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UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

Genetic Engineering and Biotechnology Monitor

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15992

Dear Reader,

It is with considerable satisfaction that I should like to inform you that substantial progress has been registered in regard to the International Centre for Genetic Engineering and Biotechnology in the course of this year. Prof. I. Gunsalus, Emeritus Professor of Biochemistry at the University of Illinois, USA, was elected Director of the ICGEB in June 1986 by the Preparatory Committee on the establishment of the ICGEB at its eighth session. The Head of the Italian component has also been nominated, namely Dr. Arturo Falaschi, Director of the Institute for Genetics, Pavia, Italy. The Head of the Indian component still remains to be nominated. The interim programme of work for the first three years of operation of the ICGEB has been approved by the Preparatory Committee and three agreements have been signed with the Government of Italy involving two projects covering the period 1986-1989 and a programme agreement between the Italian Government and UNIDO. We hope to publish news from Professor Gunsalus on the work of the ICGEB in future issues of the Monitor.

It is equally pleasant to inform you of the appointment of Mr. Fernando Simoes Souto as Deputy Director-General heading the Department for Industrial Promotion, Consultations and Technology. Until his appointment with UNIDO, Mr. Souto was Managing Director for Quality Assurance of Tectronic-Electronic Equipments in Sao Paulo. Before that he was President of the Brazilian National Institute for Metrology, Normalization and Industrial Quality.

Completed questionnaires which were attached to issue number 15 are beginning to arrive at our office, with useful comments and suggestions for improving the Monitor and we look forward to receiving the rest. In view of the need for austerity we have had to publish the Monitor in double columns, resulting in small print to save space and mailing costs. We also very much regret the delay in getting the Monitor to our readers, but distribution can only be by surface mail at this point.

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A. POLICY, NEWS AND OTHER EVENTS

UNIDO News

Seminar/Workshop on the Implications of New Technologies for Caribbean Development, May 1986

At a meeting in Barbados in November, 1984, the Standing Committee of Ministers responsible for Science and Technology requested the CARICOM Secretary General to consult with the United Nations Centre for Scientific and Technological Development (UNCSTD) and other appropriate agencies and organizations with a view to holding a regional Seminar/Workshop on new technologies and their implications for the future development of CARICOM member States.

The present workshop, from 7 to 10 May 1986, was organized jointly by the Caribbean Community (CARICOM) Secretariat and the Government of Trinidad and Tobago with the financial assistance of the UN/FCDC unit and the Commonwealth Secretariat. Technical support was provided by the Board on Science and Technology for International Development (BOSTID), International Labour Organisation, United Nations Centre for Scientific and Technological Development, United Nations Educational, Scientific and Cultural Organization, United Nations Industrial Development Organization, and the Caribbean Council for Science and Technology/United Nations Economic Commission for Latin America and the Caribbean (CCST/UNECLAC). Some of the recommendations made at this workshop were:

(a) "A workshop on biotechnology involving workers in tissue culture and applied microbiology and biological nitrogen fixation should be held late in 1986 at University of the West Indies, St. Augustine. The workshop should be convened by the University and the Caribbean Agricultural Research and Development Institute (CARDI) with financial assistance from CARICOM, CCST, UNIDO, UNDP and other interested agencies. The workshop would establish a biotechnology network (Biotechnology Resource Centre) ..."

(b) "The Biotechnology Resource Centre as proposed should tap into the UNIDO's sponsored ICGEB, and the proposed 'Sub-regional Centre for the Industrial Applications of Biotechnology and Genetic Engineering (Centro Sub-regional para las Aplicaciones Industriales de Biotecnologia e Ingenieria Genética)' based in Mexico, using regional members as focal points for entry". At the moment, only Trinidad-Tobago and Guyana within the Caribbean countries are members of the above-mentioned Centres.

(c) "Trinidad and Tobago as a signatory to the Treaty establishing the ICGEB should ratify the Treaty, become a full member, and seek affiliation status."

(d) "A regional technology assessment facility should be established on existing capabilities, which would interact dynamically with the national counterparts and have strong linkages with special programmes concerned with technology assessment in developed and other developing countries. The question of a regional ATAS project for the Caribbean and the establishment of technology advisory services particularly for small enterprises should be pursued in collaboration with UNCSTD, UNIDO, UNESCO and other interested agencies."

(e) "Relevant agencies of the United Nations System, specifically UNCSTD, ILO, UNIDO and UNESCO as well as other interested organizations such as the Commonwealth Science Council, should extend substantive co-operation and assistance where required in the design and implementation of a system for the CARICOM region, for monitoring of and access to information on new technologies."

Workshop "Biotechnology: An Opportunity for Latin-America", Ciudad de la Habana, Cuba, 2-7 February 1987

In 1981 the United Nations Industrial Development Organization (UNIDO) brought together an international group of leading scientists to see how the new biotechnologies could be deployed on behalf of the Third World to help solve problems and to advance economic development. They recommended that an international centre be created where researchers from both industrialized and developing countries would work side-by-side on a wide range of industrial, medical and agricultural applications of genetic engineering and biotechnology. At the same time, trainees from developing countries would learn the latest biotechnology techniques to take back to their home countries, in turn training others. Further, the centre would be linked to a network of affiliated national and regional research institutes.

In 1983 the International Centre for Genetic Engineering and Biotechnology (ICGEB) devoted to the problems of developing countries was officially established by 26 countries attending a ministerial-level meeting organized by UNIDO in Madrid, Spain. The following year the meeting was reconvened in Vienna, Austria, to select a location for the Centre. It decided on a dual-component ICGEB to be sited in New Delhi, India and Trieste, Italy. With the opening in 1986 of provisional facilities in New Delhi and Trieste, the Indian component will initially concentrate on agriculture and health with the Italian half focusing on industrial microbiology. The guiding principle in selecting specific R&D projects will be their priority for the Third World. At the same time, a Preparatory Committee to establish the ICGEB was set up for the purpose of guiding the preparatory process for the ICGEB. As a noteworthy point it could be mentioned that from the Latin American-Caribbean areas, so far Argentina, Bolivia, Chile, Cuba, Ecuador, Mexico, Panama, Peru, Trinidad and Tobago and Venezuela have signed the statutes of the ICGEB and are therefore members of its Preparatory Committee in which a total of 36 countries are represented at present. At the same time, institutions from Argentina, Cuba and Venezuela have requested to become affiliated centres to the ICGEB, for a further and specific vis-à-vis co-operation.

In February 1986 an agreement between UNIDO and Cuba was signed which specified that UNIDO should provide assistance in organizing a workshop on biotechnology in Cuba within the framework of the ICGEB, and oriented towards researchers of developing countries. This workshop could be considered the first of a series of forthcoming workshops and meetings for the Latin American-Caribbean region, with the objective of defining specific areas of R&D in biotechnology and genetic engineering, specially within the framework of regional co-operation.

Proposed topics for discussion are:

1. Human and animal health care
   - (i) Biotechnological production of drugs (biologically active products)
   - (ii) Development of diagnostic systems and vaccines for regional diseases.
2. Plant biotechnology
   - (i) Development of varieties resistant to diseases

(ii) Nitrogen fixation

(iii) Biofertilizers

3. Biomass processing

(i) Single cell protein

(ii) Cellulose degradation

(iii) Alcohol production

4. Food biotechnology

(i) Industrial enzymes production

(ii) Alimentary additives

(iii) Traditional fermentations improvement

5. Other topics

(i) Marine biotechnology

(ii) Mineral leaching

The objectives of the workshop are to make recommendations for the Latin American-Caribbean research centres that will serve to provide a sharper definition to the research needs in specified areas of biotechnology, particularly those germane to the needs of developing countries.

Social issues

Genetic screening raises questions for employers and insurers

As genetic tests to detect susceptibility to diseases are developed, policy-makers will have to decide how these tests are to be used, and by whom. The issues involve protecting the privacy of employees and yet protecting the interests of employers who may not want to hire or promote a person, for example, if they know he is likely to develop a debilitating genetic disease. They involve life insurance and health insurance companies.

The questions came into sharp focus when a probe for the Huntington's disease gene was discovered three years ago, allowing molecular biologists to detect a small piece of DNA that is so close to the as yet unidentified Huntington's disease gene that it is inherited along with the gene. By tracing the inheritance of this nearby segment of DNA, researchers are planning to tell many people at risk for the disease whether they inherited the gene.

Shortly after the discovery of the disease probe, molecular biologists found markers for other relatively rare classical genetic diseases - Duchenne muscular dystrophy, cystic fibrosis, and polycystic kidney disease. Now researchers are using the same techniques to look for genetic markers for more common diseases, including Alzheimer's disease, manic-depression, malignant melanoma and breast cancer.

The promise of this research is great. For the first time investigators may be able to get at the causes of these diseases by isolating the relevant genes and learning what the genes do. However the ethical problems arising from this research have no easy solutions. Already, as the search for more and more markers gets under way, a long-standing debate over the uses of genetic screening is beginning to change its content.

A decade, or even five years ago, the argument was over genetic screening of industrial workers. Researchers thought they could find tests to predict who is most susceptible to harm from toxic substances in the workplace. For example, it was suggested that workers with alpha-1-antitrypsin deficiency, which predisposes them to lung disease, might be excluded from jobs requiring exposure to asbestos or cotton dust.

Some hailed the development of such tests. Others criticized such screening as paternalistic and discriminatory.

No one has any good figures on how much genetic screening is actually going on in the workplace. The companies themselves are not releasing any figures and data are hard to come by. Perhaps because it is unclear how much testing is actually going on this particular debate has died down recently. But now, with the likely development of tests to predict susceptibility to diseases such as Alzheimer's, the same questions that were raised about genetic screening in the workplace are being asked again, and with more urgency than ever. This time the issues affect the entire population. The possibility of genetic screening is touching all groups of workers. Vexing ethical questions will ultimately have to be answered.

The ethical questions are of increasing concern to researchers and administrators at Massachusetts General Hospital and at Johns Hopkins University Hospital, which, very shortly, will be the first institutions to offer screening for the Huntington's disease gene. In this respect, the Huntington's disease screening programmes will be a test case. The ways that these programme administrators deal with the seemingly intractable problems of genetic screens will likely set the tone for screening programmes to come.

The first thing to be said about the Huntington's disease programmes is that they are moving ahead very slowly. So far, what the researchers have is a marker for the gene, not the gene itself. This means that they can tell some people whether they inherited a piece of DNA that, in their family members who got the disease, seems to travel with the Huntington's disease gene. Those who inherit such a piece of DNA near the gene have a 95 per cent chance of inheriting the gene. If they have the gene, they have a 100 per cent chance of eventually developing the disease. The molecular probe is however useless for persons who have no living family members with the disease. It can provide no information. So, until molecular biologists close in on the gene itself, the test is not universally applicable.

Nancy Wexler, who is president of the Hereditary Diseases Foundation and a faculty member at Columbia University's department of neurology and psychiatry, has asked health insurance companies whether they voluntarily will refrain from looking at the results of tests for the Huntington's disease gene. Some companies are sympathetic, yet, Wexler says, "according to our conversations with insurance companies, there is no way they can't see the results." The companies told Wexler that even if they agreed in principle not to look at the test results, they could inadvertently see them when they were reviewing patient files for other reasons.

Life insurance is a different matter. Life insurers have traditionally excluded people because their health is poor or because they are at high risk of becoming seriously ill.

These are some of the same issues now being faced by people at high risk for AIDS (acquired immune deficiency syndrome). Although there is no national legislation, some states in the USA have passed laws forbidding insurance companies to require

that members of high risk groups be tested for AIDS. Other states permit insurance companies to require the AIDS antibody test.

Then there are the questions of employment. If an insurance company pays for a genetic test, is it free to give the test results to an employer? In New York, insurance companies that require AIDS tests cannot reveal the results to employers, according to Wexler, but, once again, there is no coherent national policy, even for AIDS; and it would be hard to argue that large corporations that self-insure could somehow keep test results from themselves.

No one has any easy answers to these questions of balancing individual rights against the rights of companies and society. Yet the forthcoming genetic tests may force the issue. As tests for genetic diseases leave the protected realm of research projects, their use will be impossible to control. How, when, and by whom these decisions will be made is, of course, the issue. But as genetic testing finally leaves the realm of the hypothetical, it is becoming clear that somehow these difficult issues must be faced, and soon. (Extracted from Science, Vol. 232, 18 April 1986)

Regulatory issues

U.S. issues recombinant DNA policy

Following months of anticipation, the White House has released its plans for regulating the products of advanced biotechnology methods. The policy basically sets up a matrix establishing the duties and relationships among the several federal agencies involved in regulating biotechnology under present laws. The whole process will be overseen by an interagency oversight group.

Officially announcing the policy, David T. Kingsbury, assistant director for biological, behavioral, and social sciences for the National Science Foundation, emphasized that the White House's role is one of co-ordination, with the individual agencies having primary regulatory responsibility. For biotechnology, the responsible agencies are the Environmental Protection Agency, the Department of Agriculture's Animal & Plant Health Inspection Service, the Occupational Safety & Health Administration, and the Food & Drug Administration. Research guidelines are to be set by the National Institutes of Health and the National Science Foundation. Oversight of the regulations will be provided by an interagency biotechnology science co-ordinating committee.

The matrix of statutes and what they regulate is supposed to help companies understand what regulations they must follow to get approval for the products they produce.

The Administration's approach is somewhat controversial. Some critics of the policy believe the existing laws are not capable of properly regulating the relatively new technology and others believe the proposed guidelines are letting the biotechnology industry take too many chances. New legislation to deal with genetic engineering products is under consideration in both the House and Senate, but the committees have been waiting to see what the Administration would propose and probably will hold additional hearings on the guidelines next month.

The new proposal defines the terms intergenic organism (new organism) and pathogen. It also attempts to define exactly what is meant by "release into the environment." The new co-ordination committee is asking for comments on those definitions because of recent controversy about them. (Extracted from Chemical & Engineering News, 30 June 1986)

Brookings conference focuses on aspects of biotechnology regulation

Regulators of biotechnology need to focus on the products of the technology and not the process by which they were made, agreed most participants at the Brookings Institution's second annual conference on biotechnology in Washington, D.C. However industry representatives said that the public still fears the process more than the products of genetic engineering. Companies need to consult with all levels - national, state and local - that may be affected or perceive themselves affected by an environmental release.

Turning to regulatory issues, most participants agreed that there are three approaches to regulation: use the existing authority, modify the existing authority or adopt new legislation, or ban experimental release altogether.

Both the U.S. Administration and Congress appear to be following the first approach - the Administration, by design; Congress, because it has not yet agreed on the need for new legislation or modifications in existing legislation. Most biotechnology releases are regulated to some degree by existing legislation. The most important statutes are the Food, Drug and Cosmetic Act, which regulates human and animal pharmaceuticals, cosmetics and foods; the Federal Insecticide, Fungicide and Rodenticide Act, which covers pesticides; TSCA, which regulates chemicals used for commercial processes; and groups of statutes regulating agriculture.

The regulatory structures covering drugs, food additives and pesticides require companies that plan to distribute these substances to commercially test them for safety and provide the results to the relevant agency. Other regulatory programmes, like TSCA, require that the agency, rather than companies, gather risk assessment data.

The regulatory system often does not clearly define which agency has authority for regulating experimental release experiments, contributing to the industry's low-profile stance.

The lack of clear jurisdictional boundaries also "subjects the overall regulatory programme to turf battles among institutional actors that want a greater or lesser share of the regulatory action," according to the Brookings report.

The report recommended establishment of a registry of current users of biotechnology so that regulators will know where to look for possibilities of health and environmental harm. "Without such rudimentary information, risk assessors will be searching for needles in haystacks," it said.

The report also recommended that a registry of promising experiments be set up. The registry would assess risks in advance of commercial applications of biotechnology.

Conference participants cited the need for basic research that will lead to tests to predict released organisms' effects on their environments. Such research would span the fields of evolution, natural history, and population biology.

These areas of research are often viewed as unfashionable because they are not on the "cutting edge" of science. But regulators assessing environmental risk need information from these fields to gain an accurate picture of the environment into which an organism is being released, the Brookings report said. (Extracted from Genetic Engineering News, April 1986)

European industry reveals biotechnology safety rules position

Europe's chemical, pharmaceutical and food industries have drawn up a series of proposals and recommendations for rules to ensure the safe application of biotechnology.

In response to a request from Brussels, representative organizations from the relevant industries collaborated on proposals that will be the subject of technical discussions with the European Commission's experts.

Most important are the regulations governing the deliberate release of genetically-altered material into the environment.

Industrialists in Europe are urging the Commission to adopt a stepped approach as impact assessment of any potential risks is scientifically not well established. An approach by stages, from laboratory experiments through to full commercialization, is considered most appropriate by the industry groups. Such an approach falls in with the current positions of both the OECD and the US health institutes.

In addition, the industry groups are urging Brussels to identify a harmonized system for evaluation of risks. Any regulations would have to be consistent throughout the Community.

Nevertheless the industrialists have warned Brussels that any new guidelines and regulations should not hold back commercial application of biotechnology. Additional legislation for areas which are either non-industrial or regulated sufficiently is seen by industrialists as unnecessary. (Source: European Chemical News, 21 April 1986)

UK approves voluntary gene guidelines

Scientists in Britain who want to release genetically engineered organisms into the environment now have a set of official guidelines to work to. The guidelines, published by the Health and Safety Executive, are voluntary and the companies or organizations that approach the executive can request that the details of their experiments remain secret.

The guidelines put the onus on the scientists to assess the risk of their own proposals to release engineered organisms. At present, there is no legislation forbidding the release of altered organisms, except in specific cases, such as micro-organisms that help to control pests. These come under general legislation on the use of pesticides. The guidelines are meant to fill this gap.

The guidelines ask scientists to take into account the nature of the organism involved, including its ability to form structures that can survive in the open for long periods, and also the nature of the environment into which it will be released. There must be contingency plans in case of "unanticipated effects" of the novel organisms.

The guidelines also ask scientists to pay attention to the chances of the new organisms surviving beyond the intended period of the trial, and the possibility of the organism passing its new engineering trait to other organisms. The Advisory Committee on Genetic Manipulation, which drew up the guidelines for the Health and Safety Executive, wants to be notified in advance of any proposals to release genetically altered organisms. Although the notification will be voluntary, the committee wants them to become obligatory.

Nevertheless, the committee feels that there is no excuse for it not being told of a proposed release of a novel organism into the environment. The committee says in its guidelines that "all proposals to release genetically manipulated organisms must be notified for its consideration."

The committee also wants other bodies, such as local environmental health officers, to be told about the proposal. However, there is a clause in the guidelines that permits companies to keep certain commercially sensitive information secret. Proposals for release of gene-spliced organisms will be expected to provide data concerning procedures used for manipulation, the nature of the changes, stability of the novel organism as well as predictions of possible effects on the ecosystem. But the guidelines are intended to cover more than environmental releases and will regulate all trials outside the laboratory.

The guidelines do not apply to the use of gene-spliced organisms that have been developed for human or veterinary uses. (Extracted from New Scientist, 24 April 1986 and European Chemical News, 28 April 1986)

US to settle agency jurisdiction

After months of inter-agency wrangling, the new US federal government policy statement on biotechnology research is expected to be published in the Federal Register. Its supporters believe it will make clear the complex maze of regulatory jurisdictions among federal agencies. But even its authors acknowledge that the new document, which is two-and-a-half inches thick, will be a challenge to general understanding.

The framework is the next step in the process begun in December 1984 to co-ordinate government policy regulating biotechnology. Since last November, when an index of relevant statutes appeared in the Federal Register, the Domestic Policy Council (DPC) Working Group on Biotechnology has been conducting an intensive effort to arrive at an inter-agency consensus on how those statutes are to be applied.

The DPC working group felt that placing all products created by recombinant DNA techniques under the same regulatory umbrella was misguided. As an example, the pseudorabies vaccine developed by Saul Kit at Baylor College of Medicine uses a modified virus missing a part of its genome. Because it incorporates no new genetic material, it may reasonably be treated just like any other altered vaccine. The working group takes the approach that it is only when genetic material from organisms of different genera are combined that special attention needs to be paid to the potential hazards of a new organism.

The new document, the Co-ordinated Framework for Regulation of Biotechnology, contains policy statements by all the major regulatory agencies involved in biotechnology. Because of the "mosaic" of statutes covering biotechnology issues, "the potential for confusion is enormous." To ameliorate this problem, the new framework proposes two new definitions as a basis for co-ordinating new regulations.

The Biotechnology Science Co-ordinating Committee (BSCC), made up of senior policy officials of agencies involved in biotechnology research and products, took responsibility for coming up with the definitions. An "intergeneric organism (new organism)" is one formed by "deliberate combination of genetic material from sources in different genera." A "pathogen" is defined to include

micro-organisms that "belong to a pathogenic species or that contain genetic material from source organisms that are pathogenic." Specifically excluded from both these definitions are organisms that are "well characterized and contain only noncoding regulatory regions." BSCC is now considering expanding these exemptions, as well as defining more formally an environmental release.

A key accomplishment of the new framework is to sort out the overlapping jurisdictions of the various federal agencies involved in biotechnology regulations. The framework attempts where possible to identify the single agency having responsibility for a single product, but where overlapping jurisdictions arise, the lead agency is identified.

While sorting out overlapping jurisdictions between agencies was a major accomplishment for the BPC working group, jurisdictional issues also cropped up within the agencies. At the US Department of Agriculture (USDA), disputes arose between the science and education division and the marketing and inspection services over review issues.

One upshot of the disputes was the creation of an Office of Agricultural Biotechnology to keep track of all items either reviewed for licence or proposed as research. In addition, the Agriculture Recombinant DNA Committee (ARC) is being disbanded; an Agricultural Biotechnology Recombinant DNA Advisory Committee will now assume responsibility for review of all research projects.

Although the new framework represents a step forward in co-ordinating federal policy, some worry that the regulatory system is still chaotic. (Source: Nature, Vol. 321, 29 May 1986)

Biotechnology committee on standards begins work

With the growth of biotechnology as an industry, the USA's ASTM Committee on Research and Technical Planning (CR&TP) has been researching the possibility of standards on the subject. After doing analyses of its own, CR&TP commissioned Gerry Elman, an attorney and editor of the Biotechnology Law Report, to carry out further study. Elman's efforts indicated that several areas were appropriate for standards development. Consequently, a planning meeting was held in March 1984, which lead to the October 1985 organizational meeting of Committee E-48 on Biotechnology. Highlights of the October subcommittee meetings follow:

E48.01 on materials for biotechnology

A task group on a recommended practice for characterization of enzymes for use in research and clinical chemistry decided to look into existing practices and report recommendations at the next meeting of the group. The testing for DNA and microbial contaminants task group agreed that such testing was of concern in the use of injectable products and that any available guidelines from federal regulatory agencies should be used because the subject is in their purview. Other possible topics for this subcommittee include quality of culture media components, biological activity units, and quality control of synthetic DNA.

E48.02 on characterization and identification of biological systems

Four items by E48.02 were listed as needing classification, including cells, organisms, vectors, and viruses. The subcommittee held general discussion on issues for concentration, which include characterization of:

- Plasmids,
- Genetically modified micro-organisms,
- Viruses and viroids,
- Animal cell lines and tissues,
- Plant cell lines and tissues,
- Transposable elements, and
- Genetically modified plants.

Before forming any formal task groups, two subcommittee members will report on activities underway in organizations such as the Tissue Culture Association.

E48.03 on processes and their control

Concern about overlap with federal regulatory requirements such as process validation guidelines from the Food and Drug Administration surfaced during discussions in E48.03. Three areas were established for further research and information gathering to possibly lead to standards development. The first is chromatography which could include standards related to testing for bonded phase bleed, determination of column pressure limits and testing of column cleanup procedures. Retention measurement, porosity, flux, depth rating and molecular weight cutoff were areas for possible standards under the second heading, filtration/membrane technology. A third area to be looked into is P1/P4 monitoring, where there may be a need to monitor air flow-rates or other factors in P1/P4 processing areas.

E48.04 on environmental issues

An environmental use and monitoring task group agreed on a number of topics for further consideration. One general topic for the goup is specificity and sensitivity of monitoring techniques. The other topic is identifying and developing methods for assessing environmental fate and effects, with efforts on:

- Predictive modelling of environmental fate,
- Design features for microcosm testing,
- Design features and containment practices for greenhouse testing, and
- Design feature and containment practices for small-scale field tests.

Other areas for possible standards development by E48.04 are criteria for transportation of large quantities of micro-organisms, which may not be adequately covered by federal and state guidelines; performance criteria for measuring levels of inactivation of organisms, since present methodology may not measure such low levels of inactivation to prove that for large amounts of waste; and guidelines for design of containment facilities. (Extracted from ASTM Standardization News, March 1986)

General

Optimistic forecast

A bright future for biotechnology and other high-tech methods for increasing agricultural productivity during the rest of this century is foreseen by the US congressional Office of Technology Assessment (OTA). Biotechnology will spawn new pharmaceuticals, including growth hormones; permit

new genetic traits to be inserted into livestock and poultry; create new species by fusing different animal embryos; genetically modify plants to resist diseases, harsh environments or pesticides; increase nitrogen fixation or nutritional value; and promote propagation by regeneration of intact plants from single cells or tissue explants. But the advances will come at the cost of more than 1 million small and medium-sized farms - already struggling to survive - that will not be able to pay for the new technologies, says OTA. The OTA report predicts that about 50,000 large farms will account for 75 per cent of US agricultural production by the year 2000. Of the 2.2 million US farms now in operation, about 700,000 produce approximately 80 per cent of the food supply. (Source: Chemical Week, 26 March 1986)

Enzymes set for growth

Enzyme sales are set to grow in the US at an average annual rate of 11.4 per cent, with the greatest influence coming from the low volume, high value sectors. US sales of enzymes amounted to $105.9 million in 1985 and will reach $310 million by 1995. However, this aggregate figure hides important developments in the fast-changing enzymes business. Traditionally, the market has been dominated by the low price, high volume, bulk chemical manufacture by enzymes, but with recent cuts in oil prices and slack markets for chemicals produced by more established methods, Business Communications Company predicts that the value of the enzymes in this segment will only grow at an annual rate of 4.1 per cent to $6.4 million by 1995.

In this high volume category fastest growth will be exhibited by laundry detergents and environmental clean-up products at an annual rate of 9.8 per cent to $56.5 million by 1995.

Advances in gene-splicing methods will be responsible for moving the commercial market away from bulk chemical manufacture towards low volume, high value speciality and biomedical enzymes. Growth in this sector is expected at an annual rate of 23.4 per cent for the next decade. BCC projects that this segment will account for more than 43 per cent of total US sales in the enzyme market by 1995.

US enzymes markets ($m)

Low volume enzymes

	1984	1985	1990	1995	Average annual growth rate (per cent)
Biomedical	10.0	13.5	64.9	130.1	25.4
Speciality	2.5	2.6	3.0	3.5	3.4
Total	12.5	16.1	67.9	133.6	23.4

High volume enzymes

Food/detergents	60.0	63.3	85.3	114.0	6.1
Bulk chemical	4.1	4.3	5.2	6.4	4.1
Others	20.4	22.2	35.0	56.5	9.8
Total	84.5	89.8	125.5	176.9	7.0

(Source: European Chemical News, 21 April 1986)

Calgene files initial public offering of shares

Calgene, Inc. of Davis, California, announced that it has filed a registration statement with the Securities and Exchange Commission covering a proposed initial public offering of 1,750,000 shares of common stock through an underwriting group co-managed by PaineWebber Incorporated, Hambrecht & Quist Incorporated and Piper, Jaffray & Hopwood Incorporated. It is currently anticipated that the initial offering price for the shares will be between $13 and $16 per share.

Proceeds from the proposed offering will be used primarily for research and development programmes, facility expansion and improvements, field development programmes, joint venture arrangements and general working capital purposes.

Calgene is a leading company in the application of recombinant DNA technology to plants and currently has product development programmes in four areas: specialty plant oils, agronomically superior crops, processed plant products and forestry. (Source: Company News Release, 23 May 1986)

Celltech and Cyanamid in anti-cancer link

Celltech and American Cyanamid are to collaborate in a two-year, $7.6 million research project to develop a new generation of anti-cancer agents.

Using recombinant DNA techniques, the partners plan to make new tumour-targeted agents based on the highly specific binding portions of monoclonal antibodies.

Imaging agents for the prognosis and diagnosis of cancer will probably be ready for the market by 1990, once tumour-specific MAbs have been isolated. Therapeutic agents, including toxins, current anti-cancer treatments and radionuclides, will also be attached to the antibodies to provide a complementary regimen.

Such an approach will cut the need for speculative chemotherapy by improving prognosis. The high specificity of these anti-cancer conjugates means that toxicological data on many drugs can be reassessed as smaller amounts of the agents can be used to maintain clinically therapeutic levels.

Colon, stomach and breast cancers, all tumours that are difficult to treat with conventional chemotherapy, will be the targets for the new drugs.

Celltech had been in discussions with many other drug companies including all the major UK firms and concerns based in the US and Japan.

Though Cyanamid has all the rights to use the Celltech technology for anti-cancer drugs, the process has the potential to be adapted for other therapies including infectious diseases difficult to treat with antibiotics.

Celltech plans to use genetic engineering to shave off the surplus parts of the antibody to create the second generation MAbs. Smaller and more reproducible binding fragments will be contained that will raise both the speed of access to specific tumour sites and cut the patient's immune response to the foreign protein.

Attached to the engineered MAb fragment will be two other molecules: a carrier molecule which holds the imaging or therapeutic agents, and a linker molecule connecting the MAb to carrier. Celltech has filed a number of patent applications for the technology though none have been issued. (Extracted from European Chemical News, 28 April 1986)

Biotechnology leads the parade of new CPI technology

Biotechnology			
Product	**Process**	**Features**	**Status and remarks**
Fertilizer	Continuous culturing of a bacterium that captures nitrogen from the air and makes it available to the roots of leguminous plants	A culture medium containing the bacterium Rhizobium japonicum, glycerol, yeast extract, and various nutrients is fed at 28-30°C into a fermenter, at a rate depending upon the bacterium's optimum growth period - 70 to 100 hours. The bacterium is injected into peat that has been sterilized by microwaves or other methods.	Developed by the Technological Research Institute (Sao Paulo). Brazil's Special Secretariat for Biotechnology is negotiating with several firms to build a commercial plant this year.
Globin	Hydrolysis of hemoglobin	Alcalase enzyme is added to hemoglobin, and the mixture is aerated. The enzyme hydrolyzes the hemoglobin, separating heme from globin. The globin is then removed by centrifuge or membrane filtration, and converted into a non-bitter, water-soluble liquid, powder, or flake usable as a high-protein food additive. The by-product is oxidized to make hemin, a crystalline salt used for anti-anaemia drugs.	Commercialized by Hungary's Central Food Research Institute (Budapest). A plant is producing 3 to 4 m.t./a of globin.
Hydrolized lactose	Conversion of whey by immobilized lactase	Whey permeate solution is converted by lactase enzyme fixed to a bone charcoal support.	British Charcoals & Macdonalds (Greenock, Scotland) offers a packaged system that can operate 24 h/d. A 2-column reactor can hydrolize 15-20 tons/h of whey permeate, at a cost of 0.5 cent/lb. Price: $75,000 - $105,000.
β-lactamase protein (a treatment for penicillin allergy)	Genetic engineering	A genetic element and a host bacteria cell for the protein β-lactamase, introduced into Escherichia coli, cause the bacterium to excrete the protein into the fermenter broth in a bioreactor, where it is easily recovered and purified. (Normally, E. coli retains proteins it produces within itself, and has to be broken down and put through complicated purification steps involving 80 per cent of the total manufacturing cost.)	Developed by researchers at Cornell University's departments of chemical engineering and biochemistry (Ithaca, N.Y.).
Ligninase enzyme	Biochemical breakdown of biomass	A patented strain of the micro-organism Phanerochaete chrysosporium breaks down lignin up to 100 times faster and with a yield 30 times greater than previous strains. Efficiency has been improved by adding equal weights of hydrogen peroxide and substrate during the degradation process. The enzyme itself generates H_2O_2 when it attacks the lignin.	Developed at the Institut National de la Recherche Agronomique (Paris). A 30-litre fermentation unit is due to come onstream this year.

Product	Process	Features	Status and remarks
Biotechnology			
Livestock feed (from agricultural by-products)	Degradation of cellulose	Soaking agricultural residue for about six hours in a 1 per cent (vol) solution of hydrogen peroxide (adjusted to a pH of 11.5 by addition of a little sodium hydroxide) dissolves phenolic material in the lignin that limits its digestibility by ruminant livestock. The phenolics are removed by washing with fresh water.	Developed and patented by the U.S. Dept. of Agriculture's Northern Research Center (Peoria, Ill.), the process has been licensed to several firms.
Methane-rich gas	Anaerobic fermentation of crushed fruit pulp	Nearly 80 per cent of waste pulp - e.g., pomace from production of apple juice - can be converted into a 60 per cent methane gas with an energy value of $10-$30 per wet ton of pomace. The dried, nonacidic, odourless residue can be spread on orchards as fertilizer. The process, which can be run in either batch or continuous mode, uses only 5 per cent of the methane for heating.	Invented and pilot-tested at Cornell University (Ithaca, N.Y.)
Unsaturated wax	Biochemical conversion of tall fatty acid	Euglena, a single-cell green alga, is cultivated for three days on a glucose-peptone medium at 28°C. Then tall fatty acid, composed 60 per cent of oleic acid and 40 per cent of linoleic acid, is added. After a week of anaerobic cultivation at a pH of 6.5, the alga's cell density reaches about 20 g/L, providing a wax yield of 10 g/L. In laboratory tests, the wax is recovered with chloroform as a solvent. At commercial scale, a bio method may be developed to cause the alga to release the wax; drying and pressure filtration would follow.	Developed by Harima Chemicals, Inc. (Osaka).
Vitamin C	Fermentation of D-glucose by genetically modified bacteria	Erwinia herbicola bacteria modified by insertion of a gene isolated from a species of Corynebacterium ferment D-glucose in only one step, instead of the four needed by the older (Reichstein-Grussner) process, to the immediate precursor of ascorbic acid (Vitamin C).	Lubrizol Enterprises sponsored development of the process at Genentech. Pfizer will be the first to use it commercially; a joint venture of Lubrizol and Genentech may also build a production plant.
Pollution control			
PCP removal from soil	Microbial digestion	Soil contaminated with pentachlorophenol (PCP) is excavated and placed in a digester with caustic and water. The slurry, with a pH of 12, is then heated to 180°F and agitated for 24 hours, effectively stripping the oil-laden PCP from the soil. Cooled to ambient temperature, the slurry is inoculated with a form of Arthrobacter bacteria, allowed to sit for 48 hours, and dewatered. PCP and related polyaromatic hydrocarbons are reduced from around 500 to less than 1 ppm. Cost is $140-$180/ton.	Developed by Bio-Clean, Inc. (Bloomington, Minn.).

(Extracted from Chemical Engineering, 17 February 1986)

B. COUNTRY NEWS

Australia

Biotechnology firm set up

Monoclonal Australia is to be floated on Australian stock exchanges for Aus$2.5 m ($1.8 m). The specialist biotechnology firm is also to assume the research and development function of Australian Monoclonal Development.

AMD will now focus on production and marketing of monoclonal antibody test kits and therapeutics but will own two-thirds of the new research concern. The company is currently Australia's leading biotechnology concern with five products on the medical and veterinary markets. (Source: European Chemical News, 26 May 1986)

Contract to engineer waste degrading bacteria

ICI Australia has awarded a two-year Aus$100,000 research contract to Melbourne's Monash University to engineer waste degrading bacteria. The Pseudomonas microbe will be required to feed on chlorinated hydrocarbons now kept in concrete tanks at an ICI plant in Sydney.

The by-product from the manufacture of dry cleaning and degreasing solvents, such wastes have been disposed of by high temperature incineration in the past but this technology is no longer available in Australia. (Source: European Chemical News, 26 May 1986.

Belgium

US/Belgian biotechnology firm formed

US and Belgian partners have established Phytotec, a plant biotechnology company. The venture represents a foothold in the European market for the Salt Lake City, Utah-based biotechnology concern Native Plants Inc. which will supply the new firm with technology.

NPI is to have a $3.5 million stake in the new Belgian firm which is planned to have a total capitalization of $10 million. The balance is to be met by Société Européene de Semences, with a $3.5 million stake; Vista Ventures, a venture capital firm, with $1 million, and CDAB a biotechnology holding created in 1981 by the Walloon region. The regional government has already pledged $7 million in research contracts.

Phytotec will concentrate on producing new variations of horticultural crops, vegetables and flowers, and will use the existing facilities of Biogral, a small Belgian tissue culture operation owned by SES. The company is hoping to have its own facilities by the end of the year.

This deal represents NPI's third joint venture to capture market influence outside the US. Plantek in Singapore and Bioplants in Brazil are NPI's two other subsidiaries and though the US firm has no plans for further acquisitions it is interested in penetrating the Chinese market. (Source: European Chemical News, 28 April 1986)

Benelux biotechnology expands

Through its Brussels-based subsidiary, Compagnie de Participations et Développement Industriel (COPADI), Lafarge Coppée in collaboration with the Credit Agricole group has acquired a BF 60 million ($1.34 million), 4 per cent stake in the Belgian firm Compagnie de Développement des Agroindustries et des Biotechnologies (CDAB).

COPADI's acquisition marks the start of a push into a third area of biotechnology for the parent company. The firm is currently considering future investment in one of CDAB's subsidiaries, Ire-medgenix, as part of its push into medical diagnostics markets.

CDAB, through its subsidiaries Ire-medgenix and Ire-celltarg, specializes in medical diagnoses and therapies, while the recent affiliate Phytotec is active in plant biotechnology. In the past two years Lafarge Coppée has concentrated its acquisition efforts in the US, taking over five firms. Now the company is turning its attention to the developing Benelux market. (Source: European Chemical News, 12 May 1986)

Belgian firm plans ice-bug

A Belgian biotechnology firm, Plant Genetic Systems, is considering a plan to introduce Frostban into the European market. Developed by Advanced Genetic Science to prevent frost from forming on plants, the gene-spliced microbe has been the focus of a campaign to stop the release of such organisms into the environment.

Plant Genetic Systems, under contract from the US agrochemicals giant Rhom & Haus, hopes to field test a gene-spliced insecticide against lepidoptera larvae. Researchers at the firm have recently revealed the successful expression of a microbial toxin in the leaves of tobacco plants.

By using Agrobacterium tumefaciens as the vector for transfer, the firm is also hoping that the gene for the toxic protein can be inserted into other economically important crops. Moreover, the firm has found that different strains of the microbe, Bacillus thuringiensis, can produce a toxin against beetles.

Plant Genetics Systems (PGS), established in 1982, is the only genetic engineering company in Belgium with a direct and continuous relationship with university laboratories. This collaborative arrangement provides the company with the scientific basis for its industrially applicable technologies.

PGS applies its technology primarily to agriculture, the food and feed industries, and the food and fish processing industries. PGS was established as a joint venture with funds supplied by three companies in Belgium and one in Sweden. Their Scientific Board includes some of the world's leading specialists in the fields of molecular biology, biochemistry, plants and soil bacteria. Professor Marc van Montagu is the Scientific Director and is also Professor at the University of Ghent and at the University of Brussels. He is a member of the management group.

The laboratories of PGS are located in facilities rented from the University of Ghent. Almost $2 million was spent to build new laboratories and to provide advanced scientific equipment. The company has opened a second laboratory at the University of Brussels; it houses the molecular graphics activities of the Protein Engineering Program of PGS. At present, PGS has 60 employees, including 14 Ph.D. scientists, with expansion anticipated in the near future.

The research and development activities of the PGS laboratories are centred around three major themes: genetic engineering of plants, soil microbiology, and genetic engineering.

Because of the close association with the research activities at the Laboratory of Genetics at the University of Ghent (Professors J. Schell and M. van Montagu), PGS is particularly well suited to

tackle the challenging field of plant genetic engineering. The Laboratory of Genetics has developed efficient gene vector systems for plants which allow the transfer and expression of genes into plant cells and the regeneration of the engineered plant cells into normal and fertile plants. These systems are based on an adaptation of the Ti plasmid of Agrobacterium tumefaciens.

The current objectives of the plant genetic engineering programme are to construct:

- Insect resistant plants producing proteins which are toxic to insects; for example, the Bacillus thuringiensis endotoxins;
- Leguminous plants with higher nutritional value through the expression in the seeds of high sulphur-containing storage proteins;
- Virus resistant plants which produce antiviral agents that block the proliferation of viruses.

In 1985 PGS announced the successful engineering of plants for insect resistance. The present activities involve the construction of tissue-specific expression vectors in order to limit the synthesis of the new compounds to either the roots, the leaves, the fruits, or the seeds of the engineered plants.

Besides development of improved vectors, the research is centred around the identification of the plant genes which give advantageous properties to particular cultivars, such as growth in adverse conditions, better plant development, disease resistance, and improved nutritional value. Although the strategies vary from case to case, the approaches are based on the capacity to tag chromosomes and plant-movable DNA elements with antibiotic resistance genes by means of the T-DNA vector system.

A third focus of activity is aimed at introducing and expressing in plant cells specific bacterial genes which may influence plant cell development. It has been shown that this approach can be important for the improvement of the regenerative capacity of some plant species by altering the level and composition of secondary metabolites in plants. PGS believes that this activity will lead to the commercialization of new classes of highly valuable secondary metabolites from medicinal plants.

It is now well documented that a variety of soil micro-organisms play an important and beneficial role in plant growth. In particular, it has been shown that certain bacteria isolated from the rhizosphere (hence called rhizobacteria) are beneficial because they colonize the plant roots and protect them from the invasive proliferation of minor pathogenic micro-organisms.

Because of their previous experience with the genetic engineering of Agrobacterium and Rhizobium strains, the PGS scientists have acquired the expertise to transfer new genes into gram-negative bacteria. Recently, this expertise has been extended to gram-positive organisms for which novel multicopy cloning and expression vectors are presently being developed as well as methods for plasmid conjugation and mobilization between different types of gram-positive bacteria.

One of the main objectives of the research programme is the identification of efficient root colonisation bacteria which would be engineered genetically and used as vehicles for the engineering of genes that determine properties beneficial for plant growth. In this programme the identity and properties of the major groups of bacteria which colonise the ecto- and endorhizosphere of some major crops are being evaluated. The extent of seasonal and geographical variation is monitored. Among the efficient colonizers, those which are most accessible to gene transfer manipulation are being examined in most detail.

A second programme involves the isolation and characterization of bacteria which produce antifungal compounds that inhibit the growth of major plant pathogenic fungi; the aim is to develop systems for controlling fungal diseases in major crop plants. In certain cases it has been shown that this antifungal activity is due to the synthesis and release of small molecular weight compounds. Progress has been made in identifying and transferring to the appropriate rhizobacteria the genes which are involved in the biosynthesis of these antifungal compounds. Study of the molecular basis for the beneficial action of some plant growth-stimulating rhizobacteria is likely to identify a further set of genes which can be transferred to efficient plant colonizers.

The protein engineering activities aim at the modification of industrially important enzymes so as to improve their catalytic properties and to optimize their use in industrial processes. In the long run, the goal is to exploit this knowledge to design novel enzymes tailored to catalyze reactions that now can only be performed chemically. Such modified enzymes will have very large industrial applications in the food and feed industry, the food and feed processing industry and the chemical industry.

Protein engineering requires a complex, multidisciplinary approach involving several scientific disciplines and techniques. PGS has taken a double initiative in this rapidly developing field of genetic engineering techniques. The company has opened a second laboratory at the University of Brussels, establishing a unit of molecular modelling. The laboratory houses a powerful computer facility composed of a 32-bit minicomputer, a PS 300 colour graphic system from Evans and Sutherland, and a raster graphics system. The research team is headed by Dr. S. Wodak of the University of Brussels.

PGS is presently executing two important industrial projects in protein engineering and has also established a research programme and budget for protein engineering. This programme covers all technical and scientific aspects of the integrated approach to protein engineering; it also co-ordinates some of the most important laboratories in Europe in this field. Participating laboratories are listed in the following table.

Laboratories participating in Plant Genetic Systems' research programme for protein engineering

- Molecular Modelling Laboratory (Dr. S. Wodak), PGS and University of Brussels, Belgium.
- Nuclear Magnetic Resources Laboratory (Professors Jeener and Reissi), University of Brussels, Belgium.
- Laboratory Biological Dynamics (Dr. Y. Engelborghs), University of Leuven, Belgium.
- Laboratory of Micro-colorimetry (Professor Jaenicke), University of Regensburg, West Germany.
- Laboratory of X-ray Diffraction (Professor J. Janin), University of Paris, Orsay-Lure, France.
- Laboratory of Enzyme Technology (Professor D. Thomas), University of Technology of Compiegne, France.
- Laboratory of NMR Analysis (Professor K. Wüthrich), Swiss Federal Institute of Technology, Zürich, Switzerland.
- Plant Genetics Systems (Professors M. Zabeau, M. van Montagu), Ghent, Belgium.

(Source: European Chemical News, 5 May 1986 and European Science News, May 1986)

Brazil

Biotechnology Association

Eight Brazilian companies with biotechnological interests have formed an industry association, Associação Brasileira das Empresas de Biotechnologia. During 1986 and 1987 the group will develop a national policy for biotechnology, technology interchanges and the development of a specialized labour force. Last year the Government established a secretariat for biotechnology. (Source: Chemical Week, 28 May 1986)

Co-operation agreement with Argentina

Brazil will jointly develop vaccines and reagents for use in medicine and agriculture with Argentina. This is part of a technological co-operation agreement between Brazilian and Argentinian firms for the implementation of industrial products in biotechnology. (Source: SCRIP, 14 April 1986)

Canada

Atlantic Institute of Biotechnology officially opens

A $5.4 million research institute designed to focus the abilities of scientists from Atlantic province universities and research institutes on problems faced by industry, was officially opened recently by Supply and Services Minister, Stewart McInnes.

The Atlantic Institute of Biotechnology (AIB) at Halifax, Nova Scotia, is an independent research organization jointly sponsored by Dalhousie University, Technical University of Nova Scotia, Nova Scotia Research Foundation Corporation and the Nova Scotia Agricultural College. The Department of Regional Industrial Expansion has funded the AIB in the amount of $2.48 million over a five year period.

According to AIB Executive Director, Dr. R. G. S. Bidwell, one of the first steps will be to address what he considers an awareness problem. "Many firms are simply unaware of the enormous advantages possible through biotechnology," he said. "We encourage business people to approach us with their industrial problems or ask us for an assessment of what possibilities may be present."

The AIB, which has been in operation for six months, is already carrying out $750,000 worth of research projects ranging from cloning nursery plants, to converting potato waste to alcohol and designing computer controlled chicken coops.

According to David Leckie, Chairman of the AIB Board of Directors and Vice-Chairman of the Board of Cobi Foods, Canadian companies are going to have to be more resourceful. Leckie, who was part of a trade mission to Japan, organized by the Department of Regional Industrial Expansion and External Affairs, said that the Japanese are masters at using biotechnology to turn problems into opportunities. "Even the dust created as a byproduct in grain processing is used to make pharmaceuticals. The AIB is our way of starting that kind of thinking here," he said.

Bidwell stressed that the AIB is in business to work with and for industry and to contribute to the region's economic growth. "Research done at the AIB will not be done for the sake of science but for the sake of industry," he said.

Immediate applications for biotechnology, Bidwell said, can be readily identified in agriculture and food processing, forest technology, aquaculture and other fishery enterprises, fermentation technology and mining. (Source: News Release, June 1986)

Canada approves alpha interferon

Canada has granted Schering Canada approval to market its alpha-2 interferon. Genetically derived, the lymphokine product, developed and produced by the US-based parent Schering-Plough Corp., has been approved by the Health Protection Branch of Health and Welfare Canada for the treatment of hairy cell leukaemia.

Under licence from Biogen, Intron A, has been used to treat more than 4,000 patients for a wide range of cancer and viral diseases. In addition to Canada, which Schering sees as a major market, the product has been approved in seven other nations including Belgium, Eire, Luxembourg and the UK. (Source: European Chemical News, 12 May 1986)

Cuba

Cuban biotechnology: interferon as a model

The Centre for Biological Research (CIB) at Havana is a visible embodiment of Cuba's decision to make biotechnology development a number one national priority. Organized much like genetic engineering companies in the United States, the Centre has laboratories for in vitro gene manipulations, DNA sequencing, enzyme purification, oligonucleotide and peptide syntheses, and monoclonal antibodies, as well as a computer facility. Approximately half of the institute is given over to the production of mixed-alpha interferons from human leucocytes. Opened in January of 1982, CIB took just six months to build, and was providing leucocyte interferon for initial toxicity and clinical trials almost immediately after opening. Presently the interferon production laboratories process enough buffy coat to produce 2-4 mg per day.

The remarkable extent to which the interferon model has been successful was clear from papers presented at the Second Cuban Seminar on Interferon and First Cuban Seminar on Biotechnology held in February. Approximately 1,000 delegates from 40 countries heard researchers report the results of clinical studies on over 2,500 patients with a variety of viral and neoplastic diseases.

In the main, Cuban clinicians have been finding the same things as workers in other parts of the world. Interferon appears to be most efficacious in the treatment of hairy cell leukaemias, while its effectiveness in other leukaemias, myelomas, and sarcomas remains to be determined. One area where the Cubans are finding substantial use for their leucocyte interferon is in the treatment of papilloma virus-associated diseases. Both plantar warts and laryngeal papylomatosis are now routinely treated with interferon preparations formulated by mediCuba (a division of the Ministry of Health).

Interferon treatment of other viral diseases, such as hepatitis and a range of herpetic infections, is also the subject of investigation, with encouraging if preliminary results being reported. Significantly, the Cubans are experimenting with combined interferon therapies, which represent the most promising trend in the clinical use of these proteins.

Scientists at CIB plan to be well prepared for interferon-combined therapeutic régimes. In July of this year, researchers from the Centre moved into a new 75,000-square-metre complex, with units devoted to vaccine development, fermentation and cell

culture, energy and biomass utilization, food production, genetics and plant biotechnology. The present building will then become a lymphokine research establishment.

Extension of the interferon model into other areas of biotechnology is apparent from the range of projects actively being pursued at CIB. For example, because of the trade embargo, materials the Cubans are anxious to purchase from the United States, such as automated DNA synthesizers and restriction enzymes, are unavailable. Consequently, they have developed their own procedures. Victor Jimenez, who directs the synthesis laboratory, is able to produce two 25-mers per day using a phosphotriester protocol that has only a 10-minute cycle time and a five-minute condensation step. He has recently completed the synthesis of a 100-base-pair fragment representing the pre-S region of the hepatitis B surface antigen. Tandem constructions are being put into yeast expression systems for the production of candidate vaccines.

A variety of restriction and other enzymes are purified in a laboratory directed by Omar Saavedra. He has trained a small group of secondary-school and university-educated young people to produce sufficient quantities of XbaI, SalI, BamHI, AluI, HindIII, NaeIII, EcoRI, and Klenow polymerase to supply CIB needs as well as meet the requirements of scientists at other research institutions. The repertoire of in-house enzymes will soon be enlarged to include reverse transcriptase and deoxynucleotidyl transferase.

There is one area in which the Cubans are undertaking completely novel research. They are attempting to develop an effective vaccine against Clostridium hemolyticum, the causative agent of bovine bacillary haemoglobinuria. The approach of L. Howe and his group has been to clone and express the toxin gene of the organism, which produces a 60 Kd protein essential to the invasive process, and to modify it so that it retains immunogenicity but is no longer toxic. Protection studies with the first of these engineered proteins are about to begin. (Extracted from Bio/Technology, Vol. 4, April 1986)

European Economic Community

EEC plans biotechnology R&D to boost agro-industry

Brussels is planning a programme of biotechnology pilot projects to stimulate the agro-industrial sector. The programme will involve launching a series of demonstration projects to be conducted jointly by the scientific, industrial and agricultural sectors within the Community on a cost-sharing basis.

Possible pilot projects include greenhouse and field trails of candidate crops at the research stage and trials of new biotechnology-based processes for adding value to agricultural and animal products. Manufacture of industrial sugars and starches is at the heart of plans as well as production of alternative chemicals.

The aim of the scheme is to have biotechnology contribute to a greater differentiation of the quality of products of all fields, in response to industry's requirements. The Commission statement is now to be considered by both the Council and the European Parliament before a fuller, more precise, programme is proposed for the new R&D plans. Brussels is planning to seek advice from all interested sectors.

Brussels' plans have already received some support from the chemical industry. At a recent meeting between the Commission and representatives from both the agricultural and food industries the plans received favourable comment. Brussels is proposing to present firmer plans for projects later this year. (Source: European Chemical News, 28 April 1986)

Brussels reveals biotechnology success

Brussels has revealed the findings of the first Community biotechnology research programme launched in 1982. The scheme has established a transnational research network involving 103 laboratories.

That plant genetic engineering, sponsored by the EEC, can now be used to transfer foreign genes into onions, asparagus and daffodils is one of the highlights of the programme, according to Brussels. Moreover, researchers have identified 20 cultivated plant genes responsible for economically important properties.

Biotechnology is one of the fields to be covered in a planned co-operation deal between Brussels and Australia. The two communities have identified a need to establish joint programmes also covering medical research, minerals technology and environmental protection. (Source: European Chemical News, 5 May 1986)

EEC asked to formulate uniform biotechnology safety guidelines

The chemical industry unions of the countries of the EEC are demanding that employee interests be taken into consideration in the biotechnology research programme which is being supported by the Community.

On the occasion of a consultation with representatives of the EEC in Brussels, the chairman of the Chemical Industry Labour Union Committee in the EEC, Peter Kripzak, emphasized that biotechnology will give rise to special requirements in health protection, in job site configuration and in the training of employees. He asserted that it is therefore necessary that the EEC expend part of the provided support funds in investigating these questions.

In the opinion of the members of the Chemical Industry Labour Union Committee, biotechnology and genetic engineering will have substantial effects upon the chemical and pharmaceutical industry because with good reason the multinational chemical companies are investing millions in this area. The effects upon the number of jobs and on production methods were still unpredictable, but, as in the case of all new technologies so too in biotechnology and genetic engineering one must reckon with a possible decrease in the number of jobs rather than an increase.

In view of the unions any research subsidy out of public funds must in particular put the small and medium-sized enterprises into such a position that in biotechnology and genetic engineering they are subject to no competitive disadvantages as compared with the giants of the chemical industry. In addition, the EEC was asked to establish uniform safety guidelines for the industrial application of biotechnology within the EEC so that each member of the Community would not burden the industry with diverse regulations which in the end might interfere with the competitive capability of all enterprises. The European chemical unions also demanded that questions in the area of biotechnology and genetic

engineering be in future discussed in three-member consultations among the EEC, employers and labour unions. (Extracted from Chemische Rundschau, 24 January 1986)

Federal Republic of Germany

Financial boost for agricultural sector

The Federal Republic of Germany's Government is planning to spend $460 million on a three-year programme for applied biology and biotechnology in agriculture. The aim is to improve the agricultural sector's performance through biotechnological innovations, including product improvement and the development of new products for new markets. Special emphasis is to be placed on plant cell biology, along with manipulation of micro-organisms and enzymes. (Source: European Chemical News, 12 May 1986)

International training programme in biotechnology

The Gesellschaft für Biotechnologische Forschung (GBF), in Braunschweig, Federal Republic of Germany, with the support of the Bundesministerium für Forschung und Technologie and the State of Lower Saxony, have announced the establishment of an international training programme in biotechnology for scientists from developing countries which will become a permanent feature of GBF's activities.

The overall goal of the international training programme in biotechnology is to provide both theoretical and "hands on" experience to the participants so that they will be better able to contribute directly towards the establishment of practical programmes in biotechnology in their home countries, and to provide local training for more individuals. The programme will offer a series of formal courses in both general and specialized areas of biotechnology, covering both the relevant background knowledge and the theory and practice of advanced techniques of analysis and production. These courses will last from one to two months and be limited to a maximum of 20 students each. They are open to individuals from any developing country who already have strong training in the basic biological or engineering sciences and who hold an advanced university degree, but who lack specific experience in what is known as "modern" biotechnology. Participants will be chosen on the basis of their potential to benefit from the training offered and to contribute to biotechnology programmes in their home countries. GBF will attempt to achieve an equitable geographical distribution among the participants. The courses will be conducted in English. GBF will provide for all expenses incurred by the participants in attending these courses, including travel and living expenses.

In addition to conducting formal courses, the training programme will be able to provide individual research training for a limited number of highly capable postdoctoral and senior scientists from developing countries who will work in designated laboratories at GBF for periods of a year or longer.

The first course to be offered under this programme, introduction to industrial biotechnology, will be held at GBF from 27 April through 5 June 1987. This course will focus on techniques fundamental to industrial biotechnology, including the elements of industrial microbiology, microbial fermentation and downstream processing, including the isolation and characterization of microbial products. Organisms studied will be limited to bacteria and selected fungi (e.g., yeasts) for which there already exists a large body of knowledge and experience. The course will stress the mastery of a broad range of general methods rather than explore highly specific applications. During the latter part of the course the participants will be asked to design and execute their own projects under the general supervision of the GBF teaching staff. The course will include a brief introduction to recombinant DNA methods and some advanced seminars on special topics presented by experts in these areas.

A more detailed description of the programme and application forms are available from the embassies and consulates of the Federal Republic of Germany in all developing countries. Applications for the first course (Spring 1987) must be received at the Gesellschaft für Biotechnologische Forschung in Braunschweig not later than 31 December 1986. (Source: Announcement from GBF)

France

Rhône-Poulenc biotechnology expansion

Rhône-Poulenc is to invest $27 million to expand and regroup its biotechnology research and development base at the Vitry site near Paris. The new facilities will regroup 200 researchers who will concentrate on microbiology, genetic engineering and bioprocessing.

Located at the firm's health sector research centre, the new facilities will provide Rhône-Poulenc with a focus for design of industrial bioprocesses for both human and veterinary products. (Source: European Chemical News, 21 April 1986)

Centre of Immunology, Marseille-Luminy

The Centre of Immunology of Marseille was created following an agreement between the two French governmental research agencies, Institut National de la Santé et de la Recherche Médicale (INSERM) and Centre National de la Recherche Scientifique (CNRS). It was opened in September 1976 and represents the first Institute of Immunology built in France. The centre's two buildings are located on the University campus of Luminy (University of Aix-Marseille II) between Marseille and Cassis on the Mediterranean coast. Dr. C. Mawas is the present director.

The installation in surrounding hospitals of several laboratories associated with the Centre of Immunology has encouraged the development of medical applications. These are: Research Group in the Immunology and Pharmacology of Anti-Cancer Drugs (GRIPAC); Laboratory of Histocompatibility of the Centre for Blood Transfusion; Transplantation Unit of Moelle Osseuse; Laboratory of Genetic Recombination in vitro of Luminy and Immunotech.

The objective of GRIPAC is to develop, in a clinical environment, the study of the pharmokinetics of anticancer drugs using immunoassay techniques developed at the Centre of Immunology and to allow the benefits of fundamental research to be passed on to patients.

Immunotech, an organization for commercial development of INSERM in the sphere of immunology, has been located at Luminy since 1982 and is concerned with the industrial extension of research in immunology and, in particular, with applications of monoclonal antibodies. It is allied with the Centre of Immunology through a scientific and technical assistance arrangement with INSERM.

The general objectives of the research carried out at the Centre of Immunology is the analysis of the mechanisms of immune reaction and integrating cellular, genetic and molecular aspects. Objectives in basic research are combined with objectives for applications of immunology. Programmes in research

on the major histocompatibility complex, the functions of T-cells and immunoglobulins have been greatly influenced by methods developed by molecular genetics and by the use of cloned cells. However, research on cellular functions is also emphasized by most groups. In 1984, two new groups, one involved with the molecular biology of differentiation antigens, the other interested in immunoparasitology, were installed at the Centre of Immunology. (Extracted from European Science News, June 1986)

Hungary

New research centre

A new biotechnology research centre in agricultural services is to be set up by 1987 at Gödöllö, near Budapest. The centre, which will be equipped with the latest technology, will work out various methods for application to agriculture. The research centre at Szeged will, however, remain the centre for basic research in biotechnology.

Hungary has, for the past few years, been successfully applying biotechnology research results to agriculture. Farms have been using protoplast fusional methods for the production of non-viral plants and propagation materials on a large scale. Laboratories of the Martfüles Economic Association, set up by 10 farms and research institutes, turn out material for the propagation of millions of disease-resistant flowers bred from a single cell and for 10-12 thousand tons of non-viral potatoes every year.

The new biotechnology centre at Gödöllö will offer an opportunity for researchers from all parts of the country to use its latest technology for experiments of longer or shorter periods. The centre will also be accessible to experts from abroad.

Research is planned to go along two principal lines covering the development and application of latest molecular methods, biochemical and gene manipulation processes, as well as the study of microbiological systems operated with plant and animal cells and working out agricultural processes to be used.

Four research blocks are to be set up at the centre. The first will study genetic engineering methods for the development of new and more productive plant and animal species. The second will work to increase the capacity of micro-organisms used in agriculture. The third will strive to create new plant hybrids through genetic manipulation, while the fourth will concentrate on the advancement of embryo-transplanting and micro-surgical methods. (Source: Asia-Pacific Tech Monitor, March-April 1986 and Hungarian Exporter, Vol. 36, No. 5, May 1986)

Ireland

Biotechnology incentive

The Irish Government, in association with the National Board of Science and Technology (NBST) and the Industrial Development Authority (IDA), is creating a $10 million fund to support the establishment of four centres of excellence in biotechnology. The centres' areas of emphasis will be immunodiagnostics and mammalian reproduction of cells, food and plant technology, molecular genetics and microbial fermentation. The centres will be based in universities and supported with funds from industry and government and are expected to eventually become self-supporting through contract research.

Under their co-operative R&D Grant Programme, NBST and IDA co-sponsor up to 50 per cent of the cost of co-operative university-industry projects. Their strategic Research Grant Programme supports basic and applied research programmes in academic institutions. In addition, IDA sponsors international programmes aimed at obtaining research contracts for scientists at Irish universities and attracting foreign industry.

The Irish Government offers a variety of tax and other financial incentives to entice new businesses, including a maximum 10 per cent tax on corporate projects up to the year 2000. (Source: European Science News, May 1986)

Israel

New laboratory tool for microbiological research

One of the most basic tools in microbiological research and diagnosis is a small metal or plastic rod with a tiny loop at the end of it. It is used to test an environmental, food or clinical sample for the presence of bacteria, the sample being transferred by means of the loop onto a sterile growth medium, usually agar. The procedure, termed "dilution streaking", has usually been done with a platinum or chromium-nickel loop which has been sterilized in a flame, cooled and dipped into the sample being tested and then transferred to the growth medium. The loop has to be sterilized several times and streaked repeatedly through the agar growth medium in order to dilute the sample to a level that ensures the growth of individual colonies of bacteria. Dilution streaking with a metal loop is time consuming and is somewhat risky since bacteria might be sprayed into the air and inhaled, thereby causing infection. Disposable plastic loops, which are also used, cannot be sterilized so that several loops are needed for each sample.

Two Tel Aviv University researchers, working with a kibbutz-based plastics firm, have developed a greatly improved plastic loop, called the Multi-Loop. This loop is a slender, four-sided rod with a loop at one end and a sphere at the other. By turning the loop 90 degrees at a time, the researcher or technician can use the sphere to perform four streaking operations. One Multi-Loop thus replaces up to four conventional loops. When a specific amount of fluid is needed for the sample, the loop at the other end, which takes up to 10 microlitres at a time, is used.

The new multi-loop has been developed by Dr. Mel Rosenberg, Head of the Oral Microbiological Laboratory at the Sackler Faculty of Medicine's School of Dental Medicine, Tel-Aviv University, and Dr. Ervin Weiss of the Operative Dentistry Section. It will soon be produced commercially by Miniplast Company of Kibbutz Ein Shemer. Patents are pending in Israel, the US, Japan and ten European countries. (Source: European Science News, April 1986)

Japan

Japanese biotechnology spending jumps

Japan's burgeoning biotechnology market could be worth as much as $44.5 billion by the end of the century according to the Japan Economic Institute.

Joint ventures and international markets are likely to play an increasingly prominent role for the Japanese industry, particularly in the light of high development and marketing costs. In addition, the Japanese Government is providing some support with the creation of gene banks and a research data base.

Nevertheless, Japan's industry continues to exhibit weaknesses, the institute warns. Japanese firms may be neglecting bolder experiments and such caution could hold back any progress. To counter this, the institute urges a greater emphasis on basic research. (Source: European Chemical News, 7 April 1986)

Anti-viral monoclonal antibody developed

Teijin, the Japanese fibre producer, has developed an anti-viral monoclonal antibody which attacks the cytomegalovirus that infects patients with cancer and AIDS. Teijin is planning to ask the Ministry of Health and Welfare for permission to start clinical trials and hopes they will begin by next Spring. (Source: European Chemical News, 5 May 1986)

Takeda pushes geriatric drugs

Takeda Chemical Industries is planning to increase supply of drugs to the growing market for geriatrics.

One potential drug could be Avan, expected to reach the market between now and 1988, an improving agent for cerebral metabolism which could cure senile dementia. The Japanese firm is predicting sales of Yen 24 billion, yielding profits of between Yen 17 billion and Yen 19 billion

By the end of next year, Takeda will have an anti-osteoporsis drug on the market. Currently, there are more than 4.3 million sufferers of the disease in Japan alone. In collaboration with Abbott Laboratories, Takeda is also producing an anti-neoplastic agent. (Extracted from European Chemical News, 19 May 1986)

The Netherlands

Emphasis on biotechnology

Increasing emphasis on biotechnology is clearly in evidence in governmental programmes and initiatives in the Netherlands.

The Netherlands Government is taking an active role in stimulating the development of the biotechnology industry and offers tax and other financial incentives to emerging biotechnology companies. These incentives have already led Centocor and Molecular Genetics (US companies) to establish operations in the Netherlands. Other government initiatives include the Biotechnology Research and Feasibility Studies, in which companies can qualify for subsidies of up to 50 per cent of their investments in basic research projects. The Innovation Stimulation Scheme enables firms to apply for subsidization of R&D wage costs. Businesses can obtain government loans to support the development of new products, technologies or services through the technological Development Credits Programme. High-technology grants can total 20 per cent of a firm's investments in fixed assets.

Biotechnology research in the Netherlands emphasizes human and veterinary health care, the food and beverage industry and agricultural applications. Dutch companies active in these fields include Gist Brocades, Heineken and Akzo-Pharm. In addition, the Netherlands Industrial Commission maintains three offices in the US to assist American companies in entering the Dutch market. The biotechnology Innovation Research Programme, a joint effort of the Dutch Government, industry and academia, seeks to promote the application of research projects in academic institutions to aid the Dutch economy. (Source: European Science News, May 1986)

The Netherlands Organization for Applied Scientific Research (TNO)

TNO was established in 1930 with the aim of ensuring that applied scientific research is put at the service of the community in the most efficient manner possible. TNO is a fully independent, non-profit research organization with a staff of about 5,000 and an annual research volume of approximately F 1,560 million ($220 million). In the past year TNO executed some 20,000 contract research and development projects, commissioned by about 6,000 Dutch and foreign clients. TNO's major target group is trade and industry, the small and medium-sized firms in particular. Other important target groups are: central and local authorities, private organizations, and individuals. In some cases, collective research is carried out for specific branches of industry.

TNO's main fields of interest are industrial technology, energy, the environment, food and nutrition, health, and defence. In this connection, TNO's activities can be subdivided into three major categories: explorative research, applied research, and the transfer of know-how. The TNO consists of eight divisions (each with its own special field of research) comprising about 35 institutes:

Biotechnology:

In its research into the possibilities of extending the active life of enzymes, the Division of Technology for Society has achieved some interesting results from the application of amylase derivatives as stabilizing carriers for the immobilization of enzymes. A number of models have been developed for describing the mass transfer processes in immobilized enzymes. These are now being tested experimentally with invertase immobilized on alginate spheres.

Membrane technology:

In support of a project for the enzymatic hydrolysis of paper, studies were carried out to concentrate the dilute glucose solutions thus obtained. The method was one developed and patented by TNO, in which hyperfiltration membranes with both high and low retention are used. After experimental research on model solutions, a computer simulation programme was developed to determine the optimum configuration at minimum energy consumption. Compared with multi-effect evaporation, energy consumption which is lower by a factor of 8 appeared to be possible. The experimental results were in accordance with the theoretical basis.

Recombinant DNA research:

Research in this area is done by a number of institutes. Originally, this work was carried out only in the Medical Biological Laboratory, but now several institutes (the Radiobiological Institute, the Institute for Experimental Gerontology, the Primate Centre, and the Gaubius Institute for Cardiovascular Diseases) have topics in their research programme which require the use of recombinant DNA (rDNA) techniques. A great deal of effort is devoted to the development of vaccines. The Medical Biological Laboratory has cloned so-called "auxiliary proteins" which are of importance for the eventual preparation of a polio vaccine. In collaboration with Biogen, the Primate Centre has tested the first active recombinant DNA hepatitis B vaccine in chimpanzees. The other forms of hepatitis (non A, non B, and delta) are also being studied.

The other DNA research currently being undertaken is primarily concerned with the area of

genotoxicity (damage caused to DNA by environmental factors) and the possibilities of repairing damage to the DNA which has already occurred. In the area of host-vector systems, progress has been made with Aspergillus. This fundamental research is essential in order to achieve the optimum production of rDNA products.

Immunology:

Immunological research is carried out by a number of institutes within the Division for Health Research. The work is aimed at solving both immunological and non-immunological problems using immunological techniques. The wide-ranging nature of this research is illustrated by the number of different applications of monoclonal antibodies (Mabs) in the programme of the various institutes. In the Institute for Experimental Gerontology, Mabs are produced in connection with the early detection of tumours and also for the detection of small quantities of bacterial toxins in food.

In the Primate Centre, Mabs are produced as tracers against certain sub-classes of white blood corpuscles which are a factor in the rejection of foreign tissue. In the Gaubius Institute for Cardiovascular Diseases, Mabs are produced against hormones and apoproteins for use in basic research studies and in assay procedures.

The organ and bone marrow transplant research within the so-called "RLP" group (Radiobiological Institute, Institute for Experimental Gerontology, and Primate Centre) has acquired a considerable reputation in the field of preclinical research (in rhesus monkeys). In this work, Mabs play an important part, both diagnostically and therapeutically. It has been shown that certain Mabs from mice, directed against human tissue determinants, can be used to prevent the impending rejection of a kidney transplant. The immunological research is also carried out in conjunction with genetic research in view of the hereditary transmission of certain tissue characteristics which can predispose a person to disease. In this context, work is being carried out with rhesus monkeys using model systems for rheumatism, multiple sclerosis, and AIDS.

The Central Institute for the Breeding of Laboratory Animals supplies laboratory animals to customers outside TNO (industry, universities and other institutions). The centre also produces special laboratory animals for specific purposes closely linked to the programme of various institutes. In the field of breeding and maintenance of rhesus monkeys and chimpanzees, the TNO Primate Centre occupies a unique position in Europe. There is a clear tendency to concentrate research on non-human primates where the most expertise is available. This means that clients often subcontract their work to the Primate Centre. An isolation building developed by TNO is available for carrying out tests under conditions of strict isolation. In this building, work on primates involving viruses and other potentially dangerous material can be carried out under safe conditions.

Ionizing radiation and cancer:

The Radiobiological Institute's research programme is concerned with the role of ionizing radiation in the genesis and also in the treatment of cancer. Particular attention is paid to the possible effects of regular exposure to relatively small amounts of radiation. Among the methods used are tissue-culture techniques which are extremely useful in investigations into the occurrence of malignant changes in cells after exposure to radiation. Epidemiological data from fundamental research that relates to the occurrence of cancer in humans after exposure to relatively high doses of ionizing radiation are used to calculate the risks of the occurrence of cancer at low doses. (Extracted from European Science News, June 1986)

Saudia Arabia

Blood imports banned

Saudi Arabia has banned imports of blood in an attempt to prevent the spread of AIDS. A campaign to increase local blood donations is now under way. Incentives for donors include exemption from fees for driving licences and a donor found to be suffering from any disease will be given free medical treatment.

Kuwait, meanwhile, is setting up the Middle East's first AIDS research centre following a regional conference on the disease held there last March. (Source: New Scientist, 10 April 1986)

Spain

Centre of Molecular Biology, Canto Blanco (Madrid)

The Molecular Biology Centre is located in Canto Blanco, a suburb of Madrid, on the same campus as the relatively new Autonomous University of Madrid. Although the Centre is affiliated with the university, its primary function is research.

The Centre was organized in 1975 with the aim of providing an interdisciplinary research centre, using a common technical department, material, administrative resources, etc. To form the Centre, three institutes - one from the university and two from the Higher Scientific Research Council - joined with the Section of Developmental Genetics of the Council. They kept their autonomy but also developed collaborative programmes within the Centre and with the university. G. Ramirez is the present Director of the Centre.

A representative governing board oversees the activities of the Centre. This board is the chief governor and executor of the Centre. Members include the Directors of the three Institutes and of the Section of Developmental Genetics, the administrator, four research personnel representatives, and two representatives from the technical department.

The Spanish Government has invested substantial funds in setting up the Centre, as the buildings are modern with well-designed laboratories containing first-class equipment.

A wide range of research projects is being carried out; additional projects emphasizing the use of recombinant DNA methods are being initiated.

Some research projects at the Centre of Molecular Biology are: Metabolic regulation and ageing; Chromosome structure and function; Molecular biology of development in Drosophila; African swine fever (ASF) virus; Regulation phenomena in neural development; Developmental interactions between Schwann cells and peripheral axons; Monoclonal antibodies against developmental neural antigens in Drosophila Melanogaster; Genetics of morphogenesis in Drosophila; Antibiotics and chemotherapeutic agents; Biology of animal virus infection. (Extracted from European Science News, April 1986)

Sweden

Biotechnology venture

As a result of discussions in the past year between Alfa Laval and Pharmacia, the two companies

are to form a biotechnology venture that will supply equipment and systems for industrial scale manufacturing.

The two Swedish firms plan to pool their knowledge of separation technologies and fermentation. The new firm will incorporate Chemap, the Alfa Laval biotechnology centre, and most of Pharmacia's process separation division including an animal cell culture unit. (Source: European Chemical News, 7 April 1986)

United Kingdom

Leukaemia centre

Britain will have the world's first research centre dedicated to investigating the link between leukaemia and retrovirus. A medical charity, the Leukaemia Research Fund, will spend £2 million over the next five years on the centre, which will be built at the University of Glasgow.

The charity also funds two other centres investigating different aspects of work on leukaemia. One examines the epidemiology and the other researches into the cell biology of the disease. The new centre will come under the Department of Veterinary Pathology of the university, led by William Jarrett, who is a world authority on retroviruses.

Studies carried out at Glasgow University have shown that leukaemia in cats is usually associated with infection by a type of virus known as a retrovirus. Another retrovirus has been shown to be the cause of one rare kind of human leukaemia and yet another is known to cause AIDS.

One of the Leukaemia Research Fund's other centres has found that leukaemias occur in geographical clusters and that similar patterns occur in animal leukaemias. The Human Leukaemia Virus Centre, as the new centre at Glasgow is called, will study the causes of these clusters. (Source: New Scientist, 1 May 1986)

Production of monoclonal antibodies agreement

Celltech, Britain's leading biotechnology firm, has signed an agreement with APV International, covering large-scale mammalian cell culture technology.

APV is to offer cell culture systems for the production of monoclonal antibodies and recombinant products based on design licensed from Celltech. The biotechnology company currently operates two 1,000 litre air-lift fermenters installed by APV at its Slough culture-products facility.

The engineering company intends to offer culture systems based on the Celltech set-ups with 100 litre and 1,000 litre capacities. The package will be custom-designed and could include microprocessor control systems and downstream equipment. The company has already quoted on a 100 litre system for Bulgaria, where it operates a joint venture with BioInvest.

The link-up between Celltech and APV comes out of a three-year development effort by the two partners. APV reckons the equipment will help companies overcome the hurdles many firms face in scaling-up biological products for clinical trials and marketing. Celltech has produced over a kilogram of antibody at Slough.

Celltech is also prepared to consider licensing of its process technology, including monoclonal-producing hybridoma. Preliminary discussions have been held with Bulgaria. (Extracted from European Chemical News, 5 May 1986)

Fermentech seeks partners

Fermentech, the UK-based biotechnology company, is seeking partners with products to exploit its technology. The firm has now completed the development of a continuous fermentation process though it requires fine tuning for specific products.

One process already developed is for the production of hyaluronic acid using a Streptococcal strain. The fermentation is capable of running for more than 2,000 hours and produces the same amount of purified hyaluronic acid from 4 litres of broth as 5 kg of rooster combs, the conventional source, would yield.

Interest in the Fermentech technology is most likely to come from companies that are established in extracorporeal immunotherapy and renal dialysis. The firm already has an arrangement with Pharmacia which sells the product for eye surgery applications.

Fermentech is also hoping to find partners for its Protein A product. Sumitomo Corporation is already installed as the exclusive distributors for Protein A, from a Staphylococcus aureus strain, in Japan. The company is also supplying Imre of the US with the protein for clinical trials as well as BioTechnology General (Israel).

Plans are also afoot to develop fermentation processes using recombinant organisms. The programme has yet to be revealed by Fermentech's venture capital parent, Skandigen. (Source: European Chemical News, 26 May 1986)

UK company plans seedling centre in Japan

Twyford Plant Laboratories, the UK plant tissue culture concern, is planning to establish a Japanese seed research institute to be built in 1989 in collaboration with Nissho Iwai, a Tokyo-based trading company. Initially, the partners plan to construct an experimental farm.

Nissho Iwai and TPL have been partners since Autumn 1984 when the Japanese firm became the UK company's Far Eastern agent. The UK company produces seedlings for the Japanese market using its plant tissue culture technology.

Under the proposed deal, both the experimental farm and the new institute will use the UK concern's technology to raise tissue cultures of Japanese orchids and breeding of gerbera and carnation. Using the technology developed by TPL, plants can be obtained within six months, half the time taken for conventional methods. (Source: European Chemical News, 2 June 1986)

United States of America

Biotechnology companies to form insurance company

Representatives of fifteen companies met in February to formulate plans to create a member-owned captive insurance company. The workshop, co-sponsored by the Association of Biotechnology Companies (ABC) and Johnson & Higgins, international insurance brokers, included participants from the United States, Canada, Israel, Japan and the United Kingdom which do business in the United States.

The participants formed an ad hoc working group whose objective is to formulate and implement plans to create a captive insurance company within four or five months. The members of the working group will form the company and decide the types of risks to be

covered, extent of coverage, risk management programmes and the final structure of the insurance company.

The initial focus of the committee's efforts will be to survey the underwriting exposure of the ad hoc participants. From this survey, the insurance programme's specifications for the captive insurance company will be formulated for adoption by the ad hoc group. The scope of the insurance coverage being discussed includes commercial general liability, product liability, liability for clinical trials and directors' and officers' liability. Members will come together to determine which risks they are willing to mutually insure, develop loss prevention programmes to assist participants in reducing insurance risks and exposures, and determine what level of risk the captive will cover and what level of re-insurance will be purchased.

For further information on the ABC's ad hoc insurance working group, contact ABC's General Counsel, Bruce F. Mackler, at ABC's headquarters, 1220 L Street, N.W. Suite 615, Washington, D.C. 20005, 202-842-2229. (Source: GeneWATCH, February/March 1986)

Regulation and academic industry ties

Recent studies of the biotechnology industry reveal two important trends. First, the industry has invested heavily in academic science and may be supporting up to one quarter of the university research in biotechnology. Second, private investment capital in biotechnology has diminished significantly since 1983. Both these trends are important for understanding the current regulatory environment for biotechnology, and the response of the public sector and academic community to controls.

In a study directed by the Centre for Health Policy and Management at Harvard University (published in Science, 17 January 1986) 106 biotechnology firms were interviewed, approximately one-third of which were Fortune 500 firms. The authors of the study estimate that 46 per cent of all biotechnology firms fund university research. They reported that 21 per cent of the non-Fortune 500 companies interviewed funded academic scientists who held "significant equity" in the company. These are the conditions that foster conflicts of interest among university faculty who walk a narrow path between their academic and commercial responsibilities.

The Harvard study also reported that 32 per cent of the interviewed firms provide support to graduate students and post-doctoral candidates. Of these firms, one-third require that "students must work on problems or projects defined by the company, work for the firm during the summer, or work for the company after completing their training".

In another important result, the authors estimate from their data that 41 per cent of the US biotechnology firms with university affiliations have derived at least one trade secret from the work they have funded. This is a clear indication that the protection of proprietary information and the emergence of "limited secrecy" have become normalized behaviour in the current research environment. In this regard, the US Patient and Trademark Office reported that, between 1971-1984, 26 per cent of the patents granted in biotechnology of US origin originated from universities. The combined effect of in-house patenting and externally-negotiated proprietary information agreements has dramatically altered the culture of biological research.

Other studies of the biotechnology industry indicate that there has been a rapid decline in private investments from $849 million in 1983 to $200 million in 1985. According to Science (3 January 1986) the bottoming out of investment capital is having several effects on new biotechnology firms. First, many firms are developing closer alliances with major corporations. In some cases the large companies are either buying biotechnology firms outright or purchasing equity in them. Some of the smaller firms that are running low in venture capital or are having difficulty attracting public investments are limiting the scope of their product activities, giving up the idea that they will produce a significant product or turning toward larger companies for contract research. A firm's road to independence may depend upon its ability to get products to the market before its operating capital is depleted. As a result, the nascent industry is putting considerable pressure on regulators to ease up on controls.

The aggressive efforts of Advanced Genetic Sciences (AGS) of Oakland, Ca. to field test bacteria with the trade name Frostban, genetically modified to inhibit ice-nucleation, is illustrative of the intense competitive environment. Public interest groups have asked EPA to take a slow course of action in evaluating the deliberate release into the environment of genetically modified organisms. These requests have been met with foreboding statements from the industry representatives, expressed through congressional and agency spokespersons, warning that the American lead in biotechnology is being jeopardized by delays in product approval.

Recently, AGS has been cited by EPA for carrying out unauthorized field tests of genetically modified organisms. The permit for field testing has been suspended and AGS has been fined $20,000. EPA has not promulgated generic testing standards for assessing the risks of genetically modified bacteria nor has the agency issued standards of containment for greenhouse tests. Currently, there is a minimum burden of proof for demonstrating that a deliberate release is safe. The fact that the vast majority of molecular geneticists appear to be satisfied with the state of affairs reveals more to us about academic-industry linkages and the intense competitive environment than it does about objective risk assessment. (Source: GeneWATCH, February/March 1986. Article written by Sheldon Krimsky, Ph.D.)

Cetus links on drug delivery

Cetus has signed a joint agreement with Intelligent Medicine to develop and market new drug delivery systems.

The Emeryville, California-based biotechnology concern will have an exclusive worldwide option on certain Intelligent Medicine products. Cetus manufactures proprietary drugs and the generic anti-cancer drugs developed from its joint venture with Ben Venue Laboratories.

Intelligent Medicine, based in Denver, Colorado, has already developed a wearable pump, Intelliject, which can deliver multiple pre-programmed doses of drugs to patients. The partners plan to develop jointly certain other delivery technologies such as packaging systems for drugs. (Source: European Chemical News, 12 May 1986)

Clinical tests

Enzo Biochem is planning to start clinical evaluation of the first gene-spliced test for the identification of gonorrhea. Based on the firm's proprietary non-radioactive DNA probe technology the test will provide physicians with a faster, more specific means of detecting the disease.

Approval for the test will be sought from the US Food and Drug Administration by the company within the year. A test for the herpes virus, based on similar technology, recently received FDA approval. (Source: European Chemical News, 26 May 1986)

US biotechnology firms attract new funds in share issues

Two US biotechnology companies, California Biotechnology and Immunex, are to boost research and development efforts following successful share issues.

California Biotechnology intends to strengthen its R&D commitment. The company plans to expand its Mountain View facilities and concentrate on bringing its products to clinical trials. Currently, the firm has three projects in trials with a further seven poised to enter within the year. It focuses much of its attention on cardiovascular, anti-inflammatory and pulmonary therapies. Three major products are human lung surfactant - used to treat premature infants with respiratory ailments - a trial natriuretic factor - a heart peptide that is both diuretic and a vasodilator - and an epidermal growth factor to stimulate growth of skin and other tissues.

Company scientists recently revealed that they have accomplished the first successful cloning of fibroblast growth factor (FGF). This gene is believed to be critical to the body's ability to heal skin injuries and wounds. Fibroblast growth factors may trigger blood vessel development during wound healing and tumour growth. In addition to helping repair injured skin, inhibitors of FGF could be used to treat tumours.

Immunex Corp. plans to use the newly acquired funds to expand research in its recently initiated joint venture with Eastman Kodak and for the manufacture of lymphokines. The company is poised to conduct a feasibility study for the expansion of its manufacturing facilities.

Immunex has a couple of products approaching clinical trials. In the next few months trials with interleukin-2 are to start with a clinical investigation of colony stimulating factor. (Source: European Chemical News, 14 April 1986)

US chemicals firms invest in biotechnology companies

Two US chemicals firms are continuing to expand their biotechnology interests. Both Eastman Kodak and Du Pont have announced plans to fund research conducted by biotechnology companies.

Kodak and Cytogen have signed an accord to develop monoclonal antibody conjugates for the in vivo diagnostic imaging and treatment of human cancer. By collaborating with Cytogen, Kodak will be strategically positioned to attack the cancer diagnostics and therapies market.

Du Pont is also establishing itself further in the clinical applications biotechnology market. The company has finalized an arrangement with Molecular Biosystems (MBI), the US biomedical outfit. Under the terms of the agreement, Du Pont will receive exclusive marketing rights in Japan, Taiwan and South Korea for MBI's proprietary DNA probe technology. (Extracted from European Chemical News, 26 May 1986)

Molecular Genetics seed firm

Molecular Genetics is forming a new company that will produce and sell corn in the US in collaboration with Terra International, the largest US independent distributor of seeds. The company is also expected to announce the acquisition of a seedcorn firm in Europe some time this year. The deal with Terra is to complement the biotechnology concern's business plan. (Extracted from European Chemical News, 7 April 1986)

AIDS will increase tenfold in the US

America faces a tenfold increase in the number of people suffering from AIDS over the next five years. The threat is causing public health officials in the US to re-organize their attack on the disease. Their attention is shifting to prevention after the release of daunting figures on the disease's spread - 270,000 people will have contracted AIDS and 179,000 will have died of it by 1991 - coupled with pessimism over prospects for an early vaccine or drug treatment.

The Government's Public Health Service will be "refocusing" its goals for the next five years in the light of the latest data. AIDS will become one of the top 10 killers in the US, higher than car accidents, for instance. The medical cost to the nation in 1991 could be $8-$16 billion.

There are now 1 to 1.5 million people in the US infected with the AIDS virus, perhaps 20 per cent of whom will develop AIDS, and all of whom should be considered carriers of the disease.

The new consensus emerged from a meeting of 85 experts on AIDS held in West Virginia. The experts conclude that there must be greater emphasis on counselling those at risk who are not yet infected. (Extracted from New Scientist, 19 June 1986)

AIDS research: New foundation begins work

Support for research into acquired immune deficiency syndrome (AIDS) has received a boost from the American Foundation for AIDS Research (AmFAR). The new foundation disbursed 20 grants totalling $1.1 million, mostly for basic research on the biology of the virus associated with AIDS, with a smaller number for drug development and epidemiology. AmFAR's scientific advisory committee was looking primarily for projects demonstrating "fresh ideas", according to a spokesman for AmFAR.

AmFAR came into existence last September when the AIDS Medical Foundation, based in New York, merged with the National AIDS Research Foundation of Los Angeles. Actress Elizabeth Taylor serves as AmFAR's national chairman, and has been an active force in fund-raising. In future, AmFAR hopes to move its financial base away from special fund-raising events to long-term commitments from corporations and philanthropic foundations. Although the $1.1 million offered by AmFAR is only a small fraction of the $213 million AIDS budget of the US Public Health Service, there is always enthusiasm for a new source of funds. (Source: Nature, Vol. 321, 12 June 1986)

NAS to assess AIDS research and prevention

The National Academy of Sciences and the Institute of Medicine have begun a six-month study to assess national strategies concerning acquired immune deficiency syndrome (AIDS). Funded by a consortium of private foundations, the study aims to identify policies that are most likely to accelerate development of effective research prevention and treatment of the disease. The study will be conducted by two panels. One, headed by David Baltimore of Whitehead Institute and Massachusetts Institute of Technology, will examine whether the current AIDS research effort matches the seriousness of the AIDS problem and whether

appropriate segments of the research community are being recruited into AIDS research. The second panel, chaired by Sheldon M. Wolff of Tufts University School of Medicine and the New England Medical Centre, will look at the epidemiological evidence on AIDS incidence, review the effectiveness and cost of various treatment programmes and assess the merits of public health and education measures for slowing the spread of the disease. (Source: Chemical and Engineering News, 24 March 1986)

Union of Soviet Socialist Republics

New treatment for sewage

The Soviet Union's State Committee for Science and Technology is recommending that a new biological method of treating sewage and industrial waste should be introduced.

A pilot plant treating 2,500 cubic metres of waste water a day is already operating in Makeyevka in the Donetsk region. The plant, designed by the Makeyevka Civil Engineering Institute, comprises a long tank containing water which is kept at boiling point by hot air. Inside the tank are frames with fibreglass threads covered with micro-organisms which behave as a filter. Inlet water contains up to 15 milligrams of impurities per litre. After filtering, the impurities are reduced to 2 milligrams per litre. (Source: New Scientist, 19 June 1986)

C. RESEARCH

Research on human genes

Renin inhibitor may control high blood pressure

Compounds that inhibit the kidney enzyme renin may be effective in controlling high blood pressure. Most renin inhibitors found to date have not been therapeutically effective because they are not absorbed when taken orally or are quickly broken down in the bloodstream. Computer modelling techniques have allowed researchers at Abbott Laboratories to identify much smaller molecules that may be absorbed and will not be broken down so quickly, but still retain the potency of larger inhibitors. The di- and tripeptide analogs are more likely to be pharmacologically useful than any renin inhibitors yet developed.

Renin inhibitors block an earlier stage in the regulation of blood pressure than do existing blood pressure medications. Renin triggers a cascade of enzymic steps that produce angiotensin II, which constricts blood vessels. Captopril and enalapril control blood pressure by blocking angiotensin converting enzyme (ACE), which is involved in some other biochemical processes besides the production of angiotensin II. The existing blood pressure agents have therefore some undesirable side effects. Renin acts only on angiotensinogen, the first step in the production of angiotensin II. Blocking renin's action should therefore have no side effects. (Extracted from Chemical and Engineering News, 5 May 1986)

Malignant melanoma treatment

A monoclonal antibody linked to a toxin can effectively treat malignant melanoma, according to researchers at Xoma. A ricin-linked mouse monoclonal antibody administered to 22 patients with metastatic malignant melanoma achieved objective responses in 10 of 22 patients and stabilized the disease in five others. Side effects included a decline in serum albumin in 20 patients, which in turn was associated with falls in serum protein, weight gain and oedema. Other side effects included malaise, myalgia, fever and loss of appetite. All side effects were dose related and reversible. ES Vitetta of the University of Texas Health Science Center (Dallas) has indicated that treatment with an immunotoxin produces an immune response which in turn reduces tumor size, explaining late responses due to an immune mechanism rather than the initial injected dose. (Extracted from Medical World, 12 May 1986)

Control by maternal genes of embryonic genes

Embryo development is guided by maternal genes for at least the first few hours, until embryonic genes become active. Research by D. Melton of Harvard University into experiments with the frog Xenopus indicate that maternal genes also exert control over the embryonic genes after they have become active. Part of the control is due to differential concentrations of maternal messenger RNA in the embryo.

Among the first genes expressed in the embryo are those that encode for proteins that make up the filaments that give structure to the skin, which is the first organ to differentiate, according to T. Sargent and I. Dawid of the US National Institute for Child Health and Development. Gene expression is not triggered by contact with other cells. The main means of differentiation is apparently the suppression of gene activity.

According to J. B. Gordon of Cambridge University, a gene for muscle protein is activated slightly later than genes for keratin, the gene being turned on only in cells that later become muscle. Only cells in the middle two of four tiers of cells in the 32-cell embryo can become muscle. Only cells in tier three produce a muscle-inducing substance, which diffuses into tier two. (Extracted from Science News, 24 May 1986)

Interleukin-2 used to culture lymphocytes

According to research being carried out by S. Rosenberg of the National Cancer Institute, adoptive immunotherapy would culture lymphocytes in interleukin to turn them into killer cells for cancer treatment. The interleukin-2 used to culture the cells is made with recombinant DNA technology. Lymphocytes treated with IL-2 are able to break down fresh tumor cells in vitro. The lymphokine-activated killer (LAK) cells can even destroy tumor cells that are resistant to natural killer (NK) cells. LAK cells and IL-2 are reinfused into the patient. It is thought that the LAK cells proliferate in vivo under the influence of IL-2. LAK cells disappear when IL-2 administration ends.

IL-2 alone has an antitumor effect, presumably because it produces LAK cells in the body, but to be effective, IL-2 alone must be given in very high doses with unacceptably toxic side effects. The combination therapy of IL-2 and LAK also produces side effects such as chills, fever, malaise, breathing difficulties and abnormal liver function, but 14 of 41 cancer patients have shown regression of advanced cancers with the treatment. Despite the fact that a number of these patients have since relapsed and some have died, researchers are optimistic, because the treatment did cause some improvement in advanced tumors that had not responded to any standard therapy. A major advantage of the new treatment is that LAK cells do not attack normal cells. (Extracted from New Scientist, 8 May 1986)

Chemical cause of Huntington's chorea

The chemical cause of Huntington's chorea has been identified by researchers at Massachusetts

General Hospital. Quinolinic acid, a normal brain cell metabolite, kills neurones containing GABA and substance P but spares neurones containing somatostatin and neuropeptide Y. Other excitotoxins kill the cells indiscriminately. QA does not harm young rats, but causes the effects of Huntington's chorea in only mature animals. The neurones that are spared can apparently metabolise QA quickly. QA is a normal breakdown product of tryptophan, and in normal people it is processed for energy production or synthesis. Somehow, the gene for Huntington's chorea alters the metabolism of tryptophan or quinolinic acid. The gene might affect uptake of the acid by brain cells. The discovery will allow researchers to begin looking for a way to counteract the destruction caused by QA. (Extracted from New Scientist, 2 May 1986)

Research into beta thalassemia gene transplant

A hereditary defect in mice similar to beta thalassemia has been corrected by transplanting the proper gene into reproductive cells, according to work carried out by K. Chada and F. Constantini of Columbia University. A human beta-globin gene was transplanted into the mice. The transplanted gene was active only in red blood cells, where it normally acts, and was expressed at the appropriate time during fetal development and in adult red blood cells (but not in embryonic red blood cells). Regulatory instructions for the gene apparently are located near the gene itself. The transplant is also important because the 'bad' gene for beta thalassemia is still present in the treated mice. Gene transfers into human bone marrow cells are imminent, although it is not certain that the gene will be appropriately expressed in humans. (Extracted from Science News, 24 May 1986)

Bone-marrow transplants

Bones, besides forming skeletons, house the marrow where the key components of blood - red cells, white cells and platelets - are produced. When something is awry with the marrow drastic action is needed, such as a transplant of healthy marrow from somebody else. This has proved easier said than done. Histocompatible marrow transplants - often work well although except when donor and recipient are identical twins total histocompatibility hardly exists. In almost all cases only a partially matched donor is available - a parent, brother or sister, for example - and the transplant may then attack the recipient's tissues to cause a life-threatening disorder known as graft-versus-host disease.

The villains here are the white blood cells known as T cells. When mature, they are responsible for the mismatch between donor and recipient and thus for graft-versus-host disease. But when they begin life in the marrow as "stem cells" they are innocent. So scientists are seeking to eliminate mature T cells from donor marrow while leaving stem cells behind.

One approach that has achieved some success is to treat the graft before the transplant with antibodies that selectively destroy its mature T cells. Cells from multiple myeloma, a kind of cancer, are immortal and so can be made to produce unlimited amounts of monoclonal antibodies by genetic engineering.

So far, however, an alternative technique has resulted in fewer failures. Purified soybean extract reduces the number of mature T cells in the marrow sample that will be given to the patient. The remaining T cells are then exposed to red blood cells from sheep which cause the cells to clump. When the marrow sample is spun in a centrifuge, the clumps become separated from the surrounding stem cells and can be easily removed.

Pioneered by Dr. Yair Reisner, an Israeli scientist, and his colleagues working at the Memorial Sloan-Kettering Cancer Centre in New York City, the soybean approach is already saving lives. At the University of California at San Francisco (UCSF), for example, prior treatment of partially matched donor marrow with soybean extract has enabled seven of nine youngsters born with severe combined immunodeficiency syndrome - which makes even minor infections potentially fatal - to escape severe graft-versus-host disease. Indeed, two three-year-olds had their transplants so long ago (two and three years) that their doctors think they are cured.

Meanwhile, the soybean treatment is also showing promise for other disorders where these transplants offer the best hope of long-term survival. The disorders include leukaemia and other childhood cancers that no longer respond to other measures. (Extracted from The Economist, 26 April 1986)

Recombinant colony-stimulating factor

Saturation of blood cells is under the influence of growth factors. One such factor, the human granulocyte colony-stimulating factor (hG-CSF), is being produced in large amounts by a genetically engineered Escherichia coli bacterium and may soon be available for clinical trials. The hG-CSF gene was cloned by L. Souza and colleagues at Amgen, Thousand Oaks (CA), sequences were deduced for both the gene and the growth factor it produces, and the carbohydrate constituent and the molecular mass of the factor were determined. The purified factor causes bone marrow cells to differentiate into granulocytes and monocytes and induces some leukemic cells to differentiate into more mature cell types. Thus, potential uses of hG-CSF for the regeneration of blood cells include treatment of immunologically compromised patients, those with infections, or those with blood cell disorders like anemia. In addition, hG-CSF may inhibit growth of leukemic cells (such as the myeloid leukemia cells that have surface receptors for this growth factor) by driving the cells to differentiate and die so that they cannot continue unchecked proliferation and self-renewal. (Source: Science, Vol. 232, 4 April 1986)

How cancer cells foil toxic drugs

Cancer patients undergoing chemotherapy treatment through the use of cytotoxic drugs and who respond well in the early days of treatment become insensitive to the drugs later on. Worse still, researchers have found that once malignant cells become insensitive to one drug they become resistant to a whole range of unrelated cytotoxic drugs. For example, tumour cells exposed to certain antibiotics that interfere with the manufacture of DNA can become unresponsive both to the antibiotics and to vinca alkaloids, a group of drugs that prevent cell division. The structure of these chemicals is totally different. The only thing they have in common is that they are all lipid soluble. It is as if the cancer cells have learnt to foil the drugs.

When scientists compared notes at a workshop at the US National Institutes of Health last December, they all had a similar explanation as to why tumours might resist drug treatment. What seems to happen is that resistant cells pump out the drugs as fast as they enter, so the anti-cancer drugs have no chance to damage the malignant cells.

It looks as if this efficient pumping mechanism results from the production of a special membrane protein, which has been called P-glycoprotein - P for permeability. Molecular biologists have found probes for looking at the region of DNA that contains the gene coding for this protein. Resistant tumour cells

often have many copies of this gene in each nucleus, which would amplify the production of P-glycoprotein. The more protein that becomes incorporated into the cell membrane, the more efficiently the cell can pump out the damaging drugs.

Several independent experiments, including some work on human cancer cells, all point to the same fact - that drug resistance in tumour cells can be associated with the over-expression of a gene and the production of multiple copies of the gene.

Recent studies on several human carcinoma cell lines show that the degree of drug resistance can be directly correlated with gene expression and amplification. In the initial stages, when drug resistance begins to build up, there is a parallel increase in the amount of messenger RNA transcribed by the DNA sequence containing the multidrug-resistance gene, but the amount of DNA itself does not increase. Only at higher levels of resistance is the gene amplified, and then the cells begin to produce multiple copies of the DNA sequence. It seems that increasing expression of a previously dormant gene precedes its amplification. Some researchers have found at least two genes associated with drug resistance; others have found as many as five.

Kathleen Scotto and colleagues in New York have found that in Chinese hamster cells that are resistant to many drugs, at least two related genes show differential amplification and altered expression. However, the development of resistance to one drug and resistance to the whole array of drugs, though closely related, are not coupled.

If multiple drug resistance is caused by the production of a protein on the surface of the cell, then it might be possible to make an antibody to inactivate the protein. The membrane would then be unable to pump out the drugs which would remain in the cell and continue to exert their lethal effects. (Source: New Scientist, 15 May 1986)

Human genes for colour vision isolated

The genes that specify the red, blue and green pigments responsible for colour vision in humans have been isolated by researchers at Stanford University. The finding opens the door to direct studies of the three colour vision pigments.

The retina contains two different types of light-sensitive cells, called rods and cones because of their shapes. Both collect light and pass on the information it represents. Cones work in bright light and are sensitive to colour. Rods function in dim light, but are unable to distinguish colours.

The molecules in rods and cones that actually absorb light are called visual pigments. The chromophore in each of the molecules is 11-cis-retinal that is bound to a protein. Pigments from cones come in three types that have absorption maxima that make the cells either blue-, green-, or red-absorbing; the different absorption maxima are at approximately 420 nm, 530 nm, and 560 nm. The cones allow the human eye to distinguish colour. The brain integrates and interprets the signals from them as full-colour vision.

Jeremy Nathans, Darcy Thomas and David S. Hogness of the Stanford medical school biochemistry department have identified and sequenced the genes that encode for the three different cone pigment proteins. The deduced amino acid sequences of the pigments are identical in about 40 per cent of the amino acid units to rhodopsin, the rod pigment whose amino acid sequence had been determined previously. The researchers think that, like rhodopsin, the colour pigment proteins form seven helices and bind retinal by a Schiff base linkage to a lysine on the seventh helix. The differences in absorption spectra could be accounted for by interactions with different neighbouring charged amino acids. Genetic studies the researchers carried out with co-workers from Roswell Park Memorial Institute in Buffalo confirm the hypothesis that colour-blind people have a defect in one or more types of cone pigments. The genes for the red and green pigments are nearly identical in chemical structure and are located next to each other on the X chromosome. The genes for rhodopsin and the blue pigment are on different chromosomes, are less similar both to each other and to the red and green pigments, and may have evolved earlier, the researchers find. (Source: Chemical and Engineering News, 21 April 1986)

Discovery could unlock mystery of Alzheimer's disease

Scientists have found a protein in the brain's of people with Alzheimer's disease that does not appear to exist in normal brains. The protein may prove valuable in diagnosing the disease and may provide better understanding of its cause.

The discovery was made by a research team at Albert Einstein College of Medicine led by Dr. Peter Davies.

Dr. Davies said the discovery had two exciting implications. The first is the possible use of the protein for diagnosis. Better ability to diagnose the disease would be particularly important because there are many other causes of mental deterioration that can be confused with the Alzheimer's process but that can be treated once their cause is clarified. The second major implication is the hope of shedding light on the cause of the disease. The scientists found the protein in nerve cells that had not yet been demonstrably damaged, suggesting that it appeared relatively early in the destructive process. This was a surprise, possibly hinting that the protein was involved in the causative process.

The protein was found in relative abundance in regions of the brain known to be affected in Alzheimer's, including the cerebral cortex, which is vital to mental functioning, and the hippocampus, which is important to memory. Most other brain regions were free of it. The protein was not found in normal persons or in patients with other neurological diseases.

As a diagnostic tool the protein would be most valuable if it could be found in spinal fluid. Almost equally important is to analyze the protein totally as a step toward finding the gene that causes it to be produced. Scientists have speculated that a virus may be a factor in Alzheimer's disease. Discovery of the gene that governs the protein might shed light on this question. Identification of the gene would also help prove whether the new protein is a factor in causing the disease's effects. At present it appears to be unique to the Alzheimer's brain. (Extracted from International Herald Tribune, 26/27 April 1986)

Two new AIDS viruses isolated

Two new AIDS viruses have recently been isolated. Scientists at the Institut Pasteur, in co-operation with a Lisbon team, isolated a new virus with a substantially different genetic composition. Almost simultaneously, Harvard researchers isolated another variant of the AIDS virus. So far it is not known whether the two viruses are the same.

Observers believe the two new viruses could both simplify and complicate the task of finding an AIDS cure. So far, there is no indication whether the new viruses can be detected by those tests already on the market. (Source: European Chemical News, 7 April 1986)

New technique detects AIDS virus

A method for detecting the virus that causes acquired immune deficiency syndrome (AIDS) in cells from infected individuals has been developed by researchers at Cetus Corp. Based on what is known as DNA probe technology, the technique could lead to a routine and inexpensive assay for the AIDS virus.

The method involves amplification of viral nucleic acid sequences by a technique called a polymerase chain reaction (PCR) and rapid detection of the sequences by a technique called oligomer restriction (OR) analysis. Both technologies were developed by Cetus, based in Emeryville, Calif., which has applied for a number of patents on them.

Tests currently being used for identifying individuals who have been infected with AIDS detect antibodies to the virus rather than the virus itself. The meaning of a positive result from such a test, however, is ambiguous because individuals with antibodies may no longer have the virus and individuals with the virus may not exhibit antibodies. Detecting the virus itself is more useful both in terms of AIDS diagnosis and evaluation of various drugs designed to eliminate the virus. Unfortunately, such tests are inherently difficult. In the case of AIDS, they are particularly so because the AIDS virus is often present at extremely low levels.

The AIDS virus is a retrovirus; its genetic material is RNA. When the virus infects a cell, it triggers production of an enzyme called reverse transcriptase that causes the viral RNA to be copied into DNA. It is this DNA, some of which is incorporated into the infected cell's genome and some of which remains unincorporated, that is detected by the Cetus technique.

So far, studies have been done by culturing cells in the presence of AIDS patients' blood and semen. AIDS virus that is present in the samples infects the cells and this infection is detected by the test. Cetus researchers are working to enhance the sensitivity of the test so that the virus can be detected directly in blood samples from patients. If these efforts prove successful, a DNA probe test could be developed for introduction and evaluation in 1987, the company says. (Extracted from Chemical and Engineering News, 21 April 1986)

Antibodies used against core proteins of AIDS virus

Antibodies can be developed against some core proteins of the AIDS virus, according to researchers at the US National Cancer Institute and George Washington University. Antibodies raised against a hormone of the thymus gland were able to block replication of the AIDS virus in human cells *in vitro*. The antibodies to thymosin alpha-1 apparently can also attack the gag protein made by the virus, in which 44-50 per cent of the amino acid residues are identical in two different regions of the hormone and viral protein. Most research is focusing on making antibodies to the envelope proteins, but these change over time. The gag proteins are found in the viral core, and are probably less susceptible to change, making them better suited as a target for vaccine-induced antibodies. (Extracted from Chemical and Engineering News, 26 May 1986)

Mutant virus worries AIDS vaccine researchers

Investigators at the National Cancer Institute in Bethesda, Maryland, have created a mutant AIDS virus that appears unable to kill cultured T4 cells - the cells of the immune system that die when attacked by the normal virus.

Researchers from the laboratory of Robert Gallo have been systematically deleting nucleotide sequences from the genome of the AIDS virus. They have then studied the effects of these deletions on the virus's performance and have shown that the virus cannot reproduce without a gene known as tat. However, deleting tat did not stop the virus from killing T4 cells.

Leaving tat intact, the researchers removed several different pieces of DNA that code for another gene, 3'orf, located on the right end of the viral genome. These deletions did not affect the virus's reproduction or its ability to kill cells. However, when they also removed part of the gene's neighbour, env, they made a virus that replicates itself but does not kill T4 cells.

This mutant virus induced cells in culture to clump together, usually a sign of impending cell death. But the culture did not go on to die. The mutant failed even to kill a cell line that is hypersensitive to the normal AIDS virus.

The deletion removed the signal that tells the env gene when to finish making the virus's outer coat, or envelope.

As a result, the researchers say, the gene apparently continues to "read" some sequences that belong to 3'orf as part of the blueprint for the virus's envelope.

The researchers believe that since it is unlikely that 3'orf is pivotal to the virus's ability to kill cells, the key gene must be env. By changing the size or structure of the envelope protein, Gallo's team speculates, it made the virus noncytopathic, that is it destroyed the virus's ability to kill cells.

Much of the work on a vaccine for AIDS has centered on employing env to create an immune response. If it also turns out to be the culprit in cell death, the researchers warn, its use in a vaccine would warrant extreme caution. (Source: New Scientist, 26 June 1986)

Where is the AIDS virus harboured?

Nobody knows where in the body the AIDS virus is harboured. The virus has been found only rarely in circulating T cells, probably because it kills the cells so quickly. But researchers reason that the virus must be sequestered somewhere. A group of investigators from the University of Vienna and the National Cancer Institute have preliminary evidence that Langerhans cells, which are immune system cells that nestle in the skin, particularly in the epidermis, may serve as a reservoir for the virus. Georg Stingl of the University of Vienna presented that evidence recently at the annual meeting of the Society for Investigative Dermatology.

Langerhans cells are best known for their role in presenting antigens to T cells. They take up a foreign antigen and then present it on their surface to T cells, which then can start responding to the antigen.

Both T cells and Langerhans cells carry the T4 antigen on the cell surface; it is this antigen that the AIDS virus appears to recognise and bind

when it enters T cells. So Stingl, Erwin Tschachler, Veronika Groh, and Klaus Konrad of the University of Vienna and Mica Popovik and Dean Mann of the NCI decided to see if they could find the AIDS virus in Langerhans cells.

Skin biopsies from 25 individuals with AIDS or AIDS-related complex, the syndrome that often precedes full-blown AIDS, showed that five of these people had AIDS viruses in Langerhans cells. The skin, Mann notes, is the largest organ of the body and these biopsies were extremely small - just 4 millimeters. Because they found AIDS virus in these small samples from one-fifth of the patients, "just think of the tremendous virus load these persons have". Since they took only a small skin sample from each patient, the researchers cannot say whether those who had no detectable virus in Langerhans cells actually have infected cells elsewhere in their skin, Stingl points out.

Since the finding is so recent, the investigators can only speculate on what it means. But the prime possibility, says Stingl, is that Langerhans cells are more resistant than T cells to the lethal effects of the AIDS virus, enabling the infected Langerhans cells to serve as a reservoir for the virus. (Source: Science, Vol. 232, p. 1197, 6 June 1986)

Research on plant genes

Rice breeding

The basic techniques for the genetic engineering of rice have been developed in research institutes in Japan. The development is important not only because genetic manipulation has so far been mostly confined to dicotyledonous plants but also because rice is the staple food of half the world's population.

The transfer of genetic material into cereal plants has hitherto been held up because they cannot be infected with the Agrobacterium species which have provided a simple route to the transfer of genes in dicotyledonous plants. But two new developments have given rise to optimism that genetic manipulation of rice will be possible in the near future.

The regeneration of whole rice plants from protoplasts (single rice cells stripped of their cell wall) is one way. Success has been reported by Professor Yasuyuki Yamada's group at the Kyoto University Research Centre for Cell and Tissue Culture. Two industrial laboratories, a joint laboratory run by Mitsubishi Chemical and Mitsubishi Corporation and Mitsui Toatsu's research laboratory have also described regeneration techniques at research meetings. Each group has its own method and it is too early to know which will prove most practical.

Yamada can regenerate tissue from protoplasts by adding calf serum, commonly used in the culture of animal cells, to his medium. From one culture cell line, Yamada has been able to produce calli (undifferentiated tissue) from 10 per cent of protoplasts, many of which formed roots and shoots and developed into whole plants when transferred to regeneration medium. Although other strains produced calli, only one regenerated whole plants and there is evidence that the adult plants, now out in pots and the fields, are not entirely normal. Further work may thus be needed to make the regeneration method for general use.

The Mitsubishi group, led by Dr. K. Shimamoto, appears to have had much broader success. It has successfully regenerated whole plants from protoplasts of five different genotypes, two of them major commercial cultivars. More than 300 plants have now been regenerated, and of these 120 are now growing in paddy fields. They can later be studied in detail for differences from the parent stock.

The innovations behind the Mitsubishi group's success is that, instead of making protoplasts from rice cell lines maintained for a long time in culture, they have induced calli from rice seeds. The protoplasts so produced are "young" and have strong morphogenic potential. In the past, this approach has not been favoured because cells in fresh culture from seed do not divide - overcoming this obstacle is the secret of Shimamoto's method.

The second group of advances, for the transfer of foreign genes into protoplasts, has also very recently been reported, and depends on the observation that protoplasts prepared from cultured callus cells and treated with polyethylene glycol will take up foreign DNA. Dr. Uchimiya's group at the University of Tsukuba has successfully introduced a chimaeric gene containing an antibiotic resistance gene in experiments of this kind. He was not, however, able to regenerate plants from the transformed cells.

With both regeneration and transformation proved possible, the race is now on to produce the first genetically engineered rice plants.

The question remains of what useful application can come from the research. Rice has been intensively improved by breeders for almost a century, while large increases in production can be expected in the poorer countries of Asia simply through extending irrigation. Genetic engineering may be used to make things easier for the conventional breeder. Male sterile lines, valuable in breeding new strains of rice, are hard to produce by ordinary methods but should be easily made by protoplast fusion. One protoplast carrying the cytoplasmic male sterility factor but with its nucleus inactivated can be fused with the desired strain of rice.

In the longer term there are the possibilities of transferring genes from other cereal crops that seem to perform more efficiently, introducing viral resistance genes and altering genes to improve the quality of the seed protein. Again, there are ten wild species of rice which present an almost untapped reserve of genetic variability. Protoplast fusion will make it accessible. (Source: Nature, Vol. 321, 12 June 1986)

Resistance to viral infection

Plants can be genetically given resistance to viral infection, according to researchers at Washington University and Monsanto. Plants gain protection when the gene for a key viral substance is transplanted into the plant's cells. How this works is not known, but laboratory work with tobacco and tomatoes shows that the technique is effective. The same method might be adapted for use with potatoes, green peppers, cucumbers or any vegetable. However, the technique is not yet ready for use in crop plants such as wheat or corn. Genetic engineering can produce disease-resistant plants in six to eight months instead of the five to seven years needed with conventional breeding techniques. Genetic engineering can also provide more predictable results than cross breeding of plants. The artificial genes produced by the researchers were inserted into plant cells using Ti (tumour-inducing) plasmids from Agrobacterium tumefaciens. One possible mechanism whereby the 'vaccine' works to protect the altered plants is that the new gene product binds to binding sites generally used by the attacking virus. (Extracted from New York Times, 6 May 1986)

Novel technique used to insert DNA in plant cells

An intense electrical pulse creates temporary openings in plant cell walls for the insertion of DNA, according to preliminary research at Stanford University. The electroporation process consists of charging plant cells with an electrical pulse of 500 V/sq cm for one millisec. It appears that this pulse charges the lipids so that they develop temporary openings. The foreign DNA is then inserted through the holes. When the cells are removed from the electrical field, the holes reseal. Using electroporation to insert genes that confer resistance to the drug kanamycin, V. Walbot and colleagues of Stanford report that 1-2 per cent of the cells had incorporated the new genes into their chromosomes, vs the 0.1 per cent rate generally obtained when yeast is used as a vector. Stauffer and Pioneer Hi-Bred have also reported successes with the technique. The major hurdle now facing researchers is figuring out a way to regenerate plants out of the transformed protoplasts. (Extracted from Industrial Chemical News, May 1986)

Scientists groom Andean tubers for Ethiopia

After decades of neglect, crops in the Third World are receiving the benefits of modern science. One project that has just reached a crucial stage could help to turn some almost unknown Andean root crops into a suitable crop for the tropical highlands of Ethiopia.

Alan Brunt and his colleagues at the Glasshouse Crops Research Institute near Littlehampton, England, have been tackling virus infections, one of the main constraints to production in the root crops oca, arracacha and ullucus. Disease-free varieties of these crops are now ready for trials in their native High Andes. Eventually they could be planted in Ethiopia and other tropical highlands. The tubers' advantage is that they can survive frost.

When scientists collected stocks of the tubers from Peru and Bolivia, they found that they were riddled with viruses. The plants were stunted, with yellow and misshapen leaves, producing only a fraction of their potential yield. More important, the viruses were of unknown types, and a potential scourge of other crops.

Brunt tries to grow virus-free plants with a technique called meristem-tip culture. This means cutting off a new shoot just as it starts to develop, and growing it in a culture tube until it becomes a new plant. The idea is to catch the plant before it is infected. Between 10 and 70 per cent of plants grown in this way turn out to be free of viruses. Putting a chemical with known antiviral properties into the culture sometimes helps.

This work, Brunt believes, will help to bring the cultivation of Andean tubers into line with the agricultural practices of developed countries.

Brunt says he has been lucky to make so much progress with Andean tubers. Among the plants that could benefit from Brunt's work are sweet potatoes and yams - staple foods for hundreds of millions of people. (Extracted from New Scientist, 24 April 1986)

Scottish forest to host gene experiment

Sixteen months after setting out to gain permission, researchers at the Institute of Virology in Oxford are close to introducing into the environment a genetically manipulated micro-organism. In the first experiment of its sort ever conducted in Britain, an engineered virus will be sprayed over a hundred trees on one-twentieth of a hectare of Forestry Commission land in northern Scotland during the summer.

A team under David Bishop, the institute's director, has introduced a novel piece of DNA, a synthetic oligonucleotide, into a baculovirus which attacks caterpillars of the pine moth Panolis flammea in other parts of the country, and has been disseminated artificially for this purpose in the past. The researchers now plan to release the altered virus in a plantation of the lodgepole pine, where the caterpillars cause heavy damage each season.

The nucleotide sequence inserted into the virus does not code for any new gene products. The sequence acts as a marker to distinguish the engineered virus from other strains, allowing researchers to chart its spread in the environment.

This is unlike the "ice-minus" Pseudomonas strains which the US Environmental Protection Agency has approved, after protracted legal battles, as experimental agents to prevent frost damage to crops.

If the Scottish experiment in monitored release proves successful and safe, there are plans to introduce other new properties into the organism. These include the capacity to produce a toxin, making the virus more virulent to caterpillars than at present. Other scientists may extend the range of hosts that it infects.

A parallel aim is to splice into the virus' genetic make-up a "self-destruct" function designed to ensure that the microbe dies out a month or two after it has done its work. This is necessary because, should anything go awry, billions of virus particles could never be located and destroyed after their release into the environment. (Extracted from New Scientist, 27 March 1986)

Nitrogen fixation

Nitrate leaching is greater from soil in which legumes with nitrogen-fixing bacteria are grown, according to research from BASF. This could have serious effects on plans to insert cereals with nitrogen fixation genes. Moreover, industrial nitrogen manufacture is still more effective than biological synthesis. (Source: European Chemical News, 26 May 1986)

Research on yeast and fungus genes

Molybdenum and nitrogen fixation

After 20 years of painstaking research, inorganic chemists at the Unit of Nitrogen Fixation (UNF) at Sussex University have unravelled the chemistry behind nitrogen fixation. The enzyme nitrogenase converts the nitrogen (N_2) of the atmosphere into essential compounds that are required to make proteins and even DNA. The difficulty that nature overcomes so effortlessly is that N_2 is a very unreactive molecule.

Only a few organisms have the ability to fix nitrogen. Some bacteria such as Azobacter vinelandii, which is free-living, and Rhizobia, which lives in the root nodules of legumes such as peas and beans, can do it. So can blue-green algae. We can do it too - in costly chemical plants that react N_2 and hydrogen (H_2) to form ammonia (the Haber process) according to the equation $N_2 + 3H_2 = 2NH_3$. Curiously the reaction releases heat but it is incredibly slow at ordinary temperatures.

To be economic this reaction requires a temperature of 400°C and a pressure of 200 atmospheres - in other words, a costly input of energy. If a catalyst could be found that would make the reaction work at room temperature and pressure, the benefit to world agriculture and energy resources would be enormous. The obvious place to look for

ideas for designing a catalyst is nitrogenase itself. But even this enzyme needs a large input of chemical energy to make NH_3, although it does it at soil temperatures and does not need a high pressure of N_2 for the job. Nitrogenase gets its hydrogen from water. Deep within the enzyme is an atom of molybdenum and this is where the chemical magic behind nitrogen fixation lies. The chemists of the UNF have now exposed nature's chemical conjuring trick. They have shown that once a nitrogen molecule has been caught, it is swamped with protons (H^+) from the surroundings and supplied with electrons via the metal in a sequence of six steps.

Before this attack can start, however, the N_2 has to attach itself to the molybdenum. The metal has lots of available electrons and the ability to form double and triple bonds. In the laboratory, though, tungsten and rhenium are also used because they can form crystalline compounds that are more stable. By analysing such crystals using X-ray methods, chemists at the UNF have been able to piece together the jigsaw.

Other triply-bonded molecules react in the same way. With one of these it has even been possible to freeze the reaction at an early stage after only two hydrogens have combined. This work by David Hughes, Chris Pickett, Ray Richards and Armando Pombeiro of Lisbon concerns the reduction of cyanide by a rhenium compound. Crystals of the intermediate stage show clearly the hitherto unknown molecule CHN_2. This simple molecule is probably too unstable to exist outside the protective environment of the rhenium atom to which it is attached. The group has also recently reported how methyl isocyanide is "fixed".

The attack by H^+ on the triply-bonded molecule is only part of the nitrogen fixation story. When the second NH_3 is released the metal atom has been drained of electrons as it has had to give up one electron for each H^+ that has been used. The return of these electrons to the metal atom of the enzyme is essential if it is to repeat the fixing of another N_2.

At Sussex, Chris Pickett and Jean Talarmin discovered a neat electrical way of doing this (Nature, vol. 317, p.652). They used a tungsten compound as their model enzyme. Not only does electrolysis produce NH_3 from N_2 but it regenerates the tungsten compound which can then go through the cycle a second and even a third time. The chemists at the UNF are now turning their attention to how the natural enzyme gets its electrons back. (Source: New Scientist, 10 April 1986)

Research instrumentation

Swedish gene machine

The Swedish company Pharmacia is introducing the first European machine for assembling genes. Nucleotides can be assembled according to a pre-programmed sequence to form genes or portions of genes in a few hours and under automatic electronic control. This research machine can also help in diagnosis of genetic diseases. (Source: Le Nouvel Economiste, 7 March 1986)

New instruments to speed cracking of genetic codes

A company in Foster City, California, Applied Biosystems Inc., introduced an automated analytical instrument that will take much of the drudgery out of mapping genes. The DNA sequencer, is the latest in a series of computerized tools that are quickening the pace of biotechnology development, and invigorating the $7 billion to $8 billion U.S. market for laboratory equipment and supplies.

Essentially, the sequencer automates the tedious, manual process of gene mapping known as electrophoresis. From start to finish, mapping the base sequences of even the shortest DNA strands normally took two or three days. Now, with the Applied Biosystems sequencer, the procedure is speeded. The sequencer, licensed under an agreement with the California Institute of Technology in Pasadena, where the technology was invented, can simultaneously map 16 strands of DNA in less than 10 hours. A scientist seeking to do that with current technology would need one or two weeks.

One of the design breakthroughs enabling the electrophoresis process to be automated is the use of a laser and four fluorescent dyes to replace radioactive tracers. The sequencer's designers learned that exposing amino acids to intense light caused the dye to glow. A computer analyzes the intensity and colour and determines the identity of the nucleic acid base.

Researchers will still need to remove DNA from cells and purify it, but once the fragment is isolated, the scientist can drop it into a solution and let the $90,000 sequencer perform the biochemical reactions necessary to identify base pairs.

The DNA sequencer will help scientists to decode genetic instructions more rapidly. It will also help Applied Biosystems to continue down a path that has made the company one of the favorites of Wall Street and the biotechnology industry.

Three years ago, Applied Biosystems introduced the first reliable automated DNA synthesizer, an instrument that made artificial strands of DNA. The company, founded in 1981, now controls about 70 per cent of the world's gene-making market, according to analysts, and has sold more than 500 machines.

As successful as the gene-making machine is, company officials expect the sequencer to be an even bigger seller. The reason: making genes is important, but many more molecular biologists are interested in decoding genetic instructions. (Extracted from International Herald Tribune, 27 June 1986)

The new generation of DNA synthesizers

Rapid advances in oligonucleotide chemistry, computer technology, and instrumentation have bred a new generation of DNA synthesizers. These instruments incorporate state-of-the-art technology to automate an exacting chemistry; they are also extremely user-friendly and easy to operate.

"Gene machines" have been on the market since 1981, when Vega Biotechnologies (Tucson, AZ) introduced its first model, followed closely by Bio Logicals (Toronto, Canada) and Sequemat (now Genetic Design, Watertown, MA). Those first instruments however synthesized not genes, but merely short, crude fragments of oligonucleotides ranging from 20 to perhaps 50 bases in length. The new generation of instruments is stretching that length past the 100-mer - Biosearch (San Rafael, CA) reports a 170-mer, Genetic Design a 160-mer, Systec (Minneapolis, MN) a 107-mer, Vega three 100-mers on a multiple column model. Although today's improved chemistries result in very high purities and coupling efficiencies, it is unlikely that research scientists will use this methodology to synthesize "one-piece" genes.

TABLE I HARDWARE/SOFTWARE

	COST OF BASIC PACKAGE*	HARDWARE	SOFTWARE	USER MODIFICATIONS OF PROGRAMS	ACCESSORIES	WARRANTY
APPLIED BIOSYSTEMS						
MODEL 380B	$42,500: 1 col. $49,500: 3 col.	Integral disk drive; touch-screen	Menu-driven disk-based	Completely programmable; user controls all instrument functions, chemical procedures	Printer	1 yr. parts and labor; 90 days travel (U.S. only)
MODEL 381A	$29,500	Integral ROM programs; RAM memory	Fully-automated, menu-driven ROM		Printer	
BECKMAN INSTRUMENTS						
SYSTEM 1 PLUS	$34,500[1] $35,500[1]	IBM PC IBM PC/XT; hard disk	DNA synthesis program on diskette	Alter standard step length or flow rate; alterations stored in memory	Beckman HPLC purification system: $15,780	1 yr. parts, labor, travel
BIOSEARCH						
SAM ONE SERIES II	$29,000	Integral microprocessor	Menu-driven ROM	Fully user-programmable		
MODEL 8600	$36,000: 1 col. $42,000: 4 col.	Integral microprocessor; printer	Phosphate, phosphine routines in ROM	Fully user-programmable; 10 defined areas in RAM for user programs		1 yr. parts, labor, travel
CRUACHEM						
PS200	$12,500	None; user provides microcomputer	Control software available for IBM PC, ACT Apricot, Apple II, Acorn Micro. Semi-automatic (user must inject base)	Software options for user protocols and modifying standard program		1 yr. parts and labor; 90 days travel
PS100	$995: 1 col. $1500: 4 col.	None; manual mode	None	None		
GENETIC DESIGN						
AUTOGEN™ 6500	$39,000: 1 col. $49,000: 3 col.	Apple IIe, 2 disk drives	Proprietary: Intelligent Process Control (IPC)	Computer-directed variable cycle control; user can modify procedure during synthesis; unlimited user program storage	Modem: $900 Printer: $1195	5 yr. parts and software updates; 1 yr. labor; 90 days travel
SYSTEC						
MICROSYN 1440	$18,000	Integral microprocessor	Menu-driven, Semi-automatic (user must inject base)	Modify and store protocols in permanent memory; factory-set program called up anytime	Printer	
MICROSYN 1450A	$36,500	Integral microprocessor; printer	Digital microcassette	Custom software automating other syntheses	For all 3 models: Automatic deprotection and cleavage: $1500	1 yr. parts, labor, travel
MICROSYN 1460	$42,000	Integral microprocessor; printer	Digital microcassette			
VEGA BIOTECHNOLOGIES						
CODER™ 300	$37,000: 1 col. $44,000: 3 col.	Integral microprocessor; built-in printer	Floppy diskette	User can modify procedure during synthesis; each diskette stores 75 user programs		1 yr. parts, labor, travel

*Based on manufacturer's information 7/15/85. [1]Includes $5000 of chemicals

(Source: Bio/Technology Vol.3, September 1985)

TABLE 2 CHEMISTRY

	CHEMISTRY	REAGENTS	SOLID SUPPORT	TRITYL ASSAY FOR COUPLING EFFICIENCY	CLEAVAGE FROM SUPPORT	TIME AND COUPLING EFFICIENCY PER CYCLE	COST PER CYCLE[a]
APPLIED BIOSYSTEMS							
MODEL 380B	Patented phosphoramidite[1]; beta-cyanoethyl phosphoramidite (soon)	Prepackaged; bulk discounts available	Disposable CPG columns	Manual	Automatic	For 0.2 μmole scale: 7–9 min./ 98–100%[2]	0.2 μmole scale[2]—$1.34–$1.78 1.0 μmole: $2.68–$3.56 10 μmole: $26.80–$35.60
MODEL 381A					Manual		
BECKMAN INSTRUMENTS							
SYSTEM 1 PLUS	Patented phosphoramidite[1]	Prepackaged; bulk discounts available (RSVP Plan)	Disposable CPG columns	Coupling Efficiency Monitor monitors each deblocking step for completion	Manual	Less than 15 min. >98%[3]	1.0 μmole: $4.75
BIOSEARCH							
SAM ONE SERIES II	Modified phosphate triester; beta-cyanoethyl phosphoramidite	Prepackaged	Disposable CPG columns	Manual	Manual	10 min./ >97% (modified phosphate triester)	1.0 μmole: $3.00 (triester) $6.00–$8.00 (amidite)
MODEL 8600	Optimized triester; beta-cyanoethyl phosphoramidite			Interface for fraction collector	Automatic	5.5 min./ >99% (amidite 7.0 min./ >98% (triester)	0.25 μmole: $1.50 1.0 μmole: $3.00
CRUACHEM							
PS200	All available chemistries	Prepackaged	Reusable variable-volume glass reaction columns	Manual	Manual	10–25 min./ 95–>99%[4]	1.0 μmole: $2.00 (using OneShot pak)
PS100							
GENETIC DESIGN							
AUTOGEN™ 6500	Beta-cyanoethyl phosphoramidite; standard phosphoramidite; triester	User-supplied	User-fillable tubes; CPG or silica	On-line monitoring, built-in colorimeter	Automatic	7–10 min./ 99%+	$1.12–$1.74 (5–10 mg. step)[5]
SYSTEC							
MICROSYN 1440	Standard phosphoramidite; beta-cyanoethyl phosphoramidite; phosphotriester	User-supplied; Sigma Chemical offers kit	User-fillable cell, reusable	Manual	Manual or Automatic	10 min./ >98% (amidite) 10 min./ >95% (triester)	0.5 μmole: $2.55 1.0 μmole: $3.55 10 μmole: $10.60–$14.12[6]
MICROSYN 1450A	Beta-cyanoethyl phosphoramidite; phosphotriester[2]; standard phosphoramidite					6 min./ >99% (amidite) 6 min./ >96% (triester)	
MICROSYN 1460							
VEGA BIOTECHNOLOGIES							
CODER™ 300	Beta-cyanoethyl phosphoramidite	Prepackaged	Disposable CPG columns Fluidized bed agitation	Interface for fraction collector	Manual	Under 12 min. >98%[3]	1.0 μmole: $3.59[6]

[a]Depends on scale and bulk discounts. [1]Caruthers, Matteucci, Beaucage; University Patents. [2]Itakura, Kaplan, et al., City of Hope Research Center. [3]Includes capping. [4]Depends on protocol and chemistry. [5]Based on 2000 couplings, includes cost of column and all reagents. [6]Includes all reagents.

(Source: Bio/Technology Vol.3, September 1985)

TABLE 3 INSTRUMENT FEATURES

	REACTION SCALE	MULTI-COLUMN OPTION	VALVES	SENSING OF LOW LIQUID AND/OR GAS LEVELS	BACK-UP DURING POWER FAILURE	SPECIAL FEATURES
APPLIED BIOSYSTEMS						
MODEL 380B	Up to 10 μmole	Simultaneous synthesis; 1-col. unit upgrade; 3-col. unit	Patented solenoid-activated diaphragm	Low-level warning; can interrupt synthesis	Battery back-up, auto restart; saves synthesis parameters, user protocols	Automatically adds unusual bases
MODEL 381A		1 col. only				
BECKMAN INSTRUMENTS						
SYSTEM 1 PLUS	1 μmole 10 μmole	1 col. only	Pneumatically-activated slider	Bottle-status report; can interrupt synthesis	Standby mode; system indicates step at which power failed	Color monitor; lightpen or keyboard
BIOSEARCH						
SAM ONE SERIES II	User-selectable, 0.25 μmole up	Optional 4-col. for serial syntheses; $4000 as addition	Solenoid-activated diaphragm	None: synthesis continues	Battery backup, auto restart; saves synthesis parameters	
MODEL 8600	0.25 μmole 1 μmole 20 μmole	Simultaneous synthesis; 1-col. unit upgrade; 4-col. unit		Interrupts synthesis		
CRUACHEM						
PS200	0.5 μmole to 25 μmole	Up to 4 simultaneous syntheses	Rotary electrical	None: synthesis continues	Software-dependent	
PS100						
GENETIC DESIGN						
AUTOGEN™ 6500	0.1 μmole to 30 μmole	Sequential synthesis	Pneumatically-activated slider	Continuous self-diagnosis; can interrupt synthesis	Saves data in notebook file	Voice verification of sequence data entry
SYSTEC						
MICROSYN 1440	0.5 μmole to 10 μmole	1 col. only	Solenoid-activated diaphragm	None: synthesis continues	Auto restart	Electronic flow map for continuous update
MICROSYN 1450A		1 col. only	Rotary and diaphragm		Battery backup; restarts at beginning of last remembered step	Temperature controlled reaction cell
MICROSYN 1460		Sequential synthesis; 2-col. unit				
VEGA BIOTECHNOLOGIES						
CODER™ 300	1 μmole 5 μmole	Columns individually programmable; 1-col. unit upgrade; 3-col. unit	Proprietary	System goes on hold: can interrupt synthesis	Auto restart; resumes synthesis at stop point; keeps record	Temperature-regulated fluidized bed

(Source: Bio/Technology Vol.3, September 1985)

The automated synthesis of gene fragments evolved from work in solid phase peptide methodology, and by 1985 the first working automated peptide synthesizer was developed. The original machine featured a cycle time of four hours per amino acid residue and by the mid-1970s scientists were routinely synthesizing short peptide sequences. The automated synthesis of oligonucleotides however was not attempted until the late 1970s. The main reason for this lag in development seems to be that the parameters for solid-phase synthesis are very different to those for the liquid phase. The support materials originally chosen were not appropriate to the chemical reactions used for DNA synthesis, and conversely, the original chemical reactions were not selective and reliable enough to be used with a solid support system. The classic phosphodiester approach to DNA synthesis was not particularly suited to solid phase synthesis, but phosphate triester, phosphite triester, and phosphoramidite chemistries proved to be appropriate.

An automated DNA synthesizer is basically a precise, timed, solvent-dispensing machine. The basic components of this system include a controller, a reagent and solvent delivery system, valves and a solid-phase reactor. The chemical capabilities of the instrument are as much a function of the programming as they are of the particular reagents and solvents used. The seven manufacturers of DNA synthesizers have used different approaches to optimize each of the basic components of the system. The differences in chemistry, instrument features, hardware, and software are summarized in the accompanying charts. There are only two criteria gene machines must meet, according to research scientist in industry and academia: they must be easy to use; and they must produce what the researcher wants. The rest, as stated by a senior scientist at a major pharmaceutical company, is "just so many bells and whistles". (Source: Bio/Technology, Vol. 3, September 1985)

First automatic DNA sequencer

Three billion units long, the complete set of human genes has posed an unapproachable barrier to scientists craving access to the information it contains. The barrier still stands but technology has taken great leaps towards it in the last decade. One of the most promising is the first automatic DNA sequencer, recently announced by researchers at Caltech in Pasadena. The machine, although still a "model T" version, sharply reduces the chances of error in reading DNA while speeding the process and cutting the costs.

While the new technique is no more accurate in its ability to distinguish among bases, it all but eliminates the possibility of mistakes in the transcription of data.

The new sequencing technique, like the old one, starts by generating fragments of the DNA sequence under analysis, using analogs of the bases - cytosine (C), guanosine (G), adenosine (A) and thymidine (T) - as segment terminator molecules (DNA synthesis terminates wherever the base-analog is incorporated). By varying the concentration of the terminator molecules, a researcher can generate fragments of different lengths, each fragment representing successive occurrences of a given base. The fragments are put on an electrically charged gel column, where they migrate downward, the smallest fragments moving fastest. Because the new technique uses dye labels to distinguish each of the four terminator molecules, all the fragment subsets can be put on the column at once. Using the old method, a researcher had to examine four gel columns to determine the relative lengths of DNA fragments, and manually transfer the collated information to a computer; here, a computer automatically notes the order of the fluorescing dyes as fragments pass a laser at the bottom of the column.

The automatic sequencer allows researchers to begin projects that were beyond imagination a few years ago. (Extracted from Science News, Vol. 129, 28 June 1986)

D. APPLICATIONS

Pharmaceutical and medical applications

Two alpha-interferons win approval to treat hairy cell leukemia

Two genetically engineered forms of human alpha interferon have been approved by the US Food and Drug Administration for treatment of hairy cell leukemia. Hoffmann-La Roche will market Roferon-A alpha inteferon and Schering-Plough will make available Intron A alpha-2 interferon. About 90 per cent of hairy cell leukemia patients treated with alpha interferon achieved significant clinical remissions according to Hoffmann-La Roche. The disease, an illness of the B-lymphocytes, afflicts about 1,000 Americans, almost all men of middle age. Until now, the expected survival period of patients with the disease was several years. Both companies are presently testing alpha interferon in a number of cancers and viral diseases. Recently the British Department of Health and Social Security's Committee on Safety of Medicines approved the use of alpha interferon for the treatment of hairy cell leukemia. The UK approval covers three companies' products - Schering Plough, Wellcome and Hoffmann-La Roche. (Source: Chemical Week, 11 June 1986)

Monoclonal antibody approved for therapy

The US Food and Drug Administration has given its first approval of a monoclonal antibody preparation for therapeutic use. The product, called Orthoclone OKT*3, will be marketed by Ortho Pharmaceutical Corp. It reduces rejection of kidney tissue in transplant operations. Monoclonal antibodies are antibody preparations that have been produced from a culture derived from a single parent antibody-producing cell that has been fused with a continually reproducing, "immortal" cell. All antibody molecules in such a preparation are identical; in naturally produced antibody preparations many different antibody molecules are always produced. Monoclonal antibodies are thus more specific in the molecules they interact with and cause fewer side effects than coventional antibodies. They have already been approved for some out-of-the-body uses, such as home pregnancy tests. (Source: Chemical and Engineering News, 30 June 1986)

A device to bolster the body's immune system

A biomedical device that removes disease-related immune components from human blood will be reviewed by Takeda Chemical Industries for up to 120 days. The device, called the Prosorba column, is manufactured by IMRE (Seattle) and is undergoing clinical trials in the US for patients with certain cancers and auto-immune diseases. The column treats blood outside the body by removing such molecules as immune complexes and IgG, which may inhibit the immune system in combating disease. (Source: Chemical Week, 11 June 1986)

Du Pont offers new DNA probes

DNA probes for the quick detection of hepatitis, herpes and Campylobacter jejuni have been introduced by Du Pont. The radiolabeled probes - developed by Molecular Biosystems (San Diego) - are said to detect

the genomic nucleotide sequences of infectious diseases in less than four hours. The probes use the isotope phosphorus-32 and are contained in kits of the materials necessary for performing radiolabelling and purification. Autoradiography is used successfully to detect hybridized target sequences. (Source: Chemical Week, 11 June 1986)

Human trials with new anti-cancer drug

Cetus Corporation has become the latest biotechnology company to start human clinical testing of tumour necrosis factor (TNF), but the company does not expect the product to be approved by the US Food and Drug Administration before 1990. Several other companies are also developing TNF. Japan's Asahi Chemical announced promising initial results from the drug in cancer patients last year; Genentech started phase I clinical testing last year to determine the safety and activity of the product. Biogen is also developing TNF. Cetus and Genentech are both developing TNF with funds from R&D partnerships.

Findings published recently from these Genentech studies indicate that the company's gene-spliced TNF causes minor side effects, such as fever and chills. In vitro tests have also indicated that the compound's anti-tumour effect is markedly enhanced by its use in combination with gamma interferon.

Cetus is testing a modified, or analogue, form of TNF developed using recombinant DNA technology. The company has already developed analogue forms of beta interferon and interleukin-2 in human clinical testing. Both have been patented.

The company has three potential anti-cancer agents currently in pre-clinical development which are poised to enter human clinical trials over the next year or so. These are colony stimulating factor and immunotoxin products for the treatment of breast and ovarian cancers. Cetus is also building up a generic anti-cancer business using a joint venture approach. (Extracted from European Chemical News, 30 June 1986)

AIDS drug research continued

Rhône-Poulenc has indicated that the initial indications from clinical tests of its potential AIDS treatment, HPA 23, are of sufficient interest for its health care branch, Rhône-Poulenc Santé, to continue its commercial development.

The French chemical concern and its US subsidiary, Rhône-Poulenc Inc., have been conducting studies to determine tolerance limits and efficacy in AIDS sufferers. A new series of trials will commence shortly. The priority objective, the company says, is to determine whether HPA 23 is an effective antiviral agent and AIDS treatment. (Source: European Chemical News, 30 June 1986)

Kodak ties up on monoclonal R&D

Eastman Kodak has announced further moves into biotechnology. The photographic and chemical company has boosted its position in monoclonal antibody diagnostics via a tie-up with a small, private US biotechnology concern, Neorx based in Seattle, Washington, which specialises in monoclonal-based cancer diagnostics and therapeutics.

Alongside the equity investment, Kodak is to fund a "multi-million dollar," three-year R&D programme to commercialise a number of Neorx products. Kodak has picked up the option to manufacture and market four of these products.

Cancer diagnostics and therapeutics form a cornerstone in Kodak's strategic diversification in the health-care sector. Last month a link with the monoclonal antibody concern, Cytogen Corporation, was announced. The photographic company is funding a three-year project at Cytogen focusing on the development of monoclonal antibody conjugates for cancer imaging and therapy. (Source: European Chemical News, 30 June 1986)

Human protein slated for tests as agent against reproductive tract cancers

Production of a human protein that will be tried against several types of female reproductive tract cancer was reported by investigators at Biogen and Massachusetts General Hospital (MGH). The protein, Mullerian inhibiting substance (MIS), can be produced by recombinant genetic engineering techniques.

Until now research has been difficult because only minute amounts of MIS were available. The successful recombinant production of MIS by the Biogen-MGH team will accelerate their joint studies.

MIS is produced naturally in male embryos and causes the precursor tissue to female reproductive organs, the Mullerian duct, to shrink and disappear. In female embryos, Mullerian duct cells grow to form the female reproductive system. Because MIS suppresses the growth of embryonic female reproductive system cells, it may also inhibit tumour growth in the body in mature cells of Mullerian duct origin. Therefore MIS may eventually prove useful in the treatment of ovarian, cervical, endometrial, fallopian tube and vaginal cancers.

The potential antitumour activity of MIS is supported by laboratory studies using natural MIS that indicate the protein inhibits the growth of human cancer cell lines, principally from patients with ovarian cancer, according to Biogen.

The Biogen scientific team, headed by Dr. Richard Cate, produced recombinant human MIS in collaboration with Dr. Patricia K. Donahoe, Chief of MGH's Division of Pediatric Surgery, and her co-workers.

The Biogen researchers made recombinant human MIS by isolating the human gene that governs production of the protein and inserting it into animal cells. The inserted gene then directed the animal cells to produce MIS. (Extracted from Chemical Marketing Reporter, 16 June 1986)

Gamma interferon proves effective in treating arthritis

Gamma interferon, produced by Biogen (Cambridge, Mass.), has relieved symptoms of rheumatoid arthritis with minimal side effects in preliminary clinical studies, the company reports. In a US study at the Arthritis Center (Wichita, Kan.), 23 of 30 rheumatoid arthritis patients receiving gamma interferon injections experienced a reduction in such common symptoms as swollen joints and joint tenderness. In a similar trial in the Federal Republic of Germany, 24 of 40 patients showed improvements, particularly a decrease in pain and an increase in mobility. Biogen expects FDA regulatory approval of its gamma interferon for treatment of rheumatoid arthritis later this year. (Source: Chemical Week, 18 June 1986)

Space shuttle accident sets back experiments

A class of biomedical experiments was set back when the space shuttle Challenger was destroyed. The experiments involved the production and purification of proteins and the packaging of other biologicals in space as weightlessness is the ideal atmosphere for these experiments because the normal pull of gravity is not there to slow down or distort the shape of molecules as they grow. The result will be faster,

purer protein synthesis, more perfect crystal growth and smoother encapsulation of medicines. Once the structure of the protein molecule is modeled, scientists can use it to design new classes of pharmaceuticals, either by making modifications to boost potency of desired proteins or to block the growth of cancer cells and other harmful organisms. Schering-Plough is working on the synthesis in space of alpha-2 interferon in treating certain cancers and viral infections. Burroughs Wellcome is producing large uniform crystals of an enzyme called bacterial purine nucleoside phosphorylase, and McDonnell Douglas Astronautics is working on a protein-purification experiment with the hormone erythropoietin which stimulates red blood cell production. Vivotech is currently working to package pancreatic islet cells as an alternative to insulin shots for diabetes. (Extracted from Wall Street Journal, 23 May 1986)

Trials for TPA and hepatitis vaccine

Integrated Genetics (Framingham, Mass.) has entered tissue plasminogen activator (TPA) and hepatitis B vaccine - both produced using genetically engineered mammalian cells - in clinical trials. The company's Japanese partner in TPA research and development, Toyobo, has initiated Far East trials of the drug, a blood-clot-dissolving enzyme. BASF, Integrated's European TPA partner, will conduct trials in Europe and in the US, and will market TPA internationally outside of Japan and other Far East countries. Integrated's partner in the development of a hepatitis B vaccine, Connaught Laboratories, has begun clinical trials in the US. The current hepatitis vaccine - produced from blood collected from individuals infected with the virus - requires extensive purification and testing to ensure its safety, leading to greater cost. Integrated's recombinant vaccine, says the company, is produced in large quantities at reasonable cost. (Source: Chemical Week, 2 April 1986)

AIDS vaccine trials

US scientists have remodelled the smallpox vaccine and plan to seek approval to test its effectiveness as a possible protection against AIDS. Two groups have independently reported success in splicing a key AIDS virus gene into vaccinia virus, the only vaccine that has eradicated smallpox.

Recombinant vaccinia viruses containing an AIDS virus coat gene responsible for the production of two proteins have been constructed. The presence of these proteins is enough to fool the cell's immune system that the vaccinia virus is an invading AIDS virus.

Both groups, one from Oncogen, the Bristol-Myers subsidiary, the other with agencies of the US national institutes of Health, have demonstrated that the remodelled vaccinia virus can be used to stimulate AIDS antibodies in animal experiments. The oncogen group report that vaccinated monkeys developed specific antibodies.

Nevertheless, this ability to stimulate antibody formation does not necessarily mean that AIDS patients can be cured. AIDS patients possess antibodies against the virus, but receive no protection.

Oncogen expects to apply to the Food and Drug Administration for permission to start safety testing of its experimental vaccine in human volunteers. If the next stages of the research prove successful an AIDS virus vaccine could be available before 1990. (Source: European Chemical News, 21 April 1986)

Interferon makes cancer drugs more effective

Lung cancer is almost always a self-inflicted disease. It kills 40,000 people each year in Britain. In Scotland, where the death rate is the highest in the world, one person dies of the disease every two hours. Until doctors find a way to stop people smoking altogether, medical researchers will continue to concentrate a large proportion of their efforts and resources into the search for a more effective treatment.

Researchers from the Imperial Cancer Research Fund (ICRF) recently announced an exciting new lead in their work on lung cancer. Professor John Smyth and his team at the Medical Oncology Unit in Edinburgh have had promising results with a new form of treatment, which combines alpha interferon with a drug used in chemotherapy. Smyth and his team have tried various forms of therapy on their cultured cancers. They found that the combination of small amounts of interferon and chemotherapy is so effective that they are now planning a small clinical trial in Edinburgh. Interferon, which has been successful in treating people only with a rare form of leukaemia does not have any effect on lung cancer by itself. Smyth found in laboratory tests that if interferon is given with a cytotoxic drug, such as cisplatinum, together they caused the tumour to shrink up to six times as much as the drug alone. If the treatment is successful in the trial, then the ICRF will extend the trial to patients throughout Britain.

The combined interferon-drug treatment could have other advantages for patients. In small-cell cancers, where drugs are already effective in shrinking tumours, the addition of interferon might mean that doctors can reduce the dose of the drug - and so reduce the very unpleasant side effects that generally accompany chemotherapy. (Extracted from New Scientist 24 April 1986)

Anti-cancer trials

Human clinical trials of a potential tumour cell killer are being planned by the US biotechnology concern Immunex.

The agent, a naturally occuring protein called GM-CSF, appears to directly activate the body's defensive agents to kill tumour cells, according to Immunex scientists. GM-CSF was known to stimulate production of two major types of white blood cell, important parts of the immune system.

Immunex, in collaboration with the Hoechst subsidiary Behringwerke, has produced both native and improved forms of the protein using recombinant DNA methods. The product is now in the final stages of preclinical animal trials with human trials scheduled for later this year.

GM-CSF will be tested as a means of maintaining the immune system responses of cancer patients undergoing chemotherapy and radiotherapy, and as a direct cancer therapy through its activation of white blood cells. (Source: European Chemical News, 12 May 1986)

Test can predict rare eye cancer

Scientists at the University of Cincinnati have recently announced that they have developed a genetic test that can predict in four out of five cases whether someone at high risk for a rare form of childhood eye cancer will develop the disease. The test developed for retinoblastoma could also serve as a model for tests for other types of cancer in which

heredity plays a role. For instance, having a close relative with breast cancer increases a woman's risk of contracting the disease. In the test, DNA is isolated in a blood sample and mixed with a radioactive substance that enables scientists to identify certain genes, which are compared to those of two relatives who have had the disease. (Extracted from International Herald Tribune, 15 May 1986)

Cancer diagnostics and drugs to be developed

Diagnostic and therapeutic agents for cancer will be developed by Celltech of Slough, England, in a two-year first phase of what is expected to be a longer relationship with American Cyanamid's Lederle Laboratories. The agents will consist of binding-site portions of anti-tumour antibodies linked to spacer molecules, which in turn will be linked to carrier molecules for radioisotopes or anti-cancer drugs. In diagnostic agents, expected to be ready for marketing by 1991, antibody active sites will bind to tumours, which clinicians will locate by scanning patients' bodies for γ-rays from attached radioisotopes. Therapeutic agents, which may be available by 1994, will bind radioisotopes or drugs to tumour cells. Celltech will isolate genes for anti-tumour antibodies, excise portions that code for binding sites only, and use these to make binding-site molecules. Use of binding-site proteins may avoid current problems of nonspecific binding of whole antibodies and occlusion of binding sites during radioisotopic labeling. (Source: Chemical and Engineering News, 28 April 1986)

Agreement to develop Spirapril

Sandoz and Schering Corporation have signed a licence agreement for the development of the US firm's angiotensin converting enzyme inhibitor, Spirapril. The drug will compete in the large antihypertensive and congestive heart failure market. Spirapril is in US clinical trials.

Both firms see the project as complementing their current efforts in the cardiovascular drug market. Schering is concentrating its research efforts in developing new therapies for cardiovascular diseases and hypertension. One new product is the antihypertensive Normodyne, recently approved by the US Food and Drug Administration. (Extracted from European Chemical News, 5 May 1986)

Mutants against tooth decay

Mutant bacteria could be the next line of attack in the fight against tooth decay. Researchers at the Forsyth Dental Center in Boston, Massachusetts, have isolated a new strain of Streptococcus mutans, the mouth-dwelling microbe widely believed to be the key cause of tooth decay. The mutant fights and displaces the harmful microbes. Unlike its troublesome parent the mutant bacterium generates only a small amount of corrosive acid in the mouth. More important, it produces a protein that is lethal to the parent strain.

Theoretically, the mutant strain, codenamed JW1005, could in time completely displace the bacteria that cause caries, explained Jeffrey Hillman, head of molecular genetics at the centre. But so far, the researchers have only tested it in animals and three people. Treatment consisted of a single dose of the mutant in a suspension of water. At best, 60 per cent of the harmful microbes were displaced after one year. "Further modifications are necessary to find strains which work more rapidly and wipe out completely the S. mutans population," Hillman said. Once a fortified strain is isolated, extensive clinical trials should follow quickly. (Source: New Scientist, 10 April 1986)

Livestock applications

Biotechnology helps chicken farmers

An Israeli biotechnology company is marketing an immunological test for chicken farmers. The company says its technique could also make expensive, centralized laboratory testing, for such things as pregnancy, unnecessary. Organics, based in Rehovot, calls its product ImmunoComb. The first kit, put on the market in January, is a test for antibodies to two diseases found in poultry. Newcastle disease and infectious bronchitis

Poultry farmers vaccinate against these viruses, but the vaccine often does not "take", or requires a booster. The only way to see whether the flock has been protected is to check for antibodies. For Newcastle disease, an expensive laboratory test based on the agglutination of red blood cells must be used. No similar test is available for bronchitis. The advantage of ImmunoComb is its cheapness and simplicity. A kit for testing 30 chickens for the two diseases costs $60, which is comparable to the cost of more time-consuming laboratory tests.

Organics is discussing with several companies the development of an ImmunoComb to test for allergies in people. Currently the most common test for various types of allergy antibodies, is an immunoassay sold by Pharmacia that costs $6-$8 per test. An ImmunoComb costing $45, and carrying a range of tests for common types of antibody, could work out at a dollar a test.

Organics plans to develop tests for several human diseases. It would be possible to put chlamydia, gonorrhoea, syphilis, AIDS and others on one comb for venereal screening. The company already has a rubella test, which it wants to combine with pregnancy indicators such as HCG and alpha-fetoprotein to monitor pregnancies. Such ImmunoCombs could be available over the counter, as simple immunological pregnancy tests are now. (Extracted from New Scientist, 24 April 1986)

Synthetic foot-and-mouth disease vaccine

A chemically synthesized vaccine that protects cattle against foot-and-mouth disease has been developed by Richard DiMarchi and colleagues at Eli Lilly Research Laboratories, Indianapolis, and the Animal Virus Research Institute in the UK. The vaccine consists of a single peptide that incorporates two separate regions of the virus coat protein connected by a diproline spacer. In tests in cattle, the vaccine elicited high levels of neutralizing antibody and protected the animals against subsequent infection with the virus. "To our knowledge, this experiment represents the first example of protection of cattle against foot-and-mouth disease after a single immunization with a synthetic peptide under conditions typical of those used to test the potency of conventional vaccines," the researchers claim. (Source: Chemical and Engineering News, 28 April 1986)

Blood factors that improve horse vaccines

Neogen (Lansing, Mich.) plans to market a product that contains white blood cell factors derived from horses and is said to improve the effectiveness of horse influenza vaccines. Horses given equine influenza vaccine and equine mixed leukokines had antibody levels at least 50 per cent higher than those in horses that received the vaccine only, says Neogen. The company expects other blood-derived products to prove useful in reducing livestock disease. (Source: Chemical Week, 26 March 1986)

Anaplasmosis vaccine

Each year, 50,000 to 100,000 cattle in the United States die of anaplasmosis, a rickettsial disease characterized by severe anemia, weight loss, abortion, and death. A vaccine against the infectious agent that causes anaplasmosis is now under development through the isolation of an immunogenic protein from the surface of the disease pathogen, Anaplasma marginale. Immunization with a subunit of the protein protected cows from doses of A. marginale that caused disease in unprotected animals. The subunit is a component common to numerous isolates of the pathogen from distant regions of the United States and elsewhere and thus has the potential to provide cross-protection against infection by related strains. These experiments open the way for production of large amounts of the immunogenic subunit by cloning techniques and constitute a step toward curbing a major infectious disease of cattle. Prevalent in tropical and subtropical regions, anaplasmosis has a significant economic impact in developed and developing countries. (Source: Science, Vol. 231, 14 March 1986)

US National Institutes of Health approve genetically engineered vaccine

The US Department of Agriculture (USDA) has found a genetically engineered live-virus vaccine to be "pure, safe, potent and efficacious", and has enabled Biologics Corporation of Omaha, Nebraska, the manufacturer, to resume sales after a two-week voluntary suspension.

The vaccine was commercially licensed in January by the US Department of Agriculture. Pseudorabies causes serious economic losses for many pig farmers, especially in the Midwest.

At issue is whether the researchers had proper authorization before they conducted a field test of the vaccine, which is made from a modified live virus. The dispute over the test underscores the confusion among researchers and among federal agencies over the regulation of experiments that involve the deliberate release into the environment of genetically engineered organisms.

At a congressional hearing on 29 April, members of the House science and technology oversight subcommittee contended that the researchers should have obtained permission from their schools' institutional bio-safety committees before the field test of the genetically altered virus was performed. The biosafety committee at Texas A&M University said in a letter dated 25 April to NIH that the test should have been regarded as a deliberate release experiment by faculty member Stewart McConnell, who tested the vaccine.

The test was conducted in 1984, but only recently has received wide publicity. The experiment involved the inoculation of 1,400 pigs on a farm in Lometa, Texas, to control an outbreak of pseudorabies.

The suspension came about after charges appeared in the press that USDA had failed to follow proper procedures in approving the vaccine licence. USDA had not notified its own Agricultural Recombinant DNA Research Committee about the application. The vaccine, called Omnivac, protects swine from pseudorabies, a potentially fatal disease caused by a herpes-virus. Omnivac lacks a normally present gene for thymidine kinase that allows the virus to enter a latent state in an animal's nervous system, leading to future outbreaks of disease.

USDA's Animal and Plant Health Inspection Service conducted an "environmental assessment" of the vaccine based on available data, but critics of recombinant DNA research are not satisfied, calling instead for a full environmental impact statement. The Foundation on Economic Trends, headed by Jeremy Rifkin, has filed suit in federal court to suspend Omnivac's licence, and a congressional committee is also investigating USDA's procedures in this case. (Source: Nature, Vol. 321, 1 May 1986 and Science, Vol. 232, 16 May 1986)

Agricultural applications

A field day for gene-splicing

On 30 May, Agracetus (Middleton, Wis.), an agricultural biotechnology firm, planted genetically altered tobacco in Wisconsin, thereby beginning the first authorized outdoor test of engineered plants. How observers are saying that the industry has the opportunity to prove that gene-splicing is actually a safe, valuable science.

In Wisconsin alone, several different plant diseases cost corn farmers $50 million/year. How Agracetus has planted tobacco plants that have been modified to be resistant to crown gall disease. The tobacco is being grown on a small 2,000 sq.ft. plot to help Agracetus researchers understand the yield characteristics of disease-resistant tobacco. The experiment will not involve testing the plants against the disease in the field. The company has already shown in two years of greenhouse tests that the disease-resistance traits imparted to the plant are passed through the plant seed from one generation to the next. In the field test the total weight of leaves harvested from the plants will be compared with the total weight of leaves harvested from unmodified plants. In the greenhouse no significant difference in yields has been observed between the genetically engineered plant and unmodified ones. The reason for testing outdoors is that "the field exerts many more environmental pressures" than greenhouses.

Agracetus's test has won important endorsements. The National Institutes of Health (NIH) approved the test after receiving a positive recommendation from its Recombinant DNA Advisory Committee, a panel of scientists and public sector representatives commissioned by NIH to monitor genetic-engineering research in the US. The experiment was also reviewed and approved by the US Department of Agriculture's Agricultural Recombinant DNA Reasearch Committee and by its Animal and Plant Health Inspection Service. (Extracted from Chemical Week, 11 June 1986)

Field-testing of certain plants expected soon

Field-testing by Arco Chemical's Plant Cell Research Institute (PCRI), Philadelphia, of certain genetically engineered crop plants will start soon. PCRI has asked the US Department of Agriculture for approval to study alfalfa, cucumber, potato, tobacco and tomato plants that have been genetically engineered with the protein-coding region of one or more of 10 different genes. The research programme, so far carried out indoors, seems to indicate that the genetic information transferred may produce plants with improved nutritional quality and other beneficial traits. (Source: Chemical Week, 2 April 1986)

Monsanto's pesticide bacterium future

Monsanto may decide to shelve its pesticide bacteria project. The US firm was disappointed at not receiving a permit from the US Environmental Protection Agency to test the genetically-engineered bacteria that secretes a pesticide toxin in the field, which means that the firm cannot conduct tests

until next year. By then the technology will probably have been overtaken by others.

The EPA is demanding more data from the company despite the conclusion from the agency's scientific advisory panel that there would be minimal environmental risk from a small field test.

Monsanto is being asked to repeat a number of experiments. The agency has requested that a study of above ground colonization on plant surfaces be conducted using parental strains of the bug. If colonization is found the firm must also assess the effect on milkweed bug colonization.

Further tests are also required to determine honeybee larvae mortality rates. Initial results indicate that more than 50 per cent were killed. The company has also to determine the effects on aquatic insects and find a no-effect level on susceptible lepidoptera. Despite denying Monsanto permission the agency claims not to want to stifle biotechnology innovation, but the EPA has to insist that data supporting environmental release tests must be good enough to withstand close scientific scrutiny.

In addition to the EPA doubts, the US Department of Agriculture is not happy about the plant pathogenicity of one of the Monsanto strains and has requested repeat experiments. The company has isolated two strains of Pseudomonas fluorescens containing the Bacillus thuringiensis toxin gene and has made three derivative strains of each. (Extracted from European Chemical News, 2 June 1986)

Belgian team transfers gene to protect tobacco plants from predators

A team of geneticists from Belgium has transferred a bacterial gene into a plant and shown that it successfully protects the plant from insect predators. The results of a year-long trial on the technique are so successful that the scientists now want to test the new, genetically engineered plants in the field.

Scientists have for many years known that the toxins produced by the bacterium Bacillus thuringiensis kill insect larvae. The Belgian team transferred a gene that produces one of these insect toxins into cells of the tobacco plant.

The cells grew into normal adult plants that were highly resistant to insect larvae. Larvae feeding on the genetically altered plants became paralysed after 48 hours and died within three days. Plants then pass on the trait of insect resistance to future generations.

The scientists, who work for Plant Genetic Systems, revealed the results of their work at a conference on crop protection held in the US. The company says that its work "constitutes the first practical demonstration of the beneficial application of genetic engineering to make plants pest- and insect-resistant".

Plant Genetic Systems says that the technique will benefit countries in the Third World which cannot afford expensive insecticides. The company says that it intends to apply the technique to "all major crops suffering from lepidopteran insects".

The team from Plant Genetic Systems tried out its technique in the laboratory and in the greenhouse. Having transferred the toxin gene from the bacillus to the tobacco plant, it compared the leaves from the genetically altered plant with those from normal plants after infestation with insect larvae over a six-day period.

At the end of three days, the scientists observed "significant mortality" among the larvae feeding on the genetically altered leaves, those that did survive this period did not seem to be able to transform into the second larval stage. After the sixth day, all larvae had died, whereas only 5 per cent had died among those larvae feeding off the leaves of normal plants.

In a second experiment in the greenhouse, the team compared gross structural damage to two sets of plants infested by many larvae of insects. The first set of plants, those that contained the bacterial gene, showed minimal damage to their leaves, and all larvae disappeared after four days. In the normal tobacco plants, "considerable damage was obvious after 4-7 days and they were completely consumed after 10-15 days".

The Belgian team has compared the levels of toxin produced in the tobacco plants with the levels of toxin produced in the bacterium and found that they are comparable. The scientists also focused on the active part of the toxin protein to see whether a knowledge of the molecular basis of how it works will allow them to design new types of toxins against agricultural pests. (Source: New Scientist, 17 April 1986)

EPA reduces penalty against biotechnology firm

The US Environmental Protection Agency has reduced the penalty imposed on a California biotechnology company for conducting an unauthorized outdoor experiment with altered microbes designed to inhibit frost formation on plants. The agency also dropped a charge that the company had "falsified" experimental data and instead faulted the company for "inadequate reporting."

The company, Advanced Genetic Sciences in Oakland had conducted an outdoor experiment with the microbes without federal approval. According to the EPA, the company led the agency to believe that the tests had been performed in a greenhouse, which prompted the agency to charge it with falsifying data.

Originally, the EPA proposed fining the company a maximum penalty of $20,000, but this has been cut to $13,000. (Extracted from Science, 20 June 1986)

More latex from rubber trees

Getting almost three times the usual yield from rubber trees will be a welcome development among rubber plantation growers. An Indian company has developed a growth stimulant for natural rubber aimed at higher productivity in rubber trees using the modern technology of metabolic rejuvenation.

The rubber stimulant, named Brobastrem, is a chemical formulation consisting of phytohormones, enzymes and co-enzymes as a paste for bark application on rubber trees which metabolically increasses the latex production. It is applied externally, evenly, just like paint on a surface. It should be applied in the morning on non-rainy days. The tree should not be tapped for at least 10 to 20 days after application.

The bark of the rubber tree along the tapping panel should be scraped lightly to a depth of 2 mm just below the tapping cut, to a width ranging from 20 cm to 60 cm depending on the size of the tree trunk. Sandpaper can be used for scraping. To derive the maximum benefit, 200 gm should be applied per tree per year on healthy trees over 6 years old. It does not produce any adverse effect, but rejuvenates the metabolic activity of the trees.

The cost of equipment and machinery for making the latex stimulant is US$0.75 million and operational cost for one year comes to US$0.35 million for a production scale of 1,000 tonnes per annum. The technology is offered for transfer on licensing, joint venture or turnkey basis. For further information write to Asia-Pacific Tech Monitor, APCTT, P.O. Box 115, Bangalore 560052, India.

New cabbage variety

Takii (Japan) has developed a new vegetable that looks like Chinese cabbage but tastes like red cabbage. The plant, named Biohakuran, was created by fusing a cell from a red cabbage with a cell from a Chinese cabbage, then cultivating the hybrid cell in an artificial environment. Seeds were taken from the mature plant and raised into new plants that had characteristics of both parents. The Biohakuran contains five times more iron than red cabbage. It has 38 chromosomes, equal to the sum of red cabbage chromosomes (18) and Chinese cabbage chromosomes (20). (Extracted from Japan Economic Journal, 3 May 1986)

Commercial application of tissue-cultured plants

Crop Genetics International clones sugar cane from the disease-resistant strains of plant tissue, not seeds and the sale of the resulting plants to farmers in the USA is the first known commercial application of tissue-culture science, affording growers a 20 per cent higher yield on their crops. By altering the hormonal concentrations in the gelatin cultures that support the cells, a cell's growth pattern is changed. One cell splits into thousands of embryos rather than developing into a single mature plant. (Extracted from Forbes, 19 May 1986)

BTI enzyme success

Biotechnica International have demonstrated successfully, in a model system, its detoxification approach to herbicide resistant plants. The plants make an enzyme that inactivate the herbicides and this ability is inheritable.

BTI has now confirmed that EniChem Agricolture is to take over its nitrogen fixation programme from Uniroyal Chemical. The US company had a contract with the biotechnology firm to genetically engineer Rhizobia for use as a soyabean innoculum.

Under the terms of the agreement EniChem will support the project to the end of 1988 and provide BioTechnica with up to $6 million in funding, a significant proportion of which has already been received from Uniroyal. (Source: European Chemical News, 19 May 1986)

Plant biotechnology to play key role in agriculture

Advances in plant biotechnology will provide a new approach to the control of weed problems in agriculture. Technologies such as plant cell culture and genetic engineering are already starting to have an impact on the crop protection industry, according to Dr. Dale Shaner of American Cyanamid.

Herbicide-resistant plants are being developed using both cell culture and the transfer of genes which code for resistant enzymes. Oilseed rape resistant to the herbicide, triazine, is currently being grown in parts of Canada affected by previously uncontrollable weeds. American Cyanamid is developing imidazolinone-resistant maize while the biotechnology company, Calgene, is working on crop varieties resistant to the Monsanto product, glyphosate.

Over 180 herbicides currently exist. It is becoming more difficult and more costly to develop new, broad-spectrum products. Moreover, new products tend to have more complex chemical structures and thus are more expensive to produce. Similar problems exist in the development of new additives and safeners for herbicides.

The Cyanamid scientist predicts, therefore, that herbicide-resistant crops will play a key role in the development of integrated weed control packages. They will permit the use of cheaper, broad-spectrum products. In addition, development costs should be less than for new chemical herbicides, perhaps just 1-5 per cent of the latter. Problems still need to be overcome however, including maintaining productivity of the resistant crop, reducing development time and avoiding potential transfer of resistance to weeds.

Productivity is one of the major question marks hovering over herbicide resistant crops. The long development time for herbicide-resistant crops means that it may not be possible to come up with commercially interesting varieties within the patent life of an existing herbicide.

American Cyanamid and Molecular Genetics have successfully developed maize lines which are resistant to imidazolinones, Cyanamid's promising new class of herbicides. Once this trait is transferred to commercially acceptable hybrid maize, a potent new tool for weed control will be available to the farmer.

Although cell culture permits the rapid screening of plant cells for herbicide resistance, many important crops, such as soya beans and rice, cannot be routinely regenerated from such cultures. The use of genetic engineering is even more limited.

The transfer of herbicide resistance from the crop variety to a closely related weed is a possiblity which could severely restrict the usefulness of the procedure. Agrochemical companies will have to bear this in mind when putting together crop protection packages. (Source: European Chemical News, 26 May 1986)

Food production and processing

Industrial enzymes

Advances in industrial enzymology have improved the manufacture of a wide variety of products. Processes such as cheese-making, brewing, tanning, wine-making and baking are all dependent on enzymes produced by micro-organisms. Novo Industri (Netherlands) is one of the leading enzyme producers and is responsible for developing the enzymatic process used in the production of 'light' beers. For cheese producers, Novo has developed a microbial-produced enzyme to replace rennin, supplies of which have become uncertain due to changes in cattle slaughtering practices. For the biscuit makers, there is a new enzyme to soften the gluten in ordinary flour, allowing bakers to break away from special low-gluten flours that are still in tight supply. Yet another enzyme retards spoilage in bread. Novo's latest research involves the development of an enzyme technology to convert palm oil and stearic acid into cocoa butter, an essential ingredient used by chocolate makers. Most cocoa butter comes from West Africa and is currently supplied somewhat erratically. (Extracted from Wall Street Journal, 16 May 1986)

Provesta advances SCP project

Provesta Corporation, the biotechnology subsidiary of Phillips Petroleum, says that its proposed 1,800 ton/year dried yeast protein plant is now in the design phase. The unit will feature two

high-productivity fermenters which allow cell densities of up to 500 gram/litre.

Construction of the plant could start early next year. Completion could be achieved by the second quarter of 1988. Final cost estimates are still not known.

Based on sucrose feedstock, the unit will produce the company's Provesteen T, human and animal feed supplement, based on Torula yeast. The fermenters will be fabricated by the Fluor subsidiary, Daniel International under license from Phillips. Designed jointly by Provesta and Jacobs Engineering, the plant will be located next to the Phillips research centre at Bartlesville, Oklahoma.

Provesta already operates a large pilot plant at the site which has been used to test a variety of feedstocks, including molasses and methanol. The company has had discussions with several parties interested in licensing the technology for the production of both protein and pharmaceuticals. (Source: European Chemical News, 30 June 1986)

Chemical applications

ICI leads chemicals from biotechnology thrust

ICI is using biotechnology to produce the starting material for the engineering plastic, polyphenylene. The UK firm's bioproducts arm is poised to scale up the process to the ton scale on existing chemical plant.

At the heart of the new technology is the enzyme-catalyzed addition of oxygen to benzene to produce cis-1,2-dihydroxycyclohexa-3,5-diene - benzene-cis-glycol (BCG) for short - which can be easily polymerized into an intermediate polymer.

This product is soluble in water and can be fabricated into sheets and fibres. It is converted by heating to polyphenylene, an aromatic polymer with applications in the electronics industry. ICI's new science group at Runcorn has started test marketing of kilo quantities of this polymer.

BCG can be made chemically via chlorination of benzene but the yields are extremely low. The ICI process is based on a strain of the bacteria Pseudomonas putida the UK company's researchers found growing in benzene-polluted soil at Billingham.

The bacteria contains a dioxygenase enzyme which converts benzene to BCG in the presence of oxygen and the cofactor, reduced NAD. The ICI scientists decided to use the whole organism rather than just the enzyme since the latter is unstable when isolated.

The enzyme acts as a broad-range catalyst because of its loose substrate specificity. ICI is studying its use in the production of a range of cis-glycols and related products like phenols and catechols which cannot easily be made by conventional chemistry. The process may also be used to make fine chemicals for other ICI divisions.

The technology involves a two-stage process which can be operated "fairly routinely" on existing, non-sterile plant.

ICI has operated it on the 1,000 litre scale so far, producing tens of kilos of product. It is ready to scale up rapidly to the tonnage level when the market dictates.

The process is one of the first fruits of the major effort ICI has been putting into the biotechnology area in the wake of its financially disastrous single cell protein commitment in the 1970s. The BCG process development required a major interdisciplinary team effort.

Two areas of biotechnology research, protein engineering and non-aqueous systems, will open up further applications for the use of enzymes as catalysts for the production of fine chemicals, according to Professor Alexander Klibanov of the Massachusetts Institute of Technology. The enzyme fumarase could be redesigned to catalyze the conversion of lactic to acrylic acid, ethanol to ethylene and butadiene from butane-1,4-diol.

The use of enzymes in organic solvents would make reaction and recovery much easier on an industrial scale. Researchers have found that virtually all enzymes can be used in such solvents if they are surrounded by a thin layer of water. They become very stable to heat and capable of a larger range of reactions.

In chloroform, the enzyme polyphenol oxidase oxidizes p-cresol to the drug L-dopa giving almost 100 per cent yield. Other phenols can be oxidized in the same way. Similarly horseradish peroxidase could degrade lignin, a commercially interesting process.

Further predictions on the applications of biotechnology to chemical productions came from Soi Barer of US consultants Chem Systems. The Japanese firm Nitto Chemical is to commission a 4,000 ton/year unit this year to produce acrylamide from acrylonitrile using immobilized cells. Barer reckons that this biological route is around $15/ton cheaper than the conventional chemical process.

Mitsubishi Gas Chemical and Pfizer have both been studying the oxidative enzyme methane mono-oxygenase. Pfizer has patented its use in hydroxylation of benzene to hydroquinone. The US company's two-step process involves growing a methylotrophic organism and then using it to carry out the reaction.

Barer calculates that the biotechnology route has an economic advantage of some $440/ton at net cost of production due to lower capital costs. It is however very susceptible to catalyst sensitivity.

Celanese has patented a microbial process for the production of muconic acid, a potential monomer and chemical intermediate, from toluene. Meanwhile Amgen has demonstrated the microbial conversion of paraxylene to paracresol. The company has also been working on a biotechnological way of making the analgesic acetaminophen from substituted anilines.

Biotechnology will have important applications in the production of flavours and fragrances, according to the US consultant. The biotechnology company Synergen has shown that the odour chemical L-carvone can be made biologically from the low-priced terpene, D-limonene. (Extracted from European Chemical News, 19 May 1986)

Energy and environmental applications

Waste riches from biotechnology

Pollution from the chemical and other industries has created a multibillion dollar business. Biotechnology is expected to play a more important role in the cost-effective treatment of industrial effluent.

US industry generates around 150 million tons of waste each year and spends some $6 billion on its disposal. The chemical industry accounts for up to two thirds of all hazardous wastes. Mounting

disposal costs, adverse public opinion and increasing legislative pressures will drive the development of the pollution clean-up business.

Waste can be a valuable source of raw materials. Straw, for instance, can yield sugars, ethanol and furfural. Cellulose could one day provide up to a third of the chemicals currently obtained from oil. Lignin from waste sulphite liquors produced at pulp mills is used as a raw material for the production of vanillin.

Looking at the commercial aspects, legislation is the key factor that will dictate whether a market can be successfully developed. However, the economics of biotechnology processes must be superior to other technologies.

The cost of compliance with US waste regulations is predicted to reach some $10 billion by 1990. Companies like Monsanto, Union Carbide, Upjohn and Phillips Petroleum are spending some $20-50 million each to comply with US Environmental Protection Agency requirements.

Market opportunities lie primarily in equipment, bioformulations and microbial control. US capital expenditure for treating industrial solid waste tops $12 billion a year while bioformulations for treating toxic waste were worth $80 million in the US in 1982 and predicted to reach $400 million by 1990.

Although there are as yet no substantial industrial waste treatment businesses based on biotechnology, Biotechnica Ltd. has recently won a contract to use micro-organisms to treat a polluted site at Blackburn in the north of England while ICI has developed an enzymic product, Cyclear, for the detoxification of cyanide effluent streams. (Source: European Chemical News, 2 June 1986)

Biological pest control

New developments are establishing the feasibility of biological pest control, which uses natural enemies to control insect pests. Integrated pest management combines the use of pesticides with cultural and biological methods. Using the pesticides is difficult however, since few predators or parasites are immune to pesticides. Interest in biological control of predators waned with the introduction of pesticides after the second World War, and has only recently become the subject of intense research. Parasites may be four times more effective than predators in controlling pests, but only 200 of 200,000 parasitic species have been tested for pest control. Researchers must first identify a pest's enemies, which may occur anywhere in the world. The control organisms must then be cultured, transported to the site and released. Researchers are also attempting to identify pathogens such as bacteria and viruses that might control pests.

Several obstacles to biological pest control include the fact that natural enemies that are effective in one region or one year may not be effective in another region or year. Infestation may also occur so late in the growing season that there is no time to implement biological pest control. Still, success with biological controls outweighs control with pesticides, since six of 100 natural enemies introduced effectively control pests. Only one in 1,000 chemicals tested controls pests successfully. Savings to cost ratio with biological control is 30:1, versus 5:1 for chemical pest control. (Extracted from New Scientist, 15 May 1986)

E. PATENTS AND INTELLECTUAL PROPERTY ISSUES

Industry calls for biotechnology invention laws

Cefic, the European federation of chemical industry associations, is calling for laws to protect biotechnology invention. Current patent laws are seen by many as inadequate to protect innovations and Cefic would like rules tightened. Cefic also proposes that the other European industrial federations should co-operate to prevent non-competitive prices of raw materials - particularly starch and sugar - which, it warns, could affect the biotechnology development. (Source: European Chemical News, 21 April 1986)

Biogen wins interferon patent

The Federal Republic of Germany has awarded Biogen's affiliate, Bioferon Biochemische Substanzen gamma interferon patent for the treatment of rheumatoid arthritis.

Biogen expects to have a gamma interferon product approved for sale in the Federal Republic of Germany by the end of this year. The firm has filed and expects to secure patents for gamma interferon as an anti-inflammatory drug in the US and the UK.

Clinical trials using the recombinant gamma interferon product are currently being conducted against rheumatoid arthritis and renal cell cancer in the US, Europe and Japan. Results from these trials are encouraging, according to the company.

The anti-arthritic market is reported to be worth globally about $2.5 billion with the European contribution to this total being $800 million. Many conventional treatments are plagued by side-effects and this estimate may prove to be on the conservative side. Biogen is also investigating the use of gamma interferon against other auto-immune diseases such as multiple sclerosis.

Gamma interferon is being investigated by at least 11 other companies. Six are already involved in clinical trials. Pacesetters include Genetech evaluating the drug as an anti-viral agent and Schering-Plough in collaboration with Suntory. Europe's KabiGen and Hoechst, the US-based Interferon Sciences and Japan's Shinogi are also testing the drug against various types of cancer. (Source: European Chemical News, 28 April 1986)

AIDS patent dispute

Institut Pasteur is claiming to be ahead in the patents rights row that has followed the discovery of the AIDS virus. Moreover, the Paris concern has rejected a proposal from the US Human Health Service to pool royalties from the Institut and the US National Cancer Institute patents. Monies raised would be used to fund an international scientific trust.

At the centre of the Paris-based laboratory's first round victory claim is the acknowledgement by the US Patents Office that the Pasteur Institut was the senior party in the dispute. This statement means that the Pasteur Institut will probably win the rights claim, though it could drag on for a number of years, unless the US National Institutes of Health can prove that its request for a patent was registered before that of the French group.

The move by the US Patents Office removes any risk for Diagnostics Pasteur in France and Genetic

Systems in the US from being sued. Both firms are selling Pasteur Institut AIDS tests.
(Source: European Chemical News, 12 May 1986)

AIDS diagnostic patent

The patent battle raging between the US National Cancer Institute and the French Pasteur Institute has taken a new twist. The US scientists now admit that their keynote article on the AIDS virus, which they called HTLV III, inadvertantly used an illustration of the virus LAV, supplied by the French team. This slip may damage the US scientists' claims in the patents court.

The Pasteur Institute is currently suing the US public health service, claiming that the US AIDS research and associate patents were based on French research. Scientists at the Pasteur Institute believe that this incident confirms the charges. At stake are the royalties on sales of AIDS blood tests. (Source: European Chemical News, 21 April 1986)

F. BIO-INFORMATICS

Quelles biotechnologies pour les pays en développement?

(Author A. Sasson), is a sequel to Biotechnologies: Challenges and Promises which was published last year by UNESCO. At the moment the new book is only available in French, the English and Spanish versions will be available in due course. Copies may be obtained from UNESCO, 7, place de Fontenoy, 75007 Paris, France, quoting ISBN 92-3-202426-8.

Olsen's Biotechnology Report

A new monthly intelligence report on genetic engineering in agribusiness was launched by G.V. Olsen Associates, the New York publishers of Olsen's Agribusiness Report. "Olsen's Biotechnology Report" contains news and analysis of the biotechnology industry and its impact on agribusiness in the U.S. and worldwide. The new report provides insight into investment opportunities for individual and corporate investors. Subscribers will be informed on a regular, monthly basis of competitive developments in research, application, scale-up, commercialization and marketing of new biotechnology products and techniques in agribusiness. The following are examples of news and trends "Olsen's Biotechnology Report" will feature:

- Basic and applied recombinant DNA research, development, scale-up and commercialization,
- New companies, new start-ups, new stock issues, partnerships and financial arrangements,
- Mergers, acquisitions, joint ventures, licensing contracts and other corporate link-ups,
- Legislative and political news such as patent rights, lawsuits, tax shelters and government regulations,
- Impact of biotechnology on family and corporate farms, livestock producers and dairies, and on fruit and vegetable growers,
- Impact of biotechnology on the seed business, pesticides, fertilizers, animal drugs, energy and other agricultural inputs,
- Impact of biotechnology on food, feed and beverage industries and other users of agricultural outputs,
- Process engineering, instrumentation, and control.

For further information please contact G.V. Olsen Associates, 170 Broadway, New York, NY 10038, USA.

New tutorial software for secondary and higher education

Bioscience software

Menu-driven packages covering core areas in biology and biochemistry. Taking, on average, 45 minutes to work through, each package uses animated graphics and step-by-step explanations to demonstrate complex biological processes and communicate hard-to-understand ideas. At the end of each package there is a short section of revision questions and each package is accompanied by instructor's and students' notes. Level: Final year of secondary education or first year university. Series editor: B.D. Hames, University of Leeds.

1. Practical genetics, (D.M. Hunt, Queen Mary College, London)
2. Protein structure and enzyme activity, (M.F. Chaplin, University of Leeds)
3. Nucleic acid structure and synthesis, (J.N. Parish, University of Leeds)
4. pH/Titrations: Biological equilibria, (M.F. Chaplin, University of Leeds)
5. The Genetic code and protein synthesis, (J.N. Parish and A.J. Bleasby, University of Leeds)
6. Molecular basis of muscle contraction, (A.G. Booth, University of Leeds)
7. Photosynthesis - The light reaction, (A.J. Bleasby, University of Leeds)

Sections cover chloroplast and chlorophyll structure; evidence for origin of evolved oxygen; involvement of chlorophyll and separate light/dark reactions; photosystem structure in the thylakoid membrane; cyclic and non-cyclic electron transport.

For further information write to IRL Press Ltd., P.O. Box 1, Eynsham, Oxford OX8 1JJ, UK or IRL Press Inc., P.O. Box Q, McLean, VA 22101-0850, USA.

Provenance and genetic improvement strategies in tropical forest trees

R.D. Barnes and G.L. Gibson, eds. Proceedings of a Joint Work Conference on Provenance and Genetic Improvement Strategies in Tropical Forest Trees, Mutare, Zimbabwe, 9-14 April 1984. Commonwealth Forestry Institute, Oxford/Zimbabwe Forestry Commission, 1984, 662 pp. Price: £15 stg.

These conference proceedings contain the papers presented at a joint meeting of IUFRO working parties on Tropical Species and Provenances (52.02.06), Breeding Tropical Species (52.03.01), Breeding Southern Pines (52.03.13), held with the collaboration of the Zimbabwe Forestry Commission. In addition to 86 voluntary papers on species/provenance trials and tree improvement programmes in a number of tropical countries, seven invited papers are included in the proceedings.

Also included are four papers prepared as a result of discussions during either the conference itself or the training course held prior to it.

The proceedings provide a useful summary of present knowledge and state-of-the-art utilization of forest genetic resources. During the conference, some time was set aside for discussion, in small groups, of some of the problems and questions raised in the invited papers, followed by a general discussion in plenary.

This way of working, which allowed full, active participation on the part of all 60 participants (representing 28 countries), was found rewarding and stimulating.

The next meeting of these active working parties is planned for 1987, with the venue to be decided.

Copies of the proceedings are available from the Commonwealth Forestry Institute, South Parks Road, Oxford OX1 3RB, UK.

Cacao biotechnology by Paul S. Dimick

This new book contains contributions by several world-recognized researchers in the cacao biotechnology field. Contents: Cocoa Raw Product - Production and Problems, R.E. Larson; Chemical Changes Occurring During the Processing of Cacao, A.S. Lopez; Qualitative and Quantitative Measurements of Cacao Bean Fermentation, S.B. Shamsuddin, P.S. Dimick; Interfacing Biotechnology with Conventional Agriculture in Plantation Crops, M.R. Söndahl; Cocoa Germplasm - Some Novel Approaches to its Conservation, L.A. Withers, J.A. Yidana, M.D. Atkinson Tissue Culture Studies with Theobroma Cacao, R.E. Litz; Biotechnology - Applications to the Cacao Plant, P.J. Fritz, Z. Fanji, D.A. Stetler. (Soft cover)

1986 - 75 illustrations, 329 references, 154 pages, US$25.00, ISBN 0-9616407-0-7. Inquiry: P.S. Dimick, 116 Borland Laboratory, The Pennsylvania State University, University Part, PA. 16802, Telephone (814)863-2962, Telex 842-510.

G. MEETINGS

Macromolecules, Genes and Computers, 12-17 August, White Mtn. Conference Center, Waterville, NH. Sponsored by GenBank - Los Alamos and MBCRR - Harvard University and Dana-Farber Cancer Institute.

For further information and applications write: Dr. Temple F. Smith, MBCRR, Director, or Karen D. Gruskin, Meeting Co-ordinator, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115; (617) 732-3601.

Seventh Australian biotechnology conference, 25-28 August 1986. To take place at the University of Melbourne, Victoria, this conference is set around the theme 'biotechnology for industrial development'. Further details from K.D. Kirby, The Secretariat, 7th Australian Biotechnology Conference, CSIRO, Division of Chemical and Wood Technology, Private Bag 10, Clayton, Victoria 3168, Australia; Telephone 03-5422244.

6th Int. Symposium on Mass Spectrometry in Life Sciences, Ghent, Belgium, 31 August - 3 September 1986. Information from Prof. A. De Leenheer, Dept. Med. Biochem. Clin. Anal., Fac. Pharm Sciences, Harelbekestraat 72, B-9000 Ghent, Belgium, Telephone (091)218951.

5th Conference of European Society for Comparative Skin Biology. 1-5 September 1986, Frankfurt am Main, on Skin of vertebrates and invertebrates. Details from Prof. Dr. J. Bereiter-Hahn, AK Kinematische Zellforschung, J.W. Goethe-Universität, Senckenberganlage 27, PF 111932 D6 Frankfurt a.M. Federal Republic of Germany.

Protein Engineering, Achievements and Technologies, Churchill College, Cambridge, England, 4-5 September 1986. Contact for details and registration: Conference Secretariat, Society of Chemical Industry, 14/15 Belgrave Square, London SW1X8PS, United Kingdom. Telephone: (+44)01 235 3681. Telex: 818880 (United Kingdom)

EMBO, Basic Course on Modern Analysis of Biological Structures, 8-20 September 1986, University of Pavia, Italy. Information: Cristallografia, Dip. Genetica e Microbiologia, Università di Pavia, Via Taramelli 16, 1-27100 Pavia, Italy.

Nature, Exploring the Human Genome, Eighth International Conference and Exhibition, Boston, 15-17 September 1986. Further information from: Diana Berger, Nature Conference, Nature Publishing Company, 65 Bleecker Street, New York, NY 10012, Telephone: (212) 477-9600.

7th International Congress of Human Genetics - Satellite Workshop, Genoa, 18-19 September 1986. "New Molecular Approaches and Techniques for the Study of Hereditary Disease". For information contact: Dr. C. Romeo, Laboratory of Molecular Genetics, Instituto G. Gaslini, 16148 Genova Quarto, Italy.

The 10th Long Ashton Symposium jointly organized with the British Plant Growth Regulator Group. "Hormone Action in Plant Development - A Critical Appraisal". University of Bristol, Bristol, England, 22-25 September 1986. Further details from: The Scientific Liaison Officer, Long Ashton Research Station, University of Bristol, Long Ashton, Bristol, England, BS18 9AF.

Third International Conference on Human Leucocyte Differentiation Antigens, Oxford, UK, 21-26 September 1986. Further details from: Dr. A. J. McMichael, Nuffield Department of Medicine, John Radcliffe Hospital, Oxford, UK.

The Cambridge series on biotechnology introduces an International Conference on Enzyme Engineering. 25-26 September 1986, Churchill College, Cambridge. For information contact: Fiona Spindlove, IBC Technical Services Ltd., Bath House, 56 Holborn Viaduct, London EC1A2EX. Telephone: 01-236 4080 or Telex: 888870.

EMBO-Workshop, Eukaryotic Gene Regulation: in vivo and in vitro, Blanes (near Barcelona), Spain, 27 September - 1 October 1986. Further details from M. Beato, Inst. Molek. Biologie, Univ. Marburg, Emil-Mannkopff-Str. 1, 3550 Marburg, Federal Republic of Germany; P. Puigdomenech, Dep. de Genètica Molecular, C.I.D. (CSIC), Jorge Girona Salgado, 18, 08034 Barcelona, Spain; G. Schutz, Inst. Zell & Tumor-biologie, D.K.F.Z., Im Neuenheimer Feld 280, 6900 Heildelberg, Federal Republic of Germany.

International Conference on Prostaglandin and Lipid Metabolism in Radiation Injury. To be held 2 and 3 October 1986 at the Crowne Plaza Hotel in Rockville, Maryland. For further information, contact: Dingle Associates, 1625 Eye Street, NW, Suite 915, Washington, DC 20006.

An International Seminar on the Therapeutic and Commercial Potential of Drugs Affecting Platelet Activating Factor, Royal Lancaster Hotel, London, 13-14 September 1986. Further details from Miss Fiona Spindlove, IBC Technical Services Ltd., Bath House, 56 Holborn Viaduct, London EC1A 2EX, Telephone: 01-236 4080, Telex: 888870 IBC G.

Third European Seminar & Exhibition on Computer Aided Molecular Design, 16-17 October 1986, London. For information contact: Fiona Spindlove, IBC Technical Services Ltd., Bath House, 56 Holborn Viaduct, London EC1A 2EX, Telephone: 01-236 4080 or Telex: 888870.

China Enviro '86, will be held at the central hall of Beijing exhibition centre, 5-10 November 1986. Further details are available from Richard Woog, Modern China Ltd., GPO Box 3724, Hong Kong; Telephone 5-737335, Telex 76759 CCIRW HX.

Events. Second European Seminar on Genetic Engineering Techniques, 21-22 November 1986, Portman Hotel, London. Further details from Fiona Spindlove, IBC Technical Service Ltd., Bath House, 56 Holborn Viaduct, London EC1A 2EX. Telephone: 01-236 4080. Telex: 888870.

Cytokines and other Mediators in Inflammatory Diseases. 27-28 November 1986, Royal Lancaster Hotel, London. Further details from Fiona Spindlove, IBC Technical Service Ltd., Bath House, 56 Holborn Viaduct, London EC1A 2EX. Telephone: 01-236 4080. Telex: 888870.

Fourth International Symposium on Immunobiology of Proteins and Peptides - Presentation and T Cell Recognition of Proteins and Peptides. 30 November - 4 December 1986, Riviera Hotel, Las Vegas, Nevada. For more information, contact: Journeys Unlimited, 4528 Beechnut, Houston, Texas 77096.

The 1987 International Symposium on Viral Hepatitis and Liver Disease, The Barbican Centre, London, 26-28 May 1987. Further details from Dr. Ralph Kohn, Advisory Services Medical Symposia Ltd., 79 Wimpole Street, London W1M 7DD, UK.

International Congress on Cancer Metastasis, Biological and Biochemical Mechanisms and Clinical Aspects, 13-15 May 1987, Bologna, Italy. Sponsored by University of Bologna, Menarini International Foundation under the auspices of Metastasis Research Society. Further details from Fondazione Internazionale Menarini, Piazza del Carmine 4, 20121 Milano (Italy). Telephone: (02)874 932 - 804 739.

Fourth European congress on biotechnology, 14-19 June 1987. To be held at the RAI International congress centre in Amsterdam. Further information from Amsterdam RAI, Europaplein, Amsterdam, the Netherlands; Telephone (02) 5411, Telex 16017 and Congress Secretariat ECB4, Organisatie Bureau Amsterdam Bv, Europaplein 12, 1078 GZ Amsterdam, the Netherlands. Telephone: (31)20-44 08 07. Telex 13499 raico nl.

The first Biotechnology/Food Industry Conference, at the Rainbow Suite, Kensington, London, U.K. from 10-11 December 1987, and in conjunction with the new two-day Biotechnology/Food Industry Exhibition. Further details from Conference Secretariat, Society of Chemical Industry, 14-15 Belgrave Square, London SW1X 8PS England. Telephone: 01-235 3681. Cables: Indnchem London SW1.

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

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