of membranes used include membrane filters, ultrafiltration membranes, dialysis and electrodialysis membranes and membranes for reverse osmosis. (Source: Technology Update, 21 May 1983.)

Microorganism mines copper without making acid; metals snared selectively from waste solution

Using silver as a catalyst, a microorganism that extracts copper from copper sulfides and turns the sulfides into elemental sulfur instead of sulfuric acid can save mining companies at least five to 10 cents a pound in extraction costs, according to B.C. Research at Vancouver, Canada, a not-for-profit foundation that does contract research for government and industry. Canada's federal and provincial governments are backing the work with $150,000, and Canadian and international mining companies have invested $300,000. Patents have been filed for the process.

British Columbia mining companies produced about $483 million worth of copper ore last year by crushing the rock, then separating out the copper-rich fractions by flotation. The firms then sent the concentrates to Japan for smelting and refining. By the new catalytic process, the copper-leaching bug Thiobacillus ferrooxidans can extract copper for 25 to 30 cents a pound compared with the 35 cents a pound it costs to do the job in Japan.

Until now, for each ton of copper T. ferrooxidans leached from ore, about three tons of sulfuric acid were produced. As the acid pollutes the environment, there was little incentive to put the organism to work on a large scale, but now one can make the bug stop the oxidation of sulfide at elemental sulfur, and enhance extractions from 60 per cent to 95 per cent or better, thereby decreasing or eliminating the need to recover unreacted minerals from the leach residue by recycling. Size reduction, by milling of the concentrate to minus 400 mesh, may no longer be necessary. And chalcopyrite ($CuFeS_2$) is leached preferentially over pyrite (FeS_2). (Extracted from Newswatch, 4 April 1983.)

Recombinant process could utilize biomass component for ethanol

Rising oil prices have taken the pressure off efforts to develop fermentation processes for converting biomass into ethanol. Researchers at Purdue University have transformed yeast Saccharomyces cerevisiae with an Escherichia coli gene coding for xylose isomerase, and achieved expression of the gene. Xylose is the sugar formed by hydrolysis of hemicellulose, which makes up 30 to 40 per cent of biomass, such as wood and crop residues. When biomass of this type is hydrolyzed its cellulose is converted into glucose. Yeast can convert glucose into ethanol easily. However, yeast can do nothing with xylose because it does not produce the enzyme xylose isomerase, which converts xylose into xylulose, a sugar yeast can utilize for ethanol production. The Purdue researchers transformed yeast with the E. coli xylose isomerase gene, xylA, earlier, but the gene would not express, that is, produce the enzyme. Recently the researchers have modified the xylA gene by removing its promoter and substituting a yeast Trp5 promoter. The modified gene does express xylose isomerase, but yields are very low. The next step is to try a different yeast promoter to gain a higher level of expression. End result would be a yeast that could convert hydrolysis products of both cellulose and hemicellulose from wood or crop residues into ethanol. (Source: Genetic Technology News, June 1983. Address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Focus sharpens on how to use molecular biology to make electronic chips

Concepts of just how molecular biology might be applied to fabricating electronic devices seem to be getting a little clearer, but no one at the Second International Workshop on Molecular Devices, held at the Naval Research Laboratory in Washington last April seemed ready to actually try to design and fabricate a "biochip" yet. Molecular-scale electronic devices - whether made biologically or chemically - would open up possibilities with vastly greater capabilities than silicon chip-based computers now available. They might also be made compact enough to implant in the human body, where they could be connected to the nervous system to enhance memory, restore vision or improve other functions.

One picture of what a biochip might be like is a device constructed on a framework of protein molecules. Other molecules attached to the proteins would serve as conductors and form the switches and other elements of the chip. Porphyrins (like heme or chlorophyll), which are flat molecules with metallic ions at their centres, are often cited as possibilities. Obviously, designing a protein molecule with the proper groups attached at the right places on an accurately folded peptide chain - and then building it - will be a formidable task.

A start on the problem would be to learn how to put the structure required into a two-dimensional structure one molecule thick (a monolayer). (Source: Genetic Technology News, June 1983. Address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Bioelectronics

Scientists in the field of bioelectronics are trying to develop a molecular processor to develop computers built with such minute components that they would be 1 cm in size with 10 million times the memory of present hardware. The problem is that circuits are becoming more dense and the wavelength of optical light used in present day etching techniques will soon be longer than the circuits being drawn. New tools such as X-rays and electron ion beams will be needed but these will be too expensive to be commercially viable. R. Metzger of Mississippi University is working on a molecular switch consisting of a synthesised molecule with 2 electrons and 2 protons which change positions when a small electric charge is given. Other scientists suggest using organic materials such as monoclonal antibodies and protein. Using protein as the substrate for metallic circuitry would produce chips 100,000 times more densely packed than currently obtainable. (Source: Technology Update, 30 April 1983.)

US invests in bioelectronics

The American government wants to put money into bioelectronics. A major Congressional committee has asked the navy to tack a proposal onto the recently-produced 1984 budget requesting support for an area that could range from simple biosensors to (ultimately) complex biocomputers.

The US navy's proposal includes $20 million for 1984, $30 million for 1985 and $45 million for 1986. A large part of that will probably go to a small, entrepreneurial company in Maryland called Gentronics, whose management is in the process of casting its nets more widely in the hope of financial support from overseas. The company first received worldwide (and controversial) publicity with the two patents it received in 1978 for making a crude "protein" chip. Its work is aimed at exploiting the specific bonding capacities of molecules to make multi-layered devices from a wide range of materials to act as electronic devices. Gentronics, which has recently gone public in the US through the acquisition of a small start-up firm already traded on the US OTC market, has delineated five different areas: biomolecular electronics, biomembranes, biosensors, bioconductors and prosthetics, and hopes to exploit its development with larger companies through R&D partnerships, a method increasingly used in the US by small, high-technology firms. Gentronics has already had talks with Belgium on funding for certain areas. Any exploitable research would then be commercialised there. The Republic of Ireland also holds possibilities, particularly with its programme of grants for R&D. (Extracted from Technology, 16 May 1983.)

From genetically modified methylotrophs, a market basket of products?

A gene-transfer system for potentially useful bacteria that grow on the cheapest and purest substrates available - single-carbon methanol and methane - has been developed by microbiologist Mary E. Lidstrom at the University of Washington, Seattle. She reported her work with the one-carbon-eating methylotrophs at this year's Biotechnology for Fuels and Chemicals symposium at Gatlinburg, Tennessee.

The system's initial value may be in making bulk chemicals such as organic acids, vitamins, and amino acids.

The first application is to make more complex chemicals from simple substrates, but there is the potential, once the gene-transfer system is worked out, to make any product for which the gene is available - human growth hormone, interferon, insulin, or one of the blood-clotting factors. Or the methylotrophs could carry out new conversions, such as taking xylose to ethanol.

Imperial Chemical Industries in England is also working on a recombinant-DNA system for methylotrophs. ICI is engineering its Methylophilus methylotrophus, which it now markets in its wild-type state as a single-cell protein, Pruteen, and has contracted with Dr. Bruce Holloway of Monash University in Melbourne, Australia, to do gene transfer work on the same organism.

Dr. Richard S. Hanson, director of the University of Minnesota' Gray Fresh Water Biological Institute in Navarre, Minn., is developing a gene-transfer system in the methylotroph Methylobacterium organophillum. ICI has expressed in M. methylotrophus the Escherichia coli gene for glutamase dehydrogenase and the mammalian genes for dihydrofolate reductase and ovalbumin. Hanson has yet to express a foreign gene product.

In mutants of the facultative methylotroph Pseudomonas AM1, Lidstrom has expressed the single-carbon-metabolizing genes for methanol dehydrogenase, malyl CoA lyase, and hydroxypyruvate reductase. She did this through conjugation, the transfer of a plasmid from one bacterium to another via cell-to-cell contact, but she had to use two E. coli plasmids to do it: one, pRK2013, that would not replicate in strain AM1, and another, pVK100, that would. She used the non-replicating vector to enable the replicating one, carrying the DNA she wanted expressed, to get inside the host cell and therefore replicate.

Her ultimate aim is to put together a genetic map of the single-carbon-degrading genes in methylotrophs and to develop a vector with a strong promoter to facilitate increased gene expression in these organisms. (Extracted from Newswatch, 6 June 1983.)

Improving the splice

To obtain expression, Timothy C. Hall, Agrigenetics' research director, John D. Kemp, who heads the microbiology section, and Norimoto Murai, a postdoctoral researcher in Kemp's other laboratory at the University of Wisconsin, used as a vector the same Ti-plasmid (tumor-inducing) from the crown-gall-inducing bacterium, Agrobacterium tumefaciens, that they

deployed before, but this time they included the DNA coding for nine amino acids of the gene sequence missing in the first construction. They moved the gene to a better location on the plasmid and included the phaseolin gene promoter. It was only in late May that they saw strong evidence that the foreign protein production was actually driven by its own promoter, not a Ti-promoter. This was a point of contention when they reported their latest work in April at the Cetus - University of California, Los Angeles Plant Molecular Biology Symposium in Keystone, Colorado.

When Hall's team measures the amount of foreign protein in the genetically engineered callus tissue, it finds little full-length phaseolin. Most of it is cleaved into fragments - albeit somewhat differently by sunflower and tobacco. When he mixes pure phaseolin with ground-up callus crown-gall tissue - a process mimicking extraction - the protein degrades, but Kemp believes that the losses may occur in the cells as well. This would be one explanation of why Monsanto's gene-spliced petunias exhibit antibiotic resistance from a cloned bacterial gene, while researchers have been unable to extract any of the kanamycin degradation enzyme from callus tissue or regenerate whole plants containing the gene. So far, no one has reported regeneration of sunflower plants from callus tissue. (Extracted from Newswatch, 6 June 1983.)

E. Coli membrane gives oxygen-free boost to anaerobe researchers

Work with anaerobic microorganisms, until now difficult or impractical, can be easier thanks to a technique reported by Dr. Howard I. Adler at a symposium in Gatlinburg, Tenn., on Biotechnology for Fuels and Chemicals. By adding a partially purified Escherichia coli membrane fraction that removes dissolved oxygen from bacterial media, Adler, who is a principal biologist at Oak Ridge National Laboratory, has grown 18 different species of anaerobes representing eight genera. He has filed a U.S. patent application on his process, with himself as assignee. Adler has tested his membrane fraction on 11 disease-causing anaerobes, including Clostridium botulinum, the botulism pathogen, and species of the Bacteroides and Peptostreptococcus genera, which infect the liver and other internal organs. All these pathogens grew, and for some of them, detection time was cut in half.

This is how his anoxic process works: The cytochrome-enzyme system embedded in the E. coli membrane transfers hydrogen from substrates in the media to oxygen to produce water. Adler puts 10 ul to 20 ul of this membrane fraction in each milliliter of medium, either from resuspended freeze-dried powder or a frozen suspension. The preparation retains its oxygen-removing ability for several months, and neither the membranes nor the oxygen-consuming reaction products are toxic to bacteria. He can therefore grow anaerobes in liquid-media-filled test tubes covered with loose-fitting caps, or plate them on solid agar containing the membrane fraction, then cover them with ordinary agar. These plates are incubated aerobically.

The ultimate goal is to handle anaerobes with standard bacteriological procedures similar to those used for aerobes and facultative organisms, such as E. coli. Adler has transformed wild-type C. butyricum with DNA from streptomyces-resistant mutants of both that organism and Bacillus subtilis - but at an efficiency ratio of only 1:5,000. Many anaerobes, notably C. acetobutylicum, make solvents such as acetone and butanol. If one could change the control mechanism to increase product yield, microbial production of these solvents could become economical. (Extracted from Newswatch, 6 June 1983.)

Microbial dustmen clean up toxic waste

Few of nature's poisons can compete with man's concoctions for persistent nastiness Compounds such as hexachlorobenzene, trichloroethylene or polychlorinated biphenyls (PCBs) are increasingly building a reputation for life-threatening toxicity, and a habit of escaping from factories or dump sites to play havoc with the environment.

Now a new line of research is taking shape in the US to combat these and other toxic chemicals that are known collectively as chlorinated aromatic compounds. Microbiologists are binding the new techniques of genetic engineering to the task of training microorganisms to degrade these chemicals in contaminated soil and water. Supporting this work are the government's Environmental Protection Agency (EPA) and the US Air Force, which are responsible for cleaning up poisoned communities like love canal, or old plants that once made the herbicide Agent Orange.

Organisms are tempting detoxifiers because they have the potential to do their work on site, saving the expense and publicity of digging up tons of soil, and burning or chemically cleansing it. And because organisms replicate themselves, they could be far less expensive than chemical or mechanical methods.

The EPA plans to spend almost one million dollars over the next three years, looking for organisms that can use the chlorinated aromatics as their sources of carbon. Perhaps the most intriguing approach is a project, planned by Dr. John C. Loper, a molecular geneticist, and professor of microbiology at the University of Cincinnati in Ohio. Loper hopes to win funding for the idea soon.

Loper is following up recent research by several scientists, particularly H. Weber and colleagues of the Institute of Toxicology in Zurich, Switzerland and John Brooker at the University of Adelaide, Australia: Weber found that dogs fed massive doses of one type of dioxin, TCDD, detoxified the chemical with the liver enzyme, cytochrome p450 monooxygenase, and Brooker used chick embryos as a source of the enzyme to track down the messenger RNA responsible for producing it.

Scientists at the EPA are eager to see cytochrome p450 mon-oxygenase work on other aromatic compounds common to our polluted environment. Loper plans to isolate the gene that codes for p450 from a library of candidate mammalian gene sequences and insert it into yeast. The yeast would be manipulated to express the gene and to manufacture the enzyme in large quantities, and eventually be able to thrive on hexachlorobenzene and other offending compounds.

That much accomplished, the yeast presumably could be spread over Seveso in Italy, Times Beach in Missouri, and other places where chlorinated aromatics such as TCDD have insinuated themselves into the environment.

The EPA won't till the soil with bugs until extensive field work shows whether the microorganisms will work outside the laboratory and has already engaged an eminent pioneer in the field of biotechnology to complement Loper's approach: Dr. A. M. Chakrabarty, microbiologist at the Medical Centre of the University of Illinois in Chicago.

Chakrabarty is concentrating first on organisms he scraped up from Love Canal and other American dumpsites. The organisms had learned to live on 2,4,5-T, one ingredient of the infamous Agent Orange. Working from these, and with microorganisms he is culturing in his laboratory to metabolise related compounds from the chlorodioxin group, Chakrabarty is seeking a single culture that can degrade 2,4,5-T to the point where heavily contaminated soil can be returned in a matter of days to healthy soil that can support plant life. From his microbial mix, he hopes to find the plasmid DNA responsible for the degradative ability. He can then arm an arsenal of microorganisms with an inherited lust for a variety of dioxin compounds.

The US Air Force has also latched onto microbiology as part of a large pollution control programme run by its Engineering and Services Centre at Tyndalle Air Force Base in the Florida panhandle. In one project, scientists at Wurtsmith Air Force Base in Michigan are taking their first close look at an organism that was found happily growing in the processing tower of a mechanical device for cleaning trichloroethylene out of contaminated groundwater. Trichloroethylene is a toxic industrial solvent.

Dr. James Tiedje and Dr. Stephen Boyd at Michigan State University, are awaiting final approval of a grant to support further research of a startling and previously unknown anaerobic organism, which they found in sludge from a Michigan sewage treatment plant and in lake sediments. As yet unnamed, the organism performs a novel trick - it removes the chlorine atom from the chlorobenzoate molecule, making the resulting benzoate compound vulnerable to further degradation by known aerobic microorganisms.

Although chlorobenzoates pose little risk to the environment, this dechlorination magic might also work for other chlorinated compounds: dioxin, hexachlorobenzene, PCB, 2,4,5,-T and their irrepressible classmates. In the long run, it is hoped to pinpoint the gene that conducts this sleight-of-atom, and join other microbiologists in the latest pursuit of the perfect microbial dustmen. (Source: New Scientist, 5 May 1983.)

Microbe-made deicing agent to substitute for salt on winter roads

Field trials in two states of the USA this year and next will test a noncorrosive, biodegradable bacteria-produced substitute for highway deicing salt. Working under a half-million-dollar R&D contract from the Federal Highway Administration (FHA), scientists at SRI Internal have identified a fermentation method to produce calcium magnesium acetate in large quantities from biomass feedstocks such as corn.

To commercialize the process will require developing a more efficient mutant strain of an anaerobic bacterium, Clostridium thermoaceticum, which yields acetic acid, the main cost item in making calcium magnesium acetate (CMA). In SRI's proprietary fermentation process, the organism converts simple sugars to acetic acid, which is essentially the only product other than new cell mass that it produces. The fermentation method uses conventional techniques to convert corn to simple sugars, then ferments these to acetic acid. C. thermoaceticum was chosen for the project because it produces 83 per cent of theoretical maximum yield.

CMA produced from a corn grain feedstock would cost seven or eight times more than salt, but when the cost of salt damage to the highway system and the environment is factored in, use of CMA could be justified for special applications, such as areas where salt runoff is polluting water supplies or to protect the decks of highway bridges. A preliminary FHA study finds, moreover, that CMA is more soluble than salt and so would be more effective at deicing roadway and bridge surfaces at lower temperatures.

Extensive use of chloride salt deicers - about nine million tons each winter - has been a major cause of deteriorating the nation's transport infrastructure. Some estimates put the cost of repair at $47 billion, he adds.

In February SRI delivered 200 tons of CMA produced by conventional means to state highway departments in Michigan and Washington for deicing road tests. FHA considers CMA one of the most promising salt substitutes, Maryknowski says. It is nontoxic, noncorrosive, and the acetate ion readily degrades. But it is available now only as a specialty chemical in limited quantities at high prices.

This would change if a mutant strain of C. thermoaceticum could be isolated that was able to churn out the acetic acid at a pH of 5 or 6 rather than the 7 the wild-type organism tolerates. The lower pH is necessary because the magnesium oxides - one of the components of CMA - won't dissolve and react in alkaline conditions. If FHA funds further research and SRI wins a new contract, the scientists plan to tailor-make the low-pH, high-yield mutant by conventional selection procedures rather than recombinant DNA.

It is also reported that Union Carbide researchers, seeking a cheap way to make acetic acid, have developed a mutant organism that can tolerate a pH of 4.5, but it doesn't produce much acid. (Source: Newswatch, 21 March 1983.)

EPA aims to shoot down dioxin, funds scientists at three research centers

Engineering a microorganism that will eat dioxin is Dr. Ananda M. Chakrabarty's latest assignment. The University of Illinois microbiologist said during an international conference held at Cologne, German Federal Republic, in April on genetic manipulation that the U.S. Environmental Protection Agency (EPA) has awarded him a three-year grant for $264,000 to produce a bug that will break down the deadly chemical pollutant.

The agency is also supporting dioxin-degrading research at the University of Cincinnati and Battelle Laboratories in Columbus, Ohio.

The first step in Chakrabarty's project was to develop a minichemostat to deal with very small volumes because of the material's extreme toxicity. He will have to run this continuous culture non-stop for a year or more to select microbial strains before seeing results. His strategy is to develop any microbe that will degrade dioxin. For openers, he is working with Pseudomonas cepacia, a naturally occurring soil organism he has already engineered to break down 2,4,5-T, the refractory component of the defoliant Agent Orange, of which dioxin is a production by-product. Like dioxin, Agent Orange is a chlorinated aromatic.

Chakrabarty's P. cepacia soil bacterium could in principle be modified to break down other chemicals besides 2,4,5-T. However, as an aerobe, it depends on an adequate supply of oxygen, so can live only in the top six inches of soil, well away from some toxic chemical deposits 100 feet or so below.

The Illinois scientist plans to improve the efficiency of the microbe by constructing a plasmid that codes for the enzymes that attack 2,4,5-T and can migrate to other species of soil organisms, such as Arthrobacter and Acinetobacter. To do this he will use a cosmid vector which has the advantage that it will accept large amounts of DNA and move easily into other bacteria. The genes being dealt with are often around 30 kilobases long. Genes have already been cloned into the vector that degrade chlorobenzoate, a decomposition product of polychlorinated biphenyls (PCBs). But without practical field trials, development of the toxin-degrading microbial strains cannot proceed.

A year ago, the EPA gave microbiologist and molecular geneticist John C. Loper at the University of Cincinnati $135,000 to pursue dioxin-degradation research. Loper, also professor of environmental health, is attempting to express the cytochrome P-450 mammalian liver enzymes in the yeast Saccharomyces cerevisiae, which can live in soil. Some of these enzymes dechlorinate aromatic compounds, and Loper wants to incorporate them into the yeast system that breaks down similar agents. He is working with the dioxin surrogates, hexachlorobenzene and PCBs, but has yet to clone a P-450 gene into S. cerevisiae.

With a $96,000 EPA grant, researcher Melanie E. Davis at Battelle Laboratories in Columbus, Ohio, is trying through mutation selection of milkweed tissue-cultured cells to regenerate a plant that takes up and breaks down dioxin. She is now working with surrogate compounds - pentachlorophenol, a defoliant, and the insecticide lindane - but last year experimented unsuccessfully with hexachlorobenzene, and insoluble fungicide. (Extracted from Newsweek, 2 May 1983.)

Pyrolysis gas from solid wastes

Biomethanation of pyrolysis gas produced from solid wastes produces low-cost synthetic natural gas, according to Dynatech for DOE. The reactions necessary to upgrade pyrolysis gas to pipeline quality SNG may be accomplished in catalytic or biological processes. In the latter, the pyrolysis gas is purged into a bubble column containing selected anaerobic microorganisms that perform the shift conversion and methanation. Advantages of biomethanation versus catalytic methanation include adaptability to any mixture of pyrolysis gases, insensitivity to poisoning by sulfur compounds, simplified gas cleanup, ability to utilize nitrogen contaminants, the utilization of reaction heat to form cell mass, and minimal water use. (Source: Technology Update, 14 May 1983.)

New power source?

A University of Tokyo research team may have found a power source to be used to make a midget engine by using the natural movement inside every living cell. The team found that natural movements found in cells are generated by mutual molecular actions between two kinds of protein - actin and myosin - which form fibers. When the slender actin fibers push in between the thick myosin fibers, it causes a contraction of the muscles. When a solution with these fibers is raised to a certain level, a perfectly regular circular flow in a fixed direction is caused, as the actin and myosin react with each other by consuming ATP, an energy-creating biochemical compound. This embryonic biological engine is very fuel efficient when turning chemical energy into physical energy. (Source: Technology Update, 14 May 1983.)

A cross-section of prototype sensors

Sensor	Reference
Nitrate	Kobos, Rice and Flournoy (1979); Anal. Chem. 51, 1122.
Lactose, Urea	Mattiasson, Danielsson and Mosbach (1976); Anal. Lett., 9, 217.
L-methionine	Fung, Kung, Sung and Guilbault (1979); Anal. Chem. 51, 2319
L-glutamine	Rechnitz, Arnold and Meyerhoff (1979); Nature 278, 466.
NAD	Riechel and Rechnitz (1978); J. Membr. Sci. 4, 243.
Penicillinase	Cilliff, Williams and Wright (1979); Chem. Abstr. 90, 192596t.
Lysozyme	D'Orazio, Meyerhoff and Rechnitz (1978); Anal. Chem. 50, 1531.
Anticiuretic Hormone	Updike and Treichel (1979); Anal. Chem. 51, 1643.
Hepatitis B	Boitieux, Desmet and Thomas (1979); Clin. Chem. 25, 318.
Antigen	Aizawa, Morioka and Suzuki (1978); J. Membr. Sci. 4, 221.
Heavy metals	Mattiasson, Danielsson, Hermansson and Mosbach (1978); FEBS letters 85, 203.

(Source: Practical Biotechnology, April 1983.)

COUNTRY NEWS

Australia - Pinpoints genes for symbiotic nitrogen fixation

More than most advanced countries, Australia depends upon bacterial nitrogen fixation rather than synthetic nitrogen fertilizers. John Shine, of the Centre for Recombinant DNA Research, Australian National University (Canberra, Australia) and his co-workers have probed genes responsible for some of the first steps in establishing the symbiotic relationship between nitrogen-fixing rhizobial bacteria and clover plants. Large plasmids in Rhizobium trifoli, the bacterium responsible for nitrogen fixation in clover, contain the genes for both nitrogenase enzyme and for the bacterial contribution to formation of nodules in the plant roots. This is similar to the symbiotic system in alfalfa. Generally, rhixobial bacteria will fix nitrogen only when they are established inside nodules formed in the roots of legume plants, such as clover, alfalfa, or soybeans.

Shine's group is searching for genes responsible for each step of the nodulation process. Their approach involves detection of nodulation genes by causing a mutation in the plasmid DNA with the Tn5 transposon. The transposon interrupts a gene's DNA sequence by inserting itself into the DNA chain and inactivates the gene. If the bacterium containing the mutated gene will not perform one of the nodulation steps, then that gene is obviously involved. Once identified, the unmutated gene can be isolated and cloned and inserted into the mutated bacterium. If the mutant then functions normally, the gene's function is confirmed.

Shine has also transferred DNA sequences containing genes responsible for nodulation by R. trifoli into different bacteria, other rhizobial bacteria and also Agrobacterium species, that normally do not produce nodules in clover. He has been able to make these bacteria infect plants and produce small nodules, but the nodules do not have the complicated structure needed to provide an environment in which the nitrogenase can be produced and catalyze nitrogen fixation. Although he has identified genes involved in the nodulation process, Shine has no idea what the genes' protein products are or exactly how they function. (Extracted from Genetic Technology News, March 1983. Address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Australia - Human birth hormone agreement

Genentech, the biotechnology company from the United States has signed an agreement with the Howard Florey Institute of Experimental Physiology and Medicine in Melbourne for commercial development of the human-birth hormone, relaxin. The hormone has great potential for alleviating problems during childbirth and, perhaps, in the treatment of arthritis.

The deal follows the recent announcement of the production of a pure form of the hormone by researchers from the institute, using genetic engineering techniques. Genentech outbid rivals from Japan, Britain and the United States.

According to Dr. Derek Denton, director of the Florey Institute. the agreement with Genentech should allow clinical trials of the hormone to begin within two years. It could be on the market within four years. Under the agreement, the institute will receive royalties if Genentech successfully markets the hormone. (Source: New Scientist, 7 April 1983.)

Australians engineer vector to transform grain crops

Plant scientists in Australia are developing a vector they hope will make the genetic engineering of corn and other cereals a reality. Over 500 people who attended the Genetic Manipulation Impact on Man and Society meeting at Cologne, FRG, in April, heard how transposable elements in corn DNA, so-called Ds elements, could be turned into vectors for transforming monocotyledonous crops. Such a vector, lacking in monocot genetic engineering, could plug the gap the Ti plasmid may fill with dicotyledons such as tobacco, tomatoes, and beans.

Dr. Jim Peacock, chief of the plant industry division at the Commonwealth Scientific and Industrial Research Organization (CSIRO) in Canberra, reported on his work with mutant strains of corn containing Ds elements within their alcohol dehydrogenase (ADH) gene. Peacock has isolated and cloned the Ds element and ADH genes into Escherichia coli. Ultimately, he will try microinjecting the elements, containing foreign and ADH genes repackaged in E. coli plasmids, directly into the cytoplasm of single corn cells.

However, integration of Ds elements into the corn chromosome depends on the presence of another transposable element, Ac. Recently cloned at the Carnegie Institute of Washington in Baltimore, Md., Ac may be useful for transforming other cereals such as wheat and barley in which transposable elements have not been identified.

Microinjecting engineered Ds elements into a corn cell could be difficult. The Ds element only transforms a cell when it is inside the nucleus. On the way it could easily be degraded by enzymes in the cytoplasm. The biggest hurdle will be growing the genetically altered corn cell into a mature plant. Dr. Charles E. Green, research director at Molecular Genetics, Inc., in Minneapolis, Minn., has developed mature corn plants from aggregates of cells grown in suspension culture. By choosing cells from the embryonic part of the corn seed, then carefully adjusting the amount of proline in the nutrient medium, he can grow friable embryonic callus into adult plants. The ultimate goal is a single cell usable for genetic engineering and somatic hybridization. (Source: Newswatch, 2 May 1983.)

Australia - Government biotechnology programme

Australian government is likely to establish a national biotechnolgoy programme to fund specialist research groups at universities and to establish five or six world-class biotechnology research centres. Initial funding may be $2 million, perhaps more, rising to $13 million within three years. Australia also wants to establish a venture capital market for financing high technology firms. (Source: Genetic Technology News, June 1983. Address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Canada - biotechnology plan gets a chilly reception

For years the Canadian government has considered promoting the development of a biotechnology industry through research grants. At one point, Canada declined to join in a research effort sponsored by the United Nations. Now, in a surprise move, the government has unveiled plans to funnel more than $81 million into biotechnology research. Equally surprising, the plan is running into some sharp criticism.

Under the latest proposal from Ottawa, the biggest part of the funding will go to construct a $50 million laboratory in Montreal, which will be the cornerstone of Canada's biotechnology strategy. The strategy calls for efforts to be focused, at least initially, on animal diagnostic chemicals and vaccines, bacterial ore leaching, pest control, nitrogen fixation, and genetic engineering. Areas of prime interest to Canadian industry include forest products, food processing, mineral recovery, high-yield plants, microbial fertilization, and health care.

Construction of the biotechnology centre will begin by the end of 1983, with completion scheduled for late 1985. It will have an annual budget of $40 million and a staff of 220, including 60 scientists and 120 technicians. Canada's National Research Council will hire the researchers and administer the research centre.

Canada declined to bid on a proposed United Nations biotechnology centre after concluding that the facility would have been too costly and would have focused on biotechnological training and research which would have been of less value to the Canadian economy than a Canadian-sponsored centre. Several Canadian cities, including Montreal and Toronto, had pressured Ottawa to bid on the U.N. research facility.

Critics of the latest plan contend that the government's approach is haphazard, designed primarily as an employment measure for the vast pool of technicians put out of work by the decline of Canada's pharmaceutical industry. That decline, they note, was brought about largely through the removal in 1969 of patent protection for drugs, which prompted a number of multinational drug companies to close their Canadian research operations.

Critics also contend that there is a dearth in Montreal of the sort of industry experts needed to give proper commercial direction to projects. (Extracted from Chemical Week, 25 May 1983.)

Federal Republic of Germany - Brain drain threatens progress

As in other European countries, there are widespread fears in FRG that the country might fall behind in the fast moving field of biotechnology. The agreement between Hoechst and Harvard University to cooperate in work done in the United States has therefore caused concern, although decisions by the other two large chemical groups to support research

centres in the FRG have done something to restore confidence. Bayer has agreed to provide DM 3 million over three years to the Max Planck Institute (MPI) at Cologne for research in breeding, while BASF will fund research at Heidelberg for five years at DM 1 million per year.

In fact there has been a federal programme on biotechnology since 1979 and last August the then minister at the federal ministry of technology (BMFT), Andreas Von Bülow, proposed a 14 per cent increase in support for this year and a radical review for the future. This task has now fallen to his successor, Heinz Riesenhuber, who promised to give high priority to biotechnology research. Nevertheless, the state of biotechnology is still causing concern, as has been shown at the latest meeting of the senate of Max Planck Gesellschaft (MPG) in Stuttgart. Perhaps in response to the federal government's call for closer contacts between research and industry, the MPG president, Professor Reimer Lüst, has been pressing for more cooperative projects at the Max Planck institutes.

On the other hand, there are already numerous institutes more or less directly involved with genetic engineering and biotechnology, some with industrial support; for example biochemistry in Martinsried, biology and virus research in Tübingen, genetics in Berlin, immunology in Freiburg, experimental medicine and biophysical chemistry in Göttingen, cell biology in Ladenburg and selective breeding at Cologne.

Among the Länder, Baden-Wurtemburg is providing DM 30 million for new facilities at the University of Heidelberg; in Berlin there is co-operation between the authorities and the pharmaceutical firm Schering with MPI for molecular genetics. Support from the Länder is also being given in Munich and Cologne.

The main concern at the MPI senate meeting was the shortage of suitably qualified researchers. Many have joined the brain drain across the Atlantic and more resources are needed to stop and eventually to reverse the flow. Although these are expected to be provided by the federal ministry in part, it was felt that such funds should not be channelled into large state research centres. Thus biotechnology will do little to help BMFT to solve the problem of what to do with those centres that have outlived their original purpose. (Source: Nature, 21 April 1983.)

FRG Researchers develop new genetic engineering technique

Although at present Japan and the United States have a considerable lead over other industrial nations in various areas of biotechnology, it would be mistaken to expect news of successes only from those countries. Elsewhere as well noteworthy achievements are being made, for example in the laboratories of the Association for Biotechnology Research (GBF) in Stoeckheim near Braunschweig. It is here that in recent years the genetics section in particular has drawn attention to itself, such as through the development of the so-called cosmid method, for example, which could become an important tool in gene technology.

For the injection of the DNA material into the bacterium, this method uses so-called bacteriophages. These viruses, which are only a small fraction of the size of a bacterium and which are completely harmless to people, are bacteria killers, as their name already signifies. They can attach themselves to a bacterium in relatively large numbers. The gene chain which is accommodated in their heads then pours out into the interior of the cell and uses the cellular apparatus for its own propagation. In this process, the bacterium perishes as a rule.

The prerequisite for the development of the cosmid technique was created by British scientists, who succeeded in removing the intrinsic DNA from the heads of bacteriophages, more precisely those of the bacteriophage named "lambda", and then filling them with foreign DNA. The Braunschweig gene technologists were then able to produce a sort of optimal transport plasmid. It is very short, so that it can accommodate much foreign DNA, and it contains above all a "cos" site. This could be called the "splice" site of the ring. It is the prerequisite for the plasmid being able to be incorporated by the bacteriophage head and later, after the bacteriophage attaches to the bacterium, for being injected by this into the new host cell.

The bacteriophage is thus used as a vehicle. Since aside from the plasmid forced upon it the bacteriophage does not contain any DNA which could be dangerous to the bacterium, the bacterium also does not suffer any damage because of this bacteriophage attack. The injected enlarged plasmid is thus propagated along with the bacteria and can develop its intrinsic activities. Since the cosmid technique is still in its infancy, it is difficult to properly

assess as yet the opportunities which it offers. For basic research, the analysis of genes and their arrangement on the DNA strands, it will undoubtedly assume great significance, and it is also likely to open up new and quite far-reaching possibilities in the sector of product preparation - the utilization of bacteria as chemical factories. (Source: VDI Nachrichten, 12 November 1982.)

FRG - New process to fuse human cells has been developed

Gene transfer and production of monoclonal antibodies will be facilitated by a new process, developed by U. Zimmermann of the Nuclear Research Centre (Juelich, FRG), which uses electricity to fuse the cells. Substances within cell walls are encapsulated more easily than with current methods. Electrofusion exposes cells to a low-level, non-homogeneous electric field that orients the cells into a circle. A direct current pulse opens pores in adjoining cell walls, allowing a mixing of cell contents and their fusion. The permeability of a cell's outer wall can also be changed by the method, allowing substances the size of genes to be encapsulated. Electrofusion is 10,000 times more efficient than current methods. (Source: Technology Update, 21 May 1983.)

FRG - Genetic engineering institute established in Berlin

A co-operative venture between Schering AG and the State of Berlin, which has as its goal the establishment of an institute of genetic engineering, must be viewed as an important step for biotechnological research in Germany. For the next 10 years plans call for expenditures amounting to DM 80 million; these are to be provided equally by Schering and the State of Berlin. The cost of the building and initial outfitting are estimated at DM 20 million, the running costs at DM 6 million per year. Naturally the House of Deputies must agree to Berlin's share. In addition, an effort is to be made to attract outside funding especially from supraregional organizations involved in research support. The institute will be primarily engaged in basic research in the area of cell biology. In order to catch up as quickly as possible with the international level, the institute will also train qualified junior workers for science and industry. The director is expected to make a substantial impact on the work, and at the same time function as an advanced school instructor and represent the institute with its approximately 30 staff members.

In order to guarantee minimal breadth in the research, there is provision for departments of microbiology, biochemistry and molecular genetics. The institute will be operated as a limited liability company. It is to operate autonomously and independently and will be the source of ideas for basic research at advanced schools and other research facilities.

An option on the results developed in the institute is to be granted to Schering as a founding member. If it is exercised, then the customary compensation is to be paid. The part of the total financing which Schering is responsible for corresponds to about one-third of the total outlays which the company will provide during the same period in the area of product and method-oriented research and development in genetic engineering. There is a long tradition of biotechnology at Schering since steriod hormones have been produced by fermentation on an industrial scale. Since 1979 Schering has been testing the possible application of genetic engineering to the production of various low-molecular substances. The aim of a specific programme is the development of special methods to produce proteohormones and amino acids. In the latter area it was possible to conclude the first phase of basic research, successfully. (Source: Europa Chemie, 8 October 1982.)

Finland - Alpha-amylase gene sheds light on protein secretion by bacillus

A big advantage of Bacillus subtilis as a microorganism for cloning is that it will often secrete the product wanted into the fermenter medium rather than retain it inside the cells. Sometimes this can make purification problems much simpler. As part of their overall goal of constructing a "general" secretion vector for B. subtilis, researchers at the University of Helsinki (Helsinki, Finland) have isolated and determined the complete nucleotide sequence of the gene for an alpha-amylase and the promoter and signal sequences on both sides of it. They used this information to deduce the amino acid sequence of the alpha-amylase enzyme the gene codes for. The alpha-amylase they are studying is from B. amyloliquefaciens. The enzyme breaks down starch, chiefly into maltose saccarides. When cloned in B. subtilis, the alpha-amylase gene expressed - produced the enzyme and secreted it. The B. subtilis host processed the pre-enzyme (which contains 514 amino acid units) correctly by cleaving off the signal sequence responsible for secretion. The excreted enzyme has 483 amino acids. (Source: Genetic Technology News, March 1983. Address: 156 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

France - 95 million francs for biotechnologies in 1983, plans outlined

On 31 January Jean-Pierre Chevenement announced that the government would spend 95 million francs this year on the mobilizing programme "to stimulate the development of biotechnologies" in order to "place France among the leading nations in a field that is essential to our future".

The minister of research and industry had just attended the first meeting of the "national committee" working on these technologies. This committee is composed of about 30 people from the ministries of research and industry, health, agriculture, national education, and the budget, major research organizations. According to the minister, this committee will act as an actual parliament which will spur on the mobilizing programme, and a politically-oriented forum in the field of biotechnologies.

France cannot remain outside the field of biotechnologies. The world market for second generation bio-industries, that is, excluding the traditional fermentation industries, now amounts to nearly 140 billion francs. "Within 10 years, this market will reach the level of 250 billion", claimed Mr. Chevenement. "France's share of this market is now 7.3 per cent. Our goal is to reach 10 per cent of the market within the next 10 years."

As the minister reminded his audience, the field of applications includes the pharmaceutical and chemical industries, along with agriculture, food processing, energy, raw materials, and the environment.

According to the plan, one should expect a strong growth in the pharmaceutical and immuno-industries, a sizeable growth for the food processing industry, a potentially strong growth in the areas of water treatment and energy. Plans for some other sectors still remain to be drawn up.

While some organizations have already been created (Immunotech by the Pasteur Institute, Hybridolab by the INRA), some transfers arranged and associations established, French industry is still hesitant because the biotechnologies, despite a number of patents filed, have hardly led to any finished products yet. Some projects are now under study. The major nationalized groups will be encouraged. Support will be offered to "venture capital" companies which have been founded or which will be established in the field of genetic engineering and the production of monoclonal antibodies.

Despite the competition beginning to appear all over the world, there is at present a strong desire for bilateral cooperation agreements, between the European countries, with Canada and the province of Quebec, and even with Japan. (Source: AFP Sciences, 3 February 1983.)

France - Government investments

The government will invest F620 million over 5 years in the biotechnology industry and expects to generate a turnover of F3 billion/year by 1985. The government has already made funds of F140 million available to biotechnology companies. The Comité d'Orientation pour le Devéloppement des Industries Strategiques (Codis) has recently announced grants to three biotechnology companies: Clause, Claeys-Luck and Clonatec (all french). Clause had a turnover of F604 million in 1981-82, with 10 per cent earned from exports, in the vegetable and flower seed sector. Claeys-Luck is the leading European cereal producer and had a turnover of F1 billion in 1981-82, with 40 per cent earned from exports. Clonatec produces monoclonal antibodies for use as ultra-specific reagents in the health and agricultural food sectors. (Source: Technology Update, 21 May 1983.)

France - Purification equipment

France's Elf Aquitaine will have a high-performance liquid chromatography (HPLC) package ready for delivery before the end of this year. HPLC is widely used for accurate separations on a laboratory scale for analytical determinations. More recently HPLC equipment has been scaled-up for pilot-plant or commercial purification of proteins made by recombinant DNA processes. Elf Aquitaine's system features a column 30 cms in diameter and 3 metres high. A hydraulically driven piston can be forced through the column from the bottom to provide high pressure needed on the packing material, usually finely divided silica in a slurry. The piston can also extrude the packing material when necessary. Efficiency level is 11,000 theoretical plates per metre. Capacity is 1 kg/hr of product per injection. Flow rate can be as high as 500 litres/hr at a pressure of 500 bars. Proteins, peptides and other biomolecules can be processed, as can lower molecular weight materials. (Source: Genetic Technology News, June 1983. Address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

France - Isolating a gene for treating haemophilia

The first step toward the production of "coagulation factor 9", a genetic material used to treat one form of haemophilia, was isolated by Transgene (Strasbourg, France) as part of a joint research project with France's Institute Merieux. The development could lead to laboratory manufacture of factor 9, now obtained only from blood. Factor 9 helps blood clot in people with haemophilia. (Source: Chemical Week, 11 May 1983.)

France - New company formed

GIE-Monser-bio (France) is being formed to study and develop biotechnology, using milk as a raw material. The group will be supported by the cheese manufacturer Entremont, Sanofi, Elf bioindustries and Secta-Yves Rocher (all France). The group will develop and market various milk-based products such as lactic acid D, both for the consumer food industry and the flavour, fragrance, animal feed, cosmetic and pharmaceutical industries. As part of the agreement, Elf has acquired 19 per cent of Entremont, a leading emmenthal cheese producer and one of the most technically advanced French cheese makers. The French government will support biotechnology with grants of F95 million in 1983, versus F47 million in 1982. Some 50 per cent of grants will go to industry, versus F12.5 million in 1982. France owes 10 per cent of the $35 billion world market for biotechnology in 1993, versus 7.5 per cent at present. (Source: Technology Update, 21 May 1983.)

Italy - Genetic engineering patent

The first Italian patent in the field of genetic engineering has been issued to Assoreni, the research company of the state-owned ENI group. It concerns a new system which makes it possible to produce proteins using soil bacteria. (Source: Europa Chemie, 28 October 1982.)

Italy - R&D expenditure

Biomedical technology R&D expenditure will be Llr 139 billion in 1983-87. The government will provide Llr 73 billion and private enterprise Llr 51 billion and Llr 13 billion will come from a special grant set aside by the government for health and biomedical technology research. It is estimated that output of the sector could rise to Llr 581.5 billion/year by 1987, versus Llr 348.3 billion in 1983, and that Italy's world market share in the sector could rise to 8 per cent by 1987, versus 6 per cent in 1983. (Source: Technology Update, 21 May 1983.)

Japan - Sythetic alpha-neo-endorphin gene expresses in Escherichia coli

Cloning the gene for alpha-neo-endorphin (α-NE) is a good way to produce enough material to study. Alpha-neo-endorphin is interesting as an enkephalin (a brain protein) with very potent opiate activity. Kasuhiro Ohsue of the Osaka Research Institute for Microbial Disease (Osaka, Japan) and co-workers have developed an improved rDNA process for producing the protein. They fused a synthetic gene coding for α-NE with the gene for Escherichia coli alkaline phosphatase within a plasmid vector. The vector transformed E. coli and produced large quantities of the fused protein product. However, neither protein was transported to the periplasmic space in the bacterial membrane where it could be secreted. The Japanese group solved this problem by deleting the control region from the fused genes and substituting UV5 lac promoter region. Yield of α-NE reached 1,350 ng/ml with the new system. (Source: Genetic Technology News, June 1983. Address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

Japan - Starch converter

A powerful, diastatic enzyme that converts the starch in rice, corn and other grains into sugar without heat has been developed by the Japanese Ministry of Agriculture, Forestry and Fisheries' Foodstuff Research Institute. The enzyme may be used to produce fuel alcohol from plants and will reduce energy costs for foodstuff producers. Researchers extracted the enzyme from a black mould, which lives on the sago palm from Papua and New Guinea. After adding the enzyme, a type of amylase, over 95 per cent of the rice, corn, wheat and tapioca starches converted into sugar in two days at room temperature. With the conventional method, starch is steam heated before it converts to a paste, which is then reacted to amylase. This new amylase strain reduces the energy needed to heat the starch 20 per cent and has a 4-5 times stronger saccharification capacity, versus conventional enzymes used to make alcohol. (Source: Technology Update, 14 May 1983.)

Japan - Training and education grant

The Ministry for International Trade and Industry will grant ¥7.2 million to the Japanese Association of Industrial Fermentation to promote education and training of personnel engaged in bioindustry in fiscal year 1983. The Japanese Association of Industrial Fermentation will provide another ¥7.2 million to offer a biotechnology curriculum. (Source: Technology Update, 16 May 1983.)

Mexico - Three-nation coffee-rust program blighted

Ironically, international efforts to save Mexico's top dollar-earner (after petroleum) are being shortchanged by the country's currency collapse, economic crisis, and political changes. In 1982, Mexico exported $550 million worth of coffee, but during that year a fast-spreading fungal infection, the orange leaf rust, blanketed the country's principal coffee-growing state of Chiapas and invaded neighboring Oaxaca. Meanwhile, a three-nation biotechnology-based counter attack against the infestation, planned last year, is stalled while Mexico completes its transition from one presidential administration to another.

Plant scientists at the University of Chapingo had developed joint tissue-culture, cloning, and selection strategies with Purdue University in West Lafayette, Ind., and Portugal's Coffee Rust Research Institute in Lisbon, to propagate new rust-resistant coffee varieties. Right now, a research team at Chapingo are transplanting callus-produced plantlets from growth chambers to greenhouses. These nurseries, installed at a cost of $750,000, will soon turn out 200,000 cloned rust-resistant plants every three weeks of the Catimor variety of Coffea arabica. In June, they will be joined by a Japanese scientist, Hirofumi Uchimiya, from the University of Tsukuba in Japan's "science city", in a project to improve the Timor rust-resistant variety by protoplast fusion. Meanwhile, the Lisbon research institute is sending a supply of rust toxins newly extracted from the spores of infected coffee plants to Mexico. Researchers plan within the next six months to apply these exudates to plant cells now in tissue culture and later this year select those showing resistance for regeneration.

Chapingo is tranferring its first 10,000 cloned Catimor plantlets to Mexico's Coffee Research Institute in Jalapa, Vera Cruz. There they will be raised in nurseries for seed, from which new plants will be grown for eventual commercial distribution to coffee growers under a 10-year plan for gradual replacement of nonproductive and infested plantation trees with the new resistant varieties.

The economic benefits of cloning over chemical spraying are compelling. A year ago, spraying cost 7,848 pesos a hectare ($32 an acre). In 1983, this figure has more than tripled to 26,370 pesos a hectare. To spray Mexico's entire crop would take over $66 million a year - an eighth of its annual coffee-export income. (Extracted from Newswatch, 4 April 1983.)

The Netherlands - Split Ti-plasmid ease manipulation of DNA in plant cells

Recent successes in higher plant genetic engineering depend on using the Ti-plasmid to introduce foreign DNA into plant cells. Researchers at the University of Leiden in The Netherlands have developed a way to introduce genetic information into plants by using only part of the Ti-plasmid DNA. The Ti-plasmid is found in Agrobacterium tumefaciens, a bacterium that causes crown gall tumors in plants. When a tumor is formed part of the DNA in the Ti-plasmid, the T-DNA, becomes integrated into DNA of the chromosome in plant cells. Foreign DNA spliced into T-DNA can also be transferred into the plant cells and has recently been induced to express foreign protein in the plant cells.

The new technique involves separating two regions of the Ti-plasmid and placing them in two separate plasmids. One of the new plasmids contains the T-DNA. The other contains the vir-region of plasmid DNA, which is essential for tumor induction. The plasmid containing the T-DNA is much smaller than the original Ti-plasmid and can be transferred into and out of Escherichia coli. This makes for easy splicing of foreign genes into the T-DNA. Once small plasmids containing T-DNA and the wanted foreign genes have been constructed in E. coli, they can be transferred back into A. tumefaciens. However, the small plasmid lacks the DNA necessary to cause A. tumefaciens to develop a plant tumor, essential for transforming plant cells. This difficulty is overcome by adding a second small plasmid containing the vir-DNA. Bacteria with both plasmids will induce plant tumors and the T-DNA can be integrated into plant chromosomes. (Source: Genetic Technology News, June 1983. Address: 150 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

The Netherlands - Company receives funds for genetic research of potato starch

With the support of the authorities, the potato starch company Avébé is going to try by genetic manipulation to grow a variety of potato that yields starch that is equivalent to cornstarch. At present 750,000 guilders has been made available for the purpose. This is being done within the framework of the integral structure plan for the north of the Netherlands.

Especially in the food sector so-called branched starch or amylopectin is an important raw material. This form of starch is present only in mixed form in potato starch. At very high costs the potato starch can sometimes be purified so that the branched form is suitable for use.

Cornstarch, however, yields amylopectin in almost pure form, and it is also much cheaper. Avébé has completely lost its share of the market in this sector to the cornstarch producers.

To win that share and possibly expand it, Avébé, in collaboration with the TNO (Netherlands Central Organization for Applied Scientific Research) experiment station for potato processing and the biotechnological center of the University of Groningen, wants to develop a variety of potato that contains only starch of the amylopectin type, and this must be done by genetic manipulation. The project will probably take a considerable time. An incidental advantage is that it may also be possible to build other properties into the new potato race, such as resistance to potato blight. (Source: NRC Handelsblad, 7 February 1983.)

Sweden - Collaboration in genetic technique research programmes

A cooperation agreement concerning research and development work aimed at creating new and improved types of corn, plant biosystems and industrial micro-organisms through the application of genetic techniques has been signed by the Swedish sugarbeet seed and forest seed specialists Hilleshög AB, Landskrona, a member of the Cardo group, and Plant Genetic Systems NV, Brussels. As a result, the Swedish company will gain access to the entire EEC market, it is said.

The cooperation will consist of two R&D programmes, one concentrating on agriculture, the other on industrial applications. The agricultural programme is focussed on achieving a higher yield and increased stress tolerance in important corn types in order to reduce the amount of chemical additives needed or render them unnecessary, among other things.

The industrial programme will concentrate on improving the manufacture of industrial chemicals by using cheaper raw materials and methods leading to the reduction of undesirable by-products. It is hoped that the utilization of modern biotechnological know-now will result in changes in conventional chemical methods. (Source: SIP The Swedish-International Press Bureau, Linnégatan 42, S-114 47 Stockholm.)

Switzerland - Collaboration with Shionogi (Japan)

Biogen (Switzerland) will collaborate to develop a potential anticancer agent, interleukin-2, with Shionogi (Japan), with which it is already developing rDNA human serum albumin for use in blood transfusion and rDNA human immune interferon. The lymphokine interleukin-2 promotes most of controlled cells of the immune system, and may also be useful to treat immuno deficiency diseases. Shionogi will conduct clinical trials using rDNA interleukin-2 supplied by Biogen, as part of the commercial development in Japan. Ajinomoto (Japan) has successfully produced interleukin-2 in genetically altered E. coli bacteria, and will scale up production, with possible commercialization in five years. Biogen's rDNA human immune interferon could start European phase 1 clinical trials in a few months, with Shionogi carrying out Japanese clinical trials and commercialization. Biogen is also developing techniques to produce glycosylated immune interferon in genetically altered mammalian cells, while its Dutch subsidiary is developing 3 antitumour cultures using PBR vector in E. coli. (Source: Technology Update, 2 April 1983.)

Thailand - Biotechnology and the National Development Plan

Thailand, generally regarded as an agricultural country with a significant surplus of produces for export, intends to move toward industrialization within the next ten years. By the end of the Fifth 5-Year Plan (1982-1986) the country plans to become semi-industrialized and hopes to become a newly industrialized country at the end of the Sixth Plan. Major areas of industrial development being emphasised include agro-industry, utilization of energy and the restructuring of industry. Since the country's agricultural and industrial sectors are

very closely inter-related, it is hoped that the industrial development plan will also help promote the development of the agricultural sector and thereby the majority of people of Thailand. In order to appropriately prepare the country for the anticipated industrial development the government has felt the need to seriously review its science and technology policy and restructure its science and technology development programme and a committee for the selection and identification of technology for development has been set up. An area of industrial technology which has been considered and selected to be of high priority for intensive R&D inputs during the present 5-Year Plan is biotechnology, with special emphasis on fermentation technology. In the agricultural sector, seed technology has been emphasized.

At present several research laboratories and institutions are engaged in various research and development works in biotechnology in the fields of medicine, industry, and agriculture. While most universities are working mainly at small laboratory scale, research institutions, such as Thailand Institute of Scientific and Technological Research and Department of Agriculture, are involved at the pilot stage and large-scale operation.

Thailand - Biotechnology research and development at Kasetsart University

Kasetsart University has long been known for its excellence in the field of agricultural education and research and has given equal importance to both basic and applied research, with several technologies already successfully transferred to the user. Among the better known biotechnology research findings and their application are the following:

- The propagation of a number of high-priced and rare species of orchids through tissue culture techniques;

- The commercialization of mushroom spawn cultivation;

- The propagation of high-priced ornamental plants;

- The artificial insemination of fish.

In recent years, and with the establishment of the Biotechnology Department in the Faculty of Agro-Industry, the University has placed increasing emphasis on industrially oriented biotechnology research with the aim to increasing the effective utilization of the country's readily available bioresource materials. In addition to the in-house research, the University has also encouraged contract research work as a means to establish linkage with the private business sector, industrial as well as agricultural. As such, it was felt necessary to promote a multidisciplinary research approach and, as a result, the Research and Development Center was established - to consolidate resources. Of special interest and in relation to biotechnology research and development is the Center's recently (1980) established multi-million bahts Central Research Laboratory and Greenhouse Complex at the University's second campus in Nakhorn Prathom Province. These modern research facilities have been and are made available to research workers from other universities both within and outside Thailand, through training programmes and/or cooperative research.

Important cooperative research works in biotechnology and genetic engineering between Kasetsart University and the International Center for Cooperative Research in Microbial Engineering of Osaka University, Japan, include further development of new hybrid strains of yeasts for alcohol fermentation, based on original strains isolated and developed by the University.

Future research and development efforts in the area of biotechnology will be:

(1) Agricultural biotechnology, with the aims of improving/developing new varieties of plants, particularly cash crops, using genetic engineering techniques.

(2) Agroindustrial biotechnology, with the aims of increasing the value to the country's available low-priced raw materials and waste/by-products, or to more effectively utilize them.

Some of the research programmes being carried out or planned for implementation include the following:

- Improvement of tissue culture techniques for plant selection and propagation (particularly exotic fruits and cash crops);

- Genetic engineering technology for seeds improvement;

- Yeast fusion technology for industrial strain improvement (for alcohol fermentation);

- Microbial fertilizer development;

- Microbial pesticides development for environmentally-sound control of plant diseases;

- Agricultural wastes utilization, with emphasis on cellulosic materials;

- Mass production technology of plant cells, particularly for the production of active substances (from local medicinal plants).

The University, with its strong agricultural base, has formulated its research and development policy and programmes with emphasis in agricultural biotechnology and agro-industrial biotechnology. With Thailand being rich in bioresources, including various parent genetic stocks, and being the site of microbiological resource centre for SE Asia (Bangkok MIRCEN) and a plant genetic resource centre (plant gene bank), the University intends to bridge these facilities with the technology from advanced countries through cooperative research to achieve its goals in biotechnology R&D development.

United Kingdom - University of Wales appoints biotechnology expert

The five colleges of the University of Wales have combined to establish a Biotechnology Centre and have appointed Dr. Rod Greenshields as Director. Dr. Greenshields and his team will further develop links with industry as well as investigate new scientific techniques.

The University of Wales is one of those which has received specific Government funding to develop this technology, and it is hoped that the Centre will lead to a new industrial valley in Wales which could rejuvenate Welsh industry and provide much needed jobs.

Dr. Greenshields was formerly Reader in Biochemistry at the University of Aston. His new appointment will initially be based in the Department of Chemical and Biochemical Engineering at University College, Swansea.

United Kingdom - New research venture

Five companies have joined in supporting a new biotechnology research venture at Leicester University. The industrial partners in the Leicester Biocentre are Dalgety-Spillers; Gallaher; John Brown; Whitebread and Co.; and Distillers. Other companies have expressed an interest.

The five companies contributed £300,000 each to a five-year research programme in genetic engineering of yeasts and other plants in an effort to forge closer bonds between academic and industrial research.

Their interests lie in possibilities genetic engineering may open for new technology and products in the food, drink and tobacco industries, and in the case of John Brown for the associated bio-engineering services.

The food group of Distillers, a subsidiary, which has joined the partnership, has two yeast and six food factories for baking and catering.

The Leicester Biocentre, which came into operation a few weeks ago in a suite of university-laboratories, is closely associated with the university School of Biological Sciences, which has 50 full-time academic researchers working in genetic engineering, and has received a grant of more than £500,000 from the Wolfson Foundation for a research centre to be started this summer. The Biotechnology Directorate of the Science and Engineering Research Council has contributed £180,000 more to meet costs of getting the research programme started.

The centre is run by a management committee of senior executives from the five companies, together with staff at the university. The aim is to create a research institute of international repute having strong ties with Leicester University's schools of biology and medicine, and with industry, not only through its five industrial partners, but more widely by way of research contracts placed by companies.

The research initially will concentrate on genetic structure of yeasts and on processes which facilitate translation of yeast genes into their unique protein products.

For the genetic engineer yeast is a safe microorganism, easier and cheaper to cultivate than many others. According to one bioscientist, changes that previously took 20 years by classical breeding techniques in yeast and other plants should be possible in only two or three years by genetic engineering. (Extracted from Financial Times, 28 April 1983.)

United Kingdom - Government grants

ICI (UK) will receive government grants to develop two technologies for cultivating bacteria in continuous fermentation plants, including the Pruteen process for continuously breeding bacteria fed on methanol. The UK Industry Department's budget for new industrial biotechnology ventures is set at UK £16 million at present. ICI aims to raise the efficiency of the Pruteen process and increase the proportions of the key ingredients. Pruteen is a single-cell protein animal feed ingredient. (Source: Technology Update, 21 May 1983.)

United Kingdom - New fund set up

A fund recently set up to help British technology has just announced two research programmes in biotechnology. Cogent, set up last year with £6 million by two insurance companies - Commercial Union and Legal & General - is putting money into two programmes being undertaken by the Scottish-based contract research organisation, Inveresk Research International.

Cogent's special "angle" is its link with the 12 members of the Association of Independent Contract Research Organisations (AIRCO). It will exploit the gap between pre-prototype work and commercialisation, usually with an industrial partner. The two bio-technology projects will be aimed at products to treat and monitor thrombosis and at diagnostic kits for the herpes virus. (Source: Technology, May 1983.)

United Kingdom - New company formed

Some of the best brains from two Scottish universities are behind a new biotechnology company, Bioscot, which was launched with £1 million backing from the government and the Bank of Scotland. Bioscot is the latest attempt to channel the discoveries of British scientists swiftly to the market place by forging commercial links between research establishments and industry. It has been set up by Edinburgh University and Heriot Watt University with £500,000 backing from the Scottish Development Agency, £200,000 from the Bank of Scotland and additional financial support from Lothian Regional Council. The research team is to be led by Charles Brown and John Wilkinson, professors of microbiology at Heriot Watt and Edinburgh respectively. (Extracted from The Guardian, 6 June 1983.)

United Kingdom - Electrophoretic separator exhibited

The firm of John Brown exhibited a full-scale electrophoretic separator at the Biotech '83 show in London. The company will market the equipment, which was developed at AERE Harwell, a British government facility. The electrophoresis equipment has already been used to purify antihemophilic blood clotting Factor VIII.

Like HPLC, electrophoresis is most widely used as a laboratory method for separating biomolecules. Electrophoresis takes advantage of different rates of migration in an electric field of molecules having different electrical charges. A big problem in large-scale electrophoretic separation is that turbulence in the liquid containing the proteins interferes with separation. This is prevented in the lab by using a gel rather than a liquid. Operating in zero gravity is being tried as a means of overcoming the turbulence problem in liquids. The Harwell design overcomes the difficulty by using a rotary system to stabilize the laminar (non-turbulent) flow of a carrier solution. The solution flows upward through the annular space between two concentric vertical cylinders. The inner cylinder remains stationary while the outer one rotates at about 150 rpm. This maintains laminar flow even in the presence of the voltage gradient needed to separate the proteins. At the top of the stationary cylinder a series of 30 disks splits the stream into fractions. The price is about $85,000. (Source: Genetic Technology News, June 1983. Address: 158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA.)

USA - Health protection

A call for government rule changes concerning equal opportunity and work place health protection to accommodate emerging genetic testing technology. It is believed that the techniques are not sufficiently advanced or scientifically accepted to have significantly affected firms' hiring and firing practices, and a request has been made that NIOSH begin to work on guidelines which would specify what constitutes a valid genetic screening test.

The Equal Employment Opportunity Commission was asked to recognize the potential positive use of such methods. Previously, firms hesitated to use susceptibility to a hazard indicated by race, sex or other factors as a criteria of employment, due to fear of violating sections of the Civil Rights Act of 1964. However, if a firm declined to use such tests in the future due to fears of unfair discrimination, resulting in the serious illness of an employee, the firm could be liable to legal action for not adequately protecting the worker's health.

Legal problems concerning women of child bearing age, a group genetically predisposed to certain workplace hazards, have already arisen in regard to exposure to substances at levels considered safe for adults but hazardous for unborn foetuses. American Cyanamid is involved in a lawsuit with female employees of its Willow Island, WV, lead pigments plant. The women claim that the firm forced them to undergo sterilization so they could keep their jobs. American Cyanamid alleges that the women were offered alternative employment but instead had themselves sterilized. (Source: Technology Update, 21 May 1983.)

USA - Universities plan to speed sale of biotechnology

Universities and biotechnology companies in the US are considering a new plan to speed the transfer to industry of genetic engineering techniques developed in university laboratories. The proposal calls for the creation of a new non-profit body, the University Licensing Association for Biotechnology (ULAB), which would market biotechnology techniques patented by universities.

The biotechnology companies would then directly buy a licence for a particular technique rather than negotiate with individual universities. These universities would reap fees from the licensing. Their income would depend on how often their patented technique was used. ULAB would take a cut from the licensing to cover running costs.

The idea has been floated by Stanford University and the University of California, which together hold the patent on the Stanford procedure for gene-splicing, developed by Herbert Boyer and Stanley Cohen. Niels Reimers, director of Stanford's office of technology licensing, said that there was substantial support for the idea from both universities and industry, though the establishment of the corporation would require "considerable effort and commitment".

ULAB patents, Reimers stressed would not involve the "entire gene-cloning process", but rather specific biological tools or techniques used by industrial scientists. It was necessary, he said, to inject some order into what was becoming an increasingly complicated problem - how to give industry quick access to the growing number of biotechnology techniques being developed by universities while ensuring that the university contribution was acknowledged and rewarded.

At least 200 separate patents applications from universities existed for the biotechnology tools that industry wanted to use. In some cases, a company may need a dozen licences from a dozen universities for any particular genetically-engineered product.

Many scientists also favoured the idea of pooling biotechnology patents because it would reduce the possibility of secrecy and the delay of publication. Reimers said: "In university laboratories there has been a growing concern that desire for proprietary know-how or rights may stifle the open communication of scientists, particularly between scientists who have involvement with different companies."

Industry has already put some money into the idea. Seven companies contributed $3,000 each to finance a feasibility study by a student from the Stanford Graduate School of Business.

The student, Mark Edwards, visited 20 companies and talked to university scientists and administrators. His report is being used as the basic plan for ULAB. (Source: New Scientist, 17 March 1983.)

USSR - Enzyme discovered that will turn cotton waste into glucose

The Soviet Union is turning to biotechnology to tackle its chronic food shortages. Russian scientists are tackling any likely source of new foodstuffs, including cotton. This is the task of the National Food Programme, which works closely with the National Programme on Biotechnology.

The Republic of Uzbekistan alone produces over 10 million tonnes of cotton wastes a year. So it was inevitable that biochemical engineers such as Anatole Klyosov would try to turn this mass of cellulose into a cheap source of food for animals or humans. Klyosov described the fruit of many years of work, which has now reached the stage of setting up a small commercial plant, to an attentive audience at the Third International Meeting on Socialist Biotechnology in Bratislava, Czechoslovakia.

Turning cellulose from any source into simpler, more useful chemicals such as food sugars often requires harsh chemicals to break down the tough lignin fibres and digest the cellulose. The chemicals are then uneconomical to remove. A better way is to use a more gentle chemical pretreatment, followed by a bath of enzymes, nature's catalysts, to chew up the cellulose. But enzymes are expensive, and easily destroyed unless they are immobilised on some support, such as a special membrane.

Klyosov claims to have invented an enzyme method for converting short cotton fibres called "linters" and raw cotton plant stalks into food-grade glucose. The process runs continuously for at least two months, with the same enzymes, thus saving a lot of money. Klyosov's enzyme is a modification of one selected from 15 crude celluloses that the Ministry of Microbiology makes and markets (the ministry also owns all patent rights to the process). By studying the physical chemistry of the way enzymes absorbed onto a solid support, and testing many enzymes, Klyosov's team found one that was very good at automatically latching onto fresh substrate as the old supply was gradually exhausted. The team's system consists of a simple column, filled with a solution of enzyme. The latter attacks the mush of cotton wastes passing through.

Estimates based on an operating pilot plant indicated that a 20,000-litre production plant could turn out 90,000 tonnes of food-quality glucose a year.

Klyosov says this glucose can then be easily converted into fructose, but goes nowhere near supplying the several million tonnes that the Soviet Union needs every year. Klyosov says that by establishing several production plants, his process could supply between 2 and 4 million tonnes of fructose a year, but "this would not be wise" because it would be too expensive to move cotton wastes around the country. Instead, Klyosov favours adapting the process to suit local resources, stocks of wood from forests in Siberia, for example.

In any case, building up a network of such production plants will be unlikely to happen before the end of the decade, when the process is perfected.

The Soviet Union has genetically engineered strains of the bacterium Escherichia coli to make threanine and riboflavin, and have a lot of experience with fermentation. Satellite pictures show that every year 1.5 million tonnes of single-cell protein from yeasts, grown on paraffin, corn husks and wood chips, augment the soyameal the Soviet Union imports for feeding herds of animals. (Extracted from New Scientist, 26 May 1983.)

PATENTS

Patent Office lets Stanford off three hooks

In a cryptic letter from Stanford University's Office of Technology Licensing, the 73 licensees of the first Cohen-Boyer patent learned last month where Stanford's dispute with the U.S. Patent and Trademark Office stands in the latter's rejection last June of the second Cohen-Boyer patent.

The circular letter conveys the gist of decisions Stanford was notified of on 21 January by the patent examiner, Alvin Tanenholtz. His "Office Action" dropped three of the reasons the application was rejected:

- Erroneous description of the pSC101 plasmid;

- The hint, in a letter Cohen wrote long ago, that recombinant DNA is found in nature (products of nature are not patentable, but the Patent Office has now relaxed this strictures in this case);

- An article by Edward Ziff in the New Scientist antedating the application was deemed a nonenabling reference, not containing enough detail to constitute premature disclosure after all.

But the examiner raised two new issues:

- In their initial application in 197-, Cohen and Boyer claimed their recombinant-DNA process and its products only for bacterial host organisms. A revised submission two years later extended this to all other microorganisms, broadening the claim inadmissibly, in view of their intervening publications.

- Prior to the initial patent application but after the Gordon Conference at which the technique was first reported, did Cohen share his cloning vector too far and wide to permit subsequent patentability?

Finally, Prof. Robert Helling, now at the University of Michigan, has been invited by the Patent Office to support his claim of co-inventorship. A co-author of the initial scientific paper 10 years ago, Helling was not listed in the patent application. (Source: Newswatch, 4 April 1983.)

New patent scheme

Firms would be able to shop for biotechnological patents at US universities if a new scheme proposed by the Industrial Biotechnological Association is adopted. Under the proposal, a nonprofit corporation, the University Licensing Association for Biotechnology (ULAB), would be set up to market certain biotechnology tools patented by participating universities, which would share the licensing revenues based on the patents used by industrial customers. IBA is a high technology industry group with 25 members, many of which are among the 73 firms with licenses for Stanford's and the University of California's basic gene cloning patent.

Potential users would be able to either license patents individually or secure blanket patent rights to all patents owned by ULAB. A tentative fee of $25,000/yr or 1 per cent of net sales, whichever is greater, will enable a firm to secure blanket rights to all patents offered by ULAB. If ULAB were chartered by 10-12 businesses or universities, each initially contributing $50,000, gross revenues could total $12 million in the next 5 years. (Source: Technology Update, 2 April 1983.)

Licensor liability foreseen in patent lawsuits

At a well-attended session on "Patents and licenses - the legal jungle" at the "Biotech 83" conference, an American patent attorney warned scientists that in the U.S. they may be held liable if any of their inventions go wrong.

Thomas E. Friebel, an associate of Pennie & Edmonds, New York City, declared, "The whole field of product liability is expanding and may be reaching back to include the licensor." Conventionally, responsibility for product liability rests with the company that manufactures it and the person who "sends the goods out into commerce". These days, notes Friebel, "this may be taken to include the licensor even if the goods are never sold."

The reason, he explains, is that the public often does not know whom to sue, particularly in the case of drugs, where side effects may appear 20 years after they are taken. The public relies on the patent as an official stamp of approval, like a trademark, and the scientist licensor could be drawn into a dispute over the quality of the trademarked goods in the same way. The speaker went on to warn that juries might have "negative gut feelings" about products produced by r-DNA technology.

Friebel offered a few suggestions as to how scientists may go about protecting themselves:

- Start with a well-thought-out, solid contract, and try to make sure the licensing agreement is at the same time not licensing trademarks, which have a far greater prospective liability.

- The contract should spell out carefully the responsibilities of licensor and licensee and demand that the licensing company assume any potential risks.

- Licensor should demand that the final product comply with all the regulations of the U.S. National Institutes of Health and the Food and Drug Administration, and that the licensee agree to indemnify the injured party.

- There should be a provision that the licensing agreement be terminated at any time if the final product sold is found to be hazardous or defective.

Friedel cites one final irony: In the U.S., "strict" liability, which carries with it the strongest penalties of the four types of liability, is less likely to apply if the licensor can prove that he advised the licensee as a professional service. "The United Kingdom is very jealous of this," said a commentator from the floor. (Source: Newswatch, 6 June 1983.)

Case in point: third party sued for rabies liability

Product liability has become a pressing legal issue for the defendants in the case of Joanna Andrulonis versus United States et al. New York State is a third-party defendant in this lawsuit, now being readied for trial before the U.S. District Court here.

Mrs. Andrulonis' husband, Jerome, was a senior bacteriologist at the Griffen Rabies Laboratory in this city, a division of the New York State Department of Health. Six years ago he was working on a wildlife rabies vaccination project, allegedly utilizing a machine based on the Wurster Air Suspension process, for which the Wisconsin Alumni Research Foundation (WARF) held the patent. The project protocol was designed by specialists of the U.S. Center for Disease Control (CDC) in Atlanta and at the New York State Department of Health.

The project involved spraying sugar wafers ("pareils") with rabies virus from an aerosol encapsulation machine, adding an enteric coating, and scattering this bait in the wild. The idea was that foxes and other carrier creatures would ingest the virus-coated food and develop immunity.

Jerome Andrulonis allegedly inhaled the virus as it escaped from the aerosol and contracted rabies. He is still alive, but his brain is said to be seriously and permanently damaged. His family has brought suit for $80 million against the following roster of defendants:

- The German manufacturers of the aerosol machine, Glatt GmbH of Binzen/Loerrach, as well as this firm's U.S. distributor, Glatt Air Techniques, Inc. of Ramsey, N.J. "The ... machine was defective in design and manufacture, unreasonably dangerous, not fit for use and unmerchantable in that it leaked and failed to perform safely...." declares the complaint filed by plaintiff's attorney, Dean Higgins, Esq., of Roemer and Featherstonehaugh of this city.

- The Wisconsin Alumni Research Foundation and its spinoff, WARF Institute, Inc., as well as its successor corporation, Raltech, part of Ralston Purina of St. Louis, Mo. "did in a negligent, reckless and wrongful manner", the complaint charges, "(design) the Wurster Air Suspension process ... and (recommend) the use of the ... machine for the coating of pareils with the rabies virus material...."

- Eli Lilly & Co. of Indianapolis, which manufactured the rabies vaccine given to the laboratory workers, and Lilly's local distributor, John L. Thompson, on the grounds, says the complaint, the vaccine "failed...."

- The United States because of a federal statute that makes the federal government liable for acts or omissions of federal employees, in this case at the CDC, who developed the virus used in the machine for the wafer-coating process.

- New York State as a third-party defendant is in turn being sued by the U.S. government. Andrulonis, as a state employee, could not sue New York directly. "We deny any liability in this case," claims U.S. district attorney Jeffrey Axelrod in Washington, D.C. "If the court rules against us, we feel the third party should indemnify us."

The original complaint included as a defendant the original inventor of the aerosol equipment used, Dale Wurster, then a faculty member in the pharmacy department at the University of Wisconsin. Last year, the district court dismissed this portion of the suit, thus in effect holding him free of responsibility. (Source: Newswatch, 6 June 1983.)

Tables on distribution of patents by country, 1977 to June 1978

TABLE 1

National interest in products/purposes

	Australia	Austria	Belgium	Brazil	Britain	Canada	Czechoslovak	Finland	France	GDR	FGR	Hungary	India	Israel	Italy	Japan	Netherlands	Poland	Romania	S.Africa	Spain	Sweden	Switzerland	US	USSR	TOTAL
Polymer	-	-	-	-	6	-	2	-	2	3	2	-	-	1	1	75	-	3	-	1	-	-	-	17	3	126
Military	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1
Brewing	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	1
Baking	-	2	-	-	-	-	-	-	1	-	1	-	1	-	-	1	-	1	-	-	-	-	-	1	1	6
Cosmetic	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-
Pharmaceutical	-	-	-	-	-	-	5	-	3	6	6	1	2	-	4	156	-	7	1	-	-	3	8	33	8	240
Fine chemical	-	1	-	1	7	-	5	-	2	3	2	1	2	0	1	155	-	5	1	-	-	3	6	16	21	236
Organic acid	-	-	-	-	6	-	2	-	1	1	1	1	1	-	1	66	-	4	1	-	-	2	4	10	10	120
Amino acid	-	2	-	-	1	-	4	1	4	2	2	-	2	-	3	148	-	2	1	-	-	-	-	11	-	164
Antibiotic	-	1	1	-	6	2	6	-	2	3	6	6	3	-	4	243	-	10	5	-	2	-	6	71	7	386
Steroid	-	-	1	-	3	-	-	-	-	6	6	1	-	-	2	35	1	1	-	-	-	-	3	12	5	75
Enzyme/co-enzyme	-	-	-	2	4	-	6	-	4	8	5	3	5	-	1	163	3	11	1	1	2	1	-	21	32	265
Nutrient	-	1	-	-	6	-	3	-	6	10	5	2	3	-	3	34	-	7	2	-	-	-	1	8	6	97
Food additive	-	-	-	-	4	-	2	-	2	3	1	-	3	-	2	36	-	3	2	-	-	-	2	12	1	76
Sweetener	-	-	-	1	-	-	2	-	1	1	3	2	1	-	1	32	-	-	-	-	1	-	2	8	2	57
Biomass	-	2	-	-	5	-	12	1	8	17	11	1	5	-	3	92	-	12	1	-	-	1	4	8	10	191
Fuel	-	1	-	1	1	-	1	-	1	-	1	-	1	-	-	6	1	1	-	-	-	1	2	5	-	21
Antitumoral	-	-	-	-	-	-	1	-	-	-	-	1	-	-	-	70	-	-	-	-	-	1	-	5	-	78
Anti-foam	-	-	-	-	-	-	1	-	-	-	1	-	-	-	-	2	-	1	-	-	-	-	-	-	-	5
Vitamin	1	-	-	-	-	-	1	-	-	2	1	-	-	-	-	9	-	1	2	-	-	-	-	1	5	23
Pigment/Paint	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	-	-	-	-	-	-	1	2	-	6
Deodorant	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	1	-	-	-	-	-	-	-	3
Algotype	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Oil/Fat	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	-	-	-	-	-	-	-	1	1	10
Growth stim	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	2	-	1	-	-	-	-	-	3	-	5
Pollution control	-	-	-	-	-	-	2	-	1	-	1	1	-	-	-	26	-	2	1	-	-	1	-	6	1	42
Process inhibitor	-	-	-	-	-	-	-	-	-	-	5	-	-	-	-	14	-	-	-	-	-	-	1	1	2	23
Pesticide	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	11	-	1	-	-	-	1	1	1	-	15
Immune stim	-	-	-	-	-	-	1	-	1	-	-	-	-	-	-	5	-	-	-	-	-	-	-	-	-	7
Coating	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	1	2
Fertiliser	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1
Detergent	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	1
TOTAL	1	10	2	5	60	2	68	2	47	65	66	22	29	1	25	1427	4	81	15	1	5	10	40	244	121	2355

TABLE 2

National activity and technical integration

Level of technical integration	Australia	Austria	Belgium	Brazil	Britain	Canada	Czechoslovakia	Finland	France	GDR	FGR	Hungary	India	Israel	Italy	Japan	Netherlands	Poland	Romania	S.Africa	Spain	Sweden	Switzerland	US	USSR	TOTAL
Process Engineering	-	2	-	1	3	-	1	-	3	-	4	-	4	-	1	29	-	2	-	-	1	1	2	13	1	68
Apparatus	-	2	-	-	-	-	-	-	2	-	3	-	1	-	-	6	-	1	-	-	-	-	2	6	4	27
Bioprocess - utilising enzyme catalysis	-	2	-	2	18	1	24	1	11	21	20	5	6	1	9	480	-	18	7	1	2	3	11	64	45	752
Enzyme reactor	-	2	1	0	5	-	1	-	3	3	4	1	6	-	1	46	2	2	-	-	-	2	2	19	5	105
Immobilisation structure, organisms, cells or enzyme	-	-	1	-	2	-	1	-	2	-	1	-	3	-	-	3	2	-	-	-	-	-	0	9	1	25
Culture technique	-	1	-	-	3	-	8	-	4	6	11	4	4	1	-	109	1	9	4	0	2	1	3	29	19	216
Analytical/Diagnostic	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	11	-	-	-	-	-	-	0	1	1	13
Recycling/Reclamation	-	1	-	-	2	-	4	-	4	3	2	2	4	-	-	50	-	6	2	-	-	1	2	10	4	96
Fermentors	-	3	-	1	15	-	15	-	6	12	9	3	5	1	6	179	8	12	6	-	1	2	5	38	14	349
Genetic Engineering	-	-	-	-	-	-	-	1	1	-	3	1	-	-	-	11	-	-	-	-	1	-	-	2	1	21
Novel Result	1	2	1	-	16	2	9	-	6	6	17	3	2	-	6	420	2	12	1	-	3	-	14	74	26	625
Extraction	1	1	-	2	3	-	9	1	2	17	6	3	2	1	1	85	1	13	2	-	1	-	1	17	23	192
Mutation/New organism	-	1	-	-	1	-	6	-	-	-	-	-	1	-	2	4	-	2	-	-	1	-	2	9	2	31
Medical/Veterinary use	-	1	-	-	1	-	3	-	2	2	4	1	-	-	3	99	1	-	2	-	1	-	2	24	3	150
Chemical mod	-	-	-	-	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	4
TOTAL	2	18	2	6	73	3	81	3	46	71	84	23	38	4	29	1532	17	78	24	1	12	10	46	316	151	2672

(Source: Patterns of Change in Biotechnology, by Pauline K. Marstrand. Science Policy Research Unit, University of Sussex, June 1981, ISBN 0 903622 16 5.)

The following is a selection of recent US Patents granted:

Assignee	Title	Patent Number/ Date Issued
Salk Institute	"Mobile Phase for Liquid Chromatography." (Reversed phase HPLC technique for resolving peptide mixtures - column packed with hydrocarbon functional groups attached to carrier.)	4,377,482 22 March 83
Northwestern University	"Antigenic Linear Peptide Compounds." (Antigenic peptide compounds with chain lengths of 10 to 14 amino acids.)	4,377,516 22 March 83
Teijin (Japan)	"Antitumor Protein Hybrid and Process for Production Thereof." (Antitumor immunoglobulin combined with diphtheria toxin fragment.)	4,379,145 5 April 83
Peter Cashion (inventor)	"Immobilization of Polynucleotides and Polypeptides with Tritylated Polysaccharides." (Polynucleotide or polypeptide attached to a hydrated polysaccharide through a triphenylmethyl ether group.)	4,379,843 12 April 83
Monsanto Company, St. Louis, Mo. (Inventor: G. Edward Paget, Chesterfield, Mo.)	"Separation of Plasma Proteins from Cell Cultures". Mammalian plasma protein, such as factor VIII and albumin, are separated from microbial or mammalian cell cultures by adsorption with water-insoluble, cross-linked polyelectrolyte copolymers. Preferred copolymer components: ethylene, maleic anhydride.	4,382,028 3 May 83; 19 July 82
Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo, Okayama, Japan (Inventor: Kaname Sugimoto, Okayama, Japan)	"Mass Production of Human Hormones". These three patents cover the production of human follicle-stimulating hormone, luteinizing hormone, and chorionic gonadotropin, respectively. Human cells capable of producing the respective hormones are transplanted into warm-blooded animals where they produce more of the hormone per cell than by tissue culture methods. Alternatively, the cells can be made to multiply with a device whereby a warm-blooded animal's nutrient body fluid is supplied them.	4,383,034 4,383,035 4,383,036 10 May 83; 7 Aug. 81
Merck & Co., Inc., Ranway, N.J. (Inventor: William M. Hurni, William J. Miller, both of North Wales, Pa.; William J. McAleer, Ambler, Pa.)	"In Vitro Antibody Assay for Hepatitis A". Hepatitis A antibody is adsorbed to a surface, such as polystyrene, and then incubated for about 24 hours in the presence of cell-culture fluid containing hepatitis-A antigen. Resultant reagent: a surface with an outer layer of hepatitis-A antigen attached to an inner layer of hepatitis-A antibody, which may be used in conventional RIA assays for hepatitis-A antibody.	4,382,076 3 May 83; 1 June 82
Board of Trustees of the Leland Stanford, Jr., University, Stanford, Calif. (Inventor: Charles P. Bieber, Los Altos Hills; Frank D. Howard, Los Altos, both of Calif.)	"Antihuman T Lymphocyte Monoclonal Antibody". Monoclonal antibodies bind to alymphocyte surface antigen (Leu-5) and are specific for thymocytes, normal peripheral T cells, and some null cells. Useful in assays, cell sorting, and immuno-suppression.	4,381,292 26 April 83; 14 Nov. 80

Assignee	Title	Patent Number/ Date Issued
Meloy Laboratories, Inc., Springfield, Va. (Inventor: Irwin A. Braude, Burke, Va.)	"Purification of Human Immune Interferon". Crude immune interferon produced from mitogen-induced human peripheral blood leukocytes is purified by a series of chromatographic steps, each leading to greater purification.	4,382,027 3 May 83; 16 Aug. 81

Copies may be obtained from: Commissioner of Patents and Trademarks, Washington, DC 20231. (Sources: Genetic Technology News, May 1983. Address: 158 Linwood Plaza, Fort Lee, NJ 07024, USA and Newswatch, 6 June 1983.)

MEETINGS

Date	Title
1-5 August 1983	Advanced Biochemical Engineering '83 (course topics: modeling and analysis, design of reactors, biomass conversion, applications of biochemistry and genetics, separation processes). Troy, N.Y., Sponsor: Rensselaer Polytechnic Institute, Troy, NY 12181, Att: Joan Masterson, Director, Continuing Education.
1-5 August 1983	Biotechnology: Microbial Principles and Processes for Fuels, Chemicals and Ingredients (course topics: anaerobic metabolism, genetics of anaerobes and r-DNA technology, acidogenic bacteria, methanogenesis, thermophilic anaerobes). Cambridge, Mass., Sponsor: Massachusetts Institute of Technology, Room E19-356, Cambridge, MA 02139, Att: Director of the Summer Session.
14-20 August 1983	Third International Symposium on Anaerobic Digestion (fermentation kinetics, methane generation, solid and liquid waste treatment, biomass utilization, process design, economics, and control). Boston, Mass., Sponsor: Third International Symposium on Anaerobic Digestion, 99 Erie St., Cambridge, MA 02139.
15-19 August 1983	Fermentation Technology (course topics: metabolism, biosynthesis, genetics of industrial microorganisms, scale-up, continuous culture, computers). Cambridge, Mass., Sponsor: Massachusetts Institute of Technology, Room E19-356, Cambridge, MA 02139, Att: Director of the Summer Session.
19-21 September 1983	Molecular Biology Now and Tomorrow - 30 Years of DNA. Boston, Mass., Sponsor: 30 years of DNA, c/o Nature Pub. Col, 15 E, 26th Street, New York, NY 10010.
26-30 September 1983	Cosmid Coning (course limited to German-speaking participants; topics cover cosmid gene banks, isolation from transformed eukaryotes, colony hybridization, plasmid recombination). Braunschweig, German Federal Republic, Sponsor: Gesellschaft für Biotechnologische Forschung, Braunschweig-Stöckheim 70081, German Federal Republic, Att: Dr. John Collins.

(Source: Newswatch, 18 April 1983.)

PUBLICATIONS

Journals

The New York publishers, Mary Ann Liebert, Inc., of 157 East 86th St., publish a whole series of journals covering numerous aspects of genetic engineering such as agricultural genetics, interferon research, biotechnology law and education, etc. The 1983/84 Serial Publications Catalogue is available from the publishers upon request.

An English edition of the bibliographic journal Pascal Biotechnology (10,000 references/year) is now published monthly by the C.D.S.T. (Centre for scientific and technical documentation of the C.N.R.S. in France). This bibliographic journal is derived from the Pascal multidisciplinary scientific and technical data base and all the biotechnology references drawn from worldwide publications are brought together and treated in a homogeneous and exhaustive way. It takes into account the research in biochemistry, microbiology, cell biology and chemical engineering with a view to the industrial and agricultural applications of the resources of microorganisms and cell cultures, as well as all the resulting technologies and applications: agricultural and food industries, agriculture, health, energy, pollution, metallurgy. References are drawn from varied sources, such as periodicals conference proceedings, theses, reports, etc., and contains French, European and international patents registered at the "Institut National de la Propriété Industrielle" (Paris). Pascal enable articles dealing with biotechnology to be collected, even those published in periodicals which do not belong to the "biotechnology" list.

Biotechnology Bulletin

A monthly information source on current developments in one of the world's most rapidly developing technologies. Biotechnology Bulletin scans developments in the biotechnology field and provides itemised features to assist academics and industrialists to keep abreast of the relevant news on both a scientific and a commercial front. Biotechnology Bulletin provides you with a comprehensive briefing on recent developments and new products in a wide range of biotechnological areas. Biotechnology Bulletin is written in a succinct accessible form. Information is solid, well-founded and practical, based on a wide range of opinions with views and interpretations from many sources. Areas covered are: agricultural chemicals, diagnostics, food processing, industrial chemicals, waste disposal, pharmaceuticals, plant & animal cells, plant & animal breeding, energy production, and biomass. Published by The Publications Department, Oyez Scientific & Technical Services Ltd, Bath House, 56 Holborn Viaduct, London EC1A 2EX. Annual subscription £90.00 (UK & Overseas).

Biotechnology Made Simple

A glossary of recombinant DNA and hybridoma technology. PJB Publications, January 1983, £75 or $150 (117 pages).

This timely compilation of definitions and data is published by Scrip World Pharmaceutical News, a highly regarded series of British newsletters. Scrip advertises it as "specifically aimed at bringing the subject within the grasp of the lay executive", and the book's introduction addresses it to "the non-specialist interested in the field". (Source: Newswatch, 2 May 1983.)

This glossary is available in Britain from PJB Publications, 18-20 Hill Rise, Richmond, Surrey, TW10 6UA, UK; in the U.S. from Scrip World Pharmaceutical News, Att: Janet Gann, 500 Fifth Ave., Suite 420, New York, NY 10110.

Biotechnology

A new report from IMSWORLD publications highlights the potential growth of worldwide biotechnology. More than 800 organisations from 27 different countries are dealt with in the report. 'Biotechnology international' lists 350 universities, 300 industrial corporations, and 180 specialist venture firms, all working in health-related fields. The report contrasts the different approaches adopted in different parts of the world to exploit biotechnology: capital venture in the USA; major industrial corporations in Japan; government assistance in Europe. It also considers the possibilities for Third World biotechnology, and is available either as three separate volumes, each priced $US 400, or as a complete set, priced $US 1,000, from Dr. A.H. Sheppard, IMSWORLD Publications Ltd, York House, 37 Queen Square, London WC1N 3BL, (Tel: 01-831 5806). (Source: Chemistry and Industry, 18 April 1983.)

Guide to corporate-sponsored university research in biotechnology

For corporations seeking ways to enlist university research facilities in their R&D plans - and for universities interested in corporate financing - a comprehensive new manual of industrial-academic cooperation is now available from McGraw-Hill and Biotechnology Newswatch. This 347-page analysis reviews the basics of corporate-sponsored university research, indentifies its unique advantages in the biotechnology area, and described key options for handling product development, patent rights, and revenue. Price per copy: $187; $207, airmail, outside North America; $167 (10% educational discount) available to universities and colleges only. To order or for more information, write to or call: Valjean Bacote, McGraw-Hill Publications, Suite 1200, 1120 Vermont Avenue N.W., Washington, DC 20005; (202) 463-1700. (Source: Newswatch, 4 April 1983.)

Newswatch now on NEXIS

As of the end of May, McGraw-Hill's Biotechnology Newswatch became available to subscribers of NEXIS, the computerized information retrieval service that displays complete articles and selected data on the video screen of a user's terminal. By keying in the code name "BIOTEC" and key words of interest, users can call up any article Newswatch has published from 16 May 1983, the first Charter Issue, to within 30 days of current issues.

For details about how NEXIS works and how one can subscribe to it, write to or call: Mead Data Central, 200 Park Ave., New York, NY 10166; (212) 883-8560. (Source: Newswatch, 6 June 1983.)

The Alcohol Economy: Fuel Ethanol and The Brazilian Experience by Harry Rothman, Francisco Rosillo-Calle and Roderick Greenshields of the Technology Policy Unit, University of Aston, Birmingham (price: £13.75). Published by Frances Pinter Ltd., 5 Dryden Street, Covent Garden, London WC2E 9NW.

This book presents a comprehensive up-to-date review of developments in fuel ethanol in Brazil. The Brazilian National Alcohol Programme is a result of a constellation of unique historical, political, economic and technical factors which have combined to make Brazil world leaders in this field. In examining the component parts, the authors highlight the sterling achievement of a Third World nation pioneering the development and application of biotechnology to satisfy national economic and industrial needs on a scale yet unmatched elsewhere.

Difficulties remain, however, and the authors also examine social economic and environmental implications, including the claim and counter-claim that the production of energy crops to fuel the country's growing car fleet will be in addition to rather that in competition with food crops.

Despite these problems, Brazil's power alcohol policy represents a major contribution to industrial policy which is now attracting worldwide attention, and this book provides the first detailed study of their achievement. In conclusion, the authors offer a predictive assessment of future developments.

Assistance required: Assistance available

One of our readers has asked whether any research institution or company can supply them with information on the following:

(a) Research underway in the field of tissue culture;

(b) Institutions working on the subject;

(c) Scientists willing to help Colombia and its Association in R&D projects in the fields of genetic engineering and tissue culture:

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