OCCASION

This publication has been made available to the public on the occasion of the 50th anniversary of the United Nations Industrial Development Organisation.

DISCLAIMER

This document has been produced without formal United Nations editing. The designations employed and the presentation of the material in this document do not imply the expression of any opinion whatsoever on the part of the Secretariat of the United Nations Industrial Development Organization (UNIDO) concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries, or its economic system or degree of development. Designations such as "developed", "industrialized" and "developing" are intended for statistical convenience and do not necessarily express a judgment about the stage reached by a particular country or area in the development process. Mention of firm names or commercial products does not constitute an endorsement by UNIDO.

FAIR USE POLICY

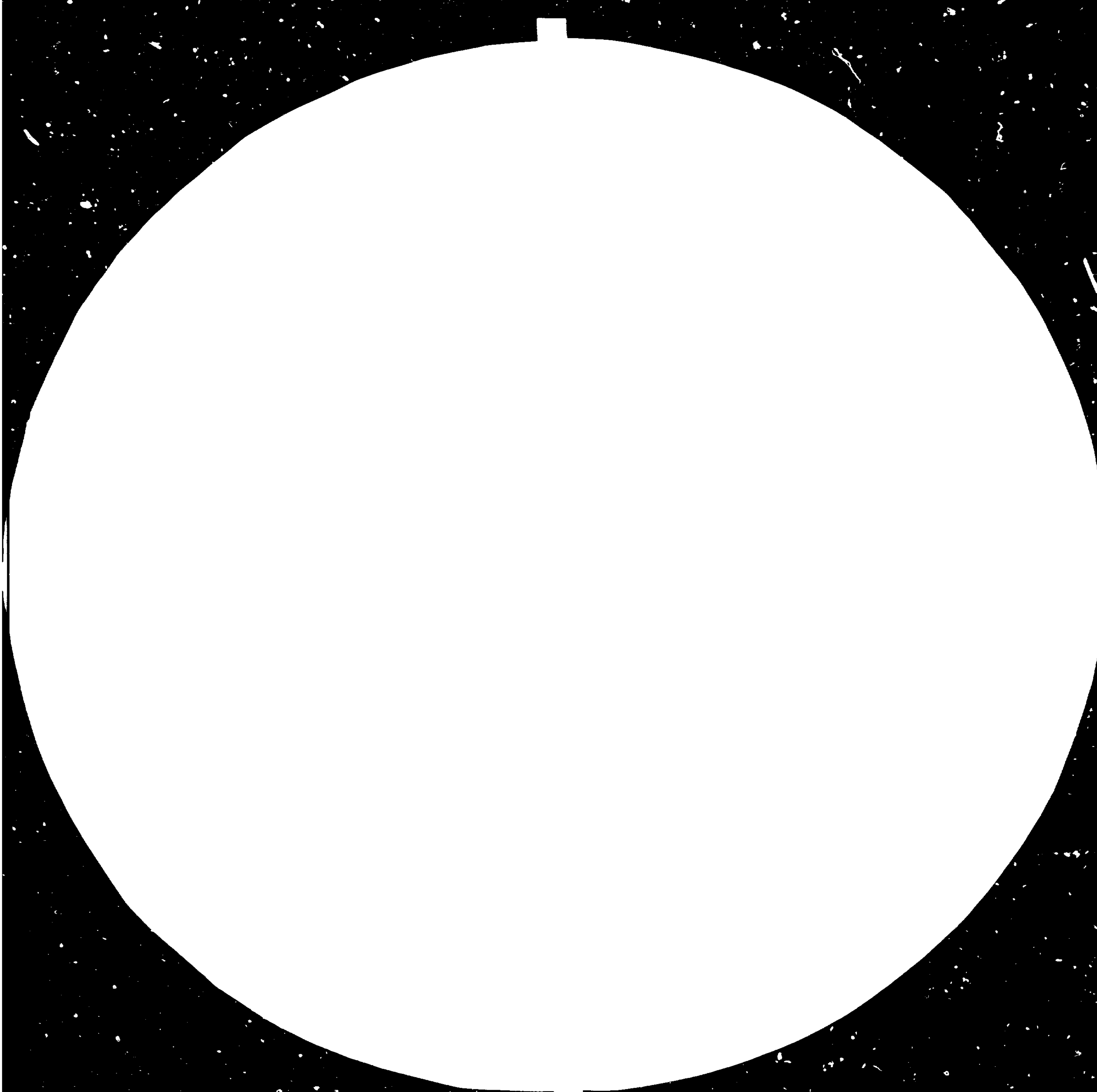
Any part of this publication may be quoted and referenced for educational and research purposes without additional permission from UNIDO. However, those who make use of quoting and referencing this publication are requested to follow the Fair Use Policy of giving due credit to UNIDO.

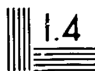
CONTACT

Please contact publications@unido.org for further information concerning UNIDO publications.

For more information about UNIDO, please visit us at www.unido.org

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
Vienna International Centre, P.O. Box 300, 1400 Vienna, Austria
Tel: (+43-1) 26026-0 · www.unido.org · unido@unido.org





MICROCOPY RESOLUTION TEST CHART

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

Genetic Engineering and Biotechnology Monitor

Issue Number 5 13216 April 1983

Dear Reader,

Events continue to move fast. Following the Belgrade meeting last December, action has been taken to set in motion the preparations for the Ministerial Level Plenipotentiary Meeting for the establishment of the International Centre for Genetic Engineering and Biotechnology. An expert team has visited sites and is preparing a report. Another team is exploring possibilities of financial and participation for the Centre. The meeting itself is now expected to take place in September 1983. You will find more details in the Monitor.

Another major event has been the International Forum on Technological Advances and Development in which experts and policy makers from 23 countries examined the impact of several technological advances, including genetic engineering and biotechnology. The Forum highlighted the fact that the industrial and technological policies for the 1980s and beyond will have to be formed in the light of the potentials and implications of the new technological advances. The results of the Forum will provide inputs for the Fourth General Conference of UNIDO which is expected to be held in Nairobi, Kenya, in July 1984. You will find more details inside.

I wish to emphasize that we would greatly appreciate more information from readers in developing countries about their present and planned activities. We would like the readers to be not simply recipients of information but active contributors as well.

G.S. Gouri
Director
Division for Industrial Studies

Compiled by the Technology Programme of UNIDO P.O. Box 300, A-1400 Vienna, Austria

Not an official document. For information only.
Opinions expressed in this newsletter do not necessarily reflect the views of UNIDO.

NEWS AND EVENTS

Tbilisi Forum considers genetic engineering and biotechnology

The International Forum on Technological Advances and Development, being one of the High-Level Expert Group Meetings Preparatory to the Fourth General Conference of UNIDO, was held at Tbilisi, Union of Soviet Socialist Republics (USSR) from 12 to 16 April 1983 in co-operation with the USSR and Georgian State Committees for Science and Technology. The objectives of the Forum were:

(a) To examine the potentials and limitations of selected technological advances for the industrial and economic development of the developing countries, in particular their industrial development;

(b) To consider the implications of technological advances in their inter-action with one another and their impact on industrial and other sectors;

(c) To identify ways and means by which specific industrial and technological capabilities may be developed by the developing countries in order to be able to avail themselves of the benefits of the advances, where appropriate and feasible;

(d) To identify policy actions to be taken by the governments of developing countries including ways of integrating policy responses to technological advances with their existing policy framework for industrial and technological development;

(e) To identify the lines of international action and in particular action by UNIDO.

(f) To make suggestions and recommendations for consideration by the Fourth General Conference of UNIDO (UNIDO IV).

The Agenda and documentation of the Forum were designed to help the development of a general perspective on technological advances based on an examination of several specific technological advances and their potentials and implications for the developing countries. Thus, the specific technologies examined were: genetic engineering and biotechnology, microelectronics, petrochemicals, renewable energy with specific reference to biomass and solar photovoltaic energy and materials and related technologies. Based on the examination of those advances, an attempt would be made to make an assessment of the combined impacts of such technologies on each other, on the industrial sectors and the international technology market structure. The experience of policy response to technological change in several developed and developing countries was also considered relevant for the developing countries in formulating their own approaches.

Conclusions and recommendations

In the different development strategies pursued by countries, there is a common recognition, with varying degrees of emphasis, of the central role of technology and the fact that it critically affects the development process. It was the unanimous view of the Forum that the impact of the emerging technological advances on development should be reviewed because of the inevitability of their diffusion in an interdependent world economy and because of their wide ranging impact, intensity and convergence. While the first order of impacts are and will continue to be felt in industrial development, the second and further order of impacts will have significance for the society and life styles of the people of the world. The technological advances contain several features which have a significant potential for the development process in all countries including in particular the developing countries. The current concerns on the rate and pattern of development make it all the more necessary to find ways and means of applying the technological advances in a manner which will benefit the development of all countries and in particular the developing countries. Those advances could help the developing countries to leap-frog some of the inherent hurdles in their traditional approaches to industrialization, agriculture, health delivery, social services etc. The advances have therefore a potential and relevance for developing countries and are feasible of application. The opportunity cost for developing countries of over-looking the technological advances is high, both in terms of acquisition of inappropriate technologies and the aggravation of their technological dependence.

There is a need for every developing country to take concrete actions of both a short-term and long-term nature. Short-term actions would include forecasting and assessment of the socio-economic impact of technological advances, careful choice of technologies and equipment to be imported, and a strengthening of the negotiating capability for their acquisition. Long term actions will call for imaginative attempts to apply the technological

advances for improving the standard of living and upgrading the general technological level of the population as a whole. Taken together, such responses should be made as a strategic activity involving, where necessary, structural changes in the industrial and economic development of the country but weaving them into the development vision of each country. It is recommended that developing countries consider establishing appropriate mechanisms individually or collectively to forecast, monitor and assess technological trends and their implications for social and economic development and develop, formulate and implement policies to maximise the potential benefits of the new technologies and to avoid their adverse consequences. Such an assessment should be an important input to industrial, technological and general development planning and the formulation of industrial, technological, commercial and fiscal policies and in decision-making on industrial projects. Such information should also be used to see how far the new technologies could be used to revitalize the development process in critical sectors.

It is also recommended that developing countries integrate their policies in regard to technological advances with the overall economic and technological policy. To enable such an integration it is recommended that the UNIDO Secretariat formulate guidelines for the consideration of developing countries on possible approaches, methodologies, models, and feasibility of alternative points of entry and targets.

It should be remembered that high technology cannot be thought of as an escape route from the problems of development, nor can the developing countries blindly follow the high technology path opened by the industrialized countries. High technology options have to be placed within the range of available technology options from the traditional to the advanced. Developing countries may have to adopt and manage a technological pluralism that will be optimal in the light of the objectives, problems and limitations of each country. High technology should also be used not only to start feasible new industrial activities but to upgrade the general industrial and technological capability of the country including its traditional and/or decentralized activities. Such application could result in advantages such as the elimination of human drudgery, prospects for substantial increases in productivity, decentralization of production and marketing and better quality control.

In considering the process of integration, it should be remembered that developing countries already suffer from weaknesses and shortcomings in regard to technology transfer and development. In the context of the emerging technological advances, it is recommended that developing countries individually and collectively, examine their existing state of technological capabilities and take steps to create or re-orient their institutions and structures as necessary and appropriate to respond to technological change in accordance with their own objectives and conditions. The application of technological advances requires significant investments in human resources in the field of technical and scientific development, the establishment of a basic institutional infrastructure for acquisition, research and development and the management and utilization of technology and the provision of internal and external financial resources in a significant and continuous fashion.

No uniform prescriptions should be sought or applied for countries at different levels of development nor indeed for each type of technological advance. It is recommended that each developing country follow a selective and differentiated approach in the light of its development objectives and present economic, social and technological situation. It will have to decide for itself the level of capabilities it wishes to acquire in the field of new technologies and in regard to the development or utilization of each technological advance. It is however suggested that each developing country give consideration to acquiring a minimum level of capability in regard to important technological advances. Apart from the newly industrializing developing countries, the case of small developing countries in the early stages of technological development should be given special attention by their respective governments. Such countries would also need to possess the same degree of technological awareness as other countries, in an interdependent world economy. In regard to acquiring capabilities in selected areas of technological advances and the application of those advances, they may have to follow initially a selective policy in accordance with their priorities. A minimum programme in this field may include awareness; monitoring; assessment; strengthening the capacity for selection and acquisition of technology and equipment; capabilities to apply the technologies; and other elements needed to facilitate autonomous decision-making. It is recommended that the UNIDO Secretariat develop guidelines for a framework of national actions, particularly for the use of newcomer countries enabling them to take decisions on priorities; points of entry; degree of penetration; linkages and inputs required etc.

Within the context of the foregoing considerations, the Forum wished to bring to the attention of UNIDO IV that the industrial and technological policies for the 1980s and beyond will have to be framed in the light of the potentialities and implications of the new technological advances. The emerging technologies make it imperative that future industrial policies should be designed keeping fully in mind the structural economic changes likely to

be brought about by the new technologies. Industrial development policy in this sense should be viewed as a strategic activity involving, wherever necessary, structural changes. The future prospects for industrialization should be viewed keeping in mind the new dimensions and perceptions that are required in the context of the technological advances. Such perceptions are required in regard to the development of transfer of technology and to the concept of technological dependence itself. A fresh look at human resources development is also required. A new type of technological capability appears to be evolving on the basis of new products, processes and matters of organization of production and other economic activities.

The new instrumentalities in this changing situation will be a technology-oriented industrial policy and the systematic incorporation of information, based on socio-economic assessments about technology trends in policy and decision-making. Special attention has to be paid to education bringing it to the level demanded by modern science and technology. In this respect it was considered appropriate that UNIDO organize a special symposium on this issue.

New mechanisms of international co-operation are also called for. These could take various forms. Firstly, it was recommended that co-operation among developing countries should increasingly incorporate activities relating to acquiring self-determination and technological capability in the field of new technologies. Since the manner in which such new technologies are applied in one developing country will be relevant to other developing countries, the need for co-operation in the exchange of information, consultancy, training, technology transfer, etc. is paramount. Collective negotiation strategies and policy responses could also be considered. The emergence of new technologies and their potentials and implications for developing countries and the challenging task of creating unique developing country applications, required consideration and attention at the highest policy-making levels in developing countries.

New ways of strengthening co-operation between developed and developing countries should also be considered. The diffusion of the benefits of the technological advances should be available to and shared by all. Developed countries are asked to give special attention in their programmes of co-operation with developing countries in providing educational and training facilities, research co-operation etc. Technologies must be made available at fair and equitable terms and conditions, and they should be adapted to the needs of developing countries. Research on adaptation, application, improvement and further innovation should be encouraged by developed country enterprises functioning in developing countries.

It is proposed that a new form of international co-operation be considered with the designation of a limited number of new advanced technologies to meet particular needs of a clear and urgent character to the human community as "Technologies for Humanity". These technologies should be developed and disseminated in the public domain. "Technologies for Humanity" should be clearly and precisely defined so that international efforts can be focused on specific problems until appropriate solutions are found and effectively disseminated throughout the world, especially in developing countries. All nations able to contribute to developing these technologies should be encouraged to do so. The UNIDO Secretariat was asked to carry out further work on the concept of "Technologies for Humanity" and present it to UNIDO IV for consideration.

UNIDO should increasingly try to augment its monitoring of key advanced technologies to disseminate the information focused on specific needs of different countries. This will involve intensifying and extending contracts between appropriate agencies and institutions in developing countries, and scientific and professional societies, universities and non-governmental organizations that are concerned with the developing countries and are based in developed countries. Additional channels of technological information should be tapped including the patent offices and plant variety registries and open proprietary sources of information on new technologies through consulting firms and business information services. Above all, developing countries may sharpen their requests for technological information through technology planning and industrial strategy groups.

It was recommended that the UNIDO programme on technological advances be expanded and diversified on the lines indicated in the reports of the expert meeting in Moscow and the Tbilisi Forum. In addition, the UNIDO Secretariat should identify and promote new mechanisms of international co-operation in particular for strengthening the technological capability of developing countries and for the development of new technologies of unique interest to developing countries. It was also recommended that UNIDO continue, together with UNESCO and other international organizations, to mobilise the co-operation of high-level scientists and technologists in the world for harnessing the new technologies for the benefit of the developing countries in particular in the field of industrial development and bring the considered views of such experts to the attention of UNIDO IV and other relevant fora.

In undertaking such activities in this field, the UNIDO Secretariat was requested to continue to maintain close co-operation with other concerned international organizations in the UN system and outside it.

It was considered that the conclusions and recommendations of the expert meeting in Moscow and the Tbilisi Forum provide a sound basis for developing further the activities of UNIDO in this field. It was recommended that the results of the Forum be brought to the attention of the appropriate bodies of UNIDO in the preparations for UNIDO IV.

Review of selected technological advances

The Forum reviewed selected technological advances in the fields indicated above. It noted that those advances had been selected for detailed review as being important to most, if not all, developing countries and as those which illustrated the mutual interrelationship among technologies. Such a discussion was intended to help provide a general framework for consideration on the basis of which the general issues of technological advances could be considered.

The Forum noted that the selected technological advances had been reviewed in depth by the preparatory expert meeting in Moscow in working groups. It took note of the observations of the report of the expert meeting and its recommendations. Limitation of time did not permit the Forum to discuss fully all the aspects involved. It was considered that the general approach adopted by the expert meeting in Moscow and its recommendations provided a sound basis for further action. Special attention was however given by the Forum to the overall policy issues arising from the review of the technological advances. The Forum also heard statements from a number of participants on the experiences of their countries and the attempts made by them to strengthen their technological capabilities in the technologies under reivew.

Genetic engineering and biotechnology

The Forum noted that though fermentation technology was known to mankind for hundreds of years, it was now possible, thanks to advances in microbiology and genetic engineering, to tailor microorganisms to specific tasks. The resultant versatility and efficiency achieved will enable the production of a wide variety of new or significantly improved products in a variety of fields such as pharmaceuticals, energy production, agriculture, mining, etc. It would provide new solutions to the basic problems of food, fodder, fuel and fertilizers. It was therefore important for developing countries to understand and acquire this technology, utilize the processes and revitalize their economies. If appropriately utilized, genetic engineering and biotechnology could open up a new pathway for industrialization. The techno-logy would also be energy-saving, of relatively low capital intensity and easy to apply and lend itself to decentralised applications. It could enable rural industrialization and improve the quality of life. With the adoption of appropriate safety regulations, the technology was not dangerous as was sometimes believed. Thus, it looked as though the new technology was particularly tailored to the needs of the developing countries where the turnover of organic material is high.

In the discussion, attention was drawn to the present asymmetry in technological development efforts in this area as between developed and developing countries. For example, from 1977 to June 1980 the patents in various product categories in biotechnology registered by the USSR, USA and Japan amounted to 121, 244 and 1,427 respectively, whereas hardly any patents were registered by developing countries.

The Forum agreed that developing countries could not be passive consumers in this area and that they should monitor what is going on and develop their own expertise and establish centres of excellence. Indigenous competence was essential to enable the developing countries to exploit their natural resources and microorganisms, specific to each country. Unless local institutional capabilities are available within the country, there is the danger that the personnel sent for training abroad might continue to stay there and as such no real local expertise could be built. The importance of setting up national groups to work in this area was stressed.

The point was made in this connection that the commercialization of R&D was expensive. But the traditional thinking of cost structure has to change, e.g. the new phenomenon is that the development time from basic research to commercial production is much shortened. Similarly, several changes in economic and industrial structures are occurring, e.g. sugar is being replaced by fructose in sweeteners. Furthermore, the production processes do not necessarily demand high cost equipment. It was noted, however, that genetic engineering involved essentially scientific research and the capital investment for genetic engineering as such was not high. Besides, in applications such as in agriculture, the production of a

new seed for example will not be an expensive proposition once the basic research is done. Capabilities of countries and the scales of production required and the cost of research personnel also varied from country to country. Development times from basic research to commercial production are getting shorter and the pilot plant production processes do not necessarily demand expensive equipment. The traditional thinking on the cost structure on R&D had to change, particularly when widespred benefits to a large number of people are to be realized. The alternative of transfer of technology also entailed high costs which may be more than the costs of development. The option of transfer of technology also entailed problems of access and suitability of technology. Further industrialized countries may not be interested in developing or using some of the biotechnologies. In any event, the opportunity cost of not developing and applying this technology is very high for developing countries.

At the same time, the problems involved in terms of the prerequisites for the introduction of the technology in terms of the infrastructure required should not be oversimplified. Besides, a measure of selectivity is required and each country has to decide at what point of technology development or application it wanted to enter. The matching of education and emerging technologies and the problems of scaling up and types of equipment needed were also necessary.

Several experts reported to the Forum on the steps taken by their countries in promoting the development and application of genetic engineering and biotechnology. The Forum noted in this connection that even a small country had a good chance of enhancing its capabilities in this field in selected aspects of technology. (The Hungarian experience cited in the meeting was a case in point.)

The Forum agreed that ways and means of possible co-operation between developed and developing countries in this field should be identified. There were already instances where some of the developed countries were co-operating with the developing countries in this area. It was suggested that such co-operation be intensified, that interaction between scientists and technologists be promoted and that developed countries should provide to the maximum extent possible the necessary financial resources and education and training facilities for developing countries in this field.

A suggestion was made to divise suitable guidelines for technology transfer in this field. Attention was also drawn to the role of payments and the costs involved in the exploitation of the patents. The question had to be considered whether the existing system of patent laws needed to be adjusted to utilize technological advances and to improve access to technologies. There was also a need for improving the terms and conditions of technology transfer.

Specific recommendations were made at the expert meeting in Moscow in regard to national and international actions and UNIDO's role (ID/WG.384/16, paras. 114-116) and other suggestions were contained in ID/WG.389/3, paras. 13-18, and ID/WG.384/4/Rev.1. There was a need to sensitise countries on the potentialities as well as the problems involved in the development and utilization of the technology and the time frames for achieving specific objectives. The Forum noted with appreciation the initiatives already taken by UNIDO in this regard and its efforts to establish the International Centre for Genetic Engineering and Biotechnology and the publishing of the Genetic Engineering and Biotechnology Monitor. UNIDO should continue to assist all countries at their request and also undertake promotional activities, it should pay particular attention to assisting newcomers, particularly the smaller ones in acquiring a greater awareness of the potentialities of the technology and the ways and means of developing a capability in this field. UNIDO should also make an effort to demonstrate that a systematic utilization of the potential of genetic engineering and biotechnology could serve as a powerful introduction to rural industrialization carried through high technology. UNIDO may also take advantage of an offer made in the Forum to prepare feasibility studies and project reports on processes that have promise for commercialization.

Experts visit sites for International Centre for Genetic Engineering and Biotechnology

Following the discussions of the Belgrade meeting, an expert team visited Belgium, Cuba, India, Italy, Pakistan and Thailand to inspect the sites proposed and discussed with the authorities the facilities offered. The team is in the process of preparing its report which will then be taken to the Ministerial Level Plenipotentiary Meeting, now scheduled for 7 to 13 September 1983. Already some 45 countries have expressed interest in attending the meeting. The members of the expert committee are:

Dr. Oscar Grau
Biochemist
Faculty of Exact Sciences
National University of La Plata
Calle 47 y 115
La Plata
ARGENTINA

Prof. Tsai-ping Li
Director
Laboratory of Molecular Genetics
Shanghai Institute of Biochemistry
Academia Sinica
320 Yo-Yang Road
Shanghai
CHINA

Prof. Dr. Peter Biacs
General Director
Food Research Institute
Herman O. u. 15
1022 Budapest
HUNGARY

Dr. Susono Saono
Head
Botanical Research Centre
(Treub Laboratory)
National Biological Institute
The Indonesian Institute of Sciences
The Botanical Garden, LBN-LIPI
Bogor
INDONESIA

Dr. R.O. Barrow
Assistant Director
Department of Medical and Natural Sciences
Federal Ministry of Science and Technology
109 Western Avenue
Iponri - Lagos
NIGERIA

Dr. Staffan Normark
Professor in Medical Microbiology
University of Umea
S-901 85 Umea
SWEDEN

Dr. Vladimir Glisin
Center for Multidisciplinary Studies
University of Belgrade
Slobodana Penezića-Krcuna 35
Belgrade
YUGOSLAVIA

Dr. David McConnell
Department of Genetics
Trinity College
University of Dublin
Lincoln Place Gate
Dublin 2
IRELAND

Two international meetings to be held in New Delhi, India

The International Congress of Genetics will be held in New Delhi from 12 to 23 December 1983. The scientific programme of the Congress consists of 34 symposia involving 100 speakers. UNIDO is expected to be one of the co-sponsors of the Congress and will help the participation of five experts. The Chairman will be Dr. M.S. Swaminathan, Director General of the International Rice Research Institute (Philippines). The Secretary General is Professor V.L. Chopra of the Indian Agricultural Research Institute, New Delhi, India.

The VIIth International Biotechnology Symposium will be held in New Delhi from 19 to 25 February 1984. In addition to the scientific programme there will be an exhibition of processes, products, equipment, books, literature, etc. pertaining to biotechnology. The Chairman of the National Organising Committee is Dr. T.K. Ghosh, Indian Institute of Technology, Hauz Khas, New Delhi, India.

Audiovisual programme on DNA

An audiovisual programme on DNA and recombinant DNA technology for classroom use is being completed by the American Chemical Society. Entitled "DNA: Master Molecule of Life," its release was scheduled for February.

The programme, believed to be the first such programme on DNA for instructional purposes, is designed to assist teachers in explaining the complex structure and functions of the deoxyribonucleic acid molecule, and the powerful new gene-splicing technology. It is expected to be especially helpful for students of general science, biology, and chemistry at the junior high through early college levels.

To be distributed in kit form, the programme consists of three 60-frame-each film strips, taped narration, 24-page teacher guide, activity sheets, suggested tests, suggestions for class discussions, class projects, resource list, and film-strip scripts. It provides the flexibility of being covered in a single class period or used as a mini-course.

Each of the film strips is about 10 minutes long. The first portion of the film is an introduction to the DNA molecule, the second a technical explanation of its structure and functions, and the final film strip portion is a discussion of implications for the future in recombinant DNA technology.

The narration and most of the visual materials in "DNA: Master Molecule of Life" were developed by the society's Office of Public Relations. The teacher guide and other auxiliary materials were prepared by MediaMark, a New York-based producer and distributor of educational aids.

The programme will be produced and marketed by Triton Scientific Corp., 2002 Colonial Gardens Dr., Avenel, N.J., 07001. Cost per kit will be about $75.

Triton also will offer for sale with the kits models of the DNA molecule of different sizes and prices, along with other DNA teaching aids. (Source: Chemical and Engineering News, 17 January 1983.)

Employment opportunity

The Federation of European Biochemical Societies is intending to set up a job-placement bureau at its annual conference from 24 to 29 July 1983 at Brussels, similar to those which have long been a feature of the annual conferences of the Federation for American Societies for Experimental Biology. Many European companies in need of particular specialist help and often unable to recruit scientists from local universities may find this venture will not only help them, but also young biochemists seeking jobs. However, language problems and restrictions prevailing in some European Community countries that employees should always be nationals, could present difficulties. Nonetheless those seeking to use the new service in July, whether potential employers or employees should write to the organizers of the 15th FEBS Conference, Brussels International Conference Centre, Parc des Expositions, Place de Belgique, B-1020, Brussels, Belgium. (Extracted from Nature, 3 March 1983.)

Biotechnology business - 1

In a sense, the field of biotechnology has mirrored the example of the hugely successful microelectronics revolution of the past decade.

Investors who looked at biotechnology and became fearful of missing out at the birth of what appeared to be a new industry with gigantic potential, rushed to set up companies or acquire existing ones, or fund research projects with the expectation of immediate returns. When the inevitable retrenchment occurred, with some companies folding in the past year and others cutting expenditures and laying off staff, interest in the field faded.

But now, there is every indication that surviving firms will be producing a wide array of products during the next ten years. Almost all observers agree that biotechnology's greatest potential to affect the shape of the chemical process industries - the production of commodity petrochemicals via biological routes - will not be realized in this decade, and possibly not in the next one either, depending on what happens with the world price of oil. Indeed, it almost would have to double in order to make biotechnology routes attractive, says one expert.

There are also technical factors that will lessen the impact of biotechnology on the petrochemical industry. Bulk-chemical conversions usually cannot be accomplished in one or two steps. With biotechnology, a protein is usually used to react with precursors so

that the protein catalytically converts to another chemical. But one needs five or six steps to produce basic commodity chemicals. This is one reason why pharmaceuticals, which usually require only a single-step process of converting one biological compound into another, will be the first commercial products to emerge from the new science.

The wall has been breached with pharmaceutical products, notably human insulin, for human healthcare, and observers see more new products coming to market in animal husbandry and agriculture.

The subject of plant life alteration poses some important questions. For instance, companies must decide whether to pursue the production of biologically based chemicals, such as herbicides, or of genetically altered plants.

In the former case, products will be sold in much the same way as fertilizers, pesticides or other agricultural chemicals are sold now. In the latter, it may occur that, once a new strain of seed is widely disseminated, further sales may be only as a high-volume, low-unit-value product.

Are agricultural-chemicals manufacturers in danger of harming some of their traditional products by coming up with a biotechnological find that would make them superfluous? Thomas Lewis, director of Monsanto's corporate research laboratory, isn't so sure this could come about. "We have been very active in applying the new biotechnology to agriculture, but it is still pretty fuzzy how best to go about this. You can build herbicide resistance into plant life, but we don't know whether when you change one attribute of a plant, you may be changing others as well."

But R.N. Dryden, president of Agrigenetics, a $100-million agricultural-products company that is moving heavily into biotechnology, sees much more definite effects. "If you could genetically provide a seed that reduces the requirements for fertilizers, pesticides or herbicides, not only do you save the cost of chemicals but you also save on tractor fuel, equipment and time," he says. The development of bacterial inoculants (to fix nitrogen in plants more quickly) "could have a significant impact on the fertilizer industry," he concludes.

Looked at another way, however, biotechnology may serve to enhance the marketing of today's agricultural chemicals. An interesting example of this is the work of Calgene, which announced a few months ago that it had successfully cloned a gene that would allow plant cells of valuable crops to withstand Monsanto's herbicide roundup.

One application of the cloning, speculates Aldis Adamson, vice-president of Calgene, could be genetically altered wheat plants able to resist repeated sprayings to kill wild oats, a weed susceptible to the herbicide Roundup.

Although Calgen succeeded in its cloning, it has not yet been able to "express" the gene - i.e., it has not passed on the genetic alteration to later generations of the cells. Still, Adamson is highly optimistic about his company's work. "This modification confirms the earlier belief that herbicide tolerance would be one of the first areas where genetic engineering would come up with commercially usable plants." He thinks that commercialization may occur no later than 1985.

Another area of potential commercialization that some observers expect to reach beyond the laboratory stage by the latter part of this decade is specialty chemicals. For some of these - high-fructose corn syrup, amino acids, enzymes and a few other chemicals - commercial production is already under way (especially in Japan), but it is expected that the refinement of biotechnological techniques will drastically change the manufacturing steps and introduce a host of new products.

In Japan, where companies have long been producers of enzymes and enzymatically treated products, Nippon Zeon Co. (Tokyo) announced last year the availability of 87 new synthetic forms of DNA. Akiya Kaneda, a Zeon specialty-chemicals engineer, says that sales of the products since September 1982 have been "better than anticipated", encouraging the company to try to realize approximately $1 million in sales by this year.

Dow Chemical Co., which has a major co-operative agreement with Collaborative Research Inc. (Waltham, Mass.), last year announced a successful cloning that could lead to genetic production of the enzyme rennin, used in cheese manufacturing. Dow has estimated the world market for that product to be $70-100 million.

Enzymes also are the basis for a joint venture between Genentech and Corning Glass Co. (Corning, N.Y.) called Genencor. That company will pursue the development of better grades of enzymes for high-fructose corn syrup production, as well as other specialty chemicals. The timetable for development of both enzymes and specialty chemicals is three to five years, notes Shirley Clayton, treasurer of Genentech.

Microbiological hurdles - even though an enormous amount of work has been done in the past decade to advance genetic engineering technology, much remains unfinished. A parallel can be drawn between the way chemical engineers have traditionally worked with research chemists, and how they will be expected to work with the microbiologists, geneticists and other scientists of the new field.

"Cloning a gene into a cell is almost - I hate to use the word - commonplace now", observes Genex's Lombardi. "It's a time-consuming process, but has a good success rate. Gene expression is the problem now. We know it is possible to do this, but finding the right biochemical environment has been difficult. It's a big problem for molecular biologists to work out."

And in a report issued by the Organization for Economic Cooperation and Development (OECD) last spring ("Biotechnology: International Trends and Perspectives"), the authors noted that too much of the work going on now is with Escherichia coli, a bacterium that in many cases has only limited capability for carrying out biological reactions. "Exclusive concentration on a few organisms has led to the neglect of large sectors of microbial life. Much is known about E. coli, which is not very useful in industry and difficult in fermentation when genetically engineered, but very little is known about other, more useful organisms." The authors recommend additional study of yeasts, fungi and plant cells, among others, as an alternative.

Chemical engineering input - at present, the complicated engineering problems associated with biotechnology are only beginning to be dealt with in a substantive way. Even so, this field promises to be as exciting as molecular genetics has been for the past decade. Some new separation and purification techniques are being developed that may even come to influence conventional CPI technology.

"There are three problems with traditional chemical-engineering unit operations when considering biotechnology", states Alan Michaels, a New York-based consultant. "First, techniques like distillation are much too energy-intensive for the dilute, highly impure fermentation broths," he says, noting that many such streams have product concentrations of only a tenth of a gram per liter, and are contaminated with isomers and closely related proteins from which the desired products must be separated.

"Second, traditional techniques are not very kind to biological products, which have very low thermal and mechanical stability. We need techniques that are more 'respectful' of these agents.

"Third, there is the question of selectivity for the products in the crazy mixtures that are found. Traditional techniques are only marginally applicable", he concludes, adding that the fermentation broths often contain many compounds closely related to the product of interest - and even optical isomerism must be reckoned with sometimes.

Nonetheless, much work is being done that looks very promising. Michaels says the most progress is being made by chemical companies, "because they know they need to make large volumes of product in order to be profitable."

Interestingly, though, many of the techniques that now look feasible originated as laboratory analytical procedures. Among these:

- Gel permeation, based somewhat on the chromatographic columns that sometimes precede use of a laboratory analyzer for species separation. In this technique, a packed column of gel particles serves to segregate larger molecules from smaller ones, as a product solution trickles through the bed. Michaels notes that there are serious mechanical problems with columns serveral feet in diameter (as compared to the less than 1 in. dia. of laboratory columns) because the gel packing cannot support its own weight. Several manufacturers are making some headway on solving this problem.

- Isoelectric focusing, a new technique similar to electrophoresis. Because most biological materials have a so-called isoelectric point (where, in a potential gradient, the molecule has no net charge), they can be separated by spreading a solution on a bed of the proper media, passing the bed through an electric-potential field, and allowing the molecules in the solution to gravitate toward their isoelectric points in the field.

- Affinity sorption, which in its eventual form may require the use of molecules derived from genetic engineering. This procedure is based on the employment of antibodies as purifying agents packed into a column much the way immobilized enzymes are used (Chem. Eng., Apr. 19, 1982, p.55). "Once the antibody is hooked onto a solid support in the column, it can act as a fishing hook for the product of interest", says Michaels. "That product, which is actually the contaminating antigen that the antibody was designed to attack in living systems, will be the only material held up (in the packed column as the fermentation broth is passed over it). Then you simply change the elution solvent, and the pure antigen uncouples from the antibody."

However getting a sufficient supply of antibodies is a major biotechnological problem itself, says Michaels. The emerging technology of producing "monoclonal antibodies" promises an answer. In this technique, a healthy cell is artificially fused with a diseased cell (when cancer cells are used in the fusion, the combination is called a "hybridoma"). The resulting hybrid is able to produce antibodies continuously; these can be collected and sent to the affinity-sorption column.

This may not be the only way to obtain needed antibodies. Certain cells can be "challenged" by culturing them in an environment that contains a high concentration of a chemical (e.g., a pollutant like phenol). The cells' DNA then begins to manufacture appropriate protective antibodies, and these antibodies, once collected in sufficient quantity, can be used in a packed column to treat, for instance, a wastewater stream containing the pollutant. "What we are talking about is an entirely new unit operation that will be developed over the next 10-15 years", says Michaels. (Extracted from Chemical Engineering, 10 January 1983.)

Biotechnology business - 2

Biotechnology products won't arrive in any numbers until the mid-1980s, and a major market impact won't occur until 1990 or beyond, much to investors' and the companies' chagrin. Investors gave millions during the late 1970s and into 1981 to garnish the riches expected later from the recombinant DNA market. Companies are now surviving on research contracts. Two early entrants, Genentech and Cetus, saw stock plummet, but still had cash. The biotech companies waiting to start up are hard hit for capital as investors dry up because of the long wait before profits. Analysts that watched other industries in this embryonic stage are not surprised, calling it a 'routine scenario'. As breakthroughs occur, the first few companies get money from excited investors; as competition intensifies, company evaluation falls or levels off and the money dries up. Many administrative changes occur and companies fail, leaving the industry to shrink.

Some veterinary-medicine rDNA products have hit the market, such as the cure for foot-and-mouth disease, but no human health-care product was approved until September 1982, when Genentech and Eli Lilly got Humulin, a highly purified form of insulin, approved by the FDA. In November, Schering-Plough announced that interferon would be on the market by 1984. Tests show that interferon can be used to treat some forms of cancer, genital herpes and prevent colds. The next biotech product is expected to be a human-growth hormone to treat dwarfism. Predicasts expects biotech's share of the US parmaceutical market to grow up to $11.7 billion in 1995, vs $230 million in 1985. The difficulty with these products is competition. Other aspects of the biotech market are included. (Source: Technology Update, 12 March 1983.)

Biotechnology business - 3

US shipments of biotech products, forecast for 1995 ($billion)

Health-care products (total)	70.0
Non-biotech	51.4
Therapeutic medicine	12.0
Diagnostic medicine	5.8
Medical research	.8
Agricultural products (total)	470.0
Non-biotech	369.0
Crops	50.0
Cattle	48.0
Seeds, veterinary, feed additives	3.3

(Source: Technology Update, 12 March 1983)

The following is a selection of the areas of greatest activity amongst the many announcements of new processes and technology reported between May and October 1982 which was published in the periodical Chemical Engineering of 24 January 1983:

Biochemical processes

Product	Process	User	Features	Status and remarks
Ammonia removal	From waste-water	Bayer AG, Lever-kusen, West Germany	Nitrogen in the form of ammonia is removed biochemically in a two-step process called The Bayer Towerbiology. Step one: ammonia is oxidized by the bacterial system Nitrosomonas/Nitrobacter to nitrates. Step two: nitrate is converted to nitrogen, water and hydroxyl ions in the presence of a hydrogen donor, e.g., methanol.	Plant built at a refinery in Germany in July 1981 is reported to be running successfully.
Diagnostic kit	For venereal disease		The assay kits for detecting chlamydia, gonorrhea, and two forms of herpes simplex are built around monoclonal antibodies that are tagged with fluorescent dyes. The antibodies are pure in that they detect and react to only specific organisms - the average time being 20 min; in contrast to current methods that take 6 days. Developed by Genetic System, a young biotechnology firm, the chlamydia kit will be on the market from February.	Awaiting approval from the FDA.
Ethanol	From cellulose	U.S. Dept. of Agricul-ture, Northern Regional Research Center, Peoria, Ill.	Partial breakdown of cellulose by acid hydrolysis forms cellodextrins. These are fermented by yeast Candide wickerhamii, in 3 to 4 days.	
Ethanol	From cheese whey		Whey feed is concentrated by reverse osmosis; the protein content is separated to be used as animal feed, and the whey is then fermented in a continuous process, using a proprietary microorganism that can be recycled.	Fermentec Corp. (Los Gatos, Calif.) is seeking patent protection, and has started up a demonstration unit (capacity: 0,5 million lb/d of whey) at Manteca, Calif.
Fructose	From rice waste	Habib Arkady Ltd., Hub Chowki, Pakistan	Rice waste is the starting material, which is converted into fructose via immobilized-enzymes treatment (at 62°C, with glucoisomerase enzymes).	A $9-million plant producing 150 m.t/d of 42% fructose and some glucose from 130 tons of broken rice will go on-stream in early 1983.

Biochemical processes (cont'd)

Product	Process	User	Features	Status and remarks
Industrial alcohol	Fermen-tation and distilla-tion		Concentrated starch-based feedstock is pumped at a fixed rate into an aerated fermenter. A portion of the broth is withdrawn continuously so that the yeast can be removed and recycled. The ethanol produced is removed in a two-stage dis-tillation that, according to the devel-oper (Alfa-Laval AB, of Tumba, Sweden): optimizes the liquid-to-vapour ratio in each stage; minimizes energy consumption; and simplifies stabilization of fermentation conditions. Reported benefits include: no need to dilute the feedstock, and little or no energy consumption for evaporation of the post-distillation effluent.	A demonstration plant producing 12,000 L/d of ethanol has been running since April 1981 in Queensland, Australia. A 20,000-L/d de-monstration plant is planned for Sweden.
Isolation of a bacterial gene that aids plant freezing.			The Intl. Plant Research Institute (San Carlos, Calif.) has announed that it has isolated and successfully cloned the gene (found in many bacteria) that ini-tiates generation of a protein that per-mits the formation of ice crystals in plants at temperatures slightly below freezing. Should the protein be pro-duced in quantities sufficient for further study, means of preventing crop freezing, or, conversely, means of quickly freezing crops for storage, may be developed.	
Methane	From bio-degradable wastes	Rank, Hovis McDougal Ltd., U.K., France, Italy	Patented enclosed digester churns in-coming wastes by a sparging stirrer. As stirrer rotates, product gas is recycled through the sparge holes to cause more vigorous mixing. A subse-quent clarification unit separates bio-mass from the treated effluent for re-cycling back to the digester. Streams having a high waste content - 4-10% biodegradable matter - are said to be converted to methane with much lower energy input than in conventional acti-vated-sludge processes. Methane yield is 0.4-0.55 m3/kg of chemical oxygen demand, and COD reduction reaches 83-98%	Developed by Bio-mechanics Ltd., Ashford, U.K., with funds from from U.K.'s Natl. Development Corp. The developer, Capital Plant Intl., a subsid-iary of Mitchell Cotts Group Ltd. (London), has the process in use at three commercial facilities in Europe. The firm plans to further market the tech-nique by empha-sizing that the route, being anaerobic, needs no oxygen, and the methane can be used as boiler fuel.
Nitrogen-fixing	Bacteria		Biotechnology General (Rehovot, Israel) is testing the ability of the bacterium <u>Axospirillum</u> for fixing nitrogen in corn-fields. The firm says Israeli tests show	A test on 300 U.S. fields was under-way in mid-1982 to determine whether

Biochemical processes (cont'd)

Product	Process	User	Features	Status and remarks
			a 25-39% reduction in fertilizer requirements after use of the organism.	the organism can survive cooler climates.
Phosphorus removal	From wastewater		Removal of phosphorus from municipal wastewater with the Phostrip process takes advantage of a phenomenon known as "luxury uptake" Normally, aerobic micro organisms, when put into an anaerobic environment, use phosphorus rather than oxygen as a source of energy. When returned into the aerobic system, these "stressed microbes" take up several times as much phosphorus as they normally would. With this process only 10% of a plant's effluent has to be treated to bring the phosphorus content of the total stream into compliance with federal standards.	Developed by Biospherics (Rockville, Md.), it is now being marketed in conjunction with Lotepro (N.Y.)
Protein supplement	From forestry waste		Cellulose forestry waste - pulp-mill sludge - combined with small amounts of chemical or organic fertilizer are fed to a fungus, which converts the wastes to protein. The protein is filtered and dried to a brown-green powder (45% of it is protein) that can be fed to poultry and livestock.	Developed by the Centre for Process Development, U. of Waterloo (Ontario). The Centre has licensed the process to Envirocon Ltd. (Vancouver, B.C.), which plans to build a pilot plant.

Ethanol and alternative fuels

Product	Process	User	Features	Status and remarks
Methanol	From wood		Wood is dried, gasified, and shift-converted to methane. The methane is then cleaned up, compressed and converted to methanol.	Battelle Pacific Northwest Laboratories (Richland, Wash.), the developer is preparing preliminary designs based on pilot-plant experience, for a plant with 1,000 ton/d methanol capacity
Methanol	From wood		Wood chips are gasified via the Texaco high-pressure process, and the resulting gas is then converted to methanol. Overall efficiency is said to be 55%.	Evergreen Energy Corp. (Waltham, Mass.) and Texaco Development Corp. are considering construction of a 330,000-gal/d methanol plant in the New England area.

Organic chemicals

Product	Process	User	Features	Status and remarks
Glucose	From cellulose		Cellulosic material is combined with a saturated acqueous solution of calcium chloride containing a small amount of hydrochloride acid. Upon heating of the mass to around 108°C, the cellulose is converted to sugar in a mildly exothermic reaction that takes about 30 min. to complete. The sugar is separated from the reaction mass by passage through an ion-exchange-resin bed: the calcium chloride liquor passes through, while the sugar is retained on the resin and reclaimed by backflushing the bed. The developer claims that conversion to sugar takes place faster and under less severe conditions than in acid-catalyzed systems.	Developed by Power Alcohol Inc. (Montclair, N.J.), which has demonstrated it on a laboratory scale.

Pollution control

Product	Process	User	Features	Status and remarks
Fluegas cleanup	Photo-synthetic bacterium		The bacterium Chlorobium thiosulfatophilum simultaneously converts hydrogen sulfide and carbon dioxide to elemental sulfur and polyglucose.	Jointly being developed by Illinois Institute of Technology (Chicago) and the Institute of Gas Technology (Chicago), which have carried out bench-scale tests.

Pulp and paper

Product	Process	User	Features	Status and remarks
Cellulose/ pentose/ lignin	Biomass fractionation		Lignocellulosic biomass, including residues, can be handled by the process, which employs a phenol as solvent for lignin, and does not require expensive chemicals or large amounts of energy. Delignification takes place at 100°C and atmospheric pressure. The fibrous cellulose fraction is separated by filtration, while the lignin and pentose are separated in a subsequent step.	Preliminary work leading to the design of a pilot plant should now be underway at developer, Battelle Laboratories (Geneva, Switzerland).

Synthetic fuels

Product	Process	User	Features	Status and remarks
Synthesis gas	Biomass gasification		Using a fluidized-bed gasifier from an unnamed licensor, this technique will convert (in a pilot unit) 12 m.t/d of biomass into around 20 m.t/d of synthesis gas suitable for methanol production. The route will comprise two stages: oxidation, followed by gasification.	Part of the European Community's solar-energy research program, the gasification pilot plant will be built in the U.K. by John Brown Engineers

Synthetic fuels (cont'd)

Product	Process	User	Features	Status and remarks
				and Constructors Ltd. and Wellman Engineering. Construction of the unit was slated to begin in Nov. 1982, with cold testing to follow 3 months later, and hot testing 4-6 months thereafter. After 10 months of testing wood gasification, researchers will test some U.K. coals as feedstocks.
Synthesis gas	Biomass gasification		The route will gasify biomass, including peat and wood, in the presence of only a minimum amount of oxygen, to produce synthesis gas for methanol production.	Developed by the Stockholm and Lund Institutes of Technology in Sweden, the process will be tested in a 12-m.t/d pilot plant that was scheduled for commissioning in Oct. 1982. Tests will be conducted for approximately two years.

RECENT DEVELOPMENTS

Hybricytes

A new cell fusion process discovered at Lovelace Medical Foundation and just to Summa Medical Corporation may make it easier to produce specialized human [illegible] protein in hybrid human or animal cells in a tissue culture system.

The new technique at Lovelace is a better way to make human hybridomas for monoclonal antibodies. The process is so efficient that it is hoped it may be used to fuse mammalian cells into "hybricytes" that could be better sources of proteins than genetically engineered microorganisms. Conventional hybridoma technique uses polyethylene glycol to promote fusion of spleen cells that produce antibodies with myeloma (malignant tumor) cells. A successful hybridoma cell will, like its myeloma parent, continue to reproduce indefinitely by cell division, just as a microorganism does. It inherits from its other parent the ability to make antibody.

Fusion efficiency is 60 to 80%, which is a vast improvement over the rate of one fusion per 100,000 cells obtained with conventional hybridoma procedure. It should now be feasible to fuse pancreas cells, for example, with myeloma cells to form hybrids that produce insulin. Hybricyte fusion might be better for products whose genes are difficult to isolate, or which are governed by more than one gene. Fused mammalian cells would also be ideal if a protein is needed in its natural glycosylated form with carbohydrates attached. Fused cells can produce glycosylated proteins. Recombinant bacteria cannot. (Extracted from Genetic Technology News, January 1983. Address: 158 Linwood Plaza, Fort Lee, N.J. 07024, USA.)

Nucleoside analogs may switch genes on or off

Analog compounds that differ only slightly from natural nucleosides making up DNA sometimes integrate into the DNA molecule. Effects can be useful:

Workers at National Institutes of Health administered 5-azacytidine, an analog of a normal DNA component, cytosine, to beta-thalassemia and sickle cell anemia patients. Apparently the compound causes genes coding for the betaglobin protein of hemoglobin to express. This raised hemoglobin levels in the blood. Defective functioning of the beta-globin gene is involved in both of these hereditary diseases. While 5-azacytidine may be too toxic for long-term therapy its success opens up a new approach to treatment.

Adenine arabinoside, an analog to adenosine, has the opposite effect on herpes simplex virus. It prevents a gene coding for an enzyme essential to viral reproduction from expressing. This drug has been used for some time to help prevent infection from spreading. However, it is not as specific as it might be and so poses problems. Better analogs are on the way, although they will also not be cures. (Source: Genetic Technology News, January 1983. Address: 158 Linwood Plaza, Fort Lee, N.J. 07024, USA.)

How to estimate costs for cloning research

The monthly newsletter Genetic Technology News (158 Linwood Plaza, P.O. Box 1304, Fort Lee, NJ 07024, USA) have recently come up with the way prospective researchers can make a rough estimate of costs for cloning enough genes for some particular protein in E. coli for testing, and we give this method hereunder:

Define some sort of researcher cost unit to work with, say a "team-year". A team would consist of a Ph.D. plus 1.5 to 3 technicians. Cost of a team-year would include not only their salaries and fringe benefits but also laboratory supplies (easily as much as salaries) and their portion of costs of shared equipment, such as centrifuges. The hard part comes in when you allocate company overhead to the team. This varies enormously from one company to another. But the total costs for a team-year comes to a minimum of $200,000 and could easily be $500,000.

Next step is to estimate the amount of team-years, or team-months needed for each step in the project. Here's what you might come up with:

To make a gene library - a series of clones containing large fragments of DNA that together represent the entire genome (DNA sequence) of the organism (say a human) whose protein you want. This might take 1 team-month.

Then you have to make a probe - DNA sequence from the gene you want. This is much easier if you know the exact gene you are looking for. This could take 2 team-months.

Use the sequence to probe the library - find the gene you want and splice it into a plasmid. This is the key step. Allow 6 to 9 team-months.

Make the gene express. Chances are your plasmids will replicate but will not produce the protein you want. So you try splicing in various promoter sequencs that could make it express. This might take 4 team-months.

Isolating the protein from the bacterial culture is difficult. It might require 12 team-months to develop a satisfactory purification process.

So you can figure on 24 team-months, a minimum of $400,000, more likely close to $1 million. Any problems and the cost could double to $2 million quickly. Elapsed time could be less, say 18 months if all went well, since in some steps two teams might be working on the same problem.

Rat growth hormone gene expresses in mice, doubling their size

You may be able to genetically engineer higher animals a lot sooner than you think. Latest success is the transfer of rat growth hormone genes into mice. The genes expressed and produced up to 1600 times the normal amount of growth hormone, causing some of the mice to grow to twice normal size. Potential application for improved meat animals and dairy cows is obvious. The research was done at four different institutions:

DNA fragments containing the gene for rat growth hormone (minus its promoter sequence) attached to the promoter sequence for mouse metallothionein were manually injected into male

pronuclei of fertilized mouse egg cells. Fertilized egg cells were obtained by flushing them from females after mating. The male pronucleus is the genetic material from the sperm cell that entered the egg cell, but which has not yet combined with the female genetic material in the cell. Injected cells were then implanted in the reproductive tracts of female mice that served as foster mothers. A few of the egg cells developed into mice containing the gene for rat hormone, and at least one passed the foreign gene on to some of its offspring. The foreign genetic material integrated into the chromosomal DNA of the mice, rather than into a plasmid outside the nucleus.

Rat growth hormone was made to express strongly by addition of zinc to the diet. This induced the metallothionein promoter to express the gene attached to it. Normally growth hormone is produced only in the pituitary gland, but transformed mice produced rat growth hormone in their livers and other tissues. It still is not certain whether they also produce it in their pituitaries.

This work follows quickly behind successful transformation of Drosophila fruit flies by injecting early embryos with a gene coding for a change in eye color. While there may be many complications to be settled before it is possible to genetically engineer livestock commercially the major obstacle appears to be overcome. University of Washington, Seattle, Univeristy of Pennsylvania, School of Veterinary Medicine, Philadelphia, University of California, San Diego, School of Medicine, La Jolla, CA and Salk Institute, San Diego, CA. (Source: Genetic Technology News, January 1983. Address: 158 Linwood Plaza, Fort Lee, NJ 07024, USA.)

Runaway plasmids increase yields from recombinant bacteria

One of the tricks to increase output of a product by genetically engineered bacteria is to increase the number of recombinant plasmids per bacterial cell. The usual way to do this is to use the antibiotic, chloramphenicol. A different way is to use a temperature-dependent technique. The Danish pharmaceutical company, Alfred Benzon, has just licensed technology in this field to Schering-Plough (Kenilworth, NJ) on a non-exclusive basis.

A big problem with a bacterium modified by recombinant plasmids is that the foreign proteins coded for by genes in the plasmids may harm the host bacterium. The idea behind increasing the number of plasmids in each cell (amplifying the copy number) is to culture the bacterium under one set of conditions to get a high copy number per cell, even though the plasmids may not be producing protein. Once a large number of cells with high copy numbers is obtained one can change the cond ions so that the plasmids produce the protein wanted. The large number of plasmids per cell means that protein production per cell can be very high. Chloramphenicol inhibits protein synthesis, and therefore growth of cells. But it does not stop replication of plasmids. Removal of chloramphenicol then permits the plasmids to produce the protein product.

The temperature-dependent technology, which Alfred Benzon calls "runaway-replication" does not require an antibiotic. High copy number is obtained by increasing the temperature, say to above 37°C. One advantage Alfred Benzon claims for its runaway-replication technology is that it does not decrease viability of the bacteria, as could happen with chloramphenicol. When temperature is lowered, the bacteria, now with large number of plasmids, are in good shape to produce the protein product coded for by the plasmid. In some cases yields can be increased so much by amplifying the plasmid copy number that it is unnecessary to improve the vector - by splicing in a promoter.

Part of the technology Alfred Benzon has available for license is confidential and part is patented. (British Patent No. 1557774 covers part of it.) (Source: Genetic Technology News, February 1983. Address: 158 Linwood Plaza, Fort Lee, NJ 07024, USA.)

Tandem genes cloned in yeast could boost protein output

The University of California, Berkeley, have been able to transform yeast with a plasmid containing the gene coding for copper resistance. In some of the transformed cells, the copper resistance gene becomes integrated into the main body of cell DNA in the chromosome. Because of a natural exchange of DNA between chromosomes when yeast divides, extra copies of the gene appear after a number of generations. The extra genes line up end to end, one after the other, as tandem repeats. A system is now being tested in which genes are spliced to the resistance gene so that they are also repeated.

Such a system should have advantages over the more common system in which cloned genes remain in plasmids. While plasmids replicate more easily than chromosomes, they are not as

efficient in translating the message in the DNA into protein, so protein production may be low. For genes in chromosomes the opposite is true. Chromosomal genes are very efficient at producing proteins, but they replicate more slowly than genes in plasmids. Having multiple copies of the gene (in the form of tandem repeats) compensates for the low frequency of replication. It is believed the system will be a very efficient general method for producing insulin, interferons or other proteins by recombinant DNA processes. A patent has been applied for.

The yeast copper resistance gene codes for a protein similar to the metallothioneins, which are responsible for resistance to copper, cadmium, mercury, zinc and other metals in many organisms. Metallothioneins have been used to promote expression of human growth hormone genes cloned in mammalian cells. About one sixth of the amino acid content of the copper resistance protein is made up of cysteine (in metallothioneins, cysteine units make up about a third of the total). The cysteine units form chelates with copper ions so they cannot damage the cell.

Adding copper ions to the medium in which the modified yeast cells are growing induces the cells to produce large quantities of the copper resistance protein and the genes spliced to it. Initiation of protein production is extremely rapid. Time from first reading of the DNA message to maximum protein production is only five minutes. (Source: Genetic Technology News, January 1983. Address: 158 Linwood Plaza, Fort Lee, NJ 07024, USA.)

SCP bacterium's ability to use methanol is not due to plasmids

Methylomonas clara, is a bacterium that has been used in Europe for making single cell protein (SCP) in high yield using methanol as its carbon source. Scientists at the University of the Ruhr (Bochum, W. Germany) find that genes coding for methanol are not coded on plasmids in the organism. This dashes hopes for genetically engineering organisms so they can utilize methanol by the relatively simple method of transferring plasmids. However, the German researchers did find that Methylomonas does have plasmids. They should make the organism valuable as a host. Genes coding for desired protein products could be spliced into the plasmids, which could then transform the host. Result: a recombinant organism that will grow on relatively cheap methanol. There is no indication that plasmids are unstable. (Source: Genetic Technology News, January, 1983. Address: 158 Linwood Plaza, Fort Lee, NJ 07024, USA.)

Scientists target algae for oil production

Microalgal culture may be useful for producing valuable chemical products such as oil, and since these organisms are simpler than plants it may be easier to manipulate them with genetic engineering techniques. The ability to genetically manipulate algae, however, is just developing and most researchers are trying to develop suitable vector systems to carry out routine cloning in these organisms. Traditionally, algal culture systems have been envisioned as potential sources of food and biomass, but scale-up has been limited by high-cost factors such as harvesting. The ability to extract oil from these organisms could make algal culture cost-effective.

The green unicellular alga Botryococcus braunii, which contains over 70 per cent oil on a dry weight basis, has aroused the interest of researchers in this area. Because of its high oil content the organism floats on the surface of water, making it easy to harvet, however, the slow doubling time of this organism - 75 hours under laboratory conditions - currently precludes its use as an economical photosynthetic oil-producer. Genetic engineering work on three other groups of organisms: the green algae Chlamydomonas sp., the blue-green algae Anacystis nidulans, and the photosynthetic bacteria Rhodopseudomonas sphaeroides, is also being undertaken.

Researchers at the Solar Energy Research Institute in Golden, Colorado have developed a cytochemical staining technique for lipids that is being used to identify organisms capable of producing intracellular oil. They have established the first comprehensive collection of oil-producing algae - 31 species within 11 genera and five taxonomical orders of eukaryotic microalgae. Among them are algae from the Chlorella and Chlorococcum genera. One species of Chlorella isolated at SERI has a mass doubling time of 10-15 hours. This organism also accumulates about 30-50 per cent of its total mass as intracellular storage oils and lipids. (Source: Bio/Technology, March 1983.)

An RNA molecule discovered

University of Colorado researchers have discovered an RNA molecule that can catalyze its own breakage and rejoining without the intervention of an enzyme. The ribozyme RNA was found in a single-cell pond organism called Tetrahymena. All previously known rearrangements of nucleic acid sequences are catalyzed by enzymes. The ability of the RNA molecule to re-arrange its internal structure by cleaving itself at specific locations and joining certain of the resulting fragments in a specific new sequence suggests that RNA, not DNA, may have been the primordial genetic material. (Source: Technology Update, 4 December 1982.)

High-resolution microscopy adapted for use on biological specimens

A type of high-resolution microscopy used primarily to study metal surfaces has been adapted for use on biological specimens by scientists of the University of Oregon and Portland State University. The research was supported by US National Institutes of Health. Photoelectron microscopy (PEM) is extremely sensitive to the topography or surface features of cells or membranes and offers certain advantages over other microscopic techniques for studying biological specimens.

In contrast to transmission electron microscopy and scanning electron microscopy, PEM uses ultra-violet radiation to photoionize electrons from the specimen's surface. An ultra-violet radiation source illuminates the specimen and photoionizes valence-shell electrons from the surface layers of the specimen, which acts as the cathode. The emitted electrons have only about 1 eV of energy and are accelerated in a strong electric field and focused by conventional electron optics. The interior of the microscope is under oil-free, ultrahigh vacuum. Contrast in the photoelectron micrograph is produced by the surface composition and its topography. The valence electrons' properties determine the photoelectron yield from any given point on the specimen. The very-low-energy photoelectrons produced by the ultra-violet radiation are deflected easily by distortions produced by the specimen surface features. Therefore, electrons emitted from a sloping surface are much less likely to enter the electron optics than those from a flat surface. This feature allows PEM to resolve changes in surface height as small as 30 A. (Source: Technology Update, 25 December 1982.)

Unusual enzyme in E. coli

An enzyme in E. coli regulates the switchover from the central metabolic pathway (the tricarboxylic acid cycle) to the glyoxylate bypass, according to researchers at the University of California (Berkeley). This unusual enzyme has 2 opposite activities - it can add phosphate groups to another protein and it can take them off - in a reaction that is not a simple reversal of the first. The enzyme may be classified with several other dual-function enzymes previously discovered that have important biochemical regulatory roles. (Source: Technology Update, 25 December 1982.)

Z-DNA

Portions of viral DNA called enhancer regions, which appear to control gene formation, may be able to assume an unusual conformation known as Z-DNA, according to Massachusetts Institute of Technology. Elimination of some or all of the 3 bits of Z-forming DNA from a particular enhancer region lowers the adjacent gene's activity, suggesting that the unusual reverse twist structure formed in Z-DNA may be important for controlling some genes. (Source: Technology Update, 26 February 1983.)

Monoclonal antibodies

Reports at the 2nd Annual Congress for Hybridoma Research suggested ways of manufacturing monoclonal antibodies with a reduced need to involve live animals or even live humans.

For relatively large volumes of antibodies, industry has relied on raising the hybrids in ascites in mice rather than in tissue culture, but a scientist working at the Basel Institute of Immunology has been able to devise a method without animals. He raises his hybrid cells under a controlled atmosphere in large jars containing a spinning mechanism turning at 15 to 20 revolutions per minute to ensure convection and prevent cells from adhering to the glass walls of the jar. This permits twice the amount of cells to grow per unit volume that will survive in tissue culture and at just below the density at which they begin to die. (Extracted from New Scientist, 10 March 1983.)

Doctors at Massachusetts General Hospital inject monoclonal antibodies labeled with radioactive technetium-99m into the coronary artery of heart patients to assess damage caused by heart attacks, using a standard imaging gamma camera. The antibodies congregate in areas of damaged heart muscle, which shows up clearly as white areas on a black background. Damaged tissue exposes the protein myosin, which can be recognized by monoclonal antibodies. The new method also exposes areas of the heart where only minor, diffuse damage has occurred, enabling detection of potential trouble. (Source: Technology Update 5 March, 1983.)

Abbott Laboratories has a new commercial diagnostic test that uses monoclonal antibodies to measure levels of prostatic acid phosphatase (PAP) in blood samples. Scientists think that elevated levels of the substances, which are produced naturally by the prostate gland, may be a good indicator of prostate cancer, a disease that finds 73,000 new victims in the U.S. each year. By periodically monitoring the PAP level of a patient with prostate cancer, physicians are able to track response to therapy. (Source: Chemical and Engineering News, 24 January 1983.)

Now that the application of monoclonal antibodies to the diagnosis and treatment of human disease has become the major goal of many investigators, a limiting factor is the availability of human rather than mouse or rat monoclonals. Human monoclonal antibodies are particularly needed for administration to patients for diagnosis and therapy in order to minimize the problems of administration of a foreign animal protein, with the risks of anaphylaxis and the clinical manifestations of immune complex formation, as well as abrogation of the antibody's effects.

The short history of human monoclonal antibody production has been fraught with technical difficulties but several novel systems now hold out promise. Initial attempts used available mouse and rat myeloma lines for fusion. Unfortunately the resulting hybridomas preferentially lose human chromosomes, eventually eject the chromosomes coding for immunoglobulin production and thus lose the ability to produce monoclonal antibodies. Although early and repetitive cloning of the hybrids can reduce the shedding of human chromosomes, the development of more stable human-human hybridoma systems seems desirable.

Accordingly several groups have developed human systems from which hybridomas may be created. Unfortunately many human myelomas are difficult to grow in tissue culture and have low growth rates and poor immunoglobulin secretion. Nonetheless, certain lines have been 'adapted' to grow in culture in genetic selection conditions in which the growth of the myeloma is suppressed but the hybridomas continue to propagate. There have, however, been difficulties with mycoplasma infection in myeloma stocks. Indeed many investigators have been unable to obtain any hybridomas at all with lines donated by certain laboratories, causing considerable controversy.

The use of several human myeloma or lymphoblastoid lines was discussed at a workshop in Cambridge held under the auspices of the Ludwig Institute for Cancer Research (LICR) last November. The ideal properties of such a cell system include high fusion frequency, high cloning efficiency, the ability to grow rapidly in non-stringent serum conditions, no secretion of myeloma or lymphoid cell immunoglobulin, and yet the production of large amounts of immunoglobulin after fusion to suitable lymphocyte donors.

Technical problems still unfortunately plague the production of human monoclonal antibodies, also discovering ways of collecting those lymphocytes that produce antibodies with the specifities being sought for different experimental purposes. It is too early yet to know whether all the current efforts will result in biologically interesting molecules with fundamental and clinical potential or just additional reagents with little difference from other available rodent monoclonal antibodies that can be obtained with significantly less effort. Nonetheless, the prospect of the former result will stimulate many groups to study and develop human hybridoma systems in the near future. The outcome could be exciting. (Extracted from Nature, 25 November 1982.)

Faster and cheaper screening tests

Quick, inexpensive tests using microorganisms and mammalian cells can successfully identify chemicals which cause mutations and are sufficiently reliable for most regulatory and manufacturing purposes, according to the US National Research Council. The screening methods can be used as alternatives to more expensive tests employing whole rodents except in cases where results are ambiguous or the chemical in question is widely used. Bacterial tests can be carried out within a few days and tests on mammalian cell cultures require several weeks, whereas tests in which mice are used require several months to complete. However, attempts to develop genetic monitoring techniques for large human populations exposed to mutagens have not been entirely successful.

The NRC committee recommended that the Environment Protection Agency adopt a 2-tiered screening process for environmental chemicals. If tests on Salmonella bacteria and mouse, Chinese hamster or human cell cultures are negative, the chemical can be presumed nonmutagenic. If 2 or more tests are positive, the chemical would be presumed to be a mammalian mutagen. According to a National Academy of Sciences panel, research should focus on hazardous chemical exposure and its possible effects on humans. The panel listed the areas in which more scientific knowledge is needed. (Source: Technology Update, 26 February 1983.)

Malaria

In the past few years malaria has resumed epidemic proportions. New drugs and vaccines are desperately needed to fight off this pernicious parasite that infects some 200 million people a year. Scientists are confident that they are nearing that goal. For instance, Professor Ruth Nussenzweig and her colleagues at New York University are expected soon to reveal that they have managed to coax bacteria to produce a protein that could form the basis of a vaccine. However, disputes over rights to products arising out of their work, could interfere with the financing of the projects.

The Wellcome team has isolated an antigen from the merozoite of the human parasite and shown that it is similar to a merozoite antigen from the parasite that infects mice. The latter antigen has been shown to protect mice injected with it against malaria and the efficacy of the human merozoite antigen as a vaccine is being tested.

There is a potential production difficulty, however, since obtaining the antigen needed for a vaccine from the merozoites themselves is difficult and costly. Far better would be to get the gene for the antigen, clone copies of that gene into bacteria and get the prolific bugs to produce the antigen. Unfortunately, isolating the gene has so far proved difficult; the concentration of genetic material in merozoites being tiny.

Professor Nussenzweig's team has been concentrating on the sporozoite form of the malaria parasite and has identified key antigens of the parasites that infect mice, monkeys and men. Until relatively recently, the team was extracting its antigens from material in the salivary glands of mosquitoes. Fortunately, it now seems that, from this material, it was possible to glean the genes coding for the antigens and then to clone them into bacteria.

There are doubts about how effective a vaccine based on sporozoite antigens alone could be; some scientists reckon that if just one sporozoite evades and immune response a severe malarial infection could result. They think that an ideal vaccine would mix sporozoite and merozoite antigens. Nonetheless, a successful cloning of sporozoite antigens would be a big step forward.

The bacteria-factory process was to be scaled up by the Californian-based genetic engineering company, Genentech. But Genentech wanted an exclusive licence to market any resulting vaccine. Problem: the World Health Organisation (WHO) has been helping to finance the research. and its contract with New York University gives it access to any new products arising for the work.

So Genentech has backed away from the project. That means trying to find another company to do the scale-up work; neither the university nor WHO is equipped to do it. Clearly, some better understanding needs to be reached in future three-way relationships of this kind.

Another line of research is being investigated in a number of countries, namely the mechanisms of natural resistance to malarial infections. Parasites already lodged inside the body's red blood cells (and presumably hidden away from the notice of the body's immune system) can sometimes be successfully attacked by the body. The explanation put forward for this phenomenon is that certain cells in the body, called macrophages, recognise a subtle alteration in the contaminated red blood cells and release electrically charged (and highly reactive) oxygen molecules when they come into contact with such cells. The reactive oxygen molecules are able to penetrate the membrane of an infected cell and, once within it, to destroy the parasite it harbours. In mice, drugs that promote the formation of such oxygen molecules kill malarial parasites. The known drugs are too toxic and too unselective to use in man.

The hypothesis neatly explains why people with one red-blood-cell disease, sickle-cell anaemia, are protected against malaria. Scientists working on sickle-cell anaemia reckon that the peculiar shape of affected cells (from which the disease takes its name) reflects an altered bio-chemistry in the cells - and that the cells have a high concentration of reactive oxygen molecules. They would be deadly targets for malaria parasites.

The hypothesis will be hard to verify. In man, the malaria parasite infects only a small number of red blood cells (in some cases as little as 0.01% of the total) and these cells are usually found deep within body tissues or firmly attached to blood-vessel walls.

Yet new drugs are needed. Only one, mefloquine from Switzerland's Hoffmann-La Roche, has become available in the past 30 years, and there are signs that the malaria parasite has been developing resistance to that. Wellcome may have stumbled on to another drug. One that promotes reactive-oxygen formation? The company, playing its cards very close to its chest, is unwilling to say. (Extracted from The Economist, 26 March 1983.)

Genetic disease diagnosed in a 10-week foetus

Mothers at risk of bearing a child with severe blood diseases can now be advised within 10 weeks of pregnancy whether or not their child will be normal. This major advance in pre-natal diagnosis is due to the successful blending and application of one existing and one new technique. The former enables doctors to diagnose the blood disease by analysing DNA taken from the foetus and was refined by Dr. John Old and Professor David Weatherall at Oxford University. The latter is a completely new means of obtaining foetal cells from the mother's womb at a very early stage of pregnancy, and this was devised by Dr. Bernadette Modell and Mr. Humphry Ward at University College Hospital in London.

In a paper published in The Lancet on Christmas Day, they describe how the technique enabled them to diagnose one foetus with thalassaemia major, and to confirm the absence of thalassaemia and sickle-cell disease in another two foetuses. They speculate that other inherited diseases such as muscular dystrophy may also lend themselves to this type of diagnosis.

Sufferers of beta thalassaemia have defective haemoglobin, the protein of red blood cells that is responsible for transporting oxygen around the body. It mainly affects people of Mediterranean and Oriental origins. It is characterised by severe anaemia and patients require frequent blood transfusions. The disease is caused by a defect in the gene coding for beta-globin, one of the sub units of the haemoglobin molecule. When this defective gene is inherited from both parents (homozygous) the disease is called thalassaemia major, and sufferers rarely used to live beyond their teens. Sickle cell disease is due to a different defect in the same gene.

At present, beta thalassaemia and sickle cell disease are diagnosed prenatally by a technique known as foetoscopy. This involves taking a sample of foetal blood (usually from the umbilical cord) bypassing a fine needle into the uterus. Analysis of haemoglobin from foetal blood cells will tell whether or not the child is affected. The drawback with foetoscopy is that it can be carried out only at about the eighteenth week of pregnancy, when termination, if necessary and desired, is a much more distressing experience for all concerned. The advantage with the new technique, is that the defect can be spotted in the DNA of the foetus; there is no need to wait until a blood sample can be obtained.

When an embryo implants in the wall of the uterus, it is surrounded by a layer of cells, called the trophoblast. These cells go on to form the placenta, and contain foetal, rather then maternal DNA. The UCH group devised a means of obtaining these cells by applying gentle suction through a thin tube which is passed through the cervix (transcervical aspiration). The next step is to analyse the DNA. Adjacent to the gene that codes for beta globin, are sites at which certain enzymes known as restriction endoculceases, can act. These sites are within a sequence of bases that do not code for any particular protein. The restriction enzymes snip the DNA strands at specific points on these sites - eacn enzyme "attacking" a specific sequence. Restriction enzyme sites, like the rest of the genome is inherited in a Mendelian fashion.

The diagnosis is made by first analysing the lengths of fragments obtained when DNA from both parents, and from a sibling is subjected to the action of a restriction enzyme (there are about six different enzymes that can be used in this way). Deciding which enzyme will yield fragments is the result of trial and error. The diagnosis depends on obtaining a pattern of fragment lengths and comparing these with the lengths of fragments obtained after subjecting foetal DNA to the same enzyme.

In one case, where a successful diagnosis of beta thalassaemia was made, the parents were heterozygous for the disease. Their beta-globin genes were carried on two different lengths of DNA in both parents. The DNA from one of their children who had thalassaemia major produced fragments of only one length that matched one of the fragment lengths in each parent. This result provided a perfect reference. The foetal DNA fragment matched the thalassaemic one perfectly, so the doctors could predict with certainty that the child would be born with thalassaemia major.

Conventional analysis of haemoglobin from the aborted foetus confirmed the diagnosis. (Source: New Scientist, 23/30 December 1982.)

A new treatment for tumors

A new product, interluken-2, that has the potential for treating tumors and immune-deficient diseases, such as rheumatoid arthritis and Addison's disease, is being developed jointly by Biogen (Geneva, Switzerland) and Shionogi (Osaka, Japan). Interluken-2 is a lymphokine that promotes the growth of control cells in the immune system. And, like interferon, it is made by white blood cells. Shionogi will conduct clinical trials with a view to commercial development of interluken-2 in Japan for human therapy. Biogen will supply the interluken-2 and has the option to manufacture all or part of Shionogi's commercial requirements. (Source: Chemical Week, 16 March 1983.)

Inorganic chemists find new cancer drug

Inorganic substances are now rarely used to treat diseases, but one platinum compound may prove to be a powerful new anti-cancer drug. The chemical, code named cis-DDP acts at the very site where cancer begins - the DNA. The inorganic compound cis-DDP can chemically bond to guanine bases in DNA and so disrupt the replication of DNA in actively dividing cells.

Cis-DDP, short for cis-diamminedichloroplatinum (II) or cis-$(Pt(NH_3)_2Cl_2)$, is a square planar complex. Discovered in 1844, it was called Peyronne's chloride after its discoverer to distinguish it from another complex with the same formula, known as trans-DDP. In 1969 researchers discovered that only the cis-DDP isomer killed tumours.

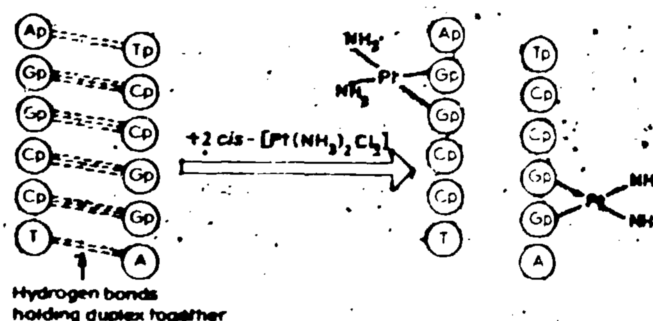
There are good chemical grounds for expecting a difference in the reactivity of the two isomers, because the chlorine atoms of cis-DDP are diagonally opposite NH_3 groups in the molecule, whereas in trans-DDP the chlorines are opposite each other. The chlorine atoms make way for the other atoms when cis-DDP attaches itself to guanine, one of the bases of DNA.

Nuclear magnetic resonance spectroscopy has confirmed that the platinum in cis-DDP bonds to the nitrogen atom in guanine's smaller one. When two guanine bases are side by side in the DNA chain, both can attach themselves to the same platinum atom, forming a stable complex.

Jan Reedijk and co-workers at the State University of Leiden in the Netherlands found that cis-DDP could bond to two guanine bases in a small chain of single-stranded DNA despite an intervening cytosine base (Journal of the American Chemical Society, vol. 104, p. 2664).

New research has gone further. Stephen Lippard and John Caradonna of Columbia University, New York, working with Michael Crait and Mohinder Singh of the Medical Research Council's Molecular Biology Laboratory at Cambridge, have shown that cis-DDP can bond to a double-stranded chain of DNA as well (Journal of the American Chemical Society, vol. 104, p. 5793).

When they reacted the drug with a self-complementary two-stranded, six-base DNA chain, they found that the hydrogen bonding which holds the two strands together cannot compete with the bonding of the platinum complex to adjacent guanine groups (see Figure).



The platinum drug disrupts the bonds holding strands of DNA together

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. For it is the hydrogen bonding ability of the existing chain that determines the sequence of bases laid down in a growing chain of genetic material.

Further research will hopefully discover more metal complexes that can bond to the nitrogen or oxygen atoms of other bases in the DNA. If these drugs can selectively block the hydrogen bonding in the DNA of cancer cells, then replication of the genetic material of such cells will be halted, and proliferation of tumours may be foiled. (Source: New Scientist, 24 February 1983.)

Detection of sickle-cell anemia

Further to our report in Issue No. 4 on a possible new treatment of the disease through the use of gene therapy, a test has been developed by research scientists at the City of Hope Medical Center and Research Institute at Duarte (California, USA).

The development of a test for a specific gene defect requires that the nucleotide sequence of that gene be known. a relatively simple matter once the culprit gene has been identified. Sickle cell anemia is caused by a single incorrect nucleotide in one of two hemoglobin genes. Using the sequence data, the research team synthesized a small piece of DNA, 19 nucleotides in length. Some of the nucleotides contained radioactive phosphorous-32 atoms instead of the normal phosphorous-31 isotope so that the probe's presence could be easily detected. The probe's sequence corresponded to the sequence of the gene surrounding and including the incorrect nucleotide. The probe points out the gene defect by binding to the corresponding region on the real gene, and this only happens if the two sequences match exactly. If one or more nucleotides between the two differ, binding will not occur. Therefore in the case of the sickle cell gene (which contains one different nucleotide), the probe will bind to the defective gene and not the normal one. Since the sickle cell defect is caused by a single nucleotide mistake, it represented the most difficult challenge for the probe test. Most other genetic defects are caused by bigger errors, so tests for the diseases should be just as accurate.

It is hoped that by the end of this year tests for at least 10 genetic illnesses will have been developed and that soon it will be possible to test a child at birth for the presence of genetic defects. (Extracted from Chemical Week, 19 and 26 January 1983.)

Chemically synthesized strings of nucleotides about 20 bases in length can be used to detect human genetic diseases, identify a member of a gene family and create specific DNA mutations, according to scientists at City of Hope Research Institute. To detect the gene for sickle cell anemia in a patient, short strands of nucleotides are synthesized, mimicking the section of the gene that has a single nucleotide difference between the normal and sickle cell genes. The normal gene binds preferentially to the synthetic strand with the normal sequence; the sickle cell gene binds to the nucleotide strand with the characteristic sickle cell sequency. This technique is being applied to other human genetic diseases, including beta-thalassemia and alpha-1-antitrypsin deficiency. Researchers have used synthetic molecules to direct specific changes in large pieces of DNA and have made a 21-nucleotide chain that pairs with part of a gene for a transfer RNA molecule. The pairing causes a specified region of DNA, in this case the intervening sequence, to loop out and be deleted from the gene. (Source: Technology Update, 12 March 1983.)

New flu vaccine

A group of American investigators has produced a live-virus flu vaccine that shows promise of being effective in humans. The results could be vaccines against flu that provide much longer immunity against influenza, than do the present killed-virus vaccines.

The new vaccine is the result of a "marriage" between a strain of flu virus that infects birds, it came originally from mallard ducks, and a strain of human flu virus. The genes that control the virus's ability to multiply come from the bird strain, and those that control the development of the virus's antigens come from the human virus.

In terms of providing protection against influenza there are two antigens of significance - haemagglutinin and neuraminidase. These antigens are part of the viral coat and stimulate the body's defences against the infection. Unfortunately, by themselves they cannot induce immunity satisfactorily. So killed virus is ineffective as a vaccine and live virus merely causes disease in humans.

Researchers at the National Institute of Allergy and Infectious Diseases at the US National Institutes of Health have overcome this dilemma by growing a bird flu virus which does not cause human disease together with a strain of human flu virus. After mating these viruses, they pull out the avian haemagglutinin and neuraminidase antigens using antisera previously produced by goats following exposure to the antigens. They then grow the virus at 42°C, a temperature at which the avian virus grows well but the human virus does not flourish.

The result is a hybrid virus that will multiply readily when given to humans but will not cause disease. At the same time, it carries the haemagglutinin and neuraminidase antigens from the human virus which are important in stimulating the production of protective antibody. (Extracted from New Scientist, 27 January 1983.)

If the work comes to practical fruition, it will still be necessary to make new batches of flu vaccine whenever a different, virulent strain of flu makes an appearance, as the viruses are notorious for the ease in which they undergo antigenic shifts, and give rise to epidemics. However, the immunity that the live virus vaccine confers may be much more effective and longer-lasting than the present vaccines made with killed viruses.

Emerging Vaccines

Emerging vaccines use genetic engineering, DNA sequencing methods, monoclonal antibodies and powerful separation and cell culture methods to treat a wider range of diseases. At various stages of clinical trials are vaccines to protect against pneumonia, gonorrhea, chicken pox, meningitis, hepatitis, etc. Over 151 million doses of 8 major vaccines worth over $300 million were distributed in the US in 1981, according to Center for Disease Control. The current agricultural vaccine market is worth $1 billion/year, according to Genentech. Vaccines stimulate the recipient's immune system to produce protective antibodies against the cause of a disease, but new vaccines can grow many pathogens, such as the hepatitis A virus and malaria parasite, in large enough quantities for detailed study, which has enabled scientists to determine which parts of a pathogen are needed to stimulate an immune response and which are involved in causing disease. (Source: Technoloy Update, 4 December 1982.)

Immune response tied to leprosy type

Dramatic differences in the immune response of patients seem to characterize the three forms of leprosy, according to a team of medical researchers at Rockefeller University in New York and the University of Rio de Janeiro, Brazil. The researchers used monoclonal antibody techniques to probe the biochemistry of the skin lesions that characterize the disease in each of its forms. In the lepromatous form, which is the most virulent, they find that almost all of the T-cells present in the lesions are suppressor cells. These cells suppress macrophages, which, in turn, kill bacteria cells. By contrast, in tuberculoid leprosy, the mildest type, suppressor cells are infrequent and most of the T-cells present are helper cells that assist macrophages in fighting bacterial infection. This difference helps explain why the spread of lesions is more controlled in the tubercular form of the disease and may help in diagnosing early forms of the disease, the researchers say. However, it's still a mystery why the immune response is not the same in all forms of the disease. (Source: Chemical and Engineering News, 3 January 1983.)

Interferon

The interferon and antiviral industries are entering a dynamic era of consolidation, technological improvement, product efficacay and safety substantiation and those companies selling the substance who are able to keep up with the rapidly changing technologies will have a competitive edge of the market as growth accelerates. It is estimated that sales of interferon treatments for prevention of the common cold alone could reach $290 million by 1990. The current $500 million per year market for antiarthritic drugs may radically change if interferon therapy for this chronic ailment proves successful, but the scarcity of obtaining large enough quantities of interferon with sufficient purity to clinical investigations has made drug development a slow process.

In France the Institut Pasteur is developing a second generation leocyte interferon (further purified 10-40X) which is presently being tested for toxicity and clinical trials are expected to begin shortly. Clinical trials of the Institute's alpha interferon have been suspended pending investigations concerning deaths of several patients, possibly caused through administering the substance intravenously instead of intramuscularly. Side effects have also been reported in the British Medical Journal on a number of patients being treated for breast cancer - they had abnormal brain waves and became lethargic and confused.

Nonetheless, research remains unchecked, also in an attempt to see whether it can be successfully used to treat human victims of rabies once all symptoms have developed. (Extracted from Technology Update, 18 December 1982, 5 and 19 February 1983.)

New tool for beauticians and plastic surgeons

A surprising new way has been developed to iron out some of the deepest facial creases and many scars. A high-technology firm in California (USA) has found a way to enzymatically alter bovine collagen to make it almost indistinguishable to the human variety. Injections of the substance, known as Zyderm Collagen Implant, can build up soft depressions in skin caused by acne, age, injury or disease. It seems to have most noticeable effects on deep frown creases on the forehead and those running from the corners of the nose on either side of the mouth, however superficial wrinkles around the eyes are not helped. Treatment involves up to 6 implants for best results and has to be repeated every 6 to 24 months since the body's enzymes gradually digest the implant. The cost can be as high as $1,500 for acnescarred skin and the firm, known as Collagen Corporation, hopes to shortly produce a concentrated product which lasts longer. The substance is a white paste packed in syringes containing collagen suspended in a salt solution and mixed with a local anaesthetic, lignocaine. Once injected, the lattice of collagen fibers is gradually invaded by cells and blood vessels and so comes to look and feel like normal skin. (Extracted from Technology Update, 19 February 1983, and from New Scientist, 24 February 1983.)

Novel way of transplanting foreign genes into plant cells

A new method for placing foreign genes into plant cells and reliably converting the infected cells back into healthy and apparently normal plants whose genes were retained through several generations of growth has been developed by University of Pennsylvania and Washington University (St Louis) scientists. The researchers used Ti plasmid, a small DNA molecule from the bacterium Agrobacter tumefaciens, which causes crown galls in infected plants. Attenuation of a gene on the plasmid can prevent it from causing tumors in the plant, which are believed to stem from a hormonal imbalance. Yeast genes for alcohol dehydrogenase which have been moved into tobacco cells via the altered Ti plasmid were retained but did not function normally since they lacked adequate genetic control signals. The resarchers are now attempting to supply the genes with appropriate signals and streamlining manipulations to avoid using the entire Ti plasmid. (Source: Technology Update, 26 Feburary 1983.)

A prostaglandin for heifers

Bovilene, a prostaglandin, will be introduced in the U.S. early this year by Syntex Agribusiness (Des Moines, Ia.), a subsidiary of Syntex (Palo Alto, Calif.). The product, a long-acting synthetic prostaglandin that acts to regulate the timing of a cow's reproductive cycle, has been approved for marketing by the U.S. Food and Drug Administration. Known generically as fenprostalene, bovilene is intended to help veterinarians and cattle-feedlot operators better manage heifers in the commercial feedlot, improve efficiency, and control feedlot costs. Prostaglandins, which are fatty acids naturally produced in animals, perform a number of hormone-like functions, including control of the reproductive cycle. Syntex has not yet set a price for the compound, which has recently been approved for marketing in the U.K. It is currently sold as Synchrocept B in a number of countries, including Mexico, Ireland and Australia. (Source: Chemical Week, 23 February 1983.)

Embryo sexing

An American company, Genetic Engineering Incorporated, claims to have developed the first reliable method of discovering the sex of cattle embryos, but other scientists in the field are sceptical. Genetic Engineering itself is in the process of filing a patent.

Predicting accurately whether an embryo would produce a bull calf or a heifer would be a money-spinner. Embryo transfer, used to maximise the number of offspring a breeder can get from prize stock, is already big business. A top cow is given fertility drugs to induce her to produce a lot of eggs (up to 40), ariticially inseminated with sperm from a high-class bull, the fertilised eggs flushed from her uterus and either introduced immediately into less valuable cows or frozen for use later.

Such embryos command high prices: several hundreds of pounds each in Britain. They would be roughly twice as valuable if the provider could guarantee whether any particular embryo was male or female. A customer with a beef herd does not want to be saddled with a cow - nor a dairy breeder with a bull. At present, each has only a 50 per cent chance of getting what he wants.

In theory, sexing embryos should not be too difficult. Scientists have known for years that a male embryo carries on its surface an antigen, or molecular identity tag, that female embryos lack. And an antibody that recognises and binds to this tell-tale antigen has been isolated. Tag the antibody with, e.g., a fluorescent marker, expose the embryo to it and you should be able to tell what you have. If the antibody binds to the embryo, it is male. If it does not, it is female.

In mice, this approach works with an 80 per cent reliability. But cattle embryos present a problem. The difficulty is that the number of antigen targets on the surface of an embryo varies over time. When the embryo comprises only eight cells - about three days after conception - a large number of antigens are expressed on its surface. Unfortunately, by the time that it can be removed from the cow - about six days after conception - this is no longer so. The upshot, says sceptics, is that an antibody sexing test is not reliable at this crucial stage.

Genetic Engineering insists that its test, using a pure antibody known as a monoclonal antibody, is reliable and the company is planning to build up a bank of frozen, sexed embryos. In support of its claim, it points to two calves born in December whose sex was correctly predicted. With a 25 per cent chance of pure guesswork turning out to be right, however, the sample is hardly statistically significant. (Source: The Economist, 19 February 1983.)

Bluetongue vaccine for cattle and sheep in the offing

Monoclonal antibodies produced at US Department of Agriculture's Plum Island Animal Disease Center may help in developing a vaccine against bluetongue in cattle and sheep - a virus disease characterised by hyperemia, cyanosis and punctate hemorrhages and by swellings and sloughing of the epithelium about the mouth and tongue.

Researchers fused spleen cells from mice inoculated with bluetongue virus BTV-type 17 with mice myeloma cells to form hybridomas. These were screened to isolate hybridoma cells that produce monoclonal antibodies specific against the number 2 protein of the bluetongue virus coat. Tests on mice and sheep indicate that the monoclonal antibody will protect these animals from infection by the virus.

The monoclonal antibodies themselves are unlikely to be used commercially to protect livestock from bluetongue, but the fact that a monoclonal antibody specific for only part of the virus-(coat protein 2)-immunizes shows the protein could be an antigen to stimulate an animal injected with it to produce an antibody that would protect the animal from the disease. Next step is to clone the virus coat protein in a recombinant microorganism so that enough protein could be produced to be used in vaccines. However, this will not be done at Plum Island, which is concerned chiefly with animal diseases that are not prevalent in the United States - such as foot and mouth disease, for a vaccine which has recently been developed by the Centre. (Source: Genetic Technology News, February 1983. Address: 158 Linwood Plaza, Fort Lee, NJ 07024, USA.)

Recombinant vaccine for animals reaches market

Salsbury Laboratories, a US member of Belgium's giant Solvay Group, is ready to market a vaccine made by a recombinant DNA process for use against scours - diarrhea in baby pigs. Antigen for the vaccine was developed by the University of Michigan and U-M Center for Molecular Genetics. The vaccine has been approved by US Department of Agriculture (USDA). Salsbury Laboratories has started manufacturing at its Charles City, Iowa, plant, where antigen is produced by genetically modified *Escherichia coli* in a 3000-liter fermenter.

Antigen consists of pili (small, hair-like protein structures that protrude from *E. coli* cells). *E. coli* bacteria are normal inhabitants of the intestines of healthy mammals, but sometimes certain strains attach to the intestinal walls, causing diseases such as scours (often fatal) in calves, baby pigs and lambs and traveller's diarrhea in humans. Attachment of *E. coli* cells to the intestinal wall involves the bacterial pili. Injecting pregnant sows with antigen causes them to produce antibodies against pili. The antibodies then pass to newborn animals when they nurse and prevent *E. coli* from attaching to the intestinal walls of the young animals.

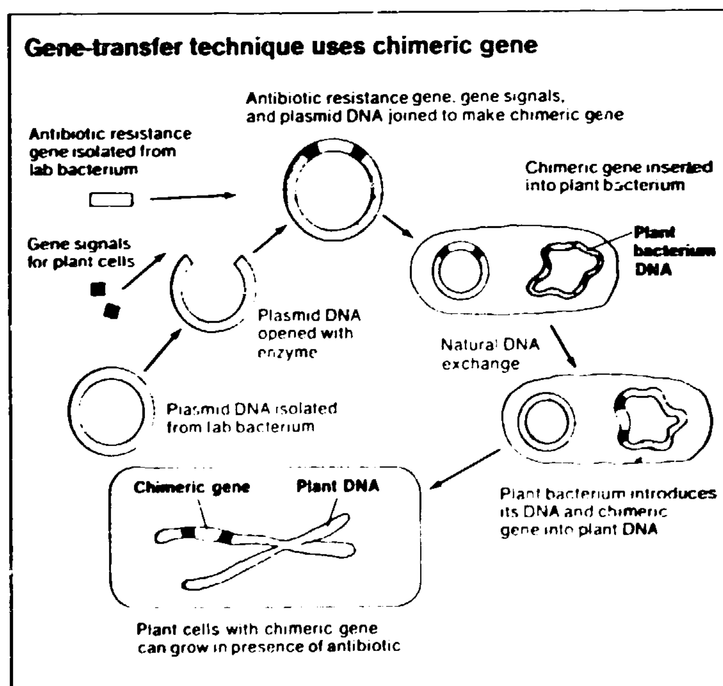
E. coli strains modified by recombinant DNA to obtain high yields of the types of pili needed and, at the same time, to supress other types. Commercial vaccine consists of a mixture of three different antigens from three different E. coli strains that may cause the disease. Molecular weights of the protein antigens are about 18,000, 20,000 or 26,000 - depending upon strain. In the production process, E. coli cells grown in the fermenter are treated chemically to cause their pili to drop off. Further processing separates pili from bacterial cells. Work is being carried out on a similar vaccine for calves and as a prevention of traveller's diarrhea in humans. (Extracted from Genetic Technology News, February 1983. Address: 158 Linwood Plaza, Fort Lee, NJ 07024, USA.)

Bacterial gene works in plant cell

Functioning genes have been moved successfully from bacteria into plant cells, marking an important milestone on the way to using recombinant-DNA technology to engineer and improve plants genetically.

Though similar successes have been hinted at previously, those efforts often failed. Genes that code for antibiotic resistance have been moved from bacteria into plant cells. In one case, the gene that inactivates the antibiotic kanamycin was placed into petunia cells growing in vitro. Ordinarily, those antibiotics do not affect plants, but they can interfere with the growth of plant cells in vitro. Key to this achievement is the method used for transferring such genes. Overall, they are introduced into plant cells by the Ti plasmid, a circular molecule of DNA from the bacterium Agrobacter tumefaciens, which can infect many plants and give them tumors. Properly manipulated, however, that plasmid becomes a useful means for bringing genes from elsewhere into plant cells.

Simply putting genes anywhere along the Ti plasmid is not good enough to ensure those genes will work once they're transferred into plant cells. The foreign genes must be attached to a "promoter region" along the Ti plasmid - that is, a part of the DNA that controls adjacent genes. Researchers hooked up the antibiotic-resistance genes to promoters that ordinarily control synthesis of an unusual amino acid whose manufacture is tied intimately to how Agrobacter established itself as a parasite in plant tissues. The system is also being tried on carrots, sunflowers and tobacco.



Though the genes for antibiotic resistance convincingly can be moved into plant cells and can function there, there is no certitude that those cells can be made to grow into intact plants. Equally, it is not known whether those genes will then continue to function once inside intact plants.

The ability to move genes for antibiotic resistance offers a convenient way of marking the progress of a gene-transfer procedure. Furthermore, these recently developed methods ought to work for transferring genes for valuable traits, such as resistance to diseases, herbicides, or insects, according to Jaworski. (Extracted from Chemical and Engineering News, 24 January 1983.)

Cleverly designed insecticide is safe poison

Researchers in the rapidly growing field of industrial biotechnology have developed a strategy for making safe and potent pesticides, using chemicals harmless to man and all other vertebrates. The chemicals are converted into deadly poison by enzymes present only in insects.

The new insecticide strategy is just one of many advances in basic research that promise to be directly useful in agriculture and plant sciences. They are all products of biotechnology, the application of basic research in biology to practical problems ranging from drug manufacture to industrial chemistry. The potential agricultural applications have only recently begun to emerge, but they include developing techniques that could lead to new breeds of more nutritious, more productive, disease-resistance plants or species that could survive in harsher environments or need less chemical fertilizer to grow.

The experimental insecticide, developed by Glenn D. Prestwich, Apurba K. Gayen, Seloka Phirwa and Toni B. Kline, researchers at the State University of New York at Stony Brook, uses plant products called phytosterols, which are chemically related to the steroids that are important to humans in such forms as vitamin D, sex hormones and drugs of the cortisone type. They added fluorine to the substances to produce compounds called 29-fluorophytosterols.

Insects have enzymes that can break these down, releasing, as one product, the deadly poison fluoroacetate. Most other forms of life, from bacteria to mammals, cannot break down the plant steroid and therefore cannot release the poison from its harmless chemical package.

The experimental pesticide has been found effective against tobacco hornworm, a pest that also attacks tomato and other plants, and the researchers believe that tricking plant-eating pests into killing themselves through their own distinctive metabolic processes will prove to be only one of many ways for biotechnology to make use of chemical differences between insects and vertebrates. (Extracted from The New York Times, 1 March 1983.)

Costly search for edible microbes

Growing microbes for food has been one of the most costly and elusive goals of industrial research and development for the past two decades. The world's chemical companies have poured hundreds of millions of pounds into the production of protein from bacteria, yeast, fungi and algae, without any commercial return on their investment.

Some firms have withdrawn entirely from the microbial protein business, writing off an estimated £100m, in British Petroleum's case, but the survivors now see encouraging signs that microorganisms will after all become a significant food source for humans and farm animals within a few years.

Rank Hovis McDougall, the British baker and flour manufacturer, is the only company close to marketing a novel human food made from microorganisms. Their "mycoprotein" received approval from the Ministry of Agriculture as a human food in 1980 after extensive toxicological and nutritional testing on hundreds of human volunteers (and on thousands of laboratory animals which ate little else for up to four generations).

Rank Hovis McDougall is now producing about a ton of mycoprotein a week from its pilot plant in High Wycombe, which is being used for culinary and marketing tests in conjuction with another British food manufacturer.

A decision to increase production to 20 tons a week in a new demonstration plant is likely before the summer. That would allow Rank Hovis McDougall to undertake extensive marketing trials before deciding whether to build a commercial factory making 500 to 1,000 tons a week and probably costing £20m.

Although the economics of the large-scale process remain speculative, RHM points out that its fungus, found in a back garden less than four miles from High Wycombe after a worldwide search is several times more efficient than farm animals in converting carbohydrate to protein.

Even if all goes well, mycoprotein foods could not become common on Britain's supermarket shelves before the 1990s. Commercialization is taking far longer than Lord Rank expected when he set the research project in motion 19 years ago; but encouraging results from the testing programme are raising a new spirit of optimism in the company.

Ranks Hovis McDougall staff canteens have sold 6,000 mycoprotein meals, masquerading as meat, poultry or fish, in competition with conventional dishes. Mycoprotein itself has virtually no colour, taste or smell, but is is very ready to accept flavourings.

The mycoprotein production process: A sterilized mixture of glucose syrup (made from hydrolized vegetable starch), water, ammonia and essential trace nutrients is pumped continuously into the fermenter, where it nourishes the fast-growing fibres of the fungus Fusarium graminarium.

At the same time liquid is being withdrawn from the top of the fermenter and heated to kill the fungal cells and destroy their nucleic acids (which are nutritionally undesirable).

The mass of mycoprotein filaments is filtered on a moving belt, and rolled and folded like a giant piece of dough. Rank Hovis McDougall's patented kneading technology makes all the fibres line up in the same direction. They can then be bound together with albumen (a cheap protein) to simulate chicken or meat. Flavouring and colouring must be added too. (Extracted from The Times, 31 January 1983)

Tomatoes

Researchers in America and Britain have developed new strains of tomatoes which last much longer than the ordinary, highly perishable tomato-on-the-shelf. The scientists working on tomato genetics are delighted with their results: producers may not be.

Tomatoes go on ripening once they have been picked and have to be sold within three or four days. After that, they start to deteriorate unless specially and expensively cooled. The new strains, which ripen much more slowly, can be left on the plant until perfect and kept for up to 40 days after picking before they start to perish.

The scientists on either side of the Atlantic have independently developed their longer-lasting strains by experimenting with different sorts of mutant plants. The American team, at Cornell University, has been using a wild, natural mutant discovered in Brazil which never really ripens at all. The British researchers, at the Glasshouse Crops Research Institute at Littlehampton in Sussex, have been working partly with artificial mutants - that is, tomatoes whose genes have been deliberately scrambled, by bombardment with neutrons.

The mutants themselves would never sell: they are green, hard and nasty-tasting at maturity. They are valuable only for their slow-ripening characteristic. Why they do not ripen normally, nobody quite knows. It may be because they produce less ethylene than ordinary tomatoes. Ethylene is known to hasten the ripening process.

Whatever the mechanism, the scientists did discover that the slow-ripening property of the mutants is conferred by a single gene. That meant they could fairly easily combine this useful mutant gene with those of a normal tomato. Not by isolating the gene and then popping it directly into the germ cells of normal tomatoes; scientists have yet to perfect such genetic engineering techniques for plants, though they are now making considerable progress. Instead, the researchers used old-fashioned, hit-and-miss breeding in order to get the desired combination of genes.

There is still work to be done to perfect the longer-lasting tomato. The new strains now have to be bred for other valuable characteristics like redness and roundess. But Dr. Martha Mutschler at Cornell reckons that her team's half-Brazilian Alcobaca strain will be ready for breeders to buy in a year or so.

Low-cost tomato growers, like those in America's warmer sunkissed climes, are enthusiastic about tomatoes that could travel to export markets, but many European growers, tied to expensive greenhouse production, wonder whether a longer-lasting tomato might mean a shorter-lived future for them.

Still on tomatoes, H.J. Heinz (Pittsburgh, Pa) has formed a joint venture with Plant Cell Research Institute, a subsidiary of Atlantic Richfield's ARCO Solar Industries (Los Angeles, CA), to improve tomatoes. Main objective is to develop a tomato with a high solids content. This would mean big savings in production of Heinz's tomato ketchup. Both tissue culture and molecular biology approaches will be used in the new programme. Work in molecular biology will be concentrated on identification of important tomato genes and development of vectors to transfer them into plant cells. It is believed work will bring breakthroughs in transforming higher plants with Ti plasmids and other vectors. ARCO researchers have already made progress in high efficiency regeneration of complete plants from protoplasts (single cells). Another part of the project will be to search for wild tomato plants growing in the Andes mountains in South America. Wild plants may carry genes for useful traits that have been lost in highly inbred domesticated plants. (Source: The Economist, 22 January 1983 and Genetic Technology News, Feburary 1983. Address: 158 Linwood Plaza, Fort Lee, NJ 07024, USA.)

Herbicide-resistant corn

Two American companies, Molecular Genetics and American Cyanamid have agreed to jointly develop strains of corn that are tolerant to new herbicides. Under the terms of the agreement, Molecular Genetics will use its know-how and plant tissue culture and will licence products to American Cyanamid, who on its part will provide expertise in herbicide chemistry and product evaluation. The new strains of corn are expected to increase the market for broad-spectrum herbicides which otherwise have limited potential when used with current hybrids. (Source: Chemical Week, 26 January 1983.)

High value products from plant cultures

Plant cell culture is unlikely to become an economic process except in cases of very high value products such as pharmaceuticals. Only when the price obtainable is greater than the manufacturing costs, estimated at around $500/kg of product, will a cell culture process pay its way.

These figures were arrived at by two independent analyses and currently only the rarer pharmaceuticals and enzymes could command this sort of price. However, the picture could change with improvements in technology, or if yields increase and the expensive medium ingredients could be reused. Two projects in Japan are showing promising results. Professor Fujita of Mitsui Research said high yields are obtainable if different mediums are used for growing the cells and producing the valuable metabolite. A species of borage, Lithospermum erythrorhizon, which produces the compound shikonin, used both as a dyestuff and a medicine for treating burns, has been made in this way in a large-scale batch culture. Cells at first grown in a 200 l tank before being transferred to a larger tank (750 l) where the shiknin is formed at a concentration of 1.5g/l of medium. 'This impressive result clearly shows that industrially acceptable yields of secondary products can be obtained by systematic optimisation of strains, media and fermentation facilities'.

At a conference in London on culture techniques, Professor Zenk said continuous culture processes may also become a realistic goal. The Japan Tobacco and Salt Public Corporation has developed a process for growing tobacco cells which also yields the drug, ubiquinone used in treating heart disease.

Plant cells are unlikely to produce the range of cheap compounds potentially obtainable from bacteria and other organisms for a variety of reasons. Fermentation takes longer because cell multiplication takes place over a period of weeks rather than days and the production phase of useful compounds is usually linked to a particular stage in the life cycle. The fermentation medium costs on average around $\$50/m^3$ as against a mere $\$6/m^3$ for a bacterial medium. Most plants excrete their products into an internal vacuole rather than the medium itself as is the case with many microorganisms.

Not all plants have been successfully cultured. Catharansus roseus, a pantropical periwinkle is the source of three separate and highly expensive anti-cancer drugs marketed by Eli Lilly. A number of research teams have attempted to culture this plant but so far no-one has produced it on anything approaching an economic level. Professor Michael Fowler's team, at the Wolfson Institute of Biotechnology at Sheffield has discovered a possible way of avoiding one of the problems with this particular species. The low sheer strength, caused by their fragile cell walls, often leads to damage when the culture is agitated in a fermenter. Long term fermentation has been selected for a strain of cells with higher sheer strengths and this could allow simpler fermentation equipment to be used, Professor Fowler believes.

Immobilised cells, either in columns or fixed beds, provides an alternative to fermentation cultures for producing plant cell products. Professor Michael Yeoman of the University of Edinburgh believes the slow growth rates associated with organised groups of fixed cells are essential if tissue cultures are to be economic. He argued that the secondary metabolites of potential value from a cell are produced at high rates when the cell has differentiated. (Source: Chemistry and Industry, 18 December 1982.)

Potentials of alfalfa

Alfalfa may be an underestimated source of fuels and chemicals by fermentation, according to Colorado State University. Alfalfa is especially suitable for conversion processes because of a high protein content that can substantially reduce the net cost of the carbohydrate fraction for fermentation. The plants's leguminous (nitrogen-fixing) and perennial qualities also make its net energy production potential excellent. Data indicate 10-20 million gallons of alcohol/year could be produced in at least 21 states. (Source: Technology Update, 4 December 1982.)

Potentials of Frankia

Strains of a relatively unknown underground genus named Frankia are being eyed as possible transforming agents to help get nitrogen fixation off the ground. So far, the front-running nitrogen-fixing soil microorganisms belong to the genus Rhizobium, but some botanists believe that actinorhizal plants modulated by Frankia may be fixing as much nitrogen in the world as the leguminous ones in symbiosis with Rhizobium.

Two independent reports of plasmids in the actinomycetic Frankia open the way to genetic manipulation of these organisms, which fix nitrogen in the root nodules of many nonlegumious plants. Frankia's wide host range - it boosts the growth of many trees, from Australian beefwood (Casuarina) to Canadian alder - makes it likely that this genus could be more readily adapted to creating new nitrogen-fixing symbiosis than Rhizobium, which increases the protein yield of soybeans and alfalfa.

Some 170 diverse species of woody dicotyledonous plants form root nodules following infection by the filamentous Frankia bacteria. Research with Frankia has lagged, because the genus was first grown in culture only four years ago. Some Frankia-induced root nodules contain high concentrations of plant hemoglobins, a finding researchers had strongly doubted. In the Rhizobium-plant association, it is leghemoglobin that reversibly binds oxygen and thereby keeps it from poisoning nitrogenase. But the role of the new hemoglobins in the Frankia symbiosis is not yet known. In order to extend Frankia's nitrogen-fixing capacity to new plants, it may be necessary to transform the new host genetically to produce hemoglobin. However there is more hope for transferring Frankia than Rhizobium since it can fix nitrogen at atmospheric-oxygen concentrations, whereas Rhizobium required microaerophilic (low oxygen) conditions.

Researchers at CNRS, the National Center for Scientific Research in Dakar, Senegal, report the first successful isolation of an infective and effective strain of Frankia from the tropical tree Casuarina, also known as beefwood or sheoak. It is one of the world's most important fuel trees. This opens the possibility of improving the strain by genetic engineering or conventional mutation and selection techniques, then distributing the symbiont to some 67 species of these trees throughout the tropics and subtropics - thus permitting them to prosper in nutrient-deficient soils. (Extracted from Newswatch, 1 November 1982.)

Pollen suppressors open new options for hybrids

Artificial plant hormones that inhibit self-pollination in important crop plants have been synthesized by scientists at two U.S. chemical companies, Rohm and Haas and Shell. These compounds should eventually enable farmers to cross fertilize with natural or genetically engineered pollens to develop superior hybrids.

Rohm and Haas claims that their new artificial hormone, has proved to be effective as a hybridizing agent for new wheat strains. Until now, wheat hybrids have been difficult to develop because each flower on the plant is self-pollinating. Within a closed wheat flower the male stamen produces pollen, which then falls onto the female stigma. After fertilization, the flower opens to release extra pollen. The company's agricultural chemical division claims that by blocking pollen formation their product causes the flower to remain open for introduction of pollen by the plant breeder, enabling plant breeders to develop new wheat hybrids within a year. Rohm and Haas already has developed several new hybrids to demonstrate the hormone's utility. Although details on them are still proprietary, the company says that the new strains produce appreciably higher yields and resist diseases better than conventional strains.

The Shell chemical hybridizing agent can be used on a large number of crops, according to company officials. The compound works by causing plants to make non-functional pollen. The end result is reportedly similar to that of Rohm and Haas. Shell scientists have been able to use the compound to develop new cereal crop hybrids in the laboratory. They are currently field testing the material with hopes of large scale use in 1984 or 1985.

The success of these chemical hybridizing agents and others under development at companies such as Eli Lilly and Monsanto may allow scientists to introduce genetically modified pollen into plants. For this purpose, John Sanford, a plant biochemist at Cornell University, has started developing methods for screening tobacco pollen cells for desirable genetic traits, such as herbicide resistance. (Extracted from Bio/Technology, March 1983.)

Not at all an evil weevil

The weevil, Elaeidobius kamerunicus, should save Malaysian agriculture around $115 million a year if things go according to plan. The weevil (actual length 4 mm) has been introduced into Malaysia from West Africa and has already greatly increased the fruit production of Malaysia's oil palms and eliminated the need for hand pollination of the trees. Since its introdution in 1981 the weevil has spread throughout the Malaysian peninsula and increases of 20 per cent in yield have been obtained. As a spin-off from this work, based on a study by Dr. R.A. Syed of CAB's Commonwealth Institute of biological Control, growers in West Africa are now keen to find means of controlling oil palm pests biologically - since the continued use of insecticides will inevitably limit the effectiveness of the pollinating weevils. (Source: Nature, 14 October 1982.)

Converting crop waste to biogas

Cornell University researchers are developing a dry fermentation process to convert crop wastes including corn stalks and wheat straw to biogas - 60 per cent methane and 40 per cent carbon dioxide - for fuel on farms and ranches where it would be produced. The process has no drainable water but the raw material can have up to 70 per cent moisture content, versus 90 per cent water content for conventional fermentation slurries.

Some 3.5 quad Btu could be produced in the US from crop wastes and up to 40 quad Btu from silvicultural energy farms. Recovery of 33 per cent of these theoretical energy yields is practical, meeting nearly 20 per cent of current US energy demand.

In the Cornell process, 1 ton of animal manure provides the bacterial innoculum/4-5 tons of straw. Moisture limitation eliminates the need for buffering with sodium bicarbonate, which was originally used to avoid formation of acids that poisoned the bacteria. (Source: Technology Update, 25 February 1983.)

COUNTRY NEWS

Arab biotechnology

Members of the Organisation of Arab Petroleum Exporting Countries (OAPEC) have thought up a new use for their natural gas: turning it into animal feed, and have recently approached Britain's ICI about the possibility of licensing their process for growing bacteria on methanol to make a high-protein animal feed. Although years of development have finally worked the technical bugs out of its "single cell protein" (SCP) process, its economics still look very dodgy in ICI's European markets.

The SCP animal feed produced by ICI has to compete with other high-protein feed additives like soya meal, fish meal and powdered milk. Subsidies and the agricultural glut have kept the price of these competing feeds down. Despite ICI's efforts to reduce the cost of producing SCP with clever process technology and a bacteria purpose-bred for its appetite for methanol, the price squeeze on SDP products is still severe in north America and Europe.

In the desert lands of the Gulf, SCP could prove more attractive. By 1985-86, when the petrochemical plants now under construction will come on stream, there will be no shortage of methanol with which to feed the bugs. The Gulf states' methanol production plans are so ambitious that some observers doubt that they will be able to sell the whole of their production to conventional markets.

The only snag could be methanol prices. If Gulf producers insist on pricing their methanol at world levels, Arabian SCP would face a price squeeze nearly as severe as that ICI now faces. But they need not be bound by the world price. Saudi Arabian petrochemical producers will pay only one half to one eighth of world prices for the natural gas from which methanol is made. If they gave a similar price edge to their methanol, SCP might look a winner after all. (Source: The Economist, 5 March 1983.)

Efforts to boost Australian biotechnology

Biotechnology efforts in Australia are lagging, and a government policy advisory group wants something done about that. The group, Australian Science and Technology Council (ASTEC), suggests that the government provide up to $10 million during the next five years to universities and industry for research and development of products and processes in biotechnology. ASTEC notes that fewer than 10 Australian companies employ techniques such as genetic engineering, cell manipulation, fermentation and enzyme technology. The new field, adds ASTEC, offers enormous potential to advance Australia's agriculture, mining and drug industries. (Source: Chemical Week, 19 January 1983.)

Australia

A transposable element of maize has been discovered by W.J. Peacock of CSIRO. Researchers cloned a maize Ds element while developing a gene transfer system. Lack of alcohol dehydrogenase (ADH) is used as a marker to determine which cells have acquired the new gene. Cells with the enzyme can grow anaerobically, so successful transfer of the ADH gene can quickly be determined. The DNA transfer can only be accomplished in cells without a cell wall (protoplasts), but it has so far been impossible to grow entire maize plants from protoplasts. (Source: Technology Update, 26 February 1983.)

Brazil

Has started up a 150,000 L/d fuel ethanol plant at São Luis distillery, the first commercial scale application of Alfa-Laval's (Sweden) Biostil continuous fermentation and distillation process. Output at São Luis is 96 per cent ethanol from a feedstock of 30 per cent final molasses and 70 per cent cane juice syrup. The plant, which started up in August 1982, achieved 94.7 per cent of theoretical alcohol yield in its 1st season, versus 86 per cent for a conventional batch plant. Stillage volume was 0.8 L/L of alcohol, versus 10-12 L/L of alcohol in a conventional plant. Alfa-Laval will co-operate with Codistil (Brazil) to market alcohol plants in Brazil, estimating that five 150,000-250,000 L/d plants will start up in 1983 and 20 in 1984. An Alfa-Laval joint venture with the Swedish Farmers Association and the W Swedish Farmers Association, Agroenergi Utvecklings, will start up a 20,000 L/d plant at Lidköping in 1983. The company plans a series of 200,000 L/d plants. (Source: Technology Update, 5 March 1983)

Bulgaria

Large quantities of enterotoxins have been produced by genetic engineering at the Academy of Sciences. The enterotoxins, used mainly to obtain antibodies, were isolated from a strain of microorganisms. The strain has the capacity to divide quickly, yielding 8-10 times more enterotoxins than colibacteria. The academy is also extracting genes from nitrogen-binding bacteria, to enable plants to use nitrogen directly from the air. (Source: Technology Update, 29 January 1983.)

Canada

Biotechnology is being developed privately by some companies, but there is no national programme. France has a $28 billion, 5-year biotechnology R&D programme, Japan and Federal Republic of Germany started national programmes in 1972 and the US gives tax incentives and corporate loans to over 200 new large and small companies and invests about $500 million to encourage biotechnology development.

Allelix was formed by Canadian Development (50 per cent), John Labatt (30 per cent) and the Ontario government (20 per cent) in 1981 for $100 million to develop new biological processes for industrialization, though it will probably not be involved in manufacturing. Philom Bios is funded completely by private interests through common shares and a limited partnership to engage in biotechnical products, especially animal health care products, alcohol production and drugs and other products extracted from plants, R&D for commercial development.

The first private venture into biotechnology was BIO LOGICALS, which underwent a major reorganization in spring 1982 because money was being spent too quickly and projects were undertaken before the ideas were fully developed. Some 50 per cent of the 53 workers, including 39 technicians and 10 scientists, are engaged in nucleotide synthesis and 50 per cent on joint ventures. (Source: Technology Update, 18 December 1982.)

China

Interferon made using rDNA technology has been produced by the Beijing Institute of Virology, producing human alpha-interferon by introducing a DNA sequence coding for the protein into E coli. (Source: Technology Update, 29 January 1983.)

France

Elf Aquitaine has developed a family of microorganisms that feast on hydrocarbons to control oil pollution at sea; available: early-1983. EAP 12 bacteria feast on phosphorous, nitrogen and carbon. By applying an emulsion containing phosphorous and nitrogen to the oil, the microorganisms consume the carbon in the oil. Once the carbon is gone, the organisms die. The strains are said to work in varying climates and conditions, a key drawback to earlier bacteria development efforts. (Source: Technology Update, 4 December 1982.)

Greece

The Greek government is expected to sign a 10-year agreement on research and technology with the U.S.S.R. The joint programme could include the areas of energy, seismology, agriculture and health. Specific applications would be developed in biotechnology, microelectronics and computers, and in solar, thermal and photovoltaic energy. The framework for the agreement was worked out during a recent visit to the Soviet Union by Greece's Minister for Research and Technology. (Source: Chemical Engineering, 24 January 1983.)

Ireland - US company to build interferon producing plant

Even though it's well aware of "the scientific and medical questions that have yet to be resolved" about the product, Schering-Plough has decided to build a plant in Ireland for making interferon. Construction began last month on the 25-acre site of the drug company's idle antibiotic fermentation plant at Innishannon, County Cork, Ireland. The product will be produced by recombinant-DNA technology. Schering-Plough says it is moving ahead with the project because it wishes to be ready to make the product available to the medical profession as soon as its therapeutic usefulness in confirmed. The company plans to submit new drug applications to the U.S. Food and Drug Administration by the end of this year and hopes to have clearance to begin marketing the product by the end of 1984. A spokesman for Ireland's Industrial Development Authority, which is reportedly putting up nearly $8 million for this project, says the company will also receive substantial tax breaks, and will provide employment for about 160 Irish nationals by the end of next year. (Extracted from Chemical Week, 23 February 1983)

Ireland: University College Cork receives EEC grant

The Microbiology Department of University College Cork recently received an EEC grant of £100,000 for research into crop development. Already, research at UCC has been tested in two local companies with encouraging results, notably in the agricultural sector. The grant will be used to make the bacteria developed even more efficient in order to push research finally

into the market place. Apart from training and industry involvement, the UCC project is anticipated to bring other benefits such as decreasing agriculture's dependence on imported energy-intensive feedstocks. (Extracted from Technology Ireland, January 1983.)

Israel

A biotechnical product to make oil compatible with water has been developed at Tel Aviv University. Based on an isolated strain of bacteria, the bacteria degrade petroleum components in oil tanker ballast water, rendering the whole mixture ecologically unobjectionable. These bacteria work by producing a compound now called emulsan, which is water soluble. A fine film of emulsan surrounds each oil drop, to produce a stable oil/water mixture, called emulsanosol. (Source: Technology Update, 5 February 1983.)

A partnership has been formed for genetic engineering involving the First Mississippi Corporation of Jackson, Ms, and the International Genetic Sciences of New York to be based at the Hebrew University at Jerusalem. Apart from the $3 million to be supplied by the 2 American companies over the next three years, the Israeli Government will also be lending their support for work on increasing productivity in crop and livestock production, development of vaccines and the production of industrial chemicals. (Source: Technology Update, 5 February 1983.)

Italy

San Marco Distilleries (Ferrara, Italy) will be the site of a new pilot plant to test a biomass upgrading process, developed by Battelle-Geneva Labs. The new process is based on the use of phenols as delingification solvents to avoid resinification. The pilot plant will process 1 tph of straw. Cellulose will be hydrolyzed into glucose for ethanol production. The hemicellulose, recovered as pentose solutions, will be tested as a carbohydrate source for producing single-cell protein. Lignin will be burned for energy and will also be tested as a raw material for glue, adhesive and phenol production. (Source: Technology Update, 5 February 1983.)

Japan: Gene Recombination Research and Development Committee

The technology council of the Ministry of Agriculture, Forestry, and Fisheries will organize a committee on gene recombination research and development in the field of agriculture, forestry and fisheries. Last April, the Ministry formed a research group made from researchers inside and outside the Ministry, and suggested priority to be given to gene recombination research, improvement of the research setup, and establishment of a committee. Last September, the Ministry revealed a report made by a research group on bioresources development and utilization. In the report the Ministry showed a direction toward utilization of biotechnology to the field of agriculture, forestry and fisheries, and applications of high technologies including gene recombination, cell fusion, bioreactor tissue culture. The technology council on agriculture, forestry and fisheries will place the planned committee as an organization which creates research and development strategy recombination and considers specific research themes. (Source: Chemical Economy and Engineering Review, December 1982.)

Japan closing biotech gap

In the past few years, there has been what one analyst described as "a mass exodus" by chemical, pharmaceutical and food companies into biotechnology. Their activity was stepped up after the Japanese government eased restrictions last year on clinical testing for biotechnology-related developments. According to a survey of more than 100 companies conducted last August by the Ministry of International Trade and Industry, private spending on biotechnology research rose 45 per cent from 1980 to 1982, to $203,5 million. A survey last year by the Organization for Economic Co-operation and Development noted that out of some 2,400 bio-industry patents issued between 1977 and 1981, 60 per cent went to Japanese applicants, compared with 10 per cent to Americans.

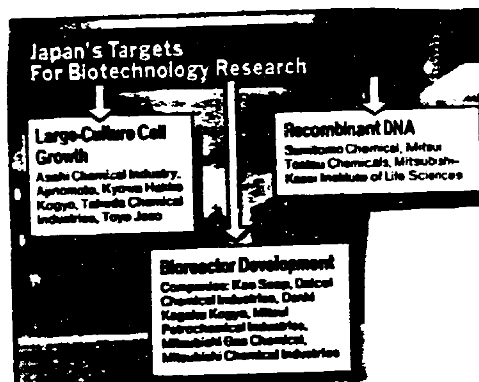
There are at least two significant differences in the development to date of the biotechnology industry in Japan compared with the United States. First, much of the initiative in the United States seems to have been seized by new entrepreneurial ventures, while in Japan the approach is to transform established companies. It is said that biotechnology has been so attractive because the field offers the possibility of new growth to companies in such stagnant industries as chemicals and food.

Hayashibara is an extreme example of a corporate transformation. Once a supplier of corn syrup and glucose to the confectionary industry, the small private company has shifted sharply in recent years toward advanced biochemical research. The company has developed an inexpensive method for producing interferon in vivo through cell cultivation, versus the in vitro method, where cells are cultivated outside a living organism. It is developing natural human interferon by transplanting cancerous human cells into hamsters, which have a low immunity and can accept up to their full body weight in human cells.

A second distinguishing feature of the Japanese biotechnology industry is that the government has marked it as a field whose development is vital to the nation's economic future. Thus a 10-year, $128-million biotechnology-research programme was started in 1981 by the Ministry of International Trade and Industry.

Thirteen major companies and one private research institute were chosen to receive the money for joint work in three broad areas of biotechnology: large-scale cell growth, recombinant DNA and bioreactors.

For most applications, the payoff for biotechnology research is likely to be years in the future. By the year 2000, the ministry estimates, the new technology will add $20 billion to $30 billion to the bioindustry in Japan, compared with $17 billion today.



(Extracted from Herald Tribune, 21 March 1983, and Technology Update, 29 January 1983.)

Japan

A new trade association for biochemistry will be formed in 1983 by the Japan Association of Industrial Fermentation, which includes 220 firms and 1,500 researchers, and MITI. Preparations are being made by 18 major companies and another 100 firms have already signed up. Officials contend that the establishment of such a committee is essential in view of the growing need to avoid duplication in the R&D field, exchange of information and efficient management on projects. The committee will open a data bank to facilitate the exchange of basic biotechnology, as well as promote interindustry co-operation. Charter members include Ajinomoto, Toray Industries, Kyowa Hakko Kogyo, Suntory, Sumitomo Chemical, Mitsubishi Chemical Industries, Sanraku-Ocean, Hitachi, Fujisawa Pharmaceutical and Meiji Seika Kaisha. (Source: Technology Update, 29 January 1983 and 19 February 1983.)

Japan's 1983 R&D biobudget jumps 5.8 per cent

Key ministries and agencies in Japan's government will spend more than of 7,906 million yen ($33.2 million) on biotechnology R&D in 1983. This represents a 5.8 per cent increase over the 7,471 million yen allocated in 1982.

Although the largest single slice of this national biobudget - 2,503 million yen - will accrue to the Ministry of International Trade and Industry (MITI), the biggest jump in funds, 7.6 per cent, goes to the Ministry of Agriculture, Forestry, and Fishery. It will dispose of 2,017 million yen this year, up from 1,874 in 1982, to fund projects in cell fusion, biological pesticides, cattle-embryo cloning, biomass conversion, and enhancement of plant

photo-synthesis. A special 208-million-yen account will support joint research with the People's Republic of China. Entitled "biological resources conservation", this relates primarily to gene-pool preservation.

Most of the Ministry of Welfare and Health's biotechnology-specific funds for 1983 have not yet been allocated. They include basic research to develop therapeutics by recombinant-DNA methods and clinical trials for biosynthetic products such as interferon, insulin, and growth hormones.

A modest but brand-new item in the MITI budget is for 203 million yen to be spent by the New Energy Development Organization (NEDO). This body will work with industry to obtain fuel alcohol from biomass by enlisting the bacterial genus Zymomonas, which has better heat resistance and faster fermentation rates than yeast.

Included in the 2,338 million yen thus far assigned to the government's Agency for Science and Technology is a 513-million-yen item for construction of a P4 containment facility at Japan's "science city" of Tsukuba. (Source: Newswatch, 21 March 1983.)

The Ministry of Agriculture, Forestry and Fisheries has successfully synthesized a reverse transcriptase enzyme which yields 100,000 iu in 3 days. The reverse transcriptase enzyme will soon be mass produced domestically, reducing dependency on US supplies. The special enzyme is used to produce DNA complementarily from m-RNA, which is easier to separate than DNA in many substances. The new method produces the specific enzyme via the cultivation of cells infected with swine leukemia viruses to yield 100,000 iu in 3 days. Studies on the vectors for eucaryote cells have been conducted at the Institute for Plant Virus Research and the National Chemical Laboratory for Industry. To duplicate recombinant DNA within a cell, a vector DNA must be present along with a signal initiating DNA. A DNA duplication initiator having 36 bases has been successfully developed using a human Adeno-virus. Both foreign and domestic patents have been applied for. (Source: Technology Update, 29 January 1983.)

Dutch soften DNA guidelines

The Ad Hoc Committee on Recombinant DNA Work in the Netherlands has proposed new guidelines for the use of genetically engineered microorganisms in cultures of 10 litres or more. Concluding that detailed regulations are neither necessary nor possible, the Committee proposed that the potential hazards of every project be judged individually, an approach similar to that proposed by the Genetic Manipulation Advisory Group in the United Kingdom. The new rulings will not be implemented until the Committee receives comment from scientists and the public.

The Committee, which has softened the guidelines year by year since their inception in 1976, is generally following the trend of the National Institutes of Health's Recombinant DNA Advisory Committee (RAC) in the United States. The Dutch advisory body, chaired by P.G. de Haan, recommended the establishment of a new class of experiments, which have relaxed safety standards relatively. Experiments in this group, called Safe Microbiological Techniques (Veilige Microbiologische Technieken), still have to be sent to the Committee, but no extensive safety evaluation will be undertaken.

The immediate benefits of this new proposal to the Dutch biotechnology industry are not apparent. Large-scale use of recombinant DNA technology has not begun in the Netherlands, but a number of large companies including Gist-Brocades, Unilever, and AKZO-Organon envision industrial scale-ups with genetically engineered bacteria in the foreseeable future. The Committee has recognized that guidelines and safety classes meant for experiments in laboratories cannot be applied on an industrial scale. For instance, it is currently forbidden in the Netherlands to introduce recombined species into the environment, a direct conflict with proposed uses in the food and waste management industries.

The guidelines in the Netherlands, like the NIH guidelines, do not have a legal basis, but an enforceable ruling is expected soon under the Occupational Health and Safety at Work Act. The work of the Committee will be modified if necessary and formalized at that time.

The Netherlands also has a two-year-old committee that concerns itself with the ethical aspects of biotechnology. The committee is expected to issue a report in the next few months. (Source: Bio/Technology, March 1983.)

Sweden

Fortia (Uppsala, Sweden) and the Swedish Government are funding a six-year research programme on biotechnology at the Institute for Cell Research at Uppsala University. Fortia is mainly involved in pharmaceuticals, diagnostics and materials and equipment for separating biological products. Some of the company's scientists will be involved in the research to be undertaken and the company will retain the right of first refusal on new discoveries.

Under the terms of the agreement, Fortia-Pharmacia will build up a research group at the Wallenberg Laboratory of Uppsala University, tailoring it to fit university research groups as closely as possible. Any discoveries or inventions made by scientists will be offered to the company under a first right of refusal agreement. If Fortia-Pharmacia passes up the offer, it can be sold to any other company, Swedish or foreign.

This is part of an overall strategy to merge key university institutes and laboratories with important segments of Swedish industry in an effort to keep Sweden competitive internationally.

What's unusual is that although the Uppsala researchers will be paid by Fortia-Pharmacia, they will work as traditional university scientists. All results of their work will be published.

United Kingdom: British venture plans mature

The British Technology Group (BTG) is likely to announce "shortly" plans for a new agricultural genetics company. The company, which has not yet been named, will have first refusal options on ideas originating from some of the research funded by the Agricultural Research Council (ARC). It will thus play a similar role to that of Celltech with the Medical Research Council.

Financial backing for the new company is expected from Ultramar, the British-based international oil company, and Advent Capital Ltd. ARC has approved the idea in principle and an announcement is expected as soon as details of the research areas to be offered to the new company have been settled.

The new company was first mooted some 18 months ago, but a variety of financial and personnel problems hindered early development of the idea. Government aid which had been sought was apparently not forthcoming, and the private sponsors were originally looking for proposals which could be brought to profitability within five years. However, the scientists who were approached apparently felt this to be an unrealistic aim. It was thought that more basic research in plant genetics would be needed before this goal could be contemplated, and the "five years to profitability" requirement was dropped. Dr. Richard Flavell, of ARC's Plant Breeding Research Institute at Cambridge, is now thought to have agreed to act as the new company's chief executive subject to details being finalized with ARC. An administrative director has also been found.

Mr. Roger Hay and Dr. Roger Cox of BTG last year set up a small holding company, New Plant Products Ltd, to carry out pilot studies for the proposed company. New Plant Products Ltd. will be incorporated within the new company when this is formed. One research area currently being investigated is the development of rape seed/jojoba hybrids produced from fused cells which have superior oil properties. Other ARC work which may form the basis of the new company's first products concerns the genetic engineering of Rhizobium and mycorhizzal innoculants for white clover, used to help add nitrogen to soil in upland reclamation schemes. New Plant Products Ltd. is already manufacturing conventional Rhizobium innoculants at ARC's Rothamstead Field Station. Mr Hay is confident that the new company will generate significant revenues "within the next five years". (Source, Nature, 10 March 1983.)

Britain backs three biotechnology projects

Three grants have been awarded under a $25 million programme set by the U.K.'s Industry Department to aid the development of biotechnology in Britain. Two of the grants go to Imperial Chemical Industries (ICI) for its polyhydroxybutyrate (PHB), a biodegradable polymer that is produced biologically, and for Pruteen, the company's animal feed made from methanol. ICI will use the money, an undisclosed sum, to try to cut the costs of its Pruteen process and to evaluate a development route for PHB in specialty medical products.

ICI has introduced a biotechnological process to produce a biodegradable plastic. Current production of polyhydroxybutyrate (PHB) from bacteria is only a few million ttpy at ICI's agricultural research division at Billingham. PHB is produced using natural bacteria, by a similar process to Pruteen. It has similar properties to polystyrene and polyester terephthalate and its melting point and tensile strength are comparable with polystyrene, and can be processed at 190-200°C. It can be used in pressure-sensitive electronic applications, as it has piezoelectric properties, generating a current when squeezed and changing shape when exposed to an electric field. It has been proven nontoxic and compatible with living tissues. A wide range of renewable feedstocks such as starch, sugars and a number of gases can be used to ferment PHB, but the price cannot compare with conventional polypropylene production, so PHB will probably be limited to special medical and electronic uses, until reserves of hydrocarbon feedstocks run short.

The third grant, for $1 million, will be used by Management Consultants P.A. International (Cambridge) and Matthew Hall Engineering (London) to build a $3 million fermentation pilot plant to encourage development of process control and electronic instrumentation for biotechnology processes. (Source: Technology Update, 25 December 1982 and Chemical Week, 9 March 1983.)

Britain's biotechnologists put monoclonals on the market

Britain's foremost genetic engineering company has beaten the world with a new range of products for identifying blood types. Celltech, financed by the government's British Technology Group and a consortium of private investors, has launched a series of laboratory reagents based on monoclonal antibodies to distinguish the main human blood types, A, B, O and AB and has been one of the few genetic engineering companies to pursue blood typing reagents as a product. The Government's blood transfusion centres have already taken delivery of the new reagents.

Although the world market for blood reagents is not enormous (about £7.5 million for hospitals and £3 million in other bulk sales), Celltech believes that its ability to grow mammalian cells on a large scale puts it in the forefront of monoclonal antibody technology. It will thus be in a good position to corner a large share of the much more lucrative market for diagnostic kits.

The advantages of Celltech's new reagents over traditional ones prepared from human blood are that the specificity of the antibody ensures a high degree of reliability from batch to batch. They also save scarce human blood for transfusions and for making other essential blood products, such as Factor VIII for haemophiliacs.

Celltech's next targets will be reagents for other main blood groups. But in the long term the company believes the major market lies with diagnosing diseases such as cancer. Recent reports show that monoclonal antibodies can pick up a variety of childhood tumours and others normally very hard to detect, in the breast, ovary, and gut.

The company has been taking on staff at the rate of one a week over the past year. It now employs about 130 people, of which around two thrids are scientists. Fairtlough hopes to increase the staff to about 180. (Extracted from New Scientist, 20 January 1983.)

USA: Faster and cheaper testing for mutagens

Quick, inexpensive tests using microorganism and mammalian cells - instead of rodents - to identify chemicals that cause mutations are sufficiently reliable for most regulatory and manufacturing decisions, according to a recommendation of a National Research Council (NRC) committee. In a report to the Environmental Protection Agency, the committee proposes that more expensive tests with mice be reserved for the relatively few cases where the results of the simpler tests are ambiguous or where a chemical is widely used. The report, "Identifying and Estimating the Genetic Impact of Chemical Mutagens", also recommends that EPA adopt a two-tiered screening process for environmental chemicals. At the first level, the chemical would be tested on the bacterium Salmonella and on mouse, Chinese hamster or human cells in culture. If these tests are negative, the chemical is presumed not to be a mammalian mutagen; if two or more tests are positive, the chemical is presumed to be dangerous. But if only one test is positive, screening should move onto the second tier, in which Drosophilia fruit flies are exposed to the chemical and the offspring are observed for signs of genetic changes. If no effects are seen in the second tier, the compound is assumed to be nonmutagenic. (Source: Chemical Week, 23 February 1983.)

USA

Functioning genes were successfully moved from bacteria into plant cells by Monsanto (St. Louis, USA) researchers and a European team of plant molecular biologists from the Max Plank Institute (Cologne, Federal Republic of Germany) and the University of Ghent (Belgium). The research marks a successful breakthrough in using DNA technology to engineer and improve plants genetically. The Monsanto group placed the gene that inactivates the antibiotic kannamycin into petunia cells growing in vitro. The genes were transferred into the plant cells by the Ti plasmid, a circular molecule of DNA from the bacterium Agrobacter tumefaciens, which can infect many plants with tumors; however, when properly manipulated, the plasmid is a useful means of transferring genes into plant cells.

Although the genes for antibiotic resistance can convincingly be moved into plant cells, it is uncertain whether those cells can be made to grow and function in intact plants. The recently developed methods, however, should work for transferring genes for valuable traits such as resistance to diseases, herbicides, or insects.

New techniques that substantially increase the scale on which mammalian cells can be grown in culture have also been developed by researchers at Monsanto. Although microbiologists can grow bacterial cells in batches of 50,000 gallons or more, mammalian cells are much more difficult to grow on a large scale. With moderate-scale (4- and 44-L) reaction vessels, continuous profusion is accomplished by attaching a satellite vessel containing a cylindrical filter, which retains the cells. Rat tumor cells were grown in the perfused vessel and in a conventional one. The cells' growth rate was about the same in each system, but cell density was 25 times in the perfusion reactor. All the cells remained alive in the reactor, versus a 30 per cent loss due to cell death in the conventional reactor. (Source: Technology Update, 5 February 1983.)

USA: Genetic testing methods

The City of Hope Medical Center and Research Institute has developed a general detection method for defects in a person's genes that could lead to early diagnosis and treatment of diabetes, multiple sclerosis, muscular dystrophy and cancer. The Office of Technology Assessment has also issued a new report on genetic testing of workers following a previous survey which showed that 59 of 366 leading US firms already use or plan to use genetic tests in the next 5 years. The tests concern genetic screening to determine traits that would make a worker susceptible to disorders from certain exposures and genetic monitoring to spot chromosomal changes that could be linked to chemical exposure. Even though workers would benefit from such tests, questions have arisen regarding privacy, discrimination and other technical issues. Some unions feel that these tests could become part of a worker's health record and create an army of 'untouchables' who are unable to get jobs. (Extracted from Technology Update, 5 February 1983 and 12 March 1983.)

USA

An interagency working group on biotechnology has been established by the US Office of Science & Technology Policy to assess the need for government policy that would sustain US scientific and technological leadership in the vastly growing field. The group will evaluate the economic and national security implications of biotechnology transfer to other countries via usual scientific and commercial channels. (Source: Technology Update, 29 January 1983.)

USA

The impact of genetic manipulation on society and medicine was reviewed by A.G. Motulsky, Director of the Center for Inherited Diseases, University of Washington (Seattle) in a recent paper. Human beings have been manipulating the genetic characteristics of plants and animals since the introduction of agriculture. Indirect manipulation of human genes occurred with widespread use of public health and medical measures that preserve genes causing disease. The production of biologicals by DNA technology raises a few ethical problems. Predictive medicine in which genetic markers (including DNA variants) are used for antenatal and pre-clinical diagnosis of genetic diseases and susceptibilities pose new questions of confidentiality, private versus societal goals, and self-determination. When normal DNA is used to treat the somatic cells of patients with hemoglobinopathies and other genetic diseases, no new ethical problems arise beyond those presented by any novel theory. In contrast, manipulation of DNA in human fertilized eggs would constitute a qualitative

departure from previous therapies since this would affect future generations. In order to be able to make wise decisions on these matters the public must be well informed. Thus, formal and informal education in human biology and genetics must be improved at all levels. (Source: Technology Update, 5 February 1983.)

PATENTS

Patents for monoclonal antibodies

Nine monoclonal antibodies that detect lymphocytes, monocytes, and certain sets of human leukocytes have been patented by Johnson & Johnson's Ortho Pharmaceutical (New Brunswick, N.J.). The three cell types play a significant role in the body's immune system. Subclasses of the monoclonal antibodies, the company says, may act to "help" or "suppress" certain immune functions. Clinical testing is under way to evaluate the antibodies' diagnostic applications in autoimmune diseases, such as rheumatoid arthritis, and for immunodeficiency states, such as leukemia and lymphoma. (Source: Chemical Week, 9 March 1983).

Prevention and dealing with scientific misconduct

In an attempt to restrict scientific fraud, a committee set up by the Mount Sinai Medical Centre at New York have laid down five guidelines to prevent a repetition of a recent case in which the Centre was involved. These are:

1. That faculties must present work frequently at seminars inside and outside the Centre and in peer-reviewed journals;

2. That laboratory heads must take responsibility for the quality of the research;

3. That all co-authors must be prepared to back work printed under their names;

4. That guidelines for reporting data in grant applications be set;

5. That a committee be set up to create and maintain specific rules to avoid research misconduct.

The Association of American Universities and the Association of American Medical Colleges also advise that institutions should set down in writing who is responsible for the quality of research, with special attention to the supervision of large research projects. Research centres should have clear rules for dealing with fraud and these should be set out in a handbook and there should be an established procedure for fairly investigating accusations of misconduct.

A survey of how 747 American research facilities handle misconduct is currently under preparation by Harvard University and should be available later this year. (Extracted from New Scientist, 6 January 1983.)

Cohen/Boyer patent

Stanford University (Stanford, CA) has decided its unprecedented decision to keep its files on the Cohen/Boyer patent open to the public was a mistake. So it is closing the files until the application is complete. Stanford feels the public has misinterpreted the Patent Office's formal rejection, which does not mean that the patent application is necessarily dead.

The two Californian inventors of the standard technique for gene-splicing waived rights to almost $400,000 in royalties last year.

Herbert Boyer donated his half-share of the $472,000 due to the University of California-San Francisco. It will be ploughed back into biochemistry research at the University where Boyer is professor. At Stanford University, the $157,000 due to Stanley Cohen, Professor of Genetics, will be used for the Medical Dean's Fellowship Fund.

Licensing of the technique raised a total of $1.5 million for the two universities last year. $200,000 was set aside as a "litigation reserve" to fight challenges to a second patent application covering products of the techniques. (New Scientist, 16 December, p.710).

Stanford also received $470,000 from the licensing of the Boyer-Cohen technique. So far, 73 companies have paid an initial $10,000 fee and an additional $10,000 annually to use it.

The division of spoils from the gene-splicing technique may soon be complicated if a claim by Dr. Robert Helling from the University of Michigan that he was also a co-inventor succeeds.

The annual report of Stanford's office of technology licensing shows that the university received a gross income of $2.5 million from licensing in 1981-82, involving 56 separate technologies. This, the office says, is more than any other US university. (Source: New Scientist, 13 January 1983 and Genetic Technology News, January 1983, address: 158 Linwood Plaza, Fort Lee, NJ 07024, USA.)

PATENTS

TITLE	ASSIGNEE	ISSUING COUNTRY & PATENT NUMBER	DATE GRANTED	DESCRIPTION
Protein Hybrid Having Cytotoxicity and Process for the Preparation Thereof	Teijin, Ltd, Japan	US 4368149	1/11/83	A protein hybrid prepared by bonding an Ig specific for a cell to be killed, to a protein-synthesis-inhibiting protein from *Momordica charantia*.
Direct Fermentation of D-Xylose to Ethanol by a Xylose-Fermenting Yeast Mutant	Purdue Research Foundation	US 4368268	1/11/83	A yeast mutant, *Candida* strain, that can ferment D-xylose directly to ethanol with at least 80% yields.
Epoxidation of Lower α-Olefins	Exxon Research & Engineering	US 4368267	-1/11/83	A process for epoxidation of certain olefins, dienes, or vinyl aromatic compounds by reacting the compounds with methylotrophic bacteria, or genetically engineered variants of such bacteria, under aerobic conditions.
Process for Producing Food Proteins of Fungal Origin From Multicellular Organisms Fermentation Apparatus and Proteins So Produced	Inst National de la Recherche Agronomique, Paris	US 4368269	1/11/83	A method for obtaining a new strain of the fungus *Trichoderma album*, and a process for recovering food proteins from the fungus.
Production of Microbial Cells from Methanol	Sekisui Kagaku Kogyo Kabushiki Kaisha and Yoshiharu Miura	US 4368271	1/11/83	A process for producing microbial cells of *Flavobacterium tosaenis* and *Flavobacterium methanolicola* in a medium containing methanol as the major carbon source.
Immunization against Group B Streptococci	Harvard College	US 4367221	1/4/83	A method of immunizing humans against group B streptococci by injecting them with a hyperimmune globulin fraction; the globulin fraction is obtained from humans injected with a streptococcal Group B-specific polysaccharide antigen.
Method for Microbial Polypeptide Expression	Genentech	US 4366246	12/28/82	Method for microbial production of a polypeptide using a plasmid that codes for precursor protein, e.g., a β-gal-somatostatin fusion protein; the precursor protein has a cleavage site next to the desired protein.
Monoclonal Antibody to a Human T Cell Antigen and Methods of Preparing	Ortho Pharmaceutical	US 4364937	12/21/82	An MCA that reacts with all human T cells and most human thymocytes, but not with prothymocytes; it may be useful in diagnosis and treatment of myasthenia gravis, multiple sclerosis, acute graft versus host reaction, and other immunoregulatory conditions.
Monoclonal Antibody to a Human Monocyte Antigen and Methods of Preparing Same	Ortho Pharmaceutical	US 4364936	12/21/82	An MCA that reacts with human monocytes and granulocytes, and that may be useful in diagnosis and treatment of biliary cirrhosis, early Hodgkins disease, hyper IgE, and other immunoregulatory conditions.
Monoclonal Antibody to a Human Prothymocyte Antigen and Methods of Preparing Same	Ortho Pharmaceutical	US 4364935	12/21/82	MCAs that react with 95% of normal human thymocytes, as well as with a human prothymocyte antigen and a leukemic T-ALL cell antigen.
Monoclonal Antibody to a Human Early Thymocyte Antigen and Methods for Preparing Same	Ortho Pharmaceutical	US 4364934	12/21/82	MCAs that react with early human thymocyte and stage II human leukemic T-ALL cell antigens.
Monoclonal Antibody to a Human Thymocyte Antigen and Methods of Preparing Same	Ortho Pharmaceutical	US 4364933	12/21/82	An MCA that reacts with about 70% of normal human thymocytes, and that could be used in diagnosis and treatment of biliary cirrhosis, myasthenia gravis, hyper IgE and other immunoregulatory diseases.

TITLE	ASSIGNEE	ISSUING COUNTRY & PATENT NUMBER	DATE GRANTED	DESCRIPTION
Monoclonal Antibody to Human Cytotoxic and Suppressor T Cells and Methods of Preparing Same	Ortho Pharmaceutical	US 4364932	12/21/82	MCAs to human cytotoxic and suppressor T cells that could be used in diagnosis and treatment of biliary cirrhosis, multiple sclerosis, hyper IgE and other immunoregulatory diseases.
Extraction of Interferon from Bacteria	Schering Corp. NJ	US 4364863	12/21/82	A method of extracting IFN-FIB from IFN-producing bacterial cells.
Recombinant DNA Transfer Vectors	Univ. of California, Berkeley	US 4363377	12/14/82	rDNA transfer vectors coding for human chorionic somatomammotropin and for HGH.
Cytotoxic Protein Hybrid and Process for the Preparation Thereof	Teijin Limited, Japan	US 4363758	12/14/82	A cytotoxic protein hybrid prepared by bonding a protein-synthesis-inhibiting substance obtained from *Phytolacca americana* to an immunoglobulin that binds selectively to an antigen on the cell to be killed.
Hybrid Plasmid and Process of Making Same	Upjohn	US 4362816 & 4362817	12/7/82	A hybrid plasmid cloning vehicle that is derived from *Streptomyces* chromosomal DNA and pBR322, and that contains a functional *tet* gene promoter.
Sandwich Immunoassay and Compositions for Use Therein	Palo Alto Medical Research Foundation, CA	US 4361647	11/30/82	A sandwich immunoassay for *Toxoplasma gondii*—which can cause jaundice and hepatomegaly—using MCAs or other antibodies.
Complement-Fixing Monoclonal Antibody to Human T Cells and Methods of Preparing Same	Ortho Pharmaceutical	US 4361549 & 4361550	11/30/82	Various MCAs that react with human T cells, including MCAs that r[illegible] with T cell chronic lymphoblastic leukemia cells, and MCAs that can be used in diagnosis and treatment of biliary cirrhosis, multiple sclerosis, mononucleosis, hyper IgE, and other immunoregulatory diseases.
Ultrapurification of Factor VIII Using Monoclonal Antibodies	Scripps Clinic, La Jolla, CA	US 4361509	11/30/82	An improved method for preparing Factor VIII procoagulant protein using MCAs.
Autonomously Replicating DNA Containing Inserted DNA Sequences	George Pieczenik, New York, N.Y.	US 4359535	11/16/82	An autonomously replicating, transferable DNA element, with an oligonucleotide sequence—such as a structural gene—inserted at a site not previously susceptible to REN cleavage.
Anti Thy 1:2 Monoclonal Antibody-Ricin Hybrid Utilized as a Tumor Suppressant	David Neville Jr. and Richard Youle, Bethesda, MD	US 4359457	11/16/82	A cytotoxic MCA-ricin hybrid protein used to suppress murine lymphomas.
Specific DNA Probes in Diagnostic Microbiology	Univ. of Washington, Seattle	US 4358535	11/9/82	DNA probes, complementary in sequence to part of pathogenic micro-organism's genome, are used as *in situ* hybridization probes to detect the pathogen in clinical samples.
Detection and Isolation of Endorphin mRNA Using a Synthetic Oligodeoxynucleotide	Harvey Rubin, San Diego, CA	US 4358586	11/2/82	A 15-base synthetic DNA molecule used as a hybridization probe to endorphin mRNA from human or rabbit cells; the endorphin mRNA can then be translated to cDNA and cloned.

(Source: Telegen Reporter, February 1983)

MEETINGS

Date	Title
14-15 April 1983	Biomass as a Source of Industrial Chemicals Conference, Paris, France. Contact: H. Heslot and R. Villet, Institute National Agronomique, ADEPRINA, 16 Rue Claude Bernard, 55231 Paris Cedex 05, France
16-22 April 1983	UCLA Plant Molecular Biology Conference, Keystone, Colorado Contact: UCLA Symposium, Molecular Biology Institute, University of California, Los Angeles, California 90024
18-22 April 1983	9th International Yeasts Specialized Symposium, Smolenice Castle, Czechoslovakia. Contact: A. Kockova-Kratochvilova, Institute of Chemistry, Slovak Academy of Sciences, Dubravska Cesta, 842 38 Bratislava, Czechoslovakia
18-22 April 1983	TNO Biology of the Interferon System International Meeting, Rotterdam, Netherlands. Contact: Congress Bureau TNO, P.O. Box 297, 2501 BD's-gravenhage, Netherlands
21-26 April 1983	UCLA Biosynthesis of the Photosynthetic Apparatus: Molecular Biology, Development and Regulation Symposium, Los Angeles. Contact: UCLA Symposium Molecular Biology Institute, University of California, Los Angeles, California 90024
23-30 April 1983	UCLA Protein Transport & Secretion Conference, Keystone, CO Contact: UCLA Symposium, Molecular Biology Institute, University of California, Los Angeles, California 90024
26-28 April 1983	Biologic Diagnosis & Treatment of Malignancies Conference, Geneva, Switzerland. Contact: Dr. W. Hennesses, Scientific Secretary of IABS, Willadingweg 37, ch-3006 Bern Switzerland
1-4 May 1983	ASM Gene Manipulations in the Exploitation & Study of Fungi Conference, South Bend, IN. Contact: Mildred Schwartznau ASM, 1913 I St, NW, Washington, D.C. 20006
4-6 May 1983	Biotech 83 Conference, London, UK. Contact: Online Conference Ltd. Argyle House, Northwood Hills, HA6 1TS, Middlesex, UK
10-13 May 1983	5th Biotechnology for Fuels & Chemicals Symp, Gatlinburg, TN. Contact: C.D. Scott, ORNL, P.O. Box X, Oak Ridge, TN 37830
24-25 May 1983	Stony Brook Experimental Manipulation of Gene Expression Sym, Stony Brook NY. Contact: Stony Brook Sym, Department of Biochemistry, SUNY at Stony Brook, Stony Brook, NY 11794
29-31 May 1983	Medic Canada 83 Conf, Edmonton, Canada. Contact: Robert S First Inc, 707 Westchester Ave, White Plains, NY 10604
7-11 June 1983	27th Wind River Genetic Exchange Conf, Estes Park, CO. Contact: Donald Morrison, Department of Biological Sciences, University of Illinois, Box 4348, Chicago, Illinois 60680
8-10 June 1983	EMBO Coronaviruses - Molecular Biology & Pathogenesis Workshop, Zeist, Netherlands. Contact: Dr. Peter J.M. Rottier Inst of Virology, Veterinary Faculty, State University, Yalelaan 1, 3508 TD Utrecht, Netherlands

Date	Title
19-23 June 1983	33rd Annual Canadian Society of Microbiologists Conference, Winnipeg, Manitoba, Canada. Contact: N.R. Cambell, Dept of Microbiology, University of Manitoba, Winnipeg, Manitoba R3T 2N2, Canada or Meeting Secretary, Canadian Society of Microbiologists, Suite 500, 85 Albert St, Ottawa, Ontario K1P 6A4, Canada
24-29 July 1983	European Biochemical Societies Fedn 15th Meeting, Brussels, Belgium. Contact: 15th FEBS Meeting, Brussels, International Conference Centre, Parc des Expositions, B-1020 Brussels, Belgium
12-16 August 1983	6th International Protoplast Symposium, Basel, Switzerland I. Potrykus, Friedrich Miescher-Inst, P.O. Box 273, CH-4002 Basel, Switzerland
21-23 September 1983	Advances in Fermentation Conference, London, UK. Contact: AIF '83 Conference Secretariat, c/o Process Biochemistry Penn House, Rickmansworth, Great Britain WD3 1SN
11-14 October 1983	1st Interntional Molecular Genetics of the Bacterial Plant Interaction Sym, Bielefeld, W. Germany. Contact A. Puehler University Bielefeld, Fakultät für Biologie, Postfach 8640 4800 Bielefeld 1, W. Germany

(Source: Telegen Reporter, February 1983.)

PUBLICATIONS

New bulletin on biotechnology

The Royal Society of Chemistry is launching Current Biotechnology Abstracts this year, covering papers, patents and articles from all fields of biotechnology, based on approximately 150 journals of all types and will have an extensive indexing system. It is hoped a computer-readable database could be provided at some future date. (Source: Aslib Information, Vol. 11, No. 3, March 1983.)

New monitor of Japanese industry

A new monitor of Japanese industry and technology, Japanscan, is available in English and is an in-depth analysis and datafile on pharmaceuticals, bioscience, food industry, ceramics and glass, medical/pharmaceutical equipment and technology, and environmental health and pollution. The monitor gives a comprehensive coverage of Japan's scientific and industrial publications, with easy and cost-effective access to that data. Further information can be obtained from Mitaka, 3-5 Tavistock Street, Leamington Spa, Warwickshire CV32 5PJ, United Kingdom.

UNIDO Documents:

ID/WG.384/4/ Rev.1	Genetic Engineering and Biotechnology and Developing Countries: Directions for Action
ID/WG.384/6/ Rev.1	Implications of Biomass Energy Technology for Developing Countries
ID/WG.384/13	Biotechnology and Enzymatic Conversion of Cellulose: Fundamentals and Applied Aspects by A.A. Klesov
UNIDO/IS.372	UNIDO Directory of Industrial and Technological Research Institutes: Industrial Conversion of Biomass

Company News

For those who would like to be kept informed of whois doing what in the biotechnology business, one source is a twice-monthly newsletter called Abstracts in BioCommerce. Further information can be obtained from the publishers, IRL Press, P.O. Box 1, Eynsham, Oxford OX8 1JJ, United Kingdom.

Biotechnology

A study by a US consulting firm claims that the new technology associated with genetic engineering will not revolutionise industry. Instead, says the study, it will allow the economic and competitive production of certain important specialties. In five volumes totalling more than 900 pages, 'The basic economics of fermentation processes based on genetic engineering' claims that these routes to new products have some serious economic disadvantages. Further information is available from Bernard Wolnak and Associates, 360 N. Michigan Avenue, Suite 706, Chicago, Illinois 60601 (Tel: (312) 782 4926). (Source: Chemistry and Industry, 21 February 1983)

FOR NEW SUBSCRIBERS ONLY:

UNITED NATIONS NATIONS UNIES

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

UNIDO MAILING LIST QUESTIONNAIRE

Genetic Engineering and Biotechnoloby Monitor
(Code: 503)

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

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

PLEASE DO NOT WRITE IN THESE SPACES

S/A ☐ CISP. CODE ☐ COUNTRY ☐☐☐

CITY ☐☐☐☐☐☐☐☐☐☐☐☐