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UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

Genetic Engineering and Biotechnology Monitor

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Dear Reader,

The Conference on South-South and South-North Co-operation in Science organized by the Third World Academy of Sciences took place on the premises of the International Centre for Theoretical Physics in Trieste from 5 to 10 July 1985. For the first time ever representatives of science and research councils of the Third World and industrialized countries met to discuss problems concerning the development of science in the Third World and examine modalities of South-South and South-North collaboration in this regard.

The specific objectives of the Conference were:

- to identify science projects in which South-South and South-North co-operation is most profitable and examine possibilities of finding financial support for these projects;
- to strengthen co-operation between between science academies and research councils of the South and promote their role in the development of science in the Third World;
- to strengthen co-operation between academies of the South and those of the North;
- to develop and set indicators to study the status of science teaching and research in the Third World and examine possibilities of South-South and South-North co-operation in the advancement of science; and
- to identify high-level scientific research performed by Third World scientists as a modality of South-North co-operation in the advancement of science.

The Conference was organized into five working groups in order to formulate proposals for South-South and South-North co-operation on agricultural sciences, biological sciences, medical sciences, physical and mathematical sciences, and chemical sciences. Problems and expectations were discussed in regional groups and the role of international organizations, science foundations and networks were reviewed. UNIDO made a presentation of its activities in promoting science and technology in the South, notably its role in the establishment of the International Centre for Genetic Engineering and Biotechnology (ICGEB) in Trieste and New Delhi.

(Continued)

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While it was agreed that the Conference was a novel approach and an important forum for scientists of the Third World and their colleagues in the industrialized countries to meet and discuss common problems, attention was given to the establishment of mechanisms for the Third World Academy of Sciences to follow. The Conference accordingly established four further committees comprised of scientists and academics to deal with South-South co-operation, North-South co-operation, global projects and science centres. The Italian Government announced the contribution of US$3 million to the Third World Academy to implement some of its recommendations and provide research grants for high-level and promising scientific work, prize awards and fellowships to highly qualified research scientists in developing countries.

Discussions covered common trends of thought, with the emphasis on science transfer rather than on technology transfer. In regard to the statements made by the Executive Director of UNIDO, Dr. Khane, great interest was shown for the UNIDO-promoted ICGEB and a proposal was made to establish a like centre for micro-electronics, a subject which is engaging the attention of UNIDO.

A proposal for strengthening biotechnology at the global, regional and country levels was made by representatives of the Latin American region as the large number of studies carried out in recent years had made it clear that the new techniques included in "modern biotechnology" revealed great opportunities to combat problems of health and food production. Despite the relative strength of biological sciences in the Latin American region, qualified researchers were few and whole areas of essential biology were very weak, in particular micro-biology, molecular genetics, plant sciences and macro-molecular structure. Networks of scientific centres existing in Third World regions have been proven to be an effective means of joining and co-ordinating resources. The Latin American Biological Sciences Network, which was also supported by UNESCO and ICSU, which has been operating for ten years with very beneficial effects for the participating countries was cited as an example. Following the networking idea, UNDP drafted a proposal to organize a Latin-American Network of Biotechnology Centres to be linked to the ICGEB at Trieste and New Delhi. Proposals for action by the Third World Academy of Sciences included financial support to strengthen deficient areas of biology; that UNDP be encouraged to approve the proposed project for the Regional Network of Biotechnology Centres; that UNIDO direct the attention of the ICGEB towards supporting these regional and national networks; that the Third World Academy of Sciences promote the adoption of policies by Third World governments towards drafting national biotechnology programmes; and assistance in providing post-doctoral fellowships and training.

The next Conference will probably be held in 1987.

For those wishing to have further information on the activities of the Third World Academy of Sciences, the address is c/o The International Centre for Theoretical Physics, 34100 Trieste, Italy.

G. S. Gouri
Director,
Division for Industrial Studies

A. POLICY, NEWS AND OTHER EVENTS

UNIDO News

International Centre for Genetic Engineering: Recommendations on work programme, affiliated centres and related issues also made by scientific panel

The Panel of Scientific Advisers for the International Centre for Genetic Engineering and Biotechnology (ICGEB), which held its first session in February at UNIDO headquarters in Vienna, concluded that the most important criterion for the Centre to be comparable in scientific stature and quality to the world's leading scientific institutions was to have a scientific staff of the highest standard. These standards should also apply to administrative and support personnel.

In order to speed up the establishment and operation of the Centre in New Delhi and Trieste the Panel recommended that the Preparatory Committee of ICGEB enlist five to ten internationally outstanding scientists to be designated as "distinguished senior scientists" of the ICGEB during 1985. They would assist the work of the Panel in enlarging the range of expertise and experience available for the Centre's establishment and make suggestions for the posts of scientific staff.

They would also assist in organizing specialized workshops in major areas of the work programme to be held in 1985 which would enable a sharper definition of research and training activities to be undertaken in each programme area. The Panel considered the activity of such a group to be a worthwhile investment for the speedy establishment and operation of the Centre and could usefully continue after the Centre is established, providing support to the Council of Scientific Advisers when it is formed.

The basic objectives of the ICGEB, as identified by the Panel, are to enhance the capabilities of biotechnology in developing countries and focus this technology on the solution of problems unique to these countries. The Panel also emphasized the importance of the Centre's activities in basic and applied research; training of scientists from developing countries; and development and delivery of technology to developing countries in key areas. The ICGEB's activities should not attempt to duplicate ongoing research and development in the advanced countries but should rather give special attention to problems unique to developing countries.

Concerning the work programme of the ICGEB, the Panel felt very strongly the importance that both the Italian and Indian components of the Centre strive to reach critical mass as soon as possible. The Panel generally endorsed the research areas proposed with some qualifications.

The concept of affiliated centres and their importance in implementing the objectives of the ICGEB received extensive discussion by the Panel. Matters such as the criteria for affiliation, the timing of the organization of the network of affiliated centres in relation to the establishment of the ICGEB, and the funding of projects in the affiliated centres by the ICGEB were addressed.

The Panel recognized that safety issues had become more than a purely scientific question, having political dimensions as well as scientific ones and occasional discrepancies between perception and facts. The Panel agreed that one of the ICGEB functions should be to consider from time to time the adequacy of safety guidelines in effect and their relevance to the actual work conducted in the ICGEB and its affiliated centres.

Social issues

International Network on the Social Impacts of Biotechnology

The purpose of the International Network on the Social Impacts of Biotechnology (INSIB) is to establish linkages among social, natural and life scientists, humanists, science writers, policy analysts, and members of public interest groups. Many individuals with an interest in the social impacts of biotechnology find it difficult to communicate with one another either because they are situated in different disciplines or they are located in different countries. The formation of INSIB is a step toward improving communications transnationally and creating a new disciplinary locus for the study of the social function of biotechnology. In addition to current writings of the network participants, the guide also offers an annotated bibliography of selected published works and public policy statements of international significance. Requests to be listed in the network guide should be directed to the INSIB co-ordinator, Department of Urban and Environmental Policy, Tufts University, Medford, Massachusetts 02155, U.S.A.

Regulatory issues

Ethical guidelines for genetic engineering recommended by Swedish government committee

A Swedish government-appointed committee on genetic engineering has, in its final report, recommended the establishment of a number of ethical guidelines rather than laws to regulate scientific research in the field of recombinant DNA techniques and to limit certain applications of it on living organisms, in particular, man. The committee says, however, that the norms it has proposed should be mentioned in the law so that their existence is manifest and the responsibility for their promulgation and supervision is clarified.

First among the recommendations is a norm proposing that research and experiments on zygotes and embryos be acceptable, providing they are medically well founded, that they are performed within 14 days after fertilization (freezing time not counted), that the donors have given their free and informed consent and that embryos in vitro are not allowed to develop after 14 days of age.

Other proposals state that human zygotes and embryos exposed to experiments must not be implanted and developed in vivo ; and that research and experiments on human somatic cells in cell or tissue culture are acceptable as well as laboratory work with human DNA outside the living cell, experiments on human germ cells (sperm and unfertilized ova) and research aimed at gene therapy on human somatic cells.

Where gene therapy on human sperm, ova, zygotes and early cells (blastomeres) is possible to perform in a reliable way and implantation is to be considered, the operation must come under strict ethical examination which should include full knowledge of all the consequences, the report states.

Experiments on a live aborted embryo or foetus should be considered in the same way as those on a child, and the use of prenatal DNA-based diagnosis should be restricted to severe genetic diseases which threaten the development of the foetus or the child.

The report says the ethical committees for research already existing in each of Sweden's university regions should bear the primary responsibility for putting the new norms into operation, assisted by the Medical Research Council, the National Recombinant DNA Advisory Committee, the National Board of Health and Welfare and the Medical Disciplinary Board.

The report also states that in regard to the use of DNA techniques for future medical care, a prohibition should be enacted in law to prevent DNA-based diagnosis without sanction by the National Board of Health and Welfare, and that Sweden's efforts to support research in the developing countries should be aimed primarily at the development of vaccines and diagnostic methods for infectious diseases. (Source: SIP The Swedish-International Press Bureau, January 1985)

U.S. biotechnology regulation

While underscoring the scientific and technical significance of genetic engineering, speakers at a recent semi-annual meeting of the U.S. Chemical Manufacturers Association also stressed the urgent need to assure the public of its safety. This is the first time that communications, public relations and just plain common sense have figured so heavily in strategic planning before a crisis has developed.

Panel moderator Howard A. Schneiderman, senior vice-president in research and development with Monsanto, suggested that genetic engineering, the core of biotechnology, was not simply another great scientific advance, as was the transistor over the vacuum tube. Despite the broadcasting genetic engineering gets, its pending impact on society and its durability as a scientific tool in the service of humanity may be underestimated. Indeed, one can argue persuasively that genetic engineering may be the most significant scientific and technological discovery ever made.

It would be a tragedy of enormous magnitude if this promise were unfulfilled. And that constitutes the challenge. It can be stated quite simply: One must ensure that the products of biotechnology are safely commercialized. And one must ensure that the public at large perceives that biotechnology is being safely commercialized.

Even within industry today, there is some disagreement about whether regulation is necessary or not. The first task is to move beyond that question as quickly as possible.

Those in the chemical industry have learned - sometimes the hard way - that when the public has a concern about how safe an industry is, that concern will be addressed by the

government. Business has two choices: to be part of a partnership to develop the guidelines ensuring adequate protection - or to be adversaries. In the latter case, regulations emerge just as surely, but they often make the industrialization a lot harder.

"The processes and products emerging from biotechnology will and should fall under the regulatory scrutiny of government."

Schneiderman went on to offer a number of suggestions:

- Regulations should be based on sound science and a firm knowledge of biotechnology and biology, and, to this end, funds that are needed to assemble an expert government staff should be allocated.
- Panels of scientists to advise agencies should be created.
- Risk assessment should be separated from regulatory policy making.
- Opportunities for building consensus among parties interested in biotechnology should be created. (Extracted from Chemical Week, November 14, 1984)

U.S. Central Science Board

Last December, a U.S. Congressional House subcommittee debated the creation of a Central Science Board within the White House Office of Science and Technology Policy (OSTP) to oversee biotechnology policy and regulation. The proposed board, which has already been dubbed "Super-RAC" by government regulators, would be patterned after RAC, the National Institutes of Health Recombinant DNA Advisory Committee. Super-RAC's mission would be to ensure uniform policies by the Food and Drug Administration (FDA), Environmental Protection Agency (EPA), U.S. Dept. of Agriculture (USDA) and other government agencies that get involved in regulating genetic engineering. The proposal, which will be described in more detail in a Guidance Document in the Federal Register, was greeted with some skepticism by those federal-agency regulators who would be regulated by Super-RAC. The document's aim is to clarify regulatory requirements; reassure the public as to the safety of new biotechnology products; and to make the regulatory process, as it involves biotechnology, more "efficient" and "certain". The document will include a "road map" to help companies through Washington's biotechnology regulatory maze; guidance from each agency involved as to how it intends to review commercial biotechnology products; and a model system for co-ordinating and sharing scientific data among agencies.

While Super-RAC would, according to Dr. B. H. Bulkley, OSTP deputy director, "promote co-operation among federal agencies on emerging scientific issues," it would leave the jurisdictional disputes in other hands. Agency disagreements will be resolved "for the time being" on an ad hoc basis by the Working Group on Biotechnology of the Cabinet Council on Natural Resources and Environment.

One area rife with possibilities for jurisdictional dispute is EPA's definition of all gene-spliced products - except drugs, plants and animals - as "new chemicals" subject to the Agency's Toxic Substances Control Act. In an "interim policy" published in the October 17, 1984 Federal Register, EPA has also claimed genetically modified microbes as "pesticides" under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). (Extracted from Chemical Week, 7 November 1984 and McGraw-Hill's Biotechnology Newswatch, 17 December 1984)

Stricter controls called for

Private genetic engineering firms should be subject to stricter U.S. government controls, according to the Foundation on Economic Trends, which has now filed a lawsuit to that effect in the District Court. Private firms now follow U.S. National Institutes of Health guidelines on a voluntary basis, but the foundation says private firms should comply with the Environmental Policy Act because they use a patent license requiring them to meet NIH guidelines. Licensees of the patent process held by Stanford University and the University of California agreed to comply with NIH guidelines, and the foundation argues that private firms must therefore meet NIH requirements for approval of experiments. NIH says the patent does not cover experiments involving deliberate release of genetically altered organisms. (Extracted from Chemical Marketing Report, 17 September 1984)

New safety rules

Biotechnology limped forward a step as a federal court in Washington laid down new rules for experiments using genetically altered organisms in the environment. An appeals court ruled that the National Institutes of Health (NIH), which funds most academic biomedical

research, must perform an "environmental assessment" of each proposed release of altered organisms. The first such experiment will be the test of doctored bacteria designed to replace natural bacteria causing frost damage to crops developed by Dr. Steven Lindow of the University of California at Berkeley. The experiment has been held up by a lawsuit filed in 1983 by environmental groups. Anticipating the outcome of the suit, the NIH has already completed an environmental assessment of the proposed experiment giving it a clean bill of health. If the assessment holds up in court, Lindow presumably may proceed. Future proposals will now get a similar review.

The court ruled that the NIH must consider performing a lengthy "environmental impact statement" covering all possible experiments outside laboratories, rather than reviewing individual proposals as they come forward. Such a statement could take years to complete. Meanwhile, private companies are sending their research proposals to the Environmental Protection Agency, the government's body for controlling pollution, where environmental assessments are routine. The result of this division of regulatory labour could be that scientists at companies will forge ahead of their colleagues at universities. (Extracted from New Scientist, 7 March 1985)

US federal agencies issue control policy on biotechnology products

The long-awaited policy statements from federal regulatory agencies that will control the products of genetic engineering and biotechnology were issued for public comment last January. Although there are no surprises in the detailed discussions for regulating biotechnology products, their publication provides a forum for discussing the proper relationships among government regulators and the scientific and business communities on this important matter.

One of the main components of the notice is a regulatory matrix prepared by the Cabinet Council Working Group on Biotechnology through the White House Office of Science & Technology Policy. The matrix outlines the laws, regulations, and guidelines that may be applicable to biotechnology products. It involves research, development, marketing, shipment, use, and disposal. It gives specific legislative references for assuming regulatory authorities, the agencies involved, the affected products, and statutory cross references.

Following the matrix section are the policy statements from the Environmental Protection Agency, Department of Health & Human Services, and Department of Agriculture. Basically, each iterates positions taken last year on that agency's ability to regulate the products of biotechnology under existing laws. Each says that in many instances regulation of genetic engineering products is going to have to proceed on a case-by-case basis, at least until more knowledge about such products and their behavior is gained.

The Food & Drug Adminstration (part of HHS), for instance, notes that its regulations are all applicable to biotechnology, in general, and that the agency's rules on process control will require inspection of laboratory operations. Among the concerns at FDA are the possible inclusion of oncogenes into mammalian cells used for products made by genetic engineering or the occurrence of mutations in the gene-coding sequences that could change the product slightly from the original.

EPA's course has been clear for some time. It has long held that it has the authority to regulate biotechnology products. For example, last October EPA published a preliminary policy statement on the regulation of genetic engineering products used as pesticides. The January statement amplifies on that as well as on controls possible under the Toxic Substances Control Act. However, EPA admits it does not expect to regulate animals or plants that are altered or produced by genetic engineering techniques.

Plants and animals fall mostly under the auspices of USDA, which has a number of statutes relating to altered organisms. It anticipates that new biotechnology-derived forestry and agricultural products will be basically similar to conventional products and will keep its policies flexible, changing as the state of the technology changes.

Because of the perceived importance of products from genetic engineering, the government is suggesting a new, two-tiered oversight mechanism to monitor the field. Each of the involved agencies would be expected to set up a scientific advisory board composed principally of scientists with demonstrated expertise in fields of biotechnology. Those review boards would examine applications regarding advanced biotechnology techniques. The five agencies include, in addition to FDA, EPA, and USDA, the National Institutes of Health (which already has the well-recognized Recombinant-DNA Advisory Committee) and the National Science Foundation. NSF is expected to examine the potential effects of environmentally related basic research in biotechnology.

In addition, a Biotechnology Science Board would be set up, composed of two members from each of the agency-based committees and chaired by the assistant secretary of health from HHS. This group would review all applications relating to recombinant DNA, recombinant RNA, and cell fusion and help develop generic guidelines for similar, recurring applications. It would also serve as the main public forum for biotechnology debates. (Reprinted with permission from Chemical and Engineering News, page 8, 7 January 1985, copyright 1985, American Chemical Society)

Another round on issue of releasing genetically modified organisms into the environment

The National Institutes of Health (NIH) and activist Jeremy Rifkin clashed again recently in federal court over the issue of releasing genetically modified organisms into the environment. If the judges' remarks in court and their past rulings are any indication, NIH may be required to produce a full-scale environmental impact statement before approving any more so-called deliberate release experiments. However, the actual ruling from the U.S. Court of Appeals for the District of Columbia, which heard the case on 5 December, is not expected for months.

NIH and the University of California are appealing a decision handed down in May by federal district judge John Sirica that, in effect, put a moratorium on all field tests of genetically altered organisms by academic and industry researchers. (Private companies are not legally bound to refrain from field testing since Sirica only halted only federally supported research, but so far companies have chosen not to go forward). Three tests had been planned when Sirica ruled in May.

Rifkin had filed suit against NIH, claiming that it had broken the law by failing to conduct a proper analysis of the environmental impact of deliberate release experiments. Sirica's ruling stopped NIH from approving any more of these experiments until Rifkin's suit is disposed of. It also halted a University of California field test of bacteria modified to prevent frost formation on potato plants, a decision that the university appealed at the same hearing.

At issue is whether NIH should have analyzed in depth a change in its policy in 1978 that allowed deliberate release experiments on a case-by-case basis.

The Justice Department, which is representing NIH, argues that a single impact statement, which is a comprehensive analysis, of deliberate release experiments is not possible because individual experiments vary too widely to be considered generically. NIH argues that the proper analysis must take place on a case-by-case basis.

Just before the December appeals hearing, NIH conceded that it would write a simpler kind of environmental impact report of the three approved field tests. These reports, according to NIH officials, basically require the same information NIH has already collected, but in a different format. (Extracted from Science, Vol. 226, 21 December 1984)

Voluntary controls placed on embryo research

A voluntary body of scientists and lay people will oversee British research into in vitro fertilisation until legislation is enacted.

The idea of a voluntary authority is part of the MRC's response to the Warnock report on human fertilisation and embryology, published last July. The Department of Health and Social Security had asked the MRC to comment on the Warnock proposals.

The voluntary body will have "a strong lay representation" but will also have members drawn from the MRC and the Royal College of Obstetricians and Gynaecologists. It will allow research on embryos that are specifically donated for the purpose of research, but it will not permit scientists to research with or handle embryos that are older than 14 days.

In general, the MRC agrees with the recommendations of the Warnock committee but feels that certain matters have been left in the air. "It is essential that these be resolved in advance of legislation," says the MRC. The council would like the term "embryo" defined to confirm that "this refers to a viable conceptus developed from a fertilised egg and not to tissue or cell cultures of human origin, as many types of research (including studies in the field of cancer) depend on such embryonic material".

The definition of research should include "new and untried treatment", and applied research on embryos should not be separated from pure research, as Warnock envisaged. The council believes that "pure and applied research are part of a continuum", and the law should reflect this.

In its response to the Warnock report, the MRC says there are three reasons why research on in vitro embryos must continue:

- for the development and improvement of methods of treating infertility,
- for the detection and prevention of hereditary disease and congenital malformations,
- for the development of safer and more effective methods of contraception. (Source: New Scientist, 24 January 1985)

Government policy and biotechnology: Four key issues, by Bruna Teso and Salomon Wald [1]

Experts agree that biotechnology is likely to be the last technological revolution of the 20th century, bringing about vast economic and social changes through its impact on health, nutrition, the environment and energy. However, biotechnology is also one of the oldest manufacturing activities. Man learned to produce bread, wine, beer and cheese very early but without understanding the process of fermentation or the fact that yeast, which has been used of thousands of years, is a living organism. What has led to the present upsurge of this technology are scientific discoveries which permit better understanding and control of fermentation as well as of many processes of microbial, plant and animal life. The invention of genetic engineering, using recombinant DNA and other methods, has provided a new and powerful tool with which to modify living organisms for industrial, agricultural and medical use, not by trial and error as in the past, but in a planned and scientific way. The economic stakes are high.

Clearly, industries that deal with living organisms have special problems and raise challenges that are different from those of other industries. These problems and challenges are faced by virtually all countries having a biotechnology potential or capability. OECD's Committee for Scientific and Technological Policy, which includes these countries (many have joint ventures across borders) has chosen to focus its efforts on what Member countries consider to be the four most crucial issues in the field.

1. Safety and regulation

As recent headlines demonstrate, safety is at the heart of public and governmental concern with biotechnology. As early as 1973, some of the scientists involved issued warnings about the potential hazards of biotechnology and particularly one of its branches, genetic engineering. Two years later, scientists themselves reached a consensus (at an international conference at Asilomar in California) on safety measures to be adopted for laboratory experiments with recombinant organisms. Specific guidelines set up then for conducting research have since been relaxed as improved scientific knowledge has indicated that the hazards were considerably overestimated at the time. Nevertheless, the original fears raised by the scientists have not been completely allayed; public understanding of the problem has not kept pace with that of the scientists.

Three recent events show that there is still serious concern over this technology. In September 1983, the District Court of Columbia, in the United States, opposed the decision of the National Institutes of Health to release into the environment a recombinant DNA organism that protects plants from frost injuries. More recently a suit was filed, again in the United States, against experiments aiming at injecting a human gene, coding for the growth hormone, into animals so that they could become a cheaper source of meat. Opposition has also been expressed in other countries.

Thus the concern focusses now not on contained laboratory research, which - after ten years of experience - is considered by most people to be safe, but on the large-scale use of modified organisms in industry or in the environment and on the ethical aspects of genetic engineering. As recombinant organisms move out of the laboratories and into the factories for large-scale production, containment becomes one of the priority issues. Safety measures in factories where the volumes handled reach hundreds of thousands of litres cannot be extrapolated from laboratory conditions where experimental cultures normally do not exceed 20 litres in volume. A rare event in the laboratory becomes much more probable on this large scale. The problem is to ensure adequate containment of the various operations in the production process, particularly when dealing with dangerous pathogens or toxins. Strict safety precautions, sometimes even stricter than required, are already being taken by industry in new production units dealing with genetic engineering.

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[1] Division of Science and Technology Policies, OECD.

Industry is confident of the safety of biotechnology for several reasons. Compared to the laboratory, industrial strains have the advantage of being well characterised before they go into production, and they are also generally enfeebled. Furthermore, industry has long experience and a good safety record in handling living organisms, harmless or pathogens, for the production of food, antibiotics and vaccines. What still remains uncertain is what safety requirements are appropriate and what levels of containment should be assigned to different organisms. Clear codes of practice should be devised in concertation with government and would benefit the public as well.

Agricultural and environmental applications raise different concerns since, contrary to what happens in industry where enfeebled strains are used, the organisms are deliberately engineered to survive in order to accomplish the desired function and are of course not contained at all. For these reasons, risk assessment must be conducted with extreme care. The difficulty in weighing the potential risks of such applications is due to the fact that there is a very complex interaction between living organisms and the ecological system - and very little information about the links is available.

How should assessment for industrial and environmental applications be carried out and what schemes of regulations or guidelines should be developed? The problem is by definition an international one: micro-organisms do not respect national borders, and different safety requirements could create trade barriers. Moreover, scientific knowledge on these matters is not limited to a single country.

It is in response to these concerns that OECD countries have set up a special ad hoc group of scientific experts having governmental responsibility to monitor the safety question and to discuss regulations and their possible international harmonisation. The group's mandate applies to "organisms" which includes, in addition to micro-organisms, plants and animals since the application of genetic engineering techniques to these higher organisms is moving very fast.

The first task of the group will be to review the differing country safety policies for genetically engineered organisms in industry, agriculture and the environment. The review is particularly timely because of the divergences between countries. Some are now discussing new legislation while others have not even assessed their needs.

The group's second task is to identify scientific criteria which could serve as the basis of guidelines or regulations. An investigation into the safety of genetically engineered organisms for industrial, agricultural and environmental purposes necessarily means entering partially unknown territory. It is very likely that handling genetically engineered organisms will not entail risks different from those raised by conventional organisms, but a prudent course of action is necessary to take account of potential dangers.

As a prerequisite to setting criteria therefore, the components of the risk must be identified and analysed. A common approach to risk assessment would allow governments to monitor the fast-moving area of biotechnology in industry and in the environment without stifling its progress.

At the present moment, more than half of OECD's 24 Member countries are already engaged, to different degrees, in industrial applications of biotechnology with genetically changed organisms. Approximately ten countries follow the United States' National Institute of Health guidelines, which entail a voluntary system of notification by industry. Whether this system is adequate is still a matter of debate. What is clear is that governments must continue to play an active role in promoting safety procedures in biotechnology. They must also ensure that such procedures are flexible enough to keep pace with the rapid development taking place in this field.

2. Patent protection

Patents can be considered an instrument of innovation policy, especially for governments which prefer indirect to direct measures, in that patents encourage inventors by providing opportunities for financial reward. This is true for all inventions, but even more so for biotechnology in that the chemical and pharmaceutical companies which presently carry out a large part of all biotechnology R&D have traditionally relied on patents and are well versed in how to handle them.

But there are more substantive reasons why the patent issue is so crucial to the future of biotechnology. There are basic differences which separate microbiological from all other inventions - first, the fact that the starting material of most biotechnological processes, the micro-organism, is living and self-replicating under suitable conditions. A second difference is that a micro-organism cannot easily be described verbally or with a formula in

the way that, say, a chemical compound can. As patent law requires that an invention covered by a patent claim must be disclosed to the public, and as this disclosure must be repeatable by a person skilled in the art, biotechnology has raised new legal and scientific questions and has challenged traditional principles and procedures of patent law which are often based on 19th century science and technology.

Many countries have found an innovative legal response as a first step in solving the difficulties inherent in the patenting of living matter. Instead of depositing a description of the invention, together with the patent claim, the micro-organism itself can now be physically deposited, not necessarily with the patent office, but with a culture collection recognised by that office.

Since the essence of patenting is that it should be valid worldwide, an accord was reached in 1977 on an international framework - The Budapest Treaty on the International Recognition of the Deposit of Micro-Organisms for the Purposes of Patent Procedure, signed by 15 countries.

However, there are differences between countries regarding some aspects of the deposit requirement, for example the time when the micro-organism must be deposited, and who may have access to this deposit. There are also differences in the laws and regulations which govern release of the deposited micro-organisms to the public. The time and the conditions of this release vary widely between countries and have led to considerable debate. Should the micro-organism be released together with the compulsory first publication of the patent application, as in some countries, or only when the patent is granted, as in others? The biotechnology industry is worried about deposit and release conditions in some countries. It fears that a competitor could take the micro-organism and replicate it before a patent is granted or, when the patent is granted, through infringement of patent rights which might be difficult to prove. Improvement of deposit and release conditions, and some additional measures of international harmonisation, would allay these and other fears.

A second issue is raised by claims to naturally occurring micro-organisms. The law says that only an "invention" is patentable not a "discovery". Accordingly, few countries accept claims to naturally occurring micro-organisms without restriction. But several micro-organisms which have been, so to say, "found" in nature have turned out to be very useful in industry. It must be added that the act of "finding" is no quick or easy procedure but one that requires years of costly R+D, involving isolation, purification, toxicity testing, etc. This work is, scientifically and technologically, no less demanding than work with genetically engineered, that is "invented" micro-organisms. Should such work not also be worthy of patent protection?

A third issue is related to the problem of plant protection. In most countries, new plant varieties produced by plant breeders fall into the domain of special Plant Variety Rights. In the past, new plant varieties have been the result of a complex, often protracted trial-and-error process which was not amenable to written, scientific description and repetition, hence not patentable. But the new genetic engineering techniques and the fast advances in plant genetics have opened up the possibility of reproducing plant breeding successes and hence pose the question: should it not be possible to cover them by patent protection as well?

A fourth issue: many inventors in the field of biotechnology are academics and have a tradition of open communication of their results. In fact they may be bound to publish or perish. But if they publish, the information comes into the public domain and can no longer be patented. So the academic choice becomes publish or patent - unless, that is, there is a "grace period" which allows the inventor to publish first, then patent within some specified time period without losing his patent rights. (If there is such a grace period, the inventor can both publish and patent.) Only a few OECD countries have a grace period, however, and this seems to give them an advantage over countries which do not.

3. Long-term economic impact of biotechnology

The likely impact of the "biotechnology revolution" on the economy and society was one of the first issues to be publicly discussed, and gave rise to strong disagreement. To some, biotechnology was simply a technical tool - one among many - of the chemical and drug industries, in their continuous search, more than a century old, for new processes and markets. To others, biotechnology heralded the greatest socio-economic revolution of man since the prehistoric invention of agriculture.

More recently, the polemic has ceased, and doubts about the prospects of this technology seem to have been largely dissipated. Interest has focussed instead on how long it will take for the "biotechnology revolution" (the term is now widely accepted) to have a major economic

impact - 10, 20 or 50 years - and in which sectors the impact will be felt first and most - public health, the pharmaceutical industry, food, agriculture etc. A number of biotechnological advances seem to have been more rapid than predicted by the experts. Already, the new technologies are penetrating industry. There are hundreds of industrial firms, big and small, in the OECD area using or producing biological molecules or micro-organisms, with a combined annual turnover equivalent to many billions of U.S. dollars, not counting any of the traditional industries involved in manufacturing fermented foods and beverages.

The basic facts and figures that would be necessary to investigate the long-term economic impact are not yet available, but the international biotechnology industry feels that it will soon be able to contribute to such a study, as many biotechnology products and processes have reached the industrial production stage.

From the beginning, biotechnology has had a strong international basis, with numerous R and D, industrial and other links extending across national borders. Also, it is a reasonable working hypothesis that the main economic and social impact of biotechnology is likely to be quite similar in OECD countries.

Some of the questions that will be addressed by OECD: What will be the capital and energy-saving effects? What will be the employment effects, if any? How about the impact on international trade in agricultural and other organic commodities? On industrial structures?

4. Government policies and priorities in biotechnology R and D

Linked to the question of long-term economic impact is that of research priorities in biotechnology R+D since, to some extent, the economic impact will depend on these R+D priorities. Conversely, government R+D decisions will depend on their appraisal of the likely economic consequences of the research as well as commercial opportunities. There is a strong and increasing interest, nationally and internationally in government policies supporting biotechnology research and development. Obviously, because of the competitive nature of this new technology, international comparisons of such policies are of particular interest to governments.

OECD's work in this field will focus on a number of issues. One is the priorities of various OECD countries in their support of biotechnology R and D; it would probably be more interesting to find out where these priorities differ rather than where they coincide. Another issue is that of so-called orphan fields in science and technology which are relevant to biotechnology - those which industry is neglecting and which may, therefore, require government support. A third issue is how to overcome the shortage of qualified biotechnologists through training and higher education. A fourth issue is how to strengthen industry-university cooperation or in some cases how the independence and openness of basic research can be protected against strong commercial interests. (Reprinted from the OECD Observer, No. 131, November 1984)

Biotechnology policies in industrialized countries

A summary of recommendations made by experts on the development and promotion of biotechnology for their respective countries or community

Criteria	Recommendations/Steps taken	
	Countries/Organizations	Description
1. Definition of biotechnology	OECD	. To adopt a common definition of biotechnology.
2. Research and Development	CSIRO (Australia)	. Give highest priority for the continued development of techniques for genetic engineering in CSIRO. . Establish an industrial microbiology unit in CSIRO for innovative research with adequate research personnel . Continue research with recombinant DNA strains.
	OECD	. To support research, especially in plant genetics, microbial physiology and biochemical engineering. . To study new organisms other than Escherichia coli.

Criteria	Recommendations/Steps taken	
	Countries/Organizations	Description
	Japan	. Classify biotechnology as one of the fields in which research and development should be emphasized. . Attention given to research which cannot be accommodated under existing research structures. . Government extending subsidies to universities, and private corporations pursuing research on biotechnology while itself also conducts its own research and development. . Government has set up a systematic programme for research and development of enzyme technology.
	France	. Government identified biotechnology as one of the major strategic areas for development on which the science law and funds will be focused. . French Government policy on R&D will give increased emphasis to high technology sectors including biotechnology.
	Chemical Economic Development Committee UK	. R&D in manufacturing industry should be increased on a selective basis. Biotechnology is one of the chemical sectors where the emphasis should be given.
	West Germany	. Government plays an active part in funding and planning biotechnology R&D in universities and industry.
	Allelix Inc. Canada	. Will spend $100 million over the next 10 years focusing on the development of biotechnology-based products and process for commercialization.
3. Manpower and Training	CSIRO (Australia)	. To consider the needs for increased manpower in industrial post-graduate training, including biochemistry, microbiology and chemical engineering. . To introduce industrial post-graduate awards financed by the Science Research Council to attract more participants.
	OECD	. To increase specific skills in the interdisciplinary context of biotechnology at university level and above.
	Second European Congress of Biotechnology	. To provide opportunities for organizations to advertise vacancies available so as to attract biotechnologists from countries whose government lack interest in biotechnology.
	Chemical Economic Development Committee UK	. Calls for an increased output of scientists with appropriate skills - biologists, biochemists, toxicologists and others.
	Royal Society, UK	. Call for a concerted drive by the British Government to develop an active national policy on education for biotechnology. . The research and teaching efforts in biotechnology should be based in a few centres which must be provided with sufficient staff and funds.

Criteria	Recommendations/Steps taken	
	Countries/Organizations	Description
4. Co-operation between Universities and relevant Research Groups and Industries	CSIRO Australia	. To take positive steps to foster close cooperation and collaborative work between the molecular and other cellular biology units, universities and other relevant research groups in Australia. . To facilitate mutual exchange of competent staff between CSIRO, universities and industries by secondment or other practical means to accelerate research and commercialization targets.
	Japan	. Private corporation advancing research vigorously in new fields through technical licence agreement with their foreign counterparts with the aim of developing commercial processes.
	Britain	. Formation of biotechnology company whose objective is to make available for use by industry a range of products and know-how derived from outstanding biotechnology research in UK. . Establishment of specialized organic SWP to coordinate the efforts of interested parties to increase the total UK effort in this field and should be actively pursued.
5. Laws and Regulations	OECD	. To investigate possible legal and institutional solutions to the problems raised by industry-university links so that trade secrecy does not prevent the dissemination of information. . To investigate and compare the various patent systems of OECD countries with a view to making them more suitable for the new realities of biotechnology and possibly achieving harmonization between various countries. . To study the problems connected with the dangers and regulations governing the use of biotechnology especially at industrial level.
	Second European Congress of Biotechnology	. To review the regulatory policy on human therapeutic products, since the present regulatory requirements may be doing more harm than good.
6. International Trade and Markets for Biotechnological Products	CSIRO Australia	. To make every effort by CSIRO to secure relevant prompt information on existing and potential international markets for biotechnological products, and to seize the world market for Australian products.
	OECD	. To undertake a serious study of the long-term economic impact of biotechnology and to examine any ensuing changes in international trade. . To evaluate raw materials needs and costs and examine the competitiveness of biotechnology compared to other technologies.
	Chemical Economic Development Committee UK	. Companies in all sectors of the industry should be alive to the opportunities for exploiting development in biotechnology to serve worldwide markets.
	Canada	. Setting up of Allelix Inc. to develop a world scale biotechnology business.

Criteria	Recommendations/Steps taken	
	Countries/Organizations	Description
7. Culture Collection	CSIRO Australia	. Conserve the existing major microbial culture collections in Australia and to accommodate future new strains in a National Microbiological Culture Collection Centre. . To facilitate national and international coordination of the component collections by supporting the World Data Centre.
	OECD	. To improve and fund microbial culture collections.

(Extracted from Asia-Pacific Tech. Monitor, November-December 1984)

Council of Europe to discuss uniform biotechnology standards

In March the Council of Europe's Conference of Ministers responsible for human rights met to examine "the challenge to human rights posed by the development of science and technology: protection of human beings and their physical and intellectual integrity in the context of the progress being made in the fields of biology, medicine, and biochemistry." This follows adoption by the Council of Europe, towards the end of 1984, of a recommendation by its Ad Hoc Committee of Experts on Genetic Engineering (CAHGE) to establish a notification system for recombinant DNA experiments. The measure was designed to harmonize practices among the 21 Western European member states.

The document incorporated suggestions made in a 1982 text prepared by the European Economic Community for its ten members, but with three differences. Because CAHGE considered the risk of a harmful gene escaping from the laboratory a "conjectural hazard" which had been overstated, the new text left individual countries to define the categories of hazard. Second, in order to safeguard scientific and industrial secrecy and protect intellectual property, member states were asked to arrange that all notifications should remain confidential unless the notifying laboratories agree otherwise. Third, the Council of Europe decided it would not yet adopt specific provisions concerning recombinant DNA techniques for transfer into human patients. In recent months CAHGE has been studying problems likely to arise from the combined use of genetic engineering and new techniques of artificial procreation. (Source: Bio/Technology, January 1985)

New biotechnology study group formed

As a result of the increasing importance of federal monitoring of genetically engineered organisms, a top farm chemical trade association has decided to form a biotechnology study group. The National Agricultural Chemicals Association (NACA) had not become involved with the issue until last summer, when critic Jeremy Rifkin petitioned federal regulators to require experimental use permits for field tests of genetically altered pesticides. The Environmental Protection Agency responded by requiring companies conducting outdoor experiments to notify EPA to determine whether a permit is necessary. NACA's new arm will study gene-splicing issues pertaining to the Federal Insecticide, Fungicide and Rodenticide Act. (Extracted from Chemical Week, 26 September 1984)

General (miscellaneous information)

Biotechnology products in FDA pipeline

In the past four years, the U.S. Food and Drug Administration (FDA) has approved for marketing 55 "devices" involved in biotechnology - mainly diagnostic test kits and enzyme assays - but only a single recombinant-derived drug, human insulin. Testifying last month before the House of Representatives' Energy and Commerce Subcommittee on Oversight and Investigations the FDA's recently appointed commissioner, Dr. Frank E. Young, submitted a list of all biotechnology drugs and devices in his agency's pipeline for approval.

Besides the 55 devices and one hormone, the list shows three hybridoma-based diagnostics as having cleared the FDA's hurdle. Fifty-one other human healthcare products, plus some 60 veterinary substances, are in or approaching investigational use. Reproduced below is the unabridged array of recombinant-DNA and monoclonal product classes, rearranged for readability. It reflects the broad sweep of biotechnology's impending impact on the practice of medicine - human and animal.

Produced by recombinant-DNA technique		Produced by
Drugs and Biologics	Vaccines	Hybridoma techniques
Hormones:	Bacterial:	In-vitro diagnostics:
Human insulin*	Bacillus anthracis	Anti-human serum*
Growth hormones	Bacillus pertussis	Anti-human serum anti-C3d*
Interferon (α, β, γ)	Clostridium botulinum	[^{125}I] antibody to hepatitis B surface antigen*
Interleukins (1, 2, 3)	Clostridium tetani	Anti-tumor antigen antibodies
Colony-stimulating factors	Diphtheria	Anti-transplantation antigen antibodies
Differentiation factors	Escherichia coli	Anti-differentiation antigen antibodies
Hormone-releasing factors	Legionella	Anti-drug antibodies
Neuroactive peptides	Salmonella	
Reproductive hormones	Shigella dysenteriae	In-vivo diagnostics, therapeutics:
Immunosuppressive factors	Staphylococcus aureus	Anti-tumor antigen antibodies
	Vibrio cholerae	Anti-transplantation antibodies antigen
Blood components:		Anti-differentiation antigen antibodies
Clotting factors	Parasite:	Anti-toxin antibodies
Clot-dissolving factors	Filaria	
Human-serum albumin	Leishmania	
Anticoagulant factors	Malaria	
Low-density lipoprotein	Schistosomiasis	
High-density lipoprotein	Trypanosomes	
α-1 antitrypsin		
	Viral and Rickettsial:	Veterinary products**
In-vitro diagnostics:	Hepatitis B	
DNA hybridization probes	Herpes simplex	Drugs:
- of genetic disease	Influenza virus	Interferons (α and γ)
- for infectious agents	Poliovirus	Interleukins (1, 2, 3)
	Rabies	Growth hormones (bovine, porcine)
In-vivo diagnostics, therapeutics:	Vaccinia hybrid	Anti-tumor enzymes
Immune-competence-test antigens		Antibiotics derived by recombinant DNA***
Infectious-agent test antigens		Food additives:
Tumor antigens		Single-cell protein
		Amino acids

* Approved by FDA for marketing; others in or near investigational use.

** FDA is processing some 60 INADS (Investigational New Animal Drugs)

*** Pre-INAD

(Extracted from McGraw-Hill's Biotechnology Newswatch, 21 January 1985)

Centre planned for study of plant genetics

A plant gene expression centre to study the application of biotechnology to agriculture will be formed as a co-operative effort of the U.S. Department of Agriculture and the University of California, Berkeley. It will be located at the Western Regional Research Center of USDA's Agricultural Research Service in Albany, California.

At a press conference, USDA assistant secretary for science and education Orville G. Bentley said that research at the centre will focus on the biochemistry of plant gene expression to develop materials and techniques that can be used to improve crop productivity and disease and stress resistance.

To facilitate application of the basic research findings, the centre will operate a consortium which, through funding incentives, will establish co-operative programmes with other research institutions and private industry. The goal of such programmes will be to use the basic knowledge generated at the centre to develop specific agricultural products, an activity not envisioned for the centre itself. (Extracted with permission from Chemical and Engineering News, page 5, 6 August 1984, copyright 1984, American Chemical Society)

Biotechnology centre for North Carolina

National Science Foundation is providing $600,000 over five years for establishment of a research centre for immunology and production of monoclonal antibodies at Duke University and the University of North Carolina, Chapel Hill. The grant is part of National Science Foundation's industry-university co-operative research centre programme to strengthen ties between industry and universities. In addition to the NSF grant, $150,000 will be provided from state funds through the North Carolina Biotechnology Center and each industrial

participant will contibute $75,000 per year to be a member of the centre. The new research centre, directed by Willard C. Hamilton, is the first NSF co-operative project in biotechnology. (Extracted with permission from Chemical and Engineering News, page 28, 28 January 1985, copyright 1985, American Chemical Society)

Chromosome-specific human gene libraries made available

Recently the first batch of 50 chromosome-specific human gene libraries was shipped from Lawrence Livermore National Laboratory to 33 researchers scattered around the world. The shipment represents a milestone in a two-year-old project at LLNL and Los Alamos National Laboratory to establish gene libraries for each of the 24 different human chromosomes.

About half of the first phase of the project has been completed, consisting of constructing libraries containing relatively short - fewer than 9,000 base pairs - stretches of human DNA. Such libraries will be used primarily by medical geneticists in what is called restriction fragment length polymorphism (RFLP) analysis, a method of screening for genetic diseases.

So far, LLNL has libraries for chromosomes 4, 6, 13, 14 and 15 combined, 17, 18, 20, 21, and Y. Los Alamos has libraries for chromosomes 1 and 2 combined, 11, 13, 16, 18, 19, and 22. Van Dilla's counterpart at Los Alamos is Larry L. Deaven.

The second phase of the project, which will get under way later this year, will aim at producing libraries containing much longer pieces of DNA, up to about 40,000 base pairs. Such pieces of DNA are long enough to contain a complete human gene and its flanking sequences: thus, libraries containing them will be useful for molecular biologists probing the structure and function of specific human genes.

Most gene libraries consist of DNA fragments derived from the entire chromosomal complement of an organism. That makes finding a specific gene or DNA fragment particularly difficult. Dr. Van Dilla, who directs the project at LLNL, says that construction of gene libraries containing DNA from single human chromosomes was undertaken at the two laboratories because both possess the instrumentation and experience to sort chromosomes and because both had received numerous requests over the past few years to provide purified chromosomes to researchers.

The laboratories decided that producing chromosome-specific gene libraries - in which the DNA from a given chromosome is cut up and packaged in phages - would be more efficient than continuing to purify chromosomes for individual researchers. (Extracted with permission from Chemical and Engineering News, page 24-25, 4 March 1985, copyright 1985, American Chemical Society)

UK establishes national collection of animal cell cultures

To meet Europe's need for an internationally recognized patent depository for animal cells, the UK has established the National Collection of Animal Cell Cultures (NCACC) under Dr. Alan Doyle. The first such facility for animal cell cultures in Europe, the NCACC is in Porton Down, Salisbury, Wiltshire. It was opened in July 1984 under the auspices of the Public Health Laboratory Service as part of the Department of Trade and Industry's programme to support British biotechnology. Previously, there had been a gap in Europe in the worldwide network of national culture collections - a gap which had become more apparent as a result of increasing emphasis placed on the use of animal cells in biotechnology.

In the past, scientists in the UK and on the Continent had to obtain animal cell cultures from the American Type Culture Collection in the US. This was expensive primarily because of the high cost of the specialized shipment required for transporting animal cell cultures.

The NCACC is envisaged as a service facility to commercial and research organizations throughout Europe, and therefore its development will depend upon the requirements of its users. Some of the services currently offered by the NCACC are as follows:

Patent Cell Depository. The NCACC is registered as an International Depository Authority under the terms and conditions of the Budapest Treaty, as administered by the World Intellectual Property Organization. In this capacity it serves as an archival holder of certified cell lines in support of patent applications.

Safe Deposit Facilities. Individual scientists and commercial organizations who wish to safeguard valuable cell stocks can deposit ampoules for a rental fee. Commercial organizations that use or supply cell cultures can use the facility to have their seed stocks expanded under certified conditions, in addition to using the safe deposit facilities.

Specialist Collections. Various collectors within a particular field, research councils, and some international organizations may require a central bank of specialized cell types for standardization purposes - e.g., biopsy cell lines with genetic or immunological markers, human homozygous typing cells, or cell lines derived from families for disease marker studies. Such lines could be available for open distribution or only within a recognized group of depositors.

National Collection. All scientists will be actively encouraged to deposit well-studied cell lines for accession to a National Cell Culture Collection in which cells, after characterization, will be available to all applicants.

National Reserve Collection. The policy is to maintain examples of all the internationally recognized and well-characterized cell lines as a guaranteed safeguard against possible imposition of import/export restrictions in the future. The aim is solely to guarantee future supplies rather than to act as a distribution agency as long as alternative sources remain available.

Distribution and Cataloguing Services. Cells obtained from individual depositors, or under contractual agreement, can be distributed from this central facility, thus relieving scientists of the burden of using their time and resources to maintain seed stocks and dispatch cells. The NCACC will accumulate data obtained within its own laboratories, and from users, on all lines held. The NCACC could also act on behalf of users as a central liaison authority with other international cell banks.

Other Services. The NCACC offers the following: (1) the freeze-preservation of cells, either by routine techniques or by determining the optimal conditions for maximum viability, together with the retention of unique characteristics or functions; (2) an identification service, including karyo-type analysis and isoenzyme analysis; (3) sterility testing for mycoplasmas, bacteria, fungi, and selected viruses; (4) functional testing for virus susceptibility, product expression, antibody studies, etc.

Research. Research topics in the general area of genome preservation, stability, product expression and identification, and quality control will be pursued. This will provide an opportunity for funding by research councils and for contract research.

The NCACC is housed in a purpose-built suite of laboratories adjacent to the main building of the PHLS Center for Applied Microbiology and Research. There are specialist laboratories for tissue culture, microbiology, and biochemistry. Dr. Alan Doyle, the curator, is responsible to the director of the Vaccine Research and Production Laboratory for the day-to-day management of the NCACC. An advisory committee representing users and funding bodies will provide an additional safeguard of the commercial integrity and independence of the culture collection as well as advising on scientific policy. There will be close liaison with other national and international culture collections.

A nondifferential charging system has been introduced and will be levied on all services, except for the deposit of a cell line which has no restrictions on its distribution; such deposits will be free of charge.

The NCACC facilities are excellent and contain the latest cell-handling equipment as well as an excellent support staff. All information on the animal cell cultures is computerized for easy access. This facility serves a very important function and has been needed for some time. The British government is to be commended for support in building and organizing facilities which will be of great help to European scientists.

Directory of courses in biotechnology available

A directory of graduate degree programmes, special non-degree courses, and internships in biotechnology for developing country scientists has been prepared.

This directory is based on information obtained earlier this year from colleges, universities, research institutes, professional associations, and industries. It includes separate lists for institutions, degree programmes, and special courses.

The institution listing includes addresses and phone numbers for key contacts as well as information on consortium memberships and previous experience with developing country scientists. The listings for the degree programmes and special courses include a title and brief description of the subject matter and admission requirements as well as information on advisors or instructors and degrees or certificates awarded. An index is also included with sectoral listings of opportunities under Agriculture, Engineering, Environment, Health, Interdisciplinary Programmes and Basic Studies, and Veterinary Sciences.

The directory is intended for use as a first step in determining where specific types of training can be obtained and to facilitate communication with the institutions identified. Full details can then be readily obtained from the institutions of interest.

For copies of this directory, please write to BOSTID Report Distribution, National Research Council, 2101 Constitution Avenue, N.W., Washington, D.C., 20418, USA.

Rockefeller Foundation biotechnology career fellowships

The Rockefeller Foundation announces a programme of career development fellowships designed to enable scientists from developing countries, trained at outstanding centres for advanced research in biotechnology, to continue to work at those or other institutions for three months each year, over a period of at least three years, conducting advanced research and keeping abreast of new developments in their fields. The programme will focus upon the development and application of advances in molecular and cellular biology and immunology relevant to agriculture, health, and reproductive biology.

Funding will be shared between the Foundation and the host laboratory, with the Foundation providing travel and per diem support. It is hoped that the fellowships will encourage the establishment of ongoing working relationships between outstanding younger scientists working at third world institutions, and research teams at advanced laboratories.

Applicants to this programme should have at least Ph.D. - or M.D. - level training, a proven record of scientific productivity, and a permanent position at a research or teaching institution in their home country. A written project proposal must be developed and submitted jointly by the candidate and the laboratory sponsor.

Information about application procedures can be obtained by writing to Biotechnology Career Fellowships, Fellowship Office, Rockefeller Foundation, 1133 Avenue of the Americas, New York, New York 10036, USA.

International Network of Biotechnology selects 40 students

The collaborative projects set up by the "Technology, Growth and Employment" working group at the Versailles and Williamsburg summits have reached the operational stage. Within the framework of the International Network of Biotechnology, some 40 students from developing countries have been selected for the academic year 1984-85.

Collaborative research programmes have also been organised in such areas as: downstream processing, cellulose bio-conversion and nitrogen fixation. Details from: Dr. Ron Coleman, chairman, International Network, Department of Trade and Industry, Laboratory of the Government Chemist, Cornwall House, Waterloo Road, London SE1 8YX. Alternatively, Marc Chopplet, executive secretary, International Network of Biotechnology, 1, rue Descartes, 75005 Paris, France or on 634.36.65. (Source: Biotechnology Bulletin, Vol. 3, No. 11, December 1984)

Market for bioequipment predicted

Three growth sectors in the bioequipment field are identified in a study published by Creative Strategies International (CSI): computerized bioreactors, automated DNA and peptide synthesizers, and biosensors and other bioelectronics equipment. According to CSI's forecasts, contained in Emerging bioequipment markets: New technologies in the 1980s, the value of the world-wide market for these three types of equipment will grow from $100.5m in 1983 to $296.1m by 1990, representing a compound annual growth rate of 16.7% (see Table 1).

Table 1: Projections for emerging bioequipment markets, 1983-1990, in $ millions

Market segment	1983	1984	1985	1986	1987	1988	1989	1990	Compound Annual Growth Rate
Computer-aided bioreactors	90.0	105.3	123.2	144.2	168.7	197.3	230.9	270.1	17.0%
Automated synthesizers	10.5	11.9	13.4	15.3	17.2	19.4	21.9	24.7	13.0%
Biosensors/ Bioelectronics	-	-	0.5	0.6	0.7	0.9	1.1	1.3	21.1%
TOTAL	100.5	117.2	137.1	160.1	186.6	217.6	253.9	296.1	16.7%

(Source: Creative Strategies International.)

Computer-aided bioreactors account for approximately 90% of the total market over the forecast period, whereas the biosensors and other forms of bioelectronic equipment will only achieve sales of more than $1m world-wide in 1989, although the growth rate in this area is forecast to be highest of the three areas studied. Details from: Dr. Giselle Toth, director of industrial biotechnology, Creative Strategies International, 4340 Stevens Creek Boulevard, San Jose, CA 95129, USA. (Source: Biotechnology Bulletin, Vol. 3, No. 10, November 1984)

Biotechnology forecast

The biotechnology industry will need 5,000 more bioprocess engineers than are now available, according to Consulting Resources (Lexington, MA). By 1995, 35,000 bioprocess engineers will be needed. A shortage of agricultural specialists knowledgeable in plant genetics, growth hormones and animal vaccines will also develop. Sources of capital for biotechnology are now shifting away from venture capital and public stock offerings to acquisitions and joint ventures. Antibiotics, antibody diagnostic kits and animal biologicals present lucrative opportunities for biotechnological research.

Sales of biotechnological pharmaceutical products are expected to rise from $35 million in 1983 to $900 million in 1988 and $4 billion by 1993. Sales of biotechnology manufactured agricultural products will probably rise from $2 million in 1983 to $200 million in 1988 and $5 billion by 2000. Sales of biotechnological chemical products will rise from $5 million in 1983 to $100 million in 1988 and $3 billion by 2000. Pharmaceuticals under development with biotechnology include urokinase, interferon, DNA probes, growth hormones and vaccines. (Extracted from Chemical Marketing Report, 31 December 1984)

British biotechnology technology transfer club

The Biochemical Separation Technology (BIOSEP), a technology transfer club for the biotechnology industries, has begun its operations from the Harwell Laboratory at Didcot. It begins with 38 members, including some of the world's largest biotechnology, food and chemical engineering companies.

The BIOSEP was set up in collaboration with Warren Spring Laboratories to develop the large-scale biochemical separation technology (down stream processing) which is essential for industrial applications of major advances in biotechnology. Its aim is to provide information rapidly. Its services include design studies, data and state-of-the-art reports, etc. for use in construction and operation of separation plant.

Key research topics include membrane separation processes, adsorption and chromatography, and primary solid-liquid separation, including gravity and surface methods.

BIOSEP membership fees are linked to company turnover, with overseas companies paying a surcharge determined by the degree of their involvement in the UK economy. (Source: Asia-Pacific Tech Monitor, November-December 1984)

Gene therapy

Investigators will soon be ready to test recombinant-DNA therapies for correcting genetic disorders. Such techniques would be applied only to certain somatic cells (body cells, as opposed to eggs or sperm); they would not create inheritable alterations in the patient's DNA or affect the human gene pool. Nonetheless, the prospect of human gene therapy has raised some worries outside the scientific community.

As part of an effort to alleviate public concern, a working group within the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health has published a draft of a document titled "Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy Protocols."

Among the diseases that might be amenable to gene therapy are disorders of the immune system that occur when the gene for a particular enzyme is deficient. To treat such a disease some of the patient's bone-marrow cells might be removed and infected with a virus into which a functioning gene has been spliced. Once such a gene has been incorporated into the marrow cells' genetic material, the cells would be reimplanted.

Preliminary attemps at such therapy may be made in 1985. Heritable gene therapy is not being seriously considered for humans because of both technical and ethical barriers. Human gene therapy could be developed for five human diseases, including Lesch-Nyhan syndrome and deficiencies of the enzymes adenosine deaminase, purine nucleocide phosphorylase, argino-succinate synthetase and ornithine carbamoyl transferase.

The draft document lists questions that will be considered by RAC when deciding whether or not to accept a proposal to test such therapy in human subjects. The list is a long one and includes many specific questions about the nature and objectives of proposed experiments. There are also quite detailed questions about the experimental methods to be followed, the theoretical and practical bases of such methods, and the safety procedures to be employed. (Extracted from Science News, 5 January 1985 and American Scientist, March 1985)

Biotechnology stock prices

The prices of biotechnology stocks still bear little relation to the field's evolution and development - at least that is what Wall Street analysts maintain. This is small consolation, however, for edgy investors who have witnessed the steady decline in these issues since the stocks peaked two summers ago. Perhaps of more concern to the companies is that the low valuations have made it more difficult for them to secure additional financing - perhaps slowing their development even further.

Stock prices of selected biotechnology specialty firms

	Price May 11	Price Dec. 10	Percent Change	52 week Hi-low	Market capitalization in $ millions (stock price x number of shares outstanding)
Companies emphasizing recombinant DNA technology					
Advanced Genetic Sciences	5.3/4	3.3/8	-41	11.1/2-2.1/4	38
*Amgen	5	4.1/2	-10	8.1/4-3.3/4	49
*Bio Logicals	1.3/4	1.1/4	-29	2.1/8-1	7
*Biogen	11	5.1/4	-52	14-4.1/2	98
*Biotech Research Labs	9.3/4	7.1/4	-26	12.1/4-6.3/4	37
*Biotechnica International	6	6.7/8	+15	9.1/2-3.3/4	26
Biotechnology General	6	3.3/4	-38	8.1/4-3.1/2	17
California Biotechnology	10	4.1/2	-55	13.3/4-4.1/4	22
*Cetus	11.3/8	8.5/8	-24	14-8.5/8	190
Chiron	5.3/4	4.5/8		8.3/4-4.1/2	33
*Collaborative Research	6.7/8	4.3/4	-31	10.3/8-4	47
CooperBiomedical	7.3/4	2.7/8	-63	9.1/8-2.3/4	51
*Enzo Biochem	15.1/2	15.1/2	0	26.1/2-11.3/4	135
*Genentech	33.3/4	31.3/4	- 6	42.1/4-28.3/4	457
*Genex	10	6	-40	17.1/4-4.3/4	77
Integrated Genetics	4	3	-25	6.3/4-2.7/8	25
*Molecular Genetics	13	7	-46	16.1/4-6	43
Companies emphasizing antibody production technologies					
*Bio-Response	12.5/8	4.3/8	-65	14.3/4-3.5/8	35
*Cambridge BioScience	3.3/4	1.1/4	-67	4.3/4-1	5
*Centocor	10.1/4	9.1/4	-10	16.1/4-8.1/4	66
*Damon Biotech	7.1/2	5	-33	10.1/2-4.3/4	96
*Genetic Systems	7	5.3/8	-23	10.3/4-4.1/2	118
*Hybritech	16.1/4	14.1/4	-12	23-11	152
*Monoclonal Antibodies	12	8.3/4	-27	15.1/2-8	41
*Summa Medical	4.3/8	3.5/8	-17	8.3/8-2.1/2	28
Companies emphasizing other products or biotechnologies					
Applied Biosystems	18.3/4	27.1/4	+45	31.1/2-16.1/2	155
*Genetic Engineering Inc.	4	2.3/4	-31	5.7/8-1.3/8	7
*Immunex	6.1/4	7	+12	9-4	41
*Interferon Sciences	3.3/4	3	-20	5.7/8-2.5/8	12
*Ribi Immunochem	7.1/2	7.5/8	+ 2	12-6	26
Vega Biotechnologies	4	1.11/16	-58	5.3/4-1.5/8	5

The BIO/TECHNOLOGY Index of Specialty Firms stands at 627 as of 10 December 1984, down from 678 on 11 May 1984. The Index is composed of the 23 companies in the chart that are marked by an asterisk. For a more complete explanation of the Index, see BIO/TECHNOLOGY 1:536.

(Source: Bio/technology, January 1985)

Biotechnology and industry

Biotechnology was expected to change medicine as radically as electronics did the information industry. The parallel is proving misleading. Genetic engineering is merely a tool; the transistor is a product. For medicine, biotechnology has simply provided another way to make drugs. Many biotechnology firms want to grow into multinational pharmaceutical companies. But to do so they are having to compete with the established giants of the drugs industry.

So far, only one biotechnology drug has reached the market - a vaccine against pig disease. Only one biotechnology company, Genentech, is anywhere near to launching a significant drug - human growth hormone. What is making money is research, not products. More and more small biotechnology firms are coming to rely on servicing the drug companies through contract research and research partnerships.

Investors are beginning to lose patience as they realise how long it takes this new industry to get its products on the market. The price of the shares of biotechnology companies has slumped, and in many firms cash is running low. Patent offices have sat on applications for biotechnology patents. Most of those they have approved are for processes rather than products - and are therefore hard to enforce.

Of the 200 biotechnology companies in the world, only a handful are still rich enough to stand a chance of becoming drug companies in their own right. The most notable are publicly-quoted Genentech and Cetus in California and Biogen in Massachusetts; and the privately-owned Genetics Institute in Massachusetts. Even these are finding the going hard, having to sack employees and prune research projects. The mass of smaller biotechnology firms may be wiser to continue as service companies.

Genetic engineers in researching a drug have a simple brief: to look for proteins important to the normal functioning of the body, and then find ways of mass producing them. On the checklists of most biotechnology firms are (a) interferons and lymphokines which trigger anti-viral or immune responses; (b) hormones such as insulin or human growth hormone; and (c) blood proteins such as tissue plasminogen activator (TPA), which dissolves blood clots during heart attacks, or Factor 8, the blood-clotting agent for haemophiliacs.

This search for suitable candidates for treatment is the easy part. The hard part is isolating the genes of these proteins and then mass producing them. As natural proteins, genetically-engineered drugs were expected by their enthusiasts to prove far more effective and safe than synthetic drugs. But, TPA apart, most of the clinical trials carried out so far have been disappointing. Side-effects are a further complication. Naturally occurring products ought to be free of side-effects common to synthetic drugs, but interferon causes a kind of fever. Genetically-engineered HGH also seems to provoke a reaction, perhaps because it is not an exact copy of the human protein (bug-produced HGH carries a different amino acid at one of the protein ends), or because it is not sufficiently pure. The regulators have asked Genentech to perform more tests on the HGH that it had hoped to market this year.

Obtaining regulatory approval has become a more protracted process than the biotechnology companies originally expected. Biotechnology drugs are as open to abuse as any others, and the risk of abuse is increased by the grandiose claims once made for biotechnology products. Regulators worry that when interferon comes to market it might again be touted as a wonder-drug by the unscrupulous.

Scaling-up biotechnology processes - getting them from the laboratory to the factory - is another problem. The E. coli bug once expected to become the all-purpose workhorse for the biotechnology industry has its flaws. First, a foreign protein made by it loses its three-dimensional structure and must be "renatured" - pushed back into its original shape. That is relatively straightforward if the protein is small, such as insulin, but impossible with larger ones, such as Factor 8 or TPA. Second, E. coli, in common with all bacteria, cannot produce a perfect copy of a human protein. It does not have the enzymes to manufacture the chains of sugar molecules which attach to proteins in the body and may be necessary for the protein to do its job.

This means that biotechnologists are having to use more expensive mammalian cell culture systems to make large sugared proteins. But most biotechnology firms other than Genentech, and perhaps Britain's Celltech, lack the expertise to scale up mammalian cells. Many are having to turn to a drug company, Britain's Wellcome Foundation, to make proteins this way.

Biotechnology products face another hurdle: proteins have to be injected into the body. If taken orally, they are broken down by acid in the stomach or prevented by their molecular structure from crossing the gut wall. New systems will have to be found if

biotechnologists are to sell drugs to patients suffering from diseases not normally treated by injection. Scientists are trying to devise biodegradable polymers, loaded with protein, which will be slowly broken down to release the drug once they are implanted under the skin. Although the implant itself may have to be injected, it should last up to a year. But these systems are still some way from the market, and will be of use mainly to those suffering from chronic diseases. These obstacles can be surmounted - at a price.

The real money-spinners may turn out to be not protein-based products, but synthetic "second generation" drugs produced by genetic engineering. Or so the big drug companies hope: these are the sort of drugs they are used to making. They plan to design products which enhance or block the activity of hormones by acting at the receptor sites on the surface of the cell. To bring this off, they first need to make large quantities of protein (this is where the genetic engineering comes in) for use in modelling the synthetic drug. Such synthetic models, their enthusiasts claim, will be patentable and easy for a patient to take. Biotechnologists disagree. They note that proteins are highly complex and may bind at more than one receptor site. Drug companies, they say, may be good at producing drugs that block activity ("antagonists"). But they will find it harder to make "agonists", drugs which enhance a bodily function - it is the difference between gumming up a lock and making a key.

The biotechnologists think they still have an edge. And they still have a world to conquer. Of the 50,000 proteins made within a human cell, only about 100 have been cloned so far. The question for investors is whether the pioneers now staking their claims will be the ones who mine the big profits. (Extracted from The Economist, 8 December 1984)

"Old" and "new" competitors

Name	Nationality	Major activity	Biotechnology
Ajinomoto	Japanese	Agro-food, chemical, pharmacy	First world producer of lysine and monosodium glutamate (amino acids)
Ciba-Geigy	Swiss	Chemical, agro-chemical, pharmacy	Large research program, especially in seed and health fields
Corning Glass	American	Glass	Enzyme bioreactors on glass slides
Dow Chemical	American	Chemistry	Enzymes for cheese making
Du Pont	American	Chemistry (1st rank in world)	Human interferon research program
ELF-Aquitaine	French	Petroleum	Seeds; research on valorization of whey through biotechnology
Eli Lilly	American	Pharmacy	A major world producer of antibiotics; considerable fermentation capacity
Exxon	American	Petroleum (world's largest industrial group)	Research program on application of biotechnology to oil industry (extraction, pollution control) and chemistry
General Electric	American	Electric & electronics industries	Research on ethanol production and industrial applications of monoclonal antibodies
Gist Brocades	Dutch	Industrial & pharmaceutical fermentation products	Second ranking world producer of enzymes
Gulf Oil	American	Petroleum	Ethanol production by cellulose fermentation
Hoechst	West German	Chemistry, pharmacy (1st rank in world)	A major world producer of antibiotics
ICI	British	Chemistry, petrochemistry	Production of unicellular organic proteins (UOP); development of a biodegradable polymer
Kikkoman Shoyu	Japanese	Fermented products (sauces, alcoholic beverages, pharmaceutical enzymes)	Largest Japanese producer of soy sauce (shoyu)
Kyowa Hakko	Japanese	Pharmacy, chemistry, foodstuffs	A major Japanese producer of amino acids
Lafarge-Coppee	French	Cement	Amino acids (ranking European producer of lysine and sodium glutamate); seeds
Meiji Milk	Japanese	Agro-food (dairy products)	Research directed toward pharmaceuticals
Meiji Seika	Japanese	Agro-food, pharmacy	First Japanese producer of antibiotics in bulk

Name	Nationality	Major activity	Biotechnology
Mitsubishi Chemical	Japanese	Chemistry (rank 1st in Japan)	Its enzyme fixation process accounts for 40% of world SHTF [expansion unknown] production
Mitsui-Toatsu Chemical	Japanese	Chemistry	Research on urokinase and interferon contracted to Genex and Genentech (USA)
Monsanto	American	Chemistry	Seeds; animal growth hormones; large genetic engineering research program
Novo Industrie	Danish	Fermentation products; industrials & pharmaceuticals	Ranking world producer of enzymes, with 30% of market
Rhone-Poulenc	French	Chemistry, pharmacy	World's third largest fermentation capacity; ranking French firm in bio-industry
Royal Dutch Shell	UK/Dutch	Petroleum	Large research program focused on petroleum recovery, ores processing, chemistry, agriculture
Roussel-UCLAF (Hoechst group)	French	Pharmacy	Leader in cephalosporine antibiotics
Sanofi (ELF-Aquitaine gp)	French	Pharmacy	Products of biological origin (serums, vaccines, diagnostic reaction agents) account for 15% of turnover
Sankyo	Japanese	Chemistry, pharmacy	First Japanese producer of vitamins in bulk
Schering-Plough	American	Pharmacy	Antibiotics; invested $100 million to produce Biogen's Alpha Interferon
Searle	American	Pharmacy	Production of aspartame, a sweetening product; research on interferon
Shell Oil	American	Petroleum	Financing ($5 million) of research on interferon conducted by CETUS [expansion unknown]
Suntory	Japanese	Agro-food (alcoholic beverages)	Research on fermentation processes, enzymatic technology, genetic recombining
Takeda Chemical	Japanese	Pharmacy	Largest Japanese producer of enzyme-based and antibiotic-based medications; second ranking producer of vitamins in bulk
Unilever	Dutch	Agro-food (1st rank in world), chemistry	Focuses large part of its research on biology: working on enzymatic systems, application of monodonal antibodies, cellular cultures, cloning of oil palms on commercial scale

(Source: L'Usine Nouvelle, 23 February 1984)

B. COUNTRY NEWS

European Economic Community

EEC - funding cutback

The European Council of Research Ministers has approved $40 million in funding spread over five years for biotechnology programmes proposed by the European Commission, a policy-making body of the European Community (EC). The award is a sharp cut from the $64 million that EC biotechnology officials had proposed. The approved funding will maintain research and training programmes that already exist. However, research contracts that the European Commission had hoped to grant to European firms and universities, as well as research on risk assessment, will not be funded. In addition, there will be limitations on the timing for spending the newly allocated funds. Only $25 million may be spent during the first two years; in mid-1986, the research ministers will meet again to review the remainder of the programmes. (Source: Chemical Week, 2-9 January 1985)

Australia

Chemicals from algae

The Australian government has awarded an A$3 35m. contract to Westralian Farmers Co-operative Ltd. of Western Australia for a project to investigate the production of chemicals from algae. Genetic manipulation of algal cells to enhance their productivity will form a part of the project. Laboratory work will be carried out at Bayswater, Western Australia, and field tests at the company's pilot facility at Hutt Lagoon, north of Geraldton, WA. (Souce: European Chemical News, 22 October 1984)

Blood clot assay

The University of Queensland has developed an assay based on monoclonal antibodies to detect blood clots more rapidly, accurately and cheaply than currently available assays. The monoclonal antibody can detect low levels of D-dimer, a byproduct of clot formation. Clinical tests have shown that the antibody can distinguish between normal D-dimer levels and those found in patients with dangerous clot formation. The assay can be completed in several minutes, as against six hours for conventional tests. MAbCo, a biotechnology firm, has developed a kit form assay and has applied for FDA (US) approval. (Source: Chemical Week, 22 August 1984)

CSIRO breakthrough

Australian researchers working at CSIRO, Canberra City, Australia, have scored a major plant biotech breakthrough using mutagenesis. They have created a linseed plant whose seeds contain an edible form of linseed oil. The development is expected to have an impact in certain wheat-growing regions of Australia, Canada, the USSR and Argentina. (Source: BioEngineering News[R], Box 290, Willits, Ca. 95490, USA, Vol. 5, No. 27, 18 December 1984)

Venture fund backs bioprocesses

An Australian venture capital firm is to fund the development of two biotechnology processes developed at the University of Queensland. The company, Queensland Science and Technology Limited (QSTL), has financed the university's marketing concern, UniQuest Limited, for the development of the Bio-Wastech protein-from-wastes process and the Sucrotech process which produces ethanol and fructose from sugar cane. QSTL is to fund R&D projects at the university and will license and market the resulting technology. The company is contemplating funding a number of projects, including an ovarian cancer diagnostic and a bovine mastitis vaccine. (Source: European Chemical News, 4 March 1985)

Austria

Austrian developments in biochemistry

Since the discovery of the acid-stable Penicillin V, Biochemie GmbH has developed into Austria's largest producer of antibiotics. The special strength and experience of the firm is in the area of the fermentative production of antibiotic substances. For some time now, the research and development department of Biochemie has concentrated its activities on the stock improvement and fermentation of micro-organisms as well as on the processing and chemical refinement of substances produced by them. Whereas hertofore there has been an attempt to achieve greater yields in the "trial and error" method through mutation, hybridization, subsequent selection and recombination of the stock material, now the spectular progress in molecular genetics is opening up possibilities to construct improvements through cloning. With the recent completion of two new laboratories, the company will also participate in basic research in genetic engineering. (Extracted from Die Presse, 21 November 1984)

Belgium

New Belgian biotechnology firm

A new biotechnology firm is being set up in Belgium to develop drug-delivery systems based on liposomes (lipid micro-encapsulation). The company, Celltarg, is a joint venture between The Liposome Company (TLC) of Princeton, New Jersey, and Belgium's Louvain University.

The two parties will each put up 40 per cent of the new firm's BF72m. ($1.2m.) capital, with the remainder to be made available to the staff. To be set up on the university's campus at Sint-Lambrechts-Woluwe near Brussels, the venture is also being supported by local government cash. Marketing of products from the new company will be carried out by a

subsidiary, Eurolip, that TLC plans to set up in Belgium by the end of the next year. TLC is currently developing its proprietary liposome technology for the controlled release of drugs and biological agents in both animal and human health-care applications. Celltarg plans to focus its efforts on systems to treat malaria, hepatitis, liver cancer and related diseases. (Source: European Chemical News, 10 December 1984)

Canada

Chair in biotechnology

Canada's first chair in biotechnology has been established at McGill University in Montreal, through a special $750 000-grant from Canadian Pacific Limited. The first incumbent, chemistry Professor Kelvin Ogilvie is known for his development of the DNA/RNA Synthesizer, better known as the "gene machine", important for the manufacturing of synthetic substances such as insulin and interferon. His current work includes the study of viroids, infectious agents made up of RNA which affect plants of commercial concern. (Source: Canada Weekly, 21 November 1984)

Canada goes for biotechnology development

A National Advisory Committee on Biotechnology has been formed in Canada with the appointment of 25 members, drawn from the private sector, universities and government agencies, by the Canadian Minister of State for Science and Technology and Economic Development.

The Committee will advise the Minister directly on the development of biotechnology areas such as energy, food, drugs, chemicals, plastics, mining and agriculture. The Committee will also provide guidelines and ensure that the opinions of the industry and the universities feature as a main factor in the Federal Government's programmes in the field.

The Federal Government of Canada has allocated C$22 million to implement the national biotechnology strategy so that Canada benefits from new developments in this area. The strategy supports research networks, involving industry, universities and government, which concentrate on using biotechnology to enhance industrial development and the use of Canada's resource base. (Source: Asia - Pacific Tech. Monitor, November - December 1984)

Rapeseed harvest improvement

Genetic engineering should improve the prospects for the industrial rapeseed harvest. Canadian rapeseed output was 3.246 million tons in 1984, about 50 per cent of which was the newly developed variety. Erucic acid content of the rapeseed was lowered by dry weather and different soil conditions to the California soil where the variety was developed. The new variety can be used for feed after the oil is crushed out. Industrial grade oil has about 45 per cent erucic acid content whereas the new variety has 41-54 per cent oil content, depending on location. Industrial grade rapeseed is generally not used for feed because of its low glucosinolate content, but the new variety has a higher concentration. (Extracted from Chemical Marketing Report, 7 January 1985)

China

China and Japan sign five-year R&D agreement

In the first R&D agreement between the People's Republic of China and a Japanese biotechnology company, Nippon Zeon Co. Ltd., and China's Biotechnology Development Center finalized a five-year pact in March. The Beijing centre and the Tokyo-based firm will undertake joint R&D in animal cell culture aimed at pharmaceuticals and fragrances. Under the first stages of the agreement, two or three Chinese senior researchers will join their Zeon counterparts at the firm's Kawasaki research centre. (Extracted from McGraw-Hill's Biotechnology Newswatch, 18 March 1985)

Discovery of N-RAS cancer gene

Assistant researcher Gu Jianren and others at the Shanghai Municipal Oncology Research Institute have discovered for the first time the N-RAS cancer gene in human primary liver cancer. Experts believe that this discovery by Gu Jianren has provided a requirement for future thorough research on molecular mechanisms of carcinomatous degeneration. (Source: RENMIN RIBAO, 10 November 1984)

US/China joint venture

Under a joint venture with U.S. and Canadian firms, China is forming its first company for making products an. supplies for biotechnology research and genetic engineering. Based in Luoyang, Henan Province, Sino-American Biotechnology Co. will receive advanced technology from Promega Biotec, Madison, Wis. - the first agreement for technology tranfer to China in this field, according to Promega. Nine senior Chinese scientists will receive training in Madison. Also a partner in the venture is SinoGenetik of Vancouver, a consulting firm. Production will start within a year, and will expand within three years to include human and animal diagnostics research, instrumentation, and agricultural applications of biotechnology. (Reprinted with permission from Chemical and Engineering News, page 23, 4 March 1985, copyright 1985, American Chemical Society)

Denmark

Human insulin production facility planned

Novo Industri is moving ahead with plans to build a commercial-scale fermentation facility to produce recombinant DNA human insulin. The plant, which will also be able to produce other gene-spliced hormones and enzymes, will be built in Kalundborg at a cost of around DKr100m. ($9.5m.) once the Danish authorities give their approval.

Since Novo cannot predict when Denmark's environmental agency will grant approval for the project, the company will not estimate completion and start-up dates. Construction will start as soon as it is obtained.

The multi-purpose plant, which is to be engineered by a Novo team, will have shared downstream purification facilities to save on capital investment costs. It will be equipped with several "standard type and size" fermenters. If the Danish plant proves a success, Novo may well build a similar human insulin unit in Canada to serve the North American market. Novo has a joint venture in Canada with Connaught Laboratories. (Extracted from European Chemical News, 12 November 1984)

Egypt

Natural pesticide

Brown algae may be a natural source of pesticides, according to Drs. M. A. Saleh and N. M. Abdel-Moein of the University of Cairo and Mr. N. A. Ibrahim of the Ministry of Agriculture. An extract from the algae reduced the appetite of the cotton leaf worm. The most active appetite suppressant is an azulene-based compound. Researchers discovered this property when they observed that house flies ignored the algae when it was left to dry in the open. (Extracted from Science News, 12 January 1985)

Federal Republic of Germany

German genetic research into plant disease

Viruses are more and more often determined to be the pathogenic agents of plant diseases. Improved diagnostic procedures now make it possible to identify these micro-organisms. To combat the pathological agents, more resistant plants need to be cultivated with the help of botanical methods. Research in Giessen has proved that plant viruses are found in rivers as well. Presumably they get into the waters directly from diseased plants or through the soil. Viruses, without causing visible damage, could lead to a reduced harvest for fruit trees.

New methods of biological plant protection are now being tried to protect useful plants from viral attack. Research into procedures that improve the resistance of plants without thereby changing their genetic constitution is being undertaken in the Federal Republic of Germany whereby virus-repulsing fungi are cultivated in a nutrient solution. The resulting product is subsequently sprayed on the underside of the plant leaves. This method apparently activates the defensive system of the plants. The same purpose is served by the development of plants resistant to viruses which will become more and more important in the future to repress disease-prone varieties. Meanwhile, with the help of gene technology, it has been possible to develop resistant plants from isolated and resistant cells of potatoes and rape. However, with the multitude of viruses and plant varieties it is still a long way to the development of permanently resistant plants. (Extracted from Chemische Industrie, November 1984)

German support for biotechnology industry expanding

Another gene centre was opened at the beginning of May 1984 in Munich. After Cologne and Heidelberg, it is the third focal point in the FRG in which there is to be basic and applied research in gene technology. What is new is that scientists from the Max Planck Institute and the university will work together supported by a non-profit association. Working groups will be established at the Max Planck institutes in Martinsried and in three departments of the Ludwig Maximilian University in Munich. Prof. Ernst-Ludwig Winacker is director of the Munich gene centre. (Extracted from Handelsblatt, 22 October 1984)

Hoechst to build r-DNA insulin unit

Hoechst has unveiled plans to build a plant to produce human insulin via genetic engineering. The move follows the pioneering work in this area by Eli Lilly and Novo.

Construction of the new unit is to begin at Frankfurt this year, with commissioning following two years later.

The capacity of the planned plant is unknown, but it may also be used for other fermentation-based processes. The amount of insulin produced will depend on market conditions. (Extracted from European Chemical News, 22 October 1984)

BASF licenses TNF from Biogen

Genetic-engineering firm Biogen, with laboratories in Cambridge, Mass., and Geneva, Switzerland, has signed a licensing agreement with West Germany's BASF for the tumor necrosis factor (TNF) developed by Biogen using recombinant-DNA technology. In vitro tests have shown that TNF kills certain cancerous cells while leaving normal cells unharmed. Biogen has cloned and expressed recombinant TNF in quantities said to be sufficient to support clinical trials, but further development is needed before the product can be marketed. (Extracted from Chemical Week, 19 December 1984)

Biotechnology sulphur process studied

Scientists at the West German mining research institute (Institut für Bergbau-Forschung) in Essen have developed a process that uses sulphur bacteria to remove more than 90 per cent of the inorganic sulphur from coal.

Amounts of fly ash and trace elements also have been reduced, the institute said. The process is currently being tested in a bench-scale unit to gather data for a pilot plant, which will be built at an unspecified date in the future.

Parallel to the experiment with sulphur bacteria, the institute is testing bacterial strains which can remove organic pollutants from process water in coal beneficiation plants. The institute said it is also working on biotechnical methods of converting coal and coal derivatives into higher added-value products. (Source: European Chemical News, 11 February 1985)

German Government sponsoring

The FRG research ministry is funding projects on nitrogen-fixing c ants to the tune of DM3.2m. ($1m.) over a two-year period. Work on soil utilization of n fertilizers is being supported with DM9.5m. annually. One project currently sponsor ses on developing a protein-rich potato.

Projects designed to promote farm animal health get DM3.5m./year.

The ministry also funds in-vitro fertilization R&D. In human health-care the government is funding the development of new types of interferon. (Extracted from European Chemical News, 5 November 1984)

France

French cement group seeks growth in biotechnology

Lafarge Coppee, the French-based international cement group, is expanding into food and agricultural-linked biotechnology activities following a series of acquisitions and expansion moves in France and the U.S. over the last few months.

Lafarge's bio-activities are centred on Orsan, a concern with its roots in the sugar business going back to the beginning of the century. Orsan, which came under Lafarge's control in its 1980 link-up with the Belgian group Coppee, got out of sugar and invested in the fermentation business during the 1960s.

Orsan provided Lafarge with the biotechnology entree it had been seeking. As a technological follow-up from its activities in sugar refining, Orsan is now one of the world's leading producers of monosodium glutamate, and under a collaboration deal with Ajinomoto of Japan signed in 1974, controls about one-third of the world market for lysine.

Lafarge was, however, determined that its biotechnology efforts should not stop at amino acids. Following months of searching, Lafarge through its Orsan unit bought the Illinois based maize seed company, Wilson Hybrids, one of some 200 smaller U.S. groups in the seed field behind the leader, Pioneer. It followed this up just before Christmas with the purchase of the seed production business of the U.S. chemicals group, Celanese, and by building up its stake in one of France's biggest seed companies, Claeys-Luck, which specialises in wheat. (Extracted from Financial Times, 30 January 1985)

French energy programme plans pilot plant to turn farm wastes into chemicals

One ton a day of chemical solvents from 47 tons of agricultural waste is the target of a large-scale pilot facility at Soustons, France. It will combine three processes, each claiming to be an advance over existing practice in biomass conversion. The aim of the project is to obtain an economically produced cellulytic enzyme to break down the B-(1-4) linkages.

The facility is scheduled to come on stream in the fall of 1986, and is part of the government's programme to produce substitute fuels from biomass in the framework of its petroleum conservation policy. The future plant is planned as the final stage before full-scale industrial production. It will process 12 tons of straw and 25 tons of corn stover to yield 0.6 tons of butanol and 0.4 tons of acetone-ethanol. (Extracted from McGraw-Hill's Biotechnology Newswatch, 15 October 1984)

Biotechnology in France

As part of French efforts to break down the distinctions between fundamental and applied research in biotechnology, Elf Aquitaine has set up a new complex at Labège to bring together key elements of the group's biotechnology efforts. The laboratory carries out genetic engineering research for development of pharmaceuticals and aromas for food and perfumes. One promising area is production of human growth hormone by general recombination techniques using cells from monkeys' kidneys. Another is the production of interleukin-2 (IL2) with potential for making good deficiencies in the body's resistance to disease. A further sign of France's interest in biotechnology, is the Banque National de Paris hiring of a research scientist to look after its expanding portfolio of participations in bio-companies (Extracted from Financial Times)

Joint venture in seeds research

The Monsanto subsidiary, HybriTech Seed International, and a French agricultural company, Coopérative de Pau, have announced plans to create a new research-oriented seeds joint venture. Its aim will be to develop and commercialize new and improved wheat and barley varieties and hybrids.

Coopérative de Pau - also known as CACBA or Coopérative Agricole de Céréales du Bassin de l'Adour - and Monsanto have been conducting joint trials for a year on genetically engineered corn. As part of the venture, Monsanto is also developing gametocides used to make hybrid cereals. (Extracted from European Chemical News, 26 November 1984)

AIDS test kit

France's Institut Pasteur Production has developed an Aids test that could be on the market next spring. The kit allows some 80 simultaneous automated determinations of the Aids virus, which has also been linked to the disease LAV. Based on anti-LAV antibodies, the test is to be made available to a dozen French blood transfusion centres and hospitals for trials. Genetics Systems, IPP's US partner in the joint venture, Blood Virus Diagnostic Inc., also plans to launch a test in the spring. The market is estimated at 50m. tests per year. (Source: European Chemical News, 10 December 1984)

Du Pont Aids test

Du Pont has started European clinical trials of its Aids test. If the multi-site trials are successful, the company predicts that the product could be available commercially early this year.

The test, which is designed to check the spread of the disease detects antibodies to the virus (HTLV-3) believed to cause the disease. Du Pont estimates that European demand for such a test could top 20m. units a year. (Source: European Chemical News, 18 February 1985)

Greece

Hellenic Biotechnology

Founded last April, Hellenic National Biotechnology Company is now performing custom peptide synthesis and developing RIAs. It is also said to be providing Greek bioresearchers with domestically-produced restriction enzymes. (Source: BioEngineering News[R], Box 290, Willits, Ca. 95490, USA, Vol. 5, No. 27, 18 December 1984)

Hungary

Hungary seeks help

Hungary is looking for help in establishing a plant to convert 140 000 ton/year of corn to enzymes, corn oil, fodder additives and other products. The unit would be built alongside an existing chemical facility.

Enzymes to be produced in the proposed plant could include thermostable alpha-amylase and immobilized gluco-amylase. Hungary is interested in receiving proposals from firms on technology and the capital costs. (Source: European Chemical News, 4 February 1985)

Ireland

Allied Irish Banks backing

Allied Irish Banks is backing a research programme aimed at cutting milk and cheese production costs, and developing new products - including innovative chemicals - from milk.

Biotechnology will be the key to this innovation, which the bank is sponsoring to the tune of £240,000. The research will be carried out over the next five years at the Agricultural Institute's Moorepark research centre in Co. Cork. The Agricultural Institute points out that the dairy industry has come through two decades of unprecedented growth in output, but the range of products made has not increased much despite this expansion.

Future profitability will depend on the ability of the dairy industry to diversify, and diversification will need new technology. The Moorepark centre researches food product innovations involving modifications in milk protein, and is concerned with new developments in cheese manufacture.

The AIB-backed project, which started last month, will pioneer developments in two important areas: Whey, a by-product of cheese and cassein manufacture, and starters essential for making cheese and other fermented dairy products. Over the past four years, Moorepark staff in collaboration with UCC have developed a new starter system for cheddar cheese now used in 65 per cent of all Irish cheddar. Now it's hoped to extend the system to yoghurt and continental cheese varieties.

The new AIB funded project will concentrate on studying the genetics of lactic bacteria, with a view to developing strains which will shorten the time needed for cheese to mature. (Extracted from Technology Ireland, January 1985)

Irish firm to develop PCB-degrading microbes

International Biochemicals is developing microbial cultures to deal with polychlorinated biphenyls (PCB) pollution. PCB disposal is a growing problem as incineration comes under continued pressure. Several other companies are hoping to develop "superbugs" to deal with the toxic chemicals.

Researchers at International Biochemicals' Dublin laboratories are also working on systems to control nitrate levels in wastewater streams. Other R&D projects focus on pure cultures to treat specific chemical and hydrocarbon-contaminated waste streams.

Sales of effluent-treatment products have been growing at an annual rate of 33 per cent over the last three years. Currently growing at over 20 per cent a year, International Biochemicals' agricultural products probably have the greatest market potential. Shell Chemicals UK is marketing the firm's microbial silage additive. Other potential areas include straw digestion and nitrogen fixation.

In the institutional area, the company sells microbial cultures to replace chemicals such as acids and caustic soda in drain cleaning and grease removal in hotels, hospitals and fast-food restaurants.

Although International Biochemicals' researchers are working on projects involving genetically altered micro-organisms, including Pseudomonas, no products are likely to be marketed until government agencies have drawn up clear guidelines covering their use.

The company has solved a number of effluent treatment problems at petrochemical complexes and oil refineries. It developed a saline-resistant bacterial culture to degrade phenol contamination in wastewater from an ethylene cracker at Thessaloniki, Greece. The Chinese Petroleum Corporation in Taiwan used its cultures to clean up oily effluent from its refinery complex. In addition, a chromium-tolerant culture was developed to treat effluent from a fertilizer plant at Pancevo in Yugoslavia. (Extracted from European Chemical News, 7/14 January 1985)

Italy

Italy wants biodegradable plastic bags

The Italian government has given the country's plastics producers until 1991 to come up with a biodegradable plastic for supermarket bags. The order does not cover industrial packaging. State-owned ENI, Italy's biggest polyethylene producer, is working on two processes. One focuses on an additive that triggers degradation of polyethylene by air and light. The other is a system that involves chemical binding of a photooxidation molecule to the polymer so that the material will disintegrate over time. (Source: Chemical Week, 16 January 1985)

Italy surveys biotechnology sector and issues report

The report on "Biotechnologies in Italy" prepared by the Federation of Scientific and Technical Associations (FAST) in Milan, was drawn up by a research group charged with surveying 142 operational units. The report was completed under the auspices of Milan Popular Bank, Caboro, Montedison, Pierrel, CNR (National Research Council). It showed who does what in Italy in the field of biotechnology, and what is the participation of the public institutions (universities, institutes, CNR [National Council on Research] centers and that of the industries or private institutions.

The first object of the report was to set up a catalogue in which research groups are listed by field of interest. Another aim of the report was to evaluate the impact of biotechnologies on the industrial production process by analyzing the present or future achievements of other countries.

Many Italian laboratories have an excellent level of skill, but without a clear view of the industrial implications of the new techniques, their skills would remain in the academic field: the report aims at stimulating relations between public and industrial research. The survey dealing with operational units is limited to certain sectors, chosen among the most promising: recombinant DNA, hybridomas, culture and fusion of cells, immobilization of bio-molecules, chemistry of proteins, chemistry of trace-nucleotids. This choice seems to exclude other biotechnologies such as fermentations, techniques which are already widely used in Italian industry but which will be strongly influenced in the near future by the latest techniques, which were of principal interest to this report. (Extracted from Biofutur, September 1984)

Japan

New rice variety

The Ministry of Agriculture, Fishery and Forestry and Mitsubishi Chemical Industries, Ltd. have reached an agreement to jointly attempt to improve rice in the first case of co-operation between the Ministry and a private enterprise. The sources said the Ministry is also studying the possibility of joining hands with some other private enterprises in biotechnological research aimed at improving rice strains.

With rice now becoming the target of the next international "seed war", the Ministry, which has a wide variety of rice seeds, is teaming up with Mitsubishi, known for its sophisticated biotechnology, to develop disease- and cold-resistant, high-yielding rice by means of cell fusion technology. The Ministry has so far worked on improving rice by the crossbreeding method. However, it has found that there is a limit to such efforts by that method, and is turning to biotechnology. Last August it revised the joint research regulations to open the way for teaming up with private enterprises in research for improvement of plants.

The Ministry now has about 16,000 varieties of rice in its gene bank but has decided to treble its seed storage capacity to 150,000 varieties. (Extracted from Asati Evening News, 16 January 1985)

Japan increases budget

While most of the items in Japan's 1985 national budget will receive level funding, biotechnology will be increased by 17.6 per cent.

For 1985 and beyond, major projects emphasized by the ministries include:

- Ministry of International Trade and Industry (MITI) - to examine recombinant-DNA safety, establish guidelines by year's end; service patents with a P2-level containment depository at the Microorganism Industrial Technology Institute, 1986 completion; recycle water by biotreatment and membrane separation, over the next six years.

- Science and Technology Agency (STA) - construct gene bank and r-DNA laboratory at Tsukuba Life Science Research Laboratory; diagnosis and treatment of cancer.

- Ministry of Agriculture, Forestry and Fisheries (MAFF) - construct gene bank; collect 230,000 plants, 13,000 microorganisms by 1992; produce fish and shellfish by parthenogenesis, over the next five years.

- Ministry of Health and Welfare - develop a faster system for examination and approval of new drugs; provide a distribution bank for 30,000 medicinal plants. (Extracted from McGraw-Hill's Biotechnology Newswatch, 4 March 1985)

Mitsui develops plant-cell selection to scale up shikonin

In Japanese folk medicine, shikonin is a traditional remedy for burn injury, inflammation and hemorrhoids. As a stimulant of granulation tissue formation, it is used for wound-healing. But shikonin's deep purple hue makes the rare root extract particularly prized as a dyestuff for silk shawls and kimonos. In nature, a stand of L. erythrorhizon takes five to seven years to reach full growth, at which point its root contains 1% to 2% shikonin. Mitsui's cell-culture process takes just 23 days to produce biomass yielding 12% to 15% shikonin, a figure now increased in the laboratory to 23.2%. Mitsui's shikonin still sells for near the price of the natural product, but the new abundance has made possible new outlets, such as a joint venture with the Kanebo cosmetic company.

Mitsui's process was developed by Dr. Yasuhiro Fujita, who built on primary studies of pigment formation in callus cultures done a decade ago by Dr. Mamoru Tabata at Kyoto University's Faculty of Pharmaceutical Sciences.

Less than a year after introducing the first biotechnology consumer product - shikonin-dye "Bio-lipstick" - Kanebo Ltd. is developing a plant-tissue-cultured perfume. The pharmaceutical firm claims its laboratories are the first to produce fragrances in vitro from geranium cells. (Extracted from McGraw-Hill's Biotechnology Newswatch, 15 October 1984 and 21 January 1985)

Proteins without use of cells

Wako Pure Chemical Industries has developed a method to utilize mRNA to produce proteins in vitro without using cells. In conventional processes, proteins are produced in vivo, but this allows impurities and is of low efficiency. The new system uses mRNA, amino acids, salts, ATP and methionine added to a substance from rabbit reticulocytes. The labelled methionine allows the protein to be separated by electrophoresis. (Source: Technology Update, 15 September 1984)

Gamma interferon

Gamma interferon with over 90 per cent purity has been successfully refined by researchers at Kyoto University. A lymphocyte of a mouse producing antibodies that attached

to gamma interferon was fused to a cancerized murine (mouse) lymphocyte with strong multiplication potential to make a hybridoma with both properties. Monoclonal antibodies binding only to gamma interferon can be produced in large amounts by cultivating this cell line. (Japan Economic Journal, 14 August 1984)

Human monoclonal antibodies mass produced

Morinaga (Japan) has successfully mass produced human monoclonal antibodies for lung cancer cells in a joint project with Kyushu University. A highly reproductive lymphoblast-type cancer cell was fused with a lymphocyte B-cell taken from a lung cancer patient to produce a human-human hybridoma that generates antibodies reactive to lung cancer cells. Diagnostic drugs using monoclonal antibodies are much more accurate than enzyme-based drugs, and Morinaga wants to commercialize a product in five years. The company hopes to develop anticancer drugs by coupling human monoclonal antibodies to anticancer agents within 10 years. (Japan Economic Journal, 21 August 1984)

Mass production of human epidermal growth factor

Earth Chemical (Japan) has developed a technique for mass producing human epidermal growth factor, a hormone that promotes epidermal cell division. The substance is a peptide made up of amino acids. Earth Chemical designed a gene that helps the growth factor remain in E. coli's periplasma. Then the gene could be transplanted into a plasmid for E. coli conversion. Yields of fused protein are currently 2-3 mg/L of culture medium. Earth Chemical will commercialize the growth factor by 1986. (Extracted from European Chemical News, 13 August 1984 and Japan Economic Journal, 31 July 1984)

Diagnostic joint venture

Two Japanese Companies have formed a diagnostics joint venture. The firms, Toray Industries and Fuji Rebio, will sell monoclonal antibody-based tests licensed from the US firm, Centocor.

The two concerns have already been distributing ovarian and gastrointestinal cancer tests developed by Centocor. Under the latest ten-year licensing agreement, the joint venture will market the US firm's monoclonal-based diagnostics for liver, breast and colon cancers. The deal gives the Japanese firms the option to include Centocor's monoclonal technology in their own products in exchange for a 20 per cent royalty payment. (Source: European Chemical News, 18 February 1985)

Biotechnology forecast

By the year 2000, biotechnology products will account for $60.7 billion of Japanese industry sales, according to a report recently completed by the Bio Industry Development Center of the Japanese Industrial Fermentation Association. The non-profit raking centre expects that 91 different industrial sectors will be producing biotechnology products within 15 years, and that products such as pharmaceuticals, commodity chemicals and specialties may account for more than one-third of the biotechnology sales, with $12.8 billion, $6.2 billion and $4.4 billion, respectively. (Source: Chemical Week, 2-9 January 1985)

Space experiment with plant seeds

T. Sakata, a nursery company, will take part in an experiment to develop new plant seeds in space. It will study the effects of cosmic rays and zero-gravity on plant seeds in a series of experiments aboard a US space shuttle. It is unknown what effects cosmic rays might have on plant ecology. Over 10 million seeds of 20 types will be sent into space, and Sakata may distribute them among schools and plant experts throughout Japan for raising. US companies have become increasingly interested in the commercial use of space. Under zero-gravity vacuum conditions, heat circulation does not occur, and this provides a good environment for a number of sensitive experiments and production processes. (Extracted from Japan Economic Journal, 23 October 1984)

Netherlands

US plant planned for Netherlands

Centocor, the US cancer biotechnology company, was last week poised to unveil plans to etablish a base in Europe. The company is to build a small manufacturing facility adjacent to the University of Leiden in the Netherlands to produce in vivo monoclonal antibody-based therapeutic products. The planned facility is to be backed by subsidies from the Dutch state investment company, Maatschaij voor Industriele Projecten. If human monoclonals prove

effective in therapeutic applications, kilogramme quantities of antibodies will eventually be required. As well as developing monoclonal-based blood tests - to detect hepatitis B and Aids, for instance - and cancer-imaging products, Centocor is working on therapeutics to treat colon, rectal and pancreatic cancers and fatal septicaemia. This spring, it put together an R&D limited partnership to raise $15m. to fund oncogene products. (Extracted from European Chemical News, 22 October 1984)

US Department of Agriculture sets up new technology exchange office in the Netherlands

Arthur I. Morgan, Jr., director of the U.S. Department of Agriculture's Western Research Center, Berkeley, CA, since 1969, has been named to head USDA's new European agricultural research and technology office in the Netherlands.

The office located in Wageningen, the Netherlands, will coordinate the dissemination of European agricultural technology to U.S. farmers and researchers, said Terry B. Kinney, Jr., administrator of USDA's Agricultural Research Service.

"Morgan's mission will be to monitor the latest foreign technological developments - especially in biotechnology and genetic engineering - assess their impact on United States agriculture, and hasten the technology transfer to U.S. users," Kinney said.

Several international agricultural organizations have their headquarters in Wageningen, which is about 30 miles inland from The Hague. Wageningen is a centre for organized meetings and courses in agriculture, especially for foreign research scientists, and has one of the world's largest agricultural libraries.

Inquiries should be directed to Agricultural Research Service, U.S. Department of Agriculture, Washington, DC 20250. (Extracted from R&DM Digest, October 1984)

Fermentation company receives government subsidy

Dutch biotechnology concern Gist Brocades has been granted D.fl. 100m. ($28.6m.) in government subsidies to help finance investments over the next four years totalling D.fl 1 billion.

The grant provides for research and for project development over and above the usual Dutch investment subsidies.

The Dutch minister of economy has set up an eight-person supervisory committee to review the various stages of the company's 30-odd projects in fermentation, pharmaceuticals, enzymes and environmental protection. Gist recently entered a recombinant DNA research agreement with Chiron Corporation of the United States on yeast improvement. The firm is also working with the Dutch blood-transfusion service on development of blood coagulant factor VIII for treatment of haemophilia. It has a biomass alcohols development project with Shell in the UK. (Source: European Chemical News, 5 November 1984)

State-owned company in TNO link

The large state-owned concern DSM, has linked up with the Dutch applied scientific institute TNO and Wageningen agricultural college in a three-year state-backed research project focusing on the production of hydroxylated aromatics using enzymes from Aspergillus mould. The new company, Holland Biotechnologie, will be based at Leiden University and will initially sell health-care products, monoclonal antibodies, enzymes and DNA fragments developed by the university and TNO.

DSM says it should take one and a half years to establish commercial feasibility. The project has received substantial government subsidies. (Source: European Chemical News, 7/14 January 1985)

Singapore

Singapore investing in national biotechnology programme

To recruit biotechnologists the government of Singapore is investing more than $30 million in a new Institute of Molecular and Cell Biology. The Economic Development Board (EDB) announced that the facility will be built near one of its sponsors, the National University of Singapore and is expected to be operational by 1986.

Singapore's own efforts to develop a national biotechnology programme have been hampered by inadequate scientific manpower and an insufficient number of companies to train workers.

Initially, the Institute's implementation committee, headed by Dr. Christopher Tan, will concentrate on developing local expertise in disease research and cell biology, but is interested in direct investment, joint ventures, joint research or other proposals.

The Institute will provide "an umbrella" for the University's joint R&D with local companies. One of the projects currently underway accelerates soy fermentation from three months to nine days, while cutting the salt content in the final product by half. (Extracted from McGraw-Hill's Biotechnology Newswatch, 17 December 1984)

Sweden

Volvo/Pharmacia controlling interest

Sweden's largest automobile manufacturer, Volvo, has acquired a controlling interest in the country's second-largest pharmaceutical firm, Pharmacia AB.

Volvo bought its equity in Pharmacia from the families of the firm's founders, who feared heavy inheritance taxes.

Volvo's latest acquisition gives the automaker a substantial position in Swedish biotechnology. It already owns a controlling interest in KabiGen AB. Also, in partnership with Alfa-Laval, it controls AC Biotechnics, Arlov, a major fermentation firm. (Extracted from McGraw-Hill's Biotechnology Newswatch, 18 February 1985)

Switzerland

Cauliflower mosaic virus

Cauliflower mosaic virus can be made into a vector system to carry foreign DNA into plants, according to researchers at the Friedrich Miescher Institute (Basel). A region of the viral genome was replaced with a gene from E. coli that confers resistance to methotrexate. Turnip plants were then inoculated with the engineered virus. Methotrexate solution sprayed on the infected plants had no effect. The new type of vector should be convenient for the rapid introduction of foreign genes into whole plants. (Extracted with permission from Chemical and Enginering News, page 23, 20 August 1984, copyright 1984, American Chemical Society)

Thailand

National Center for Genetic Engineering and Biotechnology

The Government of Thailand has recently announced the setting up of a National Center for Genetic Engineering and Biotechnology under the aegis of the Ministry of Science, Technology and Energy, Bangkok. The Center (NCGEB) will serve as a focal point to strengthen Thailand's capability in genetic engineering and biotechnology and their application to national development thereby promoting research and development, industry-university links, and co-ordinating support from Government and international sources to various institutions active in genetic engineering and biotechnology.

The aims of NCGEB are grouped as follows:

- Industrial applications
- Agricultural applications
- Public health applications
- Energy and environmental applications
- Building up of infrastructure in genetic engineering and biotechnology

Within the framework of the broad aims defined above, the Policy Board of the NCGEB has identified 12 major projects for the next five years which are:

1. Plant tissue culture for development of agriculture and agro-industry.
2. Production of improved rhizobium, organic fertilizer and mycorhiza.
3. Production of improved bacterial larvicides.
4. Production of selected enzymes.

5. Biotransformation of starch.

6. Improvement of efficiency of biofuel production.

7. Development of natural rubber.

8. Production of selected nutritional biochemicals.

9. Improvement of small and medium scale industry.

10. Utilization of industrial wastes.

11. Development and design of pilot plants.

12. Building up of infrastructure in genetic engineering and biotechnology.

NCGEB also promotes the strengthening of capability in R&D through:

- graduate fellowships in genetic engineering and biotechnology
- providing resources for, and organizing seminars, symposia, workshops, exchange of personnel, lecture tours, etc.
- promoting R&D related to genetic engineering and biotechnology outside the scope of the specific projects already outlined.

United Kingdom

Biotechnology research grants

The Science and Engineering Research Council (SERC) is offering awards for engineering graduates to undertake research into the engineering aspects of biotechnology in association with UK companies. The object of the scheme, which is launched in a pilot form this year, is to encourage the growth of engineering expertise in biotechnology production processes. Each research programme will be drawn up by an industrial sponsor in partnership with the chemical or process engineering department of a university or polytechnic. More details may be obtained from SERC. (Source: Financial Times, 31 January 1985)

New biotechnology firms set up

A new biotechnology group, Porton International, has been set up with headquarters in Washington and London, with the backing of 15 United Kingdom institutions, including the pension funds of ICI, Esso, Barclays Bank and the Imperial Group. The new group's aim will be to concentrate on manufacturing rather than research. Included in the Porton group is LH Fermentation, which specializes in bioreactors and the supply of advanced small-scale fermenters and mass cell culture equipment. Another UK subsidiary is Speywood, which specializes in purifying blood products such as porcine Factor VIII.

Finishing touches are being put on a new British biotechnology company backed by Commercial Union and the Legal & General Assurance Company's venture capital arm, Cogent. The new firm will make use of expertise at University College, London and St. Mary's hospital in London. The company will be a unique venture based on very new technology. The development of gene probes for genetic screening will be high on its list of priorities and will conduct basic research. It is to be housed in purpose-built laboratories associated with UCL's biochemistry department. (Extracted from European Chemical News, 24 September 1984 and 22 October 1984)

Biotechnology packages for schools

The Technical and Vocational Education Initiative of the Manpower Services Commission is looking at the idea of supplying "biotechnology packages" to every school in Britain. The packages would consist of equipment and instructions for simple experiments that would demonstrate the potential importance of biotechnology.

The Manpower Services Commission has asked colleges and other organisations to develop biotechnology kits. The idea is that each school should have a package costing a few hundred pounds or less to show teenagers how to manipulate biological processes. For example, one possible experiment might demonstrate how bacteria can break down waste paper into single-cell protein. Another might enable pupils to ferment sugar into alcohol and extract vinegar from the alcohol.

One problem that people who work on the package will have to deal with is safety. Luckily for biotechnology students, the processes they study do not involve working with genuine substances. For example, the biotechnology laboratory at the South Bank has a model sewage works which runs on molasses.

The Manpower Services Commission hopes to produce a plan some time this year. But the commission says that it may be necessary to train teachers in the disciplines first. (Source: New Scientist, 31 January 1985)

Plant planning

Early in 1984, the Biotechnology Unit of the U.K. Department of Trade and Industry (DTI) commissioned John Brown Engineers and Constructors Ltd. to survey "The Future Market for Process Plant for Biotechnology" in order to assist British industry in identifying future opportunities. The report is ready, and it recommends the following:

. The UK equipment manufacturing industry should think of biotechnology as a major growth industry and closely monitor its development with the aim of meeting its future requirements. In particular, it is most important for industrial companies to be aware of current process R&D. Wherever possible the end result of this research should be manufactured equipment, not a concept or a key component leaving the U.K.

. The development of cost-effective large-scale microbial fermentation systems and small- to large-scale animal and plant fermentation systems should be recognized as high priorities for a national bio-reactor research and development programme. The clear objective is that the U.K. must build on its current strengths and emerge as the world leader in these technologies. Within this programme it is recommended that immobilized bio-reactor design, development, and manufacture is a priority.

. The significant increase in the world demand for biotechnology equipment from 1990 onwards must provide the incentive for a considerably increased investment and commitment by industry and government to ensure that the U.K. is capable of meeting the needs of this market.

. The U.K. must fully recognize that the U.S.A. is the major world market for biotechnology process plants, and it must develop and implement a national policy to support U.K. marketing organizations.

. No further public funding for new anaerobic digestion projects should be allowed, and those groups requesting aid should be told to pursue other, more relevant projects.

. Measurements in and control of, bioconversion processes must be recognized as national priority since this equipment will be required for a wide range of processes.

. Those sectors of the U.K. fabrication industry capable of building large vessels should be identified and suitably trained to understand the essential requirements of biotechnology processes.

. Serious consideration should be given to the promotion of centres of excellence in U.K. universities for particular aspects of biotechnology processes - membrane technology, chromatography, and cell processing for example.

. A programme should be instigated to prepare a British Standard relating to the suitability of fabrications and equipment to meet defined levels of containment and sterility. This will increase the process know-how of U.K. suppliers and lead to greater international credibility.

. The DTI must develop ways to encourage U.K. users to take part in equipment development test programmes with U.K. rather than overseas manufacturers. Also U.K. users must be encouraged to purchase new U.K. equipment and provide a "track record" for U.K. manufacturers. (Source: Biotechnology, February 1985)

Nitrogen fixing research

Experiments on white clover could help development of efficient strains of nitrogen-fixing bacteria, according to researchers at the Welsh Plant Breeding Station at Aberystwyth. The efficiency of nitrogen fixation depends on the genetics of the bacteria and the clover. Adding the proper strain of bacterium to a field can increase the yield of clover. In order to match the proper clover with the proper bacterium, researchers have

developed a form of tissue culture which forms secondary embryos from a normal embryo, allowing cloning of clover. The technique may assist in the search for clovers resistant to pathogens. (Extracted from New Scientist, 27 September 1984)

Britain increases interferon production

A British Company, Burroughs Wellcome, is completing the largest facility in the world for growing animal cells in fermenters to produce interferon. They believe the process will compete favourably with interferon production from bacteria-based cultures.

Controversy has surrounded the Wellcome method, because its interferon is produced by cells originally derived from a human cancer. "Conventional" genetic engineering for making pharmaceuticals involves inserting the gene for human interferon into a bacterium or yeast and growing large quantities of these cells in fermenters. The microbes obey the instructions of the foreign gene and manufacture copious amounts of the precious substance.

In the case of interferon these orders are very precise: one particular interferon gene specifies only one type of interferon. So although there are more than 20 different subtypes of alpha interferon secreted in the body, the gene will code for only one.

In Wellcome's process, the human cancer cells are stimulated to produce alpha interferon naturally by an infective agent such as a virus. As their interferon is the natural product, it contains all 20 alpha interferons.

The regulatory authorities appear satisfied with the tests, because they have given Wellcome Biotechnology approval to test their product against virus infections and cancers, and the company expects a product licence in the "not too distant future".

Wellcome licensed their technology to the Japanese company Sumitomo in 1980, and are helping them build a commercial plant to manufacture interferon. Meanwhile Wellcome is applying its animal cell culture to making other scarce pharmaceuticals, such as tissue plasminogen activator, which dissolves blood clots. (Source: New Scientist, 25 October 1984)

Methane production

BioTechnica Ltd (BTL) and Aveley Methane, a joint venture between the Greater London Council and National Smokeless Fuels, have signed an R&D agreement aimed at boosting the production of methane at the Aveley refuse landfill site in Essex. Gas from the site is currently being supplied to Thames Board for steam generation. BTL is to use microbiological techniques to increase gas production under the terms of the three-year, £100 000 contract. (Source: European Chemical News, 7/14 January 1985)

United States of America

Aspartame

Pepsi-Cola USA is to abandon its use of saccharin in diet drinks in favour of aspartame which is produced by G. D. Searle under the NutraSweet label. Coca-Cola is expected to follow suit. The two US soft drinks giants have both been using mixtures of saccharin and aspartame in their diet colas. Consumer tests by Pepsi have shown that two out of three people prefer aspartame-only sweetened cola over the aspartame- and saccharin-sweetened product. While Diet Coke is the market leader in the United States, Diet Pepsi sales have been increasing at an annual rate of 30 per cent. The diet sector accounts for close on a third of the $25 billion US soft drinks market. (Source: European Chemical News, 12 November 1984)

No evidence of serious widespread side effects from aspartame, G. D. Searle's new artificial, low-calorie sweetener, was found by the National Centers for Disease Control (Atlanta). Scientists there interviewed 517 people who had complained to the Food and Drug Administration of ill effects from eating aspartame-containing foods. The researchers found no specific symptoms related to aspartame consumption and that the great majority of complaints were generally mild. The study's authors concluded that there may be a certain few individuals with some as yet undefined sensitivity to the product, but that most complaints more likely result from suggestibility or coincidence of symptoms with aspartame use. (Source: Chemical Week, 14 November 1984)

US biotechnology scene

The US position as world leader in the commercialization of biotechnology is being severely threatened as Federal support for the life sciences decline and governments of other nations select gene splicing and similar research for specific infusions of development funding.

"Japan may very well attain a larger market share for biotechnology products than the US attains because of its ability to rapidly apply results of basic research available from other countries", says a report from the Congressional Office of Technology Assessment (OTA). In addition, says the OTA report, West Germany, Britain, Switzerland and France are probable competitors of the US in biotechnology, even though those nations are not presently commercializing gene splicing as aggressively and rapidly as Japan or the US.

The authors of the OTA report argue that Federal funding of broad applied research and personnel training in bioprocess engineering and applied microbiology in the US may be insufficient to support rapid commercialization. In the fiscal year 1983, for example, the nation spent significantly more money on basic research in biotechnology than on applied research.

Another potential problem seen by OTA is financing for new biotechnology companies. The continued availability of sufficient money is unlikely, the report states. But even if new firms do not encounter funding problems, they may face obstacles in unraveling certain aspects pertaining to health, safety, environmental regulation and patenting, says the report.

In the past years, more than 100 US firms have come up to commercialize biotechnological innovations and established companies in many industries have made their own investments in biotechnology. Nevertheless, the spectre of Japanese competition looms large over US companies as the Japanese Government sees biotechnology as the key technology for the future and is financing cooperative projects within that nation's biotechnology industry.

Though the report does not say how the US can maintain its lead, it identifies 10 factors that are potentially important to the commercialization of biotechnology. They are: financing and tax incentives for firms; government funding of basic and applied research; personnel availability and training; health, safety and environmental regulation; intellectual property law; university-industry relationships; anti-trust law; international technology transfer, investment and trade; government policies; and prevailing public perceptions. (Source: Asia-Pacific Tech Monitor, November-December 1984)

Federal response to AIDS analyzed

Although federal funding of research on acquired immune deficiency syndrome (AIDS) has been substantial and has resulted in significant advances in understanding the deadly disease, the amount has not been sufficient to support the effort that individual researchers and Public Health Service agencies believe is necessary, a recently released Office of Technology Assessment technical memorandum says. The Department of Health and Human Services has maintained that funds for AIDS activities should be transferred from other Public Health Service activities. As a result, OTA says, health service agencies dealing with AIDS have been unable to plan adequately because of uncertainty about funding and personnel levels. OTA also points out that the effort thus far has emphasized a technological solution to AIDS, which doesn't seem likely soon, and that efforts to prevent the spread of the disease through education of high-risk groups has been minimal. (Reprinted with permission from Chemical & Engineering News, page 20, 4 March 1985, copyright 1985, American Chemical Society)

US company to begin field testing recombinant bacterium

Monsanto Agricultural Products Co. (St. Louis, MO) has notified the U.S. Environmental Protection Agency (EPA) that it intends to begin field testing a recombinant bacterium - perhaps as early as April. The organism - a strain of corn-root-colonizing Pseudomonas fluorescens - has been modified to produce Bacillus thuringiensis endotoxin, a potent insecticide for lepidopteral pests.

Under regulations promulgated by EPA in mid-October under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Monsanto filed an 800-page report outlining its techniques, safety analysis, and test plans for what could become the first federally sanctioned field-test of a recombinant organism. The company has no plans to seek approval from the National Institutes of Health's Recombinant DNA Advisory Committee (RAC).

Researchers inserted the endotoxin gene in the P. fluorescens genome via a proprietary transposon vector system, according to Robert J. Kaufman, Monsanto's director of plant

sciences research. The recombinant bacterium may be freeze-dried and coated directly onto seeds before planting, or it may be sprayed onto the fields.

Field experiments with naturally marked wild-type P. fluorescens and laboratory tests with recombinant microbes indicate that populations of the insect-killing strain remain active for only eight to fourteen weeks. Then they dissipate. The microbes do not over-winter and have no long-term effect on soil populations.

Monsanto officials emphasize that the current strain of recombinant P. fluorescens is a "prototype product", with too narrow a range to serve as a commercial insecticide. Salable products could appear between 1988 and 1990.

Monsanto says research workers have spent over a year testing the safety of the genetically engineered bacterium, including tests in mice, quail, fish and Daphnia. At least three common chemicals could be used to eradicate the bacteria if necessary. Monsanto says that the engineered bacteria will survive in the field about 8-14 weeks. If the tests are successful, commercial products could be available in 1988-90. (Source: Biotechnology. February 1985 and extracted from New York Times, 8 January 1985)

NASA funds university biotechnology research

NASA is supporting establishment of two university-based centres of excellence in the field of biotechnology. One will be set up by the University of Arizona, Tucson, the other by the University City Science Center of Philadelphia, with 12 higher learning institutions in the region participating. The centres will research organic separations, bioprocessing, and pharmaceutical analysis with the objective of stimulating use of the space environment as a bioprocessing laboratory. The two centres will each receive grants of $450,000 annually for a minimum of three years and will solicit additional support from industrial and educational sources. (Reprinted with permission from Chemical and Engineering News, page 10, 29 October 1984, copyright 1984, American Chemical Society)

De-contamination of soil and water

FMC Corporation's US industrial chemicals group has set up a biological reclamation business to clean up contaminated soil and groundwater. The new unit, Aquifer Remediation Systems, plans to market its pollution clean-up technology based on controlled injection of hydrogen peroxide as an oxygen source for the degrading micro-organisms. FMC has shown that the method can reduce levels of gasoline pollution at one site from 15ppm in 20 months. (Source: European Chemical News, 10 December 1984)

USSR - Moldavian SSR

New institute of ecological genetics

A decision was made to organize the Institute of Ecological Genetics in the system of the Moldavian Academy of Sciences, the 16th scientific department in the system of the Republic's Academy of Sciences, and the first institute with this specialty. A. Zhuchenko, president of the Moldavian Academy of Sciences, corresponding member of the USSR Academy of Sciences, stated that the organization of the Institute of Ecological Genetics opened up wide horizons for further work on problems of adaptive strategy for intensification of agricultural production. One of the main problems that will be solved by the scientific associates of the new institute is the genetic nature of adaptive reactions of higher organisms. On this basis, new methods will have to be developed for breeding, controlling adaptive reactions and designing fluocenoses [?]. (Extracted from Sovetskaya Moldavia, 13 July 1984)

C. RESEARCH

Research on human genes

BioTechnica files for patent on DNA fingerprinting method

BioTechnica Ltd., the new British biotechnology company, has filed a patent application on what it describes as a novel method for fingerprinting the DNA of whole organisms. BioTechnica says that the eventual patent would be applicable to two main categories of identification: (1) the identification of organisms which have reproduced by asexual means; and (2) the identification of a particular organism which is the product of sexual reproduction.

Invented by Prof. Barry Hall and Prof. Howard Slater, respectively senior research consultant and research director with BioTechnica Ltd., the process is expected to find uses

with companies wishing to protect industrial property - and it should also be of value to type culture collections. Specifically, it will enable companies to recognise microorganisms isolated from nature as their own.

The BioTechnica method exploits the minute natural variations that occur in the chromosomes of living organisms, from which a characteristic 'fingerprint' can be taken. The novelty of the invention lies in the way that highly discriminating patterns can be obtained.

It should also be useful to plant and animal breeders, in any situation where the correct identity of a unique individual, such as a racehorse, is in dispute or otherwise of some importance. Plant breeders will be able to protect unique breeding stock prior to its release to the market. Clinicians will be able to trace the source of infections. Details from: Dr R S Hogarth-Scott, BioTechnica Ltd, 5 Chiltern Close, Cardiff CF4 5DL or on 0222 766716. (Source: Biotechnology Bulletin, Vol. 3, No. 10, November 1984).

New tool for gene hunters

American scientists have persuaded an enzyme to snip out intact single genes from an organism's DNA by cutting the DNA just before and after genes but not in the middle of them. In doing so they have added a new precision tool to the implements used by genetic engineers to mix and match genes at will. Their work might also lead to new relevations about the structural features of DNA that separate useful genes from surrounding sections of so-called "junk" DNA.

The enzyme concerned is a "nuclease" (a nucleic acid-cutter) found in mung beans, long used by genetic engineers to cut and degrade sections of single-stranded DNA in a relatively non-specific manner. The trick to improve its specificity is first to feed it double-stranded DNA, and, secondly, to add large quantities of formamide which seems to force the DNA at either end of a gene into a structure that can be attacked and cut by the enzyme.

Thomas McCutchan, Joanna Hansen, John Dame and Judith Mullins of the American National Institute of Allergy and Infectious Diseases used the enzyme under the modified conditions to cut up the DNA of the Plasmodium parasite that causes malaria. They investigated five specific genes of the parasite and found they had been snipped out cleanly, to provide single free copies of the genes all about the same size (for any one gene) and not damaged by any cuts in their protein-coding sections.

The usefulness of this gene-removing reaction to genetic engineers will depend on whether or not it also works on the DNA of many other types of organism. The discovery that one enzyme can be made to snip out genes from Plasmodium DNA makes it quite feasible that other enzymes will be able to do the same job on the DNA of other organisms - even if mung bean nuclease cannot. The great advantage of the mung bean nuclease reaction is that it cuts, not at any arbitrary sequences that may or may not occur where wanted, but at the particular sites found at the boundaries of genes.

The other topic of interest thrown up by this new work is the nature of the sites that the enzyme is recognising and cutting. The reaction works on naked DNA, so it has nothing to do with attached proteins and therefore presumably depends on the specific three-dimensional structure that the formamide forces the DNA to assume. If the regions at the boundaries of genes adopt a characteristic structure in the presence of formamide, they may well also adopt a different characteristic structure in native DNA (albeit one that is not recognised by mung bean nuclease). (Extracted from New Scientist, 6 September 1984)

Alpha chain gene identified

A gene that controls the body's recognition of invading organisms has been identified by three independent groups of researchers at the National Jewish Hospital (Denver, CO), Stanford University and Massachusetts Institute of Technology. The alpha chain gene used by the thymusor is responsible for creation of a recognition site on the surface of the T-cell. Beta and gamma chain genes with similar functions were also discovered in 1984. (Extracted from Chemical Marketing Report, 7 January 1985)

Modified protein to treat emphysema

A modified form of a human protein could be used to treat emphysema, according to Dr. R. Carrell of Christchurch Hospital (New Zealand). Continuing emphysema is caused by the activity of elastase, which digests elastic proteins needed for normal lung functioning. The body is defended from elastase by alpha-antitrypsin (AT), which is a string of 394 amino acids. The active constituent of AT is methionine, which is susceptible to oxidation and

which causes a loss of efficacy. If methionine is replaced by valine, efficacy is not impaired and the compound becomes resistant to oxidation. Chiron (US) has now made human AT in yeast cells, using genetic engineering techniques. If yeast cells could make the substance in large quantities, and if it is effective in the body, the compound could be used to treat emphysema in humans. (Extracted from New Scientist, 13 December 1984)

Protein A

Protein A, obtained from Staphylococcus aureus, is well known for its ability to bind the Fc region of most mammalian immunoglobulins, particularly those of the IgG class. Consisting of a single polypeptide chain with a molecular weight of approximately 42,000, Protein A has four nearly homologous regions that possess binding activity. Pierce Chemical Co. is now offering Protein A prepared in their laboratories. It is available as a lyophilized salt-free powder and immobilised on agarose. Details from: Tim Brennan, Marketing Manager, Pierce Chemical Co., PO Box 117, Rockford, Illinois 61105, USA. (Extracted from Biotechnology Bulletin, Vol. 3, No. 11, December 1984)

Apolipoprotein-E made by biotechnology methods

Progress in work on two important biomolecules has been made by Bio-Technology General Corp. (BTG), a U.S. firm with corporate offices in New York City and laboratories in Israel. In collaboration with the Gladstone Foundation, San Francisco, the firm has used recombinant DNA methods to prepare human apolipoprotein-E, which plays a critical role in clearing cholesterol from the blood system. Apo-E's therapeutic and diagnostic potential will now be explored. (Extracted with permission from Chemical and Engineering News, page 18, 11 March 1985, copyright 1985, American Chemical Society)

Peptide may lead to rheumatic fever vaccine

Chemically synthesized peptide fragments may allow development of a vaccine against group A streptococcus infection that causes rheumatic fever, according to scientists at the University of Tennessee. The peptide mimics parts of the pathogen's M protein, and induces protective immunity in rabbits without eliciting immune responses to human heart tissue. The M protein contains the antigens that evoke immunity to group A streptococci, and also contains antigens that produce antibodies that cross-react with host tissues. These cross-reactive antibodies cause rheumatic fever. A clinically testable vaccine is still several years in the future since more than 70 strains of the pathogen exists. According to the World Health Organization six million people in India have chronic rheumatic heart disease and that rheumatic fever is a leading cause of heart disease among young people in many developing countries. (Extracted from Medical World, 10 December 1984)

Malaria research

The genes for two antigens to the blood-stage malaria parasite have been c[illegible] by Dr. M. Koenen and collaborators in France and the Federal Republic of Germany. [illegible] tigen is expressed on the surface of malaria infected red blood cells, which consists [illegible] eated sequences of nine amino acids. The sequences may allow the parasite to generate la[illegible] numbers of different antigenic appearances, thus avoiding destruction by the immune system of the infected victim. The other antigen cloned elicits a strong antibody response in monkeys, but does not work against milder infections common in humans. (Extracted from New Scientist, 8 November 1984)

Vaccine for schistosomiasis

Scientists are now becoming more confident about the possibility of making an effective vaccine to combat schistosomiasis or bilharzia. The latest work comes from Wellcome's laboratory in Beckenham, Kent, and the George Washington University in Washington DC in the US.

A vital step towards a vaccine for schistosomiasis came in 1983, when a team led by Anthony Butterworth in the pathology department of Cambridge University discovered that some people are naturally immune to the disease. This team found that about 30 per cent of children infected with schistosome larvae and adult worms experienced no relapse of the disease following drug therapy to kill the worms. The children were from an area of Kenya in which the disease is endemic.

One promising antigen has been identified which was tested as an experimental vaccine. In monkeys the vaccine made from the single antigen did not give 100-per-cent protection against infection, but it did reduce the worm load by about 40 per cent. In mice it reduced the worm load by 70 per cent.

The most important form of immunity in schistosomiasis is thought to be "delayed hypersensitivity". In this T-cells that recognise schistosome antigens produce chemicals which in turn stimulate scavenger cells (macrophages) to kill the parasites.

The search is on for schistosome antigens which stimulate delayed hypersensitivity powerfully enough to make a useful vaccine when their genes are cloned in E. coli bacteria. The antigens will have to stimulate a rapid reaction such that enough larvae are killed before they have the chance to disguise themselves with host antigens - a trick they are now known to play in order to escape immune surveillance.

The vaccine need not eliminate infection to be valuable. One that reduces the worm load by 70 per cent or even less could eliminate symptoms and also reduce by a useful amount the infected person's potential for infecting other people. (Extracted from New Scientist, 14 February 1985)

Down's syndrome research

A chromosomal abnormality can identify 30 per cent of people at risk of having a child with Down's syndrome, according to C. Jackson-Cook of the Medical College of Virginia and prevent the birth of 1,500 Down's syndrome babies per year. The abnormality, which is a marker, not a cause of the syndrome, is found in the nucleous organizing region (NOR) of chromosomes 13, 14, 15, 21 and 23. About 30 per cent of the parents with Down's syndrome children had a double NOR region in one of these chromosomes. The abnormality occurs in only 1-2 per cent of the general population. C. J. Epstein of the Down Syndrome Research Center at the University of California (San Francisco) has developed a strain of mice that produce offspring with an extra chromosome 16, providing an animal model for Down's syndrome. Affected mice do not survive to birth but it is evident they develop congenital heart disease which is also common in Down's syndrome. Another strain of mosaic mice with two cell populations has also been developed, so that the trisomy can be studied in animals that can survive one year. (Extracted from Medical World, 10 December 1984)

Ulcer causing bacterium

A bacterium that may prove to be the predominant cause of peptic ulcers and gastritis has been discovered by a researcher in Australia. If clinical trials bear out this finding, antibiotics could replace Tagamet cimetidine, the world's largest selling drug, as the treatment of choice for these disorders. Moreover, successful trials would raise the possibility that the disorders, which afflict 20 per cent of adults sometime during their lives, could be prevented if researchers develop a vaccine against the organism.

Barry J. Marshall, a microbiologist at Freemantle Hospital (Freemantle), and J. Robin Warren, a gastroenterologist at Royal Perth Hospital (Perth), reported isolating a new microorganism from the stomach tissue of patients with peptic ulcers and gastritis. The cause of gastritis, a discomforting inflammation of the stomach lining that affects as many people as do ulcers, is unknown. Fully 85 per cent of ulcer patients examined by Marshall and Warren were infected with the bacterium, as were 75 per cent of those patients with gastritis. The bacterium, which Marshall named Campylobacter pyloridis, was not present in healthy patients.

Soon afterward, two groups of researchers in England confirmed these observations, prompting Marshall to suggest that a C. pyloridis infection was the root cause of most ulcers and cases of gastritis. Another Campylobacter bacterium living in the intestines caused more cases of adult diarrhea worldwide than any other organism. Furthermore, Marshall proposed that such an infection - and, thus, both ulcers and gastritis - should be treated with antibiotics rather than with antacids.

While most researchers still view Marshall's work cautiously, many now believe that the evidence linking C. pyloridis to ulcers and gastritis is strong enough to warrant trials to test the efficacy of antibiotics in the treatment of these ailments. In fact, preliminary results of a limited study suggest that antibiotic therapy does indeed prevent recurrences. Marshall treated 16 patients with a 28-day regimen of bismuth sulfate - bismuth is the active ingredient in Pepto-Bismol - and one of three antibiotics: erythromycin, tinidazol and amoxicillin. A year after treatment, no patient has had a relapse. Marshall would like to see a vaccine developed against C. pyloridis which could be given along with any other childhood inoculations.

While researchers debate the merits of Marshall's theory and plan large clinical trials to determine that theory's merit, Marshall is working on a simple laboratory assay that can detect C. pyloridis without resorting to a stomach biopsy. The assay uses monoclonal

antibodies to identify antibodies formed by an infected patient against the bacterium. These antibodies appear in the blood of such a patient. (Extracted from Chemical Week, 23 January 1985)

Virogenes

Studies of a Gerstmann-Straussler syndrome (GSS) may provide the solution to a long-standing puzzle, the nature of the organisms responsible for the diseases kuru and scrapie. Researchers have suggested that "slow viruses" could be responsible for these and other conditions. Dr. Tim Crow and colleagues at the Clinical Research Centre Northwick Park Hospital in London, have an alternative explanation - virogenes - genes which, under special and still-unidentified stimuli, can generate viruses.

Crow and his colleagues have been studying GSS in a family in which the disease is clearly inherited. It follows the clear pattern of autosomal dominant inheritance, a condition found in 50 per cent of children of an affected parent. However, when they transplanted tissue from the brain of a patient who had died of GSS into brains of eight marmosets, all the monkeys developed GSS.

One possible explanation is that the abnormal gene giving rise to GSS might make some people susceptible to a specific and separate virus infection but, for this to be true, the virus would have to be present not only in all the affected members of the family but also in all the marmosets affected. Crow thinks the most feasible explanation is the concept of virogenes.

GSS appears to be a familial version of another degenerative brain disease, Creutzfeldt-Jakob syndrome (CJS) which has also been transmitted experimentally to monkeys. CJS is similar to scrapie, a brain disease of sheep, and kuru, a human brain disease spread by the eating of enemies's brains in New Guinea. Immunological assays show that the same antigens are present in tissue from brains affected by all these conditions. The causative transmissible agent remains to be identified. Tests have shown it is not a bacterium. Stanley Prusiner, of the University of California at San Francisco, among others, believes the agent responsible for these diseases is an infectious protein. Such a concept would require the rewriting of the central dogma of molecular biology which holds that the pathway from DNA to RNA to protein is one-way.

One hypothesis put forward to explain why prions have never been seen is that they contain no DNA, which would also explain why they are not inactivated by radiation or formalin treatment which would normally inactivate DNA. Another idea is that the prions contain only tiny amounts of DNA which act not directly, by coding for abnormal proteins, but by activating other normal genes in abnormal ways. The virogene theory could explain why no DNA has been found in prions - perhaps prions exist only fleetingly as independent entities and the rest of the time are no more than a potential possessed by virogenes.

The virogene theory may also, Crow suggests, ultimately explain aspects of Parkinson's disease, Alzheimer's disease and motor neurone syndrome. All of these show a familial pattern in about 15 per cent of cases only and tend to occur in middle age. Differences between the DNA of people affected by such conditions and that of normal people may ultimately hold clues to other conditions in which "slow viruses" have been thought to be implicated. (Extracted from New Scientist, 4 April 1985)

Monoclonal antibodies to cardiac myosin

A monoclonal antibody to cardiac myosin appears to be a more accurate imaging agent for acute myocardial infarction than the commonly used pyrophosphate, according to a report to be presented at the annual meeting of the American Heart Association (Miami Beach, 12-16 November 1984). Another report to be given at the meeting indicates that monoclonal antibodies to cardiac myosin could be used to predict complications following myocardial infarction. Centocor holds exclusive license for commercial development of antimyosin technology. The firm is developing a monoclonal imaging product which it plans to introduce in Europe by 1986, according to John W. Huss, Manager of in vivo diagnostic business at Centocor. (Source: BioEngineering News, Box 290, Willits, Ca. 95490, USA, Vol. 5, No. 22, 6 November 1984)

Reagents for cardio-vascular research

The latest additions to the product range offered by Amersham International are reagents for the radioimmunoassay of atrial natriuretic peptides (ANPs). A recently discovered series of body chemicals, ANPs are believed to be involved in heart function, specifically valve operation, and their study could be of value in combating hypertension. Also just available

are labelled (T-125) ligands for studying ANP receptors. Details from: Amersham International plc, White Lion Road, Amersham, Buckinghamshire HP7 9LL. (Source: Biotechnology Bulletin, Vol. 4, No. 2, March 1985)

Monoclonal antibodies and heart disease

Doctors are soon to begin trials in the US and in Europe of a remarkable new way of imaging disease which could save many lives. The technique employs radiolabelled monoclonal antibodies which in the case of heart disease can accurately reveal the extent of damage after a heart attack. This same type of agent can spot tiny cancer growths long before symptoms appear.

Scientists at Centocor, a biotechnology company in Philadelphia, made monoclonal antibodies that bind to myosin. Myosin normally occurs only inside the heart muscle cell, but it is released when the outer cell membrane is damaged during a heart attack.

The antimyosin monoclonal antibodies, labelled with indium, are injected six hours after the heart attack. They recognise and bind to the exposed myosin molecule. An image taken in a conventional gamma counter will outline areas of damaged tissue. By distinguishing severely damaged and necrotic heart muscle from sick cells which can be recovered, doctors can make accurate therapeutic decisions more quickly.

Post-mortem examinations were carried out on people who died because of severe heart conditions. This showed that the monoclonal images were within 10 per cent of the actual size of infarct (dead zone).

The larger trial sets out to assess the impact of different therapies, and will involve hundreds of patients at centres in Boston, New York and Atlanta, Georgia.

This technique is being extended to cancer. Centocor is testing labelled monoclonal antibodies for detecting colorectal and ovarian tumours. (Extracted from New Scientist, 28 February 1985)

TPA possibly best to dissolve blood clots

The naturally occurring protein tissue-type plasminogen activator (TPA) seems the best bet yet for dissolving blood clots that cause myocardial infarction.

TPA is produced naturally in minute quantities by the blood vessel walls. The first samples, purified by Professor Desire Collen of the University of Leuven in Belgium, were flushed out of dead animals and humans or their organs, a laborious process that yielded only a few micrograms of TPA. Then a laboratory culture of cells, the Bowes melanoma cell line, was found which produced higher levels of TPA.

The drug worked well in dogs and baboons, so in collaboration with Dr. Burton Sobel of Washington University School of Medicine in St. Louis, Desire Collen tried it in humans. In six out of seven patients, the blood clots cleared.

For bigger trials, the researchers turned to Genentech. They managed to get the TPA gene working in bacteria, yeasts and mammalian cells in culture and it is TPA from these that is now being tested in patients.

The trials were carried out at three centres: at St. Louis, at the Johns Hopkins Medical School in Baltimore, and at the Massachusetts General Hospital in Boston. Fifty patients were each given between 40 and 60 milligrams of TPA within an hour or two of their heart attacks.

One of TPA's big advantages is that it can be given through a drip into a peripheral vein. Previous clot dissolvers, such as streptokinase and urokinase, made by fungi, had to be delivered by catheter into an artery near the heart. With TPA, treatment can begin in the back of the ambulance.

TPA has a half-life in the blood of only 5 or 6 minutes, and a continuous infusion lasting 60-90 minutes is enough to dissolve most clots. TPA activates plasmin which in turn breaks down fibrin, the protein that makes platelets stick together to form a blood clot. Unlike streptokinase, TPA is a thousand times more active in the presence of fibrin as it is in free-flowing blood.

Between 80 and 85 per cent of the 50 patients treated with TPA have fully recovered. Another two trials using the drug to treat acute myocardial infarction are under way. There is hope that it might also prove effective in clearing the blood clots in the brain that

cause strokes. But, as with heart attacks, it depends on getting the drug to the patient quickly enough. (Extracted from New Scientist, 22 November 1984)

Superoxide dismutase, hyaluronic acid, edge toward clinical trials

Two substances made in the human body, and bacterially fermented by Biotechnology General, Inc. (BTG), in Rehovot, Israel, have just moved closer to market. BTG's New York-based parent company last month signed an agreement with Pharmacia, Inc., of Piscataway, N.J., to produce hyaluronic acid, HA, a high-viscosity gel-fluid used in eye surgery and expensive cosmetics.

Meanwhile, pre-clinical trials of a recombinant analog of human superoxide dismutase (hSOD) from BTG are getting under way in the heart and kidney units of the Johns Hopkins University School of Medicine in Baltimore, Md. Clinical studies are in prospect at the neonatal pediatrics department of Interfaith Medical Centre, Brooklyn, N.Y. The three clinical areas where free oxygen radicals are under closest study include the treatment of cardiac ischemia, kidney transplants and oxygen toxicity in premature infants. Animal trials of hSOD at Johns Hopkins have showed significant salvage of heart function after myocardial infarction-caused damage in dogs and rabbits. In prospect is the use of hSOD to reduce heart attack damage when a blocked coronary artery is opened up by a clot-dissolving agent, such as tissue plasminogen activator.

Bovine superoxide dismutase has been approved by the U.S. Food and Drug Administration for experimental use only. Veterinarians are giving non-recombinant SOD to horses and domestic pets to relieve inflammatory diseases, and the substance is also being considered by the medical underground as a cure-all against the effects of radiation, food additives, pollution, poor nutrition and old age. (Extracted from McGraw-Hill's Biotechnology Newswatch, 4 February 1985)

Artificial calcitonin produced

Researchers at Rockefeller University in New York have used protein engineering techniques to produce an artificial version of the human hormone, calcitonin, with the same biological activity as the natural protein. The analogue, which is 60 per cent different to nature's version, could have advantages over the natural hormone in the treatment of bone conditions, such as Paget's disease. The Rockefeller team have also modified papain to oxidize nicotinamides and have made the brain hormone, beta-endorphin, almost entirely from D-amino acids rather than the natural L-enantiomers.

The Rockefeller researchers say that their work with calcitonin is a big step toward making artificial enzymes. In principle, calcitonin is not a great deal different from the active site of an enzyme, the portion of the enzyme where a reaction takes place. The object of the work was to elucidate how each part of the calcitonin molecule functioned and then develop a technique for building new active sites in artificial enzymes.

To achieve that goal, researchers used theoretical modelling and chemical synthesis to analyze calcitonin's structure and shape. As they elucidated the function of each part of the molecule, they synthesized substitutions for those parts. Eventually they synthesized a compound that is almost completely a "nonhomologous analogue" of the hormone, an artificial version that differs from calcitonin in 60% of its components, but still functions as calcitonin.

The work, say the Rockefeller researchers, has given them a deeper understanding of the relationship between protein structure and function. A major portion of the calcitonin molecule, for example, seems to fold in such a way that it forms an amphipathic helix. Such a helix occurs when the polar amino acids line up on one side of the protein and the nonpolar amino acids line up on the other. The helix portion of calcitonin also corresponds to the molecule's binding site, which is structurally and functionally similar to an anzyme's active site.

The techniques used to analyze calcitonin and design its analogue - the artificial calcitonin - can now be applied to the active sites of enzymes.

The practical benefit of artificial calcitonin's development derives from the medical importance of the hormone. Since calcitonin regulates calcium blood levels, it is important in maintaining bone strength. In fact, injections of calcitonin are currently used to fight bone wastage diseases.

Unfortunately, calcitonin can be attacked and rendered useless by the body's immune system and by the stomach's protein-digesting enzymes, which is why the hormone must be injected.

There is also reason to believe that the artificial calcitonin could survive enzyme attack in the stomach, making oral ingestion a possibility. Another plus is the ease of its synthesis which could make it less expensive than the naturally occurring hormone.

Papain transformation. Synthesis of artificial calcitonin is only the Rockefeller researchers' most recent advance in protein engineering. Earlier this year, the researchers transformed a common, protein-hydrolyzing enzyme, papain, into a new enzyme that catalyzes the oxidation of nicotinamides, dinucleotides that are normally oxidized by a group of enzymes called flavin oxidases. Naturally occurring papain and flavin oxidases are completely unrelated compounds with few structural similarities, and the transformation by the Rockefeller researchers marked the first time that an enzyme had been changed from its original form to one capable of catalyzing a completely different reaction. The technique used in synthesizing the new enzyme is presently being applied to other enzymes that could have more immediate payoffs. (Extracted from Chemical Week, 21 November 1984 and European Chemical News, 10 December 1984)

Factor VIII produced

Genentech (San Francisco, CA) and researchers at Royal Free Hospital (London) and a team of researchers at Genetics Inst. (Boston, MA) and the Mayo Clinic (Rochester, MN) have independently produced Factor VIII from mammalian cells in culture. The two teams of researchers isolated and reproduced the entire genetic sequence and inserted it into the cells to produce the substance, which is missing or defective in the 20 of every 100,000 males who are afflicted with the most common type of hemophilia. However it may be five years before a safe product can be marketed. (Extracted from Science News, 1 December 1984)

Hormones in bread

Scientists at the Stanford University School of Medicine have found that baker's yeast contains natural estrogens. David Feldman and his colleagues noticed that a protein in the yeast could not only bind one particular estrogen - estradiol - but could also displace the animal hormone from its protein. The yeast-derived compound also showed affinity to another female hormone, progesterone.

Was the stuff really a hormone? The scientists tried it on rats whose ovaries had been removed so that they had no natural supply of estrogen. The exogenous compound acted like the natural hormone and doubled the weight of rat wombs.

The exact nature of the compound derived from this yeast - known as Sacromyces cerrisiae - is yet to be identified. (Source: Science Age, January 1985)

Mullerian inhibiting substance

Mullerian inhibiting substance (MIS), which is secreted by embryos, is reported to be able to kill certain tumours of the female reproductive system, according to researchers at North Carolina State University (NCSU). MIS normally causes some embryonic cells to die off as reproductive organs develop in the fetus. If the cells do not die, they can cause tumors. MIS could be used against these tumors. The MIS gene has been cloned from chick embryos to allow production of the compound for clinical testing. (Extracted from Chemical Week, 30 January 1985)

Potential birth control agent

A new hormone that controls both sperm and egg formation, and which could be an effective birth control agent for both men and women, has been isolated after 10 years of work by researchers at Monash University (Melbourne, Australia). The small protein, inhubin, is purified from the fluid surrounding eggs as they develop in cow ovaries. It acts as a messenger from the ovary and testes, informs the brain of the state of egg and sperm development. When sperm and egg are fully developed, the level of inhubin reaches a peak which signals the pituitary gland to shut off production of another hormone, whose function is to stimulate development of sperm and egg. Biotechnology Australia (Melbourne) has been granted licensing rights to produce inhubin using recombinant-DNA technology, and to bring the compound to clinical trials. (Source: Chemical Week, 13 March 1985)

Of pygmies and poodles

Both pygmies and dwarfs who are short because of growth hormone deficiency have low levels of the growth promoting factor, called IGF-I (insulin-like growth promoting factor). When growth hormone was administered to both pygmies and pituitary dwarfs, the IGF-I levels rose in the dwarfs only. According to Rudii Froesh and colleagues of Zurich University,

Switzerland, it is the IGF-I deficiency that makes pygmies what they are. In fact, when it comes to the growth hormone, the pygmies have just as much as their tall Bantu neighbours. Pygmies are also unresponsive to the hypoglycemic effects of insulin.

Another interesting find was that toy poodles, like pygmies, also lack IGF-I. Normal poodles have normal levels. (Source: Science Age, January 1985)

Bone-marrow transplant for genetic diseases

Over 200 inborn errors of the human metabolism are due to the deficiency of some specific enzyme or the other. Several lines of treatment have been tried out for such diseases with various degrees of success. Enzyme therapy, which seems apparently the best answer, is riddled with problems. Besides, its effect lasts only as long as the treatment is administered.

P. W. Gasper and colleagues of the Colorado State University, USA, are trying out what seems to be a more lasting and efficient therapy for a genetic disease called mucopolysaccharidosis VI which is the result of a deficiency of the enzyme arylsulphatase B. It leads to severe skeletal, cardiac and pulmonary complications.

Bone-marrow cells produce this enzyme, so the Colorado scientists have tried bone marrow transplants. If performed early in life, they could prevent deformity. Gasper and colleagues were lucky in that they had an animal model in cats. When affected cats were given bone marrow transplants from healthy litter-mates, they found their condition improved clinically. There was a marked clearance in the clouding of the cornea and the previous disability in walking and chewing also decreased. The cats also lived substantially longer. The biochemical improvement of the transplant, seen in the arylsulphatase B activity, also lasted for long: 250 days after the transplant. (Source: Science Age, January 1985)

Mammalian proteins from plants

Not so difficult after all. No, you don't have to go looking for plants that make them. Instead you could train plants to make mammalian proteins. Scientists at Monsanto's Life Sciences Laboratory, in St. Louis, Missouri, have successfully introduced human DNA into petunias. The (HCG) human chorionic gonadotropin producing gene functions in the petunia plant but the yields of the hormone are still low. The process, however, holds out hopes of using plants to produce human hormones and mammalian proteins cheaply. In fact there will be ever so many applications once the technique is perfected. (Source: Science Age, January 1985)

Cancer test based on fragile sites in human chromosomes

Susceptibility to some forms of cancer could be detected with a test based on 51 fragile sites in human chromosomes, according to Dr. J. Yunis of the University of Minnesota. Some 20 of those sites are already associated with human malignancies. Chromosomes in normal lymphocytes had a tendency to break when grown in a culture medium deficient in folic acid and thymidine. Caffeine enhanced the tendency to break, perhaps by inhibiting DNA repair during cell replication. Earlier studies have found chromosome translocations and deletions in 93 per cent of 450 cancer patients. About 7 of the 17 oncogenes that have been mapped are near fragile sites. Chromosomes were less susceptible to breakage in culture if the patients had taken 5 mg/d of folic acid for three days before the cells were cultured. Addition of folic acid prevents chromosome rearrangement in culture. Populations with diets rich in fruits, leafy vegetables and whole grains, which are rich in folic acid, are less susceptible to cancer so a diet rich in folic acid might be prudent for people with a family history of cancer or who are exposed to carcinogens. (Source: Medical World, 14 January 1985)

Cancer research

Cancer immunotherapists are trying multiple approaches to increase the effectiveness of their treatments. Combining a vaccine made from a patient's tumor cells with one made from bacille Calmette-Guerin (BCG) resulted in a 67 per cent drop in recurrence rates for colon cancer patients, according to researchers at the Litton Institute of Applied Biotechnology. Monoclonal antibodies may also be used for in vitro treatment of bone marrow for autologous transplantation, according to scientists at the Dana-Farber Cancer Center (Boston, MA). Genetic engineering could eventually produce tumor-associated antigens to make anticancer vaccines. Some cytokines that affect tumor growth directly will require more research. (Extracted from Medical World, 24 December 1984)

Cell marker for early leukaemia

Chinese scientists believe they may have discovered a way of identifying leukaemic cells early on.

Wu Qian and Zhang An, of the Chinese Academy of Medical Sciences in Beijing, compared mitochondria in leukaemic cells with those in cells taken from people suffering other blood disorders. They found a conspicuous difference in the structure of mitochondria in cells of the two groups.

Qian and An calculated the ratio of the length of cristae to the longest diameter of mitochondria in leukaemic cells and cells of non-leukaemic disorders. The ratio in the control cells was almost double that of leukaemic cells. Moreover, the researchers found that the ratio could help to predict the outcome of acute leukaemia.

This is the first time scientists have come up with a quantitative criterion for electron microscopic diagnosis of acute leukaemia. The reserrchers go so far as to say that when the ratio is "less than 1.332, a diagnosis of acute leukaemia or preleukaemia can be made if clinical findings are consistent." (Extracted from New Scientist, 13 December 1984)

CM leukemia cells produce altered protein

Chronic myelogenous leukemia (CML) tumor cells produce an altered form of a protein found in normal cells, according to O. Witte of the University of California Los Angeles. The altered protein could be a marker for the diagnosis of CML. The finding may help explain the observation that cancer-producing viruses use genes picked up from normal cells. These genes do no damage in their original cellular location, but subtle genetic differences between normal and malignant forms of these genes may induce cancer. Human patients with CML show a chromosomal break near one end of the c-abl gene, and the resultant segment attaches to another chromosome. Both the leukemia caused by a virus and the leukemia caused by chromosomal translocation involve an altered protein with tyrosine kinase activity. Similar alterations in the genes may be caused when the gene is picked up by a virus or relocated by chromosome breakage. (Extracted from Science News, 4 August 1984)

Natural anti-cancer agents found

Scientists have isolated and cloned two members of the body's armoury which they believe might lead the way to a more effective and safe way of fighting cancer.

The newly cloned proteins, called lymphotoxin and tumour necrosis factor (TNF), are genuine killers of cancer cells. The proteins are produced by white blood cells in response to contact with bacterial toxins or growth-stimulatory substances. Lymphotoxin and TNF are related; the former made by lymphocytes and TNF by monocytes, two types of white blood cell.

Cloning the genes for the two anti-cancer substances is yet another triumph for the biotechnology company, Genentech. Bharat Aggarwal and colleagues isolated the messenger RNA from which lymphotoxin is made and Aggarwal's team, with David Goeddel of Genentech cloned the gene encoding TNF.

The two proteins are present in the blood in only tiny quantities; the same problem that faced researchers trying to study the interferons. To get around the problem of sparsity of material the team "worked backwards" from the protein.

The two proteins turn out to be roughly the same size and one-third of their amino acid sequence is identical. Three regions of the proteins are very similar and are thought to be the "working" parts; those needed to attach the proteins to cancer cells in order to kill them.

The synthesised DNA was then used to make protein; the two lines of bacteria carrying the cloned genes were grown. The purified LT and TNF produced by the bacteria was injected into tumours in mice where they destroyed the tumour cells and caused regression of the cancer.

The research provides a way of obtaining enough of the factors for study. Scientists will want to find out how the substances kill tumour cells and how they manage to avoid killing normal cells. (Extracted from New Scientist, 17 January 1985)

Ricin mutation as anti-cancer agent

With a grant from Britain's Science and Engineering Research Council, scientists at Warwick University, Oxford University and the London-based Imperial Cancer Research Fund (ICRF) aim to genetically tailor the ricin toxin molecule into an effective anticancer agent.

Of the ricin molecule's two polypeptide chains, A and B, toxicity resides only in the A-chain. Thus strategy in hitching the toxin to a tumor-directed monoclonal antibody has been to extract the A chains from ricin's source in the castor bean, Ricinus communis, and link these to the antibody. However these conjugates are relatively inefficient at killing cells, states Dr. Michael Lord, who heads the Warwick team. He has found that the intact ricin molecule, containing both chains coupled to antibody, killed all cells tested, under conditions that temporarily altered B-chain function. Warwick scientists now think that the B chain plays a double role. First, it delivers the A chain to its target by binding with galactose sugars on cell surface glycoproteins. There the A chain enters the cell by endocytosis in small membranous sacs. The B chain's second play, Lord suggests, is to help the A chain escape these minivesicles and move out into the cytoplasm to exert its toxic effect.

Because B chains will bind to normal as well as malignant tissue, the team hopes to use site-directed mutagenesis to disrupt the galactose-binding sites while preserving the delivery role. It has already patented complementary-DNA clones of the ricin precursor molecule. These will be mutated once the galactose binding sites have been identified by their colleagues at ICRF. Then the altered cDNAs will be expressed in yeast cells using phosphoglycerate expression vectors developed by Dr. Alan Kingsman at Oxford. (Source: McGraw-Hills's Biotechnology Newswatch, 4 February 1985)

Anticancer action of platinum compound

A molecular probe for studying the biological mechanism of action of anticancer platinum compounds (e.g. cisplatin) has been synthesized by S. J. Lippard and colleagues of Massachusetts Institute of Technology. Their probe links a dye molecule, acridine orange, which breaks DNA chains in the presence of light, to (1,2-diaminoethane) dichloroplatinum(II) by means of a hexamethylene chain. The resulting compound binds to DNA through its platinum-containing end, and, when exposed to light, nicks the DNA chains through its acridine orange end. Given the efficiency of the nicking reaction, it should be possible to use the acridine orange moiety as an internal, photoactivated 'molecular scissors' to map platinum binding sites on labeled DNA restriction fragments.

Cisplatin is thought to kill cancer cells by binding to two guanine sites in the faulty DNA. Recent research by Kenj Inagaki, Kyoko Kasaya and Yoshinori Kidani of Nagoya City University, Japan, has proved that 1,2-cyclohexanediamine platinum (II) bonds to specific nitrogen atoms of guanine and this is how the platinum moiety would bind to DNA after it had shed the vitamin C part of the drug (see Figure 1). They experimented on tiny strands of nucleoside in which there were two guanine units adjacent to each other.

Even when it is known where the drug attaches itself to DNA, it is not known how this kills the cancer cell or prevents it reproducing itself without affecting healthy cells of the body. Perhaps the DNA repair mechanism of cancer cells is deficient. During cell division the cisplatin scrambles the genetic code - thereby producing a version that the immune system recognises as foreign. A healthy cell's repair mechanism "sees" the cisplatin clinging to the strand of DNA and removes the faulty section.

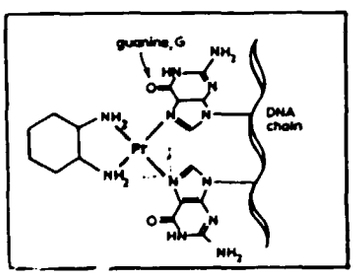

Figure 1 How cisplatin binds to DNA

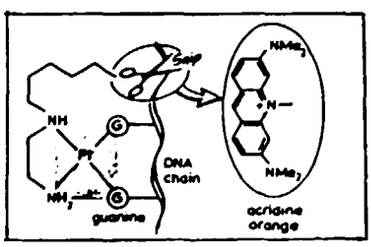

Figure 2 Acridine orange acts as a "molecular scissors", snipping the segment of DNA to which it is attached

(Extracted from Chemical and Engineering News, 8 October 1984 and New Scientist, 4 April 1985)

One-armed antibodies

Monoclonal antibodies have been made deadly enough to use in killing cancer cells without attaching toxic drugs to them, according to researchers S. Cobbold and H. Waldman. By removing one of the two arms with which an antibody fastens itself to an antigen, the antibody is made much more efficient as a selective cell killer. One-armed antibodies have also been found to be better at inducing complement to kill cells than normal, two-armed antibodies because one-armed antibodies are not thrown off; thus there are more of them to act as markers for complements. (Extracted from New Scientist, 13 September 1984)

Antibody sheds light on oncogene function

An antibody that is specific for the protein product of one of the ras family of oncogenes has been developed by researchers at Cetus Corp., Emeryville, Calif. When the antibody is injected into cultured kidney cells transformed by a ras oncogene, the cells temporarily revert to normal morphology and growth patterns, thus substantiating the direct involvement of the protein in the development of cancer. The research was a collaborative effort led by Frank P. McCormick of Cetus and James Feramisco of Cold Spring Harbor Laboratory. Ras oncogenes encode p21 protein. The complete biological activity of p21 protein isn't known; however, it is known that p21 binds cellular guanine triphosphate (GTP) and autophosphorylates by removing a phosphate group from GTP. The antibody developed by Cetus is specific for p21. In the presence of the antibody, p21 no longer binds GTP, suggesting that the binding process plays a role in ras transformation of cells. (Reprinted with permission from Chemical and Engineering News, page 15, 29 October 1984, copyright 1984, American Chemical Society)

Tumor promoters boost cell transformation

Tumor promoters apparently act synergistically with cellular oncogenes to cause normal cells to be transformed into cancerous ones. In experiments using cultured C3H 10T1/2 cells, W.-L. W. Hsiao, S. Gattoni-Celli and I. Bernard Weinstein of Columbia University found that incubating cells with the tumor promoter 12-O-tetradecanoyl phorbol-13-acetate (TPA) for a few days before and after treatment with the transforming oncogene c-ras causes a five- to 15-fold increase in the number of transformed foci obtained from the cells. In addition, the transformed foci appear earlier and are often larger than in the cells not treated with tumor promoter. The increase was greatest when TPA remained in the culture for at least four days after transfection, although a two- to three-fold increase occurred when TPA was present only at the time of transfection. (Reprinted with permission from Chemical and Engineering News, page 15, 29 October 1984, copyright 1984, American Chemical Society)

Cancer immunotherapy imminent

Research at the London Hospital and the National Institute for Medical Research at Mill Hill has led to a technique that protects mice against a disease which closely models human T-cell leukaemia. The technique is a form of immunotherapy, stimulating the mouse's immune system to react more effectively against its leukaemic cells. But whereas immunotherapy in cancer has given consistently disappointing results over the past 20 years, the work of Professor Hilliard Festenstein of the London Hospital and Drs Frank Grosveld and Kam Hui of the National Institute suggests that a new era of successful immunotherapy for cancer may be about to begin, thanks to the untiring partnership of recombinant DNA and monoclonal antibodies.

Some 40 per cent of leukemic cells in a form of mouse leukaemia have abnormally low levels of K antigen and 1-2 per cent have no K antigen at all. Although the transformed cells express viral antigens, they are recognized as foreign, and the viral antigen may be recognized as foreign only when it is expressed next to the K antigen. When the gene for K antigen was replaced in leukaemic cells, they did not grow and multiply, but were recognized and eliminated by the mouse immune system. Cells with the K antigen can also enable the immune system to cope with similar cells without the K antigen.

The hope is that it may be possible to take infected, leukaemic T cells from patients with human T-cell leukaemia, implant HLAB (the equivalent of the mouse K antigen) genes into the cells, and reinject them into the patient to make him or her recognise and reject the leukaemic cells. It is also possible that a similar technique might be used to protect people who have not contracted T-cell leukaemia from contracting it. Festenstein is now obtaining experimental material from Nigeria and if the technique looks promising after further studies it could be tried experimentally on humans within a year or so. Festenstein emphasises that it is too early to say whether it might have any value in the treatment of AIDS, which is thought to be caused, at least in part, by a human T-cell leukaemia virus.

So, for some cancers it will become possible to stimulate patients' bodies to reject their cancers by injecting them with their own tumour material, with added HLAB genes and

irradiated to prevent the injected cells from growing. Whether the antigen suppression is sufficiently similar in different individuals to allow the technique to be used to provide a vaccine to protect against cancers is another question. But for T-cell leukaemia at least it is a real possibility, though cloned virus material may provide an alternative vaccine. (Extracted from New Scientist, 22 November 1984)

Tracking the effects of oncogene proteins

An activated gene called ras is present in 20 per cent of all human tumours. This is one of the 20 or so oncogenes, genes believed to be involved in the transformation of normal cells to cancerous ones. Despite the ubiquity of ras, very little is known about the protein encoded by it, and what that protein does in the cell.

New research by James Hurley and colleagues at the California Institute of Technology and the University of Texas Health Science Center at Dallas suggests that the product of the ras proto-oncogene is responsible for modulating levels of cyclic adenosine monophosphate (cAMP) in cells. Hurley and his colleagues have found that parts of the G-proteins of bovine brain cells are very similar in sequence to parts of the ras proto-oncogene protein. In addition, a G-protein analogue called transducin, which is found in the red cells of the eye, similarly shows homology with the ras protein.

There is a whole family of G-proteins; different G-proteins are found in different cell types. But one thing that they have in common, according to Hurley, is a glycine molecule at position 12 in the amino acid chain. And the only difference between the normal ras proto-oncogene product and the product of a ras gene taken from a human bladder carcinoma is that the glycine at position 12 is replaced by another amino acid.

Other researchers have suggested that other oncogenes might code for protein kinases, some of them specifically for tyrosine protein kinases, which may not affect cAMP levels in the cell. (Extracted from New Scientist, 22 November 1984)

AIDS virus infects brain cells

HTLV-III virus not only destroys the T-lymphocytes of persons infected with the virus who develop acquired immune deficiency syndrome (AIDS) but may attack brain cells, causing serious nervous system damage. The suggestion comes from research by George M. Shaw and Robert C. Gallo of the National Cancer Institute, Bethesda, Md., and a team of colleagues there and at several other medical research institutions. Knowing that many AIDS victims develop dementia and other signs of brain cell impairment, the researchers examined the brains of 15 individuals with AIDS and brain disease to see whether the HTLV-III virus was present in brain cells. In five of the 15 cases studied, HTLV-III sequences were detectable in the brain. And in the one case checked, the concentration of HTLV-III in the brain was much greater than that found in other body tissues, such as the spleen, liver, lymph node, and lung. (Reprinted with permission from Chemical and Engineering News, page 28, 7 January 1985, copyright 1985, American Chemical Society)

AIDS victims still await vaccine

Two teams of molecular biologists, one American and one French, have published what they believe to be the entire genetic sequence for the virus that causes acquired immune deficiency syndrome (AIDS). With this sequence they can make a vaccine. Already, two other teams from commercial laboratories in the US have joined the race to find and patent the first vaccine. They claim to be on the verge of publishing similar papers which describe the virus's genetic sequence. There are two types of vaccine that could be made to fight AIDS. The first is to make fragments of the protein that coats the viral genes. This is safer than the second, which uses debilitated whole viruses. But the first type requires a knowledge of the genetic sequence. With this sequence it is possible to make the virus's coat-protein in vitro. This protein can be injected into people at risk of contacting AIDS, to help them build up a resistance to the virus. (Extracted from New Scientist, 24 January 1985)

The AIDS connection

Sleeping sickness is caused by African trypanosomes, which are protozoa. AIDS seems to be caused by a type of RNA virus. At first glance, the two diseases seem to have little in common, but several groups of investigators are currently looking to see if the trypanosomes may have similar effects to those of the AIDS viruses on the immune system and, if so, whether that can lead to new insights into either disease.

John Mansfield of the University of Louisville, for example, finds that trypanosomes produce immune system changes in mice that very much resemble the changes seen with AIDS. Whether the same effects occur in humans is unclear, but a team of scientists from the

Centers for Disease Control, the National Institutes of Health, and Zaire are currently in Zaire testing and comparing patients with AIDS to patients with any of several parasitic diseases, including sleeping sickness, to see how these parasites affect immune functions.

The investigators in Zaire are not just looking to see if sleeping sickness and AIDS produce the same immune suppression. They are also investigating a hypothesis that AIDS is prevalent in Zaire because trypanosomiasis and other parasitic infections that occur in Zaire render patients less able to fight off the AIDS virus.

A final AIDS connection is with suramin, a drug that is commonly used to treat sleeping sickness. Recently, Robert Gallo and his associates at the NIH discovered that it is effective against the putative AIDS virus in vitro. They are now beginning studies to see if it can be administered to AIDS patients. It is another intriguing link between the ancient disease of trypanosomiasis and the recently discovered AIDS. (Extracted from Science, vol. 226, 23 November 1984)

Gram-negative sepsis

Scientists at Stanford School of Medicine and the University of California, San Diego, have developed a potential treatment for a bacterial illness gram-negative sepsis, or poisoning of the bloodstream, which is a leading cause of death from infection in hospitals.

The potential new treatment consists of a protein that neutralizes endotoxin. The protein is highly effective in protecting animals from bacterial endotoxin-induced sickness and death and is thought to be the first human monoclonal antibody demonstrated to have therapeutic promise and biological effectiveness. It will be tested in humans within the coming year.

The newly engineered monoclonal antibody has been effective in preventing death in laboratory animals injected with a wide variety of unrelated gram-negative bacteria that produce endotoxin. Although different gram-negative bacteria may produce slightly different forms of endotoxin, the new antibody is thought to be capable of neutralizing them all because it recognizes a portion of the molecule which is common to all and because of this versatility it is hoped to be of broad clinical use. (Extracted from Genetic Engineering Letter, 24 March 1985)

Research on animal genes

New vector for use in animal cells

Taisho Pharmaceutical (Japan) has developed a new vector for use in genetic recombination with animal cells jointly with the University of Tokyo's Applied Microbial Research Institute. The main role in genetic recombination is currently played by E. coli, but animal cells are better suited to the production of new drugs. Basic research into manipulation techniques using animal cells is progressing in many countries. The race to develop a host-vector system using animal cells is therefore intensifying. Animal cells have low productivity versus coliform bacilli, but are able to authentically reproduce body glycoproteins. Current vectors for animal cell systems are primarily based on the simian virus SV40 or the bovine papilloma virus. The new vector is derived from a plasmid found in the mouse L-cell. The L-factor plasmid has a reproductive rate of 5,000 copies/cell, two orders of magnitude higher than any known animal vector. (Extracted from Japan Economic Journal, 7 August 1984)

Raising hair

The hair grows from a bulb in the epidermis - cells differentiate into hair. To control the hair there grows another tissue, which the dermal papilla projects into the bulb. Recent research on the papilliary cells from the sensory hair of rat's snout, when cultured, showed they retain their ability to stimulate the growth of hair.

When each cultured cell was used on rats whose dermal papiliae had been removed they grew full-blown whiskers in no time. The follicles that had received the implant developed new bulbs, with epidermal cells properly aligned around the dermal papillae.

Advances in culturing the cellular components of hair follicles are particularly significant. About two years ago, researchers showed that epidermal cells taken from follicles could be cultured in the laboratory. Now that it has been established that cultured papilla cells retain their ability to stimulate the growth of hair, researchers can

put the two types of cells together in culture and begin to explore how papilla cells induce epidermal cells to produce hairs, and how hormones such as testosterone influence their interaction.

The rat's whisker may thus serve as an ideal system in which to study the genesis of hair. (Source, Science Age, January 1985)

Research on plant genes

Hybrid bacteria fix nitrogen in crop plant

Work on transferring nitrogen-fixing genes directly into crop plants, has shown that corn and sugar beets infected with hybrid bacteria fixed nitrogen and had yields 10 per cent to 180 per cent higher than laboratory controls.

Crop Genetics International NV, of Dorsey, Maryland, claimed the results in a recent European patent application (APO 125 468). While nitrogen-fixation remains interesting, the company will focus on specialty-chemical delivery, including anti-fungals and anti-bacterials. The nitrogen-fixing hybrids are made by protoplast fusion of Azotobacter vinelandii and either Erwinia stewartii or Agrobacterium tumefaciens as the "infecting bacteria". With no field testing to date, product development could take five to seven years. (Extracted from McGraw-Hill's Biotechnology Newswatch, 4 March 1985)

Plant interferons

It seems they do. In a disease like the tobacco mosaic virus, which causes localised infections (blotches on the leaf) the surrounding tissue develops immunity and contains the viral infection. When scientists analysed the juice from the infected and neighbouring uninfected tissues of the Datura plant, they did find a virus inhibiting substance from the juice of the uninfected portion. The juice, when poured on the infected blotches, dampened the spread of the mosaic virus infection. The component that damaged the infection, like the normal interferon, was resistant to heat and extreme pH.

In many other ways too the plant product responded like animal interferon.

When infected tobacco leaves were treated with human blood interferon the growth of the virus halted and remained controlled till the interferon was washed.

It is likely that plant interferons could be used in medical therapy or they could be the starting point of new drug synthesis. (Source: Science Age, January 1985)

Protoplast fusion and plasma transfer

Protoplast fusion to produce a hybrid bearing two or more nuclei has not produced new crop plants. Protoplast can be made by a wide range of plant cells, including crop groups such as the forage legumes. They can now be produced from leaves or other tissues, but the soya bean has resisted all attempts to produce protoplast. Sugar beet protoplasts form cell walls but do not divide. Most cereal species do not form protoplasts easily. When protoplasts from very different parents are fused, many complications arise. The two nuclei may not divide together or one may not divide at all. Incompatibilities may also arise between the nucleus and organelles such as mitochondria or plastids. Research on genetic improvement of crops is now concentrating on the use of DNA vectors.

The microorganism used for genetic transfer of DNA into plants may work on a far wider variety of crops than previously thought, according to researchers at the University of Leiden, Netherlands. Agrobacterium tumefaciens causes cancer in plants by transferring a piece of plasma DNA into cells of the host plant. Once inside a host cell, the foreign DNA causes the production of a mass of undifferentiated cells known as a crown gall. Researchers have now discovered that the bacteria can infect some monocots although the plants do not produce tumors. It had previously been thought that monocots were immune to A.tumefaciens. A peculiar hormone metabolism in monocots may prevent them from responding to tumor-inducing genes in the bacterium. (Extracted from New Scientist, 1 November 1984)

Useful mutants

Plant biochemists at Rothamsted Experimental Sta[illegible] Hertfordshire have observed a different type of genetic change which could produce c[illegible]ly valuable varieties of wheat and potato. Simon Bright and colleagues found that wheat and potato plants grown from immature embryos and undifferentiated leaf tissues (calluses) often contained an abnormal number of chromosomes. About 70 per cent of the wheat plants grown from cultured cells

contained multiple sets of chromosomes. The culture medium ingredients have all been tested for their effects on genetic material, but none of them seem to be the cause.

Meanwhile, this somaclonal variation has yielded a wheat mutant which appears to be resistant to brown rust disease. One of the potato mutants is being tested in Ireland for resistance to scab. (Extracted from New Scientist, 15 November 1984)

New way to manipulate plant genes

One of the major problems to overcome in introducing foreign DNA into plant cells is knowing, for certain, that the plant cell has expressed the foreign gene. The first clear examples of such manipulation were made using the tumour-inducing (Ti) plasmid isolated from the bacterial plant pathogen Agrobacterium tumefaciens where tumour growth was the selection marker. However, because the transfer and integration of Ti-plasmid sequences into the plant genome is a natural consequence of infection by the bacterium, the possibility always remained that the transformation by purified Ti-plasmid DNA was still being effected by pathogenicity genes carried by the plasmid itself.

A group at the Friedrich Miescher Institute in Basle has shown that purified DNA can indeed be transferred to plant cells and that those cells can be regenerated into whole plants and the foreign DNA inherited quite normally through seeds to subsequent generations. This important demonstration relied on inserting into plant cells, a gene that confers resistance to the antibiotic kanamycin. The researchers obtained this gene from a bacterium.

In its natural form this resistance gene would not have been recognised by the plant systems for gene expression - the plant enzymes that make messenger RNA (mRNA) from a DNA gene and then translate it into a protein. Therefore the first task facing the group was to replace the bacterial signals with signals that a plant cell would recognise, so that the gene would produce a protein in the plant.

For this the team extracted signals from gene VI of a plant virus which does not integrate into the genome of plant cells when it infects them, but instead normally remains as a free circular molecule. Thus any integration that followed could not be due to the presence of these viral sequences.

The hybrid gene produced a fusion protein carrying the first 25 or so amino acids of the gene VI protein product joined to the bacterial kanamycin-resistance protein. The group then treated the plant cells with DNA and polyethylene glycol. After one week they began to divide, and kanamycin was then added to the culture medium. One month later, one in a million of the protoplasts had divided and grown into a small clump of cells in the presence of the antibiotic and were thus transformed. This frequency, although low, was repeatable; and clumps grew from bacteria treated with the control plasmid construction.

The researchers regenerated whole tobacco plants from the cell clumps and showed that the plants not only contained the expected kanamycin-inactivating enzyme, but also the expected DNA in a form which indicated that it was integrated into the DNA in the nucleus of the plant.

For one particular regenerated plant, 50 per cent of plantlets derived from its pollen were resistant to kanamycin. And when self-fertilised seed were tested, 75 per cent of these produced kanamycin-resistant plants. Both results indicate that the regenerated parent plant carried one copy of the resistance function per diploid cell and that the function was a dominant trait. (Extracted from New Scientist, 3 January 1985)

Important steps in tobacco research

The successful expression of the first commercially useful gene in agronomically important crop plants by recombinant DNA methods was announced in February by Calgene Inc. A team led by Dr. Luca Comai achieved the expression of the glyphosphate tolerant aroA gene in regenerated tobacco plants. The transformed plants demonstrated a significantly increased tolerance to glyphosphate when sprayed as a herbicide. Calgene first announced the cloning of an aroA gene from a genetically modified strain of Salmonella typhimurium in July 1983 and an article characterising this gene will appear in the April 1985 issue of the Journal of Biological Chemistry. (Source: Biotechnology Bulletin, Vol. 4, No. 2, March 1985)

Sweet-tasting protein's structure unraveled

The three-dimensional structure of a protein that is regarded as the sweetest-tasting substance known to humans has been determined by researchers at the University of California, Berkeley.

Professor Sung-Hou Kim and colleagues discovered that a molecule of thaumatin I, a protein from the berry of the African shrub ketemfe, contains two distinct structural regions. In one, the amino acids are arranged in sheets, while in the other, the amino acids form complex loops. The evidence strongly suggests that these loops bind to taste bud receptors that recognize sweet substances. The research is published in the March issue of the Proceedings of the National Academy of Sciences.

The researchers are close to determining the three-dimensional structure of another intensely sweet protein, monellin. The amino acid sequences of both thaumatin and monellin are known but do not resemble each other. However, they appear to possess many structural similarities suggesting that they interact with taste bud receptors in the same way.

Thaumatin may find commercial applications. It might be used as a sweetener itself - as it has been in Africa for centuries - or as a model for development of artificial sweeteners. Another property of thaumatin that could find commercial application is that it is a strong flavour enhancer. (Extracted with permission from Chemical and Engineering News, page 7-8, 11 March 1985, copyright 1985, American Chemical Society)

Research on yeast and fungus genes

Scientists exploit nature for pest control

Aphids have plenty of enemies apart from farmers and gardeners. Fungi, tiny wasps and chemicals that plants themselves produce can inhibit or kill the insects. With a little manipulation in the laboratory, and a lot of investment by industry, these natural pesticides could one day replace chemical ones.

Work at the Agricultural and Food Research Council's Rothamsted Experimental Station, near Harpenden, England, is at a most advanced stage and involves controlling aphids with a fungus that can control Aphis fabae, or black fly, out of doors.

The fungus the team chose is Erynia neoaphidis. Tests in bean-fields showed that releasing aphids infected with fungus spreads the disease into the natural population of aphids. The population of aphids declined earlier than in untreated plots. And at the most there were fewer than half the number of insects in the treated plot.

The beans did well, too. Yields went up where infected aphids were released, but nearby plots treated with a chemical insecticide did better.

The next step was to find a more convenient way to distribute the fungus around a field. The team infected aphids in the laboratory, dried them out and ground them into a coarse powder which was dusted onto plants. This seemed to work as well as releasing live infected aphids, and a farmer would obviously find it a lot easier.

Another finding is that the fungus will grow in culture dishes. Industry should be able to scale up the process. The scientists hope to start work on cereal crops next year, and to develop strategies for applying the pesticide. They will also be looking for new, more potent strains of E. neoaphidis.

Experiments have also shown that aphids themselves have chemicals that attract parasites. A lot of aphids have been crushed and dissolved in the entomology laboratories at Rothamsted, but the substance responsible has not been isolated yet.

Scientists have done better at imitating nature in another area of natural pest control. Researchers at Rothamsted have isolated and synthesised anti-feedants - substances that some plants have evolved to protect them from insect pests.

The most promising anti-feedant is called polygodial. In nature, it protects marsh pepper from aphids and main viral infections. It is relatively easy to synthesise in the laboratory, and could be sprayed onto other crops to protect them from pests.

The problem with making polygodial synthetically is that two isomers come out of the reaction. One protects crops, whereas even traces of the other erode the leaf of the treated plant. But producing the chemical biologically would avoid this problem.

Even if polygodial does not turn out to be a practical protection for crops, several other plants produce anti-feedants. An Indian tree called the neem produces anti-feedants as well as many other promising chemicals. The geranium also produces anti-feedants against slugs. (Extracted from New Scientist, 15 November 1984)

Enzyme isolated to convert proteins to amide forms

Unigene Laboratories has isolated an enzyme that rapidly and efficiently converts proteins produced by genetic engineering to their amide forms. Production of many important human proteins, such as calcitonin and growth hormone, by the single-step fermentation of bacteria or yeast was previously impossible because human proteins are amidated at the carboxyl link, and bacteria and yeast are incapable of amidating pro[illegible]. The new enzyme enables Unigene to amidate recombinant proteins in a single step following their production by a host microorganism and subsequent purification. Eventually, Unigene will incorporate the gene coding for the amidating enzyme into cells readily adaptable to large-scale fermentation. (Extracted from Chemical Week, 24 October 1984)

Cold-loving enzymes reported

By splicing genes from a cold-loving microbe into Escherichia coli, Japanese researchers plan to lower this bacterium's optimum temperature by 5°C to 10°C, thus reducing the energy costs for fermentation. Dr. Masao Kanabe of the Resource Chemistry Institute, Tokyo Engineering University, is working jointly with Hokusan Chemical Co., Hokkaido, to develop a bacterium that will produce hydrogen at relatively cold temperatures.

Kanabe spliced a chromosomal leucine-synthesis gene, β-isopropyl malic acid dehydrogenase (β-IMD) from the cryophilic Enterobacter aerogenes into E. coli via plasmid pBR322.

In E. coli, β-IMD has a temperature optimum of 45°C; the introduced E. aerogenes enzyme functions at 30°C to 40°C. Kanabi's next step will be to clone in E. aerogenes cryophilic hydrogenase genes, using the low-temperature β-IMD enzyme as a marker. (Extracted from McGraw-Hill's Biotechnology Newswatch, 4 March 1985)

Heat-stable enzyme

Wakamoto Pharmaceutical Co. Ltd. announced the development of a genetically engineered, immobilized, heat-stable enzyme that converts lactose in milk to galactose and glucose. Their β-galactosidase (β-gal) column can operate continuously at 75°C, virtually eliminating bacterial contamination.

The thermostable catalyst is produced by splicing the β-gal gene from Bacillus stearothemophilus into a strain of B. subtilis. Only the desired enzyme is heat-stable, so purification is easily achieved by raising the temperature to 70°C to selectively denature the B. subtilis proteins.

Researchers at the Genetics Department, Trinity College, Dublin, claim the gene that codes for production of a commercially important, heat-stable form of the α-amylase has for the first time been cloned and introduced directly into Bacillus subtilis.

The high-temperature amylase gene was isolated from a strain of Bacillus licheniformis that produces the enzyme, but not at commercially acceptable levels. Using recombinant DNA techniques, it was incorporated into α-amylase-negative mutants of B. subtilis, in which it produced the enzyme and remained stable. The enzyme produced by the recombinant B. subtilis is claimed to be stable up to 93°C. The α-amylase now commonly used for degradation and hydrolysis of starches in the food and distilling industries ordinarily requires a two-step process with operating temperatures that begin at 50°-80°C and are elevated slowly to about 100°C. The high-temperature enzyme could accomplish both conversions in one step, while the higher operating temperatures would also facilitate pumping of the resulting starch slurries, Ollington says. (Extracted from McGraw-Hill's Biotechnology Newswatch, 4 March 1985 and Bio/Technology, February 1984)

Research on bacterial genes

Protein patterns identify bacteria

Scientists at St. Bartholomew's Hospital, London, believe they have found a way to identify bacteria, simply and directly.

Drs. Silman, Holland and Tabaqchali label the proteins produced by bacteria with radioactive sulphur, which emits electrons. These proteins are then placed on a gel and subjected to an electric field. The proteins move down the gel to different positions depending on their size and electrical charge.

The patterns are then scanned in a few minutes by a detector. As the detector scans the picture, the pattern it "sees" is fed as a digital signal to a microprocessor which produces a pattern on a VDU.

The technique is important because hospital laboratories need to discriminate between bacteria so that doctors can decide on suitable treatment. An average laboratory may use 10 to 15 different tests, such as staining and microscopy or fermentation reactions, to narrow down the options, but often the final analysis of bacteria depends on the expertise of the staff.

Ideally, bacteria would be identified by their genes, but the proteins they produce could provide, in theory at least, an identification for each species as well as each sub species. (Extracted from New Scientist, 23 August 1984)

Advantages of host cells

Genetic engineers first tinkered with the bacterium E. coli; more recently, attention has focused on the advantages of other host cells, such as Bacillus subtilis, yeast and mammalian cells. At the Third European Congress of Biotechnology held in Munich last September, Biogen researchers Andrew Pickett and Kimber Hardy assessed the relative merits of the hosts.

Most recombinant DNA products have so far been obtained from E. coli, a gram-negative bacterium with two membranes which secretes only a very few proteins, such as haemolysin, through both membranes. The proteases of E. coli can reduce the yields of some proteins. Some protease mutants have been isolated, but it seems likely that the complete elimination of all proteases will be impossible, as some degredative activity seems to be essential for cell growth.

During downstream processing, pyrogens (lipopolysaccharide) derived from E. coli must be reduced to acceptably low levels. In practice, this does not present a significant problem since pyrogens can be removed either by column chromatography or by using the new generation of charged membrane filters.

Numerous E. coli strains have been developed and used as hosts for expressing recombinant DNA. These include strains developed for their inability to survive outside of the laboratory environment and mutants lacking a specific protein or enzyme which decreases yields from a recombinant plasmid. Strains of E. coli other than those derived from E. coli K-12 are often not used as hosts.

Other bacteria have been used on an experimental scale; for example, Bacillus, Pseudomonas, and Methylomonas. Potential advantages of other bacteria include the ability of Bacillus to secrete proteins and the possibility that certain species might produce fewer proteases (which degrade the product) than E. coli.

Bacillus species secrete many proteins, often in large amounts. Being gram-positive, they have a single, cytoplasmic membrane. However, despite this considerable potential advantage - not least for large-scale commercial production - it cannot be realized at the moment because the basic genetic systems for expressing cloned genes are not sufficiently well-developed.

In particular, strong promoters which can be efficiently controlled do not exist, although several plasmids comprising such promoters are presently being developed. Other problems associated with Bacillus include plasmid instability - both loss of the entire plasmid and also genetic rearrangements - and high levels of protease. Plasmid instability can sometimes be avoided by making sure there are no short duplications of the DNA sequence. It appears that Bacillus may have a particularly efficient system for recombination between such sequences.

Although genetically the best characterized species, B. subtilis may not be amongst the most useful species of Bacillus for expressing cloned genes because it is a highly proteolytic organism. Other Bacillus species, for example B. sphaericus, produce no more protease than E. coli.

Yeast is the most attractive alternative of the microbes to E. coli at the moment. It can be used for the production of proteins, which are difficult to make in E. coli and proteins can be secreted from yeast, for example, by using the alpha mating factor system.

At present, primary cloning is usually carried out in E. coli. Once the cloned gene is obtained, it can then be coupled to other promoters and plasmids for expression in other bacteria, in yeast or in mammalian cell cultures.

Although mammalian cell cultures are more expensive to run, they may have particular advantages for certain products or at certain stages of an investigation into a new product.

Mammalian cells may be able to secrete a protein specified by a cloned gene such that the secreted protein is in the correct conformation. In addition to correct folding, glycosylation of the molecule may also be obtained. A relatively small amount of correctly folded material may be all that is needed for preliminary tests on a new product. This can sometimes be obtained more easily from a mammalian culture, especially if it is secreted, than from a bacterial culture.

Criteria for the choice of bacteria, yeast or fungi as suitable hosts for recombinant DNA

	Bacteria	Yeast	Streptomycetes	Mammalian cells
Ease of gene manipulation	+++	++	+	++
Development of expression systems	+++	++	+	++
High density growth	+++	+++	+++	+ [microcarriers]
Ease of cell harvesting	++	++	+++	+
Ability to process cell material	+++	++	+	++
Excretion of required products	±	++	++	++
Glycosylation of required products	-	+	±	++

Comparison of Escherichia coli and Bacillus sp. as hosts for large-scale production of recombinant DNA products

	Escherichia coli	Bacillus sp.
Expression systems	+++	+
Stability of cloned genes	+++ [in certain strains]	++
Ease of genetic manipulation	+++	++
High-density growth	+++	+++
Secretion of products	+	+++
Proteases	++	++++
Product recovery	+++	+++
Safety	+++	+++
Pyrogens	+++	-
Current use as host	+++	+

(Extracted from European Chemical News, 24 September 1984)

B. brevis as high-secretion host

Selected for its ability to export proteins without degrading them, a laboratory strain of Bacillus brevis produced five times more cloned enzyme than a similarly transformed culture of the industrial microbe B. subtilis. Dr. Shigezo Udaka, professor of food engineering and chemistry at Nagoya University, claims that B. brevis can secrete three to four times its mass in the form of two high-dalton, cell-wall proteins. By linking this export system to foreign genes, his research group has boosted the yield of cloned alpha-amylase - the commercial enzyme that converts starch to sugars. Udaka's strain of

B. brevis is low in protease activity and its cells transformed with the alpha-amylase genes from B. stearothermophilus did not degrade the cloned enzyme secreted in the culture medium even after three days. The B. brevis cells produced 15,000 units/ml of alpha-amylase, compared to only 3,000 units/ml for gene-spliced B. subtilis. In another experiment, Udaka put the alpha-amylase gene from B. licheniformis into an area downstream from the high-activity, cell-wall promoter in B. brevis, and thereby increased enzyme expression 10- to 15-fold. (Extracted from McGraw-Hill's Biotechnology Newswatch, 15 October 1984)

Hybrid antibiotic

A hybrid antibiotic has been developed by combining medermycin and actinorhodin by scientists at the John Innes Institute, Norwich, UK. The antibiotic is of no medical value, but may make possible a new generation of antibiotics. Some 69 commercially important antibiotics are made by streptomycetes, which are bacteria that live in soil. The new technique involves transferring part of the package of genes coding for the antibiotic in one streptomycete into another streptomycete. The technique may enable development of new anticancer drugs, antifungals, antibiotics, and a new drug to combat leprosy. The principal antibiotic used against leprosy is rifamycin, and introducing more copies of the genes into other strands should allow more of the antibiotic to be produced. (Extracted from New Scientist, 4 October 1984)

Research on viral genes

Retroviruses linked to cancer, hepatitis and AIDS

Retroviruses have now been linked to cancer, AIDS, and hepatitis. The viruses have long been known to cause animal diseases such as cancer in chickens. They could be suitable vehicles for gene transplantation. Some of the viruses can kidnap genes from animal cells and reintroduce them into other cells. Retroviruses possess the enzyme reverse transcriptase, which can reverse the flow of genetic information from DNA to RNA so that RNA serves as a template for DNA. This DNA copy of the virus' RNA can then become a permanent part of the infected cell's genetic makeup. Intense study of retroviruses has become an important part of cancer research. The first retrovirus linked to a human cancer was human T-cell lymphoma virus (HTLV-I), discovered in 1980, and HTLV-III has now been linked to AIDS. Reverse transcriptase activity has now been discovered in blood serum samples of a patient with non-A non-B hepatitis. The viruses known to cause types A and B hepatitis are not related to the retroviruses. (Extracted from New York Times, 20 November 1984)

Hepatitis C virus found

The elusive third hepatitis virus may have been discovered. The discovery of a retrovirus or an agent with retrovirus-like properties has been reported among a group of male homosexuals and intravenous drug users. Doctors believe that some 90 per cent of cases of hepatitis in the US that are associated with blood transfusions derive from this third hepatitis C agent.

The investigators from the US and Sweden who discovered the virus say it may soon be possible to remove the virus from transfusion blood. There could soon be a vaccine which would further reduce the toll from this important and often fatal disease.

The investigators are from the US Food and Drug Administration and the University of Göteborg in Sweden. One of the investigators warned that there may be a fourth hepatitis virus. (Source: New Scientist, 25 October 1984)

Research instrumentation

Medical diagnostic technology

Chemical Sensors has been formed by Biotechnology Development to commercialize a proprietary medical diagnostic technology based on the sensitivity of piezoelectric crystals to minute changes in surface mass caused by specific adsorption of analyte molecules such as proteins and DNA segments. It can use various active agents, including monoclonal antibodies and DNA probes. The agents respond to submicron levels of analytes, and may need no sample manipulation or chemical separations. Performance will be equal or superior to current diagnostic assay methods such as radioimmunoassay and immunofluorescence. Initial applications will include measurement of therapeutic drug levels, infectious disease markers, pregnancy hormonal indicators and antibodies characteristic of immune disease. (Extracted from Chemical Week, 24 October 1984)

In-situ hybridization process

A process called in-situ hybridization uses a radioactive DNA piece to allow photographs to be taken of protein synthesis. The process is being used for basic research to allow scientists to discover which specific cells are conducting protein manufacturing. The technique will also allow research on brain development and Alzheimer's disease. The technique can be used to help understand the mechanism controlling beta-endorphin production in the hypothalamus and ACTH in the pituitary. (Extracted from Science News, 6 October 1984)

General

Amoeba transformation

International Genetic Science Partnership researchers have developed a simple, efficient method for the transformation of a single cell amoeba, Dictyostelium discoideum, that offers significant advantages over the use of bacteria for genetic engineering purposes. Being a eukaryotic organism, it routinely carries out modifications of which bacteria are not capable. Genetically transformed moulds also have certain 'industrial' advantages: large quantities of them can be easily grown in conventional fermenters to produce hormones, glycoproteins, interferons and other vital products. (Extracted from Innovation, November 1984)

EOS project fails

Despite operational difficulties experienced on the maiden flight of the NASA shuttle Discovery, it had been thought that the hormone produced by the McDonnell Douglas electrophoresis operations in space would be active, but unfortunately it is not. It looks as though bacterial contamination of the EOS system, possibly a consequence of pre-flight delays, resulted in the production of endotoxins and the destruction of the target hormones.

According to James T. Rose, EOS project director, some bacterial contamination was inevitable, but the delays compounded the problem. The equipment was sterilised two days before the scheduled lift-off and the next day a litre of pre-prepared raw material was thawed and added to 30 litres of sterile buffer solution. This was then placed in the EOS equipment, which sat aboard the shuttle for over 48 hours as one delay followed another. Later, the sample material was refrozen - and did not get into space for another month. Bacterial contamination, in these circumstances, seems to have been almost guaranteed. Details from: James T. Rose, EOS project director, McDonnell Douglas Corp., St. Louis, Missouri 63166, USA. (Source: Biotechnology Bulletin, Vol. 3, No. 11, December 1984)

DNA and the disappeared

Molecular biology is beginning to contribute to the identification of human remains. The tooth's pulp is probably the best place to dig. It lies within a protected cavity where cells are more likely to escape post-mortem degradation by microbial and chemical invasion. A variety of protein markers, such as blood group antigens, enzymatic markers and immunoglobulins recovered from teeth have allowed scientists to obtain genetic typing from skeletonised cadavers. Chromosomes, complexes of protein and the nucleic acid DNA also may survive in a tooth's necrotic pulp tissue. Japanese and Welsh scientists have determined sex by specific staining of the Y male chromosome from teeth.

As a body deteriorates, protein markers become increasingly unreliable. Foreign biomolecules borne by microorganisms from analytical procedures for recognising specific proteins are not discriminating enough to distinguish between human protein markers and the "protein noise" from soil microbes. This discrimination, however, is possible when dealing with DNA, the master molecule of genetic information. Genetic engineers can construct DNA probes that can easily distinguish sequences of human DNA from that of other organisms. Recently refined procedures allow typing of DNA fragments down to the exact sequence of nucleotide in the living organism. (Extracted from New Scientist, 15 November 1984)

D. APPLICATIONS

Malaria vaccine

A vaccine against malaria has been brought two steps nearer, with the cloning and expression of two more genes from the malaria parasite, P falciparum.

Michael Koenen and collaborators in West Germany and France have now cloned the genes for two antigens expressed by the blood-stage parasite, which causes the symptoms of malaria. One is expressed on the surface of malaria-infected red blood cells, and consists of repeated sequences of nine amino acids.

The other blood-stage antigen cloned by Koenen's group is unique among those so far examined, in that it does not consist of short, repeated sequences. It also elicits a strong antibody response in monkeys, which in turn was able to partly protect the monkeys against severe infections with malaria. It did not work against the milder infections which are common amongst humans in malaria-infested areas.

Both the recently-cloned antigens do bind to antibodies in the blood of humans who have developed immunity to malaria. But there is still no evidence that any of the antigens studied so far will elicit a sufficient immune response to malaria infection in humans. (Extracted from New Scientist, 8 November 1984.)

Smallpox vaccine modified for rabies

French scientists are working on a new vaccine to combat rabies. Trials carried out on mice seem to show that the genetically engineered vaccine is safe, effective and easy to administer. Researchers at Transgène set about producing such a vaccine by applying known biotechnology techniques. They worked with Cowpox (vaccinia) which is the basis of the smallpox vaccine to try to make it carry genes from a rabies virus. If the gene codes for antigenic protein is typical of a rabies virus then the antibody response mounted by the body would prevent rabies viruses becoming established in the body. The team at Transgène plus workers at the Wistar Institute in Philadelphia and at Inserm in Strasbourg found that, for the theory to work, hybrid vaccinia needed to carry only one rabies virus gene. This is because there is one gene that codes for a glycoprotein that sticks out of the lipid sac enveloping the rabies virus. This glycoprotein is the sole antigenic determinant of the virus. In other words it is the only part of the rabies virus that stimulates production of antibodies.

Once the scientists had successfully cloned this rabies virus gene, they incorporated it into the vaccinia. They mixed the vaccinia viruses with plasmids carrying the cloned gene, and cultured the vaccinia in chick cells. Finally, the scientists screened out the vaccinia which had taken the rabies gene on board.

To test the vaccine, mice were immunised by lightly scratching their tails and rubbing the viral suspension into the skin. The mice were given massive doses of virulent rabies virus. Those that were immunised survived.

The scientists now hope that as long as the rabies virus cannot change its antigenic determinant as quickly as the influenza virus does, they have an effective vaccine against rabies.

The rabies virus binds to the neuronal receptors designed to accept acetyicholine, according to Dr. T. Lentz and colleagues of Yale University. The viral glycoprotein and the neurotoxic proteins present in snake venom have identical sequences of amino acids in several regions. Snake venom is known to exert its neurotoxic effects by binding to the receptors. (Extracted from New Scientist, 6 December 1984 and 3 January 1985.)

Vaccine against diarrhoea

A successful vaccine against rotavirus which kills by causing acute diahorrea is nearing reality.

The vaccine consists of a live, disabled rotavirus taken from infected calves made by the Belgian subsidiary of Smith Kline and French.

Rotavirus, according to the World Health Organization (WHO), is perhaps the world's leading killer of young children. The WHO is now sponsoring trials of the vaccine in Peru and the Gambia, according to Dr. Francis Andre of Smith Kline RIT. The National Institutes of Health in the US began trials there last October of a vaccine based on a monkey virus.

Other organizations intend to clone into bacterium one of the 11 genes that make up the rotavirus. They hope to make large quantities of the viral protein which can then be extracted and made into a vaccine. One advantage of such genetically-derived vaccine is that it involves only a part of the viral DNA and so cannot harm the recipient. (Extracted from New Scientist, 25 October 1984.)

Marketing approval for met-hGH denied

Approval to market genetically engineered methionyl human growth hormone (met-hGH) for postmarketing studies has been denied. The United States FDA cannot approve the marketing of a drug for investigational use, and so requested additional follow-up data from clinical trials from Genentech who claim that met-hGH is as effective as natural pituitary growth hormone (pit-hGH). The FDA asked for more information on antibody formation in treated children, and more data should soon be available from a trial involving children with Turner's syndrome. Protropin, the final version of Genentech's met-hGH, has been used only since 1983, in 14 patients with growth hormone deficiency. An earlier preparation produced an antibody response in 21 of 22 patients. The mechanism of met-hGH antigenicity is not understood. It may be due to the presence of proteins from Eschereichia coli, which is used to produce the hormone. (Extracted from Medical World, 8 October 1984.)

Human growth hormone

Bio-Technology General is producing human growth hormone (HGH) with genetic engineering and enzymatic techniques. Genetically engineered bacteria produce methionyl-HGH, which is then enzymatically converted to true HGH. Removing the methionyl residue produces HGH that causes no immunogenic reactions in patients. HGH can be used to treat dwarfism, and may be useful in treating bone fractures, burns and ulcers. (Source: Chemical Week, 12 September 1984.)

Bovine derived growth factor

Exclusive worldwide rights to tissue culture technology that utilizes a new cellular growth factor has been granted to Nova Pharmaceutical (Baltimore, Md.) by the Children's Hospital of Boston. The factor, known as bovine derived growth factor (BDGF) is expected to support the growth of a wide variety of human and mammalian cells in tissue cultures. BDGF is said to replace partially, or completely substitute, blood serum in the growth of certain cells. In addition, BDGF - derived from colostrum, the first milk secreted by the mammary gland after birth and discarded by the dairy industry - is abundant and inexpensive to produce. The factor, Nova says, supports particularly well the growth of hybridoma cells that produce monoclonal antibodies. Nova plans to market the factor to companies and research laboratories that need to produce monoclonal antibodies in large quantities. (Source: Chemical Week, 13 February 1985.)

Diagnostic method for tumors

A staining method used inside the bladder and viewed through a fiberscope to spot bladder cancers has been developed by researchers at the University of Chicago Medical Center. The diagnostic method, said to be quick, easy and accurate, uses the dye methylene blue which binds only to tumor cells. It is put into the bladder through a catheter and flushed out; tumors, even tiny ones, in the bladder show up as blue spots and are removed. (Extracted from Chemical Week, 30 January 1985.)

Interferon effective against non-Hodgkin's lymphoma

According to researchers at National Cancer Institute and Hoffmann-La Roche recombinant leukocyte A interferon is effective against low- and intermediate-grade non-Hodgkin's lymphoma, a cancer that affects the white blood cells, and is characterized by abnormal growth of lymphocytes. The mechanism by which the interferon works is not yet known. (Extracted from Science News, 10 November 1984.)

Interferon helps shingles

After eight years of research a firm in the Federal Republic of Germany has developed an interferon preparation which is said to relieve the pain even in the worst cases of shingles in only a few hours. After one day the inflammation of the skin subsides; after two days the patient has no more pain. After about one week he is cured. Even damage resulting from this dangerous virus disease, such as loss of hearing, paralysis and neuralgic pain, can largely be avoided or at least considerably improved with this drug. (Extracted from Scala, 11 November 1984.)

Hepatitis B

Two hundred million people carry the hepatitis B virus, for which there is no known cure, yet a vaccine to prevent this disease has been available for more than two years. It remains little used because it costs too much.

That may sound a depressingly familiar story, but for hepatitis B it has an interesting twist. Certain groups of people are much more at risk than others, and one especially vulnerable group includes doctors and nurses. In parts of Asia and Africa as many as one in six people carry the virus. In Britain and America, less than two in a thousand are carriers, but with the increase of travel to the Third World the incidence in the West is rising. One in 10 sufferers still harbour the virus in their livers even after they recover and they are vulnerable to other kinds of liver damage, in particular a recently discovered and virulent agent called delta (which piggybacks into the body on the hepatitis virus). Carriers may develop cirrhosis and, every year, 200,000 of them die of liver cancer caused by the virus.

The new vaccine is effective and safe. It consists of the protein overcoat of the virus without the crucial DNA innards. This protein is made in large quantities by carriers' livers. It has to be harvested from their blood before being purified and sterilised. Hence the cost: £3.50 for a course of three injections in Britain.

Health services are unwilling to contemplate the widespread use of such a costly vaccine. Instead, they are waiting for a cheaper one. Thanks to genetic engineering techniques, one should not be long in coming. (Extracted from The Economist, 12 January 1985.)

New technique for detecting genetic defects

A method to test for genetic abnormalities in fetuses that avoids the hazards of amniocentesis has been developed by Harold Miller and Harold Sadoff, microbiology professors at Michigan State University. Their method, called ATA - for alternative to amniocentesis - involves sorting trophoblasts taken from the blood of a pregnant woman when the fetus is eight or more weeks old. Trophoblasts are embryo cells found in the mother's bloodstream at a concentration of about one for every 2.5 million red blood cells. Their function may be to prevent her immune system from rejecting the fetus. Since they are embryonic cells, they can be analyzed for genetic information about the fetus. The analytical technique uses an antibody to the trophoblasts and a fluorescent separation technique that can be used with a commercial cell sorter. A patent has been applied for and an option to license the technique has been granted to Recomtex, a Michigan biotechnology firm that sponsored the research. (Reprinted with permission from Chemical and Engineering News, page 24, 4 February 1985, copyright 1985, American Chemical Society.)

Disease-breeding bacteria "lifted" from infected wounds with new Swedish method

A completely new principle for the treatment of wounds whereby it is possible to virtually "lift off" pathogenic bacteria from the infected area has been introduced by LIC Hygien, a division of LIC, the central purchasing organization of Sweden's county councils. Developed by Professors Stellan Hjertén and Torkel Wadström, Uppsala University, in co-operation with LIC experts, the method is efficient even against bacteria that have become resistant to antibiotics.

The new system is based on the fact that many pathogenic bacteria are extremely water-repellent. Thus, over 97 per cent of the yellow staphylococci which cause blood-poisoning are strongly water-repelling. At the same time, these so-called hydrophobic bacteria adhere to other hydrophobic substances, for example fatty-acid molecules.

The products developed for the new wound-treatment method are designated Sorbact 10^5, the numerals being derived from the fact that wounds containing more than 10^5 (=100,000) pathogenic bacteria per gramme of tissue are registered as "infected". Compresses and bandages have a surface impregnated with DACC, a hydrophobic fatty acid frequently used in the food industry. Inside is a porous cellulose material for absorbing exudate from wounds.

As soon as a Sorbact compress is put in contact with a wound, bacteria are "lifted off" as if by a magnet. The more often this process is repeated, the greater the effect. The compress is subsequently replaced by a Sorbact 10^5 absorption bandage. When the healing process has begun through the creation of new cell tissue, conventional bandages can be used.

Sorbact has been successfully tested at several Swedish hospitals, even on burn cases in which severe infections prevented skin-grafting. Working according to purely physiological principles, the method is said to be natural, completely clean and without harmful

side-effects. Salts and vitamins do not adhere to Sorbact products. There are no risks for the creation of resistant strains of bacteria, nor will patients develop hypersensitivity to the material. Since bacteria adhere firmly to Sorbact, compresses and bandages will not spread bacteria in hospital environments and are simple to destroy, LIC says.

Applications for the use of Sorbact 10^5 include pressure wounds, varicose ulcers and post-operative wounds. Patents have been applied for globally and have already been granted in several countries. (Source: SIP, January 1985.)

Bandages with built-in biocide

A bandage with a micro-organism-killing disinfectant chemically bound to it which is released at a constant rate has been developed by Professor T. Ikeda of the Tokyo Institute of Technology, Japan. Although there is always a chance that infecting micro-organisms will develop resistance to antibotics, the disinfectant bound to the bandage is less likely than antibiotics to engender such resistance because it is made from synthetics. The bandage has been tested in vitro and will soon be tested on animals. Tests on human beings could begin in three to five years. The cost of the disinfectant-impregnated, gelatinlike film - called a self-sterilizing material (SSM) - "should be reasonable," Ikeda says, "because the process for making it is simple".

The SSM, prepared by radical polymerization, wards off infectious microorganisms by controlled release of a biguanide biocide - a class of disinfectant that has a broad spectrum ot antimicrobial activity, a high kill rate and extremely low toxicity for mammals. The SSM gives a constant rate of release of biguanide over a one-week period and continues to release biguanide for 30 days. In tests, Ikeda says, when SSM was placed on nutrient agar plates with bacterial cell suspensions of Escherichia coli, Bacillus subtilis and Staphylococcus aureus, no bacterial growth was found on the material after a 48-hour incubation period. But when a polyacrylamide film not impregnated with biguanide was incubated for 48 hours on agar plates with the three bacterial cell suspensions, colonies characteristic of each bacterial strain were found on the entire surface of the biguanide-free film.

Ikeda is also attempting to develop an SSM with permanent antimicrobial activity. Such material would be particularly useful, he says, in forming artificial organs and artificial blood vessels. Ikeda's current strategy for developing this material involves surface modification of polymeric materials by graft polymerization. (Extracted from Chemical Week, 2-9 January 1985.)

DNA screening device

A new DNA screening device has been developed by Georgetown University Medical Centre to screen a patient's DNA in order to determine susceptibility to diabetes, cancer, heart attack and other serious illnesses. The Automated Genetic Analyzer (AGA) can analyze DNA 10 times faster and with greater accuracy than current, manual methods, and analysis can be done in the doctor's office. The analyzer is loaded with up to 9 radio-labeled DNA probes simultaneously to identify gene sequences being investigated. The patient's DNA is placed on a thin slab of polyacrylamide gel, separated by electrophoresis, dried in a modified microwave oven and combined, or hybridized, with the radio-labeled probes. The gene probe adheres to target genes in the patient's DNA. The gel is washed, dried and placed in an electronic detection unit to measure the amount and placement of radioactivity remaining on the gel, and distinguish whether the patient's DNA has 1-2 copies ot the target gene. The detector is 400-500 times more sensitive than current methods. (Source Chemical Week, 21 November 1984.)

Coagulation disorders test

Universal Reagents, Indianapolis, Indiana, has developed a novel application for monoclonal antibodies: using them to produce test sera for the diagnosis of hemophilia and other coagulation disorders. Test sera for deficiencies of Factors V, VIII, IX and X are reportedly available. (Source: BioEngineering News®, Box 290, Willits, CA.95490, USA, Vol. 5, No. 22, 6 November 1984.)

Response to diagnostic test for herpes

Over 6,000 physicians have expressed interest in SIMPLEX-2™, a new blood test specific for herpes simplex virus 2 (HSV-2), according to Gene Link Australia, who announced the product late last year. This figure represents a 15 per cent response to a direct mail effort to physicians who are involved in the diagnosis and treatment of HSV infections. HSV-2 is the virus most commonly associated with genital herpes.

More than half of the response came from obstetricians and gynaecologists; the remainder is composed primarily of dermatologists, and is followed by specialists in public health, infectious diseases, neonatology, and pathology. The reference laboratories who will market the test to the physician are extremely encouraged by the results.

"Our studies have shown good correlation between SIMPLEX-2™ and genital herpes," said Howard I. Kim, Ph.D., Director, Immunology and Infectious Diseases, Reference Laboratory, A Damon Laboratory. "The response will certainly increase the demand for SIMPLEX-2™ testing here in our laboratory."

Nat Dworkin, Director, Physician Marketing at Metpath, said, "SIMPLEX-2™ has generated a significant physician response indicative of high interest in this area of medical concern."

Bob Savasten, Vice President Marketing and Development, Medical Laboratory Associates, said that "Gene Link Australia's mailing and our SIMPLEX-2™ testing at Medlab have both generated a good deal of interest here in the southeast, especially among Ob/Gyns."

A response level of 2% is considered very good in a direct mail effort. "Therefore, Gene Link Australia's response is exceptionally exciting and encouraging," said John Round, Vice President, Gene Link Australia. A media campaign has begun this month and Gene Link Australia will continue major efforts in direct mail marketing for this product. "Gene Link Australia is budgeting around $150,000 for direct mail and space advertising for SIMPLEX-2™ over the next 12 months," continued Mr. Round.

Gene Link Australia is a publicly-held Australian biotechnology company which was established in 1983. The company is both developing and acquiring Australian products and processes with international commercial potential in the areas of human health care, animal health care, and agriculture.

For further information, please contact John Round, Vice President, Gene Link Australia, Princeton, New Jersey. (609) 452-7100. (Source: Company News Release, 7 November 1984.)

Monoclonal assays to pinpoint oestrogen receptors in breast tumors

Abbott Laboratories has begun marketing two experimental monoclonal oestrogen-receptor assays. An immuno-cyto-chemical assay (ER-ICA) that reveals receptor distribution in tumor tissue sections was launched last month. It follows a quantitative enzyme immunoassay (EIA), first marketed in December 1984, aimed at replacing existing oestrogen-receptor binding tests.

Breast tumors with high concentrations of oestrogen receptors tend to be less aggressive than those with low receptor density. Patients with receptor-rich tumors respond to anti-oestrogen drugs, without recourse to drastic post-surgical chemotherapy. Current assays that distinguish the tumor types depend on radioactive estradiol binding to homogenized tissue samples are often inaccurate and difficult to interpret. (Extracted from McGraw-Hill's Biotechnology Newswatch, 4 March 1985.)

Rapid DNA probe-screen for Legionella

A DNA probe assay for Legionella has been developed by Gen-Probe, Inc., San Diego, California. The technique by-passes time-consuming nucleic-acid isolation steps required for conventional blot-hybridizations and is the second product developed since the firm was established in June 1984.

The Gen-Probe test takes four steps: first, a crude sample is mixed with a solution containing a lysing agent, and the radio-labeled probe. The sample is incubated at 72°C to hybridize the probe to single-stranded RNA. The DNA:RNA hybrids are separated from unhybridized probe by mixing with hydroxyapatite, which binds only double-stranded nucleic acids, and the bound label is detected in a scintillation counter. (Extracted from McGraw-Hill's Biotechnology Newswatch, 18 March 1985.)

Quicker detection of mycoplasma

A diagnostic kit that allows rapid detection of a mycoplasma species - bacteria responsible for serious infections in cell culture samples as well as in the human respiratory tract - is being introduced by Gen-Probe (New York City). The kit, which is Gen-Probe's first product, is said to obtain results in less than an hour, compared with the days or weeks needed for conventional detection methods. The assay is designed for research and industrial laboratories, where mycoplasma contamination of cell cultures is a frequent and troublesome problem. (Extracted from Chemical Week, 23 January 1985.)

HTLV-III assay

A semi-automated assay that detects antibodies to the virus implicated in acquired immune deficiency syndrome (AIDS) has proved to be highly specific and sensitive. Developed by Stanley H. Weiss at the National Cancer Institute (Bethesda, Md.), the assay, based on monoclonal antibodies, identifies those antibodies that the human immune system produces in response to infection by the HTLV-III virus. The assay will be useful in screening blood donors and populations at risk for AIDS and help define the spectrum of diseases, such as certain leukemias the virus may cause. In addition, the assay will be used to determine why only a small percentage of persons infected with the HTLV-III virus develop AIDS, while most infected persons become asymptomatic carriers of the virus. (Source: Chemical Week, 16 January 1985.)

Possible AIDS combatant being tested

The National Institutes of Health is testing a combatant for AIDS, suramin, an anti-parisitic made by Bayer (FRG). The drug can inhibit infectivity and replication of HTLV-III, a strain of human T-cell leukemia virus identified as a probable cause of AIDS. The drug can also protect a normal population of T-cells that would otherwise be killed by the virus. Tests of the drug are beginning on human patients having an early form of Kaposi's sarcoma, a disease that often infects AIDS victims, because the drug may turn out to be too toxic to give to patients with advanced AIDS. (Extracted from Wall Street Journal, 5 October 1984.)

US licenses blood test for AIDS

The US Government's Food and Drug Aministration (FDA) has approved a commercial test for identifying blood that is contaminated with AIDS (acquired immune deficiency syndrome). It could be in use at blood banks within days.

The test is known as ELISA (enzyme-linked immunosorbent assay) and detects the presence in blood serum of antibodies that the donor has produced to fight infection from the AIDS virus. Public health officials stress that a person with the antibodies will not necesasarily contract AIDS, which is really a collection of diseases that attack the victim once the virus has debilitated his or her immune system.

The US Government's Public Health Service has ordered that all blood donations taken in the US, about 1.5 million per month, should be tested. Any blood found to harbour antibodies cannot be used.

The process is not foolproof. The five companies that developed the test discovered that it sometimes registers antibodies when further tests show there are none. The rate of these "false positive" results among donors who are not at high risk of catching AIDS is only about 0.2 per cent. But when millions of samples are screened that still means many false-positive results. (Extracted from New Scientist, 7 March 1985.)

Livestock applications

Trypansomiasis vaccine

Cell biologists working at the International Laboratory for Research on Animal Diseases (ILRAD) have used trypanosome parasites grown in tissue culture to make a vaccine against trypanosomiasis, or sleeping sickness. Though only single-cell organisms, trypanosomes are extremely robust, and once in the bloodstream, they have the ability to vary the molecular structure of their surface coat to alter their antigens and keep one step anead of the host's antibodies. Sucked up into the fly, the parasites slough off their coats, becoming non-infective once more.

One of ILRAD's most important initial tasks was to culture and propagate the parasites in their infective form. The World Health Organization predicted it would take them 10 years: ILRAD's scientists have achieved it, using an isolate of T. brucei, in six months.

From that first breakthrough, work has proceeded step by step, both at ILRAD and elsewhere. In 1981, scientists at Edinburgh University developed a way to cultivate infective-stage T. congolense parasites, starting from the mouth part of the fly. In 1982, scientists from the Swiss Tropical Institute, working with colleagues at ILRAD, developed a culture system for the bloodstream form of T. vivax, the most delicate and hence most difficult species to culture.

By the end of last year, ILRAD had succeeded in culturing all three species for at least one isolate, and in some cases for several. And, using a modified version of the Edinburgh University technique, ILRAD's cell biologists were now able to produce 100 million to 200 million infective T. congolense parasites per day. Now, with sufficient T. congolense parasites available for detailed research on the forms, mechanisms and variety of antigens, researchers made an important discovery.

In its metacyclic form (that is, when it has donned its antigen coat ready for the journey into the mammalian host) the parasite appears to have far fewer antigens than it later develops once in the bloodstream. Apparently the same set of antigens appears each time the parasite returns to this stage. Thus, though it might not be possible to immunise animals against the bloodstream form, it may be possible to immunise against this initial infective form.

To test this hypothesis, the scientists produced a vaccine using metacyclic forms of one T. congolense serodeme produced in vitro, then killed and broken down by ultrasound. In the crucial series of experiments, eight goats were vaccinated. Two months later they were bitten by tsetse flies infected with the same serodeme. All eight resisted infection, whereas 11 controls caught the disease and died.

Despite this very clear-cut result, much work remains to be done before ILRAD's team can try its vaccine in the field. The next step is to test whether the vaccine, produced from a serodeme isolated in Serengeti 10 years ago, will cross-react with three new strains isolated from the Kenya coast. (Extracted from New Scientist, 18 October 1984.)

Vaccine against East Coast Fever

New vaccines being developed in Kenya could one day rid East Africa of one its most devastating cattle diseases. The techniques behind the vaccines might also eventually be developed to help in the fight against insect borne diseases in people. East Coast Fever, caused by a single-celled parasite, Theileria parva, carried by ticks is endemic everywhere below 2500 metres and kills half a million cattle each year in East and Central Africa.

The life cycle of Theileria in cattle is very similar to that of the malaria parasite Plasmodium, in humans, but unlike Plasmodium, which enters red blood cells, the fever parasite invades the lymphocytes, a type of white blood cell. There, after a few days, it stimulates the rapid division of cells and causes fever and death. So far, the principal strategy against Theileria has been to regularly dip the cattle in chemicals to kill the ticks. The process has to be repeated once or even twice every week. Most African farmers have neither the money nor the facilities for regular dipping. In any case, the ticks are becoming resistant to the chemicals.

The only way, at present, of inducing immunity is to give the cattle the disease. More than a decade ago, research supported by the United Nations led to vaccination as a combined infection-and-treatment. A controlled dose of parasites was given together with an antibiotic, oxytetracycline. Trials carried out by the International Laboratory for Research on Animal Diseases (ILRAD) showed that the treated cattle did gain immunity, but only against the strain used in the vaccination. But there are more than 20 strains of the disease. Moreover, the immunised cattle carried live parasites in their blood, and so could spread the disease.

At ILRAD's headquarters, Nairobi, researchers are looking for vaccines that are safer and easier to store and administer using monoclonal antibodies to try to characterize all the different strains of the parasite and find common antigens. One hope is that they can find a vaccine to combat the parasite at the sporozoite stage.

Another line of attack is vaccination against the ticks that carry the fever. Such a vaccine is under development at the International Centre for Insect Physiology and Ecology (ICIPE) in Nairobi. Vaccinating cattle with antigens to the ticks would mean that the ticks get a mouthful of anti-tick antibodies with their blood meal. In humans, such antibodies would probably be digested, but Israeli researchers have shown that antibodies (immunoglobulins) will pass through the gut wall of ticks.

Researchers at ICIPE, under Matt Cunningham, are making a three-pronged attack on the ticks. The first trial vaccines were, basically, squashed ticks. Now the researchers are separating out three groups of antigens. One acts against the tick's digestive enzymes, to slow digestion. Another works against the tick's gut wall, to aid penetration. A third group is prepared from various sensitive internal organs, such as the ovaries. Already, the researchers have characterized 12 gut-wall antigens. Some of them are now patented.

ICIPE has now proposed a trial to see if the various strategies can be combined to eradicate East Coast Fever from cattle in one area. They have picked Rusinga, an island 10 kilometres by 4 kilometres on Lake Victoria, in western Kenya. There are about 8000 cattle on the island. All are the indigenous short-horned zebu.

On the mainland it may prove harder to eradicate the tick because the disease is also carried in wild buffalo. But new, cheap, electric fences powered by solar energy offer the prospect of keeping the buffalo out of large areas of pastureland.

Vaccination against other blood-sucking carriers of disease is also under investigation around the world. Australian researchers are looking at another tick-borne disease in cattle, red water fever. And Dr. John Alan, at the University of Saskatchewan, has had some success against a tick that can cause a skin disease in humans.

Flying insects, such as mosquitoes and tsetse flies, will be harder to deal with because they can fly across fences to re-infect treated areas. But scientists at ICIPE have shown that antibodies will penetrate the gut wall of tsetse flies, so there may be hope here too. (Extracted from New Scientist, 7 March 1985.)

Feline leukemia vaccine

A new vaccine against feline leukemia virus (FeLV), is being sold by SmithKline Beckman's Norden Laboratories (Lincoln, Neb.). It is now possible for the first time to vaccinate a mammal against a form of cancer. The product was approved in November by licensing authorities in the U.S. and in January in Canada for sale to veterinarians.

Among cats, feline leukemia is probably the most serious disease. Studies have shown that 4 per cent of cats entering veterinary hospitals for all reasons carry the virus in their blood, although incidence of the disease in its active form is confined to no more than 1 per cent of cats.

Many cats that are exposed to the virus develop a successful immune response. But cats that don't mount a successful defense are doomed, since the disease has defied cure as well as prevention.

The virus that causes feline leukemia was isolated in 1964. Scientists first thought leukemia was passed on genetically. Only in 1974 did they learn that cats transmit the disease through social contact; this meant that the disease might be prevented, in accordance with conventional principles of inoculation. The breakthrough leading to the new vaccine came with the discovery, in 1974, that FeLV is contagious. Now, scientists know the disease may be transmitted through mother's milk or exposure to a diseased cat's urine, but the disease is definitely spread via cats' saliva. (Extracted from Chemical Week, 20 February 1985.)

Agricultural applications

Joint agreement for developing and marketing herbicide tolerant cotton seed

Calgene, Inc. and Phytogen announced a joint agreement to develop and market herbicide tolerant varieties of cotton. Using plant genetic engineering technology, the companies will jointly develop proprietary cotton cultivars tolerant to glyphosate, the world's largest selling herbicide.

According to Calgene, U.S. cotton growers annually spend more than $150 million for cotton seed planting, and more than three times that amount for herbicide and mechanical weed control. Despite these substantial expenditures, yield losses due to weed competition in cotton still cost approximately $500 million per year - or 15 per cent of the total annual crop.

"This need for improved cotton weed control can be met by the use of broad spectrum herbicides such as glyphosate if tolerant cotton varieties can be developed." said John Callahan, director of commercial development for Calgene. "We have already cloned the glyphosate tolerance gene and are curently testing its expression in commercial crops such as tobacco, soybean and tomato," added Callahan.

Under the terms of the agreement, Calgene's scientists will provide its proprietary glyphosate tolerance gene and vector systems. Phytogen's scientists will introduce the gene into elite cotton varieties, and will co-ordinate field testing.

Phytogen was the first company to successfully regenerate commercial varieties of cotton. "This co-operative effort enables us to combine and exploit the complementary technology strengths of our respective programmes," stated David Anderson, director of research for Phytogen.

Calgene and Phytogen are two of the leading plant biotechnology companies developing and commercializing new crop varieties and plant products. The companies utilize recombinant DNA and cell tissue culture techniques along with traditional biological methods such as plant breeding.

Phytogen, headquartered in Pasadena, California, is an affiliate of the J.G. Boswell Company, a leading California-based agribusiness corporation. (Source: Company News Release, 19 November 1984.)

Palm oil yield

Palm oil yield can be raised 20-60 per cent by cloning palms, according to R&D by ORSTOM and IRHO, two French agencies. Some 100,000 palm trees, which cannot be propagated using traditional methods, were studied in the Ivory Coast to determine the best producers. Some 15,000 clones were produced in one year, and production units are being built in Indonesia and Malaysis. (Extracted from Les Echos, 11 July 1984.)

Genetic engineering advances for oilseed crops

An important achievement in plant biotechnology was announced by Calgene, Inc., in an address before the Saskatchewan Brassica Biotechnology Workshop in February and sponsored by Agriculture Canada. Dr. Maurice Maloney, who leads the Brassica research team at Calgene, described the first successful recombinant DNA transformation and regeneration experiments with oilseed rape (Brassica napus), one of the world's most important oilseed crops.

According to Dr. Maloney, Calgene scientists have obtained normal Brassica napus plants from cells into which a bacterial antibiotic resistant gene was inserted and have shown that the gene is expressed in the engineered plant.

Calgene's progress in micro-injection of plant cells was also described by Dr. Maloney during the address. A micro-injection team led by Dr. Anne Crossway has obtained a survival rate of 85 per cent when the nuclei of Brassica protoplasts were micro-injected using a fine glass needle. Several hundred micro-injected cell lines are being analyzed to test for DNA integration.

"Perfection of micro-injection methods will dramatically shorten the product development cycle for genetically engineering new plant varieties," stated Dr. Maloney.

According to Lloyd Kunimoto, Calgene director of product planning, genetically engineered oilseed rape opens up significant opportunities for production of specialty, high-value oils for the oleochemical and edible oils industries. Worldwide production of rapeseed oil currently exceeds 14 million metric tons annually, and the raw material values of all plant oils exceeds $11 billion on a worldwide basis.

Calgene is developing new crop varieties and plant products using recombinant DNA and cell culture techniques along with traditional biological methods such as plant breeding. Calgene's product development programmes are focused on herbicide tolerance, carbohydrate metabolism, disease resistance and vegetable oil biosynthesis. (Source: Company News Release, 22 February 1985.)

Plant diagnostic testing

Biotechnology is being used to diagnose plant diseases, relying on monoclonal antibodies to search out and tag disease organisms; 30 per cent of US crops are still destroyed by diseases each year. Plant diagnostic tests will enable farmers to spot infection early enough to dramatically cut losses that amount to $2 billion/year in the US alone. DNA Plant Technology is working on tests for disease of citrus trees, while Agdia (Granger, IN) has developed tests to detect viral diseases in grapevines and fruit trees. Since many plant diseases can be transmitted through infected seeds or root stocks, researchers are also developing tests that will detect these diseases before the crops are planted. DNA Plant Technology has introduced test kits in 1985 that will spot the six most common grass diseases. The plant diagnostic market will take patient development since plant diseases vary from crop to crop, are localized in regions, and there is no established system of distribution. (Extracted from Business Week, 17 September 1984.)

Herbicide tolerance would be first commercial use of recombinant DNA in field crops

Researchers at Calgene (Davis, Calif.) have successfully expressed the glyphosate tolerant aroA gene in regenerated tobacco plants. Analyses of tobacco plants regenerated from transformation experiments showed that the enzyme produced by the altered aroA gene represented 25 per cent of total EPSP synthase activity measured in leaf extracts. The transformed plants demonstrated a significantly increased tolerance to glyphosate when sprayed with the herbicide.

According to Dr. Luca Comai, the Calgene science team leader, "based on these successful results, we are initiating glyphosate tolerance product development projects in a wide range of important agricultural crops. We have already introduced the aroA gene into soybean, tomato and oilseed rape cell cultures and we have a significant effort underway to transform corn." Dr. Comai added that, "tobacco plants transformed with improved constructs of the aroA gene in second generation transformed plants is also being tested".

The succcessful cloning of a glyphosate tolerant aroA gene from a genetically-modified strain of Salmonella typhimurium was first published by Calgene scientists in Science in July 1983, and an article characterizing this gene will appear in the April 1985 issue of the Journal of Biological Chemistry.

Calgene previously announced an agreement with Phytogen, an affiliate of the J.G. Boswell Company, a leading California-based agribusiness corporation, to develop and market glyphosate tolerant cotton varieties, and recently concluded an agreement with the U.S. Forest Service to genetically engineer glyphosate tolerance into forest trees used by the pulp and paper industry.

Calgene is developing new crop varieties and plant products using recombinant DNA and cell culture techniques along with traditional biological methods such as plant breeding. Calgene's product development programmes are focused on herbicide tolerance, carbohydrate metabolism, disease resistance and vegetable oil biosynthesis. (Source: Company News Release, 15 February 1985.)

Symbiosis promotes rice growth

European farmers have for centuries been looking at biological ways of fixing nitrogen into soils. In the classic four-crop rotation, clover "fixes" nitrogen into the soil one year in four. Scientists now believe that a group of blue-green micro-organisms called cyanobacteria could do the same thing for rice farmers in tropical countries, while rice is growing.

Cyanobacteria are primitive photosynthetic organisms which have the ability to exploit energy from sunlight to fix nitrogen from the atmosphere into the soil. Research in China and India suggests that inoculating paddy fields with the bacteria can increase yields of rice by as much as 14 per cent. One method may come from the symbiotic association between blue-green algae and a small aquatic fern called azolla. At least six varieties of this fern thrive in tropical and temperate regions. Experiments at the International Rice Research Institute in the Philippines have shown that with intensive managment and year-round cultivation, cyanobacteria grown with azolla can fix up to 450 kilograms of nitrogen per hectare. When grown with rice, the combination can fix between 30 and 50 kilograms of nitrogen per hectare. While farmers normally apply commercial nitrogen fertilizer at twice this rate, fixing with azolla clearly has potential. In one part of the Philippines, the fern allowed farmers to save $35 per hectare.

Despite the success of the process in carefully controlled conditions, it may run into problems in everyday use. Azolla is susceptible to pests and diseases and does not tolerate extremes of temperature, or saline conditions. Also, herbicides commonly applied to rice paddies kill the fern. A strain of azolla modified by mutation, or possibly by genetic engineering, may be more practical. (Extracted from New Scientist, 17 January 1985.)

New hybrid potato

The Canadian company Allelix has developed a hybrid potato using the standard cultivated potato together with a distant relative which does not form tubers to provide disease resistance and cold tolerance. The firm used somatic hybridisation, isolating cells from leaves of both parent plants, and removing the cell walls. The remaining protoplasm can coalesce to create a hybrid cell that can then develop into a new plant. Scientists have now produced 32 of the hybrid plants, but detailed analysis of six of them indicates a variety of chromosomal makeups. The standard potato has 48 chromosomes, while the distant relative has 24. Some of the hybrid plants had 72 or 96 chromosomes. (Extracted from New Scientist, 11 October 1984.)

New silage additive

Although Shell is itself working on a number of biotechnology projects, particularly in the fields of waste water treatment and oil recovery, Shell Chemicals UK turned to International Biochemicals (BBR 59, October 1984) to provide it with a proven product with which to enter the highly competitive UK silage additive market. The new product, "Forager", was launched in November after four years of field testing in both the UK and Ireland. It works by enhancing the efficiency of the natural silage fermentation process through the introduction of a number of key strains of micro-organisms, originally isolated from silage. Their performance has been upgraded and refined in the company's laboratories and stabilized by freeze drying. Unlike acid products, says International Biochemicals, Forager is completely safe to handle and is non-corrosive to machinery. Details from: International Biochemicals, 11 Gloucester Road, London SW7 4PP or on 01-581 4018. (Biotechnology Bulletin, Vol. 3, No. 11, December 1984.)

Food production and processing

Protein engineering makes its mark on enzymes

There is a growing industrial need for newer, tougher proteins, with special properties such as heat stability, or acid tolerance. Enzymes are a special class of protein which work within a narrow range of conditions, closely resembling those in the animal or plant cell they come from. These enzymes are expensive, and easily broken down. One way to obtain more resistant enzymes is to search for bacteria which contain them naturally, and extract them. New Zealand is rapidly exploiting its thermophilic (heat-loving) bacteria which thrive in hot water pools.

However, once protein engineering techniques become routine scientists will be able to make enzymes to order, changing not only their tolerance to heat, but their specificity, and activity as well and biotechnology companies have been quick to sieze on the practical importance of protein engineering. Only a small portion of the enzyme's surface, called the active site, is involved. So, protein engineering first of all depends on the skills of X-ray crystallographers working with computer graphics experts to pinpoint which of the many atomic groupings in the protein molecule are essential for its activity.

Once the active site to be changed is identified, the molecular biologists come into action. They synthesise a short sequence of DNA in the laboratory incorporating the sequence to be changed and insert this into bacteria.

Conventional lysozymes are already widely used as a food preservative, and in toothpaste, as well as in the growing biotechnology industry, where the Japanese are increasingly using them to break up cells. (Extracted from New Scientist, 6 September 1984.)

Porcine pancreatic lipase

An enzyme has been discovered in pigs that can work in solvents other than water, according to researchers at the Massachusetts Institute of Technology. Development of enzymes that can function without water could aid the food processing industry by eliminating contamination from water-borne bacteria. Porcine pancreatic lipase is the enzyme that has been observed to function in a range of organic solvents. The enzymes normally digest fats in the pancreas of the pig. In 'dry' conditions, the enzymes work faster at 100°C than at room temperature, although enzymes normally do not work outside a narrow range of temperatures. (Extracted from New Scientist, 4 October 1984.)

Ethanol from corn stover

Corn stover could be used to produce biogas, fuel-grade ethanol or microbial protein for animal feed, according to Drs. M. Moo-Young, J. Lamptey and P. Girard of the University of Waterloo. Corn stover could be treated with acid to yield a glucose substrate, which could be fermented in an immobilized-yeast packed-bed reactor to make ethanol, but the process is very sensitive to ethanol and raw material costs. Biogas can be made by anaerobic digestion of corn stover in a two-step process, but the method is uneconomical unless there is a good market for by-products such as compost and animal feed from solid residues of the process.

Single-cell protein (SCP) production, based on a new fermentation process developed at Waterloo, converts waste carbohydrates into SCP feed supplement. The process includes pretreatment of the corn stover with sodium hydroxide, aerobic fermentation with noncarbon nutrient supplements and separation of the product from the fermented broth. The economics of the process will be affected by the price of soymeal protein, with which the SCP would

compete. The record 1984 US harvest of soybeans will depress the price of soymeal protein in North America, making the corn stover process uneconomical, at least temporarily, but the process should be viable in Europe, Asia and Latin America. (Extracted with permission from Chemical and Engineering News, page 59-60, 14 January 1985, copyright 1985, American Chemical Society.))

New food additives through genetic engineering

Enzymes are commercially among the fastest-growing group of food additives. At a rough estimate more than 50 enzymes are used in the food industry alone. The current market for industrial enzymes, including those used in food, is around £200 million and expected to grow to between £500 and £600 million by the mid-1980s. Europe dominates the world in sales, with Novo Industrie in Denmark and Gist Brocades NV in the Netherlands controlling 60 per cent of the world market. Britain's industry remains small, with John and E. Sturges Ltd. the main producer. One of the major goals of the government's policy on biotechnology is to boost the production of home-grown enzymes: but the industry says this development may not happen if regulations are tightened.

Traditionally, enzymes have been extracted from plants and animals such as rennin, but the production of enzymes from bacteria, yeasts and fungi is rapidly becoming more common. An American company, Collaborative Research Inc., was recently granted a British patent for its version of rennin, produced through genetic engineering.

The FAO/WHO Expert Committee on Food Additives identified certain hazards associated with the burgeoning and uncontrolled use of food enzymes. It argued that these enzymes could contain potentially harmful contaminants and by-products because the commercial processes for preparing these enzymes, usually kept a closely guarded secret, varies greatly. Mutations in micro-organisms could lead to the emergence of new "potentially toxic products" which could go undetected. Other authorities in Britain, for instance, fear that workers exposed during manufacture to even a deactivated enzyme might develop allergies. Consequently, the Expert Committee deemed that chemical and microbiological specifications, and the biological control of strains of micro-organisms used to produce these microbes, were essential. It laid down guidelines for dealing with enzymes. Enzymes from micro-organisms traditionally accepted as constituents of food required only careful specification. However, enzymes derived from less well-known microbes (including those produced by genetic engineering) require extensive toxicological testing, including animal studies.

In Britain, a report published in 1982 by the Food Additives and Contaminants Committee of the Ministry of Agriculture, Fisheries and Food went further. The committee is proposing legislation that will require that all enzymes be put on a 90-day study in rats and a biological screening test (as yet not developed) for the presence of toxins. It remains "unconvinced" by the industry's claims that it makes enzymes only from strains that do not produce toxins.

The potential of such research, especially genetic engineering, is easily seen. For example, pullulanase is an enzyme that degrades pullulan, a polysaccharide, to the maltose syrups that give jams and jellies improved colour and brilliance. They reduce the discoloration of sweets during processing.

This enzyme also degrades another carbohydrate, amylopectin, to produce high amylose starches used in the industry as quick-setting, structurally stable gels, as binders for strong transparent films and as coatings. Their acetate derivatives are added to textile finishes, sizing adhesives and binders. In food, amylose starches thicken and give texture to sweets and sauces, reduce fat and grease in fried foods, and stabilize the protein nutrients, colours and flavours in reconstituted food products such as meat analogues.

A recent report from the Office of Technology Assessment in the US, dealing with the impact of applied genetics, comments that "in view of shortages of petroleum-derived plastics and the need for a biodegradable replacement, amylose's ability to form plastic-like wraps may provide its largest industrial market, although that has yet to be developed". It points out that pullulanase may never fulfil its potential without genetic engineering, because the food industry is permitted to use only enzymes that are obtained from sources "approved for food use" and the chief source of pullulanase is a pathogenic bacterium, Klebsiella aerogenes.

However, with genetic engineering the gene for this enzyme could be transferred to another, harmless bacterium such as Escherichia coli, which could then be grown cheaply to provide large quantities of the enzyme. (Extracted from New Scientist, 18 October 1984.)

Food from the sea

The University of Maryland, with its new marine biotechnology centre, is one of the hubs of marine research on the U.S. east coast. In addition to improving traditional saltwater sources of biomass, reseachers are seeking marine micro-organisms with unusual capabilities. John Waterbury of the Woods Hole Oceanographic Institution (Woods Hole, MA) and his associates discovered bacteria that can both digest cellulose and fix nitrogen. The bacteria, which are members of an as yet unnamed genus, live in symbiotic relationships with molluscs that can subsist entirely on a diet of wood. Because the bacteria are being patented, Waterbury only recently began sending out cultures.

"We've had about equal interest from academics and industry," Waterbury reports. He says the bacteria are particularly attractive for producing single-cell protein from cellulose because they would eliminate the need to add fixed nitrogen.

Such single-cell protein might conceivably be recycled back into the marine system as food for aquacultured species. Phillips Petroleum (Bartlesville, OK) is testing the efficacy of its own yeast-derived single-cell protein as a feed for such animals as lobster, shrimp and trout.

Holger Jannasch of Woods Hole is working with another unusual bacterium. Originally isolated from a deep sea hot vent, this bacterium can metabolize hydrogen sulfide, a common waste product, and procure its other nutrients from normal seawater in an "artifical vent" situation. This bacterial biomass can then be fed to mussels. Jannasch says he and his co-workers have already demonstrated that the mussels will consume the bacterium without ill effect. "All that is needed now is the bioengineering to go to a larger scale pilot plant," he says. (Extracted from Bio/Technology, January 1985.)

Improving aquaculture

Seafood is a comparatively inexpensive source of protein, so the application of biotechnology to culturing finfish and shellfish represents a real opportunity to increase food production.

Abalone is a tasty, scarce, and expensive shellfish, difficult to grow in aquaculture. Now a researcher at the University of California in Santa Barbara (UCSB) has discovered ways of overcoming the abalone's low reproduction and survival rates. These findings may also have unexpected implications for human medecine.

Daniel Morse, professor of molecular genetics and biochemistry, discovered that prostaglandin regulates reproduction in abalone, as it does in many other animals. Once one shellfish starts spawning, it releases the hormone, which triggers nearby individuals of the gregarious abalone to spawn too. This increases the chance for successful fertilization of the sperm and egg cells released into the water. Morse found that a trace of hydrogen peroxide added to the breeding tank stimulates prostaglandin synthesis, resulting in simultaneous and vigorous spawning. This simple stimulus also works on oysters, clams, scallops, and mussels. The marine biologist says the hydrogen peroxide provides free oxygen radicals needed in an enzymatic step in the formation of prostaglandin.

Successful and predictable spawning is only the first hurdle. The tiny, free-floating abalone larvae die by the thousands or millions if they do not find a suitable substrate on which to settle and grow into adults. Morse screened many rock surfaces, looking for a clue to the abalone's preference. He eventually isolated a chemical signal - a close relative of the neuro-transmitter gamma amino butyric acid (GABA) - from a red algae that colonizes rocks. Without GABA, only one per cent of the abalone larvae survive. When GABA is added, 95 per cent attach themselves to the rocks.

Morse is employing genetic engineering tools to produce and characterize the GABA-mimicking compound because it also has great potential in human therapy. GABA controls about 40 per cent of all brain nerve transmissions, involving muscle tone, sleep, wakefulness, and a range of psychological states. He hopes that GABA mimetics, which bind up to a hundred times more tightly to the GABA receptors, could one day replace commonly used drugs, which often have undesirable side effects.

The techniques of biotechnology combine with the natural biology of many fish species to offer a prime opportunity for virtuoso scientific performances. Intergeneric crosses are comparatively easy with fish, and when it comes to manipulating and improving reproduction, the potential of fish - often with many thousands of offspring per brood - can eclipse that of mammalian systems. Combine this with scientists' ability to alter the sex of young fish, and the stage is set for some truly fantastic exercises. (Extracted from Bio/Technology, January 1985.)

Mariculture

A team of American scientists has found a cheap and simple way to farm king crabs on artificial reefs in the Caribbean. The idea for these ocean farms came from research into underwater coral reefs by Dr. Walter Adey, director of the marine systems laboratory at Washington's Smithsonian Institute. Dr. Adey made detailed studies of Caribbean reefs to understand how they made the most of the nutrients at their disposal. Waves and currents proved a key element: their action constantly renews the reefs' supply of scarce nutrients. Sunlight filtering through to plants on the reefs enables them to carry on photosynthesis and thus produce carbohydrates. The water washing over the reefs contains the phosphorus and sulphur that animals and plants need to make protein.

Living things need to have access to soluble nitrogen to make protein, yet most of the nitrogen in the ocean is in gaseous form. This puzzle was solved not in the Caribbean but in Washington, where Dr. Adey's team simulated the life of a tropical reef in the Smithsonian's 12,000-litre test tank. The scientists discovered that the gaseous nitrogen was being captured and turned into soluble form by several types of blue-green algae, the primitive bacterium-like plants at the base of the marine food chain.

Soon after the Smithsonian's indoor "reef" started working five years ago, the scientists noticed something else. Some of the algae that had been floating invisibly in the imported ocean water began to stick in visible quantities to the walls of the tank. Why should they not grow equally well in the open sea, provided they were supplied with some sort of surface to take the place of the tank walls? Experiments showed that simple $6-frames of fibreglass mesh (the kind used for window screens) would do the job beautifully; they just had to be tethered six or eight inches below the surface, where there was enough wave and current action to keep the water stirred up to renew the supply of nutrients.

The next job was to find a sea creature willing to graze on the algae. Tests in the West Indies came up with an ideal candidate - Mithrax spinossissimus, the Caribbean king crab.

The crabs are now being farmed. When they are housed in underwater pens fitted with the algae-laden fibreglass mesh screens, the crabs hatch from eggs within 24 hours, and grow to a market weight of two kilograms - about 40 per cent of it meat - in just over a year. Their meat is so delectable - and so readily canned and frozen - that Dr. Adey reckons crab farming will provide jobs for thousands of people in tropical countries. Demand should grow. The previous $500m a year market for Alaskan king crab is being destroyed by over-fishing. A substitute species, the Snow Crab of Iceland and Newfoundland, is facing a similar fate. Dr. Adey's team is therefore being backed by America's Agency for International Development, the Peace Corps and Earthwatch.

Mr. Adey and his colleagues intend to adapt their technology to replace another vanishing delicacy, the Pacific abalone, for which Californian diners pay $25 a portion. The replacement will be a mottled brown and white sea snail or whelk. Mr. Adey plans to call it Caribbean abalone. He reckons that at least 100 other marine species - tropical, temperate and Arctic - could eventually be brought to market profitably by the new mariculture methods. (The Economist, 23 March 1985.)

Dipstick detects poisoned seafood

A rapid monoclonal antibody-based assay for dinoflagellate polyether neurotoxins promises seafood lovers a practical on-the-waterfront test for contaminated fish.

To absorb the lipid poisons - either ciguatoxin or okadaic acid - Dr. Yoshitsugi Hokama of the University of Hawaii's John A. Burns School of Medicine, Honolulu, spears his sample fish with bamboo skewers coated in Liquid Paper correction fluid. Bound toxin is then detected with horseradish-peroxidase-conjugated, anti-toxin monoclonals. The colorimetric test is more sensitive and specific than existing polyclonal assays, which give 12 per cent or more false positives. Hokama has sea-tested his dipstick on hundreds of reef-fish off Oahu. They include: kole, taape, palani, menpachi, nenue and wrasse, as well as on fish samples from clinically documented ciguatera poisoning cases. (Extracted from McGraw-Hill's Biotechnology Newswatch, 4 March 1985.)

Chemical applications

New chemical reagent

P&S Biochemicals (UK) has developed a ligase-based chemical reagent for genetic engineering applications. The firm previously introduced restriction enzymes with an affinity for a particular sequence of chemicals in DNA. The restriction enzyme cleaves the

DNA molecule at a certain point, allowing another piece of DNA to be inserted. The new reagent facilitates insertion and has a 95 per cent success rate. The reagent may be of use in mass production of insulin and interferon by genetic engineering. (Extracted from Financial Times, 24 October 1984.)

Energy and environmental applications

Alternative to straw burning

A cocktail of microbes may soon provide an economic alternative to straw burning. Jim Lynch and colleagues at Britain's Glasshouse Crops Research Institute have been working on ways of returning the valuable energy in straw back to the soil. Although decomposing straw produces harmful phytotoxins which can depress crop yields by as much as 30 per cent, not all the products of biological degradation are harmful. In particular, nitrogen-fixing bacteria can turn atmospheric nitrogen into a form in which it can be taken up by plants. Bacterial activity in the soil is normally curtailed by a lack of a ready source of energy. Straw, composed of 75 per cent carbohydrate, could supply this energy but the carbohydrate is mostly in the form of cellulose and hemicellulose, which most nitrogen-fixing bacteria cannot break down. However, other micro-organisms can act on cellulose and break it down into simple sugars, which can then be used by the bacteria to fuel the nitrogen-fixing reaction.

The research team has screened a number of likely microbes. The most promising is the cellulotytic fungi Trichoderma which have the added attraction of being parasitic on other fungi that cause root diseases in crops and the nitrogen-fixing bacterium Clostridium butyricum. Their relationship is mutually beneficial, with part of the fixed nitrogen being passed back to the fungus to stimulate further breakdown of the straw cellulose. Laboratory estimates suggest that about half the annual fertilizer application to crops can be produced in this way.

Another organism, Enterobacter cloacae, produces large amounts of polysaccharide gum, which binds soil particles together and thus helps to prevent soil erosion. The oxygen consumption of this organism also helps provide the right conditions for the anaerobic nitrogen-fixing bacteria.

Investigations to find the ideal combinations of microbes and how they perform under different conditions, are now underway. Straw is good for soil. Researchers at Rothamsted Experimental Station in Hertfordshire have shown that ploughing straw back into the soil can double the nutrients in it, compared with fields on which straw is burnt each year. The Rothamsted researchers have analysed samples of soil taken from two Danish fields. For the past 18 years the straw from one of the fields was burnt every year, while straw from the other was ploughed in.

The researchers measured the amount of carbon, nitrogen and phosphorus in the biomass fractions of soil from both fields. The figures for the soil in which straw had been incorporated were almost double those for the soil on which straw had been burnt. (Extracted from New Scientist, 22 November 1984.)

Ethiopians test biogas digester

The Debre Zeit research station in Ethiopia is testing a new type of biogas digester which is halfway between the Chinese hole dug in the ground with holes for the gas to escape, and the expensive industrial model designed in India.

The digester consists of a sausage-shaped plastic container, about 5 metres long by a metre across; it can be made from materials available in Ethiopia and costs about £100.

The dung from three head of cattle is sufficient raw input for the unit to produce about $2m^3$ of gas per day, and enough residue to fertilize about $10,000m^2$ of farmland each year. The gas produced by the digester would be ample for an Ethiopian farmer's lighting and cooking needs. (Source: New Scientist, 6 September 1984.)

Biomass will fuel a utility power station

Sawmill waste and tropical wood will be the fuel source for a new 6.7-megawatt power plant to be built in French Guiana. The plant is expected to save the Degrade des Cannes power station operated by Electricité de France considerable sums in heavy oil costs. Biodev International (Montreal) will supply the gasification equipment for a system developed by Omnifuel Gasification Systems (Toronto). (Source: Chemical Week, 7 November 1984.)

A safe way to kill mosquitoes

With the increase in mosquito resistance to insecticides, the World Health Organization's control programme foundered during the 1970s. Biological and physical methods provide a different approach, and the Wolfson Mosquito Control Project at Southampton has combined two such methods as part of a programme of integrated control.

A monomolecular film, Monoxci-FCM, which stays on the water surface for up to 30 days and drowns mosquito pupae and egg-laying flies is used. However, it is ineffective against young larvae which take in oxygen through their cuticle, so the bacillus, Thuringiensis israelensis (Bti), is added to the film. Bti attacks the gut of early larval stages of mosquitoes and the monolayer improves its performance by spreading it over the surface of the water.

The ecological advantage of the monolayer is that it is biodegradable and causes few problems for other wildlife, while Bti is highly selective in its target organism. The combination of Monoxci and Bti is cheaper than Bti alone. The formulation can be applied by mass spraying techniques, or by something as simple as a watering can. In the past, WHO has objected to the use of larvicides on the grounds that the breeding sites of the mosquitoes need to be known. But concentrating on community action overcomes this problem as villagers know where to find the sites in their area.

The latest report from Sri Lanka is promising; Oxfam, which funds the project, says it "definitely has potential". If the next stage of tests is successful, members of the South Asia Co-operative Environment Programme intend to apply to the EEC for funding for further studies in their own countries.

Two newly formed British companies are joining forces in this trial. Microbial Resources, based in Reading, produces Skeetal, a pesticide already marketed throughout Europe. The Environmental Protection Agency in the US approved Skeetal for sale, where it will be used to control mosquitoes and blackfly in densely inhabited parts of Florida.

Such "agrobiologicals" based on bacteria offer promising alternatives to synthetic chemicals whose toxicity and persistence may harm the environment. However, their usefulness is limited by their stability outside.

Monoxci, the film to be used in the trial, is manufactured by CI Insect Control, an offshoot of the University of Southampton and the Wolfson Mosquito Control Centre.

Test areas in Britain will include Army headquarters on Hayling Island near Portsmouth, sites of special scientific interest, and recreation areas overseen by the local councils. Because of the potential potency of this two-part pesticide, the Nature Conservancy Council will keep a close check on the ecological balance, especially its impact on larger animals which feed on mosquitoes. (Extracted from New Scientist, 13 December 1984 and 21 February 1985.)

Siberian bacterial strain cleans crude-oil spills at cold extremes

An oil-eating bacterial preparation that cleans up petroleum spills on land, and defies the extreme temperatures of Siberia was tested in simulated field trials in Novosibirsk, USSR. Developed by staff members of the West Siberian Research Institute of Geological Prospecting the preparation reportedly restores fertility to soil spoiled by accidental spillages during petroleum prospecting and extraction. The Soviet news agency Tass quotes the institute's director, Dr. Ivan Nestorov, as saying that in experimental tests the new bacterial strain - presumably Pseudomonas, continued to thrive on oil in temperatures ranging from minus 50°C (-68°F) to plus 70°C (158°F). "After treatment with the new preparation," Nesterov told Tass "a plot of land polluted by 10 litres of oil per square meter became covered with green grass after only 10 weeks."

Western European businessmen who visited the Tyumen oil and gas fields some 800 miles west of here have said that accidental spillages of crude occur frequently. Similar strains of bacteria discovered in other countries consume far less oil and cannot adapt to the extremes of Siberia's climate. The new - but still experimental - Soviet strain works 100 times faster than conventional bacterial preparations in use today, and cuts cleanup costs by 90 per cent, according to the news agency. (Extracted from McGraw-Hill's Biotechnology Newswatch, 15 October 1984.)

Bacterial remedy for acid rain

Thiobacillus ferroxidans could help reduce acid rain in the U.K. and cut back the politically troublesome export of this pollutant to other parts of Europe. According to

studies by Tony Atkins and colleagues at University College (Cardiff) and North Staffordshire Polytechnic (Stoke-on-Trent) the bacterium has considerable potential in removing sulfur from newly mined coal.

The organism converts sulfur-bearing pyrites into sulfuric acid. About a fifth of the million tons of coal normally brought to the surface in Britain each year is composed of very fine particles, mixed with both pyrites and shale. The researchers believe that T. ferroxidans should vastly speed up flotation separation of the various constituents. Mixing raw coal with water and oil in a tank normally forces oil-coated coal particles to the top, leaving shale at the bottom. But pyrites also tend to accumulate in the coal-containing froth. Although sulfur is removed by oxidation, this takes several days - making the procedure expensive and barely economic. By pre-treating coal with T. ferroxidans, however, Atkins had found that he can boost the oxidation of pyrites considerably in laboratory-scale experiments. (Extracted from Bio/Technology, February 1985.)

Industrial microbiology

Yeast developed to convert xylose sugars to ethyl alconol

Researchers at Purdue University have developed a gene-spliced yeast that converts xylose sugars into ethyl alcohol which will allow the conversion of agricultural wastes such as corn stalks and sawdust into alcohol worth $1.55/gal. Ethanol, which is used to increase octane ratings in gasoline, is expected to increase in demand as lead is phased out of gasoline. Most plants contain about 50 per cent glucose and 50 per cent xylose. Yeast is able to digest glucose, but a missing gene is necessary to digest xylose. The researchers at Purdue found the missing gene in a bacterium and spliced it into yeast. (Source: Business Week, 18 February 1985.)

New technique to produce cyclodextrin synthetase

A genetic engineering technique for producing the enzyme used to make cyclodextrin has been developed by the National Food Research Institute and Tsukuba University. Cyclodextrin synthetase is used to manufacture polysaccharide for food additives or microcapsules for drug delivery and was previously collected from micro-organisms but can now be produced in mass quantities. The gene was isolated from a microbe found in rotting potatoes and incorporated into the Bacillus subtilis host cell. (Source: Japan Economic Journal, 19 February 1985.)

Boehringer-Mannheim clones galactosidase for better beet sugar

By splitting raffinose contaminants in beet-sugar molasses, a newly cloned enzyme promises better crystallization of sucrose, thus improving yield and purity. Dr. Ralf Mattes of the Boehringer-Mannheim GmbH research center in Tutzing, German Federal Republic, reports that by genetically manipulating Escherichia coli's raffinose-operon genes, he has achieved selective expression of alpha-galactosidase, essentially free of unwanted invertase. (Extracted from Mcgraw-Hill's Biotechnology Newswatch, 15 October 1984.)

Escherichia coli altered to make lignin-degrading 'aryletherase'

A culture of sewage-dwelling Erwinia grown on Kraft black liquor, has yielded a lignin-degrading enzyme, dubbed aryletherase by discoverer V.R. Srinivasan of Louisiana State University, Baton Rouge. The highly branched, giant polymer could, if degraded to its phenolic monomers, provide high-quality feedstock for pharmaceuticals, dyestuffs and plastics. (Extracted from McGraw-Hill's Biotechnology Newswatch, 15 October 1984.)

Methane from molasses

A Japanese scientist, Masashige Tambe, has invented a new process for recovering methane from molasses waste - an obnoxious industrial residue. The new process reduces the water pollution in distillery waste by almost 99 per cent. Pollution in sugar distillery waste is 100 times the approved level.

The new process is operating efficiently in three Thai distilleries that meet more than half their fuel needs with the methane recovered. It is claimed the cost is recouped from fuel savings in about three years. (Source: South, January 1985.)

U.S. patent on biosynthesized pyrethrin

To relieve shortages of chrysanthemums from Kenya and Ecuador as a source of pyrethrin, the natural insecticide can now be biosynthesized in the laboratory. A U.S. patent to be issued shortly to the McLaughlin Gormley King Co. (MGK) describes an enzymatic method of producing the non-toxic insecticide in vitro for the $40-million U.S. market.

Unlike chemically synthesized pyrethroids, chrysanthemum-extracted pyrethrin I decomposes readily in air and light, making it an ideal spray for food-processing and grain-storage areas. Until now its only source has been from imported flowers. In research supported by MGK, a method has been developed to stabilize and immobilize enzymes from cell-free chrysanthemum homogenates that convert mevalonic acid or isopentyl pyrophosphate into pyrethrin and chrysanthemyl alcohol. (Extracted from McGraw-Hill's Biotechnology Newswatch, 4 March 1985.)

Lysozyme, proteases for dairy and detergent markets

Two proteins engineered by Genencor (California) - T4 lysozyme and subtilisin BPN - may soon find novel industrial applications, perhaps in the dairy industry and in detergent additives, fishmeal treatment and biscuit dough-making. (Extracted from McGraw-Hill's Biotechnology Newswatch, 15 October 1984.)

Industrial applications for proteins

Researchers are trying to synthesize proteins for industrial applications. The hope is that the new proteins will yield new glues, insecticides and textile fibres. DuPont and SmithKline Beckman are undertaking protein research prompted by developments in genetic research. Protein engineering involves working on genes before they are transferred to micro-organisms. Thus, bacteria or yeast are able to produce a protein unknown in nature. It is also cheaper to change a protein's blueprint as well as being more precise than trying to refine a finished protein chemically. (Extracted from Wall Street Journal, 10 October 1984.)

Spun fibres to immobilize yeast

By immobilizing yeast in 'spun fibres', the cells convert 98 per cent of the sugar in sugarcane juice to fuel alcohol - compared to only 92 per cent ethanol production for cells grown in suspension, according to research being carried out at the University of Birmingham by the Science and Engineering Council and John Brown Engineers and Constructors Ltd. The team worked with textile makers at Courtauld Ltd. to combine cell-immobilization technology with spinning know-how. The spun-fibre yeast lasted over 1000 hours in laboratory studies and produced 6.7 per cent alcohol in the product stream, compared to 6.2 per cent for the conventional continuous processes. The Birmingham team is seeking commercial partners to extend the technology to antibiotic production. (Extracted from McGraw-Hill's Biotechnology Newswatch, 15 October 1984.)

Pilot plants necessary

With the exception of fermentation, few of the techniques used in the laboratory are designed to handle more than milligramme, or possibly gramme, quantities of products, and they do not lend themselves to scale-up or continuous operation. Although biotechnology can theoretically be used to produce almost any chemical compound in any quantity, for economic reasons biologicals with pharmaceutical applications are likely to predominate for several years to come.

Chemical engineering cannot provide instant solutions to the problems of scale-up. Traditional techniques are not very kind to biological products and fermentation broths resulting from microbial growth contain many compounds closely related to the desired product. By the standards of the chemical industry, fermenter broths are highly impure and extremely dilute aqueous systems.

Scaling up laboratory processes for the recovery and purification of bioproducts - typically at the millilitre or litre level - to the thousand litre level for industrial production involves more than building bigger equipment using chemical industry techniques. It takes time and money.

The problems relate to scale-up of recovery techniques in biotechnology, such as optimization of the chemical and physical factors of the environment of micro-organisms, and the optimization of equipment and production techniques have to be addressed in pilot plants with volumes of a few hundred litres. Pilot plant studies add a couple of years and at least several hundred thousand dollars to the development process, but are of crucial importance before several million dollars can be committed to a full-scale facility. Access to a first-class pilot plant laboratory has turned out to be necessary in cutting costs and uncertainty.

Pharmaceutical producers cannot easily change their production processes once a plant is on-stream, which means that the final process plant has to be designed from the outset using

the results obtained in a pilot plant. On the other hand, with many of the biological speciality products the production plant will not be run on a non-stop basis. In such cases, it pays to build a certain flexibility into the plant, which makes it more expensive.

A major commitment in terms of capital and other resources is necessary to reach large-scale production of a biological product and the payback time is several years even for a small-scale, simple recombinant DNA product. (Extracted from European Chemical News, 12 November 1984.)

Engineers need scientific window

It is essential that the engineer looks at the future to predict what engineering skills and process technology the new biotechnology industry will require. With a thorough understanding of the current state of biotechnology and the capability of biological science, an engineer can create a strategy and a development plan to provide what will be required.

A study which John Brown recently completed for the UK Department of Industry attempted to estimate the future equipment needs of biotechnology. In spite of the differences in predicted market sizes they are of the same order of magnitude and all show that there is a substantial future market for the engineer.

Biotechnology provides an opportunity for the engineer to upgrade his normal service to include the provision of technology. There is a promising future for the engineer in biotechnology, if he can contribute to the innovation necessary to make the large-scale production by biological processes feasible.

Without a scientific window - such as an investment in a new biotechnology firm - to provide an insight into biological science, it is very difficult for an engineer to form a strategy and development plan. In putting a biotechnology strategy together the engineer needs to recognize what he is and what he wants to become.

If an engineering firm invests in a scientific window and has also put money into resources such as biochemical engineers who can predict trends, it can set about putting an investment programme together. However, unlike venture capitalists and government funders, engineers are not regularly contacted by inventors looking for investors; or when they are they do not fit in with the overall strategy. The firm must become innovative or seek inventors who are willing to become collaborators as well as requiring funds. (Extracted from European Chemical News, 12 November 1984.)

Children's genetic engineering kit

The struggling biotechnology industry may be kept afloat not by manufacturing exotic drugs but by making consumer products. The first of these are a genetic engineering kit for children.

Larry Slot of the Massachusetts Institute of Technology has produced the "Dr. Cloners Genetic Engineering Home Engineering Kit". The first step that children take is to harvest Streptococcus salivarius bacteria from someone's saliva. The cells are broken open with an enzyme, lysozyme, and the naked DNA freed from the other genetic material in the cell. The DNA is mechanically fractionated, and the fractions are separated into ones of similar molecular weight by gel electrophoresis.

The desired section of DNA is then inserted into another mouth bacteria - Steptococcus mitis - by mixing the strands of DNA with the bacteria in a test tube containing calcium chloride. The addition of DNA from S. salivarius turns S. mitis from a minor to a major degrader of sucrose. Trouble could come if the child were to drink the chemicals and perhaps the kit should be used only in schools and under supervision. (Source: New Scientist, 24 January 1985.)

Industrial equipment

Scaling-up biotechnology to commercial production

A major obstacle in biotechnology remains the process of scaling-up to commercial production, according to M. Stewart of John Brown Engineers & Constructors. The problem is that biotechnology processes cannot be mathematically modeled, and it is difficult to predict the behaviour of genetically engineered micro-organisms. There are a great many chemical and physical variables that can alter the metabolism and morphology of a microbial cell. One problem involves maintaining a homogeneous mix of oxygen and nutrients, and another problem is removing the desired products. Large quantitities of heat generated during fermentation

must also be dissipated and a sterile environment must be maintained. New fermenter designs use air bubbles to mix the broth and to provide oxygen. It may be possible to remove some of the desired product from a fermenter with an ultrafiltration system or by adding resin particles that attach to the product and can then be sieved off. Recovering the products can account for 80-90 per cent of total production costs. (Extracted from New Scientist, 6 December 1984.)

Ultrafiltration instead of centrifuges

Centrifuges are the conventional method of concentrating organisms for microbial starter cultures. However, ABC Research, Gainsville, Florida, reported at the AIChE conference that, after successful pilot-scale testing, it will be switching to ultrafiltration for concentration of its Pediococcus acidilactici cultures, which are used to initiate lactic-acid fermentation by sausage makers. (Source: Bioengineering News^{R}, Box 290, Willits, Ca. 95490, USA, Vol. 5, No. 26, 7 December 1984.)

New materials

Harwell Laboratory, Oxon, England, reports developing a range of novel chromatographic materials for use in the biochemical process industries. The new materials are said to be ideal for large fluid volume processes, and have major applications in protein and enzyme recovery, the purification of biological fluids, bio-catalysis and the production of fine chemicals and pharmaceuticals. Following a new agreement, Sterling Organics Ltd., will produce and sell the new materials, under the Macrosorb trade name. (Source: Bioengineering News^{R}, Box 290, Willits, Ca. 95490, USA, Vol. 5, No. 20, 10 October 1984.)

Isolmer kit

A kit designed for binding protein antigens to a polymer carrier, used for the affinity separation of antibodies, is offered by Sera-Lab. The resulting bound antibody is readily eluted and the regenerated polymer-antigen complex may be used several times. Details from: Jennifer Murray, Sera-Lab Ltd., Crawley Down, Sussex RH10 4LL or on 0342 716366. (Biotechnology Bulletin, Vol. 3, No. 11, December 1984.)

Biohazards

NIH director rules out environmental hazard in altered ice-minus microbe

Over half a year after a court order blocked the first deliberate release of a genetically engineered microbe, the US National Institutes of Health (NIH) has concluded that spraying gene-spliced, frost-preventing strains of Pseudomonas syringae on crops poses no environmental dangers.

At issue are field-trials of the recombinant bacterium long planned by Dr. Steven Lindow of the University of California, Berkeley. Lindow's tests of Pseudomonas were blocked last May, by a temporary injunction from District Court Judge John J. Sirica halting the experiments.

NIH's environmental assessment fulfills one part of Sirica's order but the judge also ordered the Institute to prepare a more formal Environmental Impact Statement (EIS) addressing NIH guidelines on deliberate release of genetically engineered organisms. (Extracted from McGraw-Hill's Biotechnology Newswatch, 4 February 1985.)

E. PATENTS AND INTELLECTUAL PROPERTY ISSUES

Cancer treatment method patented

The Massachusetts Institute of Technology has patented (4,496,539) a method of treating cancer in which cancer cells are brought into contact with lectin, a protein molecule that recognizes compounds unique to such cells. The lectin carries an enzyme that destroys cancer cells upon contact. (Source, New York Times, 2 February 1985)

ATCC extends its patents depository

US lawyers are not sure which plants can be patented, but they can now meet one requirement of the patent law - depositing cell lines. The American Type Culture Collection (ATCC) at Rockville, Maryland is accepting plant tissue cultures along with micro-organisms in its Patent Depository.

"We have accepted several plant tissue cultures for patent purposes for about a year, but none for a patent that has been issued yet," says Bobby Brandon, head of the ATCC Patent Depository. "To our knowledge, we are the only plant depository for patent purposes." There are also 62 other cultures available in a non-patent plant-tissue collection.

Previously plant originators used the Plant Variety Protection Act (PVPA), rather than the patent system, to protect their lines. However, the PVPA only protects the right to propagate a line, not the plant itself. (Extracted from McGraw-Hill's Biotechnology Newswatch, 21 January 1985)

Mo cell lawsuit

The University of California, Los Angeles is being sued by a leukaemia patient for a share of profits from the cell line developed from his spleen. The cell line, called the Mo cell line, is capable of continuous culture for an indefinite period of time. Thus the cells will continue to produce the desirable characteristics indefinitely without requiring the more expensive methods of gene splicing. The Mo cells also release a variety of products characteristic of activated T-lymphocytes. The patient claims the university holds a patent on his blood. The outcome of this lawsuit has possible legal implications for other patients or ordinary people with regard to blood or tissue property rights. (Extracted from New Scientist, 20 September 1984)

An anti-herpes product receives patent

The US Patent Office will issue Exovir (Great Neck, N.Y.) a patent (4,507,281) for a topical anti-herpes product, Exovir-HZ Gel. The product combines human leukocyte interferon with an antiviral in a way that in vitro studies suggest will create a two-pronged, synergistic attack on recurrent outbreaks of oral and genital herpes. (Extracted from Chemical Week, 27 February 1985)

US approval for interleukin patent

Cetus Corporation has been granted the first US patent on gene-spliced interleukin-2 (IL-2). The company expects to market the product, a potential antiviral and anticancer agent within three years.

The US Patent and Trademark Office approval covers recombinant DNA interleukin-2 "muteins", mutationally-altered proteins analogous to natural or wild-type products. The patent encompasses novel forms of IL-2 produced using genetic engineering in bacteria, yeast or animal cells, and various therapeutic formulations and gives Cetus the exclusive right to manufacture and market the muteins in the US.

Human clinical trials on the IL-2 mutein have been in progress since March last year. Phase I trials have shown that the product is well tolerated in patients. Phase II efficacy testing will focus on the treatment of leukaemias, lymphomas, solid tumours and Aids. The products will be tested in combination with other anti-cancer agents. (Extracted from European Chemical News, 18 February 1985.

Stanford wins second patent

A composition of matter patent (U.S. 4,468,464) on a recombinant-DNA molecule - known as a plasmid - and the plasmid's use in bacteria to develop and generate biological products was issued to Stanford University. Stanford feels that the new patent, in combination with a process patent on genetic engineering (U.S. 4,237,224) that was issued to the university in 1980, puts it in a commanding patent position in the gene-splicing field.

At present, 66 companies are licensing the 1980 process patent from Stanford - each for an initial fee of $10,000 and subsequent annual $10,000 payments. Those companies will also be covered under the new product patent. For the process patent, licensing fees, which Stanford shares with the University of California, San Francisco, have come to about $3 million.

At present, a number of products used by researchers, such as enzymes and other tools of recombinant-DNA, have been produced through the licensed technology and have been commercialized. But only one pharmaceutical product developed by means of the technology has been commercialized, the form of human insulin produced in bacteria, called Humulin, developed by Genentech and marketed by Eli Lilly. However, several other pharmaceuticals produced with the licensed technology - including a hepatitis B vaccine, human interferon and human growth hormone - are nearing commercialization.

Both the process and product patent are based on work carried out in 1973 by Stanley N. Cohen, professor of genetics at Stanford University School of Medicine, and Herbert W. Boyer, professor of biochemistry at the University of California, San Francisco. The patents confirm Cohen and Boyer as the fathers of genetic engineering - the first researchers to invent and produce a biologically functional plasmid, the recombinant-DNA molecule that is used to insert foreign genes into a host organism. Both researchers have waived rights to royalties from the licensing of the patents. (Extracted from Chemical Week, 12 September 1984)

The patent bug

Recently the United States patent office awarded Hoffman-La Roche, the Swiss pharmaceuticals multinational, a broad patent for alpha interferon, which shows some promise as a cancer-fighter. Biogen, a Swiss biotechnology firm, was granted a European patent on exactly the same product six months ago. The company licensed its alpha interferon to one of its shareholders, America's Schering-Plough, which has spent a substantial sum of money on further developments of the drug. Schering-Plough has won regulatory approval to market alpha interferon in Ireland and Italy, and is near to selling it elsewhere.

Two other big pharmaceutical firms - Johnson & Johnson and Becton Dickinson - are also seeing each other in court on a dispute over biotechnology patents. Johnson & Johnson claims that Becton Dickinson infringed 13 of its United States patents - eight of them for genetically-engineered monoclonal antibodies.

Without a strong ally to pay the legal bills, patent suits could damage small entrepreneurial biotechnology firms. Hybritech and Monoclonal Antibodies, the first two firms to go to court over biotechnology patents, are trying to limit the financial pain by getting into and out of court quickly. It often takes five years to resolve patent-infringement cases; they expect to resolve theirs within a year.

Stanford University and the University of California took the obvious route around lawsuits and made licences to their basic biotechnology patents cheaper and easier to obtain than the cost of a patent infringement suit.

Disputes seem certain to increase as more and more patent applications are filed. The volume of biotechnology-related patent applications has increased sharply each year for the past several years, which is hardly surprising, considering the speed with which advances are being made.

Even though small biotechnology companies get a great deal of attention, most patents in the field are assigned to large companies. Observers have criticized the patent office for processing applications too slowly and for having insufficient scientific expertise on its staff of examiners.

Well aware of such criticism, the patent office has taken a number of remedial steps, both in response to the particular complaints of the biotechnology field and as part of a broad, long-term effort to improve performance in all areas. In the general area, the patent office is moving on three major goals - to bring the period between a patent's filing date and disposal of the application down to 18 months; to bring the pendency period for trademark applications down to 13 months; and to automate search operations by 1990. The patent office currently is working on a backlog of some 1,000 applications in the genetic engineering area and 2,600 in the broader biotechnology field (including genetic engineering). (Extracted from The Economist, 30 March 1985, and Chemical and Engineering News, pages 18-20, 24, 10 December 1984, copyright 1984, American Chemical Society)

The following is a list of recent patents selected from McGraw Hill's Biotechnology Patent Watch of 15 October 1984, 17 December 1984 and 21 January 1985:

Purpose, use or process	Application System/No.	Applicant; Country
Fungal glucoamylase aids microbial ethanol production Production of ethanol by fermenting host organisms such as E. coli or Saccharomyces cerevisiae transformed by a plasmid vector containing DNA coding for Aspergillus awamori glucoamylase and a promoter that functions in the host. The glucoamylase produced hydrolyzes starch to glucose which the host ferments to the alcohol. Text includes A.awamori base and amino-acid sequences.	WO 84/02921	Cetus Corp. Emeryville, Calif. U.S.A.
Microbial synthesis of rennet for cheesemaking Plasmid vectors containing DNA coding for rennin or prorennin - obtained by reverse transcribing mRNA from calf-stomach mucosa - for expression in microbial hosts such as E. coli, B. subtilis and yeast. Rennin produced can be reactivated to produce rennet "in sufficient amounts to be useful in the clotting of milk for cheesemaking ... over 200 mg. per liter."	EPO 116 778	Genentech, Inc., South San Francisco, Calif., and Corning Glass Works Corning, N.Y. U.S.A.
Antibodies against human T cells treat autoimmune disease Monoclonals that bind to heterodimer recognition structure associated with T3 glycoprotein in membrane of specific individual human T-cell clones.	EPO 117 114	Dana-Farber Cancer Institute, Inc., Boston, Mass., U.S.A.
Antibodies to renal and colon cancers Murine monoclonal antibodies to human renal cancer cells (119 528) and colon cancers (119 556) and an "antibody panel" that distinguishes cells from different regions of the gastrointestinal tract.	EPO 119 528 EPO 119 556	Sloan-Kettering Institute for Cancer Research, New York, N.Y., U.S.A.
Hybrid human macrophage cell line produces IL-1 Interleukin-1 (IL-1) produced by hybrid cells consisting of a human non-tumor IL-1 producing macrophage cell line - such as alveolar, splenic, peritoneal, hepatic, placental or thymic macrophages or peripheral blood lymphocytes - fused with a human tumor macrophage cell line that stimulates proliferation.	EPO 118 917	Asahi Kasei Koygo Kabushiki Kaisha, Osaka, Japan
Two promoters for expression in yeast Plasmid vectors for expression of foreign genes in yeast hosts consisting of either the yeast glyceraldehyde-3-phosphate dehydrogenase promoter or the yeast pyruvate kinase promoter at the 5' end of the foreign DNA and a terminator sequence at the 3' end of the foreign DNA, as well as bacterial and yeast origin-of-replication regions. Text contains nucleotide sequences of promoter regions.	EPO 120 551	Chiron Corp. Emeryville, Calif., U.S.A.
Promoter for expression in yeast Vector, preferably a plasmid, for expression of foreign genes - such as those for bovine growth hormone, interferon preprorennin, or prorennin - in Saccharomyces cerevisiae, consisting of the yeast galactokinase promoter, the foreign DNA, and a terminator sequence. Text contains promoter nucleotide and amino acid sequences.	GB 2 137 208	Collaborative Research, Inc., Lexington, Mass., U.S.A.

F. BIO-INFORMATICS

Directory of U.S. Courses in Biotechnology for Developing Country Scientists is available from the Board on Science and Technology for International Development, National Research Council, 2101 Constitution Avenue, N.W., Washington, D.C., 20418 USA.

The purpose of this directory is to provide information on U.S. graduate degree programmes, special courses, and internships in biotechnology for developing country scientists.

The information was obtained from colleges, universities, research institutes, professional associations, and industries during the spring of 1984. Although not all of the institutions contacted chose to submit information, it represents a fairly complete picture of the types of opportunities for study that are available in the various biotechnology disciplines.

The directory includes separate lists for institutions, degree programmes, and special (non-degree) courses. The listing of institutions includes addresses and telephone numbers for key contacts as well as information on consortium memberships and previous experience with admitting developing country students. Consortium memberships can be significant because they provide expanded opportunities and resources for students.

The listings for the degree programmes and special courses include a title and brief description of the subject matter and admission requirements, information on advisors or instructors, and degrees or certificates awarded. Unless otherwise indicated, the starting time for degree programmes is in the fall and the language of instruction is English with a few courses taught in Spanish; masters' programmes require 1-2 years and Ph.D. programmes 3-5 years to complete. Information on costs is included for special courses. Cost information is not included for degree programmes because of continuing changes in tuition, fees, and living expenses.

The index is divided into sectoral listings, with courses shown under Agriculture, Engineering, Environment, Health, Interdisciplinary Programmes and Basic Studies, and Veterinary Sciences.

This directory is intended for use as a first step in determining where specific types of training can be obtained and to facilitate communication with the institutions identified. Full details on the specifics of courses, costs, timing, and prerequisites are readily available from the institutions of interest.

Related information on other aspects of U.S. colleges and universities may be obtained through such publications as:

Barron's Profiles of American Colleges. Available from Barron's Educational Series, Inc., 113 Crossways Park Drive, Woodbury, NY 11797;
Guide to American Graduate Schools. Penguin Books Inc., 625 Madison Avenue, New York, NY 10022; and
Peterson's Annual Guide to Graduate Study. Peterson's Guides Inc., P.O. Box 21[illegible], Princeton, NJ 08540

Information on U.S. educational opportunities for foreign students may be obtained from:

Institute for International Education, 809 United Nations Plaza, New York, NY 100017

Anaerobic Digestion MIRCEN

Anaerobic Digestion MIRCEN is a series of teleconferences using the Computer Conferencing System (COM) of the Computing Centre (QZ) at Stockholm University (P.O. Box 27322, S 102 54 Stockholm). These teleconferences are open to anyone with a COM account.

Computer conferencing is an asynchronized communication method where a group of people communicate by reading and typing from computer terminals rather than face-to-face speaking and listening to one another. Terminals may be personal computers that are connected to the host computer centre via a modem by telephone. Computer conferencing systems are thus designed to use the storage, retrieval and processing capabilities of the host computer to facilitate the transfer of communications between geographically dispersed people. Teleconferences may be used for (i) topic-oriented discussions or tasks, e.g. a group working towards a common goal, or (ii) the exchange of experiences, comments, ideas and announcements, as in a newsletter. Some advantages of computer conferencing are: (i) you are linked to a geographically dispersed group of people who can look at your messages and give their response in a short period of time; (ii) you can read and write at times suitable to you; (iii) the use of written language is often found to be easier to understand for a group of people with different mother tongues.

Anaerobic Digestion Mircen (ADM) aims to

(i) link individuals and organizations that are interested in methanogenic anaerobic digestion, either directly via COM or through the proceedings of the teleconference series;

(ii) to facilitate the exchange of information and encourage discussions to help solve technical questions and problems;

(iii) to enable electronic discussion of papers and posters that are presented at face-to-face conferences.

ADM currently has 4 teleconferences in the series, they are:

ANAEROBIC DIGESTION (MIRCEN) TECHNICAL
ANAEROBIC DIGESTION (MIRCEN) COCKTAIL
ANAEROBIC DIGESTION (MIRCEN) (at) BIOENERGY 84 (Gothenburg)
ANAEROBIC DIGESTION (MIRCEN) EVALUTATION (of) BIOGAS COMCON

ANAEROBIC DIGESTION (MIRCEN) TECHNICAL

This is an on-going teleconference and hopes to be a permanent operation for technical discussions and to serve as a newsletter. This conference covers all aspects of biogas, methanogenic anaerobic digestion and waste treatment - e.g.

- microbiology, ecology, taxonomy, physiology, biochemistry, genetics of methane producing bacteria;
- methanogenic fermentation processes for various plant, animal and other types of substrates;
- application of anaerobic digestion processes for energy production, waste treatment, sanitation, as in biogas plants, digesters, reactors, landfills, on-site sanitary toilets, etc.;
- uses of byproducts (biogas and effluents);
- use of biogas systems in integrated farming systems;
- implications and social and economic impact of biogas technology in various communities (rural, urban, industrial, etc.);
- etc. etc.

ANAEROBIC DIGESTION (MIRCEN) COCKTAIL

Anaerobic Digestion (Mircen) Cocktail for social and non-technical use as well as for discussions on the planning and organization of ADM, greetings, congratulations, cocktail parties, coffee breaks, corridor discussions, computer problems, information from other teleconferences, etc, etc.

ANAEROBIC DIGESTION (MIRCEN) (at) BIOENERGY 84 (Gothenburg)

This is a short-term, technical teleconference that was created for the electronic discussion of biogas papers and posters that were presented at the Special Seminar on Bioenergy in Developing Countries (15-16 June 1984) and at the Bioenergy 84 World Conference and Exhibition (18-21 June 1984) at Gothenburg, Sweden by both participants at the face-to-face conferences in Gothenburg and those who were unable to be at Gothenburg. This teleconference closed on 31 December 1984. All further discussions may be sent to ANAEROBIC DIGESTION TECHNICAL.

ANAEROBIC DIGESTION (MIRCEN) EVALUATION (of) BIOGAS COMCON

This is a short-term teleconference that was created during the Bioenergy 84 World Conference and Exhibition for the evaluation of ADM BIOENERGY 84. The conference will enable members (i) to share their views on the use of the computer conferencing technique; (ii) to provide suggestions for improvements for the organization and operation of future biogas computer conferences. This teleconference closed on 30 December 1984. All further discussions may be sent to ANAEROBIC DIGESTION COCKTAIL. For further information, contact Mr. Eng-Leong Foo, UNEP/UNESCO/ICRO Microbiological Resources Centre, Karolinska Institute, S 10401 Stockholm, Sweden

The 1985 Biotechnology Directory available

The 1980's are the era of biotechnology, reflected in a worldwide increase in biological research, the formation of new companies and large investments by nations, companies and individuals concludes the 1985 Biotechnology Directory. The Directory includes profiles of all the major nations engaged in biotechnology research in western Europe, North America, Brazil, Australia and Japan.

Commercial Biotechnology

An International Analysis compiled by OTA (Office of Technology Assessment), Congress of the United States, USA.

This report focuses on the industrial use of recombinant DNA (rDNA), cell fusion, and novel bioprocessing techniques. It assesses the competitive position of the United States with respect to Japan and four European countries - the Federal Republic of Germany, the United Kingdon, Switzerland, and France - believed to be the major competitors in the commercial development of "new biotechnology". To differentiate between biotechnology using these novel techniques and the more traditional forms of biotechnology, this report uses the terms "new biotechnology" and "old biotechnology", respectively. Thus, for example, traditional wine production is old biotechnology, but the use of yeast modified with rDNA techniques to produce wine with a higher alcohol content is new biotechnology. Published by Elsevier Science Publishers, P.O. Box 211, Amsterdam, The Netherlands. 612 pages, Price Dfl. 395.00. ISBN 0-444-99586-2. (Distributed in the USA and Canada by Marketing International Inc., Washington, DC, USA)

Elsevier have published two more titles in their "Progress in Industrial Microbiology" series. Modern Applications of Traditional Biotechnologies (424 pages, price $88.50 or Dfl. 230.00) could be valuable reading for those wondering how fermentation and other conventional biotechnologies will fare in the coming years. Edited by M. E. Bushell of Surrey University's microbiology department, the book contains many useful contributions by industrial scientists which provide new information relating to the production of wine, beer, whisky, cheese, animal health products, polysaccharides, soy sauce, cocoa, tea and coffee.

Innovations in Biotechnology (529 pages, unpriced), edited by Eric H. Houwink and Robert van der Meer, pulls together papers presented to a symposium organized by the Netherlands Biotechnological Society late in 1983. Recommended for anyone who needs to find out more about biotechnology in The Netherlands, which is this volume's primary focus. Details from: Elsevier Science Publishers, PO Box 330, 1000 AH Amsterdam, The Netherlands, or on 020 5803 911. In the USA Elsevier Science Publishing Co Inc is at PO Box 1663, Grand Central Station, New York, NY 10163. (Source: Biotechnology Bulletin, Vol. 3 No. 11, December 1984)

Biobusiness World Data Base

Draft Report by a U.S. Government Interagency Working Group on Competitive and Transfer Aspects of Biotechnology, published by Elsevier Science Publishers of Amsterdam and edited by David Leff of McGraw Hill's Biotechnology Newswatch, is now available.

The report comprises 212 pages with information on: technologies and projected start-up dates for products being developed in the USA and Japan; specific strategies for commercialization in the various countries; barriers to commercialization (financial, patent, technical and regulatory); potential products using rDNA technology (pharmaceutical, chemical, fuel, agricultural, food processing); worldwide sales projections to the year 2000; details of marketing, production and research between companies in the US, Japan and other countries; equipment sales projections, etc.

This document could be of considerable help to planning and research as it reveals proposed US Government strategies for protecting and strengthening the US biotechnology industry "frontrunners" plus information on biotechnology activities worldwide. The report was prepared by a Working Group made up of representatives from the CIA, Departments of State, Defense, Commerce, Agriculture, Health & Human Services, Food & Drug Administration, National Science Foundation, NASA, National Institutes of Health, the Office of Technology Assessment, plus many private firms active in biobusiness. 212 pages, price Dfl. 280.00 (outside North America), ISBN 0-444-99629-X. (Published and distributed in the USA & Canada by McGraw-Hill, Inc., Washington, DC, USA).

American Type Culture Collection Guide

A new, 98-page laboratory guide for use in stock culture maintenance is now available from the American Type Culture Collection. The handbook, which is free, contains over 1,000 media formulations used at ATCC to propagate strains of algae, bacteria, cell lines, fungi and protozoa. Details from: Professional Services Department, ATCC, 12301 Parklawn Drive, Rockville, MD 20852, USA or on (800) 638 6597. (Source: Biotechnology Bulletin, Vol. 3, No. 12, January 1985)

Fermentation Products and Processes

The total value of the US fermentation products industry is estimated at $37bn by Business Communications Co in its updated report, Fermentation Products and Processes (No. C-018R, price $1,500.00). By 1988, BCC expects the market to reach $59.3bn and by 1993, $72.1bn, reflecting an average growth rate of 6.9 per cent. The fastest growing sector is in ethanol/biomass. The driving force in the ethanol-from-fermentation market is its use as a

fuel additive. The use of biopolymers in enhanced oil recovery (see BB 2/10, pp 3-4) is also increasing, although their use is highly sensitive to the price of oil.

Enzymes currently represent a $157m a year US business, with $126m of that market value produced by fermentation. By 1993, BCC expects that 95 per cent of a broader range of commercial enzymes will be produced by fermentation. (Source: Biotechnology Bulletin, Vol. 3, No. 12, January 1985)

MIRDAB - Microbiological Resource Databank

Elsevier has set up a Microbiological Resource Databank of cells and their holders which will eventually be available in an on-line form. This project is for workers in animal and plant cell biotechnology and is presented by specialists in the same fields.

Particular care and attention have been given to the design of the data input forms as they have been compiled to contain the most relevant information on the cell lines.

The first catalogue of these collections comprises the following catagories:

- Animal cells - General
- Animal cells - Genetic Mutants
- Animal cells - Hybridomas
- Plant cells
- Animal viruses

MIRDAB Catalog 1/1985 will consist of approximately 600 cell and virus lines.

MIRDAB aims to:

- enable those people interested in particular cell lines to form a closer working relationship
- inform people entering the field of animal cell biotechnology of the available cells and cell lines
- prevent scientists and technologists wasting precious time generating cell lines which are already available
- fully utilise the available stored cell source material
- explore the possibilities of using cells for purposes other than for which those cell lines were originally derived
- provide information on what is available in cell terms
- set standards for cell characterisation and thus lead to an upgrading of attitudes and methods in cell biotechnology
- provide a basis for periodic meetings of the people involved to review the present situation and to point the way ahead.

New hardware and software system

TiterCalc, a new hardware and software system designed for use in biotechnology laboratories performing bioassays is the first product from HP Genenchem - the joint venture company formed by Hewlett-Packard Co and Genentech Inc. in July 1983. The system, which combines application software from HP Genenchem with Hewlett-Packard's recently introduced Integral Personal Computer, is designed to aid productivity by relieving a serious bottleneck in the labour-intensive microtitration process.

TiterCalc acquires, displays, processes and stores data from Enzyme Linked Immunosorbant Assay (ELISA) readers. Based on the use of the 96-well plate, a batch test tube, the microtitration process involves four steps: plate manipulation, fluid manipulation, plate reading and data processing.

The system lets users define the format of the 96-well plates and then choose the method of data reduction and the report format. Users instruct TiterCalc to read ELISA data by indicating on a graphic depiction of a microtitration plate the location of sample, reference, control, standard or blank wells. This allows the system to calibrate and identify the photometric measurements of the ELISA reader.

The system initially interfaces with six of the most popular ELISA readers from Flow Laboratories, Dynatech and Biotech. Because TiterCalc is multi-windowing, in addition to being multi-tasking, the system can also display more than one application simultaneously. (Source: Biotechnology Bulletin, Vol. 4, No. 2, March 1985)

EMBL and LMB build nucleic acid sequence data banks

A great quantity of data on nucleic acid sequences is becoming available which is already of considerable value in R & D carried out by geneticists, biochemists and molecular biologists. The European Molecular Biology Laboratory (EMBL) in Heidelberg is collating this data and transferring it onto a computer. The first issue of the EMBL Nucleotide Sequence Library has been released and in the UK Dr. Olga Kennard, a member of the Medical Research Council's staff at the University Chemical Laboratory, Cambridge, is developing a centralised service based on the Library and maintained on the Cambridge University computer. The service will feature bibliographic and sequence searches. Details from: Medical Research Council, 20 Park Crescent, London, WIN 4AL or on 01-636 5422. (Source: Biotechnology Bulletin, Vol. 3, No. 12, January 1985)

Battelle's CAGE/GEM simulation software

The CAGE/GEM (which stands for Computer-Aided Genetic Engineering/Genetic Engineering Machine) software toolkit now available from Battelle provides unique simulation and analytical capabilities for genetic engineers. It incorporates computer-aided design and human factors engineering techniques with a choice of relevant genetic engineering data-bases. Details from: Dr. Richard J Douthart, manager, Battelle Pacific Northwest Laboratories, Battelle Boulevard, Richland, Washington 99352, USA. (Source: Biotechnology Bulletin, Vol. 3, No. 10, November 1984)

Hybridoma Data Bank

A comprehensive data bank on hybridoma technology has been started by the US National Institutes of Health. The Hybridoma Data Bank (HDB) will expedite information on hybridomas and other cloned cell lines that produce immunoreactive substances. Duplication of effort in developing hybridomas can be avoided by searching the bank for existing cell lines. HDB will be headquartered at the American Type Culture Collection in Rockfield, MD. Computer facilities will be located at NIH (Bethesda). HDB will also co-operate with researchers in Japan and Europe. (Source: Technology Update)

European Biotechnology Information Project

The Commission of the European Communities has announced it will support the Science Reference Library's one-year project, the European Biotechnology Information Project (EBIP), to investigate information on biotechnology within the European Community.

The project has three main aims. Information sources, including databanks, organizations and published material which will be identified and documented. Information needs in biotechnology, particularly of recently established companies and research units, will be assessed primarily by visiting them and discussing their requirements. A pilot European Community-wide information and referral service will be established to deal with enquiries and publish a range of guides.

EBIP activities will be fully supported by the existing resources of the Science Reference Library. Based at Aldwych, which houses probably the largest reference collections of current life and earth science literature in Western Europe, its services will be backed by the Business Information Service, the Computer Search Service and the Industrial Property Section. In addition new methods of making services accessible will be sought. The Science Reference Library will collaborate with the Deutsches Institut für Medizinische Information und Dokumentation (DIMDI) to make EBIP services available via DIMDI's online system, the largest for biological information in Europe. A biotechnology service, Biotel, has been set up on Prestel. It is planned to make EBIP services available via the Birmingham and Loughborough Electronic Network. Facsimile transmission will be used as well as the usual methods of communication.

EBIP will be run by a team of four based at Aldwych. Project leader is John Leigh, head of the Science Reference Library biology, biotechnology and earth sciences unit; Dr Richard Wakeford has been seconded to the project and two additional subject specialists are being recruited.

Further information can be obtained from John Leigh at the Science Reference Library (Aldwych). (Source: Aslib Information, Vol. 12, No. 6)

Biotechnology of Industrial Antibiotics, edited by Dr. Erick J. Vandamme of the State University of Ghent, Belgium, and published by Marcel Dekker is available. This multidisciplinary volume examines the production of economically important antibiotic compounds by fermentation biotechnology and provides complete, in-depth treatment of their

microbiology, biochemistry, genetics, and engineering. Encompassing antibacterial, antifungal, antiviral, and antitumor compounds, as well as antibiotics used in agriculture and food practice, Biotechnology of Industrial Antibiotics offers an encyclopedic wealth of information never before assembled in any single source.

In 29 up-to-date chapters by 64 leading international experts, the book outlines industrial fermentation processes for each compound or group and provides - for the first time - "inside" information from several major antibiotic manufacturers; it investigates the latest production trends, including immobilized biocatalyst technology and the impact of genetic advances, and examines compound properties, history, screening, strain improvement, biosynthesis, production process, product recovery, applications, mode of action, etc. Price $105.

Technical Insights Inc.

Technical Insights, Inc. newest report, "Advances in Enzyme Technology: Artificial, Semisynthetic, and Designed Enzymes," organizes the current research advances being made and provides an effective comparison of the various development methods and their commercial potential. Designed to inform and enlighten people whose companies and careers could profit from significant new technologies, this 175-odd page report gives an up-to-date look at this field. A special section of the report analyzes the opinions of experts in the field and forecasts when artificial and engineered enzymes are likely to become a reality and what areas they will impact. Enzymes in current commercial use are employed either as industrial catalysts or as components of products. Thus new enzyme-like substances can find a variety of uses. The purpose of this report is to explore this potential. The report explains how new processes could benefit from catalysts with enzyme-like properties that perform better than natural enzymes and can effect transformation for which there are no known natural enzymes.

The report also contains a Technology Forecast for artificial, semisynthetic, and designed enzymes based on a survey of experts in the field. It profiles the commercial future of this technology with "inside" information on how long commercialization will take; which technical approach has the most commercial potential; what will the impact of enzyme-like substances be i.e. to improve existing products or lead to totally new products; and what the applications for these new catalysts will be.

Price $580 for US residents, $610 for the rest of the world. The report is available from Technical Insights Inc., P.O. Box 1304, Fort Lee, NJ 07024, USA.

Other reports recently available from Technical Insights Inc. are:
"Monoclonal Antibodies: Technical Opportunities" (price $645)
"Drug Delivery Systems: A Technology Survey" (price $710)
Biomass Process Handbook, A Production/Economic Guide to 42 Chemical Processes (price $540)
Genetic Technology: A Guide to Key R & D Projects, Revised, Updated & Expanded for 1985 (price $337)
The New Fourth Edition For 1985 Genetic Engineering and Biotechnology Firms Worldwide Directory, by Marshall Sittig & Robert Noyes (price $177)

Bio-Japan: The Emerging Japanese Challenge in Biotechnology

Available from Oyez Scientific and Technical Services Ltd., is a new report Bio-Japan: The Emerging Japanese Challenge in Biotechnology by John Elkington as a result of in-depth interviews and research conducted by the author during two recent visits to Japan. With the country's extraordinary track record of market dominance in so many areas of advanced technology, it is perhaps surprising that it has not yet had a comparable impact in the burgeoning field of biotechnology, which Japanese industrialists consider "the last major technological revolution of this century".

As this report shows, however, there is every chance that the gap between Japan and its competitors in Europe and the US could have closed by the end of the decade. The market implications of the trends highlighted in Bio-Japan have so far influenced the strategic thinking of remarkably few companies - and a considerable proportion of the companies which have recognised the momentum building in Japanese biotechnology have been strengthening that momentum by selling the Japanes their skills and technologies.

Increasing technological collaboration and a growing number of joint ventures are enabling Japan to reinforce its weaker areas of competence and build on its undoubted strengths. European and US companies and organizations looking for Japanese market opportunities and commercial partners will find Bio-Japan essential reading.

Other companies will be inclined to view the emerging Japanese challenge as a major threat to their established markets, rather than a series of emerging opportunities. They will find up-to-the-minute briefing on Japan's progress in such key areas as: genetic engineering; bioprocessing and separation technology; the development of new pharmaceuticals and other health care products; and the applications of biotechnology in such diverse fields as biomass energy, metal recovery, waste treatment and pollution control.

To facilitate follow-up, an A-Z directory of some of the key companies and organisations operating in Japanese bioscience and biotechnology is included. £Price 58.00, ISBN: 0.907822.52.5

New Biotechnology Journal

A major new international review journal, Biotechnology Advances: Research Reviews and Patent Abstracts, is being published by Pergamon Press. The journal will address issues related to future demands for fuels, food, chemical feedstocks, health care, and environmental pollution control. Biotechnology Advances has been conceived as a means of keeping researchers and practitioners in academic institutions up-to-date with this rapidly developing field. The journal will, therefore, be devoted to all aspects of biotechnology, including applied biology, technical biochemistry, genetic engineering, biochemical engineering, and environmental engineering. Its purpose is to provide regular, quick, but authoritative updates on the research literature. Each annual volume consisting of two issues, will contain mini-reviews plus a detailed bibliography and the abstracts of all relevant US patents. Occasionally, special supplementary issues of the journal will be published as proceedings of conferences or symposia which have addressed state-of-the-art reviews of biotechnology topics. (Source: ESN 39-3, 1985)

Patents Throughout The World, available from Clark Boardman Company, Ltd., 435 Hudson Street, New York, N.Y. 10014.

This one-volume looseleaf digest covers the patent laws of nearly 200 countries and their territories. Laws are arranged and analyzed under consistent, convenient headings. Also included are summary tables that allow for a quick comparison of the laws of different countries, as well as the complete texts of the international conventions on patents and their members.

Second Edition published 1978/1 looseleaf volume/LC No. 78-978/ISBN 0-87632-125-2 Price: $75. (Supplemented three times annually. Cost of supplementation was $45 in 1982 and $45 in 1983. No charge for current calendar year supplementation.)

Grow your own energy

Alcohol from sugar, gas from cow dung and energy from purple bacteria ... Grow Your Own Energy unfolds the potential of plant power - and of the fuels of the future. New Scientist technology consultant Mike Cross brings together an international cast of contributors in this up-to-date picture of science and scientists at work. Their struggle to unlock the secrets of the energy stored in "biomass", an ever-renewable form of power, has profound implications for the world's economy and the world's future. Price £4.95, ISBN 0 85520 7302. (Source: New Scientist, 25 October 1984)

G. MEETINGS

Date	Title
6-9 May	International Symposium on Toxicity Testing Using Bacteria, Banff, Alberta, Canada. Information: B. J. Dutka, National Water Research Institute, Canada Centre for Inland Waters, P.O. Box 5050, 867 Lakeshore Road, Burlington, Ontario, L7R 4A6, Canada
8-11 May	The Interferon System, Rome. Information: Serono Symposia, Via Ravenna 8, 00161 Rome, Italy
8-9 May	Agricultural Biotechnology - Finance, acquisitions and joint ventures, California, USA. Contact: Jodi Martin, Freshman, Mulvaney, Murantz, 8th floor, East Tower, 9100 Wilshire Boulevard, Beverly Hills, California 90212, USA
14-16 May	Bio Expo 85, Boston, MA. Information: Bill Burris, Cahners Exposition Group, 7315 Wisconsin Avenue, P.O. Box 70007, Washington, D.C. 20088, USA

14-17 May	7th Symposium on Biotechnology for Fuels and Chemicals, Gatlinburg, TN. Information: Charles D. Scott, Oak Ridge National Laboratory, P.O. Box X, Oak Ridge, TN 37831, USA
20-22 May	4th Stony Brook Symposium on Molecular Biology: Protein Engineering - Applications in Basic Science, Industry and Medicine, Stony Brook, NY. Information: Stony Brook Symposium, Dept. of Biochemistry, SUNY, Stony Brook, NY 11794-5215, USA
21-23 May	Biotech 85 Europe, Geneva. Information: Online Conferences, Pinner Green House, Ash Hill Drive, Pinner HA5 2AF, Middlesex, UK
2-6 June	Tissue Culture Association Annual Meeting, New Orleans, LA. Information: Frederick H. Kasten, Dept. of Anatomy, Louisiana State Medical Center, 1100 Florida Ave., New Orleans, LA 70119, USA
2-7 June	Mechanisms of DNA Damage and Repair: Implications for Carcinogenesis and Risk Assessment, Gaithersburg, MD. Information: Kathy Stang, A353 Physics Bldg., National Bureau of Standards, Gaithersburg, MD 208999, USA
3-7 June	United Nations Symposium on Importance of Biotechnology for Economic Development, Szeged, Hungary. Information: Industry and Technology Division, United Nations Economic Commission for Europe, Palais des Nations, CH-1211 Geneva 10, Switzerland
4-8 June	BIOEXPO 85, Paris, France. Contact: Bioexpo/Sepfi, 8 rue de la Michodière, 75002 Paris, France or on (1) 742.92.56. Telex: 211897 F TECEXPO
9-13 June	35th Annual Meeting of the Canadian Society of Microbiologists, to be held in Halifax, Nova Scotia, Canada. Contact: CSM Secretariat, 20 Hobart Crescent, NEPEAN, Ontario, K2H 5S4, Canada. Call: (613) 726-0485
9-15 June	ACHEMA 85, Frankfurt, Federal Republic of Germany. Information: DECHEMA, Organization ACHEMA, P.O. Box 97 01 46, D-6000 Frankfurt 97, Federal Republic of Germany
16-21 June	Industrial Bioprocessing: Principles and Practice of Bioprocessing Systems, Pingree Park, Colo., USA (course includes engineering principles, bioreactor developments, product recovery, fermentation costs, computer control). Contact: Colorado State University, Office of Conference Services, Rockwell Hall, Fort Collins, Colo. 80523, USA
17-19 June	Introduction to BIONET: The National Computer Resource for Molecular Biology, to be held at the Waksman Institute of Microbiology, Busch Campus, Rutgers University, Piscataway, NJ. Contact: Selma Gitterman, Director, Continuing Professional Education, Waksman Institute of Microbiology, Rutgers, The State University, P.O. Box 759, Piscataway, NJ 08854, USA
25-27 June	New Technology in Biotechnology, London. Information: Macmillan Conferences and Exhibitions, 4 Little Essex St., London WC2R 3LF, UK
14-18 July	Syntro Conference on Genetics at Stanford - The Third International Conference on Bacilli, to be held at Stanford University, Stanford CA. Contact: Dr. A. T. Ganesan, Lt. J. P. Kennedy Jr. Laboratories, Department of Genetics, Stanford University School of Medicine, Stanford, Ca 94305, USA
15-19 July	Course on Controlled Release Technology: Polymeric delivery systems for drugs, pesticides and foods, MIT, Cambridge, MA. For further information contact Director of Summer Session Office, Massachusetts Institute of Technology, Room E19-356, Cambridge MA 02139, USA
17-19 July	Photosynthesis and Genetic Engineering, to be held at Oxford University. Sponsored by the Biochemical Society. Contact: Meetings Officer, The Biochemical Society, 7 Warwick Court, London WC1R 5DP, UK
3-9 August	1985 Annual Meeting of the Society for Industrial Microbiology, to be held at the Westin Hotel, Copley Place, Boston, MA. Contact: Mrs. Ann Kulback - SIM Business Secretary, SIM Headquarters, 1401 Wilson Blvd., Arlington, VA 22209, USA

5-9 August	Biotechnology: Microbial Principles and Processes for Fuels, Chemicals and Biologicals, to be held at the Massachusetts Institute of Technology, Cambridge, MA. Sponsored by the MIT Department of Nutrition and Food Science. Contact: Director of Summer Session, MIT, Room E19-356, Cambridge, MA 02139, USA
19-23 August	International Symposium on Nuclear Techniques and In-Vitro Culture for Plant Improvement, Vienna, Austria. Sponsored by the Food and Agriculture Organization of the United Nations and the International Atomic Energy Agency. For further information contact: International Atomic Energy Agency, SM-282, Vienna International Centre, P.O. Box 100, A-1400 Vienna, Austria
25-30 August	The 13th International Congress of Biochemistry, to be held at the "International Congrescentrum RAI" in Amsterdam, The Netherlands. Organized by the Commission for Biochemistry and Biophysics of the Royal Netherlands Academy of Arts and Sciences and the Netherlands Biochemical Society. Sponsored by the International Union of Biochemistry. Contact: Organisatie Bureau Amsterdam bv, Europaplein,, 1078 GZ Amsterdam, The Netherlands
12-13 September	International Symposium - Labeled and Unlabeled Antibody in Cancer Diagnosis and Therapy, to be held at the Johns Hopkins Medical Institutions, Baltimore, MD. Contact: American College of Radiology, 925 Chestnut St., Philadelphia, PA 19107, USA
30 September-4 October	7th General Meeting of European Society for Animal Cell Technology, Baden, Austria. Contact: Mondial Congress, 4 Bösendorferstrasse, Vienna A-1010, Austria
21-23 October	Biotech 85 USA, Washington DC. Contact: Online Conferences Inc., Suite 1190, 2 Penn Plaza, New York, NY 10121, USA
27-29 November	Biotech 85 Asia, Singapore. Contact: Online Conferences and Exhibitions (Asia) Pte Ltd., Suite 0922, The World Trade Centre, 1 Maritime Square, Singapore.

See also meetings in previous issue of the Monitor.

F. REPRINTED ARTICLES

Biotechnology in Food Production and Processing

By Dietrich Knorr and Anthony J. Sinskey

D. Knorr is Professor of Food Processing and Biotechnology, Department of Food Science and Human Nutrition, University of Delaware, Newark, Delaware 19716. A. J. Sinskey is Professor of Applied Microbiology, Department of Applied Biological Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139.

This article is adapted from a position paper presented at the Institute of Food Technologists Workshop on Research Needs, 11-14 November 1984, Arlington Heights, IL.

Introduction

The use of biological technology for the manufacture of food and beverages has been practised for more than 8,000 years with sourdough, vinegar and alcoholic beverage production being the most prominent examples (1). In addition, other fermented products, food and feed additives, as well as processing aids are now produced by biotechnological processes (Table 1). This makes the food processing industry the oldest and largest industry using biotechnological processes (2, 3) to supply and preserve food. The important issue of concern today is how modern biology will impact on the food industry. Another related question is what are the constraints hindering applications of biotechnology to the food industry.

Biotechnology in food production

Biotechnology can have significant consequences on the basis of food supply, including raw material development (synthesis), modification as well as raw material preservation and bioconversion. In addition, development of production and processing aids and direct additives such as enzymes, flavours, pigments, polysaccharides and antioxidants can also be produced to improve the overall utilization of raw materials.

Critical, however, is the formulation of achievable objectives. In addition, as will be seen later, biotechnologists can make a variety of materials. What is needed is a rational basis for their utilization in food systems. Lacking is quantitative information on the structure-function relationships of food materials.

Table 1

World Production, Market Value and End use of Selected Products of the Biotechnology Based Food Industry (2)

Products	Production (metric tons/yr) 1974	1979	Market Size (millions U.S. $) 1974	1979	Primary End Use
Amino acids		455×10^3 (1982)	290	1.9×10^3	feed additive, food enrichment and flavouring agent, feed additive and preservative,
Enzymes		65×10^3 (198)	132	310-400 (1981)	food enrichment agent, processing aid
Citric acid	265×10^3	300×10^3			
Bakers yeast	0.97×10^6	1.75×10^6	380		
Beer	60×10^6	80×10^6			beverage
Cheese	11×10^6	14×10^6*			food
Vitamins				668 (1.1×10^3, (1981)	feed and food additive, food enrichment agent

* US and Western Europe

Raw material

Plant products, fewer than 30 plant species, provide more than 90 per cent of the human diet. Eight cereal crops provide more than half the world's calories (4). Animal products contribute over 56 million tons of edible protein and over 1 billion megacalories of energy annually (5). In addition, the increasing potential of marine food products and single cell protein as a raw material has recently been stressed (6). SCP is a significant source of protein in various parts of the world.

Currently, the role of biotechnology in raw material development is directed to (a) supplying the scientific tools for plant and animal breeding; (b) increasing productivity through improved efficiency of nutrient use and conversion; and (c) to identify new food sources. For example, extensive work has been carried out to increase the available supply of naturally produced nitrogen for plant growth (7). Furthermore, single cell proteins (SCP), the dried cells of micro-organisms for use as protein sources in human foods or animal feeds, are cultivated on a large scale by using photosynthetic as well as non-photosynthetic micro-organisms (8) and cultured plants and plant cells are being considered for food production (9). Additional biotechnological efforts worldwide in raw material development include genetic improvement of animal breeds, improvements in the reproductive efficiency in livestock, and the use of vaccines and monoclonal antibodies in the diagnosis, prevention and control of animal diseases; improvement of crop species via regulation of endogenous genes and the transfer of DNA from one species to another (e.g., fusion of cells, transfer of subcellular organelles, vector-mediate DNA transfer, improvement of plant resistance factors (e.g., plant and microbial produced pesticides) and improved photosynthetic efficiency (7,8,11). The use of the genetic diversity in plants, new plant and animal food sources as well as improved food production technologies (e.g., aquaculture, hydroponics, solid-state fermentation, continuous tissue cultures) are continuously sought (7,9,11).

Most of the work on raw material modification centers around the areas of stress resistance and functionality. The issue of functionality includes all properties of food or food raw material except nutritional ones that lead to its production and improved utilization. This comprises salt tolerance, herbicide and drought resistance, tolerance to

temperature stress, modification of colour, flavour and texture of raw materials, increase in essential nutrients and the reduction of undesirable constituents (11,13).

Raw material preservation by biological processes is of key importance to agriculture. Raw materials, in the form of silage, fermentation of cocoa and coffee beans and "fermentation" (oxidation) of tea leaves, as well as the conversion of raw material into single cell protein or feedstock chemicals (1,13) just pinpoint the magnitude of these microbial fermentation processes (1,13).

From a strategic-planning point of view, food manufactures or processes will pursue different strategies based on how raw materials are integrated in individual manufacturing operations.

Additives, production and processing aids

Additives and production aids used in raw material production include materials such as vaccines and growth regulators as well as microbial insecticides and herbicides in plant production (14) and on a worldwide basis these are subject to increased growth and intensive investigation (10). Historically, food additives such as vanilla flavour, vitamins B_2, B_{12}, C and D have been produced through biotechnological processes. Currently, intensive work is carried out on the production of metabolites such as flavour pigments, alternative sources of vitamins, antioxidants and lipids through plant tissue (15) and on the microbial production of flavours, pigments, vitamins, amino acids, antioxidants, bisurfactants and polysaccarides (15). For example, blue-green algae have been isolated which produce vitamin E (16), and it might be possible to increase vitamin E synthesis by altering the biosynthetic pathway in algae to fulfill the demand for this antioxidant. Aspartame (L-aspartyl-L-phenylalanine methyl ester) is a low-calorie dipeptide sweetener which has recently been approved as a food additive. Precursors such as aspartic acid and phenylalanine can be and are produced by fermentation processes (Pellon and Sinskey), (17). In addition, the production of the dipeptide aspartyl-phenylalanine has been performed at the laboratory level by recombinant DNA processes.

Polysaccharides commonly derived from algae or botanical sources and used as rheology control agents are being produced commercially through microbiological processes (18). The search for new microbial polysaccharides is of additicnal interest since additional biotechnological application of polysaccharides are possible in food related applications such as the microencapsulation of flavours, immobilization of enzymes, for the entrapment of whole cells and as a flocculating aid in food process waste management (19).

Yeasts have been used traditionally as processing aids in the production of alcoholic beverages and recently attention has been given to genetic manipulation of Saccharomyces yeast cells to increase the efficiency of the brewing process and to improve the process of preparing low-calorie "light" beers. Currently, glucoamylase enzymes from microbial sources (e.g., A. niger) are used in the production of many light beers. These enzymes are fairly thermostable and are not destroyed by normal beer pasteurization at 60-62°C. These beers become sweeter upon storage due to the release of glucose units from dextrins by the glucoamylase. Thus, the production of a thermosensitive glucoamylase by a brewer's yeast which is inactivated upon pasteurization would be of significant value (20).

Enzymes are used extensively in food production and processing with amylase, glucose transforming enzymes, proteases, pectic enzymes and lipases being the ones most extensively applied. Excellent reviews on the production and utilization of food enzymes are available (21).

Immobilized enzymes and whole cells have recently received a significant amount of attention as valuable biocatalysts for the food processing industry (22). Advantages of the application of immobilized processes include continuous operations, reuse of the biocatalyst, ease of process control, improved biocatalyst stability, and reduced waste disposal problems (22).

The most dramatic effect of biotechnology on the production of a food ingredient is exemplified by the development of high fructose corn syrup (HFCS) which involves the application of two amylases and glucose isomerase for the liquification and subsequent saccharification of corn starch into an about equimolecular mixture of fructose and glucose. Because fructose is sweeter than glucose, HFCS is about as sweet as a sucrose syrup of the same solid content and has found wide use in processed foods. In 1981, about 2.5 million metric tons of HFCS (dry basis) were produced compared to about 72,000 metric tons in 1976. Over a ten year period (1970 to 1980), HFCS increased from non-existence in the per capita consumption of nutritive sweeteners in the USA (55.0 kg in 1970, 58.2 kg in 1980) to 16.4 per cent of the total nutritive sweetener consumption while the percentage of sucrose decreased

from 84.1 to 68.0 per cent (Olson/Korus/Thijssen). The production of HFCS via enzyme technology is one of the greatest commercial successes of immobilized biocatalyst technology. Secondary plant metabolites can also be successfully produced by such processes.

The production of enzymes with enhanced temperature stability to temperasture and other processing conditions, especially for improvements in processing and processing time have recently received much attention.

Biotechnology in Food Processing

Product modification

Significant advances have been made on the modification of food components such as proteins, starches, pectins, fats, for use in foods, oils and polysaccharides. For example, protein modifications include limited enzymatic hydrolysis to alter food functionality. The reverse reaction "the plastein reaction", has been proposed as a method to create protein like materials in order to develop new food products (3).

Meat tenderization with papain (estimated annual sales in the U.S. 1975 $10.1.10^6$ \$, 1985 $16.6.10^6$ \$) is one example where large scale applications of enzymatic hydrolysis is used to modify product functionality.

Modification of the fatty acid composition of triglycerides by lipase and the enzymatic modification of olive oil and stearic acid to a cocoa butter-like fat, particularly the formation of 1-palmitoyl-2-deoyl-3-stearoyl-rac-glycerol, the major triglyceride of cocoa butter obtained on reacting oleic anhydride with 1-palmitoyl-3-stearoyl rac-glycerol in the presence of lipase present additional areas of product modifications.

Production Preservation and Stablization

The efficiency of microbial metabolism used in the food fermentation industries can also be enhanced via genetic manipulation of starter cultures. Fundamental knowledge of the molecular biology of organisms used in starter cultures is required (24).

Processing Methods

Bioreactors

With the availability of high-performance bioreactors for large scale fermentation-processes, current emphasis is on computer process control, even though there is a need to improve bioreactor performance by overcoming limitation of heat and mass transfer. This is especially important with new biocatalysts and the desire to scale-up many processes including animal and plant cell culture systems (26). The engineering problems are challenging when non-Newtonian systems are involved (25).

Currently, extensive work on immobilization techniques, reactor design and cell membrane permeabilizing procedures will help to overcome problems currently experienced with continuous animal and plant cell cultures such as shear sensitivity, slow growth rates, and release of products.

Separation and purification operations

Mechanical unit operations used for separation and purification include operations such as sedimentation, centrifugation, filtration along with dialysis, flotation, and ultrafiltration (27). Biomass separation is commonly aided by bioflocculation with or by synthetic polyelectrolytes. Recently, natural polyelectrolytes such as chitin and chitosan have been investigated in place of synthetic polyelectrolytes (28,29).

Applications of aqueous two-phase systems (liquid-liquid extraction) especially for extractive purification of enzymes (30) and that of supercritical extraction (31) for food ingredient recovery are becoming increasingly important. In the use of the latter one, carbon dioxide is favoured as dense gas because of it is non-toxic non-explosive, cheap, readily available and is easily removed from extracted products (32). As an industrial scale supercritical extraction it is currently used for decaffeination of coffee and tea.

During the past decade ultrafiltration has become a useful separation and purification process for food processes. Recovery of whey protein from cheese, cottage cheese or industrial casein processing wastes is a prominent food application (33).

Non-lipolytic enzymes have been used to enhance extractability of oil from seeds (34) and pectolytic enzymes are used extensively in the production of liquid fruit and vegetable products (35). Co-fermentation processes have also been suggested to aid the separation and purification of secondary metabolites (36). Scale-up of high performance liquid chromatography (HPLC) separation processes is being explored (37).

Product safety and quality control

Besides the use of classical methods applied to ensure quality and safety of foods (38), three recent developments seem noteworthy that are relevant to product safety and quality control. First, the potential application of monoclonal antibodies to determine optimal crop harvesting and to optimize processing and packaging techniques (39). Secondly the use of biosensors and DNA hybridization techniques for quality control (40) and thirdly the potential of tissue culture and genetic methods for toxicity assessment (41). In addition, the regulatory aspects of biotechnology as a new method of manufacture of food ingredients and its relation to food safety are being examined (42).

Waste treatment and utilization

Because of the large volumes commonly involved in the production and processing of food, food production and processing wastes create disposal and pollution problems. Substantial loss of essential nutrients can occur in work strains. For example, 20 million metric tons of whey, the fluid that results from the separation of curd from the fluid when converting milk into cheese, contains about 1 per cent protein, 5 per cent lactose, 0.5 per cent minerals and 0.2 to 0.5 per cent lactic acid, accumulate annually in the U.S. (43). Whey contains more than half of the nutrients of milk going into cheese production and only about 50 per cent of the total whey solids are disposed of by various industrial and municipal waste treatment operations (44).

Biomass recovery, especially for isolation of protein, has been carried out in the food processing industry for an extended period of time. Isolation of potato protein concentrates from potato processing wastes, for example, has been proven on an industrial scale and the product's potential for food application has been studied extensively (46). Byproduct recovery has also been studied for meat processing, cereal processing, dairy processing, fruit and vegetable processing, fish and shellfish processing and fermentation operations (45).

The potential of food processing wastes for byproduct recovery and conversion can be illustrated by chitin (poly- (1 4)N-acetyl-D-glucosamine) a waste product of the shellfish industry and one of the most abundant polysaccharides in the world. It has been used effectively to aid the separation of colloidal and dispersed particles from food process wastes, has been shown to have potential for numerous food applications including dietary fiber and functional ingredient, is used as a carrier for immobilized enzymes and chitosan (partially deacetylated chitin) is being utilized for microencapsulation of flavour and for the entrapment of whole cells (46). Numerous additional applications of chitin and chitosan are currently being investigated (47). Chitin bioconversion to single cell protein has also been examined (48).

Bioconversion of food processing wastes includes substrates such as starch by the "Symba process" which utilizes a symbiotic culture of two yeasts, the amylases producing Endomycopsis fibuliger and Candida utilis (49) or whey with Kluyveromyces fragilis and Candida intermedia, which is characterized by an exclusively oxidative lactose metabolism, being used for production of protein enriched whey (50). The use of molasses and corn steep liquor as substrate in many fermentation processes and partly the production of vinegar (e.g., from "waste" wine) can also be categorized as biomass conversion of food process wastes.

Research needs in biotechnology

As the above discussion indicates, there is a wealth of potential opportunities for biotechnology and foods. Needed is a mechanism by which the benefits of a biotechnology programme limited to the food sector can be proposed as well as a summary of the critical research needs. Fortunately, a workshop recently sponsored by the Institute of Technologists took a step in this direction. Approximately forty scientists from industry, government, and academia reviewed and summarized the following statement that defines the benefits and research needs in this important area. They are summarized below:

Biotechnology directed toward the general area of food can bring significant economic benefits at both the macro and micro levels. The U.S. national (macroeconomic) interests can be served by:

- more reliable supply of critical food and food ingredients
- more efficient use of capital employed in food processing
- lower energy consumption in food processing
- faster innovation, particularly in agricultural, raw material development, thereby maintaining a competitive international position, and
- providing an added value usage for agricultural commodities currently in surplus.

At the microeconomic level of individual food sectors, benefits will come from:

- more effective production yields
- higher productivity in processing raw materials
- improved ability to meet the consumers demand for natural foods and food ingredients
- less waste, improved processing characteristics, consistent quality, and a greater nutritional value.

The following seven programmes of research needs are not prioritized, but rather reflect needs at the various steps in the path from agricultural production through to the consumer.

The most critical research needs - in addition to basic studies on the structure/function relationship of food materials - are (1) cell physiology and biochemistry of agricultural raw materials and (2) improvement of food grade microorganisms.

1. Application of biotechnology to structural/functional relationship of food material.
   Improve the utilization of biomaterials by applying modern biotechnological principles such as site-directed mutagenesis to control the functional performance of foodstuffs. In addition, biotechnology will contribute analytical tools and processing procedures which will aid in implementation of this new knowledge.

2. Cell physiology and biochemistry of agricultural raw materials.
   The potential exists to lower the cost of agricultural raw materials, both plant and animal, by application of genetic engineering and other biotechnological techniques. Potential targets for improvement are:
   - in crops - solids content, sensory properties (colour, flavour, texture), environmental adaptation, secondary metabolites (vitamins), post harvest storability
   - in animals - feed efficiency utilization, palatability, fat/protein ratios, maturation time of juveniles.

   To realize these benefits, a vast increase is necessary in our understanding (at the molecular level) of the cell physiology and biosynthetic pathways in the appropriate animal and plant species.

3. Recombinant DNA Technologies.
   To improve the production costs, nutritional value and cost-in-use of some of the major agricultural crops, particularly cereals, further fundamental advances in recombinant DNA technologies are necessary. Critical needs are in the following areas:
   a. Vector development and transformation procedures for cereal crops,
   b. Improved regulation and expression of foreign genes, and
   c. Techniques to regenerate and propagate crops which cannot now be so handled.

4. Rapid screening.
   Reduce the time and cost of developing new crop species by confirming their genotype at the cell culture stage with desirable properties.

5. Improvement of enzymatic processing.

Enzyme processes can reduce the high cost of traditional food processes and also permit development of totally novel foods and food ingredients.

To expand the range of possible processes, and improve on the economics of current enzyme based processes, increased basic knowledge of enzymes is needed on the isolation, and characterization, mechanisms of enzyme action, and their incorporation into food processes. Specific needs are:

a. understanding the mechanisms of enzyme inactivation
b. cloning systems to permit production of new enzymes in food grade organisms quickly and cheaply
c. utilizing enzymes for biosynthetic processes and redox reactions relevant to foods, including the low cost production and recyle of cofactors
d. developing new processes/procedures using immobilized whole cells. Fundamental studies are needed on control of mass transfer in food systems, maintenance of catalytic activity and prevention of contamination.
e. understanding and modeling by computer the mechanisms of action of food processing enzymes in sufficient detail to permit systemic protein engineering of improved enzymes.

6. Improvement of food grade micro-organisms.

Micro-organisms - bacteria, yeasts and fungi - are all used extensively in various aspects of food processing. To improve the economics (yield and productivity) and new product characteristics achievable with these organisms major advances in our understanding of their biochemistry and genetics are needed.

Specific research needs are:

a. to establish food-grade recombinant DNA technologies and biochemical understanding of microorganisms useful in food fermentation and preservation processes
b. to quantitatively describe the microbial ecology and biochemistry of mixed culture and solid-state fermentations important in food-stuffs
c. to isolate, select, and genetically manipulate organisms capable of synthesizing food additives, such as biopolymers, food colourants, natural flavourings and preservations, by fermentation and cell culture
d. to develop economically viable bioprocesses as sources of raw material for the food processing industry.

7. Food safety.

There is an urgent need to improve and speed up food safety assessment techniques.

Biotechnology can contribute to food safety by developing faster and more meaningful methodologies, based on DNA hybridization, sequencing and monoclonal antibodies, for food safety assurance.

Conclusions

It is obvious that the area of biotechnology in food production and processing encompasses a tremendously diverse and large field of utilization of capabilities of biological systems with rapidly expanding new food applications and with new food sources being developed. We have attempted to highlight biotechnology in food production and processing on a very broad basis and consequently could only scratch on many of the exciting involvements of biotechnology in providing, securing and improving our food supply.

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