OCCASION

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

DISCLAIMER

FAIR USE POLICY

CONTACT

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

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

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

Genetic Engineering and Biotechnology Monitor

Issue No. 25 1988/IV

Special in this issue: An article by Dr. F. L. Singleton and J. C. Kramer of the Center of Marine Biotechnology, Maryland, USA, on the biotechnology of marine algae and their opportunities for developing countries. (See page 83).

This publication is distributed free of charge

The *Genetic Engineering and Biotechnology Monitor* proposes to accept industry-related advertisements from companies interested in reaching planners and policy-makers as well as entrepreneurs and members of the scientific community in some sixty developing countries throughout the world and inform them about their products and services.

The *Monitor* is published four times a year and distributed free of charge to individuals and institutions on an approved mailing list which includes at the moment 2500 entries. The *Monitor* has been published since 1982 and has built up a sound reputation both in developed and developing countries.

Our activities in the field of advertising are directed towards helping to finance the preparation, publication and mailing of the *Monitor*, which will continue to be distributed free of charge.

Advertisements will be printed in black and white and in English only. Prices in Austrian Schillings or the equivalent in $US will be AS 5,000 for a full page; for half page advertisements, AS 3,700; and for a quarter page, AS 2,500. Requests for placing of advertisements, accompanied by a layout, illustrations and text, should be submitted to the Editor, *Genetic Engineering and Biotechnology Monitor*.

CONTENTS

CONTENTS (continued)

CONTENTS (continued)

A. POLICY, NEWS AND OTHER EVENTS

UNIDO news

New Director for the International Centre for Genetic Engineering and Biotechnology

Arturo Falaschi (Italy) was elected as the new Director of the International Centre for Genetic Engineering and Biotechnology (ICGEB) by the Centre's 41-nation Preparatory Committee's thirteenth session. He will take up his post on 1 July for five years, succeeding the current incumbent, Irwin Gunsalus (USA).

The Committee also considered a re-scheduled work programme for the ICGEB for 1989-94, as well as progress on the interim programme, finances, training, affiliated centres, intellectual property rights and work of the Panel of Scientific Advisers.

Head of the twin-component Centre's Trieste laboratory since 1987, Mr. Falaschi has been a prominent molecular biologist since becoming a fellow of the National Committee for Radiation Research at the University of Ferrara in 1959. From 1961 to 1965 he was a post-doctoral fellow at the University of Wisconsin and, subsequently, Stanford University. In 1965 he was a researcher with the Italian National Research Council (CNR), 1966 to 1979 Acting Professor of molecular biology and 1978 to 1984 Director of the Post-graduate School, all at the University of Pavia. In 1978 he became President of the Ministry of Health's Committee for the Studies of Activities on Recombinant DNA.

Approving ICGEB's work for 1989-94, the Committee decided that it should be treated as a "rolling five-year programme", to be reviewed and extended on an annual basis.

Of the estimated $56 million for the programme, some $46 million are already available from the host countries, India and Italy. Contributions in kind of the order of $4 million will come from member countries participating in specific programmes of the Centre. A further $6 million in voluntary contributions are expected during the five-year period, to finance training programmes and other co-operative activities.

The main features of the programme include research on agriculture and animal and human health at the New Delhi component, while industrial biotechnology and bioprocessing will be the focus at Trieste. Both laboratories will each train 20 scientists annually as space becomes available.

Twelve collaborative research projects between ICGEB and affiliated centres are scheduled for 1989, increasing to 20 in subsequent years. Short-term training will be organized for visiting scientists and biotechnologists. In addition, affiliated centres are expected to organize laboratory courses and meetings. The Centre will also provide advisory services to member countries.

Members of ICGEB so far are Afghanistan, Algeria, Argentina, Bhutan, Bolivia, Brazil, Bulgaria, Chile, China, Colombia, Congo, Cuba, Ecuador, Egypt, Greece, Hungary, India, Indonesia, Iran, Islamic Republic of, Iraq, Italy, Kuwait, Mauritania, Mauritius, Mexico, Morocco, Nigeria, Pakistan, Panama, Peru, Senegal, Spain, Sudan, Thailand, Trinidad and Tobago, Tunisia, Turkey, Venezuela, Viet Nam, Yugoslavia and Zaire.
(Source: UNIDO Press Release, 28 April 1989)

ICGEB meetings - courses - workshops to be held in 1989

To complement the list printed in the last issue of the Monitor, hereunder are the details of the Practical Course on Genetic Pathologies and the Human Genome to be held from 6 to 10 October 1989 in Trieste, Italy.

Organiser(s):

L. L. Cavalli-Sforza, Stanford, USA
A. Cao, Cagliari, Italy
D. Shaw, Cardiff, UK
Y. W. Kan, San Francisco, USA
L. Luzzatto, London, UK
C. Schneider, Trieste, Italy
G. Romeo, Genoa, Italy
U. Gyllenstein, Uppsala, Sweden

Lecture topics:

RFLPs:

- Human and genetic diseases
- Chromosomal genetic maps
- Major diagnostic applications

PCR:

- Genetic polymorphisms
- DNA regions
- Major diagnostic applications

Population genetics:

- Equilibria for genetic markers
- Linkage analysis
- Linkage disequilibria
- Association of disease and genetic markers

Human genetics and DNA maps:

- Normal and pathological human variation

The course is open to member country scientists nominated through their National Scientific Focal Point.

Requirements: Participants with a basic knowledge of molecular biology, biochemistry, and involvement in research on application of course material. Submit resumés to Ms. Diana Viti, ICGEB, Padriciano 99, 34012 Trieste, tel. (040) 22 60 333. Telex 460396 ICGEBT I. Fax (040) 22 65 55. Closing date for nominations 31 July 1989.

ICGEB Trieste will provide accommodation and transport from the hotel to the laboratory. The travel to and from New Delhi will be borne by the participants.

UN and other organizations' news

UN considers biodiversity convention

Concerned that existing international laws are not sufficient to halt the rapid disappearance of many of the world's species, the United Nations Environment Programme (UNEP) has taken the first step, in what is usually a 10-year process, to draft a new global convention for the conservation of biological diversity.

The proposal is likely to be controversial, as several other global conventions already address biodiversity, and few countries want to add another layer of international bureaucracy or to support another secretariat.

The problem with the existing instruments, according to an ad hoc experts panel that met at UNEP in Nairobi, Kenya, in early September, is that they provide at best only patchwork coverage of biodiversity; thus the need for a new "umbrella" convention to fill in the gaps. The idea is not to have another "motherhood" convention, but rather one with a funding mechanism that can be used for training or establishing reserves, among other things.

However, getting nations to kick in a substantial share to international agreements has proved difficult in the past. The United States, for one, is notably behind on its payments to all the global conventions and to the United Nations, though the latter is at last being at least partially addressed.

The reason an umbrella convention is needed, is that each of the existing conventions protects only a very small percentage of global biological diversity, and each is signed by a different set of nations. Most of these conventions, like those to protect world cultural and natural heritage, migratory species and endangered species, were established for other purposes and protect biodiversity as a by-product.

Moreover, while these global and regional conventions add prestige and underscore the importance of certain areas, they do not add much in terms of real estate or new land, since many of the sites they designate are already protected by national laws.

Perhaps the key element of the convention, as now envisioned, is a funding mechanism to support conservation efforts in countries that could not afford them otherwise. The nations with the greatest diversity are often least equipped to deal with it, financially and technically.

The tricky question, obviously, is where money for the fund will come from. One possibility is voluntary contributions by Governments, another is a tax on the use of genetic resources.

As described in the expert panel's draft report, which is just the first of many versions, the convention would also establish a technical committee that would maintain a world list of areas particularly important for biodiversity.

This same technical committee would review grant applications to the fund, which would be used, for instance, for establishing new sites or improving existing ones. The fund would also provide long-term financial support, where needed, to the international research and training centres, such as those in Serengeti and the Galápagos Islands.

The next step is a meeting of government experts in Switzerland. That panel will review the biologists' report and advise UNEP on how it might be shaped into a politically acceptable convention. Mostafa Tolba, UNEP's executive director, will return to UNEP's governing council with his recommendation in early 1989. Meanwhile, IUCN is already working on a draft of the convention, incorporating ideas from the Nairobi meeting. (Source: Science, L. Roberts, Vol. 241, 23 September 1988, copyright 1988 by the AAAS)

The OECD's view of the impact of biotechnology

The industrialized world still lacks adequate risk assessment of biotechnology, according to a new OECD report, entitled "Biotechnology and the Changing Role of Government". Many companies are unwilling to conduct field tests of altered organisms because of the inadequate procedures for risk assessment. Furthermore, biotechnology could worsen already critical surpluses of agricultural products. Governments have failed to assess the impact of biotechnology on their agricultural policies. Another area of concern is that biotechnology might provide diagnosis of animal diseases without also providing cures. Biotechnological treatment of waste has been advanced the most in Japan, the Netherlands, France and the Federal Republic of Germany, but industry in general finds it more economical to pay fines for pollution rather than install pollution control equipment.

This is the fourth in a series of OECD reports on biotechnology. The first, "Biotechnology: International Trends and Perspectives", appeared in 1982; "Biotechnology and Patent Protection: An International Review" in 1985; and the third, "Recombinant DNA Safety Considerations", in 1986.

Details from: Publications Service, OECD, 2 rue André-Pascal, 75775 Paris Cedex 16, France. The report can also be ordered through Her Majesty's Stationery Office. (Extracted from Chemical Week, 10 August 1988 and Biotechnology Bulletin, Vol. 7, No. 7, August 1988)

General

Human genome organization launched

What was five months ago merely an idea for an international council to promote collaboration on the mapping and sequencing of the human genome has now coalesced into a bona fide organization with money in its pocket.

HUGO, the Human Genome Organization, held its first council meeting on 6 and 7 September 1988 in Montreux, Switzerland, and newly-elected president Victor McKusick of Johns Hopkins University in Baltimore expects that HUGO will have opened offices around the world by the end of the year.

HUGO was born at a rump session of a Cold Spring Harbor meeting last April. According to McKusick, James Watson, director of the laboratory, Leroy Hood of the California Institute of Technology, Sydney Brenner of the Medical Research Council Laboratory of Molecular Biology in Cambridge and Kenichi Matsubara of Osaka University were HUGO's intellectual godfathers.

The European Molecular Biology Organization (EMBO) is the model HUGO intends to follow, and to that end it was incorporated in Switzerland. HUGO will be an extra-governmental organization, but will depend on government contributions for its existence. It will give fellowships, conduct mapping workshops and issue annual reports.

Another possible function is to serve as a clearing-house for information about the growing number of international groups focusing on the genome project.

The HUGO Council proposed in Montreux that the organization should also start planning for the day when international centres will be set up around the world to do the immense - but mostly routine - task of sequencing identified fragments of DNA. McKusick says it is premature to consider establishing such centres now, but that they will be needed and it would help to establish HUGO's identity if it were to take the lead in planning for them.

HUGO has established five areas of special interest: data banks, physical mapping/sequencing, other species, ethics and human disease. More co-operation is particularly to be encouraged between those involved in constructing genetic maps of the genome and those involved in physical mapping and sequencing efforts. HUGO will have to be conscientious in addressing the ethical issues raised by the mapping effort.

The council membership is international: 12 are from the United States, 7 from Britain, 5 from the Federal Republic of Germany, 4 from France, 3 from Japan, 2 each from Canada, the Netherlands and Sweden, and 1 each from Australia, Greece, Italy, the Soviet Union and Switzerland.

HUGO does not yet have a fixed budget, but is aiming for several million dollars a year to support its activities. (Source: Nature, Vol. 335, 22 September 1988)

ABC offers higher limits, lower prices on bio-insurance

The US Association of Biotechnology Companies (ABC) has successfully negotiated with London underwriters and is offering a product and professional liability insurance programme including an additional $1 million of primary limits and up to $2 million per policy-holder. Additional capacity of up to $10 million will be available on a case-by-case basis. Details from: Association of Biotechnology Companies, 1120 Vermont Avenue NW, Suite 601, Washington, DC 20005, USA. (Source: Biotechnology Bulletin, Vol. 7, No. 7, August 1988)

Molecular aging

A European network of collaborative research in the molecular biology of aging and age-related diseases is to be formed with the aim of reducing costs and increasing the international competitiveness of European research. Collaboration will be initiated at the first meeting of the Eurage Molecular Biology Group, held in Crete on 7-10 October 1988. At the meeting, recent developments will be outlined by experts in the field from both in and outside Europe and the exchange of materials will be discussed. (Source: Nature, Vol. 334, 11 August 1988)

New model predicts future of HIV in Africa

A model of the spread of AIDS in Africa is relying on data on infection with HIV, sparse though they are, rather than reported cases of AIDS. The model suggests that there may be 10 times as many cases of AIDS in Africa than reported by many nations.

The model has been developed by scientists from the World Health Organization. James Chin, of the WHO, told the Third International Conference on AIDS in Africa, held at Arusha, Tanzania in September, that out of 111,000 cases of AIDS reported to WHO to date by 140 countries, only just over 14,000 are from Africa.

Methods of forecasting that rely on extrapolation from the reported cases of the disease are not useful in developing countries which do not have reliable reporting. Chin, together with Steve Lwanga, also from WHO, decided to develop an alternative method.

The first step is to estimate when HIV began to spread extensively in the population. If no data are available, Chin said, 1980 should be the starting-point. The second stage is to estimate the prevalence of the virus in the country at a specific time - for example, in the current year. The accuracy of the predictions from the model are quite sensitive to this figure, Chin said.

People found to be infected in one year will not all have caught their infection in that year. The model allows for this, and calculates the expected number of cases of AIDS using data which suggest that 15 to 20 per cent of people develop AIDS within five years of infection, 50 per cent within 10 years and 75 per cent within 15 years.

Finally, the model needs an estimate of what the continuing incidence of HIV infection might be. This figure is difficult to estimate, Chin said, but it will not greatly influence the predicted number of cases of AIDS within the next four to five years because most of these will come from the pool of people already infected with HIV.

Lwanga and Chin found that their model's predictions of the number of cases of AIDS in the US and Europe agreed well with projections from other methods. They then used the model to examine what the situation might be in a hypothetical East African country with a population of 16.1 million. They gave the country a typical population structure with 15 per cent living in urban areas.

The next stage was to fit data on the prevalence of HIV infection in different groups to the population. Surveys have shown that in 1986, in some urban areas, up to a quarter of the most sexually active age groups (20 to 40 years old) were HIV-positive. A tenth of children under five years of age are also HIV-positive due to transmission from infected mothers. Few children aged five to 14 years are infected.

Overall, 12 per cent of the hypothetical urban population are infected, and fewer than 1 per cent of the rural population. Throughout the country, the overall infection rate would be 2.6 per cent. Overall, there would be about 416,000 HIV-positive people in the hypothetical population in 1986. (Source: New Scientist, 22 September 1988)

AIDS reagent repository opens

After years of preparations, an AIDS reagent repository containing deposits from AIDS researchers world wide has been opened by the US National Institute of Allergy and Infectious Diseases (NIAID). The repository contains over 100 reagents, virus stocks, cell lines and clones drawn from contributions solicited from nearly 1,500 researchers.

The repository was established in April of this year through the efforts of John McGowan, chief of the Developmental Therapeutics Branch of NIAID's AIDS programme. McGowan says the two aims of the repository are to make reagents freely available to draw in new researchers to study AIDS, and to offer standardized protocols and reagents so that results can be compared between laboratories.

The NIAID repository is part of the World Health Organization AIDS reagent repository programme, and is collaborating with similar

repositories in Paris and London. The repository's reagents are free to industry, government and academic researchers, to be used for research purposes only. (Source: Nature, Vol. 335, 27 October 1988)

Critical period ahead for biotechnology firms

Many US biotechtechnology companies face a difficult period that will likely extend through the next 12 to 18 months.

The problem, like being between the proverbial, "rock and a hard place," stems from the combination of dwindling cash and mounting expenses. This is one of the conclusions of a new industry study prepared by analysts at Consulting Resources Corporation, the Lexington, Mass.-based consulting firm.

Financing has become more difficult since the stock market crash last year, especially for younger companies. According to the study, many of the more established companies will also be forced to raise money within the next several years.

On the expense side of the income statement, mounting costs relating to scale-up, patents and regulations seem to be growing much faster than product revenues.

On the legal front, courtroom battles over biotechnology patents are heating up. As more new patents are issued, many of their holders will be following the strategy of suing other companies developing similar products to delay their entry into the marketplace. The study, however, questions the long-term value of this strategy. It is believed biotechnology patents may not be as critical as some of the companies contend. The reasons are, first, that it is difficult to patent a "natural" product in the pharmaceutical area and, second, the technology for developing second- and even third-generation products is changing too rapidly.

Cross-licensing or other types of settlement may be more beneficial to both parties as well as to the industry, the consulting firm says.

In the regulatory arena, Food & Drug Administration is in the midst of restructuring certain operations to improve its evaluation of biotherapeutics. Two separate centres - one for evaluating biologics and one for evaluating drugs - have been set up, and strategies are being formulated to better facilitate the assignment of a product to the appropriate centre.

As for EPA, the agency has proposed that all micro-organisms not already on the market or regulated by a federal agency would be subject to the Toxic Substance Control Act. The proposal would cover naturally-occurring soil bacteria, and, along with other regulations, hamper US progress in agricultural applications of biotechnology, according to the study.

In examining critical success factors among the various functional skills, the consulting firm's study concludes that "marketing" will steal the limelight from "R&D" in terms of relative strategic importance. Management style and corporate strategy will need to shift as cost control and even cost-cutting become more important.

What is the outlook for biotechnology? Despite the problems, the study concludes that biotechnology is moving into a rapid growth phase. The flow of products has so far been only a trickle. The rate of product introduction will increase dramatically in the next few years, beginning with the expected US approval of Amgen's erythropoietin late this year or in early 1989.

Most of the new products will be for the pharmaceutical market, where the technology is further along than in other sectors and where profit expectations are highest. However, research in the agricultural and specialty chemical areas has advanced faster than first anticipated and is generating increasing excitement among major companies.

Large drug companies believe biotechnology will soon become a lucrative source of new products and are racing to form ties with promising biotechnology firms. Before, these capital-starved companies had to license or sell technology to their larger patrons. Now, major drug makers are treating the leading biotechnology firms as equals. Industry executives and analysts say this will enable more biotechnology companies to follow the example of Genentech. Some 60 per cent of 291 biotechnology firms surveyed by Arthur Young, the New York accounting and management consulting firm, indicates that now is a good time to form strategic tie-ups with large drug companies. (Source: Chemical Manufacturing Reporter, 22 August 1988 and New York Times, 30 September 1988)

Neurological market offers opportunities for new products

More than one in five Americans are affected to some degree by a neurological or mental illness, at a total economic cost of more than $150 billion. According to "Market opportunities in neurological diagnosis and therapy", a new report from Biomedical Business International (BBI), "initial diagnostic workups for these patients range from $500 to more than $2,500, while total diagnostic billings for the US alone are estimated to exceed $5 billion. The world-wide market for neuropharmacological agents could also reach $5 billion by 1990, based on annual per patient drug expenses of $1,000 for chronic disorders."

Yet, says BBI, new product development opportunities exist because current diagnostic and therapeutic techniques have been largely ineffective. Diagnostic techniques are often insensitive, lack specificity, are usually effective only late in the course of the disease and only rarely do they provide definitive diagnoses. In addition, few screening tests have been available.

The treatment of neurological disorders has been difficult because of a lack of understanding of the disease processes, the relentlessly progressive nature of many neurological disorders and late-stage diagnoses. Nevertheless, BBI concludes, recent product developments are improving the diagnosis and treatment of neurological and mental disorders and are creating new market opportunities.

Developments in diagnostic technologies include laboratory diagnostic and screening tests (chromosomal mapping techniques, DNA probes, monoclonal antibodies, biochemical markers), electrical/magnetic field monitoring devices, imaging devices and agents, and intracranial pressure systems.

Therapeutic products include new pharmaceutical agents, drug delivery technologies (with an emphasis

on mechanisms for crossing the blood-brain barrier), tissue transplantation and other therapeutic devices.

Details of the report, priced at $2,850, from: Biomedical Business International, 17722 Irvine Boulevard, Tustin, CA 92680, USA. (Source: Biotechnology Bulletin, Vol. 7, No. 10, November 1988)

ATCC offers gram-negative ring-forming micro-organism

The search for new antibiotic-producing micro-organisms has traditionally been focused on soil surveys. In recent years new ecological niches have come under investigation based on the premise that different environments are likely to support different types of antibiotic-forming organisms. The American Type Culture Collection (ATCC) has available a varied group of micro-organisms from the marine environment. One recent acquisition, which came from the Woods Hole Oceanographic Institution, is a gram-negative ring-former, Flectobacillus marinus, isolated from 2,000 metres depth. Details from: American Type Culture Collection, S/M Box NR9, 12301 Parklawn Drive, Rockville, Maryland 20852, USA. (Source: Biotechnology Monitor, Vol. 7, No. 7, August 1988)

Participants needed for ASTM Sub-Committee on biological systems

Participants are needed for E48.02 on Characterization and Identification of Biological Systems, a sub-committee of ASTM standards-writing Committee E-48 on Biotechnology. This group has recently developed standard guides for the characterization and identification of the bacterial virus lambda and the animal virus herpes simplex. Similar standards development activities are currently under way within the sub-committee.

All interested parties are welcome to participate. The next meeting of the sub-committee is 17-19 April 1989 in Atlanta, Georgia. More information is available from sub-committee chairman Larry E. Bockstahler, Food and Drug Administration, Rockville, MD 20857, 301/443-7287 or 7160; or John Vowell, ASTM, 1916 Race Street, Philadelphia, PA 19103, USA. (Source: ASTM News Release, 28 November 1988)

Japan's Human Frontier Project

Promoting a biological revolution in business over the next two decades has become a top national priority in Japan. This commitment is most evident in the Human Frontier Project, Japan's most ambitious new science programme. Officials at Japan's Ministry of International Trade and Industry (MITI) hope this project will result in innovations ranging from computers built from living cells to the production of polyethylene plastic by photosynthesis.

The Human Frontier Project represents a departure for Japan. Typically, the Japanese Government organizes narrowly targeted government/industry projects to advance recently developed technologies that are not quite ready for aggressive commercialization. Biotechnology ventures that are now under way include studies of protein engineering, the molecular breeding of micro-organisms, and new ways of producing ethanol by such methods as fermenting cellulose.

In contrast, the Human Frontier Project aims to pursue fundamental research in co-operation with foreign Governments. Japan is seeking co-sponsors and funding.

The Human Frontier Project has two key goals. First is the understanding of brain functions, which could lead to artificial brains made from living cells. Japanese computer makers such as Fujitsu and NEC take this effort very seriously. Fujitsu, for instance, is exploring "bio-elements" in its laboratories and hopes to apply them to its work on "neurocomputers", or computers that emulate the human brain. The second goal involves understanding biological functions at the molecular level, through such techniques as gene splicing. The project might also examine how nerves interact, with hopes of letting man-made devices communicate directly with the body.

Japan's deep commitment to biotechnology has gone beyond chemical and pharmaceutical houses such as Takeda Chemical and Green Cross Inc. into a variety of companies whose business involves an understanding of biology. These mainline companies, which include Kikkoman, Kirin Brewery and Ajinomoto, possess some of the world's richest knowledge of micro-organisms. Kirin Brewery, for example, is involved in eight Government-sponsored biotechnology projects. (Source: High Technology Business, August 1988)

Parallel thinking takes on the human genome

Twelve of the world's most prominent computer scientists and biologists gathered in Chicago to evaluate the computational needs of the project in the US to map the human genome. Teams from each of the computer centres involved were invited to attend, as well as representatives from the European genome project, and from Japan's Institute for New Generation Computing Technology. The delegates have compiled a report on their discussions, which they intend to publish.

Many of the largest computer centres in the US will work on the project, and each will specialize in one aspect of the work. The Los Alamos National Laboratory, for example, will look at the needs of the project's data base, while the Argonne National Laboratory in Illinois will handle those parts that require intensive use of computers.

"These are limited but significant aspects of the project," says Ross Overbeek, who heads the computer work at Argonne. Researchers cannot carry out these areas of the project on conventional sequential computers, which act on one piece of data at a time in a specific sequence. Overbeek will have to use parallel computing to avoid routines which would take thousands of hours to run, even on some of the world's most powerful supercomputers, such as the Cray.

Overbeek has chosen to use Strand, a new programming language, to carry out this work. The language, developed in Britain by Artificial Intelligence, is designed to run on parallel computers. Its closest rival is a language written in Japan under its fifth-generation computing program, Kernel Language 1. Overbeek says he never considered KL1 to be a serious contender for the genome work because it is not yet available as a commercial product.

Overbeek will try to match any new sequence of the nucleic acids which make up a sequence of DNA with sequences that have already been identified. His work also involves the identification of sequences that are known to code for particular

proteins. The problem is ideally suited for solving by parallel processing, where a computer can match several pairs of nucleic acids at once.

According to Artificial Intelligence, Strand - which stands for "Stream-And" parallelism - will run on a large number of different parallel architectures. This means that computer users can rewrite reliable pieces of software which are now running on sequential machines, so that they will run on a number of different parallel machines.

Parallel processors will be the answer for many applications that need huge amounts of processing power. Large computer sites will find they need to move over to parallel computing as their processing needs swell. Unfortunately, parallel computers are notoriously difficult to program, so users want to avoid rewriting their trusty software too many times.

The advantage of Artificial Intelligence's new language is that once software is rewritten in Strand, the user can, in theory, run it on virtually any parallel machine, even if they buy a new system in the future.

At the moment, Strand is written to run on Intel's Hypercube system, on any array of transputers which runs an operating system known as Helios, or on Meiko computing surfaces, also based on transputers. It will also run on Sun workstations, so software developers can write an entire program themselves in the knowledge that it can easily be made to run on a parallel machine.

Strand works by adopting what is known as a "virtual machine" concept. This allows the software developer to write a program as if there were an unlimited number of processors available on which to run parts of it.

Strand will also allow a user to embed pieces of software written in another language, such as C or Fortran, so that a user can run these within one larger Strand application. This protects what can be a huge investment in successful software, and is the way Overbeek plans to use the new programming language. He will run software that he has already written in C as part of a larger Strand program.

Strand has its roots in a language called Prolog. This was the first of what are known as declarative languages. These languages can handle computer instructions regardless of the order in which they are laid down in a program, and do not require the program statements to be written in an exact order, unlike their predecessors, which are known as procedural languages.

Declarative languages are the best type of language to use on parallel computers, because software developers can scatter the instructions that make up a program across any number of processors. There is a parallel version of Prolog, known as Parlog, and some of the characteristics of Parlog have been incorporated into Strand.

Although a programmer does not have to know how to program parallel machines in order to work with Strand, the new language will let the user design a program very specifically, so that parts of a program can be written to run on particular processors. In the US, two universities are soon to use Strand to teach students how to program parallel computers. Case, the British telecommunications company, and Edinburgh University, will test Strand from January, and it should be released on the market in February. (Source: New Scientist, 12 November 1988)

B. COUNTRY NEWS

European Economic Community

EEC research programme in predictive medicine

Predictive medicine seeks to predict susceptibility to diseases with a view to their prevention and early diagnosis, as well as to improved prognosis and eventual treatment. The Commission of the European Communities has proposed a new Community Research programme in this field, based on the use of new biotechnologies, and especially on human genome analysis. The programme is expected to run from 1989 to 1991 at a total cost of 30 million ECU. It is proposed that the Community contribution should be 15 million ECU, with matching funds from national sources.

The programme will be implemented through cost-shared or marginal cost contracts, support to centralized facilities and networks, training contracts, training grants, courses, consultations with national experts, organization of study group meetings, participation in seminars and symposia, and publications. The Commission's participation may range from about 50 per cent in the case of cost-shared contracts and may reach 100 per cent in some cases.

Participants may be research institutions, universities, industrial enterprises or combinations of them, located in EEC Member States or in certain non-EEC countries. Projects must be carried out by participants from more than one country and include at least one participant from one Member State. (Source: Biotechnology Bulletin, Vol. 7, No. 7, August 1988)

Draft bio-regulations published

The official texts of three draft directives which are designed to help create an EEC regulatory framework for biotechnology have been published. They cover the contained use and deliberate release of recombinant organisms (Official Journal C198, Vol. 31, 28 July 1988) and the protection of workers exposed to biological agents (Official Journal C150, Vol. 31, 8 June 1988). (Source: Biotechnology Bulletin, Vol. 7, No. 8, September 1988)

A bridge too far

Over-ambitious targets, poor funding, a shortage of staff and a lack of co-operation with industry have all conspired to ensure that the European Community's two major biotechnology research initiatives to date have produced few useful results. This is the conclusion of a report just produced by the Biotechnology Evaluation Panel for the Commission of the European Communities.

At a time when the commission is planning to launch its third major biotechnology initiative, the Biotechnology Research for Industrial Development and Growth in Europe (BRIDGE), the problems which have dogged the two previous programmes were obviously worth looking at in detail.

The Biomolecular Engineering Programme (BEP) lasted four years, ending in 1986, while the Biotechnology Action Programme (BAP) began in 1985 and ends in 1989. Both programmes were designed to promote collaboration between public laboratories, universities and industry. In the event, however, the average size of a project (50,000 ECUS or 33,000 a year) turned out to be "too small to

attract either significant industrial participation or (in some cases) leading academic groups".

Given the need for increasing intra-EEC co-ordination and collaboration in biotechnology in the build-up to the single European market, the Commission clearly has an important role to play. The question raised by this report (Evaluation of BEP and BAP, Report 32, Office for Official Publications of the European Communities) is whether it is still trying to run before it can walk. (Source: Biotechnology Bulletin, Vol. 7, No. 9, October 1988)

EEC announces proposals on biotechnology patent rights

The EEC Commission has published a draft directive on harmonizing legislation over biotechnology patent rights to "increase the certainty of obtaining legal protection by patent for discoveries involving living matter under various forms" and establish an adequate internal market for biotechnology products.

The aims of the directive are to ensure wider legal protection for the various genetic engineering techniques used to modify living organisms and modified living organisms and the more efficient issue of patents covering genetically manipulated products such as micro-organisms, plants and so-called "improved" animals.

Intellectual property in the EEC is governed by the Convention of Paris of 1961 and Convention of Strasbourg of 1963 to which all Member States are party but which were drawn up at a time when biotechnology was barely in existence. Trends in biotechnology since have not been matched by revisions in the two conventions which are in any event interpreted differently by different EEC States.

For example, a European patent covering a biotechnology product and delivered to the German patent office in Munich, could have its validity questioned by Governments which believe that a biotechnology product or process should not be patented.

The EEC Commission argues that such an example is not an isolated one and more legal certainty is required, not least to remove the disadvantages faced by EEC companies in relation to US or Japanese competition which benefits from more protective legislation.

The directive envisages that a patent would also protect the generations emerging from the patented organism throughout its legal existence, i.e. 20 years from the date of registration.

It would not cover plants produced by an already known biotechnology process. The Commission says that the adoption of this directive (the draft has to be approved by the Council of Ministers), will have positive effects on the achievement of the single European market because it will help minimize the legal differences in the protection of intellectual property in biotechnology and genetic engineering between the EEC Member States and will help expand intra-Community biotechnology business.

The possibility of obtaining a patent will be an additional spur to companies to engage in biotechnology measures and will help the industry improve its competitiveness. (Source: Manufacturing Chemist, November 1988)

Australia

Joint venture on algae production

Australian and British scientists are combining to test the potential of a method of rapid production of commercial algae products. A plant at Luton, UK, and another near Melbourne, Australia, are testing a British-developed device called a biocoil photobioreactor.

Algae products, among them beta carotene, essential fatty acids, some forms of protein and food colours, are usually produced in open ponds, hence risk contamination by unwanted airborne organisms or other pollution.

The biocoil photobioreactor, developed by the British company Biotechna, uses a different method in that algae are totally enclosed so that they can be grown in a controlled environment. It consists of thousands of metres of small-bore plastic tubing wrapped around a central tower ensuring far greater exposure to light, which is critical to algae production.

An Australian company, Wallace Biotechna Proprietary, has been testing the biocoil system at Laverton on the outskirts of Melbourne. The plant produced algae far in excess and at a greater rate than had been indicated to date in any available documented evidence of production by conventional methods. The plant is producing one specific type of algae at five g/l doubling its weight every two and a half days, and is currently analysing another 24 species of algae which may be grown in the biocoil photobioreactor. The company planned to have a full-scale commercial plant in operation by July 1989.

Some products to be produced by the new method would be used in food colouring, such as additives for poultry farm food, to produce a stronger yolk colour.

Among priority products would be gammalinolenic acid for use in the reduction of cardiovascular risk factors, alginates for surgical dressings, and decolourized protein. (Source: Manufacturing Chemist, November 1988)

Establishment of a micro-organisms depositary

One of Australia's biotechnology consultative group's recommendations is that a depositary institution in Australia be established as a matter of urgency.

It has recently been announced that the Australian Government Analytical Laboratories (AGAL) would acquire the status of an International Depositary Authority under the Budapest Treaty as from 30 September 1988.

The New South Wales Regional Laboratory of AGAL, located at 1 Suakin Street, Pymble, NSW 2073, will act as the Authority.

AGAL will accept for deposit bacteria, including actinomycetes, yeasts and fungi (other than known human and animal pathogens) that can be preserved without significant change to their properties by the methods of preservation in use (currently freezing and freeze drying). AGAL will not at this time accept for deposit animal, plant, algal and protozoal cultures, cultures of viral, rickettsial and chlamydial agents, micro-organisms prohibited by Australian law, or fastidious

micro-organisms which may require, in the view of the curator, special attention to handling and preparation for storage. Thus it appears that hybridoma cell lines must be deposited overseas.

Further information can be obtained from: Dr. Ken Newton, Australian Government Analytical Laboratories, P.O. Box 385, Pymble, NSW, 2073, Australia. (Source: ABA Bulletin, Vol. 3, No. 5, October 1988)

AMRAD Pharmaceutical announced

AMRAD Corporation Ltd., the commercial arm of Victoria's major research institutes, joined forces with the Australian subsidiary of the world's largest pharmaceutical company, Merck & Co., Inc., in a unique majority Australian-owned joint venture in August.

A new pharmaceutical company, AMRAD Pharmaceuticals Pty. Ltd., will commercialize products of original Australian medical research and co-market certain pharmaceutical products. It will be 55 per cent owned by AMRAD Corporation Ltd. and Merck Sharp & Dohme (Australia) Pty. Limited will hold the remaining equity.

AMRAD Corporation Ltd., is a company established in 1987 by the Victorian Government with some of Australia's premier research institutions. The Walter & Eliza Hall Institute of Medical Research, Fairfield Hospital, Royal Children's Hospital Research Foundation and Murdoch Institute for Research into Birth Defects hold equity in the company. The Victorian Government is a major shareholder of AMRAD Corporation Ltd. (Source: ABA Bulletin, Vol. 3, No. 5, October 1988)

Canada

Regulatory system concerns the focus of biotechnology advisory committee report

A sound regulatory system is vital to development of the biotechnology industry in Canada, according to the report of an advisory committee released by William Winegard, Minister of State (Science and Technology).

The report, prepared by the National Biotechnology Advisory Committee, expresses the concerns of industry about regulation of the products of biotechnology under the new Canadian Environmental Protection Act. It also emphasizes the need for a predictable regulatory climate that furthers industrial development and application of biotechnology products while ensuring the safety of workers and the environment.

In releasing the report, Dr. Winegard reiterated the Government's ongoing support for industry efforts to develop strategic technologies such as biotechnology, information technologies and advanced industrial materials, and acknowledged the legitimacy of concerns about regulatory issues.

"An effective regulatory system for the products of biotechnology is crucial, not only to our researchers and industries, but also for the protection of human health and the environment" he said.

To improve the climate for development of biotechnology, the report recommends that priority be given to: establishing an office within Industry, Science and Technology Canada to co-ordinate information on regulatory issues related to biotechnology; helping companies finance the research and testing needed to meet regulatory requirements for new classes of products; and continuing support for the recently established Expert Subcommittee on Regulations, which provides advice to the Government on this subject.

Entitled "The Regulation of Biotechnology: A Critical Issue for Canadian Industry and Industrial Development", the publication is the third annual report of the National Biotechnology Advisory Committee.

One of the priorities of the newly established Industry, Science and Technology Canada is promoting development, exploitation and application of strategic technologies to improve Canada's international competitiveness. (Source: News Release, 15 February 1989)

New Federal programmes encourage excellence in biotechnology

The new Federal Department of Industry, Science and Technology (ISTC) has identified biotechnology as a strategic technology essential for Canada's competitiveness and future prosperity.

The Government has pledged to support industries to develop, acquire and apply biotechnology in co-operation with the private sector and universities. Firms are encouraged to make alliances and create networks, thereby sharing the costs and risks of accelerating the development and application of technology.

These alliances will undertake pre-competitive R&D or leading edge technology applications, in order to create technological capabilities and position Canadian firms to capture future markets in a myriad of industrial sectors profiting directly from advances in biotechnology.

Technology Application Alliances will fill the "development gap" between research projects and commercial production where government funds, venture capital and bank loans are often not available. Research groups from industry, universities, institutes or government laboratories can be partners in alliances. (Source: Bioscope, Vol. 1, No. 3, Winter 1988)

Exploratory programme in anti-inflammatory field

Rhône-Poulenc Pharma [illegible], a leading Canadian pharmaceutical company, and Allelix Inc. have concluded an agreement to study the role of a natural protein known as Interleukin-6 (IL-6) in inflammation. This work may lead to a new approach to develop novel pharmaceuticals for the treatment of inflammation in disorders such as arthritis. Rhône-Poulenc will fund research and development work by Allelix and its partner, Dr. Jack Gauldie of McMaster University, Hamilton, Ontario.

Rhône-Poulenc has a long tradition of anti-inflammatory research both in France and the United Kingdom which has already yielded internationally known drugs.

Inflammation is a complex biological phenomenon of which a thorough understanding has not yet been attained. Acute or chronic inflammation is present in most, if not all, human disease. Over one third of visits to physician's offices can be attributed to episodes of clinical inflammation. For this

reason, the search to understand and modify the inflammatory response is very active.

Last year, Dr. Gauldie discovered that IL-6, which has been known for some time to be involved in the regulation of blood cells, is also involved in alerting the body to produce a number of other proteins which naturally limit the inflammatory response. Since then Dr. Gauldie has been collaborating with Allelix Biopharmaceuticals to produce IL-6 in quantity to better characterize its effects and mode of action.

Recently, it has been demonstrated that the level of IL-6 is elevated as much as 100 to 1,000-fold in burns and arthritis. While the study of the role of IL-6 is in its infancy, Dr. Gauldie's discovery has opened a new avenue in the search for more effective anti-inflammatory pharmaceuticals. (Source: Company News Release, 8 September 1988)

Joint effort to develop better canola varieties

Three leading Canadian research institutions have announced they will combine expertise to develop technologies used to genetically engineer canola. The joint effort from l'Université Laval, Allelix Agriculture and Agriculture Canada is made possible by a grant from the National Research Council for a three-year project under the Programme for Industry/Laboratory Projects. The project will develop new techniques in molecular transformation and result in canola varieties which can tolerate herbicides and disease-causing fungus.

Canola, as Canada's second most valuable crop, has an annual market value of $1 billion. However, annual losses to weeds and fungal diseases can reach $85-100 million. This co-operative effort will develop improved canola cultivars by isolating genes from organisms where the resistance occurs naturally or chemically synthesizing such genes and then inserting them into canola.

Dr. Guy Bellemare of the Biochemistry Department at l'Université Laval is a renouned expert in plant gene regulation and will collaborate on aspects of the project related to the control of the inserted gene. He became familiar with the canola development at Allelix last year when he did his sabbatical as a visiting research scientist.

Allelix Agriculture develops improved crop seeds and microbial seed treatments using plant breeding, cell biology, molecular biology, and agricultural microbiology. The canola research programme, with 35 scientists and technicians, is believed to be the largest in the world and one of the few which encompasses all types of rapeseed. Canola is a high quality rapeseed used for food and feed and is the third largest source of vegetable oil world wide. It is the most widely planted oilseed in Canada and Europe and is drawing attention in the US. (Source: Company News Release, 23 September 1988)

Flax seed collaboration

Biotechnica Canada and Australia's CSIRO are collaborating to develop a new edible vegetable oil from flaxseed. Under a proposed joint venture the partners will develop varieties of flax which produce oil similar to sunflower or corn oil. By the mid-1990s edible oil flax will be grown on several million acres as an alternative crop to wheat. (Source: European Chemical News, 22 August 1988)

Research target: Osteoporosis treatment

Reversing osteoporosis, a bone-thinning condition that affects one in four women after menopause, is one of the immediate goals of a new research collaboration between Glaxo Canada and Allelix Biopharmaceuticals. According to the Osteoporosis Society of Canada, approximately 800,000 Canadian women have this condition.

The work will be done under a $10 million five year (renewable) agreement with Glaxo Canada to develop new drugs to treat bone disorders. Allelix and Glaxo will share patent rights and Glaxo Canada, the country's second largest pharmaceutical company, will have world-wide marketing rights.

"The work on osteoporosis is part of a larger effort to develop pharmaceuticals from recent discoveries of how bones form, repair themselves and decay, and how cells affecting bone development communicate at the molecular level", says Jacques Lapointe, President and CEO of Glaxo Canada.

Allelix will concentrate on producing some of the known protein factors that affect bone growth, using their own genetically-engineered fungi as mini-factories. Researchers will also apply cell biology, molecular biology and biochemistry to discover and develop new factors that regulate bone growth and repair.

Factors which can accelerate new bone formation would have potential use in orthopaedic, oral and cosmetic surgery. A better understanding of how the body's natural growth and healing processes work would have applications in the treatment of bone cancer, bone malformations, fractures and breaks, as well as osteoporosis, the most prevalent bone disorder.

One of the first projects will be the production by genetic engineering of parathyroid hormone (PTH), which preliminary evidence indicates can reverse osteoporosis.

PTH as produced by the body, is a protein made of a string of 84 amino acids. Most work to date has relied on the first 34 amino acids in the chain, which can be produced by chemical means. Producing the full-length molecule by genetic engineering is the next step becuase only the full molecule is likely to have the desired properties of the natural molecule.

Allelix plans to produce the large quantitites of PTH required in clinical trials, the only way to substantiate the promising early findings, but it will be a year or two before patients can be enrolled. Dr. Richard Bozzato, research manager in the collaborative programme said that "It is a grim reality that even if we were to find the answer today, it could take five to ten years for testing. That underlines the urgent need to advance this research."

A number of other hormones similar to PTH may have equal potential in the treatment of specific bone disorders, he says. One group of researchers will focus on PTH while another will explore known and unknown factors related to bone formation. These factors will also likely be produced by genetic engineering.

An important part of the collaboration is the development of close ties with leading bone researchers across the country. Dr. David Goltzman,

professor and chairman of the Department of Physiology at McGill University, is providing scientific direction. Several of the projects in the research programme involve active participation by other leading academics. (Source: Company News Release, 24 October 1988)

Canada pioneers national screening for Huntington's disease

Scientists in Canada have begun the world's first nationwide screening programme to identify people at risk of developing Huntington's disease. The programme, which began earlier this month, was formally announced in Toronto at the 16th International Congress of Genetics by the project leader, Michael Hayden of the University of British Columbia.

Huntington's disease is an inherited, ultimately fatal, neurological disorder that affects approximately one in 10,000 people in the Western world. Either parent can pass the disease to a child, who has a 50-50 chance of inheriting the defective gene that is responsible for the disease.

Because there is no known cure and because victims of the disease generally do not develop symptoms until middle age, predicting the presence of the Huntington's gene before the onset of symptoms is critical for many people at risk, says Hayden.

If parents know that they carry the gene, they can choose not to have children or to abort affected foetuses. The new programme, based on a pilot scheme that began in 1986, will be open on a voluntary basis to any Canadian who is 18 years of age or older, and who has a parent who either has Huntington's disease or who died from it. All participants must agree to extensive pre- and post-screening counselling to help them understand their test results and to cope emotionally with the findings.

Blood from participants and their close relatives will be collected at 14 genetics clinics across the country. Analyses will be conducted in Vancouver using three established gene markers known as D4S10, D4S62 and D4S95.

Depending upon the amount of useful genetic information available from family members, Hayden predicts the tests could be "99 per cent accurate" in establishing an individual's risk of developing the disease.

Theoretically, if Huntington's disease is caused by a single genetic mutation, and if the mutated gene can be isolated and cloned, detailed family histories and blood samples from relatives will not be required. It should be possible to detect the presence or absence of the defective gene in samples taken solely from the individual at risk. (Source: New Scientist, 22 September 1988)

Biotechnology skills required by the year 2000

A report outlining biotechnology skills requirements of the human health care industry to the turn of the century has been completed on behalf of BIONET by McIntyre Engineering Consultants of Ottawa.

BIONET is a national network of government, academic and industry representatives with common interests in the application of modern biotechnology to the human and animal health care industries.

Based on national industry surveys and interviews with company executives, the report predicts an impending shortage of biotechnology specialists by the year 2000 unless steps are taken to increase the supply of qualified manpower.

By applying different growth rates to the companies surveyed, it was estimated that employment of scientists and engineers would increase threefold by the turn of the century.

The report forecasts a demand exceeding supply for experienced bioprocess engineers, molecular biologists, biochemists, cell and microbiologists, and geneticists.

Human health care biotechnology companies project a demand for employees with specialized skills in biological sciences, especially graduates with bachelor or doctoral degrees.

Strategies are suggested in the report to alleviate the potential shortage including:

- Introducing novel approaches to education and training;
- Improving the level of student/industry interaction;
- Promoting co-operation among companies with similar employment needs;
- Developing in-house corporate training and education programmes.

These strategies address current changes and opportunities and require industrial associations to play a major role in co-ordinating events. The human health care sector has traditionally involved collaboration between universities, teaching hospitals, health care delivery services and product manufacturers, and government educational and health care funding services. (Source: Bioscope, Vol. 1, No. 3, Winter 1988)

Membrane centre of excellence proposed

The University of Ottawa Industrial Membrane Research Institute (IMRI) is a major participant in the proposal for a National Centre of Excellence for membrane separation science and technology. Dr. Srinivasa Sourirajan, the Institute's director, points out that membrane separation processes have broad application in Canada's chemical, biomedical and biotechnology industries.

The proposed network will be centred in Ottawa at IMRI and will include researchers from several universities, government laboratories, and a number of companies. The network will incorpoate the research activities and expertise of over 26 professionals, 25 graduate students and additional people providing technical support. Researchers from universities across the country pledged support for the network.

The Centre of Excellence application was a collaborative effort on behalf of proposal participants and the National Research Council, who provided a number of extremely valuable networking contributions.

The proposed research programme addresses all aspects of synthetic permeation selective membranes and processes. The general objectives are to:

- Advance the fundamental understanding of membrane separation science;
- Identify the parameters which influence the quality and performance of membranes;
- Develop compounds and techniques for the manipulation of these parameters;
- Develop compounds and improved membrane materials;
- Establish definitive and empirical relationships between membrane preparation parameters, membrane morphologies and membrane materials, membrane separation processes, and applications.

(Source: Bioscope, Vol. 1, No. 3, Winter 1988)

Ottawa bioresearch data base completed

The Ottawa-Carleton Biotechnology Business Development Initiative (OCBBDI) has compiled a bioresearch data base for Ottawa-Carleton to showcase the region's expertise. The computer data base will be updated regularly to reflect new researchers and capabilities in the region.

Approximately 260 principal investigators, laboratory heads, and in some cases, research directors from nine biotechnology and bioscience organizations in Ottawa-Carleton are listed in the 1988 version.

Listings are categorized into almost 50 research specialities, and each of these researches are listed alphabetically by organization and department. The specialities range from analytical chemistry, animal health and cardiology, to molecular biophysics, soil microbiology and X-ray crystallography. (Source: Bioscope, Vol. 1, No. 3, Winter 1988)

China

Biotechnology is key in national reforms

As China defines its niche in a capitalist world, reforms continue on all levels, including science and technology. With a population of one billion, China needs the products that can come from biotechnology - crops with improved yields and resistance to adverse environmental conditions, higher-quality livestock, animal health care products, new antibiotics, diagnostics, vaccines and cures for "malignant diseases of high influence".

This need is so pressing, in fact, that the Chinese Government - now in its seventh five-year plan - has set biotechnology at the top of its priority list. The main objective is to improve the population's health by the 21st century. To achieve this, the State Science and Technology Commission (SSTC) has essentially demanded that research scientists and their institutes link upstream basic science with downstream industrial production. The Government has even encouraged contractual arrangements between individual institutes and Chinese or foreign enterprises to make products and earn profits.

To co-ordinate the biotechnology activities of Chinese Academy of Sciences (CAS) research institutes, the Ministries of Public Health and Agriculture, and other government organs, SSTC established the National Centre for Biotechnology Development in 1983. The Centre also helps the State Council set general policy on biotechnology and promote international co-operation. Along with joint R&D efforts, training courses, exchange of scientific information, technology transfer, and joint ventures, such international co-operation will promote China's move towards maturity in biotechnology R&D.

For all their positive aspects, however, training and research collaborations with foreign universities and corporations still have drawbacks. For one thing, the Chinese patent and copyright system falls short of the coverage and reliability most foreigners have come to expect. Officials are much less enthusiastic about academic ties than industrial ones: Chinese students, once abroad, often stay there; if they do return to their research institutes, it is difficult to reintegrate them into the system.

China's biotechnology showpiece is intended to be the Shanghai Centre of Biotechnology. Still under construction (like the rest of China), the Centre's physical facilities - including a pilot plant - may be finished by mid-1989. The Centre is designed to provide that desperately needed "bridge" between basic and applied science, between research and production.

But establishing that link is one of the most monumental tasks the Chinese face. And they fully realize the enormity of the problem. For one thing, they have limited expertise in scale-up or downstream processing. For another, they lack trained personnel, especially R&D engineers. Thus, one function of the Shanghai Centre of Biotechnology is to serve as an information and training centre open to both Chinese and foreign scientists. In fact they have already reached an agreement with the US National Academy of Sciences for a series of co-operative programmes.

Although many of the institutes possess sophisticated equipment, the Chinese must import many of the materials and reagents needed to use such equipment.

Despite these difficulties, Chinese scientists have made considerable progress in genetic engineering over the past five years: in health care this includes hepatitis B vaccine, K88-K99 vaccine for acute diarrhoea in piglets, penicillin acylase, human insulin, interferon, interleukin-2, growth hormones, atrial peptides, and monoclonals for hepatoma, lung cancer, and neuroactive peptides. Although most developments are still at the research stage, several products are now in clinical trials, and a first generation hepatitis B vaccine is already available. (Source: Bio/Technology, Vol. 6, August 1988)

Federal Republic of Germany

Biotechnology law may force research abroad

The Federal Republic of Germany's enthusiasm for environmental controls may force the nation's chemical firms to site their R&D activities elsewhere in the world.

Over 50 per cent of biotechnology research by FRG firms is conducted abroad, notably in Japan and the US, according to RauCon Biotechnology Consultants (Dielheim). Federal safety regulations may make it more difficult and expensive to use genetically engineered organisms for industrial purposes in the FRG than elsewhere in western Europe. Industrial and government biotechnology R&D exceeded $600 million in 1987, an increase of 30 per cent over 1985. Government biotechnology research subsidies have risen to $135 million in 1988 as the country attempts to catch up to the US. FRG firms have attempted to catch up by forging research links to US companies or universities. Some 67 per cent of the population has reservations about genetic engineering, and the Green Party has called for abandonment of genetic engineering. Public opinion has led to a difficult permitting process. Some firms have therefore moved their biotechnology operations to the US. Although about ten biotechnology products have been developed in the FRG, only tPA is actually produced there.

BASF has plans to build a DM 130 million ($69.5 million) biotechnology research centre but the new law, which came into operation on 1 September 1988, has forced the company to rethink its plans. BASF was planning to site the new facility in Ludwigshafen but is now considering sites in other countries. A company spokesman said: "The first choice is the US with the UK the second choice." (See article under USA in this section of the Monitor)

The chemical major is at an advanced stage with two biotechnology derived pharmaceuticals. BASF is developing tumour necrosis factor and a second generation tissue plasminogen activator. The BASF board will make its final decision at the end of the year.

Environmentalists in the FRG are mobilizing to appeal against the approval awarded to Invitron at the eleventh hour on 31 August, before the new rules came into effect. Opponents of the planned Invitron facility claim that they will use every legal means possible to stop construction.

Hoechst has also found its gene-splicing ambitions thwarted by environmentalist pressure. Plans for a plant to produce gene-spliced insulin have been disrupted for almost two years now.

Each time the company receives approval from the Hesse authorities, local opponents submit objections. The most recent involves objections from a coalition of Greens, Communists, the German Peace Union, the German Association for Nature Protection and Höchster Schnüffler und Maagucker.

Behring, a division of Hoechst, is also facing trouble from environmentalist groups. The Marburg-based concern is applying for permission for a facility to produce erythropoietin using genetically engineered mouse cells. Under the new regulations, amending the federal law on emissions, public participation in the licensing procedure is mandatory. (Source: Chemical Week, 10 August 1988 and European Chemical News, 26 September 1988)

Researchers win US patent for pollution detection system

Plant protoplasts immobilized in a matrix of calcium alginate or lanthanum alginate are the heart of an environmental pollution detection system developed by the FRG's Kernforschungsanlage GmbH. After the protoplasts have been exposed to a pollutant, it can be detected by measuring evolution of ethane or blocking of ribulose-diphosphate-carboxylase. The protoplasts can be made up either in the form of spherical particles or of ribbons. The system has received a US patent. (Source: Biotechnology Bulletin, Vol. 7, No. 8, September 1988)

Europe fumbles towards agreement on embryo research

European scientists, lawyers and theologians met in Mainz, for the first international bioethics conference on human embryos and research. The European Commission initiated the conference to promote agreement on guidelines for research on human embryos in Europe.

For the FRG research on the human embryo has become a pressing political issue. The federal parliament is expected to pass legislation this session that would ban any research on human embryos. Such legislation would put the nation at odds with other countries in the EEC.

Albin Eser, the director of the Max Planck Institute for Foreign and International Criminal Law in Freiburg, defended strict legislation and insisted that the price of modern reproductive medicine was "first and foremost, the victimization of those embryos that need to be 'used up' for the development and investigation of in-vitro fertilization".

Accordiang to Eser, embryos that are left over after artificial insemination are subject to protection under the FRG Constitution. "A legal standpoint", he says, "gives an embryo the right to personhood and protection under the Constitution". (Extracted from New Scientist, 19 November 1988)

Finland

Microbiological treatment system for organic radioactive waste

The system, including a 38 m3 bioreactor is now being planned for Loviisa Nuclear Plant, Finland. The system including all auxiliary components will need some 600 m3 of room volume. Provision is made for the second bioreactor which will need an additional volume of 200 m3. There must be water and normal electricity connections in the room where the system is operated.

The first bioreactor is planned for wastes such as:

	(Weight %)
Paper	63.9
Boards	7.3
Plastics	6.7
Wood	4.1
Cloth	17.7
Others	0.3

It is estimated that the portion of the easily decomposable material is 90 per cent. Laboratory and pilot plant tests to decompose the waste have been finished.

Spent ion exchange resins will be handled in the second bioreactor. Laboratory tests were started in 1986 with inactive resins and in 1987 with active resins.

Before taking the waste into the microbiological treatment system, the waste is categorized and stored separately. Depending on the waste type, several pretreatment systems can be utilized. All waste is torn up before feeding with the recirculated water in the bioreactor.

In the bioreactor, the lag time is wholly dependable on the composition of the waste. The pilot-plant tests performed gave lag times from 7 to 10 days for the waste types presented above. When decomposing the waste, essential micro and macro nutrients are added. In addition to this, stabilizers are used.

The output product contains inorganic material (ash), dried bacteria mass (dried soil) and some amount of undegradable organic material. No pathogenic bacteria exist in the output product. The reduction factor for the weight of the waste is between 10 and 20. The volume of the dried output product is less than 10 per cent of the volume of the corresponding waste when packed into steel drums.

The output product is periodically taken out of the bioreactor. The activity level of the waste and the amount of undecomposable material are the main factors affecting the length of the period. The dregs are settled on the bottom of the clarifier and water is recirculated. The dregs are collected into containers and dried to the form of hard mass. Solidifying of wet slurry with cement is possible.

The gas production of the system can vary from 0.4 m3/kg TS (Total Solid) to 1.9 m3/kg TS. The production rate depends on the quality of the input material. The gas from the pilot-plant consists of 50 to 80 per cent of methane 20 to 50 per cent of carbon dioxide, and minor amounts of nitrogen and hydrogen sulfide. The gas produced can be burned. No release of radioactive substances with the gas was measured in the pilot-plant experiment.

The system cannot handle metal and glass. Traditionally undecomposable plastics can be pretreated and decomposed.

The system can be constructed so as to be operated manually or fully automatically. The monitoring of the process depends on the selected level of automatization. The manual system needs a whole-time operator, whereas automatization reduces the need of manpower.

The system, IVO Mic-Treat, can substitute, for example, for incineration or supercompaction in the management of organic waste. The system is technically uncomplicated, inexpensive and does not cause radioactive releases. Further information may be obtained from Mr. Esko Tusa, , P.O. Box 112, SF-01601 Vantaa, Finland. (Source MIRCEN Anaerobic Digestion, August 1988)

An advance in protein engineering

The Biotechnical Laboratory of the Technical Research Centre of Finland has developed a novel way of developing new enzymes and other proteins.

The new technique involves producing a pool of mutants from which those with suitable properties can be identified and selected.

The new method for the generation of novel enzymes and proteins for industry and medicine starts with the production of a library of all the possible mutants in a gene. This corresponds to the natural occurrence of mutants over a long period of time.

The library of mutants is then expressed in a suitable host organism, where the mutant genes produce their modified protein products. The process of natural selection is replaced by sophisticated screening systems, and the best proteins and corresponding mutants are picked up for further testing.

The new method has advantages over those that have been used in the past. It is comprehensive in that it produces a complete set of all the possible single base mutants in the gene. Moreover, proteins with the desired properties can be developed even before their structure is well known.

The new method is already being used to develop industrially and medically significant proteins, such as new alpha amylase enzymes. Patents covering the method have been applied for in the United States and in other countries. (Source: VTT Newsletter, February 1988)

France

French drug stunts the progress of AIDS

A new drug for treating people with the human immunodeficiency virus (HIV) appears to delay the onset of AIDS. Populatations of T cells, which decline as someone progresses towards AIDS, increased in recipients of the drug.

Ditiocarb (trade name: Imuthiol) is taken orally and seems to have only minor side effects. Institut Merieux, a French company makes ditiocarb.

The study involved more than 80 patients infected with HIV. For the first 16 weeks, half of the patients received ditiocarb, the others a placebo. During the second 16 weeks, the drugs were reversed.

None of the patients in the group that received ditiocarb for the first 16 weeks went on to develop AIDS. Three in the placebo group did.

Doctors scored the patients' condition after 16 weeks as improved, stable or worse. More than 42 per cent of patients who received the drug had improved, compared with only 5 per cent in the placebo group.

The mode of action of the drug is not clear. Experiments have shown that ditiocarb encourages the formation of mature T cells, but because the drug binds to heavy metals, it might also inhibit viral enzymes dependent on copper. The researchers suggest that this property might affect a protein produced by HIV. Without it, the virus can make no other proteins. (Source: New Scientist, 29 September 1988)

Researchers find protein switch

French scientists at Inserm and CNRS have developed a potenitally important system for the industrial production of proteins. Pierre Chambon and his colleagues at the French institutes have grafted the human genetic blueprint for an oestrogen receptor into yeast's genetic machinery.

In human beings this receptor when in contact with the female development hormone oestrogen, is responsible for switching on protein synthesis.

Chambon and his colleagues have demonstrated that when yeast genes are linked to the receptor they too are switched on in the presence of oestrogen.

Biotechnology firms already employ yeast to make recombinant proteins. The yeast is more closely related to higher animals than bacteria and makes proteins in a similar way. Chambon believes the receptor system could be used commercially as the yeast would not make the desired proteins unless oestrogen was present. (Source: European Chemical News, 31 October 1988)

New biotechnology research centre

French chemicals major Rhône-Poulenc (Paris) has inaugurated its new $32 million biotechnology research centre at Vitry, south of Paris. Pierre-Etienne Bost, research director of Rhône-Poulenc Santé, the French group's pharmaceutical subsidiary, says the new centre gives Rhône-Poulenc the techniques to start work on new methods of pharmacological targeting, in turn opening the way to tailor-making drugs. The centre will also be working on molecules produced using recombinant DNA techniques and products extracted from plants and micro-organisms. Biochemical process design is also being carried out at the Vitry centre, with work going on industrializing production using a new fermentation route for human albumen, enzymes for use in stereospecific syntheses, as well as improving existing processes for established products like vitamin B_{12} and antibiotics. (Source: Chemical Week, 26 October 1988)

Aid for AIDS in France

Claude Evin, the French health minister, announced that he would triple funds for research on AIDS to $15 million in 1989. A committee to co-ordinate the research, and another to oversee the ethical aspects of AIDS testing and treatment, will come into being. Preventive educational campaigns in 1989 will receive an extra 10 million pounds sterling, and 43 million pounds sterling will go to the care of AIDS patients in hospitals. The cases of AIDS in France are expected to quadruple from 4,874 to around 20,000 by the end of 1989. (Source: New Scientist, 12 November 1988)

Foundation promotes flexibility

Earlier this year, Luc Montagnier, who isolated the AIDS virus five years ago, established the European Federation for AIDS Research (EFAR) in an attempt to counter some of the deficiencies he sees in French support for AIDS research. In particular he hopes that the independence afforded by private funding will complement public funds and provide the flexibility missing in directly State-financed research.

The organization will build upon a collaboration among scientists in several other European countries that has, for the past two years, been paid for out of the $1.1 million Korber Prize donated by a Hamburg physician. EFAR will bring together fundamental researchers, clinicians and pharmaceutical company scientists and executives.

Although the main scientific and clinical input has so far come from France, commercial interest has been shown by a range of companies in both Europe and the United States. One of EFAR's first events, for example, was a workshop held in Paris last month on possible new therapeutic protocols combining antiviral and immunostimulant agents. Sponsored by ViRx Inc. of San Francisco, the meeting's participants included, in addition to research workers and clinicians from many leading French hospitals, representatives from companies such as Bristol-Myers, Roche, Wellcome, Hoechst and Rhône-Poulenc.

Funding for research will be sought from banks and insurance companies, as well as from both national and international government agencies. EFAR will subsequently be able to subcontract research work to groups in France and elsewhere. (Source: Science, D. Dickson, Vol. 242, p. 509, 28 October 1988. Copyright 1988 by the AAAS)

Italy

Biomedical institute established in Bari

The University of Bari is founding an international biomedical institute to be located near Brindisi. The institute will focus research on (1) identification and mechanisms of macromolecules influencing cellular growth, differentiation, transformation and defense: (2) biomembranes; and (3) activities of molecules of pharmacological interest. (Source European Science News, March 1988)

Cell proliferation protein discovered in Milan

Researchers in Milan have isolated a protein considered to be responsible for the abnormal proliferation of cells, causing tumours of the hypophysis. The protein acts on cyclic adenosine monophosphate (CAMP), one of the factors regulating cell proliferation, producing abnormal CAMP activity and continuous cell proliferation. This "Q" class protein has been isolated only in hypophysis tumours, but the researchers do not exclude its presence in other tumours. (Source: European Science News, March 1988)

Erbamont builds "Research City"

Erbamont, a company of the Montedison Group, is building a research city at Nerviano (near Milan) which will focus on pharmaceutics and biotechnology. When completed in 1990, the centre will employ 1,000 researchers working to develop new drugs for oncology, cardiovascular diseases, immunology, anti-infective drugs and drugs for the central nervous system. In 1988, Erbamont will spend 200 billion lire (about $164 million) for research. (Source: European Science News, March 1988)

Natural substance acts as cerebral antidepressant

Professor Erminio Costa recently identified a peptide in mammal brains that links up with the same receptors that are bound by traditional antidepressant drugs called diazepam binding inhibitor (DBI). Researchers hope the peptide will lead to new types of natural antidepressants, thereby avoiding the use of substances considered to be alien to complex cerebral chemistry. (Source: European Science News, March 1988)

Japan

Japan keeps its options open on genome sequencing project

Japan's role in world-wide efforts to sequence the human genome remains undecided in a report to the Science and Technology Agency. Perhaps for

political reasons, given that the powerful Ministry of Finance has yet to back the project, all possibilities are left open.

The 40-page report, compiled by the Council for Aeronautics, Electronics and Other Advanced Technologies, covers all aspects of human genome analysis, including chromosome sorting, gene mapping and sequencing, automation of analytical procedures, cell banks, data processing and storage and international collaboration. But apart from stressing the need for automated analytical techniques and the importance of human genome analysis for diagnosis and treatment of genetic disease. the report gives no indication of the future course Japan is likely to take.

For example, no indication is given of whether mapping or sequencing of genes should be stressed, although this is a major point of contention among proponents of the human genome project in the West. The report says it is very important to consider the possibility of setting up one large-scale facility to carry out the analysis, but it then calls for careful examination of whether one or several small facilities should be established. The council report makes a vague call for international co-operation. The Science and Technology Agency opened a window of communication with the US Department of Energy last year. (Extracted from Nature, Vol. 33L, July 1988)

Specialized mice developed for cancer research

Mice that possess special genes for a cancer-inhibiting enzyme have been developed by the Japan Cancer Research Institute. The objective is to perfect an enzyme that can be used in human cancer patients to repair cells damaged by the disease. Cancer researchers around the world have in recent years concentrated more on improving the body's regenerative capabilities. The enzyme gene was derived from colon bacteria by another group of Japanese researchers. The Japan Cancer Research Institute group then successfully injected the isolated gene into fertilized mouse eggs and implanted those eggs into a host mouse. (Extracted from Asian Wall Street Journal, 19 September 1988)

Blood coagulant research

Blood plasma derivatives produced using recombinant DNA technology could be developed by the Japan Health Science Foundation (JHSF), which will attempt to co-ordinate government and private research. Blood coagulants will be a first focus of the research. JHSF will also promote research into neurosciences.

The Ministry of Health and Welfare has also announced its allocation for AIDS-related research in FY 1989. The allocation for anti-AIDS drugs will rise from Y300 million in FY 1988 to Y430 million in FY 1989. the budget for AIDS research will rise from Y200 million to Y250 million, and project support will rise from Y260 million to Y390 million. Another Y70 million will be spent on developing technology for making blood derivatives without using blood as a raw material. (Extracted from Japan Chemicals, 29 September 1988)

Korea, Republic of

More firms enter bioengineering

As development and commercialization of bio engineering related technology become more active, industries that manufacture devices and facilities needed in bio-engineering and associated plant design services are becoming popular and more firms are entering such industries.

According to an industry source, Koryo Synthetic Fibers, Korea Engineering, Iron Manufacturing Chemistry [Chechol Hwahak], and Korea Enzyme Machinery [Han'guk Hyosogi] are already participating in facilities manufacturing and plant design services related to bio-engineering.

Koryo Synthetic Fibers has a technical co-operation programme with Hitachi of Japan for bio-plant engineering technology and is already involved in the bio-engineering facility industry.

A consortium was formed by Koryo Synthetic Fibers, which will provide expertise on plant construction; Hitachi, which will contribute engineering expertise; and by the Korea Chemistry Research Institute, which will provide bio-engineering software. The consortium is currently building a pilot plant.

Korea Engineering, an engineering service firm, is considering participating in the bio-engineering facility industry, using its accumulated expertise. Using its subsidiary research laboratory, Korea Engineering has chosen the development of design technology for bio-engineering plants as an important goal and is surveying appropriate development topics.

Iron Manufacturing Chemistry has developed a waste water processing microbe column that uses microbes and is testing the column now. It is planning to commercialize a waste water processing system that uses such microbes.

Korea Enzyme Machinery is fully participating in the bio-engineering facility industry by developing and commercializing a domestically produced cultivating facility. Hyundai Facilities and Kumho Petrochemical are also joining the bio-engineering facility industry. (Source: Maeil Kyongje Shinmun, 2 March 1988)

Technology acquisition from overseas Koreans and laboratories

Domestic firms in genetic engineering are actively seeking consultation and exchange of technical information with overseas Korean researchers and well-known research laboratories, thus opening new dimensions in international co-operation between industries and academic institutions.

According to industry sources, this type of co-operation and exchange is actively promoted to effectively obtain technical consultation through overseas Korean scientists, collect information on state-of-the-art technology, and conduct joint research.

Green Cross is consulting a research group led by Dr. Wu Che at the New York Hematology Center on formulating hematic drugs, such as a vaccine for hepatitis. The Center is also co-operating on clinical tests.

Also, Dr. Chillyong Kang of the University of Ottawa in Canada is providing technical consultation on the AIDS virus and diagnostic reagents for AIDS. The Alpha Omega Laboratory (a Korean subsidiary) incorporated in the United States is also playing an important role in collecting advanced technology information.

Lucky Biotech, a subsidary of Lucky [Gold Star] in the United States, is maintaining close ties with Cairo Company. Lucky Biotech is also using Dr. Songho Kim of the University of California as a technical consultant.

Yujin Tech, a subsidiary of Cheil Sugar in the United States, is acting as a window for advanced technology information and technical exchange for the parent company. Donga Pharmaceutical has arranged to have Otsuka University of Japan and the Sloan Kettering Center of the United States provide technical training and consultation.

Yuhan Corporation maintains a co-operative programme with Dr. Sangsin Pak of the United States National Institute of Health; Pacific Chemical Industrial has a co-operative programme with the Institute of Physical and Chemical Research [Riken] of Japan.

Other co-operative programmes for training and technical consultation include: the Doosan Group research laboratory with Quos [phonetic translation] of the United States; Chong Kun Dang with Hokuri [phonetic translation] University and Kyoto University of Japan; and Miwon with MIT of the United States. (Source: Maeil Kyongje Shinmun, 26 March 1988)

Genetic engineering patent applications increase

Patent applications in genetic engineering have greatly increased during the past few years. Most of these applications concern mass production technologies for products such as hepatitis vaccines and interferon, indicating that technology development in genetic engineering is maturing.

According to an announcement by the Patent Office on 16 March, patent applications in genetic engineering by Koreans began to increase in 1985 - reaching 25 applications in 1985, 45 applications in 1986, and 37 [577] applications in 1987, an annual increase of 31 per cent on the average.

This trend of increasing applications indicates that the R&D investments made in the early 1980s in genetic engineering are now beginning to pay off in the form of recent patent applications.

In particular, early patent applications in genetic engineering were mostly concerned with restricting enzymes and simple gene manipulations. Recent patent applications, however, mostly concern mass production of products and techniques to manufacture therapeutic agents or antibodies using genetic engineering, indicating that the genetic engineering technology is progressing.

Patent applications by foreigners mostly concern basic technology, while those by Koreans tend to be improvements on existing inventions, such as increased product yield. (Source: Maeil Kyongje Shinmun, 16 March 1988)

The Netherlands

Gist-Brocades links with Mogen

Gist-Brocades is moving back into the plant biotechnology field by forming links with the Leiden, Netherlands-based agrobiotechnology company Mogen International. Both firms have agreed to work together on plant improvement technologies. Mogen has the gene-splicing technology while Gist-Brocades possesses the rights to commercialize a number of significant patents.

These patents were originally registered by Professor Schilperoort, who recently headed Greengene, a joint venture between Gist-Brocades and several institutional investors, but the Dutch company recently withdrew from this joint venture. Gist-Brocades intends to take a stake in Mogen but would not reveal how large the investment will be. (Source: European Chemical News, 12 September 1988)

United Kingdom

Biotechnology a policy pawn

The Biotechnology Directorate of the UK Science and Engineering Research Council (SERC), whose future is already under review, now seems to have had the misfortune of becoming a pawn in a much larger game in British science policy. The end result could be the formation of a new biological research council responsible for all non-medical biological research, including that currently funded by SERC. Ironically, an independent - and simultaneous - evaluation of the Biotechnology Directorate has strongly recommended that it should stay within the SERC.

The evaluation, prepared by Jacqueline Senker and Margaret Sharp of the University of Sussex's Science Policy Unit, also concludes that it would be a bad mistake to wind up the seven-year-old Directorate: instead, the Directorate should build on its past achievements, while changing its ways slightly.

Among its recommendations for the future, the report suggests that more efforts be made to persuade small firms to partake in the schemes promoted by the directorate and - controversially - that foreign firms be allowed to participate. But the report warns that the future of UK biotechnology is seriously endangered by the scarcity of good quality post-doctoral recruits. It urges SERC to take up this "crisis" immediately with the University Grants Committee - which provides UK universities with internal funds for research. Recent monetary cutbacks are forcing the committee to evaluate the relative merits of different universities as a prelude to supporting only the best. Preliminary work on this painful process is about to get under way.

The outcome, which will probably be to concentrate research in a few universities, has already been endorsed in a general way by the Advisory Board for the Research Councils (ABRC), which represents the interests of all five existing research councils.

More recently, ABRC has encountered problems within its own ranks on a different matter concerning biological research. The debate centres on whether it continues to make more sense to have biological research scattered among the research councils rather than concentrated in a single council. Strong differences of opinion have emerged. SERC argues for the status quo, whereas the Medical Research Council (MRC) would like to take on SERC's biology - including biotechnology. On the other hand, the National Environment Research Council, which funds the genetic manipulation of viruses for use in biological control, favours its own fusion with the Agricultural and Food Research Council, which in turn argues for the foundation of a new research council for all non-medical biology.

That the current situation creates schisms in biotechnology is illustrated by the fact that, although MRC supports some of the best basic

research on protein engineering (largely within its own institutes), it is SERC's Biotechnology Directorate that runs the Protein Engineering Club, which brings together several universities and companies. SERC considers itself uniquely able to bring together biology, chemistry, and engineering for the benefit of biotechnology, as well as being better at solving the manpower problem than the other research councils. MRC, under a new director with many years' experience in industry, clearly feels it should take over minority interests in biolcgy and belatedly provide the lead in biotechnology.

In a recent policy document "SERC Biotechnology Support 1980-2000", the directorate's management committee argues for a continuation of the present arrangement in expanded form. (Source: Bio/Technology, Vol. 6, August 1988)

SERC publishes revised strategy for core science

At a time of continuing concern about the erosion of Britain's scientific research base, a new edition of Strategy for Core Science, first published in 1984, has been produced by the Science and Engineering Research Council (SERC). The SERC Science Board has revised and updated its strategy in the light of trends in its funding, the evolution of its programme, developments within science and the evolving policy of the Council, the Advisory Board for the Research Councils (ABRC) and the Government.

The largest single component in the Science Board funding is made up of research grants, including both responsive grants and strategic initiatives. At present, the Board spends 32 per cent of its budget on grants and this fraction will rise to 40 per cent over the next three years. The Board has decided that, of its grant funds, 50 per cent should be used for responsive funding and the remaining 50 per cent directed to a number of co-ordinated strategic research initiatives.

An important component of the Board's strategy has been the identification of research themes within the areas covered by its remit. This approach has allowed subject committees to study trends in research grant funding; to identify areas of research requiring stimulation; to establish interdisciplinary linkages; and to provide "earmarked" funds and studentships against special activities.

Strategic research initiatives continue to be an important part of the SERC's strategy. The present initiatives can be grouped under three main headings: materials and related technologies; mathematics, computational and cognitive science; and molecular sciences and biotechnology. The Board is involved with four LINK programmes and is developing several more.

The Board continues to endorse the principle of scientific selectivity and concentration being achieved through peer review. The SERC Council has decided to encourage the greater consolidation of research programmes, to be supported through the "rolling grant" mechanism.

Beyond the normal scope of a conventional "rolling grant" lies the Interdisciplinary Research Centre (IRC). This is a substantial multidisciplinary research group based at a higher education institute, often involving academics in nearby institutions and having interactions with industry.

Details from: SERC, Polaris House, North Star Avenue, Swindon, Wilts. SN2 1ET. (Source: Biotechnology Bulletin, Vol. 7, No. 9, October 1988)

SERC launches new "LINK" biotransformations centre

A new LINK Biotransformations Club, involving ten UK-based companies and three universities (Kent, Warwick and Exeter) has been set up as part of the Science and Engineering Research Council's drive for a world lead in the use of enzymes in industrial chemistry.

Enzymes have become amazingly efficient at their job over millions of years of evolution. That efficiency, says SERC, is a natural resource as real as coal or oil - but renewable, potentially inexhaustible and capable of further improvement through genetic engineering.

The new Biotransformations Club is part of the Government's Biotransformations LINK programme, which aims to encourage collaboration between industry and universities. It is being funded by SERC (through its Biotechnology Directorate), by the Department of Trade and Industry (through its Biotechnology Unit) and by industry.

So far, ten companies are involved: Glaxo, Beecham, ICI, Quest International, BP, Shell, Courtaulds, Enzymatix, International Bio-Synthetics and Pfizer. Work already in progress is searching for novel enzymes to perform key steps in the sequence of reactions which ultimately produce products such as pharmaceuticals and plastics. The key is to find the right enzyme to do the job on the scale which industry requires. Genetic engineering enables the participating scientists to build up a better understanding of the way particular enzymes work - and of ways in which their performance can be improved. (Source: Biotechnology Bulletin, Vol. 7, No. 10, November 1988)

Agricultural and food research cuts feared

Up to 33 million pounds sterling per annum could be cut from public funding of agricultural and food R&D if a recent government review is implemented, according to the Agricultural and Food Research Council (AFRC). The review has identified areas of work totalling 33 million pounds sterling a year in the programmes funded by the Ministry of Agriculture, Fisheries and Food (MAFF) and the other agricultural departments which are judged to be close to the market place and thus more appropriately funded by industry. The implications for the AFRC are thought to be serious.

A quarter of the commissioned research MAFF places with the AFRC has been deemed to be "near market", representing a potential loss of almost 11 million pounds a year. All AFRC institutes are likely to be affected, but a withdrawal of MAFF funding on this scale would hit the Institute of Horticultural Research, the Institute of Food Research and the Institute of Grassland and Animal Production especially hard. (Source: Biotechnology Bulletin, Vol. 7, No. 10, November 1988)

Committee to screen bio-imports

A new advisory committee established by the Department of the Environment (DoE), the Interim Advisory Committee on Introductions, will advise the DoE on the ecological implications of proposed imports of organisms to the UK, i.e. whether or not they have been genetically manipulated. The

committee's status is "interim" because the Government is still awaiting the conclusions of the Royal Commission on Environmental Pollution, whose report on the deliberate release of recombinant organisms is due for publication early in 1989. (Source: Biotechnology Bulletin, Vol. 7, No. 8, September 1988)

New effluent processing clubs

Companies in the specialized organics sector are finding it increasingly difficult to treat and dispose of effluents generated during chemicals production. To help them, the National Economic Development Office (NEDO) has linked up with the Laboratory of the Government Chemist (LGC) to form the Industry Waterman Club.

The Club has two main objectives: (1) to raise company awareness of the tightening environmental constraints on their operations; and (2) to identify and commission public sector research and development projects designed to improve effluent treatment technology. State-of-the-art reports will focus on the use of technologies such as anaerobic digestion for organic wastes, electrolytic detoxification and the chromatographic identification of pollutants.

Full membership is open to any European chemical firm, with a fee of 4,000 pounds for firms with a turnover in excess of 25 million pounds and of 2,000 pounds for firms with a turnover below that figure. Associate membership is available to firms with a turnover of less than 1 million pounds a year at 750 pounds a year, but excludes participation in the Industry Waterman P&D programmes. Details from: Sue Armfield, Biotechnology Research Group, Laboratory of the Government Chemist, Cornwall House, Waterloo Road, London SE1 8XY.

Representatives of 30 industrial companies met at Harwell in November to launch the Effluent Processing Club (EPC). The Club combines the experience, technologies and services of Harwell and the WRC to provide companies with quick and cost-effective solutions to liquid effluent problems.

The EPC is open to companies worldwide and aims to help members make best use of available technology and to identify where today's technology is inadequate to meet strict environmental standards. By identifying these gaps, the EPC will define research needs through separately funded groups of members and develop industrially relevant research programmes.

The Club will provide members with a comprehensive Manual of Effluent Processing Technology. This will comprise 12 volumes consisting of in-depth reviews of the science and engineering of processes used to treat liquid wastes. Also to be included are a practical guide to process selection and a review of environmental legislation.

Technologies to be covered in the Manual will include common processes such as biological degradation of organic wastes and the neutralization/precipitation of inorganic effluents. Also to be included are more specialized processes such as adsorption and ion exchange for heavy metal removal, and chemical or catalytic processes for the destruction of toxic compounds.

The EPC will also keep members abreast of novel and highly promising techniques like ultrasonic irradiation, membranes and electrochemical processes. The cost of membership is 5,000 pounds sterling a year. Details from: Dr. Ewan Macdonald, Effluent Processing Club, Process Engineering Research Centre, B488.T6, Harwell Laboratory, Oxfordshire OX11 0RA. (Source: Biotechnology Bulletin, Vol. 7, No. 8, September 1988 and Vol. 7, No.10, November 1988)

National Centre for School Biotechnology

Formed in 1985 and based in the University of Reading's Department of Microbiology, the Centre aims to promote the teaching of biotechnology in schools. Sponsors include the Department of Trade and Industry, the Royal Society, the University Grants Committee and the Manpower Services Commission. The project is co-ordinated by Dr. Paul Wymer, who edits the NCSB newsletter and will also be the editor of a new journal, Biotechnology Education, to be published in 1989 by Pergamon. Details from: Dr. Paul Wymer, NCSB, Department of Microbiology, University of Reading, Reading, Berks. RG3 1JL. (Source: Biotechnology Bulletin, Vol. 7, No.10, November 1988)

New laboratory established to fight cervical cancer

A major cancer charity has opened a new laboratory in Britain as part of a drive to develop a vaccine against cancer of the cervix. Worldwide, an estimated 300,000 to 500,000 women develop cervical cancer each year.

The scientists involved say that it may be some years before a candidate vaccine will be available. The charity involved, the Imperial Cancer Research Fund, is one of Britain's biggest cancer charities. The laboratory, in Cambridge, will house the fund's Tumour Virus Group, which will work closely with the university's department of pathology.

Researchers involved will investigate how cervical cancer develops. The main theory is that some strains of the human papilloma virus (HPV), when they infect cervical cells, eventually cause cancer. Other strains cause a variety of warts, including those that occur on the external genitals.

Initial studies have already shown that the tumours grow more slowly in animals earlier "immunized" with transformed cells that have been made harmless by irradiation. In future, the researchers plan to prime mice with vaccinia virus (which induces immunity to smallpox in humans) that has been genetically modified to carry genes from HPV.

It may also be possible to treat women with precancerous changes in their cervices by "turning off" the growth of cells infected by HPV. Research has already identified E7, a protein of HPV, that appears to be important in transforming cells. If E7 is turned off, transformed cells stop growing. It might also be possible to immunize a woman so that her immune system recognizes, attacks and eliminates cells infected with the HPV. (Source: New Scientist, 19 November 1988)

First steps towards a vaccine

Tests on humans of potential components of a vaccine against AIDS may begin in Britain within the next few years. Such studies would be the first

clinical tests to take place as part of the Medical Research Council's direct programme of research into AIDS.

An initial study would probably include about 100 volunteers. Two or three antigens (proteins) from the human immuno-deficiency virus might be tested. It would take two or three years to obtain results. These trials would not be evaluating candidate vaccines, but might be seen as clinical research to see how human beings respond to HIV antigens, and generate critical information vital for further development of vaccines.

One of the antigens which scientists would test would "certainly" be a large part of the envelope protein of the virus, called gp120. The research council has asked the pharmaceuticals company, Wellcome, and the biotechnology company, Celltech, to collaborate in producing this viral protein using genetic engineering.

Another question that remains unanswered is on what kind of population would researchers choose to test a vaccine?

The directed programme has set up a committee to produce technical, practical and ethical guidance on clinical studies of promising viral antigens. There is also a working party specializing in ethical aspects of such trials. (Source: New Scientist, 8 October 1988)

Transgene invests in British firm

Pharmaceutical Proteins, the Edinburgh-based biotechnology concern, has raised 1.2 million pounds ($2 million) to fuel its expansion plans. The original backers of the firm, Prudential Venture Managers, Transatlantic Capital and the Scottish Development Agency, have now been joined by venture capital fund Alan Patricof Associates and the French biotechnology outfit, Transgene.

The company plans to use the additional funds to expand its commercial activities. First products in the firm's portfolio will be alpha 1 antitrypsin, factor VIII and factor IX. These will be produced by farm animals that have been genetically modified and programmed to produce the proteins in their milk. (Extracted from European Chemical News, 12 September 1988)

Crop plan seeks funds

A consortium of two Scottish and one FRG institutes is applying to the Science and Research Directorate General at the EEC for a grant to develop potatoes that can produce commercially important chemicals and drugs. The Scottish Crop Research Institute (SCRI), Paisley College of Technology and the Institut für Genbiologische Forschung have applied for a laboratory twinning grant.

The researchers are planning to conduct more fundamental research into the genetics of the gene responsible for the soluble protein patatin. Scientists at the institutes have already discoverd that the gene possesses variable regions and have sequenced the DNA.

The institutes expect to apply for an EEC Eclair programme at a later stage and hope to attract interest from firms. (Source: European Chemical News, 5 September 1988)

United States of America

Genome pact drafted

The National Institutes of Health (NIH) and the Department of Energy (DOE) have drafted a memorandum of understanding for interagency co-ordination on the genome project, the $3 billion effort to map and sequence the human genome.

The agreement sets up a joint mechanism for receiving outside advice and otherwise provides for communication and co-operation between the two agencies.

The memorandum marks a turning point for the agencies, which have consistently maintained that informal co-operation and co-ordination were sufficient to run the project. Congress, however, worried about accountability and redundancy in this costly effort, has been less convinced and is considering a bill that would set up a formal interagency structure.

Both agencies have been vehemently opposed to legislation. The hope among officials in both agencies is that their memorandum of understanding will remove the incentive for this and other bills.

The brief agreement calls for the creation of a joint scientific advisory group for both agencies that would draw members from the two existing advisory committees: DOE's Health and Environmental Research Advisory Committee and the newly created NIH Program Advisory Committee on the Human Genome. (Source: Science, L. Roberts, Vol. 241, p. 1596, 23 September 1988. Copyright 1988 by the AAAS)

James Watson to head NIH human genome project

The National Institutes of Health (NIH) have announced that Professor James Watson, the director of the Cold Spring Harbor Laboratory, will become associate director of NIH. Watson will head a newly established office that will co-ordinate NIH efforts to map and sequence complex genomes.

The genome office, part of the office of the director, will not distribute research grants, but will instead provide general policy direction, identify neglected research topics and target new technology. Watson has said that he also intends to encourage active investigations into the ethical issues raised by a genetic map of the human genome. Decisions about research grants will continue to fall to the National Institute of General Medical Science.

Watson, who shared the 1962 Nobel Prize for his work with Francis Crick on the structure of DNA, will be a part-time associate director of the OHGR, continuing as director of the Cold Spring Harbor Laboratory in New York. He will advise NIH director James B. Wyngaarden on the direction and co-ordination of the NIH's human genome iniative.

Currently, the NIH has budgeted some $28 million for human genome work for the fiscal year 1989, but Wyngaarden forecasts that the figure will reach $200 million by 1993 or 1994. The total cost of mapping the human genome has been estimated at $3 billion. (Extracted from Nature, Vol. 335, 15 September 1988 and Biotechnology Bulletin, Vol. 7, No. 9, October 1988.

NIH delay first gene transfer

James Wyngaarden, director of the National Institutes of Health (NIH), has decided to defer approving the first human gene transfer experiment. Although the NIH Recombinant DNA Advisory Committee (RAC) approved the experiment at a meeting earlier in October, Wyngaarden decided the protocol be re-evaluated on the basis of "unresolved questions" raised by the RAC's human gene therapy subcommittee and the NIH Institutional Biosafety Committee.

The experiment, proposed by W. French Anderson of the National Heart Lung and Blood Institute and R. Michael Blaese and Steven A. Rosenberg of the National Cancer Institute, involves putting a bacterial antibiotic-resistance gene into human lymphocytes specially selected for their ability to attack cancer tumours.

These "tumour infiltrating lymphocytes" are grown in culture, activated with interleukin-2, and then injected into the patients from whom they were originally obtained. The bacterial gene provides no direct benefit for the patient, but will enable researchers to track how well the lymphocytes reinfiltrate their target tumour.

The gene therapy subcommittee was established to evaluate the details of the Anderson, Blaese and Rosenberg protocol, and at a meeting in July it asked for additional data about the experiment which was submitted in early October.

In addition to the re-review by RAC and its subcommittee, the protocol must also be approved by the institutional review boards of the two NIH institutes involved, and the NIH Institutional Biosafety Committee. (Source, Nature, Vol. 335, 27 October 1988)

BASF plans a laboratory in Boston

BASF Corporation of the FRG has reported that it will build a $45 million biotechnology laboratory and pilot plant facility in the Boston, Mass. area at a site currently being selected.

The installation is expected to be operational by 1991 and should ultimately employ about 230 persons, including 60 scientists. They will concentrate on developing pharmaceuticals for the treatment of cancer and immune diseases.

The new facility will complement BASF's biotechnology research centre in Ludwigshafen, FRG, where the company reports recent developments in processes for vitamin B2 and natural flavours as well as D-lactic acid and TNF. The latter are under development for treatment of certain forms of cancer. (Source: Chemical Manufacturing Reporter, 14 November 1988)

New field-test report

Washington, D.C. Because of "gaps in regulatory coverage", the US General Accounting Office (GAO) recommends that two federal agencies modify current policies for the field-testing of genetically engineered organisms. Meanwhile, by continuing to follow a "prudent" case-by-case approach, agencies can "accumulate experience in evaluating organisms and eventually develop generic regulation", the GAO says in a recently issued report, "Biotechnology: Managing the Risks of Field Testing Genetically Engineered Organisms". The report provides a concise snapshot of deliberate release regulatory dispositions within several key federal agencies. In summarizing risk management policies and procedures for several key federal agencies, it complements a recent Congressional Office of Technology Assessment (OTA) report, "Field Testing Engineered Organisms: Genetic and Ecological Issues".

The GAO report focuses on polices of the US Department of Agriculture (USDA), Food and Drug Administration (FDA), and the Environmental Protection Agency (EPA).

In referring to the Toxic Substances Control Act, the report notes that certain sections of the law provide EPA with "insufficient authority" when evaluating microbes in a "lower risk category". This limitation could be remedied by subjecting all genetically engineered micro-organisms to the category of rules involving either a "premanufacture notice" or a "significant new use".

Officials from EPA say that pending agency rules will address issues raised by the report. For example, the agency expects to implement an earlier proposal to establish local environmental biosafety committees (EBC) for reviewing most proposals; it will also implement a new proposal to require "significant new use notices" before release of altered micro-organisms for commercial use that are not specifically excluded from such treatment. Academic research without "immediate or eventual commercial purpose", for example, will not be subject to such requirements.

"Biotechnology: Managing the Risks of Field Testing Genetically Engineered Organisms", GAO/RCED-88-27, can be obtained from the US GAO, Post Office Box 6015, Gaithersburg, MD 20877. The first five copies are free, with additional copies available for $2.00. (Extracted from Bio/Technology, Vol. 6, August 1988)

Request to test bioengineered organism

Monsanto Company and the US Department of Agriculture's Agricultural Research Service, in co-operation with Washington State University, have requested permission from US Environmental Protection Agency to conduct a small-scale research field test of a genetically engineered micro-organism.

The field test is proposed for WSU's Spillman Agronomy Farm near Pullman, in eastern Washington.

In the research test, scientists want to assess the anti-fungal activity of a naturally-occurring microbe against wheat take-all disease, a fungal disease which attacks the plant roots and causes dry rot and premature death.

Monsanto researchers genetically engineered the microbe to contain two additional "marker" genes, which serve as a reliable and sensitive tracking system for environmental monitoring of microbes.

The naturally-occurring bacteria, strains of fluorescent Pseudonomonas, were field tested for seven years in Washington as biological control agents effective against take-all, which causes millions of dollars of damage annually.

The genetically engineered microbe will be coated on wheat seed and then planted. Scientists

plan to routinely check and monitor for traces of the marked bacteria on the wheat roots and in the soil. The winter wheat crop will be periodically evaluated for signs of the take-all disease and then harvested in ten months.

A related small-scale research field trial of Monsanto's genetically engineered microbial tracking system began in November 1987 at Clemson University's Edisto farm. Recent harvest results from the first phase of the 18-month test at Clemson successfully confirmed very limited movement from wheat roots.

The model tracking system genetically engineered into the natural strain consists of two genes from a benign strain of E. coli. lacZY and lacy, which are normally present in humans, animals, and soil.

The genes will enable the natural microbe to use lactose as a nutrient - something that non-engineered, naturally-occurring pseudomonads cannot do. This allows the engineered organism to be readily distinguished from others, thus enabling scientists to track the movement and disease suppression activity of the marked microbes in the soil and environment.

When a special dye compound is added to culture dishes, the lacZY marked bacteria produce bright, blue-coloured colonies - a visual sign that clearly differentiates them from other bacteria, which produce yellow-coloured colonies. (Source: Chemical Marketing Reporter, 26 September 1988)

Congress passes first AIDS bill

In its first major legislative response to the AIDS epidemic, Congress passed a bill that calls for a suite of AIDS education and prevention programmes and establishes a home health care programme for those suffering from the syndrome.

The legislation skirts the issue of confidentiality of test results. It is also silent on the issue of discrimination against persons with AIDS or those testing positive for the virus. Many public health officials, as well as the President's AIDS commission, fear that those who need to be tested and counseled most may refuse to come forward without guarantees of confidentiality and protection.

The bill calls for broader clinical trials for AIDS drugs, and requests the National Institutes of Health to evaluate more rigorously unlicensed treatments used by AIDS patients and to expand its investigation of experimental drugs outside clinical protocols. (Extracted from Science, W. Booth, Vol. 242, 21 October 1988. Copyright 1988 by the AAAS)

AIDS treatment drug imports

US Food and Drug Administration commissioner Frank Young announced last week that the Government would no longer try to stop the import of unapproved drugs for the personal treatment of AIDS.

The decision will affect most strongly the import of dextran sulphate, a drug manufactured in Japan for the treatment of high blood-lipid levels and shown to hinder HIV virus binding in cell culture. The drug has become a popular self-treatment for AIDS patients in the United States. Imports by mail will now be permitted provided the amount is no more than a three-months' supply.

Only one drug, AZT, has received FDA approval for the treatment of AIDS and it has such powerful side-effects that many AIDS patients have abandoned therapy with it.

Free availability of dextran sulphate may make it harder to test new therapies against AIDS. Many doctors running clinical trials report that their patients were taking unknown quantities of other untested drugs. In tests of AZT, some patients took their medicine to independent laboratories for analysis; those who found they had been given a placebo dropped out of the trials, making assessment of the treatment more difficult. Interpretation of phase I toxicity tests of dextran sulphate were also complicated when patients boosted their hospital doses with dextran sulphate bought from health clubs. (Extracted from Nature, Vol. 334, 4 August 1988)

AIDS test for one-in-three newborns

The United States has begun a programme to test nearly one-third of all newborn babies for the presence of antibodies to human immunodeficiency virus (HIV). The study will provide information on the prevalence of HIV infection that is more representative of the general population than that being gathered elsewhere. Other studies are focusing on military recruits, patients at selected hospitals, women attending prenatal testing and abortion clinics and people seeking treatment at sexually transmitted disease clinics.

The tests will be administered as part of a standard series of blood tests to screen for metabolic disorders and infectious diseases that are performed shortly after birth. The results of the tests will be completely anonymous: the mother will not be told whether the results are positive or negative, and the data reported to the US Centers for Disease Control will contain only the mother's age and race. The zip code of the mother's address will be recorded so that regional assessments may be made.

Because there is no cure for AIDS, it is not considered unethical to perform anonymous blood tests for HIV without notifying the donor of the results. Anonymous testing is supported by both homosexual rights groups and the American Civil Liberties Union because it guarantees that the test results cannot be used to discriminate against individuals who test positive.

The newborn study is based on one begun in Massachusetts in 1986, which revealed that 2.1 in every 1,000 babies born alive in that state were infected with HIV. Thirty US states and the District of Columbia are expected to participate in the new study, so that a third of the babies born next year in the United States, estimated to number about 3.9 million, will be tested.

The state of New York also began testing newborn infants for antibodies to HIV last year. The New York study has so far shown a statewide infection rate of 8.6 in 1,000 and an infection rate for New York City of 16.4 in 1,000. (Source: Nature, Vol. 335, 1 September 1988)

Synergen announces second quarter results

Synergen's second quarter results reflect increased investment in evaluating pharmaceutical products in models of human disease.

Preparations for clinical testing of Fibroblast Growth Factor (FGF) for treating skin ulcers continued to accelerate and it is anticipated that evaluation of this compound in patients will begin in the first half of 1989. During the quarter, in partnership with CIBA-GEIGY, Synergen made substantial progress in the development of elastase inhibitor (SLPI) for the treatment for emphysema and other respiratory diseases.

The firm is encouraged by initial results of studies, performed in partnership with DuPont, showing the potential of FGF in helping brain cells to survive injury. Similarly encouraging initial results have been obtained when FGF has been used to stimulate bone growth. Studies of FGF for cardiovascular uses, also done in collaboration with DuPont, are less promising than originally hoped, however.

Synergen also focuses on the application of biotechnology to diseases of the central nervous system.

While the causes of Alzheimer's and Parkinson's diseases remain to be discovered, it is known that these diseases result in the death of particular types of neurons. Synagen's participation in the search for treatments for these disorders centres on the development of factors that stimulate the growth and survival of specific types of neurons within the brain. FGF is one such protein being investigated for these uses. Other agents with these desired effects also have been identified and are being investigated by Synergen's scientists.

Another part of the company's neuroscience programme involves the isolation and study of receptors, one of the most important classes of biological molecules. Receptors reside on the outside surface of cells, receive chemical messages and thereby regulate cellular responses to changing conditions within the body. Receptors located in the brain are involved in every aspect of both conscious and unconscious behaviour. The ability to produce these highly specific receptor proteins would allow researchers to rapidly design new compounds that stimulate or inhibit the chemical signals associated with behavioural disorders and disease. Synergen's efforts are focused on receptors for the chemical messages involved in such important functions as sleep, memory and control of blood pressure.

Another major goal of research in neuroscience is the application of technology to one of the major challenges of neuroscience - how to deliver pharmaceuticals across the "blood/brain barrier". A novel approach to this problem has been developed which is currently undergoing testing in animals. If successful, this delivery system would be useful for conventional pharmaceuticals as well as biotechnology products.

Synergen has recently been awarded new research grants by the Federal Government under the SBIR programme (Small Business Innovation Research). One of the studies will evaluate a compound for use in treating adult respiratory distress syndrome (ARDS), an often fatal inflammatory condition that commonly afflicts patients in intensive care units in hospitals. Another study will extend Synergen's knowledge of the synthesis of a class of high value antibiotics, which could lead to new methods of producing these anitibiotics more efficiently. (Source: Company News Report, 3rd Quarter 1988)

Cell-growth regulator joint venture

Collagen Corp. and Bristol-Myers Co. will jointly develop a genetically engineered cell-growth regulator that may be used to treat certain skin disorders (including psoriasis and eczema), rheumatoid arthritis and cancer. The regulator, known as transforming growth factor beta-type 2, will enter trials with psoriasis patients in 1989. Details from: Collagen Corp., 2500 Faber Place, Palo Alto, CA 94303, USA or on +1 (415) 856-0200. (Source: Biotechnology Bulletin, Vol. 7, No. 8, September 1988)

Union of Soviet Socialist Republics

A biotechnology enterprise Soviet style

In 1989, for the first time, Soviet biologists may be able to enjoy a convenience that American scientists have long been accustomed to. They will be able to obtain restriction enzymes, a fundamental research tool in biotechnology, within days or weeks after ordering them from a new Soviet scientific association, instead of waiting up to a year to obtain them from foreign suppliers.

This modest, but significant development, is part of a larger experiment under way in Soviet science to spur industrial innovation and invigorate the country's ailing economy.

As part of General Secretary Mikhail Gorbachev's drive for economic reform, the Soviet Academy of Sciences and the government ministries in charge of manufacturing have teamed up to form 21 different enterprises to collaborate on research and development and the manufacture of a wide variety of items, including biotechnology products for medicine and agriculture, industrial robots, industrial chemicals, personal computers, and machine tools. These enterprises, known generically by their Russian acronym as MNTKs, will do everything from research to production of products.

Under the MNTK plan profit is the stimulus to improvement. In a major reform, the MNTK enterprises can keep the money made from sales to develop other products rather than funnel the profits back into the general government treasury. One of the ultimate aims of this change is to make research self-financing. Before, researchers have depended on the Government for virtually all their support.

Under the MNTKs, the research institutes of the Soviet Academy for the first time control several of the enterprises. Academy institutes historically have had little experience in production, but Gorbachev considers them to be "more enlightened" about technology and management methods.

One of the most ambitious of the MNTKs enterprises is the biotechnology association. It is a collaborative enterprise that includes about 20 Academy institutes and the ministries of Health, Microbiology and Agriculture and is headed by the Shemyakin Institute, the country's leading research facility in bio-organic chemistry.

The biotechnology association plans to produce not only restriction enzymes, but also a wide range of recombinant DNA products for medicine and agriculture and equipment for the laboratory and industrial production. The biotechnology association also hopes to set up joint ventures with

foreign firms and to eventually compete in the international market. It just completed preliminary field trials of bovine growth hormone in co-operation with the Monsanto Company, for example.

The programme was recently promised at least 50 million roubles (about $80 million) for 1989. About 70 per cent of these funds will come directly from the State budget for the first time. Until now, the biotechnology association has been funded mainly by member institutes and ministries from their own budgets. The money will in part go towards the development of 32 products, 24 in medicine and 8 in agriculture. These include hepatitis B vaccine, which is in clinical trial, alpha interferon and human growth hormone, which are close to clinical trial, hepatitis A vaccine, amino acids peptides, and even diagnostics for the AIDS virus.

While many of the pharmaceuticals under development are commonly available in the West, they are in short supply (or nonexistent) in the Soviet Union. Foreign trade is extremely complicated by the fact that the rouble is not an exchangeable currency.

The Shemyakin and the biotechnology association are tightly linked. Researchers at the Shemyakin can divide their time between institute work and the biotechnology association. At present, one-third of the "intellectual power" at the Shemyakin is devoted to projects related to the biotechnology association. The other two-thirds focus on fundamental research.

In a change that is likely to benefit both organizations, Shemyakin staff members, for the first time, can be hired, fired, or promoted based on merit. In July 1988 the biotechnology association introduced a competitive grants system - a rarity in Soviet science.

Efficiency at the institutes and in science in general may also improve because layers of bureaucracy are being trimmed away.

Despite the adoption of many reforms, the biotechnology association faces enormous hurdles. Reducing red tape in purchasing will not compensate for the fact that laboratory supplies and machinery, from the simple to the sophisticated, are in short supply. Even the Shemyakin, which is one of the best equipped biological laboratories in the country, must cope with chronic scarcity.

The biotechnology association itself is wrestling with institutional problems. The research institutes and the production ministries still struggle with how to decide what products to target for development.

Whether the biotechnology association can sell its future products at reasonable prices and still make a profit is unclear. (Extracted from Science, M. Sun, Vol. 241, pp. 1154-1155, 2 September 1988. Copyright 1988 by the AAAS)

USSR approves alpha 2 interferon

The Soviet Union has approved the use of recombinant alpha 2 interferon for treating viral hepatitis and for several other applications, according to the head of the Moscow Institute for Genetics and the Selection of Industrial Micro-organisms, Professor Debadov.

Meanwhile, the UK's health care concern, Wellcome, expects the Soviet pharmacological committee to make a decision on Wellferon within the next two months.

The approval of alpha 2 interferon represents a first for recombinant product in the Eastern bloc. Debadov explained that the protein has been purified using monoclonal antibody affinity chromatography. The Moscow institute has other recombinant proteins, such as interleukin-2, tumour necrosis factor and insulin, at advanced stages of development.

It was also revealed that the Soviet Union intends to increase its production of single cell protein (scp) to more than two million ton/year. In 1987 the Soviet Union, the world's largest producer of scp, manufactured 1.73 million tons.

The USSR has developed scp production processes based on natural gas and other hydrocarbon feedstocks. This avoids using n-paraffins, an expensive feedstock because of the high cost of Soviet oil. Professor Debadov believes that the natural gas based technology could be of interest to other petroleum product manufacturers.

Wellcome expects an answer on its submission for Wellferon before the end of 1988. Unlike the Soviet alpha 2 interferon, which is made using a gene-spliced bacterium, Wellferon is a cocktail of highly purified alpha interferon sub-types from mammalian lymphoblastoids. Wellcome believes that the Soviets may require some USSR-based clinical studies to back up existing company data. (Source: European Chemical News, 19 September 1988)

C. RESEARCH

Research on human genes

Teams pinpoint schizophrenia gene

Independent research teams hunting a genetic cause for schizophrenia each claim to have the answer. Their conclusions, which disagree, have fuelled controversy among psychiatrists seeking to explain the disease.

Psychiatrists now believe schizophrenia has a genetic base. Timothy Crow, head of psychiatry at the Clinical Research Centre at Northwick Park Hospital in Middlesex, claimed that the gene for schizophrenia was located on the sex chromosomes. Crow says that his theory explains the intimate link between gender and schizophrenia. He believes it also explains a second major mental illness - manic depressive psychosis.

Although equal numbers of men and women are affected by schizophrenia, gender appears to have an important role. For instance, the onset of schizophrenia is earlier and the outcome is worse for men than for women. Pairs of schizophrenic siblings are more often of the same sex than would be expected by chance. The disease is particularly common in people who carry an extra sex chromosome.

Crow suggests these findings could be explained if the gene for schizophrenia and the gene for manic depressive illness were located on either of the sex chromosomes - the X and Y chromosomes. The site that Crow believes carries the gene is known as the "pseudoautosomal" region. This site behaves like

the other 22 pairs of chromosomes - the autosomes - during the production of sperm and eggs. During a cell's reproductive phase (meiosis) the autosomes and the pseudoautosomal area of the sex chromosomes exchange information.

Crow says a gene in the pseudoautosomal region could, therefore, sometimes behave like a typical sex-linked gene, such as the gene for haemophilia, which is sited on the X chromosome. Sometimes, he says, a gene in the pseudoautosomal region would behave like an autosomal gene with rather more random movement.

This theory contradicts another explanation for schizophrenia. Researchers led by Hugh Gurling at the Middlesex Hospital in London claim firm evidence for a gene for schizophrenia on chromosome 5.

Studies on two related Chinese people with schizophrenia who had unusual physical characteristics led Gurling's team to the chromosome. In both cases, one particular segment of chromosome 5 was duplicated. The find prompted Gurling to look more closely at chromosome 5 in other people with the illness. The analyses of chromosomes from more than 100 members of seven families prone to the disorder, including 39 people with schizophrenia, identified an abnormal gene on chromosome 5.

Psychiatrists at the Middlesex Hospital interviewed all the members of five Icelandic and two English families and used their medical records to establish diagnoses.

By searching genealogical records, they established, as far as possible, that there was a single source for any gene for schizophrenia now carried in each family. The researchers established a variety of different types of schizophrenia.

Gurling admits that the genetic model is not straightforward. The disease does not always affect both members of a pair of identical twins, and some people with schizophrenia have no history of the illness in the family.

Gurling's results support the model of a single dominant gene that is not fully penetrant so that expression of the gene would depend on other genetic and environmental influences.

Douglas Blackwood, David St. Clair and Walter Muir at the Royal Edinburgh Hospital announced that they had failed to confirm Gurling's results. Blackwood used one of Gurling's marker genes to investigate chromosome 5 in 10 families in Edinburgh that were prone to schizophrenia. The group says that it obtained a negative result that rules out close linkage of the marker on chromosome 5 and the schizophrenia gene.

Both teams admit that chromosome 5 is still not beyond suspicion. They stress that Blackwood's findings are preliminary, and that a number of gaps in the research could have caused the negative result. Meanwhile, work by Swedish and American researchers, led by James Kennedy of Yale University School of Medicine, has been unable to confirm a link between chromosome 5 and schizophrenia. The team used a battery of gene markers, including those used by Gurling's team, to investigate the genetic material of over 30 people with schizophrenia and that of members of their families.

Kennedy and his colleagues say that their work does not disprove Gurling's findings but provides strong evidence for a number of different loci - c. sites on chromosomes - that lead to a "final common pathway" to schizophrenia. (Source: New Scientist, 12 and 19 November 1988)

Protein helps cells survive heat shock

Living cells can survive the stress of exposure to heat by producing special protective proteins, the heat shock proteins (HSPs). Even cells with a relatively simple structure, such as bacteria, protect themselves with HSP. Once a cell has produced the protein in response to heat, the HSP moves from the cytoplasm of the cell into its nucleus. Recent rersearch in the US has shown that only those cells with fully functioning HSP manage to survive exposure to heat; cells without it die.

Karl Riabowol and his colleages at Cold Spring Harbor Laboratory, New York, inactivated HSP in fibroblast cells from rats. The researchers found that fibroblast cells were unable to survive at a temperature of 45° C. They injected some cells with abtibodies that specifically bound to molecules in one group, the 70K HSPs; once bound to antibody, the HSPs are inactivated. The researchers injected other cells, as controls, with antibodies that bound to other proteins.

Ninety per cent of cells that had not been injected survived heat shock. Similarly, the cells that were injected with control antibodies survived, with no apparent damage. HSP had entered the nuclei of all the control cells, the researchers found. But the cells containing antibodies to the HSP did not survive. These cells either disintegrated, or their outer membranes became torn and leaky. The nuclei of these cells did not contain HSP.

Riabowol and his colleagues also examined cells from other sources, including cells derived originally from humans (HeLa cells). None of the cells they studied survived heat shock after injection with HSP antibodies, although HeLa cells, the researchers found, survived better than the cells obtained from rats. Their better survival, suggest the researchers, may be due to their production of two different 70K HSPs: rat cells, by contrast, produce only one. (Source: New Scientist, 5 November 1988)

Antigens like mother's make for smoother transplant

Organ transplants are less likely to be rejected by the recipient's immune system if the donor and recipient share the same family of "self-marker" antigens. These markers form the complex of major histocompatability lymphocyte-A antigens, or HLA system. However, it is often difficult to find a perfect match of such antigens between donor and recipient, and doctors frequently have to resort to "permissible mismatches".

A new study by researchers in the Netherlands shows that recipients are often able to tolerate kidneys bearing HLA antigens that were expressed by the patient's mother, but not inherited by the patient.

Frans Claas and his colleagues at the University Hospital in Leiden studied patients who had received many blood transfusions. These transfusions exposed

them to foreign HLA antigens so that their immune systems were already primed to reject most "non-self" HLA antigens.

They found one exception: kidneys that matched the HLA type of the patient's mother were less likely to evoke an immune response. Exposure to the mother's HLA antigens in the womb or at birth is apparently enough to create a life-long tolerance to such "foreign" protein. In the patients studied at Leiden, 85 per cent of the transplanted kidneys were still functioning a year later. (Source: New Scientist, 29 October 1988)

Cross-species alliance combats cancer

Antibodies that are part rat and part human have stopped a tumour from spreading in a 70-year-old woman. The treatment, which lasted 30 days, is the first time that doctors have used antibody chimeras to combat a disease.

Greg Winter, a researcher from the Medical Research Council's Laboratory of Molecular Biology in Cambridge, told the Royal Society that the woman, from Cambridge, was suffering from an enlarged spleen that had pushed her intestines to one side. Conventional treatment, including injections of rat monoclonal antibodies engineered to recognize and destroy cancerous cells, had failed.

There were signs, Winter said, that the woman's immune system had rejected the rat monoclonal antibodies because they were too alien for the body. Doctors therefore tried a new type of antibody chimera, designed by Winter and colleagues, that has a largely human component attached to the active, cancer-destroying part of the rat antibody.

Winter said that after 15 days, the treatment had cleared the woman's blood of lymphocytes, including cancerous ones. After 20 days, the "humanized" antibodies had cleared lymphocytes from the bone marrow. The woman's bone marrow began producing normal lymphocytes once more, and the spleen became less swollen.

"The results are promising," Winter said, but he stressed that they are not conclusive. The researchers plan to carry out further clinical trials.

Celltech, the biotechnology company that has non-exclusive rights to the patent on Winter's humanized antibodies, is trying to sell the technique to Japanese companies. (Source: New Scientist, 22 October 1988)

Inherited genes in rectal and colon cancers

University of Utah researchers have reported finding strong evidence that about 33 per cent of all white Americans inherit one or more genes that make them highly susceptible to developing adenomatous polyps, which according to researchers must be present for a rectal or colon cancer to develop. The new evidence bolsters the claim that genes are instrumental in the development of colon and rectal cancers. Led by L. Cannon-Albright, M. Skolnick and R. Burt, the researchers found evidence of the genes during colon examinations of 670 people in 34 families with family histories of cancers. The study centred on Utah Mormons. As a consequence, findings concerning racial groups other than whites were unavailable. The results of the study will be published in the New England Journal of Medicine. A separate study, which will be published in the same journal, was led by B. Vogelstein at Johns Hopkins University School of Medicine. This study reported evidence that four to five genes must be mutated for a colon or rectal cancer to occur. (Extracted from Wall Street Journal, 1 September 1988)

Colon cancer inherited

One of the most common forms of cancer, colorectal, is partly inherited, according to a new study of 670 Americans. Moreover, 19 per cent of the relatives of such cancer patients were found to have at least a benign form of colon cancer, adenomatous polyps.

Researchers from the University of Utah examined 34 familes of cancer patients for colon cancer and signs of colonic adenomatous polyps, which are precursors of the cancer. They conclude that genetics and environmental factors work in concert.

The researchers calculate that at least 53 per cent of their patients with colon cancer inherited a predisposition to the disease. No gene for this predisposition has been located yet. Finding the one or more genes responsible will require large studies to search for genetic landmarks in the genomes of many generations within families whose members have colon cancer or the polyps. In the mean time, close relatives of people with colorectal cancer should be screened for signs of polyps.

About 45,000 people contract colorectal cancer each year in the US. It is the most common killer among cancers in the US next to lung cancer in men and breast cancer in women, and has a cure rate of about 50 per cent. (Source: New Scientist, 8 September 1988)

Whooping cough vaccine

The toxin that is produced by Bordetella pertussis, the organism that causes whooping cough, has both positive and negative effects: it elicits protective and neutralizing antibodies in host animals, but, through a biochemical cascade initiated by enzyme activity in its S1 sub-unit (it has five sub-units), pertussis toxin produces in the infected host the pathobiologic effects that are hallmarks of the disease. Because currently available whooping cough vaccines may at times induce dangerous side-effects, including permanent neurologic damage and death, attention has been directed toward uncoupling antigenicity and toxicity through the use of recombinant DNA techniques. W. Neal Burnette of Amgen, Thousand Oaks, California, USA and colleagues prepared a series of anologues of the S1 sub-unit by site-specific mutagenesis; alterations appeared in residues in a stretch of eight amino acids that, if completely deleted, leaves the molecule devoid of enzyme activity and with reduced antigenicity. The most promising analogue was one in which just a single amino acid was changed - a lysine was substituted for an arginine. The molecule had substantially reduced enzyme activity but continued to react with toxin-neutralizing antibodies. The attributes of this altered molecule are suitable for a vaccine that might have few or no negative sequelae. (Source: Science, Vol. 242, 7 October 1988. Copyright 1988 by the AAAS)

Improvement to influenza vaccine

The influenza vaccine can be made more effective in the elderly by adding a diphtheria toxoid, according to D. Gravenstein of the University of Wisconsin (Madison, WI). Older people are frequently unable to mount an antibody response to the trivalent influenza vaccine, but a T-cell response is improved if the diphtheria toxoid is bound to the vaccine's haemagglutinin. The conjugated vaccine produced a 79-89 per cent antibody response, as against a 38-63 per cent response for the conventional vaccine. Response to protein-based vaccines appears to diminish with age, although polysaccharide vaccines, which are T-cell independent, still produce a response. The next step is to determine if the increased antibody response actually provides more protection. (Extracted from Medical World, 8 August 1988)

Of mice and men

A new approach has been taken for studying the human immune system: SCID mice, a strain with severe combined immunodeficiency disease, are given human cells and tissues and then go on to live healthy lives, apparently no longer susceptible to the opportunistic infections that usually kill them before they are four months old. The mouse-human chimeras were developed by J.M. McCune and colleagues at Stanford University, California, USA, and are produced by transplanting into mouse hosts human foetal liver hematopoietic cells (a source of lymphoid precursor cells) and human foetal thymus and lymph node tissue (the environments in which the stem cells can differentiate, proliferate, and apparently function). Both human antibodies and human lymphoid cells were detected in the circulation of the mice several weeks after the tissues had been transplanted. The characteristics of SCID mice that make this model workable and the anticipated uses of the chimeras for studying the normal and pathologic workings of the human immune system - with AIDS being perhaps the chief disease to which the system is relevant - are discussed by the authors. (Source: Science, Vol. 241, p. 1567, 23 September 1988. Copyright 1988 by the AAAS)

Protein kills broad spectrum disease organisms

A protein in human white blood cells - granulocidin - kills a broad spectrum of infectious disease organisms, according to Invitron (St. Louis, MO), which isolated the protein from granulocytes. In in vitro experiments, granulocidin killed minute quantities of certain Gram-negative and Gram-positive bacteria and certain fungi.

Invitron has also announced that it has ended its agreement with G.D. Searle over commercialization of azurophil-derived bactericidal factor (ADBF), a protein derived from human white blood cells that has antimicrobial activity. (Extracted from Chemical Week, 31 August 1988)

Lasers used to determine functions of cell surface proteins

Specific cell surface proteins can be destroyed by laser to determine their function, according to D. Jay of Harvard Medical School. Chromophore-assisted laser inactivation requires a chromophore (light-absorbing molecule) to be attached to an antibody to the target protein. Pulses of laser light are absorbed by the chromophore, and the energy so absorbed disrupts the target protein. The temperature of the target protein may rise to 130° C, but the temperature just a few hundred atomic widths away rises only 2° C. A major use of the new technique will be to determine the role of cell surface proteins in determining the growth of neurons. (Extracted from Science News, 13 August 1988)

Hybrid protein destroys HIV-infected cells

US National Institutes of Health scientists have fashioned a hybrid protein that works like a self-guided missile, searching out and destroying only cells that are infected with human immunodeficiency virus. The hybrid protein was genetically engineered to contain key portions of the human CD4 protein and a potent toxin made by Pseudomonas bacteria. The CD4 portion homes in on HIV-infected cells and binds to gp120, an HIV glycoprotein found on the surface of infected cells that are manufacturing new HIV particles. The toxin portion of the hybrid protein then kills the cell and the fledgling viruses within it. In in vitro experiments, the CD4-toxin hybrid has killed infected human white blood cells while leaving uninfected ones unharmed, according to NIH's Ira Pastan, Bernard Moss, and five co-workers. Pastan says it will be at least a year before tests in humans can begin. A soluble version of the CD4 protein itself is currently in clinical trials as a possible means of inhibiting the infectivity of HIV. (Reprinted with permission from Chemical and Engineering News, 26 September 1988, p. 22. Copyright (1988) American Chemical Society)

H-DNA contains single, triple strands

DNA most often adopts conformations in which two strands of nucleotides wind around each other in a double helix. But one form of DNA, called H-DNA, is unusually sensitive to enzymes that cut single strands. The H-DNA conformation arises from the interaction of a strand containing all purine bases (adenine and guanine) with one containing all pyrimidine bases (thymine and cytosine). Physiological chemistry professor James E. Dahlberg and his co-worker Han Htun at the University of Wisconsin, Madison, have marshalled evidence that H-DNA does indeed contain single strands of nucleotides, and triple strands as well. "The structure results from a disproportionation of a DNA duplex into a triplex plus single-stranded polypurine sequences," the researchers write. Although it is unclear whether H-DNA actually exists within cells, the researchers note that its stability at neutral pH indicates it could exist at low levels under physiological conditions. (Reprinted with permission from Chemical and Engineering News, 3 October 1988, p. 22. Copyright (1988) American Chemical Society)

Fingerprints reveal the genetics of aging

A team of Dutch scientists has developed a new technique for studying the genetic changes that take place as people grow old. The technique improves the accuracy of the revolutionary process known as genetic fingerprinting, which can distinguish between individuals by analysing the DNA in their cells.

Forensic scientists already use genetic fingerprints to confirm whether a suspect was present at the scene of a crime where the police have found body tissues, such as blood. The process is extremely accurate at distinguishing between

individuals, but not so good at revealing minor genetic differences between cells of the same individual, such as mutations that can occur during the aging process.

The Dutch scientists, working at the Institute for Experimental Gerontology in Rijkswijk, part of the Netherlands Organization for Applied Scientific Research (TNO), have taken this a stage further. In addition to an electric field, which separates the molecules of DNA according to size, the scientists repeat the process in a gel that has been infused with two chemicals that separate, or "denature", the double strands of the DNA molecule.

The gel contains a concentration gradient of the two chemicals so that, as the double-stranded molecules move through an increasing concentration of the denaturing agents, the molecules begin to separate into single strands. At a certain concentration they separate completely. The two denaturing chemicals are urea and formamid, and the process was pioneered by Stewart Fisher and Leonard Lernam working in laboratories in New York.

There is a point when the DNA is part double-stranded and part separated. These "branching" molecules move much more slowly in the gel than completely double-stranded or single-stranded molecules. Andre Vitterlinden from TNO calls this "melting", and says that molecules with minor genetic differences melt into single strands at slightly different concentrations of the denaturing agent. The effect is to separate the DNA molecules both by size, due to the electric field, and by genetic mutations, due to the concentration gradient in the gel of the denaturing agents.

The great advantage, says Vitterlinden, is that this "two-dimensional" approach to genetic fingerprinting can separate DNA fragments which have been split into almost identical sizes. This technique can handle more than 600 DNA fragments.

Vitterlinden envisages many applications for the new technique. The great advantage is that the technique can help scientists to analyse the complete genetic complement of the cell at one go, rather than just a small portion of it.

The Dutch scientists hope to publish the full details of their two-dimensional genetic fingerprinting in the near future, Vitterlinden says. One of the research projects that they have begun looks at how the genetic material inside cells changes as people age. Vitterlinden says that the technique can identify extremely minor mutations, such as a single base change in a DNA molecule. These can tell us what happens inside our cells when we grow old. (Source: New Scientist, 18 August 1988)

Killer protein punches holes in cell membranes

A new "killer protein", aptly named perforin, joins the ranks of the immune system's battalion. Yoichi Shinkai of the Juntendo University in Tokyo and his colleagues working on the Frontier Research Programme in Saitama, have determined the structure of the protein from the natural killer cells of mice.

The Japanese researchers' discovery confirms a long-standing suspicion that perforin would turn out to be remarkably similar to another molecular killer - the final protein (C9) in the "complement" cascade of the immune system. In this cascade a series of enzymatic reactions end in the destruction of a foreign or infected cell. The discovery provides new evidence for an evolutionary link between two quite different branches of the immune defence system.

Perforin has the lethal quality of being able to "punch" a hole in a cell membrane, leading to its rapid death. A molecule of the protein binds to a target membrane and then links with its fellows, polymerizing to form a channel through the membrane. Killer cells of the immune system that make perforin, the natural killer cells and the cytotoxic T cells, treat it with respect, and confine it in robust granules within the cytoplasm of their cells until it is ready for release. The discovery that perforin is so similar to the C9 protein highlights the links between the killer cells and another death-dealing arm of the immune system - "complement".

The complement system is typically activated by the binding of antibodies to a foreign cell. It consists of nine proteins that act in sequence, one activating the next to create a cascade effect that is amplified as it proceeds. Thus the triggering of one molecule in the first step of the chain can lead to the activation of thousands of molecules later in the chain.

The last protein, C9, teams up with five other members of the cascade to form a "membrane attack complex" that delivers the fatal punch to the target designated by the immune system. Thus C9, in concert with other terminal components of complement cascade, acts in much the same way as perforin.

Perforin and the complement proteins are similar in their molecular structure over just a short part of their length, and this information helps to clarify the picture of how they kill cells.

The central question is how a protein dissolved in the watery environment around cells manages to transform itself into one that can enter the lipid-dominated habitat of a membrane. The study of these interesting proteins of the immune system thus also promises to reveal the ways in which proteins interact with the lipid bilayers that form cell membranes.

Two steps seem to be involved: first, the molecule must bind to the membrane and then invade it. The key to both steps is probably a region common to both perforin and C9 - a helical portion of the proteins that has both hydrophilic and hydrophobic aspects. (Source: New Scientist, 18 August 1988)

Protein cleaves DNA sequence-specifically

Chemists at California Institute of Technology have designed and synthesized a sequence-specific DNA cleaving protein that consists wholly of naturally occurring α-amino acids. Caltech chemistry professor Peter B. Dervan and graduate students David P. Mack and Brent L. Iverson attach the tripeptide glycine-glycine-histidine, which is a consensus sequence for the copper-binding domain of serum albumin, to the amino terminus of the DNA-binding domain of Hin recombinase to produce a new 55-residue protein with two structural domains with distinct functions - sequence-specific recognition, and cleavage of double helical DNA. The hybrid protein, which was synthesized by solid-phase techniques, binds to four Hin sites,

each 13 base pairs in length. In the presence of Cu(II), hydrogen peroxide, and sodium ascorbate, strong cleavage of DNA by the protein occurs at one of the four sites. Previously, Dervan and co-workers had converted the DNA-binding portion of Hin into a sequence-specific DNA cleaving protein by covalent attachment of an iron chelator, ethylenediaminetetra-acetic acid (EDTA), to the amino terminus of the protein. The present research demonstrates that EDTA can be replaced by a sequence of α-amino acids that binds transition metals capable of facilitating oxidative cleavage of DNA. (Reprinted with permission from Chemical and Engineering News, 31 October 1988, p. 17. Copyright (1988) American Chemical Society)

Single-chain antigen-binding proteins made

Three genetically engineered antibody-like molecules that bind to antigens with the same specificities and affinities as the antibodies they are modelled after have been prepared by Robert E. Bird and a team of researchers at Genex Corp. The work follows closely on the heels of a similar construction by James S. Huston and colleagues at Creative Biomolecules, Massachusetts General Hospital, and Harvard Medical School. Both groups synthesize their new proteins as a single-chain peptide containing the antigen-binding regions of the native antibody - the variable regions of two different chains, called light and heavy - with a synthetic linker between the two regions. The linker is designed to cause the peptide to fold up after synthesis so that the binding regions will be correctly oriented. The engineered genes are expressed in Escherichia coli, then isolated and refolded. Such engineered proteins may have advantages over native antibodies in such uses as providing imaging applications, penetrating to solid tumours, and being more quickly cleared from the bloodstream. (Reprinted with permission from Chemical and Engineering News, 24 October 1988, p. 20. Copyright (1988) American Chemical Society)

Building a protein backwards

Lynne Regan and William DeGrado, of E.I. du Pont de Nemours in Wilmington, Delaware, designed a model protein of four linked α-helices. The α-helix is found in proteins throughout nature, such as the keratin of hair and nails, and has been well studied. The helix produces a characteristic X-ray crystallographic pattern.

Regan and DeGrado designed a sequence of amino acids that would produce an α-helix when joined together. They designed shorter sequences of amino acids that would link four such helical units together to produce a stable, folded structure. The researchers predicted how the four α-helices would arrange themselves and the X-ray crystallographic pattern they would produce in the finished protein. A would-be designer of proteins needs to know how proteins will fold once their constituent amino acids have been linked together.

Biochemists think of four levels of organization in a protein. The first level, its primary structure, is the sequence of amino acids that make up the protein. Certain sequences of amino acids result in the chain forming a helix. The α-helix, and other types of helix, are examples of a protein's secondary structure.

Covalent bonds between the sulphidryl (-SH) groups of molecules of the amino acid, cysteine, produce the kinks and folds in a protein which make up its tertiary structure.

Some proteins are composed of groups of polypeptides - long chains of amino acids. These large molecules are called globular proteins. Taken together, the four levels of structure account for the overall "shape", or conformation, of the protein.

Regan and DeGrado synthesized a gene to encode the four polypeptide sub-units they had designed and inserted the gene into a bacterial plasmid. The gene also encoded sequences that would link the four sub-units together. They then introduced the plasmid into the bacterium, Escherichia coli, which expressed the whole protein.

X-ray analysis of the resulting protein confirmed their predictions of the protein's structure. The researchers had also made samples of the constituent helical sub-units. They raised antibodies against the sub-units which enabled them to test that the product made by E. coli was indeed the protein they had designed. (Source: New Scientist, 8 September 1988)

"Achilles' heel" method cuts DNA selectively

A technique for selectively cutting DNA should aid the mapping and manipulation of large DNA molecules, according to researchers at the University of Wisconsin's McArdle Laboratory for Cancer Research. Michael Koob, Eric Grimes and Waclaw Szybalski have dubbed their new method "Achilles' heel cleavage". The restriction enzymes currently used to cleave DNA cut the molecule on average about once every 65,500 bases. The Wisconsin scientists limit the site of attack of those enzymes to a specific region by modifying the target DNA molecule. First, the DNA is treated with a protein that binds tightly to a region of the DNA. Then a methylase enzyme adds methyl groups to the portions of the DNA that are not protected by the protein complex. The protein is then removed, exposing an unmethylated site that is vulnerable to attack by a restriction enzyme. The researchers have explored two systems so far, but suggest the method could be used with a wide range of other proteins that form sequence-specific complexes with DNA. (Reprinted with permission from Chemical and Engineering News, 29 August 1988, p. 28. Copyright (1988) American Chemical Society)

Contraceptive vaccine effective in guinea pigs

A vaccine based on antibodies to a protein found on the surface of sperm cells provides 100 per cent effective contraception in male or female guinea pigs, show studies conducted by Paul Primakoff, Diana Myles, and colleagues at the University of Connecticut Health Center. The vaccine inhibits a protein called PH-20, which plays an essential role in the adhesion of sperm to the extracellular coating of the egg, a necessary initial step in fertilization. The contraceptive effect is long-lasting and reversible; female guinea pigs progressively regained fertility in the period from six to 15 months after immunization. How closely human fertilization parallels that of the guinea pig at the molecular level is not known, the scientists say; however, they suggest that "a human functional analogue of PH-20 would be a candidate for an effective contraceptive immunogen". (Reprinted with permission from Chemical and Engineering News, 10 October 1988, p. 21. Copyright (1988) American Chemical Society)

Protein is possible monitor of toxics exposure

Fluctuations in the serum or urine levels of metallothionein, a low-molecular-weight, metal-binding protein found in vertebrates, invertebrates and micro-organisms, may serve as a biomonitor of heavy metal exposure or pathological states characteristic of certain metal-related diseases, according to Justine S. Garvey, professor of immunochemistry at Syracuse University. Research in Garvey's laboratory has resulted in development of a radioimmunoassay and an enzyme-linked immunosorbent assay (ELISA) for metallothionein, which normally appears to play a role in the metabolism of zinc and/or copper. The protein is induced by a number of elements, including zinc, copper, cadmium, mercury, platinum, gold and lead, as well as by stress and by food and water deprivation. Garvey has shown, for example, that humans exposed to cadmium in the environment exhibit increased urine levels of metallothionein, and that experimental animals exposed to airborne cadmium exhibit increases in the level of the protein in lung cells. Additionally, the protein may serve as a monitor of toxicity associated with gold- and platinum-containing drugs used to treat rheumatoid arthritis and certain tumours. (Reprinted with permission from Chemical and Engineering News, 10 October 1988, p. 32. Copyright (1988) American Chemical Society)

Flaw in muscular dystrophy theory

The gene responsible for muscular dystrophy, the largest gene that researchers have studied so far, continues to defy scientists' attempts to explain the disease. The theory for muscular dystrophy that researchers currently accept neatly explains how apparently similar deletions of genes on part of the X chromosome cause remarkably different forms of muscular dystrophy. However, new results from the US may mean that scientists will need to rethink their present model.

The most common and most severe form of muscular dystrophy is the Duchenne type (DMD). A mutation in the same gene causes the much less severe form of the disease - Becker muscular dystrophy (BMD). People with the disease who lose their mobility before they reach 16 are considered to have a more severe form of BMD. Others, with the mild form of BMD, may lead a normal life to the age of 50.

Earlier this year, researchers in Boston, Massachusetts, identified the protein dystrophin, encoded in the mutant gene for DMD. The researchers also found that dystrophin was absent (or present in only small amounts) in the muscle cells of boys affected with DMD. In BMD, dystrophin is present, but the molecule is abnormally small.

The current theory for muscular dystrophy appeared to fit both these observations. When genes are transcribed into proteins, messenger RNA copies the DNA template in the cell nucleus. Before mRNA leaves the nucleus, the inactive areas of mRNA known as introns, are excised and the areas that code for proteins, the exons, are spliced together. The activated mRNA then becomes the blueprint, or reading-frame, from which proteins are synthesized. The code is read in triplets, each triplet coding for a particular amino acid.

The current theory says that, if something disrupts the reading frame - for example, a gene deletion - the sequence of triplets will be disturbed. The message will be "scrambled" and no protein will be produced. If, however, the disruption leaves the triplet sequence intact, scientists believe that a smaller but partially functional protein may be produced.

New work by R. Worton from the University of Toronto and colleagues has put the theory to the test. The researchers analysed gene deletions in 29 patients with both types of muscular dystrophy. In all the patients, a previous study had located the deletion to the first 10 exons of the gene.

The researchers identified the specific deletion for each patient. They then established the sequences of nucleotides at the exon-intron boundaries, from which they calculated the number of nucleotides and intact triplets in the deleted exon and so see if the reading-frame had shifted.

All 13 patients with DMD had frame-shift deletions. However, 13 patients with BMD also had the deletions, seven of whom had the more severe form of this condition. According to the researchers, this unexpected result does not invalidate the frame-shift theory for muscular dystrophy. But it does suggest that an alternative mechanism may exist to generate a protein with partial function. (Source: New Scientist, 19 November 1988)

Antibody trap for skin cancer

Researchers in Australia have begun clinical trials of an antibody that could stop the spread and growth of malignant melanoma cells in humans. If the trials are successful, doctors could start treating patients within months.

Gordon Burns and colleagues, at the Institute of Medical and Veterinary Science, in Adelaide, have spent five years testing the antibody in the laboratory which they injected into patients three weeks ago. The trials will be completed in about six months.

The antibody disables cells in the skin tumour by preventing them from attaching themselves to other cells. Once disabled, the cells should not grow or move to other parts of the body and form new tumours.

The researchers developed the antibody using standard techniques for the culture of monoclonal antibodies in mice. The antibody binds to two specific substances called gangliosides - a building-block of fat - on the walls of melanoma cells. These gangliosides, called GD2 and GD3, normally enable the melanoma cells to attach themselves to other tissues in the body.

Once coated with the antibody, cells cannot join onto endothelial cells which line blood vessels. The melanoma cells should, therefore, be trapped in the bloodstream, preventing the formation of metastases - subsidiary tumours formed by cells that break off from the primary one. The researchers also discovered that the cells that were exposed to the antibody do not attach themselves to other proteins and so cannot grow.

Doctors still have to destroy the disabled cells to ensure a complete cure because there is still a risk that the cells could regenerate. Cells coated with the antibody in the laboratory are more vulnerable to attack with drugs than untreated melanoma cells, say the researchers, so doctors may be able to destroy the malignant cells.

Trials of the antibody, which have begun in Adelaide, will test whether it is safe to use in humans and, during a second stage, how effective it is when injected into tumours.

A disadvantage of the treatment is that patients may become immune to the antibody after two or three doses. Because a patient with melanoma may have many tumours on their skin, the effect of the treatment could wear off before the treatment is complete.

The next step of the trial will be to try to develop a preparation of the antibody that doctors could infuse directly into the bloodstream. (Source: New Scientist, 1 September 1988)

Molecular shears to attack viral diseases

Genetic engineers have developed a new set of molecular scissors that may ultimately form novel weapons against viral diseases. Australian researchers have devised ways to target these "ribozymes" to cut molecules of RNA at specific sites.

Jim Haseloff and Wayne Gerlach of the CSIRO Division of Plant Industry in Canberra developed the new molecular shears from small virus-like molecules found in plants that can undergo "self cleavage". The researchers identified the RNA-cleaving section of the satellite RNA linked to the tobacco ringspot virus. Experiments involving mutated forms of this RNA enabled the researchers to devise a model of what a molecule must have to be a ribozyme. The model assumes that the RNA enzyme and its target (or substrate) interact through the pairing of their constitutive chemical "bases". This pairing precisely positions the region of the enzyme that is essential for its cutting function - the "conserved domain" - next to the site for cleavage. Haseloff and Gerlach synthesized three RNA enzymes which did indeed cut strands of RNA to order.

This new technique offers many potential applications. The ribozymes are likely to become a standard part of the molecular biologist's toolbox, enabling researchers to produce particular RNA fragments in bulk and to construct physical maps of RNA strands. These molecular scissors may also be able to cut and thereby inactivate messenger RNA transcripts from genes, thus interfering in the production of the protein encoded by a particular gene. Using this approach, researchers could effectively inactivate specific genes by inserting a gene into animals or plants that would produce one particular ribozyme. (Source: New Scientist, 25 August 1988)

Tangled transport blamed for dementia

Alzheimer's disease might be due to a breakdown of the machinery inside brain cells that tranports molecules. As Alzheimer's disease develops, tangles of abnormal paired helical filaments (PHFs) fill nerve cells and build up within plaques. Researchers from the Medical Research Council's Laboratory of Molecular Biology and the University Clinical School in Cambridge have found these filaments contain tau protein. Tau protein is normally associated with microtubules, the sub-cellular organelles involved in transporting molecules along the extended axons of nerve cells.

Plaques and tangles can be found in small numbers in healthy brains, but when diseased areas increase beyond a certain threshold the brain begins to malfunction and senile dementia ensues.

The amyloid beta protein, which accumulates in the centre of plaques, may play an important role in the development of the disease. There has been progress in analysing the amyloid gene but it is still not clear what the protein does or why it accumulates in the brain. There is no proof that deposits of amyloid cause Alzheimer's disease.

The group at Cambridge began to examine the structure and identity of PHFs several years ago. Tony Crowther and Claude Wischik produced three-dimensional pictures of the PHF from images taken using an electron microscope. They found that filaments are surrounded by a fuzzy coat which can be stripped away by enzymes to leave a resistant core. The core is made up of paired C-shaped sub-units stacked together like coins. The team injected a suspension of PHF cores into mice, from which they isolated a monoclonal antibody which recognized the stripped filaments. Wischik extracted a protein fragment from the cores that the monoclonal antibody recognized. The researchers sequenced the fragment and isolated and sequenced corresponding cDNA clones. These clones showed that the protein fragment from the core was part of human tau. The team suspects that nerve cells may malfunction as the PHFs in plaques and tangles immobilize tau. Current work aims to identify the remainder of the PHF core and the factors that cause the abnormal assembly.

The group has joined forces with ICI to carry on with its basic research which the researchers hope will lead eventually to a way to dissolve the filaments or prevent their formation. (Source: New Scientist, 25 August 1988)

Immunex clones IL-1 receptor

Researchers at Immunex have cloned and expressed the gene for a receptor protein of interleukin-1 (IL-1). This IL-1 receptor is a potential treatment for rheumatoid arthritis and other auto-immune diseases which have been linked to excess production of IL-1. The research is being conducted on behalf of the Immunex and Eastman Kodak joint venture Immunology Ventures.

While IL-1 promotes inflammation, an important immune response to injury and infection, if the response is prolonged it can cause excessive pain and even bone and cartilage degradation. (Source: European Chemical News, 8/15 August 1988)

Human cytochrome c cDNA cloned

Scientists at Suntory Ltd.'s (Osaka) Institute for Biomedical Research are developing rDNA techniques for producing human heme proteins, such as superoxide dismutase (SOD), in yeast. They have cloned the human cytochrome c cDNA, linked it to a vector containing the promoter for yeast 3-phosphoglyceraldehyde, and expressed the human protein in yeast. The ability of SOD to destroy activated oxygen promises to be an important tool for treating inflammatory disorders (including rheumatism, ulcerating gastroenteritis, and Behcet and Crohn diseases), and for preventing damage to heart muscle following heart attacks. (Source: Bio/Technology, Vol. 6, August 1988)

Drug firms enter space race

Chemicals firms took advantage of the last space shuttle mission to investigate protein structure. Wellcome, Du Pont and Upjohn paid for experiments to be conducted in the microgravity of the orbiting craft.

Determination of the precise three-dimensional structure of proteins is important in the quest to understand some drugs' action.

Growing protein crystals for X-ray crystallographic analysis, however, is difficult to attain. The three firms hope that the microgravity environment will make this easier.

Wellcome sent a project into space aimed at growing the key retrovirus enzyme, reverse transcriptase. Wellcome's AIDS therapy zidovudine operates by inhibiting this enzyme.

Better structural information of the enzyme could lead to a clearer understanding of zidovudine's mode of action. Furthermore, it may be possible to design other molecules which will inhibit the enzyme's activity.

Similarly, Du Pont is also hoping that the shuttle mission will bring back protein structural information. The US major funded an experiment to grow the polypeptide-1-B, a model system for protein structural analysis. Upjohn hopes to have perfect structures of the proteins renin and phospholipase AZ. All firms hope the mission will aid the design of future drugs. (Source: European Chemical News, 10 October 1988)

Research on animal genes

Genetic diversity

Recent research on a complex of genes important for the body's immune response, the major histocompatability complex (MHC), has shed new light on the origin of species.

One thing that fascinates biologists about the MHC is its genetic diversity. There are three groups of genes in the MHC, known as classes I, II and III, with several genes in each, but for each of these genes, there may be many different "types", or alleles, within any species. Any individual has two alleles for each gene. Among natural populations of mice, for instance, biologists have found more than 100 alleles for each gene in the MHC.

Genetic diversity, or polymorphism, is important for the body's ability to recognize "self". Many genes direct cells to manufacture proteins so differences between genes means differences in those proteins. The more different types of any one gene there are in a population, the more likely it is that individuals will have MHC genes and proteins that are unique.

Biologists have, until fairly recently, assumed that the polymorphism shown by different species arose after each species had evolved.

New research by Felipe Figueroa, of the Max Planck Institute for Biology, in Tübingen, Federal Republic of Germany, and colleagues there and the US, suggests a different origin for genetic diversity. They found that not only do different species of mice (Mus) have many of the alleles in common, they also share with them at least some strains of Norway rats (Rattus norvegicus).

Figueroa's group focused on a particular gene of the MHC, the Aβ gene. About a third of the populations of wild mice that they studied have alleles of this gene that lack short sequences of the DNA, and so produce a protein lacking two amino acids - the building blocks of proteins. The rest of the populations produce proteins containing these two amino acids. The researchers detected the Aβ polymorphism in several different species of Mus, as well as in some strains of rats. And, not only do the different species have the same kind of polymorphism, the researchers found, the rats have the deletions in exactly the same place in the DNA as the mice.

Figueroa believes that the particular kind of polymorphism his group studied already existed in the last common ancestor of rats and mice. The MHC polymorphisms show how stable some of these genes are. The genes have a remarkably long ancestry - the ancestor of rats and mice probably lived at least 10 million years ago.

A long ancestry can also be traced in human MHC genes - and predates the separation of humans from closely-related species. Like rats and mice, we share many MHC polymorphisms with chimpanzees, even though the evolution of humans and chimpanzees diverged more than five million years ago. David Lawlor and his colleagues, at the University of Stanford in California, compared some of the alleles of the MHC in humans and chimpanzees. The researchers at Stanford found that the proteins produced by this MHC gene in both species were identical.

Indeed, the two species are so similar that the researchers located some human alleles which were more similar in structure to the chimpanzee alleles than they were to other kinds of human allele. So, although the MHC genes show considerable diversity, that diversity existed before the two species diverged.

Jan Klein, from the University of Miami, Florida, believes that MHC polymorphism arose instead through "trans-species evolution". According to this idea, the ancestral species already possessed many alleles for the same gene. As new species evolved from this ancestral species, each receives some of the collection of alleles from the ancestral form: so, the polymorphism persists in each new species. (Source: New Scientist, 22 September 1988)

Gene sets the time in hamster's clock

Circadian rhythms of activity in hamsters can alter as a result of mutation in a single gene. Martin Ralph and Michael Menaker, of the University of Oregon, noticed that a single male hamster had an abnormally short cycle when it was in total darkness. The animal's activity peaked and dipped every 22 hours, rather than the usual 24 hours. Even when the researchers exposed the hamster to 14 hours of light and 10 hours of dark each day, the hamster's period of activity began four hours earlier than usual. Golden hamsters have cycles of activity of about 24 hours when they live in total darkness.

Ralph and Menaker mated the abnormal hamster with females that had 24-hour cycles, to study the way in which the abnormality of the cycle was inherited. By interbreeding the offspring of this first generation, the researchers identified three different groups of hamsters: one group had a normal cycle about 24 hours long; another group had a cycle 22 hours long, like the original males; and a third group had a cycle lasting 20 hours.

Genes for a characteristic are always paired. The researchers suggest that the animals with the cycle lasting 22 hours are heterozygous - that is, they have one normal and one mutant gene. They

suggest that the animals with 24-hour cycles have two normal copies of the gene, and that those with a 20-hour cycle have two mutant copies.

The mutant gene seems to be associated with an intrinsic cycle that is abnormally short. The researchers suggest that these results are the first evidence that a genetic mutation can affect natural rhythms in vertebrates, in a similar way to the mutations already familiar to biologists in fruit flies (Drosophila). Studying the inheritance of the mutant gene may allow biologists to find out how circadian rhythms are regulated. (Source: New Scientist, 29 October 1988)

Body plan gene caught in the act

The first clear evidence that pins one part of vertebrate development to a particular gene has been uncovered by researchers working in the US. Understanding the role of that gene addresses one of the central mysteries of biology - how a mass of embryonic cells develops into specialized tissues.

Richard Harvey, an Australian biologist currently researching at Harvard University, recently found a way of circumventing the limits of conventional genetics. His prize was the first evidence to implicate a homeobox gene from the African clawed toad (Xenopus laevis) in the formation of somites. Somites are the tissues that give rise to the segmented structures - such as the spinal column and ribs - of vertebrates.

For a fruit fly to develop normally its homeobox genes must switch on at the right time and in the right place. Harvey knew that the messenger RNA (mRNA) encoded by the toad's homeobox gene was, similarly, produced only in tiny amounts early on in the toad's development. His approach was to flood Xenopus eggs with large amounts of the mRNA of the toad's homeobox gene.

Harvey reasoned that overdosing developing eggs with the product of the homeobox gene might severely disrupt embryogenesis, particularly if, like its fruit fly counterparts, the toad homeobox gene helps to organize the body plan.

Harvey cloned the homeobox gene of Xenopus and induced it to make large amounts of mRNA. He then injected the synthetic mRNA into one of the two cells resulting from the first division of a fertilized Xenopus egg. By injecting only one of the sister cells, Harvey ensured that only those cells destined to form one side of the tadpole would be affected by the surplus mRNA. The progeny of the untouched sister cell should remain normal and serve as a control.

The resulting tadpoles grew with kinks in one side. In each case the kinked side was the one that received the overdose of homeobox mRNA.

Dissecting the tadpoles, Harvey saw that the orderly array of somites was completely disrupted on the kinked side, whereas the control sides retained their normal structure. Only somite tissue of the tadpoles appeared to be affected. Harvey showed that the kinks were not simply a result of puncturing the egg or of a non-specific toxic effect of mRNA by injecting a mRNA known to play no part in differentiation. Injecting the mRNA for the blood protein globin failed to produce kinked tadpoles.

Although the surplus mRNA was introduced at the earliest stage of development, it had no effect on any of the developmental steps prior to the formation of somites. Nor did it influence the differentiation of somites into muscle tissue. The only thing it appeared to affect was the structure of the somite array. Toad homeobox mRNA seems to produce a protein that is specifically involved in forming that array.

Harvey sees a parallel between the role of the normal toad homeobox gene in laying down the segmental pattern of the vertebral trunk and the role of its counterpart in the fruit fly lays which gives rise to the segmental pattern of that insect.

That toads and flies share stretches of homeobox DNA suggests that ancestral homeobox genes supervised pattern formation in general rather than in segmentation in particular. Not every animal is segmented, but every animal needs a body plan. (Extracted from New Scientist, 18 August 1988)

Research on plant genes

Possibility of cold weather forage grass

Researchers are attempting to develop a forage grass that grows actively even in cold weather. A cool spring can wreak havoc with livestock farmers, who depend on grasses. The Welsh Plant Breeding Station (Aberystwyth, UK) is trying to determine how cold weather affects plant growth on a cellular level. Highly sensitive measurements indicate that grasses respond to cold weather immediately, with no time lag. This probably indicates that cold affects the expansion of existing cells, rather than the formation of new cells. Plants still have materials available for growth even as the temperature drops, and turgor pressure is unaffected, so the cold response must be due to a mechanism to prevent the expansion of cell walls.

Research has now focused on a variety of barley called "slender", which keeps growing to a temperature 10° C lower than that at which barley normally stops growing. Its cell walls are about three times as plastic as normal barley cell walls. Slender may have a defective gibberellin regulatory mechanism. Cold shock proteins (CSPs) may also be produced by some plants exposed to cold. How CSP might work is unknown, but one possibility is that they may be cold-hardy forms of enzymes. Some plants make no CSPs. Some grasses store energy as fructans, which are produced by enzymes that are still operating at temperatures when starch-making enzymes have ceased to operate. Frost hardening is another phenomenon that must be better studied. It may be that in 10-15 years we will have a genetically engineered supergrass that continues to grow in cold weather. (Extracted from New Scientist, 28 July 1988)

Better crops from foreign genes

Biochemists in London have developed a new method of inserting foreign genes into plant chromosomes. Once implanted, these foreign genes can replicate hundreds of times in each cell. The foreign gene is not only present in high numbers within a cell, and therefore more efficiently expressed, but is also present in most cell types throughout the plant.

The technique was demonstrated in dicotyledons, but it should work just as well in monocotyledons, such as wheat, rice and maize, on which the world relies for more than 70 per cent of its food. The ability to introduce foreign genes into crop plants,

in such a way that those genes are expressed, would dramatically cut the time and cost of traditional plant breeding. Genetic engineering can produce plants with resistance to insects, fungi, bacteria and viruses. It can also give researchers a valuable tool to study the function of plant genes.

Until now, molecular biologists have relied on two techniques to carry foreign genes into plants. The first uses Agrobacterium tumefaciens as a carrier for the foreign gene. A. tumefaciens has a circular piece of DNA called T_i plasmid which is a convenient carrier for genes. Researchers attach the foreign DNA to the T_i plasmid of the bacterium and then grow the modified bacterium in culture. They then add various plant hormones and nutrients to the culture medium and incubate a leaf in it. Eventually the leaf forms callus tissue, clumps of undifferentiated plant cells which, in time, produce primitive roots and shoots. After seven to 10 weeks the callus tissue can be grown into whole plants. The more copies of a gene in each cell, the more efficiently that gene is expressed. However, cells of transgenic plants made using this method each have no more than five or six copies of the foreign gene.

The second method gets around the difficult and time-consuming process of growing plants from callus tissue by allowing cauliflower mosaic virus (CaMV) to infect a whole plant. Here, the foreign gene is first attached to a particular segment of the CaMV genome. This modified CaMV is then attached to the T_i plasmid, inserted into A. tumefaciens and grown in culture. Once injected into a plant stem the virus spreads throughout the plant. It incorporates itself into the cellular DNA and begins to replicate itself, together with the "passenger" foreign gene attached to it.

There are two main drawbacks to using CaMV as a carrier. First, the virus will only remain infective if it is allowed to produce its protein coat. This means that any foreign DNA attached to it must be small enough to fit into this coat. If the gene to be introduced is too large to fit neatly into the protein coat when the viruses assemble within infected plant cells, the particles will not be infective and the technique will fail. Secondly, CaMV will infect only a few families of dicot.

Robert Hayes and colleagues, at Imperial College, London, have managed to overcome the drawbacks of both methods by using another virus, called tomato golden mosaic virus (TGMV) to carry the gene. They removed the gene for the coat protein of the virus and attached it to a foreign gene, in this case a convenient marker gene called neo.

They made dimers of the gene construct - that is, two of the TGMV-neo constructs joined head to head. The researchers then attached the dimers to the T_i plasmid of A. tumefaciens.

Once injected into the stems of Nicotiana tabacum the TGMV-neo - TGMV-neo dimer becomes incorporated into the cellular DNA. The dimer then splices into two monomers. One TGMV-neo monomer leaves the cell and infects adjoining cells. The other remains as a master copy within the cellular DNA.

The result is that each cell in the plant will make between 200 and 500 copies of the foreign gene, courtesy of the TGMV gene for self-replication. TGMV spreads rapidly throughout the plant, infecting most cell types.

Unlike CaMV, TGMV will infect a wide range of monocotyledons and dicotyledons. According to Hayes, evidence of expression of the foreign gene takes only about 10 days. By 21 days, the virus should be present throughout the plant.

The researchers say the technique will be invaluable in studying the functions of plant genes. The technique holds enormous potential for improving commercial crop plants by allowing genetic engineers to get desirable genes, coding perhaps for resistance to common pathogens, where they want them and in large enough numbers to make a noticeable difference in productivity of the crops. (Source: New Scientist, 18 August 1988)

Icy alfalfa warms up in the greenhouse

Scientists at McGill University in Montreal, Canada, have identified four genes that team up to help alfalfa plants to survive the long, cold Canadian winter. These are the first results from a revolutionary complex of greenhouses, called a phytrotron, with very tightly-controlled atmospheres.

Ronald Poole, a plant physiologist at the university, says the team hopes to transfer these "antifreeze" genes into strains of alfalfa that have commercial use - for example, fast-growing varieties. The long-term objective is to transfer genes from alfalfa that has adapted to the cold into different species, such as wheat or corn.

In order to isolate the genes, the researchers worked with alfalfa seedlings and a "DNA library", cloned from RNA that they had removed from seedlings that tolerated freezing well. To find the hardiest candidates for cloning, the researchers subjected seedlings from two varieties of alfalfa, Anik and Saranac, to cold stress at McGill's phytotron.

Poole acclimatized the seedlings to temperatures near freezing, in order to trigger the expression of the genes which make the seedlings tolerant to freezing. Some of Poole's seedlings weathered the process better than others. Roughly 50 per cent of the Anik variety of seedlings survived in temperatures that dropped as low as -15° C.

Once Poole had identified the toughest seedlings, molecular biologists at the university prepared a DNA library from these particular alfalfa plants. They built up the library by inserting the genes into the bacterium Escherichia coli. As the bacteria reproduce, they create vast quantities of the alfalfa genes. The scientists were then able to locate and clone the specific genes that are responsible for the seedlings' tolerance to cold.

Poole says the researchers plan to search through the whole genome of their alfalfa seedlings, to find the DNA sequence which "turns on" the four genes, and then study the way it works. They are also trying to identify the proteins produced by the genes. If the team can find these proteins, it may be possible to determine whether they serve as enzymes for particular reactions that are critical to the development of the plants that tolerate freezing.

Possibly within the next two years scientists will be able to develop a kit for testing plants permitting plant breeders to determine which of their plants have a genetic predisposition to tolerate cold. (Source: New Scientist, 8 October 1988)

Caterpillar-resistant cotton

Using genetic engineering techniques, scientists at Agracetus (a joint venture between W.R. Grace and Co. and Cetus Corp.) have developed cotton plants that are resistant to major insect pests. Under laboratory conditions, the new plants deter feeding and kill certain caterpillar pests of cotton. A bacterial gene, coding for an insecticidal toxin produced by the bacterium Bacillus thuringiensis, was introduced into the cotton chromosome. The bacterium itself has been sprayed as a pesticide for more than 20 years to protect plants from caterpillar attack.

Control of caterpillar infestation is a major problem of cotton growers, who currently use chemical insecticides to protect their crops. Worldwide, about 27 per cent of the $5 billion insecticide market is directed at the control of cotton insect pests. The Bt toxin is an attractive insecticide because it does not kill beneficial insects. Details from: Agracetus, 8520 University Green, Middleton, WI 53562, USA or on + 1 (608) 836 7300. (Source: Biotechnology Bulletin, Vol. 7, No. 10, November 1988)

Viroid induces changes in host plant protein

Viroids are very small pieces of RNA that can replicate and cause severe diseases in plants. Just how they do it is puzzling; unlike RNA viruses, they do not serve as the template to trick the plant's genetic machinery into making viral proteins. A clue to how viroids may work comes from plant scientists H.J. Hiddinga, D.A. Roth, and colleagues at the University of Wyoming who have found a viroid that alters a protein in its plant host, phosphorylating it into a form that has enzyme activity. The potato spindle tuber viroid infects tomato plants where it selectively alters the phosphorylation state of one of the host proteins, the researchers find. This protein is an enzyme of the family known as protein kinases. Although the function of this particular protein is unknown, similar proteins in mammals help regulate protein synthesis and replication, suggesting a way the viroid could be producing its effects in the tomato plant. (Reprinted with permission from Chemical and Engineering News, 25 July 1988, p. 23. Copyright (1988) American Chemical Society)

Flavonoids give a clue to how your garden grows

British researchers may be closer to solving the mystery of how plants regulate the transport of the growth hormone, auxin. New work at the University of Cambridge suggests that flavonoids, a class of phenolic compounds found in flowering plants whose function has never been fully explained, may inhibit the transport of auxin from where it is produced to where it acts.

Auxin was the first plant hormone to be discovered. The hormone is produced, among other places, in shoot tips and young leaves. One of its effects is to stimulate growth. Auxin also influences the differentiation of phloem and xylem, the vascular tissues of plants. To carry out its many functions, auxin often has to be transported from the top to the bottom of the plant. This activity is known as polar transport and exactly what controls it still baffles plant physiologists.

French researchers showed, in the late 1970s, that tomato plants fed with a precursor of flavonoids accumulated high levels of phenolic compounds. The plants were dwarfed and the movement of auxin from apical buds - buds high on the plant - to roots was reduced. Both observations suggested that the transport of auxin might be affected by the high levels of phenolic compounds. The problem then was how to test that hypothesis.

The search for herbicides during the Second World War led to the discovery of synthetic chemicals that would inhibit polar transport of auxin. One of these chemicals, naphthylphthalaic acid (NPA), binds to a protein receptor in the plasma membrane of plant cells. The receptor has since been referred to as the NPA receptor.

Mark Jacobs and Philip Rubery, at Cambridge, have now shown that a variety of flavonoids also bind to the NPA receptor. They have also shown that these compounds affect the transport of auxin in segments of stem, in the same way that NPA can. It is still too early to say that flavonoids made by the plant regulate polar transport of auxin. Jacob and Rubery have shown NPA-like activity only in free flavonoids and not in their glycoside derivatives. Flavonoids exist mainly as glycosides, in the vacuoles of plant cells. Researchers have done very little work to estimate levels of free flavonoids in the cytoplasm.

Researchers still have to show in vivo a correlation between cellular flavonoids and the inhibition of polar auxin transport, but the in vitro evidence for flavonoids as candidates for regulating polar auxin transport is strong.

Biochemists have identified hundreds of flavonoids. A handful of those are found in plants and have now been shown to mimic the effects of NPA in vitro. Levels of phenolic compounds, including flavonoids, increase at sites of damage. Auxin is important in healing wounds, in stimulating the growth of new tissues and helping in the formation of new vascular tissues. Flavonoids may allow auxin to accumulate in wounded tissue and, by inhibiting its movement, keep it where it is needed. (Source: New Scientist, 1 September 1988)

Miniature bullet shatters traditional crop engineering

A new method of inserting genes into plants will enable geneticists to transfer DNA into plants that were previously inaccessible to genetic engineering. Using a "shotgun" technique, researchers will be able to insert genetic material into the cells of plants without having to strip the cell wall. The technique will allow geneticists to study gene expression in single cells of cereals, and to grow whole plants from cells without having to dismantle them first.

Geneticists at present have to remove the tough cell wall before they can insert nucleic acid into the cell's nucleus. An alternative method is to bore a hole through the wall of a cell and insert genetic material through it. Both approaches are laborious and depend upon the success of regenerating entire plants from a small handful of individual cells - a process that is possible only for plants with very prolific tissues, such as those of tobacco plants.

American horticulturalists from New York, California and Iowa have designed a novel technique for engineering plant genes which will have many uses in cereal research.

The researchers construct the genetic material for transfer into the cells into circular carriers of viral DNA, called plasmids. These plasmids are literally blasted into the host cells. First, the researchers mixed the plasmids with tiny particles of tungsten, each about 1 micrometre across, and stuck these tungsten microprojectiles onto the front face of a cylindrical plastic "bullet".

The device works like a miniature pistol. A firing pin detonates a blank gunpowder charge that propels the bullet down a barrel onto a plate. The impact of the bullet hitting this plate jerks the tungsten microprojectiles off the bullet's surface through an opening, across a vacuum to their targets in the plant cell. The particles of tungsten are large enough to penetrate enough cells to be effective, but not so large that they destroy the cells.

The researchers tested the effectiveness of the method of delivering the genetic material by propelling plasmids containing DNA that encoded chloramphenicol acetyltransferase (CAT) into cultures of maize cells. The plasmids also contained a viral promoter and a piece of the genome from the maize plant - a prerequisite for the expression of the gene that codes for CAT in the host cell.

After one bombardment with plasmid-coated particles of tungsten, the cells produced up to 200 times the normal amount of CAT, showing that the CAT gene and promoter had been incorporated successfully into the DNA of the host cell.

The gene transfer was as efficient as with conventional means of transfer, in which the cells are first stripped of their walls. (Source: New Scientist, 29 October 1988)

Plant biotechnology novelties

Specialized plant structures with odd biochemistry may bring long-term payoffs if persevering researchers prove successful. Investigators are finding that structures as diverse as plant roots and microscopic "cones" found on some leaf surfaces can produce potentially useful secondary metabolic products.

For instance, recently Hector Flores and his collaborators at Pennsylvania State University (University Park) have begun to uncover some potentially valuable biochemical mysteries by growing plant roots in culture. When seedlings are infected with Agrobacterium rhizogenes, critical changes result which enable plants to organize into root cultures that grow efficiently on defined media. Cultured in such a fashion, root structures produce greater-than-usual amounts of specialized biochemicals (including alkaloids and sweeteners). Hence, such culture systems could become a source for otherwise rare and potentially highly valuable plant secondary metabolites. Flores and his collaborators are developing techniques to grow the fragile root cultures in large-scale bioreactors.

Likewise, the spiked, conelike structures along leaf surfaces of some plant species have been neglected in biotechnologists' search for novel compounds. None the less, several wild varieties of commercially important plant species, including tomatoes and potatoes, appear to contain valuable anti-pest concoctions within their trichomes - a finding that may eventually prove valuable for farmers, according to John Steffens, Ward Tingey and Robert Plaisted, Cornell University, Ithaca, NY who have found that these specialized biochemicals seem to confer protection against preying insects. For instance, the trichomes on wild potatoes produce an exudate that helps protect the plants against aphids. The exuded material, when exposed to air, changes from a clear liquid to a viscous brown syrup, acting as a natural glue trap for insects. The material also plugs insects' mouths. Plant breeders are trying to incorporate the polyphenol oxidase-catalyzed reaction that produces the "glue" into domesticated potatoes.

The leaves of wild tomato plants also contain trichomes producing anti-pest substances. The protective mechanism, however, is very different from that observed in wild potatoes. The trichomes on wild tomatoes produce various fatty acid-containing glucose esters, which act as aphid repellants. The hybrid progeny of wild and domesticated tomato plants - somewhat surprisingly - produce both glucose and sucrose fatty acid esters, Steffens notes. He hopes such breeding efforts eventually will lead to production of insect-resistant crop plants. (Source: Bio/Technology, Vol. 6, August 1988)

Herbicide-resistant transgenic plants

Genetic engineering of tobacco plants with a non-plant catabolic gene has made the plants resistant to the potent herbicide bromoxynil. The gene bxn from soil bacteria detoxified the herbicide by breaking it down to a non-toxic metabolite. In the experiments carried out by David Stalker and colleagues at Calgene, Davis, California, tobacco plants were given a chimeric gene - bxn - under the control of a light-inducible promoter that works only in photosynthetic tissues. Control plants were bleached by the herbicide, but such bleaching - a sign of inhibited photosynthesis - did not occur in the transgenic plants. Herbicide resistance was inherited by progeny transgenic plants. The approach of detoxification by degradation has caused no adverse effects in transgenic plants; such plants should be valuable agricultural resources. (Source: This Week in Science, 21 October 1988)

Alga increases its rhythm

Biologists have accelerated the body clock of a single-celled alga by exposing it to creatine, a compound found in the muscle of vertebrates that controls the storage and release of energy. Although the researchers could not say exactly how creatine affects the alga's body clock, they suggest there might be some link between the production of energy in cells and daily rhythms in the alga.

Till Roenneberg and colleagues at Harvard University also found an unidentified substance occurring naturally in the alga. The substance had the same effect as creatine on the cells' body clocks - suggesting this substance might be an analogue of creatine. Hideshi Nakamura, a member of the research team, says they have almost isolated this "very small compound".

The researchers monitored the daily rhythm of the alga, Gonyaulax polyedra, by measuring the glow its cells emitted - one of several activities that follow a daily rhythm, including photosynthesis and cell division. Cells receiving no creatine and cultured in constant dim light and stable temperature, to eliminate other stimuli to the internal clock, reached their peak of brightness every 23 hours. Cells receiving creatine glowed

brightest earlier each day depending on the dose given. The cells receiving the maximum dose of creatine peaked on average four hours earlier than the control cells - every 18.8 hours. (Source: New Scientist, 18 August 1988)

Research on yeast and fungus genes

Newly-discovered yeast keeps fruit from rotting

Research by American and Israeli scientists has identified a type of yeast which can protect fresh fruit against the depredation of fungi that cause the onset of rot. The project, financed by the Israel-US Agricultural Research and Development Foundation, was carried out by Dr. E. Halutz, of the Agricultural Research Organization here, and by Dr. S.L. Wilson, of the US Department of Agriculture Research Station in West Virginia.

In their search for organisms capable of suppressing the action of the fungi that cause green and blue rot in citrus fruit, the two scientists identified a yeast which naturally occurs on lemons and has the desired effect. Further experimentation proved that this does not only work with all citrus fruit varieties; the same protection is also available to apples, grapes, tomatoes and many other types of farm produce.

Although how this yeast acts is not yet understood, one thing is already clear beyond all doubt: it does not do so by producing some antibiotic substance. This is an important point, since regulatory authorities are even more sensitive to the presence of active biochemicals.

Efforts are now under way to develop a simple method for the establishment of rot-preventing yeasts on fruit before it is shipped. An application for patent protection of this method has also been filed. (Source: Innovation, March 1988)

New enzyme discovered

An enzyme that breaks down plant and animal protein stains more rapidly and at higher temperatures than the enzymes currently utilized as detergent additives has been discovered by researchers at Cornell University. The enzyme was obtained from a microbe taken from a swamp in Mexico. It is called YX protease, and the university has applied for a patent. The enzyme remains active in alkaline conditions and at a wide variety of temperatures. It is also active even when exposed to chemicals that damage most other enzymes. Possible applications include the production of protein-packed therapeutic diets. It could also be used to clean ultrafiltration membranes and other filtration devices soiled by proteins. A cleaner using the new enzyme could complete a job in just one hour. Existing enzyme-based cleaners take 24 hours. (Extracted from Chemical Week, 12 October 1988)

Cellulose production in living cell

The method by which living cells produce cellulose was recently defined by a team of Hebrew University scientists, headed by Prof. Moshe Benziman. This discovery, the result of more than a decade of research, may prove the first step towards economically important developments.

Past efforts to observe the manner in which living cells convert glucose into cellulose failed, simply because that production stops as soon as the cell wall is broken. That obstacle was overcome five years ago, when Prof. Benziman managed to demonstrate the synthesis of cellulose in the laboratory. At that time he discovered that guanosine triphosphate (GTP) activates synthase in a test tube; synthase is the enzyme that polymerizes glucose into cellulose within the cell.

Taking their departure from this fact, other members of the research team then found that GTP is only a precursor of the molecule which really activates the synthase: that is cyclic diguanylic acid (CDA), a substance never before found in nature. Later they discovered a second enzyme system, which deactivates CDA and halts cellulose production.

Prof. Benziman and his associates focused on the production of cellulose in a single micro-organism, Acetobacter xylinum, long known for its ability to convert wine into vinegar. However, they believe the same or a similar mechanism is used for this purpose also in higher plants, and efforts to verify that assumption are now under way.

At the same time, efforts have begun in co-operation with molecular biology laboratories in Norway and the United States, towards identifying the specific gene that controls cellulose synthesis. Once that has been accomplished, it may become possible to speed that process in various plants, in order to enhance their production of wood, straw or cotton. Ultimately this effort may even lead to some revolutionary development, such as the large-scale production of cellulose by advanced biological engineering methods. (Source: Innovation, March 1988)

Research on bacterial genes

Ice-minus bacteria protect against frost

Genetically modified bacteria are safe and effective in protecting crop plants from frost damage, Steven Lindow, associate professor of plant pathology at the University of California, Berkeley, told the annual meeting of the American Phytopathological Society in San Diego. As a result of court challenges stemming from concern over the safety of releasing genetically modified micro-organisms to the environment, Lindow and Berkeley colleagues waited four years to conduct field tests of ice-minus Pseudomonas syringae, a common bacterium that colonizes the surfaces of numerous plants. Using recombinant DNA techniques, Lindow and Berkeley professor of plant pathology Nickolas J. Panopoulos deleted a portion of the P. syringae gene that encodes a protein that acts as an ice nucleus. In field tests at the university's Agricultural Field Station in Tule Lake, Calif., the researchers applied the modified bacteria to potato seedlings before naturally occurring P. syringae could colonize the plants. They found that the seedlings with the ice-minus bacteria incurred, on average, only one third the frost damage of unprotected plants, and that the modified bacteria did not spread beyond the experiment's 30-metre buffer zone. (Reprinted with permission from Chemical and Engineering News, 21 November 1988, p. 26. Copyright (1988) American Chemical Society)

Bacteria grow fitter on foreign DNA

The release of genetically-engineered organisms carrying foreign DNA may be riskier than scientists have supposed. New research by Judith Bouma and Richard Lenski of the University of California at

Irvine suggests that bacteria can evolve so that they tolerate and even benefit from carrying extra genetic material.

Biotechnologists have often argued that bacteria engineered to carry extra genes, in the form of a circular strand of DNA known as a plasmid, suffer from the costs of accommodating and producing proteins from this additional genetic material. According to this hypothesis of "excess baggage", engineered bacteria released into the environment are unlikely to spread when forced to compete with native bacteria. The new research by Bouma and Lenski casts doubt on such a notion of inherent safety. They produced a strain of the bacterium Escherichia coli that evolved a liking for its extra DNA.

The researchers introduced a plasmid that initially reduced the reproductive fitness of the bacteria in ordinary culture media that lacked antibiotics, but enabled the bacteria to grow more vigorously in the presence of antibiotics. However, the relationship changed after the researchers cultured the bacteria for 500 generations in the presence of an antibiotic. After this, the plasmid increased the fitness of the host, even in the absence of antibiotic.

Further experiments revealed that it was the host, not the plasmid, that had adopted. The evolved colonies of E. coli benefited in the same way when given copies of the original plasmid.

The researchers do not yet know what genetic changes are responsible for this "evolutionary transition from antagonism to mutualism". They hope to determine whether any particular region of the plasmid is essential in increasing the fitness of the host, by systematically removing portions of it from the host. (Source: New Scientist, 29 September 1988)

Bacteria can act as natural fertilizer

Los Alamos National Laboratory researchers found that plant-killing bacteria can also act as a natural fertilizer. Certain bacteria called rhibozia normally attach themselves to the roots of legumes like alfalfa and soybeans, feeding their hosts by extracting nitrogen from the air and creating nitrogen-rich ammonia which can be used by the plants. When scientists added a variety of pseudomonas bacteria - which normally kills non-legumous plants - to rhibozia, alfalfa plants were found to double their foliage and weight. On their own, pseudomonas bacteria make a toxin that blocks a step in plants' intake of ammonia from the soil. When rhibozia and pseudomonas are combined, researchers theorize, the plant resorts to emergency routes for getting ammonia when the toxin blocks the usual route. The new routes do not have normal chemical stop-and-go signals, so the rhibozia and host plant take twice as much nitrogen out of the air as normal. Discussions are being held with a biotechnology company to determine if pseudomonas bacteria can be genetically altered so it can be used on entire fields of alfalfa and soybeans. Under normal conditions, the bacteria does not survive very long in soil. (Extracted from Wall Street Journal, 5 October 1988)

PSTI mass-produced in E. coli

Scientists at Mochida Pharmaceutical Co. Ltd. (Tokyo) have been developing recombinant DNA techniques to mass-produce small proteins in Escherichia coli. In general, E. coli has proved a difficult host for proteins smaller than 10,000 MW because they tend to form insoluble clumps or be degraded by bacterial proteases. Mochida scientists have constructed an E. coli strain that lacks lipoprotein; they have used it to mass-produce human pancreatic secretory trypsin inhibitor (PSTI), with yields 40-fold higher than previous levels. The protein has all the physical and biological properties of authentic PSTI. Mochida scientists chose PSTI as a model small protein because it is readily degraded by intracellular bacterial proteases and has a relatively complex structure: the active protein has three disulphide bonds. The Mochida strain could potentially increase the yields of other small proteins such as somatomedin, insulin, and epidermal growth factor. (Source: Bio/Technology, Vol. 6, August 1988)

Myxobacteria attract new interest

Even simple, single-celled bacteria are capable of advanced social behaviour. A single cell will amass with its kin: together they move in co-ordinated fashion across a solid surface, accumulate into aggregation centres, and go on to form morphologically complex fruiting bodies containing spores. This behaviour is a hallmark of the Myxobacteria.

Organized masses of myxobacterial cells grow and feed in soil; they produce various hydrolytic enzymes that allow them to degrade proteins, microbial cell walls, cellulose and other insoluble materials. When faced with starvation, however, vegetative growth comes to a halt. Instead, the bacteria begin an orderly process of multicellular development and differentiation - culminating in spore formation within the fruiting body. The thick-walled, dormant myzospores will germinate only when favourable growth conditions return, thus completing the organism's life-cycle. Because the Gram-negative Myxobacteria can be manipulated genetically, they provide an attractively simple experimental system for studying the biochemical events that trigger and regulate cellular morphogenesis and differentiation.

Myxobacteria respond to morphogenic factors and signals. In fact, the bacteria themselves produce many of these signals. For instance, wild-type Myxococcus xanthus cells release a heat-labile protein that triggers an early developmental event. Adam Kuspa and his associates, working in Dale Kaiser's laboratory (Stanford University, Palo Alto, CA), have identified and isolated this protein - A-factor. They have found that mutant bacteria incapable of releasing A-factor are also incapable of producing spores. M. xanthus cells release another protein - C-factor - that functions later in the developmental cycle; this signal is also necessary for normal sporulation. Both A-class and C-class mutants can be rescued if the factors are supplied exogenously.

Myxobacteria also respond to light stimuli. Stationary-phase cultures of M. xanthus accumulate orange or red carotenoid pigments after they have been exposed to blue light. Apparently, the pigments protect the bacteria from the damaging effects of light, such as photo-induced cell lysis. Francisco J. Murillo and co-workers (University of Murcia, Spain) have detected the light-inducible promoters (through beta-galactosidase expression) that control carotenoid synthesis.

While Myxobacteria's developmental characteristics continue to appeal to research biologists, their potential as a source of new antibiotics has attracted biotechnologists. Because the common soil organisms can be found almost anywhere on rotting wood or other decaying organic matter, it is easy to obtain many different, albeit impure, strains. Most strains are culturable on simple laboratory media. Hans Reichenbach and associates (Gesellschaft für Biotechnologische Forschung Mikrobiologie, Braunschweig, FRG) have screened over 800 different strains for anti-microbial activity; of these, 60-80 per cent were positive. The resulting array of antibiotics exhibited very different structural characteristics - quinones, lactams, lactones, polyenes - many of them completely unique.

The myxobacterial antibiotic, saframycin, appears to have promising anti-tumour activity in addition to being very effective against various bacterial species. And the antibiotic soraphen, by disturbing the eukaryotic cell growth cycle, appears to have excellent activity against fungi and moulds.

Among known myxobacterial antibiotics, TA appears the most promising as a potential therapeutic agent: it shows a wide spectrum of activity and low toxicity for the host. According to Eugene Rosenberg (Tel Aviv University, Israel), TA, which many strains of M. xanthus produce, inhibits bacterial cell wall synthesis and has unusual adhesive properties. TA's adhesive nature may prove useful in certain clinical situations, such as the treatment of catheters or artificial devices to prevent infection. Rosenberg adds that the antibiotic is now being evaluated in the clinic, and his group is constructing M. xanthus strains capable of producing TA commercially. (Extracted from Bio/Technology, Vol. 6, August 1988)

Bacteria take the chance out of evolution

Bacteria can mutate in ways that specifically enhance their survival. This discovery, by John Cairns, Julie Overbaugh and Stephen Miller at the Harvard School of Public Health in Boston, challenges one of the cherished tenets of Darwinian natural selection - that mutation is spontaneous and random.

Evolution by natural selection has been considered to be a two-stage process. First, mutations crop up with no regard for what is happening to the organism. They occur at random. If one of those mutations confers a reproductive advantage on its holder, that mutation will be favoured by natural selection and the genetic make-up of the population will change. It is selection that adds the directional component to evolution by filtering out almost all of the randomly-produced mutations. In Cairn's experiments, by contrast, bacteria produced mutations in direct response to a change in their environment.

The apparent proof that mutation occurs independently of selection came from the so-called slot-machine experiments conducted in the 1940s by Salvador Luria and Max Delbrück. Cairns, however, points out that these classic experiments have a flaw. Although they prove that some mutations do arise spontaneously and at random, they do not rule out the possibility that others might be non-random and directed at meeting a particular environmental challenge. Phage, for example, kills all bacteria that are not resistant. The bacteria have no chance to "try" to become resistant. To overcome this objection, Cairns and his colleagues studied less drastic selection, where mutants are rewarded by better growth, but non-mutants survive so that, in Cairn's words, "they can at least have the opportunity to perform directed mutation".

In the first experiment, the team looked at bacteria unable to use the sugar lactose. They have a mutation which prematurely stops the decoding of the gene for beta-galactosidase, one of the enzymes involved in lactose fermentation. When a culture of these bacteria was transferred to a medium that contained lactose, colonies appeared of mutants that were now able to use the lactose. Some of these were clearly the result of spontaneous mutations that had occurred while the cultures were growing. But others took much longer to appear, suggesting that the mutation took place late in the experiment, once the bacteria had been forced to try to use lactose. The number of these "late" mutants followed a Poisson distribution, as would be expected if they occurred in response to selection.

In this first experiment, then, E. coli somehow produces the most appropriate mutation, one that changes the full stop in the beta-galactosidase gene into a readable codon for the correct amino acid. The replication of DNA is an error-prone process at the best of times - with special proofreading enzymes that correct the many mistakes - and so, as Cairns admits, this one result does not seem too hard to believe. He followed it up by looking for much larger mutations which would seldom, if ever, arise by chance.

The final experiment that Cairns and his colleagues report comes even closer to the sort of selection one might expect in the real world. It exploits a technique developed early this century for classifying bacteria according to their ability to use certain sugars. Wild E. coli, for example, can ferment lactose whereas Shigella and Salmonella cannot. Some species, however, are so-called "late" fermenters of certain sugars. That is, it may take a week or more before the bacteria start using an unusual food source. Shigella sonnei, for example, is a late fermenter of lactose.

In fact, bacteria possess several such cryptic genes, which are brought into play only when needed. The mechanism of activation varies. Sometimes, another piece of DNA is inserted upstream of the desired gene and switches that gene on.

In other cases, the DNA sequence needs several specific changes before the cryptic gene will function properly. Cairns and his group studied one such cryptic gene which allows E. coli to ferment lactose even when its beta-galactosidase gene is not working.

The gene is call ebg, and it needs at least two mutations to turn it on. The first is a change in the repressor, a DNA sequence which codes for a protein that normally keeps ebg inactive. The second is a change to ebg itself. The enzyme produced by the usual version of the gene cannot, in fact, break down lactose; it needs a mutation to make it effective. Under normal circumstances, each of these two mutations happens roughly once in every 100 million generations. Both mutations are needed, which would happen by chance roughly once every 10 million billion generations.

"That such events ever occur seems almost unbelievable," says Cairns, yet colonies do appear after about two weeks. That they do, without at the same time gathering a lot of neutral and outright harmful mutations, suggests to Cairns that bacteria must have access "to some reversible process of trial and error".

Cairrs suggests that the cell might make a set of variable RNA messages - which carry the genetic instructions from the DNA to the machinery that makes proteins according to those instructions - and reverse-transcribe the most effective of these back into DNA.

It would need some way of monitoring "effective" RNA, but if it reverse-transcribed only those messages present when it started to grow again, it would most likely capture the message that had indeed enabled growth to resume. (Source: New Scientist, 22 September 1988)

Newly developed bacterial strain removes organic sulphur from coal

Investigators at the Institute of Gas Technology (IGT) have produced a strain of bacteria that selectively removes organic sulphur from coal without degrading the coal itself. With further genetic engineering of the bacteria - to increase the rate of sulphur extraction - a process for the complete pre-combustion desulphurization of coal may be possible.

This research, funded by the US Department of Energy, is part of an expanded biotechnology effort at IGT. Environmental microbiologist John J. Kilbane II, who heads up the research, notes that up to 90 per cent of inorganic (pyritic) sulphur in coal can be removed either biochemically or by other means. The organic sulphur - sulphur chemically bound within the molecular structure of the coal - is another matter. Until 90 per cent of all the sulphur, organic and inorganic, can be removed, it will be necessary for those who burn coal to buy and maintain expensive post-combustion desulphurization equipment and to dispose of great quantities of solid sulphurous wastes.

If the sulphur could be removed prior to combustion, that would be of great advantage, particularly if little or no additional pre-treatment equipment were necessary. Low-sulphur or no-sulphur coals are not abundant enough to meet anticipated energy needs, although they are certainly of great value in the total energy picture. The area of greatest potential impact is that of large coal-burning steam generation plants used to produce electricity. Other large industrial uses would also be affected.

For some time, it has been observed that there is acidic drainage from stockpiles of coal resulting from bacterial action. However, this microbial action is almost entirely limited to inorganic sulphur. It is the result of action by the bacteria Thiobacillus ferro-oxidans, Thiobacillus thio-oxidans, and Sulfolobus acidocaldarius. The thrust of Kilbane's research is the development of bacteria that will similarly remove the organic sulphur at rates that will be commercially attractive.

For developing a microbiological process to remove organic sulphur from coal, the first need is for one or more micro-organisms that have an affinity for cleaving carbon-sulphur bonds - that is, which are capable of sulphur-specific metabolism of organic compounds. Two such organisms have been produced at IGT. One of them is a mixed bacterial culture designated IGT-S7, which selectively extracts only sulphur. A second extracts sulphur but also degrades the adjacent carbon to some extent.

The general technique for producing IGT-S7 and other cultures of interest is selective and controlled feeding of the bacteria. The challenge to Kilbane was to operate laboratory culture media such that they favour only the organism of interest. The general idea is to devise a system that permits only the fittest strain to survive the culture.

The discovery of IGT-S7 by Kilbane's group is an integral part of a broader biotechnology effort at IGT. Cavit Akin, associate director of the IGT biotechnology group, notes that IGT has been pursuing biotechnology research for about 15 years, all of it generally aimed at assisting the energy industry in the areas of energy utilization and supply and environmental improvement. Until recently, much of the effort focused on increasing the supply of methane via microbial conversion of biomass.

This methane research continues, but other efforts are also under way, including biochemical degradation of heavy chemicals in the soil and microbial clean-up of waste at former town-gas manufacturing sites. Similar procedures are being employed in groundwater clean-up. It is also anticipated that coal desulphurization techniques, such as that expected to develop with IGT-S7, will be applicable to the desulphurization and denitrification of Eastern oil shales.

Yet another research effort is aimed at the biological solubilization of coal for eventual biomethane production. Microbial solubilization of coal has been observed with pure cultures of lignin-degrading fungi and streptomyces. However, solubilization with other microbial species seems to depend on the oxygen content of the coal. Lignite appears to be the easiest coal to solubilize, and there is further evidence that increasing the oxidation state of coal by pre-treatment with nitric acid or hydrogen peroxide produces the highest degree of solubilization. This may be as high as 80 per cent of the coal. IGT is now examining the microbial activity of several cultures, including Phanerocheate chrysosporium and Cunninghamella YML-12.

IGT has also begun an investigation of the biochemical production of chemicals from methane. At present, the product of choice is methanol, already a high-volume commodity chemical. The IGT researchers speculate that a successful microbial production technique for methanol would circumvent some of the homogeneous catalytic problems that are currently experienced. All told, IGT is currently pursuing at least 15 biochemical projects in the general areas of gas supply, gas utilization, and environmental clean-up. (Abstracted with permission from Chemical and Engineering News, 29 August 1988, p. 37-38. Copyright (1988) American Chemical Society)

Hybrid bacteria may help to treat AIDS

A toxin that binds selectively to HIV-infected cells could help treat AIDS, according to researchers at the National Cancer Institute and NIAID. The

toxin is a hybrid protein, consisting of a molecule that binds to gp120, attached to a cell-killing toxin. The newly-engineered protein does not attack the HIV itself, since it is generally hidden within cells. The hybrid bacterium is produced in engineered E. coli bacteria, which produces CD4 receptor molecules that bind to the gp120 expressed on the surface of infected cells and the toxin normally produced by Pseudomonas. (Similar technology is being developed to recognize and kill tumour cells.) The engineered hybrid protein is effective against infected cells in culture. Animal studies will be needed before the technique can be tested in humans. (Extracted from Science News, 24 September 1988)

Technology for cell fusion of Bifidobacterium

Snow Brand Milk Products Co. Ltd. has succeeded in obtaining protoplasts of Bifidobacterium which exist in human intestines and also succeeded in regenerating these protoplasts. As a result, it is now posible to achieve cell fusion of Bifidobacterium.

The company earlier isolated a variety of bacterial components and metabolic substances displaying excellent biological effects from Bifidobacterium such as suppressing the cholesterol level in blood and suppressing tumour activities. These bacterial components and metabolic substances are expected to lend themselves to the manufacture of metabolic functional foods and medical drugs. Therefore, the company is presently performing research with the aim of fusing the cells of these Bifidobacteria, further improving the species of bacteria possessing desirable functions and utilizing them for producing fermented lactic products.

The bacteria succeeded in protoplast form and regenerated successfully consisted of two kinds - Bifidobacterium pseudolongum SBT2908 excelling in acid resistance and Bifidobacterium longum SBT2933R that has been proven to suppress the cholesterol level in rat blood. The company plans to delve further into research with the aim of fusing different kinds of bacteria. Further details from Snow Brand Milk Products Co. Ltd., 13 Honshio-cho, Shinjuku-ku, Tokyo, Japan. (Source: JETRO, September 1988)

Research on viral genes

Hormones turn virus into cancer agent

Human papilloma virus, which causes genital warts, is able to interact with a common virus to cause cancer, according to a laboratory model of the development of cancer. If the same mechanisms operate in people, women infected with the virus who also take oral contraceptives could be more likely to develop cervical cancer.

The Canadian researchers who carried out the work have called for new epidemiological studies to examine the incidence of cervical cancer in women infected with this virus who also take oral contraceptives.

The scientists, from the Memorial University of Newfoundland, tested two types of human papilloma virus, HPV-16 and HPV-11. HPV-16 (or closely related strains) is present in almost three quarters of cervical cancers. HPV-11, by contrast, causes benign warts on the external genitals. The researchers found that only HPV-16 caused cancerous changes in the presence of the hormone, and not HPV-11.

Mary Pater and Alan Pater and their colleagues carried out the study on kidney cells which are closely related to the cells of the cervix: both types are epithelial cells, the only kind of cell in which HPV will grow. The researchers added the genetic material of either HPV-16 or HPV-11 to the kidney cells, as well as a human oncogene which seems to be activated in all tumours of the cervix studied to date. When they added a chemical called dexamethasone, the only cells to become "transformed" into cancer cells were the ones containing the genes for HPV-16.

The growth of the cancerous cells was dependent on the presence of dexamethasone - a synthetic analogue of a type of hormone known as a glucocorticoid. When dexamethasone was present, cells grew five or six times more rapidly.

The natural hormone progesterone is also a glucocorticoid. Oral contraceptives contain synthetic hormones, called progestagens, which act in a similar way.

The researchers found that kidney cells containing the DNA for HPV-16, as well as the appropriate oncogene, did indeed become transformed into cancerous cells in the presence of progesterone. These cells also caused tumours when injected into suckling rats.

The researchers decided to study the ability of glucocorticoid hormones to cause cancerous changes in the presence of HPV because earlier work, by German scientists, had shown that the genetic material of the virus contained a sequence which normally responds to glucocorticoid hormones. This research was probably the closest correlation that anyone had made between HPV-16 and cancer of the cervix. The problem with epidemiological studies that had been carried out so far was that they had looked at women taking the pill, but had not examined separately the incidence of cancer in such women infected with HPV-16 and not infected with HPV-16.

The team is now trying to grow cervical cells in culture, which is technically difficult. (Source: New Scientist, 5 November 1988)

Pinpointing the chinks in the HIV's armour

The mysteries of the molecular biology of the virus are yielding new targets for antiviral drugs. Jim Neil of the Beatson Institute in Glasgow reviewed the possible approaches.

The very complexity of the genetic structure of the human immunodeficiency virus and its life-cycle could make it vulnerable to interference by drugs. One promising example is a variety of compounds that inhibit the uncoating of viruses within the host cell. Michael Rossmann at Purdue University in Indiana has identified compounds that inhibit the uncoating of picornaviruses which act by fitting into a cleft in the core shell of picornaviruses. These viruses do not have a fatty envelope layer as HIV does, but the compounds are soluble in lipids, so the lipid membrane of HIV should not prove too great an obstacle.

Rossmann is now studying the core protein of HIV to determine its structure. The next stage of

the research would be to design compounds that fit in a cleft of this protein.

Another approach that has come to the fore in recent months is to interfere with the action of the protein products of HIV's regulatory genes. These genes are called tat, rev and nef. The products of the tat and rev genes seem to be essential if the virus is to make any of its other proteins. The protein made by the nef gene down-regulates the production of the virus's structural proteins, without which viral replication is impossible.

Any of these proteins could be useful targets for anti-viral drugs. The first step is to work out their function more precisely. Researchers at the Medical Research Council's Laboratory of Molecular Biology in Cambridge are producing the tat gene product in bacterial cells using genetic engineering. Other researchers at Oxford are also trying to produce biologically-active protein from this gene. They have injected the protein into the nuclei of toads' eggs and it appears to be active.

Once scientists have the purified proteins manufactured by these three genes, they can study the functions of these molecules by blocking parts of the proteins with monoclonal antibodies. Researchers will also be able to study the effect of the proteins on cells.

Eventually, the aim would be to inhibit some of these proteins, perhaps with short synthetic segments of protein that resemble the protein's active site. An alternative might be a short sequence of genetic building blocks which would bind irreversibly to the virus's genetic material, preventing manufacture of the protein.

Another vulnerable point in the life-cycle of the virus might prove to be during the assembly of viral particles. Raymond Dwek of the University of Oxford has identified substances that could inhibit enzymes known as glycosidases. These have the task of adding sugar molecules to the proteins of the virus, an essential step in the manufacture of infectious viral particles.

One further strategy that researchers funded by the directed programme are working on is to interfere with the maturation of the new viral particles in the cell. Viral enzymes called proteases play a vital role in cleaving large precursor proteins into smaller molecules which form the mature virus. The fact that a viral enzyme carries out this step, rather than one supplied by the host cell, suggests that human cells have no closely related enzymes. So it might be feasible for researchers to inhibit this enzyme specifically without adverse effects on the cell's enzymes. (Source: New Scientist, 8 October 1988)

Decoy protein enters human trials

A novel treatment for people infected with HIV began trials at three medical centres in the US. The substance is a protein which normally occurs on the cells which HIV infects, and to which the virus binds in order to enter the cell. The theory is that if there are quantities of this protein, called CD4, in the blood of an infected person, the molecule will mop up the virus, preventing it from attacking cells.

The Californian biotechnology company Genentech has produced the protein in bulk using genetic engineering. They have called the recombinant protein rCD4. The American Food and Drug Administration approved within two weeks the application for trials of rCD4 in humans.

About 50 volunteers with AIDS will take rCD4 for six months to determine whether it has serious side-effects. If these people tolerate the protein well, more volunteers will test its effectiveness in curbing the decline of the immune system following infection.

CD4 occurs in the body on the surface of cells such as T-helper cells and macrophages, the main cells which HIV infects. Until recently, scientists believed that the virus could enter the cell only if the CD4 molecule was present on the cell's surface. Some researchers now believe, however, that the virus may be able to enter the cell via another receptor.

Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland has found that the virus can infect immature blood cells found in the bone marrow, which do not have CD4. Other researchers are not yet convinced of the evidence for anothe. receptor. Some of them believe that HIV's ability to bind to and infect a cell may be the most sensitive test we have for the presence of CD4. The virus needs only one receptor in order to enter the cell, and currently available tests may not be sensitive enough to detect such low concentrations of CD4.

A second group of researchers in the US, some of them from the biotechnology company Genelabs, also based in California, is planning more cautious tests of a fragment of CD4. Jeffrey Lifson, Lee Eiden and their colleagues reported recently that they had identified a short segment, or peptide, of CD4 which could prevent HIV from infecting its target cells.

They prepared a range of peptides from the CD4 protein, and found that a mixture of one of these with some of the by-products of synthesis could block the ability of HIV to induce the fusion of cells grown in the laboratory. To their surprise, subsequent tests showed that the active ingredient was not the peptide itself, but one of the by-products of synthesis.

Further investigations identified a second peptide, called CD4(83-94), with a benzyl group at two positions, as the active component. (Scientists need to add and then remove "protecting" groups, such as the benzyl group, during the automated synthesis of peptides.) It appears that the attached benzyl groups alter the conformation or shape of the peptide, so that it more closely resembles its conformation in the whole protein.

This group of researchers believes that a peptide of CD4 may prove more useful than the whole molecule, for several reasons. First, many proteins, because of their size and/or electrical charge, cannot cross the blood-brain barrier - the tightly-linked cells which isolate the central nervous system from the blood. Any effective therapeutic agent against AIDS would have to be able to enter the brain, because the brain often contains infected cells and may form a reservoir of infection.

Peter Nara, one of the researchers involved, from the Frederick Cancer Research Facility at

Frederick, Maryland, says that CD4 is too big to cross the blood-brain barrier. The team hopes, however, that a peptide would be small enough to pass into the central nervous system.

Secondly, the whole protein may stimulate the immune system to produce antibodies against it. Small peptides are less likely to provoke this reaction. A third reason for using a peptide is that, unlike whole proteins, peptides are more resistant to attack by enzymes called proteases which break down protein molecules.

The team found that the active peptide could prevent four isolates of HIV-1 with widely variant envelope proteins from infecting cells. In addition, it blocked infection of cells by the simian immunodeficiency virus (SIV). This virus also uses CD4 to enter cells of its host.

As a result, the researchers can test the peptide's therapeutic effect initially in rhesus monkeys infected with SIV. Before the research reaches that stage, however, the scientists intend to conduct studies in healthy uninfected animals to determine how these primates metabolize the peptide. (Source: New Scientist, 18 August 1988)

US researchers find pathogen

US researchers have discovered that the pathogen causing the pneumonia which kills AIDS sufferers may be a fungus. Jeffrey Edman at the University of California at San Francisco and co-workers at other laboratories report that the genetic code for ribosomal RNA of the pathogen Pneumocystis carinii is more related to yeast than to protozoan RNA.

Presently it is not possible to grow the pathogen in vitro but, Edman explains, it will now be possible to isolate and clone those genes that may be potential targets for drugs.

Edman and his co-workers at the Hormone Research Institute, University of California, in collaboration with researchers at the National Jewish Centre for Immunological and Respiratory Medicine, at Denver, Colorado and the National Institutes of Health, plan to look at the human pathogen.

To date research has focused on the rat pathogen and there is some suggestion there may be differences between rat-infecting and human-infecting strains. This will also have an important bearing on subsequent drug testing with animal models.

Eventually the scientists intend to pull out the genes that will be targets for drugs. (Source: European Chemical News, 8/15 August 1988)

Advances on a vaccine

Researchers from Zaire, France and the US say that they have identified two regions of HIV's envelope protein which may be useful components of a vaccine against the virus.

The latest results show that, in laboratory experiments, T cells from most of the people who had been immunized recognized two peptides (short fragments) of the envelope protein. The cells responded by proliferating. T cells from three people who had been boosted with envelope protein plus antibodies, however, showed a more vigorous response. The researchers say that boosting with antigen-antibody complexes may be especially effective.

The two peptides which the T cells recognized seem to be in regions of the envelope protein which mutate less rapidly than other parts of the protein. One of them overlaps a portion of the protein which other researchers have suggested is involved in binding to the CD4 receptor on the surface of the T cell. As a result, the scientists say, these peptides "should be effective in eliciting immunity cross-reactive with a large number of viral isolates". (Source: New Scientist, 1 September 1988)

US scientists unveil potential AIDS therapy

US scientists may have come up with a strategy which could prove effective in combating AIDS. Researchers at the Carnegie Institution of Washington, in Baltimore, Maryland have genetically engineered mouse cells to produce a mutant viral protein which makes the cell resistant to infection by the virus.

Steven McKnight and his colleagues have introduced a gene from the herpes simplex virus type 1 (HSV-1) into mouse cells that produces a mutant form of a protein called VP16. This protein, in its normal form, is responsible for sticking to, and switching on, the HSV-1 reproduction system.

The US scientists say the mutant form binds to the reproductive genes but fails to switch them on. This means the cells are effectively immune to the herpes virus because once inside the cell it is unable to reproduce.

Nobel Prize winner and director of the Cambridge, Massachusetts-based Whitehead Institute for Medical Research, David Baltimore heralds this research as a possible basis for combating AIDS and other viruses.

AIDS is primarily an infection of blood cells, T lymphocytes and monocytes/macrophages which derive from haematolymphoid stem cells. It has already been demonstrated by a number of research groups that these stem cells can be engineered to switch on foreign genes introduced using a retrovirus.

Baltimore suggests that bone marrow cells, including the important stem cells, could be taken from an AIDS sufferer and infected with either a virus or piece of DNA coding for a protein that can interfere with intracellular growth of the AIDS virus. The modified stem cells would then be injected back into the patient.

Baltimore contends that it is unlikely that such a procedure would be used for uninfected people but would be used as a therapeutic on AIDS carriers. However, he adds that it is still at the cellular level, a form of immunization, not a therapeutic attack on the virus.

Designing a molecule that interferes with the AIDS reproductive cycle, however, may not be as easy as McKnight's mutant VP16 for the herpes virus. (Source: European Chemical News, 3 October 1988)

AIDS virus coat activates T cells

Gp120 is not simply an inert protein that forms the outer coat of the AIDS virus. The molecule, which is being used as the basis for several experimental AIDS vaccines, appears to have

biological activity of its own. New information on the behaviour of gp120 may help researchers understand more about the complex biology of T lymphyocytes.

Gp120 stands for the coat glycoprotein of the AIDS virus, which has a molecular weight of 120 kilodaltons. When it binds to its receptor - the CD4 antigens on the surface of normal T4 lymphocytes - it triggers a rise in intracelluiar calcium and stimulates resting T cells to enter the cell cycle, according to David Center and Hardy Kornfeld of Boston University School of Medicine and their colleagues. Other researchers who have attempted similar studies do not obtain the same responses, however.

It is not clear whether the new information will help to explain how the AIDS virus, called human immunodeficiency virus type 1 (HIV-1), kills T4 lymphocytes or causes disease. Rather, it supports a previous finding that the CD4 molecule may act as a receptor for a naturally occurring growth factor, possibly a lymphokine secreted by T8 lymphocytes. Gp120 mimics the action of the lymphokine because it induces fresh, uninfected T4 cells to become motile and it stimulates more of them to express the interleukin-2 growth factor receptor on their surface - an indication that the cells are activated from the G_0 or resting phase of the cell cycle to the G_{1a} phase.

Center does not yet know the amino acid sequence of the lymphokine, which he calls lymphocyte chemoattractant factor, nor does he know how closely it might resemble gp120. But both molecules bind to CD4 and stimulate the breakdown of phosphatidyl inositol, a membrane lipid, to form inositol trisphosphate. They also induce about a twofold rise in intracellular calcium ions, largely from intracellular sources. Contrary to data from other experimental systems, the calcium concentration in the lymphocytes increases before the concentration of inositol trisphosphate reaches its peak. (Source: Science, Vol. 242, 28 October 1988)

The AIDS virus can take on many guises

The AIDS virus, unlike the leopard, not only can change its spots but does - often and fast. Researchers have known for some time that the virus genome may differ from one infected person to the next. They are now learning that it can even show dramatic variation within a single individual. Moreover, the AIDS virus may be spinning off so many variants because it is inherently prone to make mistakes when it reproduces itself.

These genetic changes may be reflected in the behaviour of the AIDS virus variants, perhaps influencing the course that the disease takes in infected individuals. In particular, they may help the virus escape from the body's immune defences. The extreme genetic variability of the AIDS virus also appears to be still more bad news for efforts to develop a vaccine to protect against AIDS.

AIDS virus variability was the major focus of a "Conference on Genetic Variation of Immunodeficiency Viruses", which was held on 19 and 20 July at the National Institutes of Health in Bethesda, Maryland. At the conference, for example, George Shaw of the University of Alabama in Birmingham described his group's characterization of the variation in human immunodeficiency virus 1 (HIV-1), as the AIDS virus is known scientifically. The variation turned out to be extensive.

Shaw and his colleagues, including Michael Saag and Beatrice Hahn of Alabama and Wade Parks of the University of Miami School of Medicine, cloned individual virus genomes from samples isolated from two patients. Seventeen of the 27 HIV-1 clones prepared from one patient's virus turned out to be genetically different, as did 9 of the 17 clones obtained from the second patient.

The researchers estimate that the nucleotide sequences of the various cloned viruses obtained from one patient at a given time vary by 2 to 3 per cent. "The data imply," Shaw says, "that there is no such thing as an [AIDS virus] 'isolate'. You probably have enormous numbers of slightly different viruses in an individual."

Moreover, the virus apparently continues to mutate as time goes by. The clones derived from another virus sample obtained from the second patient 16 months after the first showed even greater genetic variation. Thirteen of 18 were different and all were distinct from the earlier viruses.

Also at the meeting, Thomas Kunkel of the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, North Carolina, presented new data that may help to explain why HIV-1 mutates as readily as it does. The HIVs are retroviruses and have RNA as their genetic material. During the retrovirus life-cycle, an enzyme called reverse transcriptase copies the RNA into DNA. The DNA, which may become integrated into the genomes of infected cells, then directs the synthesis of new RNA molecules for packaging into viral particles during reproduction.

Kunkel and his colleagues have been studying the reverse transcriptases of several retroviruses, now including that of HIV-1. These enzymes generally tend to be somewhat inaccurate. The enzymes that make DNA copies of DNA have a proofreading activity that allows them to recognize when they have made a mistake and then remove it. The reverse transcriptases studied so far lack this ability.

The NIEHS researchers have found that the HIV-1 enzyme errs even more often - by a factor of roughly 10 - than other reverse transcriptases. The generation of numerous variants may thus be an intrinsic property of HIV-1.

Peter Nara of the Frederick (Maryland) Cancer Research Facility of the National Cancer Institute described results that further buttress this idea - and also bode ill for efforts to develop an AIDS vaccine. As part of the NCI vaccine project, Nara and his colleagues injected chimpanzees with HIV-1. The researchers then began isolating HIV-1 from the animals at two-week intervals. The very first HIV-1 samples recovered were already resistant to neutralizing antibodies raised specifically against the parent HIV-1 strain even though the animals had not yet mounted detectable antibody responses to the virus.

Even though HIV-1 variants may not be arising as a result of immune selection, their generation may none the less help the virus escape control by the immune system. David Looney of the Walter Reed Army Institute in Washington, D.C., in collaboration with Flossie Wong-Staal and Robert Gallo of NCI, has shown that a change of a single amino acid in the HIV-1 envelope protein is sufficient to make the virus resistant to antibody neutralization.

In addition to showing altered resistance to antibody neutralization, the genetic variants of HIV-1 may also differ in their biological activities. These differences may influence the course that AIDS takes in infected individuals. In some patients, for example, suppression of the immune system is the principal manifestation of the disease, whereas for others neurological degeneration may be dominant. What happens may be determined by the type of cells infected by AIDS virus variants, which researchers are now finding to differ in their cell preferences.

In one such demonstration, Wong-Staal, Gallo, and Amanda Fisher, who is also a member of the NCI group, took envelope gene sequences from six of the variant HIV-1 clones produced by Shaw and his colleagues and used them to construct hybrid HIV-1s that were identical except for their envelope proteins. The researchers found that the hybrids differed widely in their ability to grow in cells, including T cells and monocytes, which are the major cell types that HIV-1 infects in AIDS patients.

Another indication that HIV-1 variants differ in their ability to infect cells comes from Yoshio Koyanagi, who works with Irvin Chen at the University of California School of Medicine in Los Angeles. Koyanagi isolated two genetically distinct HIV-1s from an AIDS patient who had had severe neurological deterioration before he died.

One variant, which had been obtained from cerebrospinal fluid, infected glial cells (a sort of accessory cell for neurons), but reproduced very poorly in monocytes. The other variant, which had been isolated from the brain, displayed the opposite cell specificity. Since monocytes probably carry HIV-1 from the bloodstream into the brain, it is not surprising to find a brain isolate with a preference for infecting monocytes.

Cecilia Cheng-Mayer, from Jay Levy's group at the University of California School of Medicine at San Francisco, reported at the genetic variation meeting that the HIV-1s isolated from AIDS patients become more effective at killing cultured cells as the patients' symptoms worsen.

The time needed for cytopathic HIV-1 variants to emerge may contribute to the long lag period between infection and the development of AIDS symptoms, although other factors, such as the ability of the infected person's immune system to fight off the AIDS virus, might well be involved, too.

What researchers have not yet done is identify the particular changes in HIV-1 that influence the virus cell's specificity or ability to kill cells. Results with a feline AIDS model that were described by James Mullins of the Harvard School of Public Health may provide some clues to the features that influence the virulence of immunodeficiency viruses, however.

The feline leukaemia virus work also implies that current techniques for isolating HIV-1 may not detect an important subset of pathogenic variants. The replication-defective feline viruses were cloned directly from cat tissues, whereas the HIV-1's are generally obtained by culturing cells from AIDS patients with other cells in which HIV-1 will grow. This co-culture step might result in a loss of cytopathic variants, which will kill the cells they infect. Meanwhile, recipient cells that have acquired variants that are not very effective cell-killers will survive and multiply.

Whether these HIV-1 variants have anything to do with the development of human AIDS remains to be seen. Nevertheless, the ability of HIV-1 to generate so many variants may help to explain the unusual pathogenic features of AIDS, at the same time that it helps to frustrate researchers' efforts to produce a vaccine for the disease. (Source: Science, J. L. Marx, Vol. 241, p. 1039-1040, 26 August 1988. Copyright 1988 by the AAAS)

HIV: more tricks up its sleeve

Two recent studies suggest the AIDS-causing virus, HIV, may create much of its biologic havoc not only by destroying the body's immune cells, but also by interfering directly with the function of other cells. One report provides the first evidence that HIV may by itself be carcinogenic. The other indicates that a protein found on the viral surface can - without any help from the rest of the virus - kill nerve cells. This could provide an explanation for AIDS dementia in patients who show no signs of immunosuppression.

Using gene transfer techniques, Jonathan Vogel and his colleagues at the National Cancer Institute in Bethesda, Md., along with researchers at the University of California, Davis, created a line of mice whose cells had permanently incorporated a critical HIV regulatory gene called tat.

By splicing the tat gene into mouse embryo cells, they created three lines of mice that continuously expressed tat protein in their skin cells. After four months, microscopic examination of the skin cells from these mice showed cellular changes similar to those seen in the early stages of Kaposi's sarcoma. At 12 to 18 months of age, 10 male mice, or about 15 per cent of the male mouse population, developed skin tumours. Others showed a propensity for spontaneous bleeding into the skin. Microscopic analysis again revealed many similarities between the mouse tumours and those seen in Kaposi's sarcoma - all the more significant, the researchers say, because Kaposi's-like lesions are not seen in mice.

In a second study, researchers at the National Institutes of Health in Bethesda tested the effects of an HIV envelope protein, gp120, on cultured brain cells isolated from foetal mice. Brain cells, like immune system cells, have so-called CD4 receptors on their outer membranes, which serve as "docking sites" for HIV's gp120 glycoprotein.

While neuropsychiatric deficits, including early memory loss and progressive dementia, often accompany AIDS, scientists have remained uncertain whether these effects result directly from HIV infection of nerve cells. Douglas E. Brenneman and his co-workers found that gp120 alone could bind and kill mouse neurons.

Moreover, they showed that a hormone called vasoactive intestinal peptide (VIP) - which shares many of the same genetic sequences found in gp120 - can prevent neuronal death when nerve cells are exposed to gp120, perhaps by blocking gp120 binding to nerve cells.

On the basis of their findings, Brenneman and his colleagues suggest that gp120 - which can be produced and secreted by HIV-infected white blood cells - may in some patients travel to the brain, where it can cause neuronal abnormalities even without obvious sign of infection there. (Source: Science News, Vol. 134)

Teams unmask the real seal virus

The virus that has infected thousands of seals around the coasts of Europe is neither canine distemper (CDV) nor rinderpest (RPV), as reports had originally suggested. Instead, the virus appears to be a new species, in the same genus as CDV and RPV, which some researchers have called phocine distemper.

Two teams in Britain, who used different methods to investigate the new virus, drew broadly similar conclusions. Brian Mahy and his colleagues at the Agricultural and Food Research Council's Institute for Animal Health at Pirbright in Surrey analysed genetic material from the virus, in tissue from the spleen of a common seal. Louise Cosby of Queen's University of Belfast in Northern Ireland and colleagues examined the antigens in serum from a seal.

The team at Pirbright used DNA probes - cloned, radio-labelled sequences of single-stranded DNA that code for particular proteins - to analyse the degree of similarity between the RNA of the seal virus and genetic material from the four other known species of the genus of morbilliviruses - CDV, RPV, measles and peste des petits ruminants (PPRV). If the sequence of RNA from the unidentified virus is sufficiently similar to a particular probe, the strand of RNA will bind with the probe, forming a radioactive patch.

Mahy's team found that a morbillivirus was present but that it was not CDV. The researchers also found some relationship between the RNA of the seal virus and the gene for a protein, called the nucleocapsid protein, in RPV and PPRV. However, they concluded that the new virus was "neither RPV nor PPRV" because the match with the gene was only partial and because the probes for this protein in RPV and PPRV distinguish the viruses "unequivocally" from each other.

Cosby's team used monoclonal antibodies - specific, purified antibodies that recognize and bind to particular antigens - to compare the antigenic properties of the seal virus with the other morbilliviruses. They found that the virus is closer to CDV than to RPV or measles, but that some of its proteins are different. They tested the seal's serum against 17 anti-CDV antibodies. Only 12 of the 17 recognized and bound to antigens from the seal's serum, compared with a complete match - 17 out of 17 - in serum infected with CDV. The researchers suggest that the seal virus is a new species, rather than a new strain of CDV, because the five different strains of CDV have almost uniform profiles for these 17 antigens.

Chris Bostock, a member of the research team, says that the vaccines against CDV that some captive seals have now received will almost certainly have immunized them, at least partially, against the new morbillivirus. (Source: New Scientist, 18 November 1988)

Research instrumentation

A new gel for viral purification

Chisso Corp. (Tokyo) and the Chemo-Sero-Therapeutic Research Institute (Kumamoto City) have jointly developed Cellufine Sulphate cellulose gel for adsorption of viruses and proteins by affinity chromatography. The purified viruses and proteins are used to produce vaccines. Chisso will soon begin commercial production of the gel; Seikagaku Kogyo (Tokyo) and Amicon Div. (Danvers, Mass.) of W.R. Grace will market it. The product represents a combination of Chisso's know-how in chromatography gel production and the institute's basic technology for inserting sulphuric esters into cellulose, which gives the gel its selective binding characteristics. The institute, known for vaccine development and production, says Cellufine Sulphate is "the first efficient chromatography gel for virus purification". The gel has affinity for rabies, Japanese encephalitis, influenza and other viruses as well as hepatitis B virus surface antigen. It also has affinity for some proteins, including complement (C)5, C6, C8 and C3 activator as well as trypsin. (Source: Chemical Week, 9 November 1988)

New column for plastic purification

Designed exclusively for plasmid purification, the new Plasmid Isolation Column System (PICS) from Applied Biosystems utilizes paired ion reverse phase chromatography (RPC). Applied Biosystems claims that it is "the first company to recognize the benefits that this technique can offer plasmid purification". Separation is rapid and is complete within 30 minutes, compared with 50 minutes using anion-exchange chromatography (AXC) and at least 4 hours 40 minutes with ultracentrifugation. Details from: Applied Biosystems Ltd., Kelvin Close, Birchwood Science Park, Warrington, Cheshire WA3 7PB or on 0925 825650. (Source: Biotechnology Bulletin, Vol. 7, No. 9, October 1988)

New type of bioreactor using fibre support

The Research Institute for Polymers and Textiles of the Agency of Industrial Science and Technology at Tsukuba, Japan, has fabricated a new type of bioreactor using a fibre support.

An extremely fine polyvinyl alcohol (PVA) filament with a diameter of about 1 μm is formed into a braid capable of immobilizing various kinds of micro-organisms and enzymes without causing any clogging or compaction.

The fibre support used in the Research Institute's experiments is made of PVA fibres into which ammonio groups are introduced, and the positive charges of the ammonio groups attract the negative charges possessed by yeast fungi. However, accommodating this support intact into a column resulted in compaction, with gaps between the fibres getting extremely small and the micro-organisms themselves clogging the gaps, thereby entirely obstructing the substrate's passage.

The Research Institute has been engaged in research for several years with the aim of eliminating these phenomena and to develop a technology for utilizing the fibre support.

A distinct characteristic of the new bioreactor is that it uses a braid made of the fibre support. Simply winding the thread in a solenoid coil will increase the pressure drop and impair the substrate's flow, making the assembly unusable for the bioreactor. To cope with this, the Research Institute wound the thread in spiral braid form on a porous plastic core. Since the thread was wound with great tension, a very strong support with numerous gaps was obtained and voids were left even after continuous operation. As a result, a very strong support with numerous gaps was obtained.

In alcohol fermentation tests using yeast fungi the bioreactor was confirmed to be operable

continuously for as long as 10 days. Details from: The Research Institute for Polymers and Textiles of the Agency of Industrial Science and Technology, 1-4 Higashi 1-chome, Tsukuba City, Ibaraki Pref., Japan. (Source: JETRO, September 1988)

New gene assembler

Designed with particular concern for ease-of-use, a new fully automated oligonucleotide synthesizer - Gene Assembler Plus - was recently introduced by Pharmacia LKB Biotechnology AB. With the help of on-line monitoring, Gene Assembler Plus automatically calculates the coupling efficiency and yield of each cycle. Pharmacia LKB is also introducing a new range of PAC amidites and supports with Gene Assembler Plus, which permit deprotection in an hour. Details from: Pharmacia LKB Biotechnology AB, Molecular Products, S-751 82 Uppsala, Sweden. (Source: Biotechnology Bulletin, Vol. 7, No. 10, November 1988)

Uses of biosensors

Biosensors, discrete devices that incorporate biological - even living - components as part of a sensor or probe, will meet important measurement needs in medicine and veterinary medicine, biotechnology, environmental studies, food and agriculture and military applications, according to G.A. Rechnitz of the University of Delaware. Some of the research is a truly novel synthesis of biological and analytical concepts, and offers new ideas for measurement techniques by focusing on environmentally benign natural materials. Biosensors are comprised of a molecular recognition element (the biological component) and a transducing or signal-generating element (the instrumental component). Biosensor research blends molecular biology, chemistry, physics, materials science and bioengineering. Biosensors could be used to measure biochemical parameters for peanuts, cereal grains, fermentation broths, dairy products, wine and food additives; however, most researchers feel that success will first be achieved through contributions to medicine. Military uses could include detecting chemical and biological warfare agents.

Chemoreceptors are involved in chemical senses (e.g. olefaction and taste), metabolic and neural biochemical pathways and in various other physiological functions. Problems with interferences in immunological biosensors remain to be solved. (Abstracted with permission from Chemical and Engineering News, 5 September 1988, pp. 24-36. Copyright (1988) American Chemical Society)

General

Gelatin sponges used in research

Gelatin sponges can contain genetically-engineered cells within animal bodies to keep them functioning. Cell-impregnated sponges might even be developed as artificial organs to secrete desired proteins, according to W.F. Anderson of the National Heart, Lung and Blood Institute. In the mean time, the sponges will allow researchers to study the long-term behaviour of engineered cells in animals. Simply injecting engineered cells into animals is unsatisfactory, since it is hard to recover the cells to study them. The new system uses Upjohn's Gelfoam, which dissolves in the body after four to six weeks. Previous attempts had failed because the cells lacked sufficient blood supply. The new system uses a hormone that stimulates the growth of new blood vessels. (Extracted from Science News, 10 September 1988)

Silk studied by army

Researchers at the US Army Natick Research, Development and Engineering Center, Natick, Mass., USA are studying the use of genetic engineering and protein engineering techniques to modify silk proteins for enhanced high tensile strength fibres.

Silk was extensively studied at Natick in the 1960s due to its exceptional structural properties, including anti-ballistic performance. Now, using protein engineering, protein structures based on silk will be produced with the aim of higher strength, higher extensibility fibres for ballistic and other high performance fibre applications.

Silk is a natural crystalline protein polymer with a predominance of alanine and glycine amino acids. The excellent strength properties of this fibre come, in part, from the primary structure and, in part, from the conformation of the polypeptide chains, particularly the stacked B-pleated sheets. The excellent extensibility properties are derived from the amino acid sequences in the amorphous regions.

Modifications of the natural sequence of amino acids in the silk protein may offer a unique approach towards the development of high-performance fibres, according to the Army.

Genetic engineering and protein engineering techniques, chemical synthesis of model proteins based on silk and computer modelling of optimized silk-like proteins will be studied.

Techniques involving the modification of natural proteins through genetic engineering, the de-novo synthesis of new proteins through peptide chemistry, or the construction of synthetic genes for protein production will be investigated for their application in modifying natural silk protein for improved properties. (Source: Chemical Marketing Reporter, 5 September 1988)

Biodegradable plastic from cellulose acetate

A researcher at Purdue University has found a way to make biodegradable plastic that retains its strength and will not introduce micro-organisms into food that is packaged in plastic. Most biodegradable plastics are made with starch, which can be decomposed by bacteria or fungi, but the use of starch weakens the structure and can leach bacteria into food. By using cellulose acetate in place of starch, R. Narayan may have solved the problem. Cellulose acetate is a natural plastic derived from wood pulp instead of starch, and is subject to decomposition only after a reaction with soil alters its chemical structure to cellulose. Narayan developed a co-polymer that binds the cellulose acetate molecules with those of the synthetic plastic, allowing its strength to be maintained. Dow Chemical and Mobil have shown some interest in the process. (Extracted from Wall Street Journal, 2 September 1988)

Mass production of luciferase

Kikkoman Corporation (Japan) has succeeded in applying genetic engineering by using E. coli for the mass production of luciferase, the substance

excreted when a firefly (Luiciola cruciata) generates a glow.

Luciferase is an enzyme that generates a luminous glow by chemically changing the light-emitting substance luciferin with the aid of a substance known as adenosine triphosphate (ATP). ATP is a vital substance that serves as an energy warehouse in living bodies, so all kinds of organisms are known to contain ATP.

Accordingly, using luciferase and detecting the minute quantities of ATP existing in organisms will enable the number of organisms to be measured. Also, luciferase can be diagnostically used in biochemical determination of some materials in blood, and in enzyme immunoassay. Up to now, immuncassays were performed effectively using radicisotopes, but since they are expensive and also require rigid control, the use of these substances is limited.

In this respect, the light-emitting reaction of luciferase is quite sensitive, which enables recording on a photographic film and safe handling. However, since luciferase had been extracted directly from fireflies up to now, it was expensive and technology for its mass production was needed.

The new mass production technology consists of extracting luciferase genes from tail cells of the firefly and inserting it inside E. coli. Since these E. coli are highly reproductive and increase by 260,000 times in half a day it will be possible to mass produce luciferase effectively.

The utilization of luciferase still lies in its initial stage but embodies a broad range of possibilities, the more immediate of which include its application to (1) blood examinations, (2) checking of beer, fruit juice and other beverages against contamination by various kinds of germs, (3) examination of water and air contamination in clean rooms used in the process of semiconductors, and (4) application to various other industrial fields in which the existence of bacteria is detrimental.

The company plans to commence practical use of luciferase in 1989. Further information is available from Kikkoman Corporation, 25 Kanda-Nishiki-cho 1-chome, Chiyoda-ku, Tokyo, Japan. (Source: JETRO, September 1988)

Bioreactor for efficient production of plant hairy roots

Professor T. Kobayashi and his research group of the Department of Chemical Engineering, Nagoya University, the Department of Agronomy of the same university, together with food manufacturer Kinjirushi Wasabi Co., Ltd. have succeeded in developing a bioreactor for the efficient production of plant hairy root cells. This reactor uses a support of meshed construction for cell adhesion. Its lower part is equipped with a stirring mechanism and the system is designed to permit nutrients such as polypepton to be added from time to time.

In experiments to culture the hairy root cells of horseradish, it was confirmed that 11 grams of the useful hairy root cells were produced per litre of culture bed, a production efficiency that is twice that of conventional culturing systems.

Up to now, hairy root cells cultured with conventional types of reactors have been unstable, making their mass production impractical. To cope with the problem, the new reactor's support for immobilizing the hairy root cells is made of foamed polyurethane and a soft stirring mechanism equipped at the reactor's lower part for regular circulation of nutrients.

When culturing plant hairy roots, difficulty is encountered in selecting the optimum culture bed and nutrient supplementation conditions, but with this newly developed reactor, the two-stage dosage system is adopted and adds 1 gram of polypepton per litre of culture bed in the initial stage, and 5 grams in the latter stage. In horseradish culturing experiments, the growth of hairy roots started in two weeks and 11 grams of hairy root cells were produced per litre of culture bed by the 31st day.

The research group measured the culture bed's electric conductivity and discovered, in the process of the bioreactor's development, that the electric conductivity can be used for evaluating the total volume, making continuous production possible by using the new reactor.

Horseradish produces peroxidase, an enzyme that is used today as a marker enzyme in medical diagnosis, and its demand is increasing from year to year. Since the raw material for this expensive reagent is available from plants, related research is being undertaken by various research organizations, but the bioreactors developed so far, with rare exceptions, have failed to be commercially feasible for mass production due to their slow culturing speeds. Further details available from Department of Chemical Engineering, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya City, Aichi Pref., Japan. (Source: JETRO, August 1988)

New type of cell-binding factor

Nichirei Corporation and Associate Professor H. Murakami of Kyushu University have jointly discovered a new type of cell-binding factor and have succeeded in its purification and characterization.

Recently, various kinds of biological modulators such as cytokines featuring excellent immunal reinforcements have attracted attention, triggering active research to establish animal cell mass production systems.

With the exception of haematopoietic cells, cultured cells generally grow by adhering to the walls of culturing containers. Proliferation is not initiated without cell attachment and the suspended cells generally lose their viability. Cell binding factors promoting cell proliferation and differentiation like fibronectin and laminine have been discovered from animal tissues and these substances are now under study.

This time, the company used a protein-free culture system for HmLu-1 cells belonging to a cell stock derived from a hamster lung, and extracted a macromolecular substance possessing two sub-units with a molecular weight of about 200,000 from the supernatant fluid of the culture medium. This is considered a new type of cell binding factor. The substance promotes excellent cell proliferation on various kinds of cells in a DME.F12 culture medium.

So far, there had been no alternative but to use a natural serum culturing medium (foetal calf serum) imported at high cost, but the discovery of this cell binding factor now enables mass culture

and manufacture of an animal cell with a basal medium whose components are chemically defined.

The company has a plan to elucidate the substance's structure and biological activity and to establish its mass production process as soon as possible, but since it is produced in a protein-free cell culture, purification and mass production are expected to be accomplished with relative ease.

Further details available from Nicherei Corporation Research Laboratory, 52-14 Kumegawa-cho 1-chome, Higashimurayama City, Tokyo, Japan. (Source: JETRO, September 1988)

D. APPLICATIONS

Pharmaceutical and medical applications

Antibody bridge leads to better vaccines

A new technique could soon allow researchers to produce tailor-made vaccines which protect against several diseases at once. The method makes it possible to isolate from a virus the specific proteins that stimulate an immune response and present them in such a way that they induce a highly effective type of immunity in the immunized animal.

The technique could eventually pave the way for making vaccines to diseases such as herpes, hepatitis, influenza and even AIDS, but the researchers emphasize that extensive tests of the safety and effectiveness of the method would have to be carried out before trying such vaccines in humans.

Rick Randall and Dan Young of St. Andrew's University in Fife are developing the new type of vaccine. The starting point is a solid particle, roughly the size of a bacterium. The researchers link this solid matrix to monoclonal antibodies. When these complexes are mixed with material containing the antigen that the monoclonal antibodies recognize, the antigen sticks to the antibodies.

The result is a complex consisting of solid matrix and antigen, bridged by a monoclonal antibody. This complex forms the vaccine. By attaching several different antigens to the solid matrix (by using a variety of monoclonal antibodies) it is possible to make a single vaccine that will produce immunity to several diseases, or a vaccine against disease that incorporates several antigens.

The technique could avoid some of the limitations of conventional methods of making vaccines. One problem is how to purify individual proteins from viruses and other micro-organisms. The monoclonal antibodies attached to the solid matrix make this process easy. They "hook out" the proteins they recognize.

This method is also helpful where researchers have produced the required proteins by growing them in genetically engineered bacterial or yeast cells. Current techniques of purification may alter the protein so that it no longer produces a strong immune response. But monoclonal antibodies cause less damage.

The group at St. Andrew's has already successfully induced both antibodies and cell-mediated immunity to several different viral diseases in laboratory mice and rabbits. For this work, the researchers used monoclonal antibodies derived from mice. Human monoclonal antibodies will probably have to be developed before the vaccine is suitable for people. (Source: New Scientist, 29 September 1988)

Double action against waterborne disease

The world's first vaccine to protect people against both cholera and typhoid could be on sale within five years, say researchers in Australia. They reported that initial trials in the US of the vaccine, which is given orally, were successful. If further trials in 1989 are equally satisfactory then they plan to undertake large-scale field tests in countries where cholera and typhoid are endemic. Existing vaccines against cholera and most against typhoid must be injected. They often do not work and produce side-effects, says Derrick Rowley, head of the team at the University of Adelaide that developed the vaccine.

No oral vaccines against cholera are available. The World Health Organization does not back the use of the injectable vaccines. The Australian vaccine is the first oral cholera vaccine to be evaluated in clinical trials on humans, though others are under development.

In trials on a small group of volunteers at the Center for Vaccine Development at the University of Maryland in Baltimore, the vaccine proved effective against heavy doses of cholera bacteria. None of the volunteers showed significant side-effects and one quarter of those vaccinated showed no symptoms of cholera. Each member of an unvaccinated control group caught the disease.

The organizers of the trial cured infected volunteers with rehydration therapy and a five-day course of tetracycline to combat the most severe symptoms.

The vaccine consists of live salmonella bacteria. The bacteria contain stretches of DNA from the organisms responsible for cholera and typhoid. The gene from each organism codes for a protein which is produced by the salmonella.

The proteins are normally on the disease organism, and stimulate the immune systems of recipients to react against the pathogens. (Source: New Scientist, 29 October 1988)

Safe whooping cough vaccine moves closer

A vaccine for whooping cough that has none of the damaging side-effects of the current vaccine could be available in the future. Researchers from the US and Japan have succeeded in altering the toxic part of the existing vaccine, dramatically reducing the virulence of its active part.

Whooping cough is caused by the bacterium Bordetella pertussis, which produces pertussis toxin (PTX). The present vaccines can have severe side-effects on the child, which has persuaded increasing numbers of parents not to allow their children to be vaccinated setting the stage for a possible epidemic of whooping cough in the near future.

Neal Burnette and Vernon Mar from Amgen, a company in Thousand Oaks, California, and researchers at the National Institute of Allergy and

Infectious Diseases at Hamilton, Montana, and the National Institute of Health in Tokyo, have succeeded in divorcing the virulence of the vaccine from its antigenic properties.

They focused their efforts on PTX, which causes the symptoms of the disease and underlies both the toxic effects of the vaccine and its ability to stimulate immunity to the disease. However, these two features appeared inextricably linked. In the past, researchers who cultured non-toxic, mutant forms of PTX found that these invariably lost their ability to stimulate the production of antibodies, rendering them useless as vaccines. The new research may have overcome this problem. (Extracted from New Scientist, 22 October 1988)

Malaria drug launched

"Halfan" (halofantrine) a new antimalarial that treats all forms of multi-drug resistant malaria, has been launched worldwide.

Today, malaria is one of the most common and most virulent of all tropical diseases. More than half the world's 5,000 million people live in areas where malaria is endemic, mainly in the third world. An additional 20 million people worldwide travel annually to areas of malaria transmission. An estimated 100-300 million new clinical cases occur each year, of which 1 per cent prove fatal.

Although more than 30 countries have either eliminated malaria or drastically reduced the number of cases, the global transmission of the disease is rising. This is because of the enormous increase in travel to endemic areas and widespread resistance of malaria parasites, especially the deadly P. falciparum, to the most potent and widely used drugs now available for treating malaria, including chloroquine.

Dr. John Horton, medical director for SmithKline and French Laboratories, Hertfordshire, UK, said, "'Halfan' has been developed to the stage where doctors using it to treat chloroquine-resistant falciparum malaria may expect a dramatic increase in their ability to cure it. 'Halfan' is effective against all types of malaria, particularly multi-drug resistant strains of P. falciparum, which accounts for most of the 3 million malaria deaths each year." The new drug was originally developed by Walter Reed Army Institute for Research (WRAIR) after screening 300,000 compounds for antimalarial activity. Only two of the compounds proved clinically useful - mefloquine and halofantrine. SK & F in-licensed halofantrine from WRAIR in 1982 and set up a co-operative research programme with the Institute. SK & F developed the chemical for clinical use and carried out Phase II and Phase III clinical testing.

Some scientists fear, however, that when the manufacturer makes halofantrine available worldwide from next year, indiscriminate use of it could induce resistance in the malarial parasites.

The launch of the drug could also jeopardize an agreement between the World Health Organization (WHO) and a rival pharmaceuticals company to limit the marketing of a second drug for malaria, called mefloquine, to developed countries.

Halofantrine (whose trade name is 'Halfan') has been approved for use in France, Côte d'Ivoire, Togo and Congo. Registration of the drug in a further six West African countries is expected before the end of the year and in the rest of the world by the end of 1989.

'Halfan' is administered orally in 250 mg tablet form, two tablets three times during a 12-hour period. This treatment reportedly returns a patient's temperature to normal in about 24 to 36 hours and clears parasites from the blood in about 36 to 48 hours. A pediatric dose is available in liquid form. Three 8 mg/kg doses are prescribed at six-hour intervals.

Side-effects - slight abdominal pain and diarrhoea - are mild and soon clear up, Dr. Horton said. However, the drug was toxic to embryos in animal experiments. But even if it is inadvertently taken by a pregnant woman, the risk, Horton said, "is extremely low at the human doses prescribed. There may be a very slight risk of foetal death if the drug is taken in early pregnancy."

Halofantrine is likely to prove a serious competitor to mefloquine, particularly for use by the 20 million people who are estimated to travel every year to the 102 countries where malaria is still active.

Before launching mefloquine, Hoffmann-La Roche made an agreement with WHO to limit marketing of the single drug to developed countries. The aim of the agreement was to prevent resistance to the drug from developing through overuse, says Jürg Handschin, the medical manager of Hoffmann-La Roche. SK & F's plans for rapid world-wide distribution of halofantrine may now persuade Hoffmann-La Roche to reconsider its agreement with WHO rather than lose out on a massive market for their drug. (Source: Chemical Marketing Reporter, 26 September 1988 and New Scientist, 19 November 1988)

Modified vaccinia virus used in tests

Bristol-Myers' experimental AIDS vaccine will soon be tested in the US on human volunteers, according to the US National Institute of Allergy and Infectious Diseases. The tests will take place at six university medical centres. Six people at each centre will be given the AIDS vaccine, which is a genetically modified version of the vaccinia virus. For years the vaccinia virus has been used to vaccinate people against smallpox. Bristol-Myers modified it to produce the type of surface protein found on the AIDS virus. Since the vaccine does not contain actual immunodeficiency viruses, alive or dead, there is no chance that the volunteers will get AIDS. They will be given blood tests before the experiment to make sure they are not already infected with the AIDS virus. Three volunteers at each medical centre will be given the vaccinia vaccine by itself. They will serve as controls.

Earlier in 1988 human trials began with an AIDS vaccine produced by Microgenesys (West Haven, CT). Meanwhile there has been a wave of promising results from laboratories around the world.

In France, a drug called ditiocarb (sodium diethyldithiocarbamate) appears to have been successful in forestalling the development of full-blown AIDS in infected patients taking it for four months in a double-blind clinical trial on 83 people.

Meanwhile, research by scientists at the National Institutes of Health in the USA suggests

that the "magic bullet" concept, first put forward as a potential way of treating cancer, may be a way to kill cells infected with the human immunodeficiency virus (HIV) that causes AIDS. Using genetic engineering to link a bacterial toxin to a protein receptor that recognizes cells infected with HIV, the NIH team have made a hybrid protein that will kill such cells in vitro.

Other scientists are trying to find good animal models for AIDS, in order to be able to test potential drugs and vaccines. Only the chimpanzee, an endangered species, has previously been infected with AIDS.

Two groups in California have been able to place human immune systems in mice. Scientists at Stanford University used liver, thymus and lymph cells from aborted human foetuses and keep them alive for a couple of months. At the Medical Biology Institute in La Jolla, the second team injected mice with human white blood cells.

In Italy, scientists at medical schools in Pavia and Genoa have succeeded in infecting rabbits with HIV by injecting the virus, or infected cells, into the peritoneum. They have not yet seen any symptoms in the animals, but are continuing their work in an effort to develop the rabbit as a model for preclinical studies of candidate vaccines and drugs. (Extracted from New York Times, 26 August 1988 and Chemistry and Industry, 3 October 1988)

New treatment against hepatitis B

Immune-suppressing steroids combined with alpha interferon can effectively treat hepatitis B infection, according to R. P. Perrillo of Washington University (St. Louis). If steroids are administered long-term, they increase viral replication, but when administered in high doses for short periods, they cause a rebound effect of enhanced immunologic activity. The new regimen includes a six-week course of prednisone, followed by alpha interferon treatment. The virus disappeared in 9 out of 18 treated patients. In four of the patients, who had been infected for a relatively short period before treatment began, both the virus and the hepatitis B antigen HBsAg disappeared, and hepatitis B antibodies appeared. A larger follow-up study is already under way. The treatment will probably not work for all patients, since the stage of disease may be a critical factor. Worldwide, there are some 200 million people chronically infected with hepatitis B. In the US, there are one million chronic carriers, with 300,000 new cases a year. About 5,000 deaths a year are attributed to complications of the disease, including cirrhosis and liver cancer. (Extracted from Science News, 6 August 1988)

Company turns plants into sunscreen factories

With growing concern about the state of the Earth's protective ozone layer, which filters out most of the incoming ultraviolet radiation from the sun, there has been a good deal of talk about the prospects for manufacturers of sunglasses and sunscreens. Biosource, meanwhile, has come up with an idea which sounds extraordinary: it has genetically engineered plant cells in such a way that they produce the skin pigment melanin by the kilogramme.

Plant biotechnology has two key possibilities when it comes to plant cells: either they can be persuaded to produce something they did not produce before, or they can be induced to make more of something they did not make much of before. Examples of the first approach would include plant cells engineered in such a way as to produce melanin or insulin, while examples of the second approach include attempts to boost plant cell production of such products as alkaloids, aromas, hormones, oils, pigments, sugars, tannins, vitamins and so on. For example, it should be possible to engineer plant cells to produce the plant alkaloid vincristine, an anti-cancer agent that currently sells for perhaps $1,200 a pound, for just a few dollars.

The company, which dubs the genes it uses to reprogramme plant cells "geneware", inserted melanin genes into tobacco cells. They promptly turned black. The next stage will be to make melanin in 100-pound quantities, probably inside germinating barley seeds. Details from: Robert L. Erwin, president, or David R. McGee, chief operating officer, Biosource Genetics Corp., Vacaville, California, USA. (Extracted from Biotechnology Bulletin, Vol. 7, No. 9, October 1988)

Genetically engineered mice to be marketed

Early next year, Du Pont will begin marketing mice with cancer-causing genes (oncogenes) inserted into their cells. Aimed at cancer research, these animals - to be marketed under the trade name OncoMice - are the first to be commercialized under the first patent ever granted for genetically engineered animals.

The mice are expected to be useful for studies of cancer development, screening of anticancer drugs, and testing of compounds for carcinogenicity. Because the mice provide close models of cancer development, fewer animals may be needed for each such study than is now the case.

The company, through its medical products department, will sell the mice initially to academic and government laboratories at less than commercial prices. Du Pont has not yet set pricing policies, but such sales to non-profit laboratories may be at less than $50 per mouse. In a sense, the mice are seen as an additional research tool in a line of offerings that includes radiochemicals, laboratory centrifuges and a DNA sequencer.

The first mice to be shipped will bear an oncogene called Ha-ras. The company plans to introduce two other strains with the myc and neu oncogenes later in 1989. The oncogenes are linked to a deoxyribonucleic acid promoter sequence isolated from mouse mammary tumour virus. The promoter sequence triggers expression of the oncogene in response to hormones in lactating mammary tissues. Thus, although the oncogenes are located in every cell in the body, they lie dormant until the mice are bred, after which the mice will develop breast cancer within 90 days. Offspring will inherit the oncogenes without further need for genetic engineering. (Abstracted with permission from Chemical and Engineering News, 21 November 1988, p. 6. Copyright (1988) American Chemical Society)

α type interferon as kidney anti-tumour agent

Hayashibara Biochemical Laboratories Inc., Otsuka Pharmaceutical Co. Ltd. and Mochida Pharmaceutical Co. Ltd. have jointly developed natural α type interferon (α-IFN) using the hamster process (Hayashibara's method), and have obtained

approval from the Ministry of Health and Welfare for manufacturing it as an anti-tumour agent for kidneys. This is the first time that the manufacture of a natural bio-active substance with the hamster process has been approved by the Government in Japan.

Interferon is available in three types: α, β and γ. In Japan, the α type is manufactured by four companies and the β type by one company, all by the method of tank culture or gene recombination. By contrast, Hayashibara's α-IFN is cultured and separated by directly implanting interferon-producing human lymphoblastoid cells into newly-born hamsters. These cells are then proliferated, harvested and induced with appropriate inducers. That is, the hamster serves as a tank under nearly the same conditions as in the human body for cell propagation, with the result that interferon production efficiency is high, of moderate cost and mass production.

The Ministry of Health and Welfare's investigations centred on confirming the safety of the hamster process and questioned whether there was any fear of the hamster's proteins getting mixed in the substance, whether adverse influences would be exerted by hamsters, whether the quality of the substance extracted from numerous hamsters would be uniform, etc. Hayashibara Biochemical Laboratories eliminated these concerns by demonstrating that a technology has now been established for checking the substance during its purification process against extraneous proteins or impurities generated by hamsters. Data obtained through four years of animal experiments and clinical tests was supplied.

Up to now, anti-tumour agents for the kidneys have been quite rare. The newly-developed α-IFN displays an efficacy of 23 per cent with respect to cancer of the kidneys, strengthens the human immune structure and helps kill cancer cells.

Hayashibara Biochemical Laboratories is presently engaged in research to develop other anti-tumour agents such as an n-TFN and γ-IFN by the same process. Further details are available from Hayashibara Biochemical Laboratories Inc., 2-3, Shimoishii 1-chome, Okayama City, Okayama Pref., Japan. (Source: JETRO, August 1988)

High-performance antihypertensive agent

Asahi Breweries Ltd. has succeeded in developing a substance that displays an excellent antihypertensive (high blood pressure) agent effect over a long period of time.

The new substance is a derivative of 4-piperidyl alkyl and has the effect of inhibiting the action of the angiotensin converting enzyme (ACE) that triggers vasoconstriction and sodium retention. Experiments in vitro and in vivo using animals are already in progress, and so far the substance has been confirmed to be more than doubly active compared with its existing antihypertensive agents, for instance captopril and enalapril.

The blood pressure is raised by the angiotensinogen generated by the liver being converted by resin into angiotensine I, whereupon ACE acts to convert it further into angiotensine II (potent vasoconstrictor). The new substance inhibits this ACE activity.

This new substance comes in more than ten types depending on the differences in chains, among which several types display an ACE inhibitory activity (concentration of 50 per cent inhibition) from 1.1 nmol to 0.5 nmol which is better than the 1.3 nmol of enalaprilate, an active form of enalapril, or the 4.0 nmol of captopril that belongs to the same system. Further details from Asahi Breweries Ltd., 7-1, Kyobashi 3-chome, Chuo-ku, Tokyo, Japan. (Source: JETRO, August 1988)

Collagen signs pact with Bristol-Myers

Collagen Corp. has reached an agreement with Bristol-Myers to develop a potent new cell growth regulator known as transforming growth factor beta, type 2. Collagen owns the patent on the substance, TGFb2, a potential treatment for psoriasis and eczema, rheumatoid arthritis and cancer. Research will first target immune-based skin diseases such as eczema and psoriasis. Preclinical studies are already under way and clinical trials for psoriasis are scheduled to start next year.

The US patent office has recently granted Collagen an extension to its patent for TGFb2 which covers its use as a cancer therapy and in immune suppression. In studies conducted by Celtrix, TGFb2 was shown to be over 100,000 times more potent than cyclosporine-A, the immunosuppressant usually used to prevent organ transplant rejections. Research apparently indicates that TGFb2 can differentiate healthy and abnormal cells, which may lead to novel cancer therapies. (Source: European Chemical News, 12 September 1988)

New enzymes aid viral therapy

Researchers at the CSIRO division of plant industry, Canberra, Australia have designed, built and tested enzymes which may have important implications for research and medicine. The enzymes made by Jim Haseloff and Wayne Gerlach are made of ribonucleic acid (RNA) and have been dubbed ribozymes.

Haseloff and Gerlach isolated the features linked to RNA's ability to cleave itself and designed three synthetic RNA molecules that are active against particular sites in RNA molecules. The two researchers see their ribozymes being used in the laboratory in the mapping of large segments of RNA.

More significantly these ribozymes could be used to cleave and inactivate messenger RNA from particular genes keeping them switched off. This could be the basis of therapies against genetic diseases and viral infections. (Source: European Chemical News, 29 August 1988)

Diagnostic kit for Alzheimer's disease

Alzheimer's disease is a difficult disease to diagnose. Doctors have tended to rely on subjective assessments of the mental capacity of their patients. Senetek, the British biotechnology company chaired by Sir Hans Kornberg, is planning to test a new diagnostic kit which can detect levels of "paired helical filaments" (PHFs) in the cerebro-spinal fluid of patients. Large quantities of PHFs build up in the brains of patients suffering from Alzheimer's disease. The tests should start early in 1989. (Source: Biotechnology Bulletin, Vol. 7, No. 9, October 1988)

Possible drug against Parkinson's disease

Dr. M. Shulman, based in Canada, is seeking a pet food company to underwrite tests of Eldepryl, a supposedly life-lengthening drug. Shulman, once on the brink of death from Parkinson's disease, claims Eldepryl saved his life. The drug was invented in Hungary by Dr. J. Knoll, whose research showed that rats fed the substance lived long past their normal life span. Shulman wants to replicate the tests on rats and dogs but has so far been unable to find backing. Shulman has formed a company called Deprenyl Research to market Eldepryl as an animal feed additive in the US and Canada. Somerset Pharmaceuticals, based in New Jersey, owns US rights for human consumption of the drug. It is worried that Shulman's plan will delay FDA approval of its use as a Parkinson's treatment. It might also hurt plans to sell Somerset to Sandoz Pharmaceutical. In tests, Eldepryl is claimed to slow the action of enzymes that break down dopamine, an amino acid in the brain. A lack of the substance is a main cause of the muscle rigidity seen in Parkinson's victims. Eldepryl also has anti-oxidant properties, preventing free radicals from damaging cells. (Extracted from Business Week, 3 October 1988)

Commercialization of factors VIII and IX from milk

Pharmaceutical Proteins (Edinburgh, Scotland) will produce Factors VIII and IX, alpha$_1$-antitrypsin and other high-value proteins important in clinical medicine from farm animals' milk. It will commercialize Transgene's (Paris, France) procedure. Factors VIII and IX are blood-clotting proteins needed by haemophiliacs who lack them. Alpha$_1$-antitrypsin may be used to treat emphysema. Genes expressing the proteins are transferred to sheep, which produce them in milk. The genes are inherited from one generation to the next. (Reprinted with permission from Chemical and Engineering News, 3 October 1988, p. 22. Copyright (1988) American Chemical Society)

Roche hormone deal

Hoffmann-La Roche has agreed to market a blood cell growth hormone for cancer patients in Europe. Neupogen, developed by California-based Amgen, is under test at the moment and will go on file for approval in 1989. The hormone is a gene-spliced version of a natural hormone which stimulates white blood cell production, thus strengthening the immune system. (Source: Manufacturing Chemist, November 1988)

Ampligen proves less than able against AIDS

A trial of a drug being tested against AIDS has come to a premature halt in the US. A spokesman for one of the companies funding the study, Du Pont of Wilmington, Delaware, said that interim analysis of the results provided no evidence that ampligen worked.

The termination of the trial is surprising because researchers reported encouraging results with ampligen earlier this year.

Ampligen consists of special sequences of the genetic material RNA. Normally, RNA consists of only one strand of smaller molecules. But ampligen consists of two strands wrapped round each other. Its mode of action is not known, but it seemed to be able both to stimulate the immune system and to inhibit the virus from action.

Following the initial encouraging results, an enlarged trial began in the US, which recruited almost 300 people with severe symptoms of HIV infection, though not AIDS. Participants were to remain in the trial for nine months unless they developed AIDS during that time.

Interim analysis of the results, and of the expanded pilot study, showed that people taking ampligen were progressing to AIDS no more slowly than HIV-infected men in San Francisco. Du Pont and HEM Research, who were jointly supporting the study, decided to pull out after considering these results.

The National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, is testing ampligen not for effectiveness but for toxicity and safety. These studies will continue. (Source: New Scientist, 5 November 1988)

Biotechnological approach to AIDS

A biotechnology-derived, synthetic hormone being studied for anaemia has shown promising preliminary results against the severe anaemia experienced by AIDS patients undergoing AZT therapy, reported Dr. Seth Rudnick, vice-president of biotechnology research and development for Ortho Pharmaceutical Corporation, a Johnson & Johnson subsidiary.

"Human recombinant erythropoietin is not being tested as a treatment for AIDS, but rather a treatment for the severe anaemia in patients undergoing therapy for AIDS which may remove the need for transfusions," Dr. Rudnick emphasized.

"From our preliminary data, there appears to be a reduction in blood transfusion requirements. Based on these findings, we are continuing these studies," said Dr. Rudnick.

The use of natural erythropoietin and now, recombinant erythropoietin means another therapeutic approach is possible. In addition, lessening the dependence of these patients on transfusions can have a postive effect upon the public blood supply.

In Ortho's first trial, a subset of AIDS patients receiving "Eprex" (r-HuEPO), recombinant human erythropoietin showed a decrease in their transfusion requirements. The biotechnology-derived erythropoietin, virtually identical to the natural human hormone, works by stimulating bone marrow to produce red blood cells. (Source: Chemical Marketing Reporter, 17 October 1988)

AIDS trials for soluble CD4

Biogen Inc. began clinical Phase I trials for "Receptin" its brand of recombinant soluble CD4, an experimental AIDS therapeutic in October. The trials are being carried out in collaboration with the National Institute for Allergy and Infectious Diseases (NIAID). The material for the trial is being manufactured by Biogen in a mammalian cell expression system.

The clinical trials are being conducted at two centres, Massachusetts General Hospital (MGH), a Harvard Medical School affiliate and Cedars-Sinai Medical Center, Los Angeles.

Phase I human clinical trials are designed to determine the safety profile of an experimental drug. Data obtained in the trial will be used to

expand the testing of the drug into larger study groups where an evaluation of its effectiveness against AIDS will be carried out.

CD4 is a natural surface molecule found on certain immune system cells. Research has shown that HIV binds to CD4 as the first step in gaining entry into T-helper cells, a subset of a class of white blood cells. Among the clinical manifestations of AIDS is a decline in the number of T-helper cells and the collapse of the immune system.

Scientists at Biogen in collaboration with researchers at MGH were first to demonstrate in test tube experiments that "Receptin" blocked both direct infection of T-helper cells by HIV and cell-to-cell transmission of virus. (Source: Chemical Marketing Reporter, 17 October 1988)

Antiviral hormone

A new treatment for AIDS, developed in Ireland, may soon begin clinical trials in North America and Holland. The Elan Corporation of Athlone, in the Republic of Ireland, is applying to the Food and Drug Administration in the US for permission to test a compound called EL10 on humans. EL10 is a synthetic chemical similar to hormones produced by the adrenal cortex. The substance was discovered by a group of Irish scientists, who filed global patent applications.

The researchers' preliminary work convinced them that the hormone could be a potential treatment for HIV infection. After they undertook a small pilot study on humans in Paris, Elan approached them to set up a licensing agreement. (Source: New Scientist, 1 September 1988)

Direct diagnostic test for HSV

Enzo Biochem (New York, NY) received FDA permission to market a direct test for herpes simplex virus (HSV). Enzo, a biotechnology concern, claims its test can detect the presence of an active herpes infection within two hours after sampling a suspected lesion. The test is non-radioactive and is based on a DNA probe. Enzo says its test is the first that detects HSV without first culturing a sample, which can take up to seven days. The test was first marketed in January 1988 under the name Colorgene DNA Hybridization Test. (Extracted from Wall Street Journal, 9 September 1988)

Roche signs deal with Amgen

Hoffmann-La Roche and California-based biotechnology firm Amgen have reached agreement to market the recombinant cancer drug granulocyte colony stimulating factor (Gcsf) in Europe. Upon launch the drug will be sold under Amgen's Neupogen trade mark by both firms.

Gcsf is a naturally occuring hormone which stimulates the production of neutrophils, the body's first line of defence against bacterial infection. Amgen was the first biotechnology firm to clone and produce a recombinant version of the hormone. Gcsf may have the potential to treat patients whose immune systems have been weakened.

Amgen and Roche expect to apply for marketing licences in Europe and the US next year. The product is currently in phase III human clinical trials being used to treat patients suffering from various forms of cancer. (Source: European Chemical News, 10 October 1988)

More ammunition to fight tooth decay

Despite their sugar, some sweets (notably those made of liquorice or chocolate) can help to fight tooth cavities. There is even a kind of sugar that seems to prevent them. Xylitol is found in such foods as plums, raspberries, strawberries and cauliflower, and can be made from some raw materials: e.g., birch bark, corn cobs and sugar cane bagasse. Ounce for ounce, xylitol contains as many calories as - and is as sweet as - table sugar (sucrose) or fructose. (Fructose is substituted for sucrose in many processed foods because it is cheaper.) The bacteria that predominate in most mouths cannot ferment xylitol. So, unlike sucrose and fructose, it does not generate acid or promote decay.

This knowledge could be a boon in poor countries, where more and more people - many of them children and teenagers - are losing their teeth, mainly because they are consuming more of the conventional sugars and have few dentists. It may also be helpful in the developed world, which has many more dentists.

The consumption of conventional sugar has been rising in the developed world too. But thanks mainly to the fluoridation of drinking water, fluoride toothpastes, the direct application of fluoride to children's teeth and fluoride-enriched diet supplements, the number of teeth which people have lost or had filled by the time they are adults has dramatically declined in many developed countries, from Russia to America. Field studies conducted by the World Health Organization and others on school children in countries as diverse as Thailand, French Polynesia, Hungary, Finland and Canada have found that fluoride alone helps to prevent cavities, but that xylitol by itself also helps - and a combination of the two is still better.

The results of a Finnish study, which compared fluoride alone to fluoride and xylitol, stood out. In the study's first (two-year) phase, some 11- and 12-year-old children chewed gum containing xylitol every day while a control group of similar children did not. After two years the gum chewers had up to 80 per cent fewer cavities than those in the control group. None of the children used the gum for the next three years. When almost all of them were later re-examined, the one-time gum chewers still had 51 per cent fewer cavities: xylitol seems to have lasting benefits.

According to papers at the Washington meeting, another dental villain turns out not to be quite as bad as it is painted. Dr. Stephen Moss, chairman of paediatric dentistry at New York University, found evidence that plaque (a mixture of saliva, carbohydrates and bacteria on teeth) can store fluoride and release it into the saliva to protect tooth enamel from decay. Dr. Newell Johnson of the British Medical Research Council's Dental Research Unit offered some reassurance about the link between plaque and dentistry's other main foe: periodontitis, or infections of the gum which erode the bone supporting teeth and eventually make them fall out.

Dr. Newell's studies suggest that it is not so much plaque itself that determines whether people get periodontitis, more the nature of the bacteria living in their mouths and, crucially, how their immune systems respond to the toxins which the bacteria produce. Just as some people become oversensitive to grass pollens or cat fur, the same

seems to be true of sensitivity to these toxins. And since the toxins are produced by bacteria, the best way to protect the people who are most susceptible to them may well be a vaccine. Animal studies, he reported, already suggest that such a vaccine is feasible.

Another approach is also on the horizon: simple diagnostic tests - based on genetic-engineering technology - that can be used to identify high-risk patients before they get into trouble, and to monitor the effectiveness of therapy. The tests analyse samples of fluid taken where the teeth and gums meet. One such test is already on the market, made by BioTechnica Diagnostics in Cambridge, Massachusetts. It detects periodontal disease and has been approved by the American Dental Association. But Dr. Johnson argues that such tests should for now be regarded only as research tools. The mouth is, after all, still full of mysteries. (Source: The Economist, 26 November 1988)

Cardiovascular biodrugs on the way

Cardiovascular drugs - compounds that treat ailing hearts and control blood pressure - are fast becoming the new frontier of the biotechnology revolution. Indeed, research into new cardiovascular products now accounts for more than 25 per cent of the total research and development spending of the US drug industry.

Almost every major pharmaceutical company is involved, including American Home Products, SmithKline & French, Upjohn and Sandoz. Such biotechnology companies as California Biotechnology, Chiron and Procyte are active. And joint efforts between majors and biotechnology companies are common, as exemplified by collaboration between Eastman Kodak and Enzon, as well as between Bio-technology General and Bristol-Myers.

Genentech's Activase tissue plasminogen activator (TPA) - a blood-clot-dissolving compound that treats heart attacks - is the first biotechnology-based cardiovascular drug to reach the market, and other cardiovascular products are now in clinical trials, including another clot dissolver, pro-urokinase, as well as the enzyme superoxide dismutase (SOD), which scavenges oxygen-free radicals, thereby preventing the damage those compounds can cause in heart muscle that has been deprived of oxygen during a heart attack. Also in clinical trials are two peptides that treat congestive heart failure, known, respectively, as atrial peptide and peptide with vasomotor activity.

Numerous other cardiovascular drugs are in the pipeline, moreover, with the majority of those products aimed at blood pressure control.

The compound renin is an example of a biological molecule that could lead to development of a blood pressure drug. Renin is an enzyme uniquely specific for converting proangiotensinogen to angiotensin II in the body. Angiotensin II is a molecule that the body uses to raise blood pressure. Researchers believe that developing a drug that inhibits renin could result in a better means of controlling blood pressure than the current use of angiotensin-converting-enzyme (ACE) inhibitors, which also block the conversion of proangiotensinogen to angiotensin II.

A drawback with ACE inhibitors is that ACE is involved in other physiological reactions in addition to regulating blood pressure. Thus, patients taking ACE inhibitors run the risk of developing side-effects. Yet despite such risks, Squibb's Capoten (captopril), an ACE inhibitor, has become a dominant player in the hypertensive drug market.

Vasoactive intestinal peptide (VIP) is another biological compound that could lead to a blood pressure drug. VIP, a hormone produced by the gut, actually raises blood pressure by constricting blood vessels. But Eisai has synthesized an analog of VIP that dilates blood vessels.

Yet biotechnology-based cardiovascular drugs could have drawbacks, too. TPA is an example. The compound's improved specificity for the fibrin portion of a blood clot - touted as giving TPA an advantage over such conventional clot dissolvers as streptokinase - may, in fact, work against TPA. Sol Sherry, a cardiologist at Temple University (Philadelphia), has documented incidences of severe internal bleeding following administration of TPA. Sherry explains that TPA - in addition to dissolving the clot responsible for a heart attack - appears to dissolve haemostatic plugs, the beneficial clots that stop the small holes in blood vessels that occur through normal wear and tear.

Also, doubt exists whether the more targeted nature of biological drug development will mean significant time and cost savings compared with the 10 years and $125 million expense of developing a drug through traditional methods. Traditional development involves random screening of compounds in animals to discover desired effects against a specific disease. Development of biolcgical drugs, on the other hand, involves using the body's own chemicals to achieve desired effects against a disease. The protein atrial natriuretic factor (ANF) is such a chemical. ANF - under development as a blood pressure drug - is a hormonelike substance made by the heart that can have a dramatic effect on salt balance and water retention and, as a result, blood pressure. (Extracted from Chemical Week, 17 August 1988)

Epidermal growth factor: anti-tumoural too?

The discovery a few years ago - that the v-erbB oncogene encodes a truncated form of the human epidermal growth factor receptor (EGF-r) - provided a first look at the structural biochemistry underlying malignant cell transformation. And the subsequent findings - that a number of human neoplasias (including squamous cell carcinoma and breast cancer) are characterized by elevated levels of EGF-r - have made therapeutic approaches targeted to the receptor very attractive. Most of the protocols presently being developed rely on monoclonal antibodies directed against the receptor, or recombinant fusions of the ligand (EGF) and a cytotoxin. Until now no one had seriously considered that saturating these over-expressed receptors with EGF alone might have clinical utility.

Ramón Fonseca and Rolando Pérez of the Cuban National Center for Oncology and Radiology reported in a recent seminar at the country's Center for Genetic Engineering and Biotechnology that after laboratory demonstrations subcutaneous administration of EGF to mice also inhibited incorporation of ^{3}H-thymidine into the DNA of Ehrlich ascites tumour cells in vivo. The team designed an animal-model protocol using athymic mice and when they were able to produce a transient inhibition of tumour growth in both vulvae

epidermoid carcinoma and lung epidermoid carcinoma xenografts by recombinant human EGF at 20 mg/kg, they were encouraged to begin human trials.

For the pilot trial, the investigators chose 10 advanced skin carcinoma patients who had unsuccessfully responded to conventional therapies. None of the patients received any treatment for at least four weeks before the study.

After daily topical administration of a 1 per cent silver sulphadiazine creme containing 10 μg/gm of recombinant human EGF for three weeks, the researchers obtained two partial remissions, and five patients showed an intense evaluable objective clinical response as measured by a dramatic change in the macroscopic morphology of the lesions. Even those patients who did not demonstrate an objective clinical response none the less showed no progression of their malignancies.

The microscopic anatomy of the EGF-treated tumours was perhaps even more dramatic. Six of nine evaluated patients showed degeneration of tumour cells, marked enhancement of stromal tissue, and an acute inflammatory reaction.

While continuing to treat and evaluate these first patients, the research team is beginning a larger study, and collecting biochemical data on the number and occupancy of the receptor sites, both on the tumour cells and the newly resident stromal cells. In the light of these results, the constantly expanding relationships between growth factors, their receptors and the oncogenic process may now have to be further expanded to include the direct therapeutic use of the hormones themselves. (Source: Bio/Technology, Vol. 6, September 1988)

Mopping up a lingering threat

A new treatment for breast cancer, the most common cancer among women and the third most common in the world, could save thousands of lives each year, according to the head of the US National Cancer Institute.

NCI studies have shown that more women patients would survive if they received additional therapy after surgery. NCI director Dr. Vincent De Vita estimates this would save 5,000 lives a year in the US alone.

But the findings only apply to patients whose cancer is caught in its early stages. So it is unlikely that as many lives will be saved in developing countries, where early detection is less common.

Although breast cancer is more common in the developed world, it is expected to strike an increasing number of women in developing countries as a result of urbanization and the adoption of western life styles.

The NCI studies looked at two kinds of auxiliary therapy: chemotherapy, which destroys cancer cells, and hormonal treatment, which inhibits their growth. Doctors have been reluctant to administer these additional treatments unless they find cancer cells in the lymph nodes, since the majority of node-negative patients survive without any recurrence of cancer.

Two of the studies showed chemotherapy benefited women thought likely to suffer cancer relapse. The findings suggested that women who received Tamoxifen - a drug which inhibits the growth of cancer cells by blocking the oestroge. that stimulates cell division - were more likely to avoid a relapse.

De Vita says Tamoxifen may be particularly useful for treatment in developing countries because it has few side-effects - an important consideration where people have to travel long distances to see a doctor. The drug may induce hot flushes and accelerate the onset of menopause. The chemotherapy agents used in the other studies are also easy to administer and cause few serious side effects, he says.

Despite these findings, Tamoxifen and chemotherapy will probably have limited applications in developing countries. Dr. Pouru Bivandiwala, chairman of the board of directors of the International Women's Health Coalition and former medical director at the Washington-based Family Health International, says they will have more impact in big city hospitals, where early detection is more common.

In rural areas and among the poor, early screening for breast cancer, like most preventive health care, is often unavailable. (Extracted from South, August 1988)

Cetus will "revolutionize" DNA probes

Sales of DNA probes - used primarily as diagnostic tools to identify pathogens by binding to pathogenic DNA have been disappointing. The problem has been that DNA probes are not sensitive enough. They might bind to a target strand of pathogenic DNA, but that strand is only a tiny fraction of the total DNA in a sample containing the pathogen; detecting that strand has been much like searching for a needle in a haystack.

Cetus (Emeryville, Calif.) has now developed technology - called polymerase chain reaction (PCR) - that amplifies minute amounts of target DNA a millionfold. The result is that researchers can make a million copies of the one needle they are looking for in a haystack, in essence creating a haystack of target needles.

Cetus has already received 70 applications to license its PCR technology - covered by US patents 4,683,195 and 4,683,202 - in applications as diverse as genetic disease research and forensics. Cetus's strategy is to make the technology available as broadly as possible. To universities that want to use PCR in basic research, Cetus will license the technology without charge. Companies interested in PCR, though, will be charged licensing fees and royalties on sales of products developed through PCR.

PCR goes a step further than DNA probes. PCR's role in detection of the AIDS virus, which can hide in as few as one in one million white blood cells, is one example. With DNA probes, researchers first heat a blood sample from a person suspected of carrying the virus. That causes the double-stranded DNA in the cells in the sample to separate into two single strands. A DNA probe targeted to a portion of the AIDS virus's DNA is added. If that portion of viral DNA is present, the probe binds to it, forming double-stranded DNA.

PCR amplifies the targeted DNA, which might otherwise be too small to study. The DNA is heated, so the double strand separates into single strands. Next, short pieces of DNA specific to those single

strands, called primers, are bound to each of the strands. The primers mark the strands for duplication, which happens when the enzyme DNA polymerase is added. Thus, each single strand of DNA is now double-stranded. Thereafter, every time the procedure is repeated, the DNA is doubled. In such a geometric progression, 20 repetitions copy the original portion of viral DNA one million times, generating enough of that DNA for further study.

Some of the most exciting PCR work has been done in AIDS virus detection. The virus is now detected indirectly, by testing a person's blood for the antibodies that the body produces in response to the AIDS virus. Direct detection of the AIDS virus itself requires culturing it from the blood of an antibody-positive person. That procedure takes 3-4 weeks and lacks sensitivity, because the virus is sometimes present in minute amounts or else it is latent inside infected blood cells.

PCR, for its part, is even more direct than viral culture, as it detects viral genes and, therefore, does not depend on the release of the virus from infected cells. Moreover, PCR requires only four days. In fact, PCR has detected the AIDS virus in patients who have not formed antibodies to the virus. This finding supports other studies that have shown that some people with the AIDS virus do not form antibodies for many months or even years. PCR has also detected the AIDS virus in babies born to antibody-positive mothers. Those babies do not always carry the virus, but such determination has been hampered by the fact that maternal antibodies to the virus persist in the babies for 15 months. (Extracted from Chemical Week, 10 August 1988)

Septic shock breakthrough soon

Two US biotechnology companies, Xoma Corp. and Centocor Inc., are racing to bring to market a drug for the treatment of septic shock, a condition caused by a bacterial infection often acquired in hospitals that kills tens of thousands of people each year.

Whether the drug will work is still not known because the results of tests are not yet available, but some preliminary evidence suggests that the drug should work, and excitement has been rising in the medical and financial communities that the treatment could drastically cut the death rate from such infections.

The main treatment for such bacterial infections so far has been antibiotics, which kill the bacteria. But that alone often does not save the victim because the toxins are already in the blood. In some cases, killing the bacteria can actually aggravate the problem by causing the bacteria to split apart and release all their toxin.

The treatment being studied by Xoma and Centocor would use monoclonal antibodies that would latch onto the toxins in the blood stream and neutralize them.

Xoma has potentially the most to gain. It also expects to file by the end of the year for approval to market another monoclonal antibody product aimed at treating graft/host disease, often fatal, which strikes recipients of bone-marrow transplants.

Xoma's product has been shown to result in dramatic improvement in some patients.

While the market for this product will probably be smaller than for the septic-shock product, the same antibody product might also find uses in treating other diseases, such as rheumatoid arthritis.

Centocor has pursued an opposite strategy, developing a wide range of monoclonal-antibody-based products for use in diagnostics, in imaging and in treatment of diseases.

Its septic-shock product will be its first drug, but even if it fails, the company has many more baskets.

While Centocor is behind Xoma in the race to market, its product is a human antibody, while Xoma's is an antibody that comes from mice. That could make Centocor's more useful in some cases, because people are more likely to develop reactions against a mouse antibody than a human one.

Other competitors are entering the septic-shock treatment race but are far behind. Cetus Corp., a biotechnology company in Emeryville, California, is only now getting ready to start clinical trials. Chiron Corp., another Emeryville biotechnology company, is developing antibodies not for the bacterial toxin but for a substance produced by the body after it is exposed to toxin.

This substance, known as tumour necrosis factor, is thought to do much of the actual damage from septic shock. While the treatment has worked in baboons, it has not yet been tested in people.

The big question now is whether Xoma's and Centocor's treatments will work. The main basis for confidence is a study done several years ago by researchers at the University of California at San Diego.

Volunteers were inoculated with killed bacteria. The volunteers developed antibodies to the endotoxin. When the blood serum of these volunteers was used to treat patients with bacterial infections, mortality was reduced 40 per cent compared with that of a control group.

Despite the success, using human volunteers to produce such a drug was considered impractical. So since those results were published six years ago, the medical community has been waiting for monoclonal antibodies to be made in large quantities in biotechnology factories.

Xoma's earlier trials showed some promise, though the number of patients tested was far too small to be meaningful.

There are reasons for caution. The results of a Swiss study published this summer showed no effect on mortality. That study used a different kind of antibody than Xoma and Centocor are using, an antibody that some evidence suggests would not be as effective. (Extracted from International Herald Tribune, 23 September 1988)

Livestock applications

Cattle vaccine turns the tables on ticks

Researchers in Australia have developed the world's first vaccine against the cattle tick, Boophilus microplus, which causes damage worth millions of dollars to herds in Australia and Latin America.

Scientists working for the Commonwealth Scientific Industrial and Research Organization (CSIRO), in Canberra, developed the vaccine jointly

with a team from Biotechnology Australia, the largest biotechnology company in the country. It should be on the market within three years.

The team has identified a key protein, made by the tick itself, which stimulates an immune response in the cattle. They have also isolated the gene that codes for the protein. The researchers, led by Tony Johnston, from the CSIRO's Division of Tropical Animal Production, began work on the project in 1980. In 1983 they successfully isolated antibodies produced by the cattle, which attack the guts of ticks as they feed on the cattle's blood.

They then purified the protein, or antigen, from the tick's gut that produces the immune reaction in vaccinated cattle. The isolation of the individual protein is a multi-stage process, which starts with crushing and centrifuging the ticks to extract the glycoproteins attached to their cell membranes. These are then separated further with a detergent, chromatography and other fractionation methods. Peter Willasden, who heads the team, is about to publish a paper on the details of their work.

Each experiment involved between 40,000 and 60,000 ticks, individually picked with tweezers from cattle. Antigen produced from these ticks was sufficient to vaccinate only three cattle.

The researchers were then able to study the structure of the protein and identify the tick gene which codes for it. This gene was then cloned by Biotechnology Australia, manufactured in large quantities and used to produce the anti-tick vaccine.

The research team is now trying to develop a related vaccine to combat the various species of tick which infest cattle in Africa. The team expects a great demand for the vaccine, which would mean a reduction in the level of pesticides used to control the tick at present. These pesticides leave toxic residues. (Source: New Scientist, 18 August 1988)

Genetic hoofprints

Researchers in New Zealand have devised a genetic fingerprinting technique for horses that will enable race officials to determine with certainty a particular horse's parentage.

Tom Broad and colleagues at the Department of Scientific and Industrial Research at Palmerston North have identified multiple bands in horse DNA fragments using electrophoresis. The pattern of bands is effectively a "bar code" that is unique to each animal, and identifies the animal's parents. The researchers have tested the technique on 12 horses and identified their parents and offspring.

To ensure the credentials of a horse that is registered to race, scientists confirm its parentage using up to 20 blood tests. Yet, as with humans, blood grouping cannot provide absolute proof of the horse's parentage. Genetic fingerprinting reveals with certainty who the parents of a particular foal are. (Source: New Scientist, 29 October 1988)

CAH develops sheep vaccine

Coopers Animal Health (NZ), in collaboration with scientists at the University of Melbourne and the New Zealand Ministry of Agriculture and Fisheries, has developed a recombinant vaccine against tapeworm parasites. Commercial production of the vaccine - which will give sheep up to 95 per cent protection - will begin within two years in New Zealand where sheep measles is a major problem.

In 1971, scientists at the University of Melbourne proved that antigen material from the egg state of the sheep measles parasite was effective as a vaccine. Now the teams have identified the necessary genes for this antigen and introduced these into E. coli to produce commercial quantities for vaccines. (Source: European Chemical News, 10 October 1988)

Twin calves produced by transfer of blastocyst matured, fertilized and cultured in vitro

Japan's National Institute of Animal Industry, Ministry of Agriculture, Forestry and Fisheries, has advanced the technology of producing "twin calves", which combines transfer of in vitro fertilized oocyte and artificial insemination. Up to now, in vitro fertilized eggs (oocytes) were cultured in rabbit oviducts, but the development of the new system for complete in vitro culture has paved the way for performing in vitro fertilization at a low cost.

The technology of producing twin calves involves the method of transferring a blastocyst originated from in vitro fertilization into the inseminated cow in order to give birth to twin calves, and was developed by the same institute last year. Since two calves can be produced at the same time, this technology is expected to alleviate the burdens of dairy farmers substantially.

With the technology, the in vitro fertilized eggs to be transferred were prepared by first collecting the ovaries of dairy cows at a slaughterhouse, then mixing them with frozen-thawed sperm for vitro fertilization, followed with transfer into a rabbit oviduct for culturing up to the optimum transplantation stage. Five days later, blastocysts developed in the rabbit oviduct were transplanted into the mother cow's uterus. With this method, the fertilized eggs are cultured in the rabbit's oviduct, involving much time and expense.

To cope with this situation, research was conducted on an in vitro fertilized egg culturing system, by which the first twin calves were born in May 1988. In contrast to the method of using rabbits, the processes involved are controlled much more easily and the way is paved for production of twin calves with more stability.

The mother cow used in the experiment was a dairy cow and the sperm of a dairy bull was used for artificial insemination. Meanwhile, the sperm of a Japanese Black bull was used for fertilizing the oocytes of slaughtered dairy cows. The twin calves consisted of a dairy calf, and a hybrid between a dairy cow and a Japanese Black beef bull. Further details available from: National Institute of Animal Industry, Ministry of Agriculture, Forestry and Fisheries, Tsukuba Norindanchi P.O. Box 5, Ikenodai 2, Kukisaki-machi, Inashiki-gun, Ibaraki Pref., Japan. (Source: JETRO, September 1988)

AFRC scientists hunt for more effective salmonella vaccine

Research at the AFRC Institute for Animal Health, Compton, UK, has demonstrated that calves can be protected against salmonellosis - an enteritis and/or a generalized infection resulting

in death - by suckling from vaccinated dams for two days followed by bucket feeding immune colostrum for eight days. This has been achieved with a vaccine prepared from killed bacteria, but researchers have now identified the group of plasmid genes responsible for virulence and are progressing with the identification of the gene products with a view to producing more effective future vaccines by genetic engineering. (Source: Biotechnology Bulletin, Vol. 7, No. 9, October 1988)

Investigation on bovine somatotropin and milk production

A four-year investigation by the UK Agricultural and Food Research Council (AFRC)'s Institute for Grassland and Animal Production, Shinfield, on the effect of the administration of bovine somatotropin (BST) has shown that milk yields are increased by 20 per cent, while milk composition remains unchanged. At the same time, feed intake increased by 12 per cent and feed conversion improved by eight per cent. Any loss of condition was regained by the start of the next lactation.

There were no adverse effects on animal health, as long as the animals were well managed. The interval between calving and conception increased, on average, by 11 days, although the percentage of successful pregnancies remained unaffected. The institute suggests that BST, now produced by genetically engineered bacteria, be used to: enhance forage intake; improve milk quota management; and to overcome seasonal variations in production. (Source: Biotechnology Bulletin, Vol. 7, No. 9, October 1988)

Agricultural applications

Growing compounds from plants

Now that techniques with plant cells have advanced to the point where it is possible to grow relatively large amounts of biomass together with the synthesis of natural products, the prospects for exploiting the biosynthetic potential of cultured plant cells industrially is subject to critical scientific and commercial scrutiny.

Over a period of 300,000,000 years, plants acquired biosynthetic routes enabling the assembly of a wide range of complex compounds which are often quite specific to particular plant groups. These natural products are termed "secondary metabolites" in reference to the fact that they are not regarded as essential to the primary growth of the plant. Nevertheless, in evolutionary terms, these secondary metabolites play a crucial role in the competition for survival since they include compounds which are highly poisonous to predator animals and micro-organisms, attract insects for pollination, or have attractive flavours, aromas and colours for fruit dispersal.

We have found uses for many of these natural, plant-derived compounds and they feature prominently in our everyday lives. Compounds of medicinal value have been documented in pharmacopoeias since the 16th century; even today, despite the advances of synthetic chemistry, at least 23 per cent of all prescriptions in industrial countries depend upon plant products; compounds such as the anti-tumour alkaloid Vinblastine, and the triterpene Diosgenin used as the steroid skeleton in the synthesis of oral contraceptives. Plants are also the source of many compounds important in the agri-food industry; flavours, fragrances and pesticides. Furthermore, in recent years, there has been a gradual realization that many compounds created by the chemical industry to replace natural compounds (e.g. pigments, sweeteners, insecticides) have carcinogenic potential for man. This has led to a reassessment of natural (or "nature identical") products.

However, there are often uncertainties associated with commercial marketing of field-grown crops, for example, fluctuations in supply of quality as the result of climatic changes, diseases or political unrest. Therefore the prospect of stable production of natural products by plant cells in a bioreactor, close to quality control laboratories, would offer many advantages. The biotechnological realization of natural products through plant cell culture methods will depend upon commercially determined market forces. One of these is that production in vitro must be cheaper than by traditional field-grown methods.

During the last 10 years it was found that the yield of plant cell suspensions can be markedly enhanced by a programme of cell screening which exploits the high level of variation in product accumulation between cells. Cell screening is greatly facilitated if the product of interest is coloured so that high-yielding colonies can be selected by eye. It is no accident that the earliest high-yielding cultures synthesized pigmented compounds, e.g. shikonin; berberine. Analytical screening methods have been developed for compounds that fluoresce in ultra-violet light such as ajmalicine using semi-automated radio immunoassay to cope with the very large number of samples that need to be assayed. More recently the advantages of new methods of fluorescence-activated cell sorting (FACS), which can quickly analyse and sort millions of cells, holds promise for future progress.

At first sight it might be supposed that plant cells could be grown using established microbiological methods for large-scale liquid culture. It is now realized, however, that cultured plant cells have characteristics which require special bioreactor designs. Individual plant cells are highly vacuolated, surrounded by a relatively thin cell wall and, by contrast to many micro-organisms, some 200,000 times greater in volume. As a result plant cells have relatively slow division rates, doubling times of 50 hours are usual by comparison with less than one hour for bacteria. Plant cells are also much more sensitive to the shearing forces developed as the result of stirring in a bioreactor. These requirements place constraints on bioreactor design. Special attention must be given to air filtration to keep the culture sterile over long culture periods. And, since fast spinning turbine blades can cause serious cell damage, alternative designs such as slowly rotating paddles or air-lift stirring are being considered.

A different approach to this problem is currently being investigated in a joint project by the Departments of Botany and Chemical Engineering at University College Dublin, Ireland. This approach is to measure the shear sensitivity of plant cells quantitatively and establish how this relates to the structure of the plant cell wall. With this knowledge it may be possible to develop shear-resistant cell lines which could be grown in efficiently stirred bioreactors. A second aspect is that of extraction of the product. By contrast with many micro-organisms which excrete their metabolites

Table 1.
Some important plant-derived natural compounds together with maximum yields reported in cell suspension culture.

Compound	Application	Plant Origin	Cell Culture Yield
	Medicinal		
Ajmalicine	anti-hypertensive	Catharanthus roseus	368 mg/l
Vinblastin	anti-tumour	Catharanthus roseus	Not found
Codeine	analgesic	Papaver somniferum	1.5mg/g
Digoxin	Cardiatonic	Digitalis lanata	700 mg/l*
Quinine	Anti-malarial/ bittering agent	Cinchona ledgeriana	Not found
Diosgenin	Oral contraceptive	Diocorea deltoidea	18 mg/g
Ubiquinone-10	Heart diseases	Nicotiana tabacum	5.2mg/g
Berberine	Antiseptic	Coptis japonica	130 mg/l
Fragrances/Pigments/Flavours/Insecticides			
Jasmine Oil	Fragrance	Jasmin	Not found
Saffron	Pigment	Colchicum sp.	
Shikonin	Pigment	Lithospermum erythrorhyzon	140 mg/g
+(−) nootkatone	Flavour	Grapefruit	Not found
Anthocyanin	Pigment	Vitis sp.	332 mg/l
Stevioside	Sweetener	Stevia rebaudiana	1.5mg/g*
Thaumatin	Sweetener	Thaumatococcus danielli	**
Pyrethrum	Insecticide	Chrysanthemum sp.	0.1mg/g

*By biotransformation from a fed precursor;
**Plant gene cloned into a bacterium E. coli

Table 2.
Examples of yield increases in cultured plant cells obtained by screening and cloning.

Product	Cell Culture	Increase of yield (x)
Anthocyanin	Vitis	3 - 4
Berberine	Coptis	2
Ubiquinone-10	Nicotiana	15
Shikonin	Lithospermum	20

(Source: Technology Ireland, October 1988)

into the medium, plant cells commonly retain these compounds within the cell vacuole. Consequently downstream processing for these cell lines involves sacrificing the valuable biomass, quite apart from the expense of solvents and the additional costs of purification. Recently some cell lines have been isolated which leak their metabolites. These might then be adsorbed onto resins. Other recent work on the mechanisms of transport of alkaloids across plant cell membranes may also lead to non-destructive methods of stimulating product release.

Obstacles to commercial realization

The successful isolation of some 20 cell lines which are capable of accumulating secondary metabolites, at levels exceeding that occurring in the plant, represents a really substantial advance over the position that existed 15 years ago. Furthermore, the technology has developed sufficiently up to 20,000 litre capacity for the commercial exploitation of a high yielding strain at least for one or two examples, Shikonin, and Ubiquinone-10. Shikonin is a napthoquinone used in Japan for treatment of burns and skin diseases, and also as a red pigment for dyeing silk and in the cosmetic manufacture of "bio-lipsticks". Traditionally shikonin was extracted from the roots of Lithospermum erythrorhyzon imported from China. Its production fills a niche for high value compound within a local ethnic market. This example emphasizes the importance of identifying a specific market and of producing a high-value product not obtainable by a less expensive route such as by either chemical synthesis or from a microbial fermentation.

Further commercial developments in this form of plant cell biotechnology will depend upon the ability of biologists to isolate stable, high-yielding cell lines. Many of today's high-yielding plant cell strains produce low-value compounds of no use

industrially (e.g. anthraquinones). Many compounds that would be of high potential, e.g. vinblastin, have not yet been isolated in sufficiently high yield. Furthermore, highly selected cell lines, with the capacity to produce a valuable product (e.g. ajmalicine), demonstrate a tendency for production instability which is too quickly expressed to enable a sufficiently large culture to be grown from a small inoculum.

The desirability of being able to dissect out and harness the diverse biosynthetic capacity of the plant kingdom in the test-tube was first recognized as long ago as 1900. The ways and means to achieve this objective have been continually changing as our knowledge of biological systems has increased, and never more so than in the present day. Since cultured plant cells are such expensive delivery systems it might be advantageous to extract and immobilize the necessary enzymes into an enzyme bioreactor, or alternatively, to use engineered micro-organisms to express a plant biosynthetic pathway. At present, however, not enough is known about how pathways are controlled to make this possible. In the short term it may be more realistic to constrct an engineered micro-organism to synthesize a single useful plant enzyme which could be used to undertake a synthetic step presently impossible by conventional chemistry. Already the gene for the peptide sweetener thaumatin has been transferred from the plant to a bacterium E. coli. Alternative approaches, such as culturing the fast-growing "hairy roots" are also showing promise for the synthesis of root natural products.

From a more general point of view the main problem is one of finding out how secondary metabolic pathways are regulated in plant cells, what switches pathways on, and what limits the maximum product accumulation in the cell. At present this subject is only dimly understood. In whole plants secondary metabolites are often found in specific structures (e.g. pigments in petals, the ginseng saponins in roots) and so their synthesis may be developmentally regulated through the expression of selected parts of the plant cell genome. Unravelling regulation at this level will require the application of molecular genetics. It is clear that exploiting plant cells requires a broad range of scientific expertise together with support from the pharmaceutical and agri-food industries.

Monsanto testing recombinant micro-organisms

The US Environmental Protection Agency (EPA) has given Monsanto Agricultural Co. permission to conduct a small-scale research field test of a genetically engineered micro-organism in Pullman, Washington State. In the test, scientists from Monsanto and the US Department of Agriculture (USDA) want to assess the anti-fungal activity of a naturally-occurring microbe against wheat take-all disease, a fungal disease which attacks the plant roots and causes dry rot and premature death.

Monsanto ressearchers are genetically engineering the microbe to contain two additional "marker" genes, which serve as a reliable and sensitive tracking system for environmental monitoring of microbes. The naturally-occurring bacteria, strains of fluorescent Pseudomonas, have been field tested for seven years in Washington as biological control agents effective against take-all, which causes millions of dollars of damage annually. Details from: Monsanto Agricultural Co., 800 N Lindbergh Boulevard, St. Louis, Missouri 63167, USA. (Source: Biotechnology Bulletin, Vol. 7, No. 9, October 1988)

Weevil pesticide reduced

Destroy their food and protective winter homes, and pesticide use can decrease as much as 80 per cent. That is the result of a seven-year Department of Agriculture study on boll weevils in the Lower Rio Grande Valley of Texas. The study led to a new Texas law requiring farmers to destroy harvested cotton plants and to an inexpensive, USDA-devised system for detecting plants that are illegally left untouched which give weevils a food source, a place to reproduce during autumn and winter and protection when they are in their dormant stage, according to entomologist Kenneth R. Summy of USDA's Agricultural Research Service.

At the start of the study, farmers applied pesticides 15 to 18 times a year in 1980 and 1981. In 1984, following a year of moderate stalk destruction, pesticides only had to be applied three or four times. From 1985 to 1987, pesticide use went back up, sometimes equalling 1981 levels, because farmers did not destroy stalks.

In 1987, the Texas legislature passed the law requiring cotton growers to destroy stalks annually by 15 September. Stalk destruction procedures call for stalk shredding followed by deep ploughing, he said.

To help state officials enforce stalk destruction, ARS scientists worked out a surveillance system for cotton fields. "With aerial infrafred photos," Mr. Summy said, "you can easily detect unploughed cotton at a cost of only about a half-a-cent per acre." Scientists also used the system to track how well farmers had ploughed their fields during the study.

In co-operation with James R. Cate of Texas A&M University and officials of the Cotton and Grain Producers Association of the Lower Rio Grande Valley, the scientists went to the fields to investigate exactly why there were fewer weevils after farmers had destroyed stalks.

They found that without cotton plants to serve as hosts, the weevil's survival is greatly reduced and remaining weevils cannot reproduce during autumn and winter. As a result, the weevils do not build up heavy populations to reinfest in the spring.

The Texas Boll Weevil Law established pest management zones where cotton stalk destruction and deep plough is enforced by the Texas Department of Agriculture. Cotton plants must be destroyed by 15 September in the Lower Rio Grande Valley, but the deadline is later in other zones. (Extracted from Chemical Marketing Reporter, 26 September 1988)

Genetic first breeds hardy mushrooms

The world's first strain of mushrooms designed by biologists to withstand both changes in temperature and disease is growing in plastic beer cups in a laboratory in rural Canada. Paul Horgen and James Anderson developed the new strain, named the "Erindale Hybrid Ag95", at the University of Toronto.

Early indications are that the mushroom, a cross between a commercial and a wild strain of Agaricus bisporus, grows faster than existing commercial varieties and has a similar yield. Horgen and Anderson say that such hybrids may lead to mushrooms that are less sensitive to temperature than existing strains, and more resistant to the bacteria and viral diseases common to many commercial crops.

According to Horgen, the problem with existing commercial strains is that they derive from a few strains, isolated 300 years ago in France. This lack of genetic variety makes mushrooms extremely sensitive to temperature; the yield of one strain called C-4 drops by 20 per cent if the temperature varies by as little as 0.5°C during the sensitive periods of its development.

Horgen and Anderson treat the mycelial cells with enzymes to eat away the cell wall, creating protoplasts. In these pieces of fungi, approximately one in 10 of the protoplasts have chromosomes inherited from only one parent, making it easier to isolate particular traits. The protoplasts can then be fused to form new strains.

The researchers crossed commercial parental types with wild parental types to produce a hybrid of the desired characteristics. These hybrids can be "DNA fingerprinted" to confirm their paternity.

The scientists are trying to establish a test farm with the Canadian Mushroom Growers Association by next year. If all goes well, Horgen is optimistic that a genetically engineered mushroom could be on the market in less than five years. (Source: New Scientist, 22 September 1989)

Let's talk tomato

A genetically engineered tomato is now the subject of "serious discussions" between ICI Seeds and Calgene. Both companies have filed patents on a means of genetically blocking the production of an enzyme that softens the tomato during ripening, opening the way to the development of new varieties with longer shelf-lives.

Dr. Simon Bright, of ICI Seeds, has indicated that Professor Don Grierson of the University of Nottingham, and Wolfgang Schuch and others of ICI, had succeeded in engineering tomatoes that have reduced levels of the enzyme, polygalacturonase (PG). This enzyme breaks down pectin and helps to cause softening in ripening tomatoes.

The tomatoes were engineered by creating a synthetic gene related to the DNA sequence of the PG gene, and introducing it into the chromosomes of normal tomatoes. Once in place, the synthetic gene produces strands of antisense RNA that bind specifically to the RNA from the natural PG gene, and so prevent it from being translated into the PG protein. In this way, the UK team were able to bring levels of PG down to 10-40 per cent of their normal level in tomatoes at each stage of ripening, Bright said.

Meanwhile, in work funded by Campbell Soup, the US biotechnology company Calgene has independently used the antisense RNA method also for reducing PG levels in tomatoes. The two companies have been talking about their patent positions for a month or so, trying to keep a potential conflict out of the courtroom.

For ICI Seeds, the research represents a model experiment on a crop that has not - until now anyway - been a serious commercial target. It is much more interested in developing, among other things, new varieties of maize - a race in which it is somewhat behind competitors like Pioneer and Ciba-Geigy.

PG is only one of the enzymes responsible for tomato softening. So further genetic tinkering with this humble fruit will be needed before supermarkets, and soup companies, get exactly what they want. Bright thinks it will take at least another five years before all the components of ripening are brought under genetic control in a new commercial variety.

Meanwhile, the antisense RNA method has potential for improving on nature in other plants. It could be used, for example, as a way of reducing erucic acid levels in oilseed rape, or the levels of toxic alkaloids in potatoes. And one Calgene idea is that it could be used in trees for creating varieties with reduced lignification. (Source: Chemistry and Industry, 19 September 1988)

Mass culture of biotic insecticide for gold bug larvae

The Laboratory of Insect Pathology of Japan's Forest Experiment Station, Ministry of Agriculture, Forestry and Fisheries has discovered a new species of nematode that displays a strong insecticidal effect with respect to injurious soil insects such as gold bug larvae and has developed a technology for the mass production of the nematode. A new method of eliminating injurious soil insects by utilizing the nematode in place of ordinary insecticides is now a probability.

The larva of the gold bug is known as a highly injurious insect not only for forestry seedling farms but also for vegetable farms, tea estates and golf courses. Insecticides have been used up to now, but they have not necessarily proved effective and since they also produce environmental polution problems, the development of some effective means for control other than the use of insecticides is necessary.

The laboratory had been probing for natural enemy organisms existing in the gold bug in order to develop some effective biotic method for gold bug larva control. While searching for natural enemy organisms by using Anomala cuprea (a species of the gold bug) larva extracted from soil sampled in Hamakita City, Shizuoka Prefecture, in 1984 a parasitic nematode was discovered which causes a high mortality rate among these larvae. This nematode is a new species belonging to the Steinernema family.

Several families of this species of nematodes are known to exist, invariably killing insects by causing septicaemia (blood poisoning) with the aid of coexisting bacteria. By utilizing this characteristic, some of these nematodes are being processed and put on the market as biotic insecticides in the United States and Australia. More recently in Japan attempts are being made to utilize these nematode groups for various kinds of insect control. However, up to now, no nematode has been discovered which displays a strong infectious effect with respect to gold bug larva.

According to experiments conducted by the laboratory on a Japanese cypress seedling farm, the

nematode displayed 100 per cent efficacy when over 100,000 nematodes were used per square metre.

At present, this new nematode can be obtained at an average rate of several tens of thousands of units or a maximum of 400,000 units per Anomala cuprea. It is also possible to culture them by using dog food or chicken culture beds, but this proliferation rate will be insufficient for commercialization. The laboratory therefore developed the new artificial culture bed, by which one barrier has been cleared for the application of this new nematode as a biotic insecticide. Further details available from Forest Experiment Station of Ministry of Agriculture, Forestry and Fisheries, 1, Matsunosato, Kukizaki-machi, Inashiki-gun, Ibaraki Pref., Japan. (Source: JETRO, September 1988)

Technology for mass culture of F_1 vegetables

Kirin Brewery Company, Limited and Plant Genetics Inc. (US) have jointly come out with a technology for the mass culture of F_1 hybrids of celery and lettuce as well as a mass production technology for rice somatic embryos.

Research is in progress to create new species of plants by mating, gene recombination or cell fusion. However, establishment of mass production technologies for seeds and seedlings will be indispensable for the commercialization of these newly created plant species. Especially as regards F_1, their excellent genetic properties are limited to a single generation and not passed on to the second generation; therefore the establishment of mass production technologies for F_1 seeds will be necessary when supplying these seeds on a commercial basis.

These new technologies are essentially based on two technologies, one for the mass production of somatic embryos and adventitious shoots (both of which are cells deriving from fertilized eggs and/or tissues with the same construction, which are divergences of ordinary plant cells), and the other for their encapsulation.

Technologies for culturing and proliferating somatic embryos and adventitious shoots from the cells of plant leaves, stalks and roots have already been commercialized for some varieties of vegetables and flowers, but the number of plants that can be produced in six months after a given growth stage has been limited to about 200 to 300.

Kirin and Plant Genetics studied and improved culturing conditions, and established small tank culture and technologies for efficient culture of somatic embryos of celery and adventitious shoots of lettuce which are generally characterized by uniformity and a high germination rate. Through these efforts it is now possible to culture roughly 10 million somatic celery embryos and 100,000 lettuce adventitious shoots from one gram of callus in about six months. At the same time, a technology has been established for rice plant culture that now enables roughly 2,500,000 somatic embryos to be produced from one gram of callus in about six months. Further details available from Kirin Brewery Company, Limited, 26-1, Jingumae 6-chome, Shibuya-ku, Tokyo, Japan. (Source: JETRO, September 1988)

Herbicide-resistant cotton

Monsanto Company has announced that its scientists have genetically engineered cotton for tolerance to the company's non-selective "Roundup" herbicide, a trait of major potential commercial significance.

The cotton plants tolerant to "Roundup" herbicide are being researched to aid farmers to better control such weeds as cocklebur, morning glory, prickly sida and johnsongrass, which costs farmers millions of dollars annually in weed control.

Monsanto recently announced success in genetically engineering soybeans for "Roundup" herbicide tolerance - a milestone for the biotechnology science of crop transformation. The company also has reported success in genetically engineering various agronomically-important traits into canola and tomato, and field testing those crops this past summer.

Genetically engineered cotton plants were produced using an Agrobacterium-mediated gene transfer system. Agrobacterium tumefaciens has the natural ability to transfer some of its own DNA into plant cells. However, the result is usually a type of injury known as crown gall. Monsanto researchers developed a method to stop the Agrobacterium from causing crown gall, while at the same time keeping its ability to insert DNA into plant cells. The altered plant cells were then regenerated into healthy cotton plants through a process called tissue culture. (Extracted from Chemical Marketing Reporter, 21 November 1988)

Ice-minus minus risk

A plant pathologist from the University of California at Berkeley, who was at the centre of a controversy two years ago for wanting to use genetically-altered bacteria to protect plants from frost damage, reported this week that his experiments had proved effective and the environment had not been damaged. Over the past two years, on a small plot in northern California, Steven Lindow has been spraying potato seedlings with Pseudomonas syringae, a strain of common bacterium. Lindow deleted a frost-forming gene from the bacterium. Lindow told a meeting of the American Phytopathological Society in San Diego in early November 1988 that the seedlings protected with the ice-minus bacteria received, on average, only one third as much frost damage as the unprotected plants. The altered bacteria were not detected beyond the 30-metre buffer zone around the experiment. (Source: New Scientist, 19 November 1988)

A new duo in biorational pest control

Phillips Petroleum's biotechnology arm Provesta (Bartlesville, Okla.) and Dow Corning's Dow Corning Enterprises (Midland, Mich.) are joining to manufacture and market biorational pest control and monitoring systems for agricultural applications. The joint venture, Agrisense, will develop systems based on the use of chemical indicators - pheromones - which insects employ in communicating with each other. Provesta will supply expertise in pheromone synthesis and marketing, and will provide a manufacturing plant in Bartlesville. Dow Corning will offer its polymer technology for season-long, sustained release of pheromones. (Source: Chemical Week, 17 August 1988)

Particle guns for plant biotechnology

Plant biotechnology has been slow to develop. One reason has been a lack of scientific advances in areas important to the technology. For example, no single technique exists to engineer the genes of each of the wide range of important crop plants.

Moreover, current techniques generally require regenerating single plant cells into whole plants, an arduous and time-consuming task that does not always work.

An instrument is now available that should allow researchers to modify the characteristics of all important crops via genetic engineering and to reproduce copies of the engineered plants, without recourse to regeneration by culturing single plant cells. Both Agracetus (Middleton, Wis.) and Biolistics (Geneva, NY) have developed versions of a machine - called a particle gun - that shoots tiny pellets coated with genes for such desired traits as insect resistance into plant seeds or seed tissue. The seeds or tissue then grow into plants that exhibit the traits and pass them on to succeeding generations.

Biolistics and Agracetus - both of which have applied for patents on their guns - have starkly different business strategies. Biolistics is making its gun widely available, as it wants the technology to advance rapidly. The company has leased its gun for a 10-year period to eight US companies and universities and has entered into collaborative research agreements with Calgene, Pioneer, Agracetus, Amoco and Embrex. Under those research agreements, Biolistics supplies its gun and technical support, while the companies conduct research.

Agracetus, conversely, is keeping its gun in-house and is currently negotiating with a number of companies to do contract research. Those companies will supply Agracetus with the plants and the genes they want put in those plants. Agracetus will return to the companies the genetically engineered plants they desire.

The Agracetus and Biolistics guns are quite similar. In its model, Agracetus makes use of a shock wave generated by an electric discharge. The gun - which operates under a partial vacuum - is made up of a spark discharge chamber 13 mm in diameter, inside of which are a pair of electrodes. A drop of water that is placed between the electrodes is vaporized by a charge of 15,000 V applied across the electrodes. That sends a shock wave through the chamber to a carrier sheet, which is positioned above the chamber.

The carrier sheet contains gold spheres 1-3 micrometers in diameter that are coated with polylysine and the DNA to be inserted in the target seeds; polylysine prevents DNA degradation for a period of several weeks. The carrier sheet - propelled by the shock wave - strikes a stainless steel retaining screen. The screen stops the carrier sheet but allows the DNA-carrying gold spheres to continue to the target seeds. The spheres penetrate the seeds, inserting in them their DNA.

The Biolistics gun differs from its Agracetus counterpart in two important ways. Rather than using an electric discharge, the Biolistics gun uses a gunpowder explosion to propel its DNA-carrying spheres. Also, the Bolistics gun uses a plastic container to carry those spheres, instead of a carrier sheet. (Extracted from Chemical Week, 31 August 1988)

Food and food processing applications

Test detects salmonella in food

An on-site test for salmonella in food has been developed by Gene-Trak Systems, Framingham, Mass. The test takes two days compared with four to six days for conventional microbiological methods. A 24-hour pre-enrichment and six-hour selective enrichment régime encourages any salmonella present to grow while inhibiting other bacteria. Users then add a lysing solution that breaks up cells and denatures DNA. Next, users add a specific DNA probe with a tail of polydeoxyadenylic acid (poly-dA) and insert a dipstick. The dipstick bears DNA with a polydeoxythymidylic acid (poly-dT) tail. Poly-dT anneals to poly-dA, letting users pull salmonella DNA out of the sample. The dipstick is then inserted into another solution containing a DNA probe labelled with horseradish peroxidase. The intensity of a colour change, if any, is read from a colorimeter and compared with those of negative and positive controls. (Reprinted with permission from Chemical and Engineering News, 3 October 1988, p. 22. Copyright (1988) American Chemical Society)

Pectinase offered for improved fruit juice yields

Food grade pectinase for fruit juice processing is now available from Biocatalysts, the specialist supplier of enzymes. Pectinase, derived from Aspergillus niger, can be used to obtain increased juice yields, reductions in viscosity, increased colour extraction and enhanced clarification. The formulations are designed for various applications in fruit juice processing such as wine making, apple juice, blackcurrant juice and lemon juice manufacture, and flavour syrup production. Biocatalysts Ltd., Main Avenue, Treforest Industrial Estate, Pontypridd CF37 5UT, UK. (Source: Biotechnology Bulletin, Vol. 7, No. 8, September 1988)

Chemical applications

New enzyme for detergent

Novo Industri (Bagsvaerd, Denmark) claims to have produced the first commercial detergent that can dissolve fatty spots at low, energy-conserving temperatures.

Detergent enzymes now in use include proteases that work on protein stains such as egg and blood and amylases that dissove starch-containing stains such as cocoa and gravy. One stumbling block has been removal of fatty stains; most surfactants remove only part of a stain from butter, margarine, salad oils, sauces and cosmetics.

Enzyme sales for household laundry products in the US total about $50 million/year, with Western Europe roughly the same. In Japan, the laundry enzyme market hovers at $24 million.

Novo's first consumer of the enzyme is Japanese detergent maker Lion Corp. (Tokyo). The company says sales of its lipase have begun in Europe, but the company will not release names of it customers. Sales in the US are still about two years away. One deterrent to using Novo's lipase may be its cost, which is not disclosed by the producer or its one user.

Novo's success came in developing a fungus of the Aspergillus type that can produce lipase in considerable amounts. For years, researchers in Novo's genetic laboratory had worked on the development of the fungus Aspergillus as a host for a lipase gene. Last summer, researchers succeeded in isolating the lipase gene, its structure was determined, and the gene was modified so that it would fit into the Aspergillus fungus. Several genetically engineered strains were tested, and one

of these, A. oryzae, proved to be more than willing to produce the coveted enzyme.

The company then looked for the fastest path to commercial production. To make Lipolase at Novo's plant in Kalundborg would have required going through Denmark's lengthy procedure for approval of production via genetic engineering, so Novo applied simultaneously for permission to produce the enzyme in its new factory at Hokkaido, Japan, which is run by Novo's Japanese arm, Novo Biochemical Industry Japan (NBIJ).

Four months later, last December, Japan's Ministry of International Trade and Industry gave NBIJ permission to start using A. oryzae as host for detergent enzyme lipase production. It was unlikely that the Japanese would sit on Novo's application, considering A. oryzae has been used in the country for centuries in production of sake, bean paste and soy sauce. An NBIJ scientist called the enzyme's production start "a marriage of things old and new".

The company plans to do a lot more work in the laboratory. For one, Novo hopes to use its laundry lipase know-how to develop lipases for food synthesis. The enzymatic action that attacks and cleaves particular bonds in fat molecules can also be used to form new molecules out of two simpler ones. Such technology, for example, might allow the company to develop a product chemically identical to human mother's milk and to concoct high-priced cocoa butter out of palm oil and cheap animal fats. (Extracted from Chemical Week, 27 July 1988)

Unusual porphyrin analog promises many applications

Chemists at the University of Texas, Austin, have synthesized an analog of porphyrin that has five, rather than the usual four, co-ordinating nitrogen atoms. Unusual properties of its metal ion complexes suggest that the ligand may serve as a springboard to cancer therapy, medical diagnostic imaging, solar energy devices, and theoretical investigations of aromaticity and co-ordination chemistry.

The Texas group, consisting of organic chemistry professor Jonathan L. Sessler, post-doctoral fellow Toshiaki Murai, graduate student Michael Cyr, and crystallographer Vincent Lynch, linked three molecules of pyrrole and one of o-phenylenediamine through alternating methine (= CH -) groups to form the macrocyclic compound. Their work was supported by the Research Corp., Procter & Gamble Co., the Camille & Henry Dreyfus Foundation, and the National Science Foundation.

Sessler is struck that the symmetrical structure of the expanded pentaco-ordinate compound resembles the five pointed star of Texas. Moreover, the large central cavity seems to him to be naturally in keeping with the tradition that anything accomplished in Texas tends to be bigger. These features have moved the Austin group to name the ligand texaphyrin.

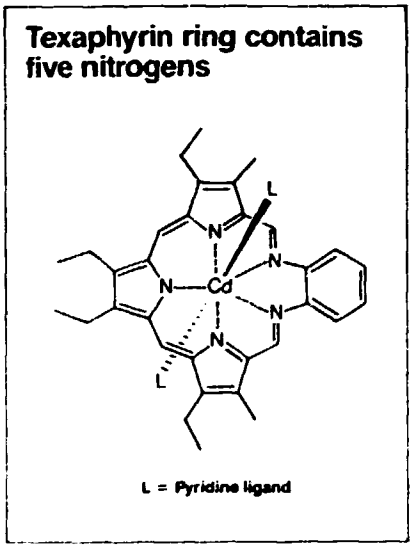
The macrocyclic ligand itself absorbs at 752 nm and its cadmium complex at 767.5 nm. The Austin researchers ascribe these long-wavelength absorptions to delocalization through either a 22-π electron system that includes a fused benzene ring or an 18-π electron system not involving the fused benzene ring.

Sessler says that the long-wavelength absorptions of such compounds also make them attractive to look at as photodynamic therapeutic agents. In such therapy, compounds such as haematoporphyrin are known to localize in tumours. If tumours lie close to body surfaces, exposure to light causes porphyrins to generate singlet oxygen molecules, which are toxic to tumour cells.

But the absorption maximum of haematoporphyrin lies close to haemoglobin's. Thus, irradiation at that wavelength also damages haemoglobin. Sessler suggests that the longer wavelengths of his "expanded porphyrins" might avoid this problem.

In addition, rare-earth complexes of texaphyrin may find use in magnetic resonance imaging. This is because the larger cavity of the molecule accomodates such ions as neodymium (III) better than porphyrins, making complexes that are more stable to water in the body. If these rare-earth complexes also localize in tumours, they would change the relaxation times of water protons there, producing an image of a tumour.

More immediate benefits, however, will come in modelling and understanding multistep electron-transfer reactions akin to photosynthesis and exploring the nature of aromaticity and transition metal ion bonding.



Texaphyrin also stabilizes unusual bonding by metal ions. X-ray studies of one cadmium complex of the new ligand show that it is a pentagonal bipyramid with pyridine molecules at the apical sites. (Abstracted with permission from Chemical and Engineering News, 8 August 1988, p. 26-27. Copyright (1988) American Chemical Society)

Energy and environmental applications

Walt Disney experiments with its garbage

Researchers at Walt Disney World (Orlando, Florida) are studying ways to produce low-cost methane from solid waste. The project is being supported by the US Energy Department's Solar Energy Research Institute (SERI) and the Gas Research Institute and Southern California Edison. SERI says municipal solid waste consists of 50 per cent organics, 25 per cent inorganics and 25 per cent

moisture. Once the inorganic material is removed, the organic waste is ground up and then broken down by anaerobic digestion. This is a biological process in which acetogen bacteria hydrolyze the waste into organic acids, according to Barbara J. Goodman, co-ordinator of SERI's Energy from Municipan Waste programme. A second group of bacteria, called methanogens, converts the acids to a 50-50 mixture of methane and carbon dioxide. Anaerobic waste treatment has been limited to laboratory research and one large-scale project, called RefCoM (refuse conversion to methane), built in 1978 at Pompano Beach, Fla., but RefCoM produced methane costing $5/million Btu, or twice the current market price; the facility no longer exists. The work at Walt Disney World is focused on cutting that price by increasing the solids concentration in each digestion reactor, thus producing more methane per reactor. (Source: Chemical Week, 28 September 1988)

Bacteria enlisted in the battle to clean nitrates out of water

Researchers in the Netherlands have devised a new technique for extracting nitrates from groundwaters which produces far cleaner water than current methods. It could soon be used across Europe to reclaim contaminated water.

The scientists, at the Agricultural University of Wageningen, have been sponsored by the Dutch Government, which is concerned over the levels of nitrates in Dutch groundwater. The Association of Dutch Water Production Companies estimates that soon more than a quarter of the country's supplies will exceed the European Community limit of 50 milligrams of nitrate per litre.

The new process combines two existing nitrate extraction techniques - ion exchange and biological denitrification. Ion exchange methods are used in the US, but most of them produce water that is very salty and has a high chlorine content. Biological extraction processes often run the risk of contaminating the water with either the bacteria themselves or the methanol they need to survive.

In the Dutch technique the water flows through the ion exchanger where the nitrate ions are extracted and replaced by bicarbonate ions. These are generated by the action of Hyphomicrobrium bacteria on the methanol they feed on.

The nitrate ions then pass through a second column where they are "consumed" by these same bacteria. The bacteria eat the nitrate, and transform it into innocuous nitrogen gas. The water never comes into direct contact with the bacteria, which eliminates the risk of contamination.

The end result is water that is free of nitrate and has a bicarbonate concentration of 100 milligrams per litre for every 50 milligrams of nitrate removed. It is slightly salty to the taste but is quite safe because such concentrations of bicarbonate are harmless. The system, for which a patent is pending, has only to be topped up with methanol which the bacteria use to generate bicarbonate.

The new method is expensive, costing about 100,000 pounds sterling for apparatus to purify 75 cubic metres of groundwater per hour. This would inevitably raise the cost of drinking water, the researchers say, but is cheaper than finding alternative supplies. They estimate that the system would cost 2 pence per cubic metre for drinking water if applied nationwide. (Source: New Scientist, 18 August 1988)

A beautiful killer redeemed

The water hyacinth, a native of South America, is called the beautiful killer. It is now widely distributed in the tropics and subtropics, choking rivers, streams, lakes and reservoirs, and hampering drainage and navigation.

Yet the plant is redeeming itself by providing a fuel which could help to prevent deforestation. It is being used to purify water and produce organic fertilizer, plastic, paper and commercial feed. In India the water hyacinth has been converted into biogas.

Thailand's National Energy Institute, part of the Ministry of Science and Technology, has developed an alternative fuel to wood and charcoal by drying and pressing the water hyacinth. The institute has even developed machines which can mass-produce this green fuel.

It costs US 50 cents to produce a million calories of green fuel energy and US 60 cents if water hyacinth is mixed with other fibrous weeds, straw, sugar cane waste and lignite powder. To obtain the same amount of energy from wood costs US 71 cents and from charcoal, US 75 cents.

The green fuel block made from water hyacinth yields 3 million calories per kilogram; the mixed type yields 4 million.

Up to 40 private companies are considering producing green fuel commercially. Small gasifying units will enable villages to generate electricity, power water pumps and develop cottage industries.

The Thai army is helping the Government on an ambitious project to turn part of the parched north-east into a green belt by digging wells and canals and replanting forests.

Energy research and development division director Sompong Chantavoraparp says the Government will open three green fuel factories in the area this year.

Meanwhile, an Esso refinery in California is growing water hyacinth to feed a water treatment plant.

The plant is nature's pollution scavenger: it takes in chlorine, cobalt, lead, chromium and bismuth, until its absorption threshold is reached. The Commonwealth Science Council and the United Nations Environment Programme have been working for some years on water purification schemes for rural areas using water hyacinth.

In Bangalore, the Application of Science and Technology for Rural Areas (ASTRA) has shown that water hyacinth can also be turned into biogas. (Extracted from South, August 1988)

Water purification and energy recovery system using the water hyacinth

Japan's Government Industrial Research Institute at Osaka is commercializing technology relating to a water purification and energy recovery system using aquatic plants. The basic idea of the system is to use aquatic plants to absorb and remove phosphorus from eutrophic lake and marsh water and then recover the floating plant for re-utilization in the manufacture of methane gas and liquid fertilizers.

The generic method for removing phosphorus and nitrogen generally consists of utilizing a chemical reaction and settling these components, then treating the sludge. This method is disadvantageous in that much time and expense are required for treating the sludge itself. In this respect, the new system is designed not only to resolve this problem but also has an economic advantage.

The bioreactor used in this purification system is the floating weed A. pinnata var. imbricata (the water hyacinth) which survives by absorbing dissolved phosphorus and nitrogen from the water. The research institute selected the water hyacinth since it displays an efficient insolation shielding effect in addition to a high water dephosphorization effect. Test results have corroborated that the system displays an excellent dephosphorization effect, and that it reduced the element's concentration in a tank to as low as one hundredth part.

The fully grown plant is harvested, pressed and separated into fluid and residue, with the fluid fermented to produce methane gas and the residue likewise converted into methane gas over a longer period of time. The residue after gas synthesis is exposed to the air and eventually utilized as liquid fertilizer containing rich quantities of phosphorus and nitrogen.

Over the next year, the plan is to conduct various tests including a test to confirm that the liquid fertilizer exerts no adverse influences prior to the system's commercialization. Further details from: Government Industrial Research Institute, Osaka, 8-31, Midorigaoka 1-chome, Ikeda City, Osaka, Japan. (Source: JETRO, August 1988)

Aerobics rubbished

For almost a year two oxygen-hating types of bacteria, methanobacterium autotrophicum and m. arbophilicum, have been munching their way through the muck churned out by an ice-cream factory near Gloucester, UK. This is a carefully planned experiment, which has shown a lot about the best ways to use bugs to dispose of rubbish. It is also well-timed.

It shows that such "anaerobic" bacteria can dispose of rubbish 35-50 per cent more cheaply than their "aerobic" cousins, which need oxygen in order to live. One apparent snag with anaerobes is that they work much more slowly than aerobes at breaking down organic waste, but they avoid the need for two expensive things: oxygen, and the equipment to keep stirring or blowing it into the bioreactors in which they work.

Last April four groups of researchers and the UK Department of Trade and Industry set four different reactors - each holding five cubic metres of effluent - to work on the sugars and fats flowing from the Gloucester ice-cream factory.

According to Dr. Kenneth Anderson of Newcastle University, who directed the project, the results have clearly shown that the best reactor for the job is the so-called upflow reactor, in which muck is pumped in at the bottom and rises up the reactor past pieces of plastic which provide a large surface area for bacteria to grow on. This is easier to use and more reliable than other designs. It was expected to handle about 6 kg of organic waste per cubic metre of reactor each day; in fact it got through 9 kg.

Different sorts of waste call for different micro-organisms to eat them, but researchers think that the ice-cream results will be useful for plenty of other branches of the food industry. The Gloucester test rig is portable and will be towed off to compare the different reactors' performances in treating other food-industry wastes.

Many food factories across Europe will soon have to take a fresh look at the way they dispose of their wastes. They are gradually succumbing to creeping national and EEC regulations which say that organic wastes dumped into estuaries must be turned into fluid first. The new rules impose a new cost on those businesses; anaerobes mean that it could be much lower than they once feared.

Inland producers of food wastes usually dump their untreated effluent into sewers and pay local authorities to treat it for them. The now-proven lower cost of anaerobes and good performance of upflow reactors could mean that such companies will start to do more of their own dirty washing. The wastes could then be reduced to harmless chemicals before they leave the factory gates, instead of overloading sewers. (Source: The Economist, 27 August 1988)

Waste treatment biotechnologies reaching the market

The hazardous waste problems now dogging countries like the United States are opening up a range of potential new commercial opportunities for specialist biotechnology companies.

Depending on how the problem is defined, between 150 million and 300 million tons of hazardous waste are generated in the US every year. Additionally, there are approximately 900 designated "Superfund" sites - chemically polluted sites that have been abandoned by their owners and left to the Goverment to make safe. Indeed, the US Environmental Protection Agency (EPA) has identified nearly 2,500 additional sites that will eventually need to be cleaned up. In total, it is estimated, there may be as many as 425,000 potentially hazardous waste sites in the United States alone.

Dozens of new high technology companies have been offering new products and services targeted at this emerging new market. A forthcoming survey, Cleaning Up, produced by the US World Resources Institute (WRI), highlights the wide range of technologies that are now being developed in this field. And, according to a market report just released by Business Communications Co. (BCC), Hazardous Waste Control: Advanced Waste Treatment Technology (Report No. C-059), the largest sub-sector of the high technology waste treatment market in the US is for advanced chemical treatment.

The market is made up of a lot of dissimilar segments, including heavy industrial construction (for incinerators), biotechnology (for waste-treatment microbial cultures), commodity and speciality chemicals, fabricated polymers (like geosynthetic liners or membrane filters), and electrical components or equipment. Compared to the total US spending on environmental protection, the high technology hazardous waste treatment market is relatively small: worth only $215 million.

BCC foracasts, however, that the market will grow at an annual average rate of 10 per cent over the next five years, topping the $0.5 billion mark by 1998. By then, BCC estimates that environmental

biotechnology - mainly in the form of microbial cultures - will be a $14 million-a-year industry, in constant 1988 dollar values. Genetically engineered bacteria and yeasts will not have a major impact within this time-frame, BCC suggests.

Recent events in the UK suggest that environmental biotechnology could take off in Europe, too, although hazardous waste treatment seems unlikely to be the most active area. As part of a joint technology venture programme, for example, Biocatalysts Ltd. is pooling its environmental biotechnology resources with those of Probac Ltd. Probac will exclusively market Biocatalysts' enzyme systems for use in municipal water treatment plants and effluents from the chemical and agricultural industries. Biocatalysts has developed a range of specially tailored enzyme systems for the food, dairy, beverage, confectionery, leather and slaughterhouse industries.

Biotreatment is involved in the construction of the world's first "designer" refuse tip, built as a "bioreactor", at Arpley, near Warrington. The project is managed by four organizations: in addition to Biotreatment, they are the Manchester Ship Canal Co., Cheshire County Council and CPC Consultants. Waste from Cheshire and Merseyside will be microbially treated to produce more than six million therms of methane gas a year, which will be sold cheaply to local companies.

Details from: Biocatalysts Ltd., Main Avenue, Treforest Industrial Estate, Pontypridd, Wales CF37 5UT, UK. Biotreatment Ltd., 5 Chiltern Close. Cardiff CF4 5DL, UK. Business Communications Co., Inc., 25 Van Zant Street, Norwalk, CT 06855, USA. World Resources Institute, 1735 New York Avenue, NW, Washington, DC 20006, USA. (Source: Biotechnology Bulletin, Vol. 7, No. 7, August 1988)

Treasures from biomass

It is no secret that waste biomass is a treasure waiting to be tapped. Such wastes as sugarcane bagasse, cereal straw and scrub trees contain valuable fuel, chemicals and feed. Indeed conversion of the world's waste biomass solely to feed would more than triple the feed supply and, subsequently, the supply of milk and meat.

Now a continuous process is catching on that uses high-pressure steam to convert biomass into feed, chemicals and fuel, as well as pulp. Developed by Stake Technology (Oakville, Ontario), the process breaks down biomass into its three major components - cellulose, hemicellulose and lignin - which are then made into products.

Although several companies are working on continuous steam conversion of biomass, Stake Technology is the only one with such a process on the market.

The process is already on line. Finnish Sugar (Helsinki) uses it to convert hemicellulose in birch chips and oat hulls into the sugar xylitol; the remaining lignin and cellulose are made into cattle feed. Bio-Regional Energy Associates (Floyd, Va.) uses the process to make furfural from the hemicellulose in hardwoods, as well as adhesives from the lignin and ethanol from the cellulose.

Stake Technology is also involved in numerous negotiations. The provincial government of Saskatchewan recently agreed to use the process in a $65 million pulp mill that will produce 100,000 tons/year of pulp from such local hardwoods as aspen for use in paper and tissue. Rhodia, the Brazilian arm of France's Rhône-Poulenc, intends to use the process to make furfural from bagasse. And Forte America (Jackonsville, Fla.) plans to use it to make cellulose from hardwoods for production of chemicals like carboxymethyl cellulose, which is used as a thickener in foods and cosmetics.

Though Stake Technology makes the equipment for its process, its strategy has been to license engineering firms to build plants using the technology. The company - which holds 110 patents around its technology - has licensed Technip (Paris) to build plants worldwide. However, in the US Technip shares a license with Vulcan Cincinnati (Cincinnati).

Key to the Stake Technology process is the breaking of the lignin bond in biomass. Lignin chemically and physically holds together the cellulose and hemicellulose. In fact, one kind of biomass differs from another in its percentage of lignin. Grass, for example, is 7-10 per cent lignin, while trees are 19-33 per cent lignin. The increased lignin gives plants their strength and rigidity and hence reduces their digestibility by animals.

The Stake Technology process is straightforward. A feeder compresses raw biomass into a dense plug that is fed continuously into a steam digester, where it is carried to a discharge device at the digester's rear. Steam supplied to the digester - at pressures up to 450 psi and temperatures as high as 230°C - breaks the lignin bond between cellulose and hemicellulose. Release of the material through the discharge of mechanism to atmospheric pressure and temperature "freezes" the material, preventing the lignin bond from reforming.

The process - which has a reaction time of 1-6 minutes - requires 1 lb of waste biomass, or equivalent energy, to convert 9 lb of biomass into lignin, cellulose and hemicellulose, says Stake Technology's President Jeremy N. Kendall. Each plant using the process is individually designed to turn those biomass components into pulp, feed or other products, depending on the producer's needs.

Stake Technology believes its pulp is superior to pulp produced by other methods. Compared with pulp made by chemithermal mechanical pulping, Stake Technology pulp is 50-80 per cent stronger, with energy costs that are 53-82 per cent lower. Moreover, the Stake Technology process is ideal for hardwoods, which are not currently used for pulp production, and has pulp yields of 92-94 per cent. The flexibility of Stake Technology's modular pulp production units - each of which produces 50,000 tons/year of pulp - makes production feasible in areas without abundant forests or sufficient cash for full-scale plants. (Source: Chemical Week, 28 September 1988)

Perspective on biomass conversion

Uncertainties about future oil prices make it impossible to predict the timescale over which biomass-derived liquid fuels might become fully competitive with petroleum products. However, developments in biotechnology will open earlier opportunities in the chemicals-from-biomass sector. Initially, these will be based on conventional sugar and starch feedstocks and direct cultivation and husbandry of new and modified plants and animals.

These are some of the conclusions that emerge from Strategy for Biomass Conversion, a paper produced by Bertus van der Toorn of Shell International. He is head of Shell's Non-Traditional Business organization, which is involved in activities including forestry, solar and biomass-derived energy and phytobusinesses worldwide. Details from: Shell International Petroleum Co. Ltd., Shell Centre, PAC/233, London SE1 7NA, UK. (Source: Biotechnology Bulletin, Vol. 7, No. 10, November 1988)

Bugs clean up waste

The chemical industry is becoming increasingly concerned with finding permanent solutions to its hazardous waste problems, the result of growing awareness of liability rules. Rather than transport their problem to another site, chemical companies are looking more and more to bioremediation as one of their waste clean-up alternatives.

At the same time, the bioremediation industry is going through a period of consolidation. More waste treatment businesses are trying to broaden their range of services to include the newer technology, while small companies which offer bioremediation are readily taking advantage of the improved market positions resulting from joining forces with a larger company.

The most formidable example of this is Du Pont Biosystems, established last April, which is led by the pioneer of bioremediation technology, Richard Raymond.

Dr. Raymond holds the patents for the earliest work of this kind - utilizing indigenous bacteria to clean up spills of straight-chain hydrocarbons like gasoline and diesel fuel. Representing newer directions are Du Pont's patent for biodegradation of a range of chlorinated compounds, awarded last summer based on work in the laboratory.

As a growing number of hazardous waste dump sites are discovered and blame is assigned, chemical manufacturers find it increasingly attractive to rid themselves of hazardous waste once and for all by using bacteria to degrade it into harmless component compounds.

Under the 1980 CERCLA rule, government officials trying to get a Superfund site cleaned up do not need to prove negligence or intent on the part of the potentially responsible party (PRP). Further, if only one PRP can be identified for a particular site, that party must pay for the entire cleanup of the site, regardless of how little that party may have contributed to the problem at the site.

Those who offer bioremediation services consistently claim that, in most cases, their method for handling waste is more cost-effective than competing approaches. At the same time, though, the cost of bioremediation is often condensed; that is, more money must be paid in a shorter period of time than in a decade-long operation like air-stripping.

Most of those who offer bioremediation agree that increasing numbers of companies are shifting their focus of concern from short-term cost to long-term liability.

Waste treatment companies, in the mean time, are hard at work studying ways to expand the range of compounds they can degrade by manipulating naturally-occurring bacteria. Hunter Biosciences advertises two dozen chemical and fuel-type compounds that they have successfully biodegraded, including acetone, ethylbenzene, ethylene glycol, methyl ethyl ketone, styrene and xylene.

Many companies are working to perfect degradation of chlorinated solvents and other chlorine-containing compounds, generally seen as the most ubiquitous and toxic of waste-streams produced by the chemical industry.

In studying these more complex compounds, many researcher. have found that the best way to degrade them is to allow micro-organisms to feed on a co-substrate, such as methane. Upon digesting this, the bacteria will secrete enzymes which do the actual work of breaking down the target compound.

Laboratory work has been done on biodegradation of polychlorinated biphenyls (PCBs), a highly toxic chemical that is also strongly resistant to breakdown. The latest report of successful biodegradation of PCBs was reported from Michigan State University where researchers found that micro-organisms taken from the sediment of New York's Hudson River, which suffers from PCB contamination, were able to dechlorinate PCBs from another source. This presumably made the compounds far less toxic, although researchers say that toxicity data have not yet been gathered.

New Jersey Institute of Technology recently dedicated an Advanced Technology Center, which will house the Hazardous Substance Management Center. Researchers there are working on reactor designs that will allow the breakdown of chlorinated compounds using white rot fungus, rather than bacteria, with o-chlorophenol as the target material. (Extracted from Chemical Marketing Reporter, 21 November 1988)

Wanted: Microbes to clean up aquifers

Discovering underground micro-organisms that can remove pollutants from aquifers is the aim of a project in which researchers will collect sediment up to 2,000 ft below the Earth's surface. The project is part of the US Department of Energy's (DOE) Deep Microbiology Programme, a co-operative study between government and university laboratories. Sediment is currently being collected at a site near the DOE's Savannah River Plant (Aiken, S.C.). (Source: Chemical Week, 28 September 1988)

Industrial microbiology

A superior enzyme for commercial use

An enzyme from a microbe found in a Mexican swamp can break down animal and plant protein stains much faster and at higher temperatures than can enzymes now used as detergent additives, according to Todd W. Gusek, a Cornell University graduate student. Cornell has applied for a patent on the enzyme called "YX protease". Gusek says that plans are under way to mass-produce the enzyme from genetically altered organisms. He says that the enzyme is active at a broad range of temperatures, as well as in alkaline conditions. It also maintains its activity in the presence of a variety of chemicals that harm most enzymes. The new enzyme also could have application in the food industry. Because it breaks down proteins, it could find use in the production of protein-rich therapeutic diets, known as protein hydrolysates, for patients who

cannot take solid food. In addition, the new product could be used to clean protein-soiled filtering devices, such as ultrafiltration membranes that are used to concentrate milk. A cleaner made up of the enzyme can do the job in an hour instead of the 24 hours it now takes with commercial enzyme-based cleaners, says Gusek. (Source: Chemical Week, 12 October 1988)

Biopol - the biodegradable polymer

Biopol is a polyhydroxybutyrate co-valerate polymer.

Biopol is a polymer of the future. Made by bacteria in a fermentation reaction it has many interesting properties. These include the ability to be moulded and extruded in the same way as thermoplastics such as polypropylene and P.E.T. Bacteria will also destroy it and Biopol items in waste water, sea water, sewerage and landfill in time will simply disappear. This suggests an ideal packaging material, but present costs are high and eventual costs are expected to be four times the price of traditional synthetic polymers.

The natural origins of Biopol have given it great compatibility with animal tissues, and this coupled with the ability to make it in a variety of particulate forms has opened up many veterinary and human applications.

Biopol porous particles (microspheres) can be impregnated with active ingredients and either injected or placed subcutaneously. As the polymer is bioabsorbed by animal tissue the active ingredients are released progressively. Vaccines, steroids, growth promoters, hormones and cytotoxic drugs for cancer treatment are all possible active ingredients to be delivered in Biopol microspheres.

Fabricated Biopol components are compatible with all animal tissues and can be used for example in bone repairs where it will eventually metabolize away as new tissue grows to replace it.

The progressive release of insecticides, as microspheres biodegrade in soil, is another possibility.

If you have a requirement for a polymer which is fully degradable and can be supplied in particulate or fabricated form, please contact: Dr. Mike Robey, ICI Research Group, Newsom Street, Ascot Vale, Victoria, 3032, Australia. (Source: ABA Bulletin, Vol. 3, No. 5, October 1988)

Designs on silk weave stronger fibres

Scientists hope to use genetic engineering to manufacture the silk with which spiders weave their webs. The silk could form ultrastrong fibres for military and biomedical uses.

Nick Ashley, a consultant microbiologist at the research centre of the technology consultancy, PA Technology, Cambridge, UK, was inspired to look at the biotechnological possibilities of the silk produced by the common orb web spider (Araneus diadematus) after a research programme of genetic engineering on the silk of silkworms.

Spider's silk combines flexibility with strength. It is five times stronger than an equivalent filament of steel. In terms of speed per unit of weight, a spider's web withstands the impact of a jet fighter every time it ensnares a fly.

The orb web spider produces five kinds of silk: cocoon silk; web silk; anchor silk; catching silk - found in the sticky central part of the web; and dragline silk. The last kind is the sort spiders dangle on, and is the one that Ashley is studying because it is easy to obtain. It is simply pulled out of the spider, and is extremely tough.

The secret of the silk's unusual properties lies in its molecular architecture. It is a very large, pure protein with a molecular weight of around 300,000 daltons. It consists of repeating ordered regions, six amino acids long, called crystalline domains. These alternate with disordered, or amorphous regions. The crystalline domains give the silken strands their strength, while the amorphous regions provide elasticity.

The silk is secreted from the spider's silk gland in a dilute salt solution, then squirted as a liquid through the spinnerets - organs which apply shear forces that cause the molecules to align into a solid filament.

Ashley has sequenced the single amino acids and the chains of more than one amino acid, or peptides, that make up the ordered and less ordered regions. From this sequence, he can deduce the corresponding DNA sequence, or gene, which is responsible for producing the silk protein. Ashley then creates a synthetic version of this gene, and inserts it into the bacterium, E. coli. This bacterium produces the "biosilk" as granules inside its cell wall. The silk is then dissolved in a solution of lithium bromide. The conditions in this solution mimic those found in the spider's own silk gland, so that the protein can be spun into fibres.

Biosilk could have many applications because it is so light and tough. It could be incorporated into reinforced composites for satellites and aircraft, and even bulletproof vests. At the moment, Ashley is looking for business partners who might help to fund his work. (Source: New Scientist, 29 September 1988)

High-accuracy automatic sampling filtration apparatus of products

Kirin Brewery Company, Limited and Toyo Roshi Kaisha Ltd., both in Japan, have jointly developed a high-accuracy "Automatic Sampling Filtration Apparatus of Products" that is capable of extracting samples of beer and other fermentation liquors without human assistance, and also of continuously changing the filters used for filtering yeast and other substances which denature the samples.

Normally, fermented beer is sampled manually from the fermentation tank and the yeast removed with a centrifugal separator requiring much time and the liquor component's denaturing by yeast action has been unavoidable. Also, the analysed value, a maximum error of about 10 per cent, equivalent to one day of fermentation, used to be generated.

With the newly developed apparatus, the liquor is sampled from the tank directly by suction pump, the yeast is then removed with plastic filters and the sample stored in a cryogenic storeroom. Up to 48 filters are accommodated in a cartridge and controlled with a computer which replaces them before they become clogged. Therefore, up to 9.6 litres can be sampled continuously around the clock with a single cartridge. Another distinct advantage is that the error in analysed values is

lowered to about one per cent thereby enabling accurate sample analysis and permitting product quality to be improved substantially.

The brewer plans to use a bitter substance analyser in combination with this sampling system in the future, and to come out with an automated distillery in which even the hop addition ratio will be adjusted by computer. Further details from Kirin Brewery Company, Limited, 26-1, Jingumae 6-chome, Shibuya-ku, Tokyo, Japan. (Source: JETRO, August 1988)

A small, low-cost MAB reactor

A continuous, immobilized-cell bioreactor for mammalian cells that is said to be 2-3 orders of magnitude smaller than conventional batch reactors, has been developed by Brunswick Biotechnetics (San Diego, Calif.). Brunswick has set up a facility to do contract production and has been making clinical-grade monoclonal antibodies (MAB) for about a dozen customers since early 1988.

The two key features of Brunswick's process are the design of a membrane system to contain the cells and the decoupling of the nutrient supply from the cells' oxygen and carbon dioxide needs. Separation of the air supply from the nutrient permits the design of a much more efficient system. Oxygen is conventionally provided in the nutrient solution, so the O_2 supply is limited by its solubility in the solution. While air-lift fermenters work well and can be scaled up, they are very expensive. The main competitors in air-lift technology are Britain's Celltech and the US company Invitron.

Brunswick's basic reactor core consists of four compartments, made up of flat-sheet membranes that are stacked on top of each other. Liquid-borne nutrient is fed into a chamber that has walls of hydrophilic membranes and diffuses through the membranes into adjacent compartments that contain the mammalian cells or seed material. The O_2-CO_2 mix goes into a chamber that has hydrophobic membrane walls and is similarly located between two seed chambers. Nutrient, gases and seed material are fed in through ports located on the sides of the reactor (nutrient and gases are fed at right angles to each other).

Twenty of these basic units are assembled into a module. A 10-module system, measuring about 1 ft. square by 6 in. nigh, can handle the equivalent of a 1,000-litre suspension reactor, says Wolfgang Wrasidlo, Director of Research. Yet, the membrane reactor uses only 4 litres of nutrient that is circulated back and forth through the system. (Extracted from Chemical Week, 24 August 1988)

Integrated processes in biotechnology

For a long time, product formation and downstream processing have been separate stages of production processes, and are often performed in two different buildings. However, there can be several reasons to integrate these different process stages, including problems of product inhibition, product instability, and high broth viscosity, among others. In several production processes, cell growth or product formation (or both) are reduced with increasing product concentration. This inhibition or repression at high product concentrations is a frequent phenomenon in biotechnology. Most researchers have considered the inhibitions caused by ethanol or butanol and the possibilities for their removal. Many separation processes have been tested in these investigations, and are outlined below.

Adsorption of the product on solid sorbents has the drawback that the loads are fairly low. Large amounts of sorbents are needed to remove small amounts of solvents. Adsorption is only economical at low product concentrations (e.g., adsorption of cycloheximide from culture broth by Amberlite XAD-4).

Extraction is impaired by the low partition coefficients of the product between the solvent and aqueous phases, if the solvent is biocompatible. Solvents with high partition coefficients cause cell damage. Therefore a direct extraction in solvent contact with the cells is not practical; for this type of extraction, a prior separation of the broth and cells is necessary. This problem can be avoided if one uses two aqueous phases. For example, during the microbial transformation of hydrocortisone to prednisolone, the product can be extracted from the broth by biocompatible polyethylenglycol (PEG) solutions.

A novel technique uses extraction with liquid membranes in which an enzyme is encapsulated. The fermentation product permeates from the cell-free broth through the liquid membrane to the inner aqueous phase, where it is converted by the encapsulated enzyme to an end product that is accumulated. This technique is used to remove unstable products from the broth during product formation and to reduce product losses. The insoluble liquid membrane phase (paraffin) is biocompatible. Carries (water-insoluble secondary and/or tertiary amines) are used to increase the permeation rate of the product through the membrane. This technique was tested for integrated penicillin recovery and conversion.

Evaporation of the solvent at reduced pressure (vacuum fermentation) has the disadvantage that only the highly volatile components are removed. Components with higher boiling points (e.g., higher alcohols) continue to accumulate. They are sometimes more toxic to the cells than the more volatile products.

Membranes can be used alone if the molecular weight of the product is much smaller than that of the educt. This is the case when polymers are decomposed enzymatically and the low molecular weight products, which often act as enzyme inhibitors, are removed by permeating them through an ultrafiltration membrane.

If educts and products have similar molecular weights, the use of membranes must be combined with another separation technique.

Pervaporation is a combination of evaporation and membrane permeation. This technique has the disadvantage that it works only at higher ethanol concentrations. Membranes that ensure selective ethanol permeation at low product concentrations are not yet on the market. Many research groups are active in this field. It is expected that, within a few years, suitable composite membranes (e.g., combinations of silicon and polysulfon) will be available with high ethanol selectivity.

Membrane distillation is a combination of membrane permeation and distillation. When a temperature difference is maintained between the two sides of a membrane, a partial pressure gradient can

be created. The more volatile components are thereby enriched on the high-temperature side of the membrane. However, the throughput of this separation technique is very low.

Perstraction is a combination of extraction with membrane permeation. Solvents with high partition coefficients can be used if their solubility is low. In this case, the solvent concentration in the broth can be kept below the critical level that is toxic to the cells. Silicon membranes have been used for alcohol separations of this type.

In another combination of membrane permeation and extraction techniques, one separates the fermentation broth from the cells with a microfiltration module first, and then treats the cell-free broth with solvents that are insoluble in the aqueous phase. To avoid the contact of solvent droplets with the cells, the broth is fed back to the fermentor through an ultrafiltration membrane after the extraction.

Persorption is a combination of membrane permeation and adsorption. The solubility of the product in the membrane can be increased considerably if the sorbent is included into the membrane (e.g., silicalite into silicon membrane). When using this membrane for pervaporation, increased separation rates can be achieved.

A novel combination of adsorption and membrane permeation is the so-called continuous affinity recycle extraction (CARE) for the separation of proteins from culture broth. With this technique, β-galactosidase has been recovered and purified in continuous mode.

Electrodialysis uses cation- and anion-exchange membranes and a potential difference between the two sides of the membrane. It is suitable for the removal of salts, acids, and bases from fermentation broths by means of the electric charges of particles. It is usually necessary to remove the cells from the broth before the electrodialysis (e.g., by means of microfiltration modules).

This technique has been applied for the recovery of lactic acid and various amino acids from fermentation broth.

A novel technique that utilizes exclusion chromatography to recover the product and reduce the broth viscosity has been used during the production of xanthan gum with Xanthamonas campestris. In this process, the cells were immobilized in Celite filter aids, and the product accumulated in the pores of the Celite particles. This was due to diffusion limitations that prevented the transport of the gum from the porous matrix to the external medium.

Many proteins produced by recombinant micro-organisms are not stable. During their storage, their biological activity diminishes. Their stability can be improved by genetic techniques as well as by improving product formation or product recovery and purification. The investigation of the complex interrelationships allows the development of an integrated process which can yield the suitable quality and stability of the product. (This article, by Prof. Dr. Karl Schügerl, Institute for Applied Chemistry, Hannover University, FRG, is reprinted from BioTechnica Journal, No. 5, 1988)

E. PATENTS AND INTELLECTUAL PROPERTY RIGHTS

Help for US Patent Office

In an effort to reduce the huge backlog of biotechnology patent applications, a group of biotechnology companies will help the US Patent Office develop an educational programme for patent examiners.

The announcement, made at the Industrial Biotechnology Association's annual meeting at Coronado, California, publicizes an effort under way since late summer when IBA proposed the Biotechnology Institute and other initiatives to help reduce the existing 6,000-plus backlog of US biotechnology patents. Biotechnology patents currently take an average of 32 months to be reviewed by the Patent Office, a year longer than the average time taken to approve patent applications in most other fields.

The delay has been blamed on the highly technical nature of biotechnology patent claims and the large increase in the number of applications filed over the past six years. (Extracted from Chemical Manufacturing Reporter, 7 November 1988)

House of Representatives to decide on animal patents

The US House of Representatives Committee on the Judiciary in early August considered two drastically different ways to resolve the complex ethical, procedural and economic issues surrounding the patenting of animals. The Committee was to decide whether Congress should establish a two-year moratorium on the granting of patents covering animals, or allow the patenting of animals to continue, but exempt researchers and farmers from paying royalty fees after breeding the animals.

Congress became obliged to set policy over the patenting of animals after the US Patent and Trademark Office decided in April of last year to accept applications for animal patents. The Patent Office ruled that it could no longer stand in the way of patenting animals simply because they were higher life forms. During the public furore that then erupted, the Patent Office made clear that its hands were tied by the judicial interpretation of current patent laws, and that it was up to Congress to weigh the implications and set down new laws if the policy was unacceptable.

While Congress has been in a flurry of activity to come to grips with the technology to create "new" animals, the Patent Office has continued to process the roughly 20 applications it has on hand. It granted a patent to Harvard University in April when all of the legal hurdles to patentability were jumped by "myc-y mouse" - a mouse made susceptible to the development of cancer by the insertion of the myc oncogene into its genome.

Critics of the patenting of animals state that it equates "cows with toasters", and that it will lead to higher prices for farm and laboratory animals and reduce the genetic diversity of animals important to US agriculture. Proponents claim that it encourages innovation, and contend that the patenting of plant varieties - permitted since 1970 - has not been the cause of a recent escalation in seed prices.

But some are not prepared to wait for Congress to resolve these issues: the Animal Legal Defense Fund, an animal rights organization, has filed suit against the US Patent Office accusing it of violating the Patent Act, and the laws governing the establishment of new policies by Federal agencies, by granting animal patents. (Source: Nature, Vol. 334, 4 August 1988)

House approves genetic animal patent bill

The US House Judiciary Committee has passed legislation, H.R. 4970, reinforcing the Patent and Trademark Office's April 1987 assertion that, under current law, genetically altered animals are patentable matter, by neither changing current law nor imposing a moratorium on the issuance of such patents. However, the bill would provide limited protection for farmers who purchase genetically altered animals by proving that on-the-farm reproduction and/or sale of a patented animal or its offspring does not constitute patent infringement. However, sale of embryo, germ cells, or semen of a patented animal would be an act of infringement. The bill also clarifies the Patent Commissioner's authority to require deposits of biological material to support a patent application and states quite definitely that "human beings are not patentable subject matter". (Reprinted with permission from Chemical and Engineering News, 19 September 1988, p. 18. Copyright (1988) American Chemical Society)

EEC drafts revised biotechnology patent law

Europe's 17 Commissioners were in October 1988 considering details for a proposed directive to harmonize EEC Member State patent laws for biotechnology. The draft directive proposal is designed to simplify the patchwork of existing national regulations and broaden patent protection for EEC-derived biotechnology products.

Officials at the Commission are concerned that the more developed patent protection offered in the US and Japan may encourage European firms to export their technology. The proposals will not undermine either the European patent conventions of Paris and Munich or the role of the European Patent Office.

"The thrust of the proposal in front of the Commissioners is to provide legislative guidance through a set of principles designed for applications of patent law for biotechnology inventions," a Commission spokesman explained. The directive is likely to confirm that biotechnology products must be novel, inventive and industrially applicable.

The directive will attempt to define patent limits. "There is a gap in European patent protection particularly as the European patent conventions have exclusions written into them." The key is Article 53 (b) of the European Patent Convention which states: "Patents shall not be granted in respect of plant or animal varieties or essentially biological processes for the production of plants or animals. This provision does not apply to microbiological processes or the products thereof."

"Neither Japan nor the US has these exclusions so individuals are not excluded from making patent claims, while in Europe such claims would automatically fail," added the spokesman. In fact, in US court law the patentability of plants and animals is accepted.

To complicate matters, however, some member States have embodied in law so-called breeders' rights which offer protection for plant varieties. The proposed directive will however attempt to reconcile patent law with such breeders' rights. "The eventual directive will not specifically look at patents but will attempt to harmonize our understanding of the rights and applications of patents within the Community," the spokesman explained.

Patent laws in the European Community are based on the outmoded patent conventions held in Paris (1961) and Strasbourg (1963). At the time, as the Commission itself points out, "biotechnological processes were either non-existent or in their infancy". (Source: European Chemical News, 10 October 1988 and Biotechnology Bulletin, Vol. 7, No. 7, October 1988)

Patent bonanza

The invention business is booming for the European Patent Office in Munich. The EPO's latest annual report says that after only a decade of operation, applications are running at 46,000 a year. Income is DM 25 million higher than estimated when the office was being set up and expenditure DM 30 million lower.

To keep applications flowing smoothly through the office, the EPO is trying to find more examiners, especially in the field of electronics. The EPO is also investing in the future by computerizing its records and patent files. It will now accept applications from inventors in a form that can be read by computers, for example on floppy discs.

European industry has had to deal with Dickensian national patent offices for so long that companies have so far been slow to respond to the EPO's enthusiasm for new technology.

The report notes that there is now a lull in applications in biotechnology and a "staggering increase" in the number of firms who publish their biotechnology inventions in scientific literature instead of patenting, thereby preventing anyone (including themselves) from securing patent monopoly.

Surprisingly few firms are filing patent applications on the new generation of high-temperature superconductors. They know that once a patent application has been filed, its secrets are published after just 18 months.

With money to spare, the EPO has set up a fund of DM one million which will promote research into such problems, where commercial reality and legal nicety come into conflict. (Source: New Scientist, 25 August 1988)

Rights of patients to immortalized cells

A surprise ruling by a Californian court backs the notion that patients have the right to control what happens to samples of tissue and body fluids taken from them, and have a financial interest in any products developed from them.

The case arose after a Seattle businessman, John Moore, filed a suit against the University of California at Los Angeles (UCLA) Medical Center where he had been successfully treated for hairy-cell leukaemia. Cells from his spleen, which was removed as a standard part of his treatment were

found to have unique properties that made them useful as a cell-culture source of interferons and colony-stimulating factor. UCLA researchers established a cell line from the spleen cells which the university then patented and developed in collaboration with two biotechnology companies.

The case may continue for years and eventually be appealed in the Supreme Court of California. In the interim, biotechnology companies will have to prepare themselves for the possibility that they will have to share profits from cell lines with the patients who provided the cells. (Source: Nature, Vol. 334, 11 August 1988)

Group wants to speed up biotechnology patents

The United States Industrial Biotechnology Association, in co-operation with the United States Patent and Trademark Office, is setting up a technical and legal education programme for patent examiners who work in the field. Called the Biotechnology Institute, it will develop a series of seminars to be taught by outside experts to help train new examiners on legal and scientific developments in the biotechnology field. Mini-seminars on specialized topics could also be offered to ensure that the current examining corps is kept up to date on the latest innovations in the field. The institute would also help co-ordinate visits by examiners to biotechnology companies so that they can experience at first hand the realities of biotechnology research and help the PTO update its library of biotechnology books and journals. There is currently a backlog of about 6,500 biotechnology applications; it takes about 27 months for the PTO to process such applications compared with 22 months for other types of applications. The IBA hopes that this new programme will help cut several months off that processing time. (Reprinted with permission from Chemical and Engineering News, 7 November 1988, p. 14. Copyright (1988) American Chemical Society)

First patent granted for herbicide-resistant corn

Molecular Genetics has received a patent (US 4,761,373) for biotechnology-derived corn plants that resist several commercially important herbicides. The patent also covers corn tissue cultures and seeds from which the plants can be generated. The plants are a suitable food source for both animals and humans. Molecular Genetics expects the patented technology to result in the first large-scale commercialization of a biotechnology-derived plant. American Cyanamid has exclusive rights to commercialize herbicide-tolerant corn hybrids resulting from the technology. (Extracted from Chemical Marketing Reporter, 8 August 1988)

Allelix wins plant breeding patent

A US patent has been issued to Allelix Inc., the Canadian biotechnology company, for a novel process which facilitates the development of hybrid canola, a high-quality rapeseed used for food and feed. It is the third largest source of vegetable oil worldwide and the most widely planted oilseed in Europe and Canada. Canada alone has an annual production of $1 billion, making it Canada's second most valuable crop.

The patent covers a unique process of using pollen to transfer genetic material from one canola plant to another. It is notable because it challenges an established genetic principle of inheritance, according to which certain genetic material inside a cell (but outside the nucleus) is transferred to the offspring only from the mother. This has been a major obstacle to agricultural scientists trying to improve various plants using traditional crossing methods, especially when the desirable traits are carried only outside the nucleus.

Details from: Allelix Agriculture, 6850 Goreway Drive, Mississauga, Ontario, Canada L4V 1P1 or on + 1 (416) 677-0831. Source: Biotechnology Bulletin, Vol. 7, No. 8, September 1988)

T-PA patent issues

The Belgian technology-patent firm Innovi N.V. - and its exclusive licensee Genentech (South San Francisco, CA) - have been awarded a broad US patent on t-PA. Precictably, the pair immediately sued the Wellcome Foundation (London, UK) and its partner Genetics Institute (GI, Cambridge, MA) for infringement. Genentech will also try to bar the Wellcome/GI team from making or selling its version of t-PA in the US.

The composition-of-matter patent apparently covers any purified t-PA, irrespective of how it is produced. Most analysts agree that the patent is strong; some even cite this as the reason that SmithKline Beckman (SKB, Philadelphia, PA) has terminated its t-PA joint development arrangements with Damon Biotech (Needham Heights, MA) and with Biogen (Cambridge, MA). SKB will shift its focus to second-generation t-PA, in collaboration with Bio-Technology Ltd. (Oxford, UK).

Meanwhile, Genentech Inc. and Invitron Corporation have reached an out-of-court settlement of their differences in the trade secret suit filed by Genentech last February. Both companies said the amicable resolution of differences would allow them to return their full energies to the development of new health care products to treat major diseases. (Source: Bio/Technology, Vol. 6, August 1988 and Chemical Marketing Reporter, 26 September 1988)

Cartilage growth factor patents granted

Collagen (Palo Alto, CA) has patented two proteins to stimulate the body to produce cartilage. Transforming growth factor beta 1 and beta 2 apparently stimulate the growth of new cartilage, an essential first step in repairing damaged bones. Collagen has also identified the protein that stimulates bone growth, and has applied for a patent. (Extracted from New York Times, 1 October 1988)

Cetus awarded US patent on PEG interleukin-2

The United States Patent and Trademark Office has granted a patent to Cetus Corp. covering PEG interleukin-2, an advanced form of the company's investigational anti-cancer agent, interleukin-2 (IL-2). Cetus began human clinical testing of PEG IL-2 in April 1988. In preclinical animal studies, Cetus' PEG IL-2 demonstrated longer activity in patients, permitting lower dosage rates.

PEG refers to polyethylene glycol, which exists in the form of polymers that can be attached to the

IL-2 molecule to increase the length of time it remains active in the body and improve its solubility. The patent covers composition of matter claims for the PEG polymer conjugates, as well as composition of matter claims for polyoxyethylated glycerol (POG) conjugates. All "native" and analogue forms of IL-2, to which PEG or POG are attached are broadly covered by the patent. Details from: Cetus Corp., 1400 Fifty-Third Street, Emeryville, CA 94608, USA. (Source: Biotechnology Bulletin, Vol. 7, No. 8, September 1988)

A patent covering brain cancer treatment

The Massachusetts Institute of Technology (MIT) has received a US patent for a biodegradable polymer that the university and Nova Pharmaceutical (Baltimore) hope to use in treating brain cancer. The polymer is made of 20 per cent carboxyphenoxypropane and 80 per cent sebacic acid. BCNU carmustine - a widely used brain cancer drug - is mixed with a solution of the polymer and pressed into a wafer, forming fairly rigid tablets about the size of a small coin. Implanting such wafers in the brain has two principal advantages over other methods, says Nova's technology development director, Mark Chasin: "It can deliver thousands of times higher drug concentrations directly to the malignant cells than any other form of therapy." And unlike other biodegradable polymer which undergo bulk erosion, says Chasin, "in our polymer water does not penetrate the polymer matrix, and the rate of degradation can be controlled precisely." (Source: Chemical Week, 27 July 1988)

F. INFORMATICS

ATCC catalogue of human DNA probes, cloned genes and chromosome specific genome libraries

The American Type Culture Collection (ATCC) has issued the second edition of its NIH Repository of Human DNA Probes and Libraries, a 140-page reference catalogue listing materials deposited at the ATCC as part of the genetic repository supported by the National Institute of Child Health and Human Development, and the Division of Research Resources. Details from: American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD 20852-1776, USA or on +1 (301) 881 2600. (Source: Biotechnology Bulletin, Vol. 7, No. 10, November 1988)

ATCC catalogues

ATCC Catalogue of Cell Lines and Hybridomas 6th Edition, 1988

The ATCC collection of cell lines and hybridomas now contains some 2,800 lines derived from 75 different species, including 150 human skin fibroblast lines derived from apparently normal individuals and from patients with various states (including genetic disorders). This catalogue lists these.

Plant tissue cultures are included in this catalogue (64 lines).

This 380-page catalogue is prepared in the usual detailed and meticulous manner of the ATCC catalogue series, with full introductory information, listings of media, and literature references. The catalogue is divided into the following major listings:

Cell Line Descriptions

CCL - Certified Cell Line Bank (142 pages)
CRL - Cell Repository Line Bank (36 pages)
- Genetic Variant and Normal Human Skin Fibroblasts (13 pages)
HTB - Human tumour cell bank (54 pages)
TIB - Tumour immunology bank (17 pages)
NBL - Naval Biosciences Laboratory Collection (14 pages) Plant Tissue Culture Collection 3 pages)

Hybridoma Descriptions

Monoclonal Antibody Index (8 pages)
CCL and CRL Hybridomas (9 pages)
HB - Hybridoma Bank (31 pages)
TIB - Hybridomas (12 pages)

The catalogue is available at a nominal charge from the ATCC to cover postage costs.

ATCC Microbes and Cells at Work
1st Edition, 1988
Edited by M.J. Edwards and others

This new publication is an index to ATCC strains with special applications. The index is an alphabetical listing of compounds which can be accumulated, produced or acted upon by strains available from ATCC in some manner or other. This book is of special interest to biotechnologists because it lists applications, and includes literative references to most listings.

Previously, applications had been indexed in some catalogues of ATCC. Now, they have combined and expanded this approach. In this regard, they are well ahead of most other collection catalogues who only list very rudimentary application information.

The book contains some 115 pages of applications information and 108 pages of fully-titled references. This book is useful as a source of ideas for research projects and new areas of research.

The book is available for US$50.00 outside the USA. ISBN 0-930009-21-5. Order from: ATCC, 12301 Parklawn Drive, Rockville, Maryland 20852-1776, USA. (Source: ABA Bulletin, Vol. 3, No. 5, October 1988)

ASTM publications catalogue available

The 1989 ASTM Publications Catalogue describes 67 volumes of the Annual Book of ASTM Standards and several hundred ASTM Special Technical Publications, Compilations, Data Series, and Standard Adjuncts. ASTM standards and its related technical publications are used world-wide to specify materials, assure quality, integrate production processes, promote trade, and enhance safety.

The Catalogue is available free from ASTM Customer Service, 1916 Race Street, Philadelphia, Pennsylvania 19103, 215/299-5585. (Source: ASTM News Release, 18 October 1988)

The 1989 ASTM Directory of Testing Laboratories

Each laboratory listing contains complete information including contact name, phone number,

address, speciality, fields of testing covered, materials and products analysed, equipment, staff, and branch locations. The Directory features 1,100 laboratories, contacts and phone numbers, and detailed indexes. Please note: the laboratories listed perform services for a fee. They are not certified or endorsed by ASTM; they are listed as a service to ASTM members and customers. List price: $50.00. ASTM member price: $40.00. ISBN 0-8031-1212-2. Publication code number: 04-333289-32. (Source: ASTM News Release, 18 October 1988)

Three new information brochures from US Industrial Biotechnology Association

The Industrial Biotechnology Association (IBA, Washington, DC) has three new biotechnology brochures, available to the public at little or no cost. The brochures cover regulation of biotechnology, biotechnology's impact on US competitiveness, and medical applications of biotechnology. (Source: Bio/Technology, Vol. 6, August 1988)

Free information

The World Health Organization, in collaboration with the Bureau of Hygiene and Tropical Diseases in London, is bringing out a new journal, the WHO AIDS Technical Bulletin, which will be distributed free in developing countries. The journal aims to provide people who find it difficult to gain access to original papers with information on AIDS. The emphasis will be on advances relevant to developing countries.

The bulletin will provide four extended precis of major papers followed by critical editorial comments, in the style of the Morbidity and Mortality Weekly Report. It will also supply abstracts and bibliographical citations. There will be English, French and Spanish editions. People wishing to obtain the bulletin should write to: Global Programme on AIDS, WHO, CH-1211 Geneva 27, Switzerland. (Source: New Scientist, 1 September 1988)

Biotechnology in Eastern Europe

In the wake of the Gorbachev reforms, the political climate in Eastern Europe is increasingly favourable for science and technology. Biotechnology in Eastern Europe: Opportunities for International Business, a new market study from Financial Times Business Information, provides a database on biotechnology in Bulgaria, Czechoslovakia, German Democratic Republic, Hungary, Poland, Romania, the Soviet Union and Yugoslavia. The study indicates the main areas of opportunity for Western suppliers, traders and investors and points to potential low-cost suppliers of biotechnology research, product facilities and manufacturing inputs. Details from: Judy Ashby, Financial Times Business Information, 7th Floor, 50-64 Broadway, London SW1H 0DB. (Source: Biotechnology Bulletin, Vol. 7, No. 8, September 1988)

Survey indicates biotechnology industry is moving towards profitability

Costs in the biotechnology industry still exceed revenues by 9 per cent, but the industry is moving towards profitability, according to a survey by Arthur Young (New York, NY), an accounting and management consulting firm. As of now, only 26 per cent of all biotechnology companies are making money. Some 50 per cent of suppliers are profitable. Some 17 per cent of companies involved in therapeutics are in the black, as against 29 per cent of those involved in diagnostics and 10 per cent of those in agricultural areas. Total product sales have risen 25 per cent in 1988 over the 1987 level, and the industry expects an increase of 69 per cent in two years and 389 per cent in five years. Diagnostics companies believe that by 1990 their sales will rise 87 per cent, and a 606 per cent increase is expected by 1993. Foreign sales by US biotechnology companies will grow 30 per cent in five years. They currently account for 17 per cent of total industry sales. Diagnostics companies say their foreign sales will grow 39 per cent by 1993. US biotechnology companies tend to join forces with other US companies to gain additional capital and with foreign companies to acquire marketing know-how and regulatory expertise. Some 19 per cent of the industry's financing comes via strategic alliances.

US biotechnology companies will spend $51 million on plants over the next five years, with foreign plants accounting for 25 per cent. Spending on foreign plants during the period will be 90 times higher than current levels. R&D outlays have grown 32 per cent over the 1987 level and now average about $4.4 million per company. Some 43 per cent of the sector's total product sales are ploughed back into R&D. R&D spending for agricultural companies is equivalent to 116 per cent of sales. For diagnostic companies the figure is 35 per cent of sales and for therapeutics companies it is 104 per cent of sales. (Extracted from: Chemical Week, 21 September 1988)

Investment opportunities in biotechnology

Supermarket freshness indicators that change colour as the pack of food gets stale and the grading of fruit and vegetables in terms of taste (rather than just of size or shape) are two of the impending applications of biotechnology in the 40 billion pounds sterling food sector. These are examples of a growing spectrum of financial and technological opportunities in the food and agricultural sectors outlined in a new report, Biotechnology for Businessmen.

The UK Department of Trade and Industry commissioned the report, which gives a good deal of information about the value of particular markets. It is designed to tell financiers and commercial managers, in non-scientific language, of the potential for diversification, profit and product improvement in the biotechnology field. Many applications are ripe for small companies and can cost as little as 10,000 pounds sterling.

David Thelwall of Prospect Management Services notes that UK Government agencies are currently spending 20 million pounds sterling a year on biotechnology research. Opportunities have already been taken up in the human and animal health-care sectors, he says, but "in the food area this is not yet so - as the technology and its commercial application gather pace, this is bound to change. The window of opportunity is narrow," he urges. "Action should be taken now."

Food sector applications include a salmonella dipstick to replace current complex test methods for this most widespread fresh food hazard. The report envisages its use in 500 UK factories. Special modified atmosphere packs, such as we already have for fresh meat, tailored to specific crops such as apples or tomatoes, as well as novel coatings to

preserve processed fresh vegetables could transform the fresh produce market, currently worth some 3 billion pounds sterling a year.

Micro-encapsulation of food enzymes is expected to bring significant quality advantages in processes where the enzyme affects flavour and texture, such as in cheese ripening. The UK cheese enzyme market is worth some 8 million pounds sterling at present and the EEC food enzyme market is expected to more than double to a value of around 75 million pounds sterling during the next decade.

Details of the report from: Prospect Management Services, Prospect House, Copt Hewick, Ripon, North Yorkshire HG4 5DB or on 0706 2514/3581. Price 25.00 pounds sterling, incl. p & p. (Source: Biotechnology Bulletin, Vol. 7, No. 9, October 1988)

World market by 1998 for delivery of drugs and imaging agents to brain

Technologies designed to deliver drugs and imaging agents across the blood-brain barrier will hold the key to the treatment of many neurological diseases, psychiatric disorders and other conditions in the next decade. This is the overall conclusion of Business Opportunities in Crossing the Blood-Brain Barrier - A Worldwide Study on Delivering Drugs and Other Products, a report just published by the Technology Management Group. Such technologies will have a high value, since without them many neurotherapeutics will be limited in their efficacy.

The world market for the delivery systems themselves is expected to exceed $1 billion by 1998, with the US market alone projected to pass the $100 million mark in 1993. Brain imaging will be the largest single application for the next decade, with over a third of the total market.

The blood-brain barrier protects the brain from common infections, but also prevents many drugs from penetrating the brain. A wide range of conditions may ultimately be tackled by delivery systems able to penetrate this barrier.

There is no single approach that appears to solve all the problems or to work for all substances. Over 20 companies and 27 other organizations are currently working on relevant technologies.

Twenty-six neurological conditions in seven categories in which crossing the blood-brain barrier may be significant in treatment (Source: TMG)

Reproductive conditions

Impotence
Birth control

Psychotropic disorders

Depression (all forms)
Schizophrenia
Epilepsy

Degenerative neural diseases

Alzheimer's disease
Other senile dementias including:
Huntington's disease and Jakob-Cruzeldt disease
Parkinson's disease
Multiple sclerosis
Amyotrophic lateral sclerosis (Lou Gehrig's disease)

Cancer

Prostate cancer
Brain cancer

Infections

Newborn cytomegalovirus
AIDS dementia
Encephalitis

Meningitis
Brain abcesses
Brain inflammation
Herpes

Behaviour modification

Anti-hypertension
Appetite suppression

Anti-pain or anaesthetics
Tranquilizers

Brain imaging

Diagnostic procedures
Prognoses
Surgical targeting

Numbers of companies and other organizations working on eight different methods to deliver drugs to the brain (Source: TMG)

Method/ technique	Companies	Other organizations	Total
Carrier transport	9	2	11
Polymer implants	2	2	4
Receptor transport	1	1	2
Liposomes	1	1	2
White blood cells to open junctions	1	0	1
Prodrugs	0	3	3
Sugar-rich injection to carotid artery	2	2	4
Implanted pumps	-	1	1

Note: Some companies or organizations are pursuing more than one method.

Details of the 76-page report, priced at $875.00, from: Technology Management Group, 25 Science Park, New Haven, Connecticut 06511, USA. (Source: Bio-technology Bulletin, Vol. 7, No. 8, September 1988)

World-wide immunomodulators for cancer market possible by 1997

Over 180 firms are now involved world-wide in the search for new immunomodulators for use in cancer therapy, according to a study published by the Technology Management Group (TMG). Immunomodulators for Cancer Therapy: A Worldwide Study on Markets and Activities predicts that the world-wide market for such immunomodulators will be worth $3 billion by 1997.

Despite a disappointingly slow start, interferon has been approved for hairy cell leukaemia and approvals for other immunomodulators are expected between 1989 and 1991. Beta and gamma

interferons (approvals expected between 1990 and 1992), interleukin-3 (1990-1991), tumour necrosis factor (1990-1991) and granulocyte-macrophage colony stimulating factors (1989-1990) are also being tested.

Interleukin-2 (IL-2) is thought likely to find the largest market. It may be approved in 1989 for kidney cancer and malignant melanoma, neither of which can be cured by existing chemotherapies. IL-2 is also showing promise against lung cancer, colorectal cancer, multiple myeloma and non-Hodgkin's lymphomas. Immunomodulators may also be used to treat Kaposi's sarcoma (part of the AIDS syndrome), leukaemia, and breast and lung cancer. Details of the report, price at $2,650.00, from: Technology Management Group, 25 Science Park, New Haven, Connecticut 06511, USA. (Source: Biotechnology Bulletin, Vol. 7, No. 7, August 1988)

Herbicide resistant wheat

In November 1987, Professor Jonathan Gressel of the Department of Plant Genetics of the Weizmann Institute of Science warned the British Crop Protection Conference of the imminent possibility that major groups of herbicides currently used to control weeds in wheat would become ineffective due to the evolution of resistance by economically damaging weeds. Failure to control such weeds, he said, can cause yields to fall by 60 per cent.

Some of the most pernicious of these weeds, including blackgrass and wild oats, are not just evolving resistance to the current, very expensive herbicides but are also developing a new and potentially even more damaging characteristic: multiple resistance to virtually every chemical presently in use - and, indeed, to new herbicides to which they have never been exposed.

A study written by Professor Gressel and published by Biotechnology Affiliates, Wheat Herbicides: The Challenge of Emerging Resistance, analyses both the problems and possible solutions. He believes that genetic engineering's ability to modify basic wheat biochemistry has much to offer. He also shows how modifications to the wheat genome can be used to cut the cost of producing hybrid wheat seed, making recombinant hybrid wheat profitable for agro-chemical, seed and biotechnology companies and cost-effective for farmers and consumers. Details of the report, priced at 1,000 pounds sterling, from: Biotechnology Affiliates, PO Box 8, Checkendon, Reading RG8 0BP, UK. (Source: Biotechnology Bulletin, Vol. 7, No. 7, August 1988)

European Foundation for the Improvement of Living and Working Conditions focuses on biotechnology

Four studies on biotechnology-related themes were completed on behalf of the Foundation during 1987. They examined the impact of biotechnology on: living and working conditions; agriculture; the environment; and social conditions. Details from: European Foundation for the Improvement of Living and Working Conditions, Loughlinstown House, Shankill, County Dublin, Ireland. (Source: Biotechnology Bulletin, Vol. 7, No. 9, October 1988)

New report available on US investment in biotechnology

The Congressional Office of Technology Assessment has released its latest report, New Developments in Biotechnology: US Investment in Biotechnology. The study analyses overall federal, state and private spending, and also compares three R&D areas: human therapeutics, plant agriculture, and hazardous waste management. Copies of the report (GPO stock number 052-003-01115-8) are available from the US Government Printing Office. (Source: Bio/Technology, Vol. 6, August 1988)

Biotechnology Directory 1989

J. Coombs and Y.R. Alston. Now with more than 1,600 new entries and vital revisions, this new edition is more complete, more current, more useful than ever. This new edition includes more than 800 new organization listings; 865 other updated and/or revised entries, information on more than 6,150 commercial and non-commercial organizations, a greatly expanded Buyers' Guide of products, research and services, and alphabetical and classification indices for quick access to all information. Available from December 1988, 640 pp., 0-935859-50-0, price $170.00. Details from: Stockton Press, 15 East 26th Street, New York, NY 10010, USA.

Biotechnology Guide USA

Companies, Data and Analysis, by Mark D. Dibner. This guide is a desktop reference that provides specific and detailed information on US biotechnology companies. Focusing on 360 key firms working with the new technologies, this book gives comprehensive details of each company and an analysis of the industry as a whole. The Guide also describes the involvement of large corporations in the biotechnology industry and offers information on the work of the State biotechnology centres. Available from July 1988, 396 pp., 0-935859-40-3, price $175.00. Details from: Stockton Press, 15 East 26th Street, New York, NY 10010, USA.

Virology

Directory and Dictionary of Animal, Bacterial and Plant Viruses. Edited by R. Hull, F. Brown and C. Payne. This is an indispensable reference work for all scientists working with viruses as biochemical tools or as the agents of infectious disease. Many general as well as technical terms are defined including aspects of molecular biology and genetic manipulation. Compiled by internationally renowned authors, this comprehensive work also lists cell lines and provides equations, formulae and definitions. Available from November 1988, 368 pp., 0-935859-59-[illegible], price $79.00. Details from: Stockton Press, 15 East 26th Street, New York, NY 10010, USA.

Biotechnologies: challenges and promises

By Albert Sasson. Paris: UNESCO 1987, 315 pp., price 12.75 pounds sterling/FF85, ISBN 92 3 102091 9. This is the second volume in the UNESCO "Sextant" series designed to provide the general reader with a state-of-the-art review of important topics in clear language. While the subject of biotechnology is very complex and covers many facets, its impact on the whole population can be expected to be similar to the industrial revolution of the late eighteenth century. The aim to put the subject into clear language is an exciting challenge.

Following a basic introduction to the subject, the varied nature of its processes and its impact on the health, food and energy industries, the remaining eight chapters describe various aspects in more detail. The discussion of genetic engineering and genetic recombination occupies a major portion of

the text and presents the subject by way of discussion of the applications developed in the medical health field rather than from the more common theoretical considerations. The subjects of monoclonal antibodies and hybridomas and their applications are covered in a brief chapter. In maintaining the emphasis of application-based discussion, the subjects of plant productivity and its development through biotechnology, the production of useful substances by industrial microbiology, the conversion of wastes and agricultural or industrial by-products and energy production by microbial conversion of biomass are covered.

The two final chapters deal with the development of bio-industry and the perspectives and problems inherent in the new technology. The contents of these chapters include discussion of training of qualified staff, relationships between academics and industry, patents and their exploitation, risk prevention, ethical problems and international co-operation. Both these two chapters provide a much awaited discussion of many aspects of the subject which are not normally included in standard texts.

The text is equally readable to the non-expert decision-maker and the man in the street. It would not be suitable for those wanting an in-depth discussion of the subject but academics would find it a useful text for an introductory course at undergraduate level. (Reviewed by C.A. White and J.F. Kennedy) (Source: Chemistry and Industry, 3 October 1988)

Directory of British Biotechnology 1987/88

Published by Longman, 1988, 185 pp., 65.00 pounds sterling/$120.00, ISBN 0 582 90347 5. Biotechnology, being a multifaceted subject which covers a wide range of disciplines and services, is not necessarily a co-ordinated subject. Cross-fertilization of ideas between the different groups of workers is sometimes difficult and frequently operates only on the personal level. The production of a directory of British biotechnology in 1984 did much to improve the contacts between academic institutions and industry. The 1987/1988 directory, which is a revised, updated edition of the original directory, retains the aims and pattern of the earlier edition while the influence of the Association for the Advancement of British Biotechnology (AABB) has given valuable background information to this volume.

Following a brief resumé of British biotechnology, the AABB and government involvement in biotechnology through the Biotechnology Unit and SERC, a summary is given of some of the recent British achievements in biotechnology describing developments in the fields of health care, agriculture, chemicals and culture collection. This illustrates that biotechnology does have its successes and that Britain is involved in their development.

The main body of the text contains, in alphabetical order, brief profiles of almost 500 organizations (together with contact names and telephone numbers) which are involved in biotechnology. Each is classified into product manufacturer, equipment manufacturer, contract researcher or academic department, and provides details such as general area of involvement, annual R&D budget, number of graduates employed and links abroad. Indexing of the entries has been significantly improved compared with the 1984 edition with organizations represented in the directory being listed under one or more of the following subject areas: agriculture, bioelectronics, commodity chemicals, environment, pharmaceuticals and speciality chemicals.

The text is concluded by an index of venture capital companies, their interests in biotechnology and brief summaries of their level and mode of involvement to date. This is a useful compilation and helps the innovator select potential funding for development from the deluge of (conflicting) information which floods the field of biotechnology.

This is a very useful directory which enables: workers in biotechnology to contact groups in allied or complementary fields; sales personnel to contact key workers in research organizations; journalists and information officers to obtain accurate information from experts in a chosen field; and overseas companies to select companies for interaction and joint ventures. It is hoped that the continued revision of the material will keep the information up to date in an ever-changing field. (Reviewed by J.F. Kennedy and C.A. White) (Source: Chemistry and Industry, 3 October 1988)

Micro-algal biotechnology

Edited by M.A. Borowitzka and L.J. Borowitzka, published by Cambridge University Press, 1988, 477 pp., 45.00 pounds sterling/$79.50, ISBN 0 521 32349 5.

There exist several thousand species of micro-algae and nearly 2,000 literature references are cited in this volume. These figures are a testimony to the intensive study of this vast subject. About 300 species are referred to in the text, though less than 50 have been studied in some detail with respect to their metabolism and chemical composition.

Only a few genera have so far been identified for commercial use. These are described in six chapters of section I: Chlorella, Dunaliella, of which some strains tolerate up to 35 per cent salt in water and which are noted for producing glycerol and β-carotene, Scenedesmus, an attractive source of single-cell protein, Spirolina, of potential use as human food and animal feed, and Porphyridium, a source of polysaccharides and miscellaneous other micro-algae with various potential uses. Nutrient requirements, growth conditions, cell morphology, chemical composition, mass cultivation and commercial production are discussed for these genera.

The second section covers the production of vitamins, fine chemicals, fats and oils, and hydrocarbons; and the use of micro-algae for human consumption, in aquaculture, agriculture and in waste-water treatment. This section is so rich in information and commercial leads that only one example must suffice within this brief review: the single-cell oil production by micro-algae such as Prymnesiophyceae, Chrysophyceae and Chlorophyceae which under specific conditions produce 48-72 per cent of total lipids on a dry weight basis. These lipids are a mixture of neutral glycero-, glyco- and phospholipids. Some of these lipids are rich in essential fatty acids such as α-linolenic 18:3 ω3, eicosapentaenoic 20:5 ω3 and arachidonic 20:4 ω6; these are not only essential components of the diet of humans and animals but are also becoming important feed additives in aquaculture of molluscs, fish and shrimps.

Section III deals with the technology of micro-algae mass culture including engineering aspects of large-scale culture systems and methods for harvesting biomass.

What makes this volume so valuable is that along with scientific information, practical economic data are given including costs of production. Complete operating plants are described and there are informative photographs of commercial plants in several countries. Typically, on page 404 there is a table comparing investment costs for commercial micro-algae biomass separation by centrifugation, sedimentation, flotation and filtration. Energy consumption and maintenance costs are given in the same table. The final chapter on genetic engineering of micro-algae describes possibilities of the use of genetic manipulation to improve product yields, to expand the range of products, to promote faster growth and better adaptation to the environment. This is an indispensable book for all working in this area of biotechnology. (Reviewed by M.K. Schwitzer) (Source: Chemistry and Industry, 3 October 1988)

Software for drug design

Proteus Biotechnology, a private company set up by academics from the University of Manchester, has developed what it considers to be the most sophisticated computer drug design software available.

The software system, called Prometheus, allows the investigator to find a succession of potential ligands on the basis of mathematical input, enabling many potential compounds to be abandoned in only a short time in favour of a few promising options. The company says the system is "objective" compared with existing systems for drug design which are "subjective" in that potential receptors and ligands have to be judged from what is represented graphically on screen.

Proteus envisages three potential markets for the system. The first involves companies being able to buy a licence for the software by the end of 1988. Secondly, drug companies could contract with Proteus to work on specific drug design projects. Finally, it is possible to design drugs in-house using the system. This latter option is already under way, says Proteus

Proteus is situated at Proteus House, 48 Stockport Road, Marple, Cheshire SK6 6AB (Tel.: 061-426 0191) (Source: Manufacturing Chemist, November 1988)

Directory of molecular biology data bases

The recent thrust to decode the human genome has provided a strong impetus for creation and maintenance of a computerized directory of molecular biology data bases. Such a "database of data bases" has now been compiled at Los Alamos National Laboratory and is available to researchers without cost on electronic mail, floppy disk, or in printed form. Called the Listing of Molecular Biology Data Bases, or LiMB, it contains information on about 60 data bases, and the number is continuing to increase. LiMB is expected to evolve into a system directly supporting communicative software. Current information in LiMB includes the names of the data bases, the type and amount of data they hold, descriptions of the hardware and software, and details about access to the data. According to LiMB project leader Christian Burks, the human genome project will involve efforts to generate new data sets in a systematic way. There will be a strong need, he says, to keep track of the data bases spinning off the genome project. (Reprinted with permission from Chemical and Engineering News, 26 September 1988, p. 22. Copyright (1988) American Chemical Society)

Microcomputer software compares 2-D gels

High-powered image-processing workstations dedicated to image-analysis are one way of approaching the daunting task of analysing 2-D electrophoresis gels. But personal computer based software can get the job done for less - about $100,000 less, to be exact. Some can perform automatic global comparisons between two gels - the drawing card of premier minicomputer systems such as those offered by Bio Image (Ann Arbor, MI) and Large Scale Biology Corp. (Rockville, MD).

Of course, these PC packages do not offer nearly the data storage capacity or computing power of the fancier systems. Users can view only two to four images at a time, and must perform more manual adjustments and wait longer for results. But for the average laboratory it is adequate.

Most personal-computer-based image analysis works on an IBM AT or 100 per cent compatible clone with 640K, using either a camera or a densitometer to acquire images. Interactive programs let the user edit and select spots of interest.

Efficient algorithms are the key to running automatic global comparisons on a personal computer program, according to Charles Tseng, vice-president of Indiana Biotech (Highland, IN), which has developed the IB-1000 image analysis system (marketed by Isotech, Oak Ridge, TN, at a cost of $50,000).

Potential customers should note, however, that unlike Indiana Biotech's system, Bio Image's Visage series compares and quantifies an unlimited number of spots, and offers extensive database and quantitative report-generating capabilities. The new Visage 60, priced at $34,500, is cost-competitive with several of the PC-based systems.

Biomed Instruments (Fullerton, CA) offers PC-based image analysis software that does global comparisons - and is also part of the least expensive system available. For $17,000, Biomed offers a package that includes the computer, software, a printer, and the company's patented laser scanner, which scans a 20 x 20 cm 2-D gel in one minute. Biomed's system superimposes images from different gels and performs Gaussian deconvolution to separate unresolved 2-D spots.

Molecular Dynamics (Sunnyvale, CA) has taken a different approach to PC-based image analysis. Its new 300A Computing Densitometer combines a microcomputer with a fast-scanning densitometer. The $29,500 system (not including printer) uses software based on Microsoft® Windows™, which permits transfer of image data to statistical programs and data bases. This instrument provides a well-defined image (88μ spatial resolution; optical density resolution up to 3.5 with one per cent variation). It acquires images in three minutes, much faster than most densitometers, which can take up to six hours for a typical 2-D gel. The densitometer scans the whole area of the gel as opposed to scanning individual lines, improving its accuracy.

Though the Molecular Dynamics system cannot perform global comparisons, its capabilities serve the needs of many researchers. The computing densitometer is well-suited for expression studies, purity testing and quality control.

Component-based image analysis systems offer researchers the option of simply buying software and using it with PCs and densitometers that are already in the laboratory. Haake Buchler (Saddle River, NJ) offers its Q-Gel 2-D analysis software for $3,400. It integrates spot density and computes molecular weight and isoelectric point, but cannot match spots from one gel to those in another.

LKB (Bromma, Sweden) also offers a component-based system. Its Gel-Scan XL software, available for $2,695, helps researchers compare two 2-D gels by superimposing the images and showing areas of overlap or non-overlap in contrasting colours. (Source: Bio/Technology, Vol. 6, September 1988)

G. MEETINGS

1988

4-6 April - San Servolo Island, Venice, Italy. Seminar on Regulation of Cell and Tissue Function by Peptide Growth Factors. Further information from the Secretariat - NI, The European School of Oncology, Via Venezian 1, 20133 Milan, Italy.

5-7 April - Christ Church, Oxford, UK. International Conference on Vaccines for Sexually Transmitted Diseases. Further information from Diane Cogan, Butterworth Scientific Ltd., P.O. Box 63, Westbury House, Bury Street, Guildford, Surrey GU2 5BH, UK.

6-7 April - Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK. Symposium on Psychiatric Neuropathology and Neurochemistry. Further information from Nadine Morgan, Conference Office, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK.

7-10 April - St. Petersburg Beach, Florida, USA. First US-Japan Symposium on Biotechnology. Further information from Showa University Research Institute, 10900 Roosevelt Boulevard, St. Petersburg, Florida 33716, USA.

10-11 April - Bethesda Marriott Hotel, Bethesda, Maryland, USA. Conference on Multidrug Resistance: Molecular Biology and Clinical Relevance. Further information from Abbe Smith or Debra Casey, Technical Resource Inc., 3202 Tower Oaks Boulevard, Rockville, Maryland 20852, USA.

12-14 April - Cambridge, UK. Research Symposium on Ion Transport. Further information from C.D. Keeling, Smith Kline and French Research Ltd., The Frythe, Welwyn, Hertfordshire AL6 9AR, UK.

12-16 April - Chichester, West Sussex, UK. NATO Advanced Research Workshop on Recognition and Response in Plant-Virus Interactions. Further information from Dr. R.S.S. Fraser, AFRC Institute of Horticultural Research, Worthing Road, Littlehampton, West Sussex BN17 6LP, UK.

17-19 April - Atlanta Hilton and Towers, Atlanta, Georgia, USA. ASTM Committee Meeting on Biotechnology. Further information from ASTM, 1916 Race Street, Philadelphia, PA 19103, USA.

17-20 April - Sheffield University, Sheffield, UK. International Conference on Studies Involving Nucleic Acid Recognition. Further information from Dr. G.M. Blackburn, Department of Chemistry, The University, Sheffield S3 7HF, UK.

17-20 April - Gennep, the Netherlands. Congress on Idiotype Networks in Biology and Medicine. Further information from OBU Utrecht Congress Office, P.O. Box 14214, 3508 SH Utrecht, the Netherlands.

17-21 April - Loughborough, UK. Basic Microbiological Methods for the Analytical Chemist. Further information from Dr. R.K. Dart, Department of Chemistry, Loughborough University of Technology, Loughborough, Leicestershire LE11 3TU, UK.

17-22 April - International Conference Center, Havana, Cuba. Third Cuban and International Seminar on Interferon, Second Cuban and International Seminar on Biotechnology and First Iberoamerican Congress on Biotechnology. Further information from Fairs and Exhibitions, Palacio de las Convenciones, Apartado 16046, La Habana, Cuba.

18-19 April - The Wistar Institute, Philadelphia, USA. Symposium on New Perspectives on Evolution. Further information from External Affairs Office, The Wistar Institute, 3601 Struce Street, Philadelphia, PA 19104, USA.

20-22 April - Université Libre de Bruxelles, Brussels, Belgium. First European Symposium on Calcium Binding Proteins in Normal and Transformed Cells. Further information from Dr. R. Pochet, Laboratoire d'Histologie, Faculté de Médecine, Université Libre de Bruxelles, 2, rue Evers, B-1000 Brussels, Belgium.

25-28 April - Rancho Mirage, California, USA. Conference on Structural and Chemical Basis for Cell Function. Further information from The Secretariat, Annenberg Center, 39000 Bob Hope Drive, Rancho Mirage, California 92270, USA.

26-30 April - Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA. Meeting on Genome Mapping and Sequencing. Further information from Meetings Co-ordinator, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724. USA.

1989

1-5 May - Paris, France. Seminar on BMT in Lymphomas. Further information from ESH, Hôpital Saint Louis, Centre HAYEM, 1, avenue Claude Vellefaux, 75475, Paris, Cedex 10, France.

3-7 May - Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA. Cold Spring Harbor Laboratory Conference on Regulation of Liver Gene Expression. Further information from Meetings Co-ordinator, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York 11724, USA.

9-12 May - Baltimore, Maryland, USA. International Study Group for Tryptophan Research. Further information from Dr. R. Schwarcz, Maryland Psychiatric Research Center, P.O. Box 21247, Baltimore, Maryland 21228, USA.

15-16 May - Scanticon Conference Center, Princeton, New Jersey, USA. Fourth Princeton Liposome Conference - From Bench to Bedside. Further information from P. Pluta, Conference Co-ordinator, The Fourth Princeton Liposome Conference, c/o The Liposome Company, Inc., One Research Way, Princeton, New Jersey 08540, USA.

16-18 May - Edinburgh, Scotland, UK. International Symposium on Biothermic Medicines: From Laboratory to the Patient. Further information from the Symposium Secretariat, CEP Consultants Ltd., 20-28 Albany Street, Edinburgh EH1 3QH, Scotland, UK.

16-18 May - Tara Hotel, London, UK. Biotech '89. Further information from Blenheim Online Ltd., Blenheim House, Ash Hill Drive, Pinner, Middx. HA5 2AE, UK.

16-20 May - Island of Les Embiez, France. Fourth European Network of Immunology Institutes Conference. Further information from Dr. Diane Mathis (1989 ENII Conference), INSERM U.184/LGME, 11, rue Humann, 67085 Strasbourg, CEDEX, France.

17-20 May - New Brunswick, New Jersey, USA. Second International Conference on Mathematical Population Dynamics - Cell and Molecular Biologists, Oncologists, Mathematicians. Further information from Dr. Marek Kimmel, Department of Pathology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA.

18-20 May - Santa Margherita Ligure, Italy. International Workshop on Chromosome 21: Impact of the New Genome Technology in Human Genetics. Further information from International School of Pediatric Sciences, Direzione Scientifica, Istituto G. Gaslini, 16148 Genoa, Italy.

18-23 May - Capo Caccia Hotel, Alghero, Sassari, Italy. Sardinia Symposium on Advances in Biotechnology: Control of Gene Expression. Further information from Organizing Secretariat, Dr. Salvatore Rubino, Istituto de Microbiologia e Virologia, Viale San Pietro 40B, 07100 Sassari, Italy.

22-26 May - London, UK. Course of lectures on Receptors, Autoradiography and Image Analysis. Further information from the Conference Office, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 ONN, UK.

22-26 May - Paris, France. Seminar on Allogenic Bone Marrow Transplantation. Further information from ESH, Hôpital Saint Louis, Centre HAYEM, 1, avenue Claude Vellefaux, 75475 Paris, Cedex 10, France.

25-26 May - Les Pensières, Veyrier du Lac, Annecy, France. Vaccines of the Future. Further information from Fondation Universitaire des Sciences et Techniques de Vivant, 55, route d'Annecy, 74290 Veyrier du Lac, France.

29 May - 3 June - Aussois, France. Structure, Metabolism and Genetics of Glycoconjugates. Further information from Dr. J. Montreuil, UST, Lille Flandres-Artois, Chimie Biologique, 59655 Villeneuve d'Ascq, CEDEX, France.

31 May - 7 June - Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA. Symposium on Quantitative Biology: Immunological Recognition. Further information from Meetings Co-ordinator, Cold Spring Harbor Laboratory, Bungtown Road, Cold Spring Harbor, New York 11724, USA.

10-17 June - New Haven, Conn., USA. Tenth International Workshop on Human Gene Mapping. Further information from Prof. F. Ruddle, HGM10 Executive Office, 25 Science Park, Suite 457, New Haven, CT 06511, USA.

21-23 June - London, UK. 6th International Meeting on Advances in the Applications of Monoclonal Antibodies in Clinical Oncology. Further information from The School Office (SSC), Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 ONN, UK.

25-28 June - Cornell University, Ithaca, New York, USA. Second Symposium on Genetic Engineering of Animals. Further information from Dr. W. Hansel, Department of Physiology, 816 Veterinary Research Tower, New York State College of Veterinary Medicine, Cornell University, Ithaca, New York 14853-6401, USA.

26-30 June - Vienna, Austria. Second International Symposium on Positive Strand RNA Viruses. Further information from Dr. F.X. Heinz, Institute of Virology, Kinderspitalgasse 15, A-1095 Vienna, Austria.

25 June - 8 July - Gran Hotel del Sella, (Ribadesella), Asturias, Spain. Advanced Study Institute on Molecular Basis of Plant Aging. Further information from Prof. Dr. Roberto Rodriguez, NATO ASI on Molecular Basis of Plant Aging, Laboratorio de Fisiologia Vegetal, Dpto. Biologia de Organismos y Systemas, Universidad de Oviedo, calle J. Arias de Velasco s/n, 33005 Oviedo, Asturias, Spain.

28-30 June - Les Pensieres, Veyrier du Lac, Annecy, France. Seminar on Frontiers in Eukaryotic Transformation. Further information from Fondation Universitaire des Sciences et Technique du Vivant, 55, route d'Annecy, 74290 Veyrier du Lac, France.

4-7 July - Cambridge, UK. International Symposium on Brain-Gut Interactions. Further information from Joyce Fried, Brain Research Institute, University of California, Center for the Health Sciences, Los Angeles, CA 90024-1761, USA.

6-7 July - Minto Place Suite Hotel, Ottawa, Ontario, Canada. First Canadian Workshop on BioInformatics. Further information from Ottawa Carleton Research Institute, 300 March Road, Suite 204, Kanata, Ontario, Canada K2K 2E2.

9-14 July - Helsinki, Finland. Thirty-first International Congress of Physiological Sciences, Helsinki, Finland. Further information from The Finnish Fair Corporation, Ms. Anja Böhling, P.O. Box 21, SF-00521 Helsinki, Finland.

14-30 July - Denver, Colorado, USA. Workshop on Somatic Cell and Molecular Genetics. Further information from Program Director, Somatic Cell and Molecular Genetics Workshop, Eleanor Roosevelt Institute for Cancer Research, 1899 Gaylord Street, Denver, CO 80206, USA.

17-28 July - Bar Harbor, Maine, USA. 30th Annual Short Course in Medical and Experimental Mammalian Genetics. Further information from Dr. T.H. Roderick, c/o Training and Education Office, The Jackson Laboratory, 600 Maine Street, Bar Harbor, ME 04609-0800, USA.

24-29 July - Churchill College, Cambridge, UK. Imperial Cancer Research Fund Meeting on DNA Tumour Virus. Further information from Mrs. Clare Middlemiss, ICRF DNA Tumour Virus Meeting Secretary, Imperial Cancer Research Fund, Lincoln's Inn Fields, London WC2A 3PX, UK.

26-28 July - Pennsylvania State University, Pennsylvania, USA. Eighth Summer Symposium in Molecular Biology - DNA-Protein Interactions. Further information from Symposium Program Co-ordinator, Eighth Summer Symposium in Molecular Biology, 208 South Frear Laboratory, The Pennsylvania State University, University Park, PA 16802, USA.

30 July - 5 August - Berlin, FRG. Seventh International Congress of Immunology. Further information from the Congress Bureau DER-CONGRESS, Congress Organization, Augsberger Strasse 27, D-1000 Berlin 30, FRG.

2-7 August - Stockholm, Sweden. 32nd IUPAC Congress. Further information from 32nd IUPAC Congress, c/o Stockholm Convention Bureau, P.O. Box 6911, S-102 39 Stockholm, Sweden.

27 August - 1 September - Assmannshausen/Rhein, FRG. Sixth International Conference on Partitioning in Aqueous Two-Phase Systems - Biochemistry, Cell Biology and Biotechnology. Further information from DER- Congress, Att. Mrs. Brigitte Schönfeldt, P.O. Box 100701, D-6000 Frankfurt, FRG.

4-7 September - Roscoff, France. Gene Regulation in Development. Further information from Dr. Walter J. Gehring, Biozentrum der Universität Basel, Abt. Zellbiologie, Klingelbergstrasse 70, CH-4056, Basel, Switzerland.

17-20 September - College Station, Texas, USA. Third International Meeting on Membrane Biotechnology. Further information from Mrs. Catherine Meyer, Biophor Corporation, College Station, Texas 77840, USA.

21-23 September - Stockholm, Sweden. Fourth International Symposium on VIP and Related Peptides. Further information from Registration VIP Symposium, Biochemistry II, Karolinska Institute, P.O. Box 60400, S-10401, Stockholm, Sweden.

25-29 September - Ashford, Kent, UK. Fourth Wye International Symposium on Agriculture and Global Climatic Change. Further information from Dr. G.P. Chapman, Wye College, Nr. Ashford, Kent, UK.

25-29 September - Roscoff, France. Hormone Signals and Plant Growth. Further information from Dr. J. Guern, Physiologie Cellulaire Végétale, CNRS, Bâtiment 15, avenue de la Terrasse, 91198 Gif-sur-Yvette, Cedex, France.

28 September - Ghent, Belgium. Third Forum for Applied Biotechnology. Further information from Scientific Center FAB, p/a L. Demey, Coupure 653, B-9000 Ghent, Belgium.

22-25 October - Siena, Italy. International Conference on the Molecular and Cellular Biology of IL-1, TNF and Lipocortins in Inflammation and Differentiation. Further information from the Scientific Secretariat, Sclavo Research Centre, via Fiorentina 1, 53100 Siena, Italy.

1990

12-15 February - Massey University, Palmerston North, New Zealand. Fermentation Technologies: Industrial Applications. Further information from the Director, Biotechnology Department, Massey University, Palmerston North, New Zealand.

11-13 September - University of Reading, Reading, UK. Second International Conference on Separations for Biotechnology. Further information from the University of Reading, Reading, UK.

B. REPRINTED ARTICLES

Biotechnology of marine algae: opportunities for developing countries

F.L. Singleton, Ph.D., and J.G. Kramer, Ph.D.
Center of Marine Biotechnology
Maryland Biotechnology Institute
University of Maryland
600 East Lombard Street
Baltimore, Maryland 21202, USA

ABSTRACT

Recent advances in molecular biology provide the means to exploit the unlimited potential of marine resources, especially finfish, shellfish and algae. This is true especially for countries with significant coastal resources, although other countries can also take advantage of the benefits of marine biotechnology. One of the most accessible marine resources of the coastal zone are the macroalgae or seaweeds. The marine macroalgae are comprised of several distinct taxonomic groups typified by a wide range of sizes, pigmentation, chemical composition and physiology. A common feature for most however, is a macroscopic life history stage distinguished by substrate-attached individuals. Historically, these plants have been cultivated with great success.

Seaweeds are used in various ways - from food for humans and animals, primarily in the Far East, to energy production, to a source of the specialty chemicals known as phycocolloids (agar, alginate, and carrageenan). The world market of phycocolloids alone exceeds $250 million per year. This market will continue to expand as the demand for such products increases.

The application of modern biotechnology to the problem of efficient exploitation of algal resources (macroalgae and microalgae) presents developing countries with opportunities to expand existing markets and develop new markets. The potential of marine algae for developing countries and for developed countries is unlimited; this potential can be realized with a concerted effort to employ the powerful techniques of modern molecular biology in conjunction with both historically established mariculture techniques and new developments in aquacultural practices.

Advances are being made in the area of "genetic engineering" of seaweeds and microalgae. Thus, we should soon realize the goal of hybrid strains of

marine algae that have desirable features such as rapid growth rate or "hyper-producers" of valuable compounds (e.g., phycocolloids).

By carefully developing a strategy to take advantage of the results of genetic selection of macroalgal strains and appropriate cultivation techniques, developing countries with favourable climate and coastal resources can make significant gains in their national and international market-places. Of primary interest is the potential to establish new industries based upon the production of highly valuable specialty chemicals such as phycocolloids, nutritional supplements, vitamins, fertilizer, and pharmaceuticals.

Biotechnology of marine algae: opportunities for developing countries

F.L. Singleton, Ph.D., and J.G. Kramer, Ph.D.
Center of Marine Biotechnology
Maryland Bictechnology Institute
University of Maryland

Marine waters cover approximately 71 per cent of the earth's surface and harbour a wide variety of highly diverse biological communities. In all probability, the oceans contain more than one million species of animals, algae, bacteria and fungi. For centuries, humans have depended on harvests of some species of fish, shellfish and algae from the oceans as a staple food. Also, we have relied on the oceans for raw materials for some industries and as an avenue of travel and trade.

Our long-standing dependence on natural stocks of marine life, especially finfish and shellfish, has resulted in the lack of incentives to enhance production of desirable species. The lack of progress in this area is in sharp contrast to our progress in food production on land. We have advanced from hunter-gatherers in exploiting terrestrial food crops to our current stage of producing food supplies from a technologically-advanced agricultural industry. The development of agriculture has included the application of appropriate technologies to maximize production of desirable crops. Those technologies range from developing hybrid strains of plants and animals to the application of molecular genetics in agricultural biotechnology. Thus, we are able to capitalize on the metabolic potential of key crops, livestock and terrestrial micro-organisms. We have not made similar accomplishments in utilizing marine resources.

Our awareness of the productivity of the oceans is changing as we become more appreciative of the fact that natural stocks cannot meet tne demand for many marine organisms and their products. For example, it has been estimated that the maximum world-wide harvest of wild seafood is between 100 to 150 million metric tons (National Oceanic and Atmospheric Administration, 1977). The current harvests of approximately 70 million metric tons of seafood cannot be sustained in the long term. In the United States, harvests from natural stocks cannot meet the demand and, as a result, the United States imports billions of pounds of finfish, shellfish, and algae (National Marine Fisheries Service, 1980).

Only in a few countries have there been sustained efforts to apply some of the experience gained from agriculture to cultivating and harvesting marine organisms. China and Japan have been at the forefront of farming coastal waters (Tseng, 1981; 1984). The successes realized in China and Japan as well as increased demand for products from marine organisms are enhancing incentives for adapting successful agricultural practices to farming some regions of the marine environment. Compared to terrestrial crops, the concept of farming the oceans is in its infancy.

The benefits of the development of new and, perhaps, high technology marine-based industries will be many, especially in developing countries. One benefit to societies in all countries will be to reduce (or eliminate) threats posed to sensitive habitats and organisms by harvesting natural stocks of marine life. In many instances, the genes which code for a particular product or process can be cloned into a micro-organism amenable to laboratory cultivation and, as a result, eliminate the need to harvest organisms from the wild.

The application of techniques of modern molecular biology and molecular genetics to marine organisms presents many unique opportunities and unlimited potential for many facets of society (see review by Colwell, 1983). Indeed, through marine biotechnology we can exploit the genetic diversity of marine organisms to obtain particular products while promoting economic development. Concomitantly, the development of marine biotechnology-based industries will require efforts to be directed towards basic studies on commercially-important marine species. An investment in studying the basic biology and ecology of marine organisms will ensure increased productivity of mariculture-based industries and, equally important, that there will be a continual influx of innovative ideas to stimulate new marine biotechnology initiatives.

In order for any country to expand existing industries and to develop new industries based upon marine biotechnology, it is essential to institute policies which are sound ecologically as well as economically. Countries with abundant coastal resources should benefit most from marine biotechnology and, as such, they must ensure that the development of this field does not harm their coastal resources. Considering this, we must evaluate which strategies have the greatest probability of success.

The potential of marine biotechnology can be considered in terms of the **genetic potential** and **crop potential** of marine organisms. Genetic potential includes an organism's metabolic products (i.e., pharmacologically-active compounds, fine chemicals, etc.) and the processes it mediates in situ. The crop potential of marine organisms includes their use as food and food supplements and, perhaps, in applications of their biomass (i.e., as a substrate for methane production).

Marine organisms possess a remarkable phenotypic diversity and, therefore, a.. even more varied genotypic diversity. Of the hundreds of thousands of species of marine organisms, only relatively few have been studied in any detail. Fewer still have been examined at the genetic level; of those, only a very limited amount of information has been obtained. Compared to what is known about the molecular genetics of Escherichia coli, we have, at best, only a rudimentary appreciation for the genetic diversity of marine life. However, on the basis of the very limited amount of information available, a great deal of knowledge is to be gained from studies on the genetics of marine organisms.

Marine organisms survive and grow in habitats characterized by physico-chemical environmental parameters not encountered by terrestrial or

freshwater organisms. As a consequence, marine organisms must cope with habitats characterized by seemingly harsh conditions. In addition to high salinity, many species of marine organisms must contend with high hydrostatic pressure and low temperature (typical of the deep sea) or high hydrostatic pressure and high temperature (typical of deep sea hydrothermal vents [Baross and Deming, 1983; Deming and Baross, 1986]). Much of the biota of tropical marine waters possess specific traits for survival in highly diverse and competitive habitats; because of this, they are subjected to strong selective pressures from biotic and abiotic factors in their environment.

In order to survive and grow in highly competitive habitats, marine organisms must compete for limiting resources. A variety of offensive and defensive mechanisms have evolved to allow organisms to gain a selective advantage and to cope with competitors. The physiological manifestations of offensive and defensive abilities of marine organisms are in the form of bioactive metabolites (i.e., toxins) (Martin and Padilla, 1973; Scheuer, 1973; Hashimoto, 1981). Many marine animals produce specific toxins that are used to capture prey or to deter predators. Many marine algae produce metabolites that function as feeding deterrents (Burreson et al., 1975; Targett, 1979; Faulkner and Ghiselin, 1983; Tachibana et al., 1984, 1985). These and other bioactive metabolites are excellent candidates for a variety of applications in, among others, the pharmaceutical, agrochemical, and food industries (Scheuer, 1973; Baslow, 1977; Cardellina, 1986).

Compounds produced by marine organisms, especially marine algae, represent a variety of (potentially) lucrative markets. An increasing appreciation for the unlimited potential of food and products from the sea is stimulating the development of marine biotechnology-related industries in many countries. This is true for products with pharmacologic activity and those that have applications as fine chemicals. The momentum to capitalize on the potential of marine biotechnology should increase dramatically in the future.

It has been estimated that the majority of people inhabiting developed countries have some daily contact with products originating in marine algae (Abbott and Cheney, 1982). These products are present in toothpaste, shampoo, many dairy products as well as many other consumer goods. As such, marine algae are the most obvious candidates for enhancing the development of marine biotechnology-based industries in developing countries.

Marine algae have many features that make them ideal organisms on which to base initiatives in marine biotechnology. Although other organisms (i.e., finfish, shellfish and micro-organisms) hold great potential for marine biotechnology, marine algae may represent the greatest market potential due to the diversity of products that can be obtained from them (see Waaland, 1981; Abbott and Cheney, 1982; Tapie and Bernard, 1988). Also, industries based on exploiting marine algae have a long history (Waaland, 1981). As technology advances, those industries will expand to meet an increasing market, and new industries will be formed to satisfy new markets.

Many types of marine algae, both macroscopic and microscopic forms, can be used in marine biotechnology industries. However, significantly different types of technology and facilities are required to capitalize on these very different groups of organisms. Representatives from both groups have been used as a food for humans and animals and for a variety of useful products (Abbott and Cheney, 1982; Tapie and Bernard, 1988). Compared to macroalgae, there has been remarkably little exploitation of microalgae. Borowitzka (1989) has estimated that only 60 of over 22,000 strains have been screened for vitamins, pharmaceuticals or biochemicals. Only a relatively modest effort has been directed toward commercial cultivation of a few species of microalgae. These include producing algae as a source of food or food supplements or for fine chemical production. However, the market potential of these organisms has not been exploited to any significant degree. This should happen in the future as improvements are made in the technology required for their cultivation and as more strains with highly desirable characteristics are isolated or developed in the laboratory. For instance, we now have the capability to culture Dunellialla salina in such a manner that over 50 per cent of its dry weight is glycerol (Borowitzka, 1988; Borowitzka and Borowitzka, 1988; Moss and Doty, 1987). Currently, glycerol production is petroleum-based but it is reasonable to assume that current production can be supplemented by utilizing algal products.

The economics of microalgal production of specific chemicals will improve as technology advances (see Hartig et al., 1988). For example, cells of some strains of microalgae comprised of as much as 72 per cent lipid have been isolated. These lipids can be converted to a high quality energy source. However, this fuel is still far more expensive than conventional fossil-derived sources (McIntosh, 1984). The application of techniques of molecular biology and molecular genetics to these organisms may result in strains with faster growth rates and increased production of lipids and other biochemicals. Additional research is required if we are to capitalize on these organisms.

Metabolic products of marine algae, especially microalgae, have significant potential as pharmaceutical compounds (see Baslow, 1977). The pharmaceutical industry is very large (multi-billion in the United States) and requires a constant influx of new compounds. Marine algae have yielded many natural products with unusual structures and activities (see reviews by Fenical, 1982; Faulkner, 1984, 1986, 1987). The reported activities of natural products isolated from marine algae range from antimicrobial to antihelminthic to cytotoxic to anticoagulant to, among others, hypocholesterolemic (see Scheuer, 1973; Baslow, 1977). Thus, these organisms are excellent candidates for use in developing industries in marine pharmacology.

Bioactive metabolites from marine algae may also have applications in agriculture. "Agrochemicals" have a multi-billion dollar market. Marine natural products from algae have great promise in this market and emphasis should be placed on developing this potential (see review by Cardellina, 1986). Because a relatively large percentage of food crops is lost to insect pests, there are urgent needs for effective and environmentally-safe pesticides.

Studies have demonstrated that plant growth-promoting compounds are common in marine algae (Bentley, 1958; Abe et al., 1974; Augier, 1978; Kingman and Moore, 1982). More work is required to determine the chemical structures of the growth-promoting substances as well as their specific role(s) in the developmental biology of

marine algae. Likewise, studies are needed to evaluate the feasibility of exploiting the applications of these compounds (see Cardellina, 1986).

Although bioactive metabolites and other specialty chemicals have significant potential in markets that will develop in the future, in all probability they may be minor in comparison to existing and future markets for other compounds from marine algae, especially from seaweeds. In Western cultures, emphasis is placed on using those marine plants as a source of useful chemicals (e.g., phycocolloids) but in Eastern cultures, the culinary aspects of seaweeds are exploited.

All three groups of macroalgae (Chlorophyta, Phycophyta and Rhodophyta) can provide digestible proteins, essential vitamins and trace minerals when consumed by humans. Indeed, in many cultures, these plants are considered delicacies. Macroalgae have been utilized to supplement both human and animal diets (Waaland 1981; Hansen et al., 1981). Certainly, the greatest use of seaweeds is found in the Orient. However, there is a long tradition of regional harvesting of macroalgal stocks in Europe and North America as well.

Macroalgae have been used as food in the Orient and in some Pacific cultures for centuries. Representatives of the three types of macroalgae are consumed, although consumption of the red and brown seaweeds is more common (Stickney 1988). The seaweed industry, including uses and cultivation techniques, was summarized recently by Tseng (1984).

Of the red seaweeds, Porphyra spp. are the most widely utilized (see Dawes, 1981). These species have been recognized as a delicacy for more than 1000 years. Porphyra (or "nori" in Japan and "zicai" in China) is harvested, dried and processed into thin sheets (Hansen et al., 1981). The processed Porphyra is then used in a variety of manners in cooking. Its major uses are as flavouring in soups and as wrappers for sushi. Many species of seaweeds other than Porphyra are consumed directly as vegetables, in soups, or in jellies and puddings. More than 30 types of red algae were consumed by early Hawaiian cultures (Hansen et al., 1981).

In comparison to Oriental cultures, the amount of seaweeds consumed in Western cultures is relatively small. Chondrus and Gigatina are consumed in the largest amounts. In general, the consumption of seaweeds tends to be a localized phenomenon. For example, Porphyra (or "laver") is eaten in the British Isles (Hansen et al., 1981). Similarly, along some coastal areas from Scotland to Alaska, Palmaria palmata (or "dulse") is consumed as a snack in taverns or as a vegetable with meals, used in cooking breads and puddings, or chewed like "chewing-tobacco".

Whereas the historical basis for the use of macroalgae as food can be traced back for centuries, industrial uses of chemicals extracted from them is a more recent development. It is apparent, however, that the role played by biochemicals extracted from these plants is far more pervasive in modern societies than is the direct utilization of the plants themselves.

Estimates of the world market for macroalgae vary. However, in general terms, the wholesale value of chemicals extracted from macroalgal sources was approximately $500 million in 1983 (Moss and Doty, 1987). This, combined with a estimated value of over $1.2 billion for seaweeds used as food sources in Japan and China, demonstrates the potential world market size for marine algae (Moss and Doty, 1987). It has been predicted that these markets will continue to expand in the future. An interesting development which may have potential for developing future markets is the use of macroalgae as sources of biomass to be converted to fuels such as methane gas. However, the feasibility of this remains to be established (Ryther, 1984).

The structural polysaccharides (phycocolloids) of marine algae are in the most demand. Phycocolloids from seaweeds are nearly ubiquitous in Western households and in a variety of industries (Waaland, 1981; Abbott and Cheney, 1982). Alginates, carrageenans, and agar all comprise the three general classes of phycocolloids. They are utilized predominantly as gelling agents, stabilizers and emulsifiers. Alginates derived from brown algae (Laminaria, Macrocystis, Ascophyllum) are found in milk products and baked goods as well as toothpaste, and shampoo. They are also used in dyes and paints. Over 60 per cent of the world's supply of alginates is utilized in the paper and textile industry. Carrageenans isolated from red algae (Chondrus crispus, Gigartia) can be found in a variety of processed foods.

Agar, extracted primarily from Gelidium sp., has perhaps the longest history of use as a gelling agent (Marine Algae Text). Several different types of agar with differing chemical purities are now being used. Lesser grades find applications in foods while more purified forms are chiefly used in microbiological culture media. As an indication of the demand for agar, consider its retail price during the 1980s. From 1981 to the present, the retail price for laboratory agar has increased by approximately $70 per pound (from $14 to $84 per pound). During the past year alone, the price has risen by approximately 55 per cent.

Dramatic increases in the price of agar has an impact on research related to biotechnology. Gel electrophoresis, a corner-stone technique in biotechnology, requires the use of a highly purified form of agar, agarose. The price of agarose has increased proportionately to that of agar during the past few years. Indeed, the current retail price of agarose ranges from hundreds of dollars to thousands of dollars per pound, depending on purity and other properties. Such high prices may restrict some research efforts.

The inherent demand for algal products provides a powerful incentive for development of industries based on macroalgal resources. In a simplistic sense, success or failure will depend upon how well appropriate technologies can be applied to cultivating this biological resource in what is essentially a hostile environment. Given this, it is necessary to consider "biotechnological innovation" in a broad context. The two facets most applicable to this case are the engineering of ecologically sound, efficient culture systems and, secondarily, the genetic manipulation of macroalgal stocks to produce plants with physiological and chemical characteristics most beneficial to the nascent industry.

To begin to appreciate what will be required to farm marine macroalgae, it is necessary to understand that these plants are very different from terrestrial plants. Macroalgae do not form seeds; they rely upon dispersal of fragile spores for reproduction (see Dawes, 1981). The life cycles of algae require two or three generations which

alternate between sexual and asexual forms. The diploid, asexual generation (sporophytes) typically produce motile haploid spores. After release, the spores must settle onto a suitable substratum so they can attach and begin growth. They then develop into male or female plants (gametophytes). Fusion of the gametes produced by the gametophytes yields diploid zygotes. The zygotes mature, forming the sporophyte generation. In general terms, the sporophyte generation is macroscopic, whereas the gametophytes may be macroscopic or microscopic and spores and gametes are microscopic.

An understanding of their life history is essential to cultivate macroalgae on an industrial scale. This is exemplified by the success of the Chinese seaweed industry which is based, in large part, on an understanding of their basic biology and ecology (see review by Tseng, 1984). Currently, several varieties are under cultivation, especially in China. However, improvements in technology are required in order to enhance the continued development of the burgeoning industry. Certainly, efforts must be directed at increasing productivity of the seaweed mariculture industry as a means of making it more profitable and less labour-intensive.

Mariculture techniques can be broken down into two general patterns: (1) outplanting and (2) growth in closed systems. Outplanting can be accomplished by either of two approaches. The first takes advantage of the alternating stages of macroalgal life cycles and the second involves vegetative propagation of mature plants.

Historically, the best examples of outplanting are found in the Pacific. Laminaria japonica, a phaeophyte, is grown attached to weighted cords suspended from floating rafts (Tseng, 1981). Zoospores are attached to cords and allowed to develop under ambient conditions. As they grow, the kelp plants are raised or lowered in the water column in order to maintain them under appropriate light intensity for maximum productivity. Scientists determined in the mid 1950s that reproduction was linked to ambient water temperatures (see Dawes, 1981). The natural reproductive cycle starts in the autumn and culminates with spore release in the early winter. However, studies demonstrated that if warm-adapted plants (i.e., "summer sporelings") were exposed to cold temperatures for short periods during the summer, sporulation could be induced artificially. Thus, reproduction and setting could be controlled. The technique not only excluded unwanted sets of weed species from the culture ropes, but the production of the young kelp was increased by 50 per cent because the effective growing season could be lengthened by several months.

Another important commercial species, Porphyra, a red alga, is consumed in many countries and, consequently, has a large market. The Chinese have directed efforts at farming Porphyra for more than 200 years (Hansen et al., 1981; Tseng, 1984). Initial efforts in Porphyra farming were very simple. Rocks in coastal areas were cleaned free of attached seaweeds, barnacles, and other sessile marine organisms in the fall, immediately prior to the natural release of Porphyra spores. Because the surfaces of the rocks were clean, the Porphyra spores had a substratum to attach to and grow. The local people harvested the crop the following year.

Today, Porphyra farming is based on the use of floating rafts (Tseng, 1981). This development was the result of basic studies on the reproductive biology of Porphyra by Chinese and Japanese phycologists during the 1950s. Mariculture of Porphyra begins in the spring when water temperature increases and it induces development of Porphyra carpospores. These spores are isolated from reproductive tissues and suspended in seawater in tanks lined with shells. The carpospores settle on this substrate and the filamentous or conchocelis stage develops over the summer. Autumn cooling induces a second round of spore formation, this time from the conchocelis filaments. The process is easily manipulated so that the released conchospores settle on layered nets which may be suspended in situ. Adult Porphyra develop from these spores.

The best example of exploiting vegetative growth can be found in the Philippines where Eucheuma sp. are cultivated. In this process, fragments from plants are fixed to artificial substrata (typically monolines) and grown suspended just below the mean low tide level. Approximately two months are required before a harvestable quantity of biomass is produced. Maintaining the crop is very labour-intensive. This type of mariculture can be improved by employing new approaches to growing the crop and by developing new strains of Eucheuma that are more amenable to mariculture. The latter can be accomplished either through strain selection by classical genetics or by employing techniques of recombinant DNA technology. In order to maximize the probability of success, efforts should be directed in both directions.

In all three of the examples given above, the culture systems rely upon very simple technologies coupled to an understanding of the ecology and reproductive biology of the species. In addition, by employing the process of outplanting, coastal resources are used directly, thereby eliminating the need for expensive land-based cultivation.

The labour-intensive nature and unpredictability of ocean farming are major obstacles that must be overcome in order to ensure the continued development of this industry. The advent of intensive, enclosed culture techniques helps to alleviate these difficulties. Western mariculturalists have been cultivating the red alga Chondrus crispus for many years (Hansen et al., 1981). Large-scale suspension cultures maintained with flowing seawater and nutrient enrichment are required. By manipulating nitrogen loads it is possible to shift the alga's physiology towards growth and biomass production, or alternatively, to the synthesis of the desired biochemical, carrageenan.

In Taiwan, cultures of Gracilaria are successfully raised for the production of agar. Vegetative cultivation of the plants is done in tidal enclosures, of approximately one hectare. The cultivation of Gracilaria requires fresh seawater and, in most situations, addition of fertilizer. Usually, fertilizer is added in the form of urea or manure. In most situations, fertilizer is required to meet the demand for the limiting nutrient, nitrogen. The crop is then harvested at 10 day intervals over a six-month long peak growing period.

The addition of fertilizers can also be used in outplanting techniques. Typically, additional nitrogen is applied directly to the crops. This practice enhances growth of the mature plants, thereby increasing productivity and yield of the crop.

Natural stocks as well as mariculture crops of Gracilaria and other agar producing seaweeds cannot meet the demand for agar. This has resulted in a variety of commercial initiatives directed towards

the cultivation of Gracilaria sp. in the West (see Waaland, 1981). Certainly, developing countries with appropriate coastal features and climate should take advantage of the opportunity presented by the market for agar and its derivatives.

The harvesting of natural algal stocks is conducted on a world-wide basis. Gelidium sp. (and many other species) are taken in Japan, while in the Northeastern United States and Canada natural populations of Chondrus are collected. Chondrus or "Irish Moss" is typically collected by raking shallow beds from small dories. On the Californian coast of the United States the giant kelp Macrocystis pyrifera grows in forest-like stands rising from the sea floor to form an algal canopy. This canopy vegetation is harvested with specially designed boats equipped with cutting blades (Jackson and North, 1973). Harvesting macroalgae in this manner is not lethal to the plants, thus permitting a sustainable crop.

When natural stocks of algae are harvested, the plants must be considered in the same context as fish or shellfish in a traditional fishery. Therefore, the effects of over-harvesting, water quality, herbivores (e.g., sea urchins) as well as natural climatic and biological cycles must be considered. It is reasonable to assume that harvesting of natural stocks of algae can be supplanted by mariculture-grown crops.

In most of the cases of macroalgal culture described in the literature, advances in the understanding of the physiological ecology of the plants and the technological innovations required to grow them have spawned efforts to improve production through genetic screening and selection. The Chinese began breeding different strains of Laminaria in the 1960s (Neushul, 1981; Tseng, 1981; Fang, 1983). Plants with specific traits were used as sole sources of spores. These were inbred and progeny sporophytes were derived from the gametophytic generation. Strains with variable thallus morphologies and iodine content were selected. A more extensive selection programme for plants combining both iodine content and high production resulted in the generation of two Laminaria strains for commercial cultivation (see review by Mathieson, 1981).

Spore selection has been practised within the Oriental Porphyra industry for many years. As for other species, emphasis has been placed on selecting strains with desirable growth or chemical characteristics. Hansen et al. (1981) note that additional laboratory-based attempts have produced distinct morphological variants which grow much more rapidly and to considerably larger size than parental stocks. Strains selected in these manners have projected yields that are three to five times greater than the wild type.

The most notable example of strain selection in the West can be found in the Canadian Chondrus industry. During the 1970s a strain particularly suited to growth in suspension culture was isolated. The strain designated "T4" has a very rapid growth rate and fragments spontaneously, in effect, "re-seeding" itself (Hansen et al., 1981). Both of these characteristics are important in increasing production of Chondrus.

In the examples described above, the strains of macroalgae that were cultivated were obtained as a result of selecting from wild stocks those varieties that expressed desirable characteristics. These approaches to strain selection are based upon simple screening for desired characteristics and normal manipulation of plants during the mariculture process. Despite the drawback that this may require a considerable investment of time (i.e., several generations through successive growth cycles), it remains a proven and effective means to increase production.

Given the incentive to speed the selection process as well as develop new hybrid strains with exceptional characteristics, research efforts have been directed towards more direct approaches to strain selection. These techniques are based on inducing mutations, either with ionizing radiation of chemical mutagens. For example, ultra-violet and X-ray irradiation have been used to induce mutations. Exposure to chemical mutagens has also been used very effectively (Neushul, 1981).

An alternative approach to developing new strains of seaweeds involves hybridization of gametes from separate populations. Such intra-specific crosses have been very successful with kelps (Sanbonsuga and Neushul, 1980; Bolton et al., 1983). In addition, there have been reports of success in inter-specific crosses yielding true inter-generic hybrids (Lewis et al., 1986). Experiments of this type have been performed on members of the Laminariales (e.g. Macrocystis X Nereocystis). Unfortunately, the hybrid plants were infertile.

Even though progress has been made in macroalgal genetics in recent years, it is reasonable to assume that, with the techniques of modern molecular biology and molecular genetics, substantially more progress will be made relatively quickly. Efforts are under way to elucidate the molecular genetics of marine algae through direct manipulation of specific genes (Cheney et al., 1981; Cheney, 1988; Goff and Coleman, 1986, 1988). As the information base on macroalgal genetics increases, the rate of progress should increase also. This has been true for all aspects of modern molecular biology.

On the basis of historical perspectives, current research initiatives and future potential, the biotechnology of marine algae represents a remarkable opportunity for developing countries. However, in order to take advantage of this opportunity, developing countries should develop strategies that are based on a combination of economic and scientific factors. Whereas the corner-stone of an economic strategy may be an evaluation of the exciting and potential markets for products from marine organisms, production of the product will be based on appropriate scientific principles.

In evaluating the potential of marine biotechnology of marine algae for a country, consideration should be given to many important factors such as natural resources, work force, technology transfer, university-industry relationships, and, among others, government funding of basic and applied research. These factors and others that may be considered as country-specific, will determine the success or failure of an initiative in marine biotechnology.

It is difficult, if not impossible, to attempt to prioritize the relative importance of economic, scientific, regional, or other factors that will influence initiatives in this field. However, when a programme in marine biotechnology is initiated, a country should not depend on harvesting natural stocks of an organism. Serious consideration should

be directed towards crop production in coastal areas or, alternatively, in enclosed systems. The success of this approach will be due, in large part, to an understanding of the biology and ecology of the species being cultivated. Such knowledge is required in order to optimize environmental conditions for growth and reproduction of the species being cultivated. Also, it is essential that appropriate consideration be given to the environmental impact of mariculture initiatives. No initiative that would damage (either short-term or long-term) the environment should be undertaken.

The coastal zones of all countries represent a resource that is under-utilized (Epstein and Norlyn, 1977). Coastal regions can make significant contributions to a nation's economy, especially in developing countries. In order to do so, efforts must be directed to developing mariculture programmes and the supporting industries. Thus, the results of developing coastal resources should extend beyond the primary mariculture industry and into many facets of the private sector.

The economics of some biotechnology initiatives dictate a significant commitment of financial, physical, and intellectual resources. An understanding of the biological principles of a system will be a significant contributing factor to the overall success of any industry that is based on producing large quantities of an organism. Thus, studies are required on the basic biology and ecology of the species in question. Usually, small companies cannot provide funds or personnel to carry out such studies. However, gaps in our knowledge can be overcome by forming co-operative partnerships between government, industry, and academia. Basic studies on the biology and ecology of organisms, especially commercially-important species, should be government supported. Furthermore, a combination of industrial and government support is required for carrying out applied studies. This is true especially in the early stages of the development of an industry. However, appropriate safeguards to intellectual property rights are required to ensure the success of such co-operative ventures and to guarantee continued support for basic research in academic institutions.

Support for basic research can contribute greatly to a well-trained work force that is required to enhance an existing industry and to develop new markets and new industries in the future. This type of support will also ensure that: (1) society gains an appreciation for the ecology of the species being exploited and for the environmental impact of the industry; and (2) basic research leads to technological advancements that will be available for transfer to industry. In this manner, for most situations, marine biotechnology initiatives can, and should, begin as "low-tech" and then develop into "high-tech". Regardless of the degree of sophistication of a marine biotechnology-based industry, the best efforts of traditional techniques, genetic selection, or even molecular manipulations will be of little use if mariculture techniques are inefficient ecologically or socially.

An understanding and appreciation of their genetic diversity can lead to a realization of the benefits of marine organisms. The potential of marine organisms and the process they mediate can be of profound importance to many aspects of society, both in industrialized and in developing countries. The development of modern molecular biology has provided the foundation for understanding the molecular biology and molecular genetics of marine organisms and the processes they mediate. Thus we can best use modern molecular biology to derive benefits from marine organisms if we understand their basic biology and ecology.

Developing countries can speed the development of marine biotechnology-based industries by forming partnerships with industrialized countries. Also, developing countries should consider pooling resources in order to attain goals that could not be reached otherwise. The latter approach can allow countries without significant marine resources to benefit from this rapidly emerging field. Certainly, agreements between nations can be complicated because of different laws pertaining to patents, international technology transfer, intellectual property rights, etc. However, such differences can, and should, be overcome so that all agreements are mutually beneficial.

The application of the techniques of modern molecular biology and molecular genetics to marine algae is a discipline that is in its infancy. A combination of these powerful techniques and an understanding of the basic biology of marine algae can result in significant economic benefits to developing countries. As such, the impact of farming marine algae on a nation's economy can be analogous to that of some crops in terrestrial agriculture. In order to achieve the goal of realizing the potential of the biotechnological applications of marine algae, nations must develop a strategy that accomplishes specific economic objectives while stimulating both basic and applied research without adversely affecting the environment. Such an approach will ensure the success of this field.

REFERENCES

Abbott, I.A., and Cheney, D.P., 1982. In: J. Rosowski and B. Parker (eds.), Selected Papers in Phycology, Vol. II, Phycological Soc. Amer., Lawrence, KS, p. 779.

Abe, H., Uchiyama, M. and Sato, R., 1974. Agr. Biol. Chem. 38:897.

Augier, H. 1978. Bot. Mar. 21:175.

Baross, J.A., and Deming, J.W., 1983. Nature 303:423.

Baslow, M.H., 1977. Marine Pharmacology. R.E. Krieger Publ. Co., Huntington, NY. 327 pp.

Bentley, J.A. 1958. Nature 181:1499.

Bolton, J.J., Germann, I. and Luning, K., 1983. Phycologia 22:133.

Borowitzka, M.A. 1988. In: N.A. Borowitzka and L.J. Borowitzka (eds.), Microalgal Biotechnology. Cambridge Univ. Press, NY, p. 153.

Borowitzka, N.A. and L.J. Borowitzka (eds.), Microalgal Biotechnology. Cambridge Univ. Press, NY.

Burreson, B.J., Scheuer, P.J., Finer, J. and Clardy, J., 1975. J. Am. Chem. Soc. 97:4763.

Cardellina, J.H., II. 1986. Pure Appl. Chem. 58:365.

Cheney, D. 1988. Abstr. 1st Internat. Symp. Marine Molecular Biology. Baltimore, MD., Oct. 1988. Abstr. 31.

Cheney, D., Mathieson, A. and Schubert, D., 1981. Intl. Seaweed Symp., 10:559.

Colwell, R.R., 1983. Science 222:19.

Dawes, C.J., 1981. Marine Botany. John Wiley and Sons, NY.

Deming, J.W., and Baross, J.A., 1986. Appl. Environ. Microbiol. 51:95.

Epstein, E. and Norlyn, J.D., 1977. Science 197:249.

Fang, T.C., 1983. In: C.K. Tseng (ed.) Proceedings of the Joint China-U.S. Phycology Symposium, p. 123. Science Press, Beijing, China.

Faulkner, D.J. and Ghiselin, M.T., 1983. Mar. Ecol. Prog. Ser. 13:295.

Faulkner, D.J., 1984. Nat. Prod. Rep. 1:551.

Faulkner, D.J., 1986. Nat. Prod. Rep. 3:1.

Faulkner D.J., 1987. Nat. Prod. Rep. 4:539.

Fenical, W., 1982. Science 215:923.

Goff, L.J. and Coleman, L.W., 1988. Abstr. 1st Internat. Symp. Marine Molecular Biology. Baltimore, MD., Oct. 1988. Abstr. 30.

Goff, L.J., and Coleman, A.W., 1986. Amer. J. Bot. 73:1109.

Hansen, J.E., Packard, J.E. and Doyle, W.T., 1981. Mariculture of Red Seaweeds. Calif. Sea Grant College Program Publ. No. T-CSGCP-002, 42 pp.

Hartig, P. Grobbelaar, J.U., Coeder, C.J. and Groenweg, J., 1988 Biomass 15:211.

Hashimoto, Y., 1981. Marine Toxins and Other Bioactive Marine Metabolites. Japan Scientific Societies Press, Tokyo.

Jackson, G.A., and North, W.J., 1973. W.M. Keck Laboratory, Cal. Tech. Final Report No. N60530-73-MV176, 135 pp.

Kingman, A.R. and Moore, ..., 1982. Bot. Mar. 25:149.

Lewis, L.J., Neushul, M. and Harger, B.W.W., 1986. Aquaculture 57:203.

Martin, D.F. and Padilla, G.M., 1973. Marine Pharmacognosy: Action of Marine Biotoxins at the Cellular Level. Academic Press, New York.

Mathieson, A., 1981. In: C. Sindermann (ed.), Proc. 6th U.S.-Japan Meeting on Aquaculture. U.S. Dept. Commerce Report NMFS Circ. 442.

McIntosh, R., 1984. In: M.Z. Lowenstein (ed.), Energy Applications of Biomass. Elsevier Applied Sci. Publ., NY., p. 169.

Moss, J.R., and Doty, M.S., 1987. Establishing a Seaweed Industry in Hawaii, An Initial Assessment. Aquaculture Development Program, Hawaii State Department of Land and Natural Resources, 73 pp.

National Marine Fisheries Service, 1980. Fishery statistics for the United States, 1979. Current Fishery Statistics No. 8000. Washington, D.C.

Neushul, M., 1981. Proc. Internat. Seaweed Symposium, 10:71

National Oceanic and Atmospheric Administration, 1977. In: J. Glude (ed.), NOAA Aquaculture Plan, Washington, D.C.

Ryther, J.H., 1984. In: M.Z. Lowenstein (ed.), Energy Applications of Biomass. Elsevier Applied Sci. Publ., NY., p. 177.

Sanbonsuga, Y. and Neushul, M., 1980. In: E. Gantt (ed.), Handbook of Phycological Methods, Vol. 3. Developmental and Cytological Methods, p. 69. Cambridge Univ. Press.

Scheuer, P.J., 1973. Chemistry of Marine Natural Products. Academic Press, New York.

Stickney, R.R., 1988. World Aquaculture 19:54.

Tapie, P. and Bernard, A., 1988. Biotechnol. Bioeng. 32:873.

Tachibana, K., Sakaitanai, M. and Nakanishi, K., 1984. Science 226:703.

Tachibana, K., Sakaitanai, M. and Nakanishi, K., 1985. Tetrahedron 41:1027.

Targett, N.M., 1979. Bot. Mar. 22:543.

Tseng, C.K., 1981. Int. Seaweed Symp., 10:123.

Tseng, C.K., 1984. Proc. 11th Int. Seaweed Symp., Hydrobiologia 116:7.

Waaland, J.R., 1981. In: C. Lobban and M. Wynne (eds.), The Biology of Seaweeds, Botanical Monographs, Vol. 17. Univ. of Calif. Press, Berkeley, CA., p. 726.

For new subscribers only

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

UNIDO MAILING LIST QUESTIONNAIRE

(Code 503)

The UNIDO Newsletter is sent free of charge to an approved list of readers

To be considered for inclusion on the UNIDO Newsletter mailing list, please complete questionnaire and return it to

UNIDO MAILING LIST, INDUSTRIAL INFORMATION SECTION,

P.O. BOX 300, A-1400 VIENNA, AUSTRIA

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

PLEASE DO NOT WRITE IN THESE SPACES

S/A DISP. CODE COUNTRY

CITY

T TYPE OF ORGANIZATION Identify below the type of organization to which you belong, checking the box(es) as appropriate (e.g., for a research centre at a university, boxes 20 and 23 would be applicable).

01	UN, specialized agency or other UN body	12	Trade centre or association	23	Research centre/laboratory
02	Other intergovernmental organization	13	Professional association/learned society	24	Library/documentation centre
03	International non-governmental organization	14	Bank or financial institution	25	Information centre
04	UNIDO National Committee	15	Industrial enterprise	26	Publisher
05	Embassy or Mission to UNIDO	16	Public utility	27	Bookseller
06	Government body for development aid	17	Trading concern	28	News agency/press
07	Ministry for industry	18	Engineering organization	29	Radio and television
08	Other governmental department	19	Consultant		
09	Non-governmental aid agency	20	University		
10	Chamber of industry or commerce	21	Vocational or technical institute/school		
11	Manufacturers' association	22	Industrial training or productivity centre		

F FIELD OF INTEREST Check the appropriate box(es) which reflect your *main* field(s) of interest

MANUFACTURING INDUSTRIES – PLANTS, PROCESSES AND PRODUCTS		017	Electrical machinery	030	Industrial legislation
		018	Transport equipment	031	Industrial property
		019	Precision instruments	032	Transfer of technology (licensing)
001	Food processing	020	Agricultural machinery	033	Industrial research and development
002	Beverages			034	Standardization
003	Tobacco	NON-MANUFACTURING INDUSTRIES AND PROJECTS		035	Industrial organization and administration
004	Textile and garment			036	Industrial co-operatives
005	Leather	021	Mining and quarrying	037	Industrial information and documentation
006	Wood processing	022	Utilities (including power plants)	038	Industrial promotion
007	Pulp and paper	023	Public services (transport, communications, tourism)	039	Industrial training
008	Petrochemical and plastics	024	Construction (civil engineering) projects	040	Industrial management
009	Industrial chemicals and fertilizers			041	Industrial consulting services
010	Pharmaceuticals and other chemical products	SUPPORTING INDUSTRIAL ACTIVITIES		042	Development of small-scale industries
011	Rubber			043	Industrial estates
012	Non-metallic mineral products and building materials	025	Industrial planning and programming	044	Appropriate technology
013	Iron and steel	026	Industrial policies		
014	Non-ferrous metal	027	Industrial financing and investment promotion		
015	Fabricated metal products	028	Promotion of export-oriented industries		
016	Machinery	029	Industrial development surveys		

LANGUAGE Indicate below in which language you wish to receive the NEWSLETTER

ENGLISH [ ] FRENCH [ ] SPANISH [ ] RUSSIAN [ ]

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

Price List for Advertisements in the Publication

Genetic Engineering and Biotechnology Monitor

General Provisions

1. UNIDO activities in the field of advertising are non-profit-making and are carried out to cover the cost of preparing, publishing and mailing its publications, which are sent to readers all over the world *free of charge*.
2. Requests for placing advertisements in the UNIDO *Genetic Engineering and Biotechnology Monitor* should be made in writing. They should be accompanied by a layout, illustrations and a text containing all necessary information.
3. Advertisements are printed in black and white and in English only.
4. UNIDO reserves the right to reject advertisements without giving reasons, to suggest amendments or to hold advertisements if space is not available.
5. UNIDO cannot guarantee to print advertisements on specific pages of the *Monitor*. Page proofs will not be provided to advertisers.
6. Payment of invoices is due immediately after receipt and should be made within 30 days in United States dollars or Austrian schillings to the UNIDO bank account (see below) or to the Treasurer, UNIDO, Vienna International Centre, P.O. Box 300, A-1400 Vienna, Austria (telegrams: UNIDO Vienna Austria; telex: 135612). Upon payment, please advise the Head, Development and Transfer of Technology Division, at the same address.

Bank accounts

For dollar payments:

"UNIDO dollar account" No. 29-05115
Creditanstalt Bankverein
Schottengasse 6, A-1010 Vienna, Austria

"UNIDO general account" No. 949-2-416434
The Chase Manhattan Bank
International Agencies Banking
380 Madison Avenue, New York, New York 10017
United States of America

For schilling payments:

"UNIDO schilling account" No 29-05107
Creditanstalt Bankverein
Schottengasse 6, A-1010 Vienna, Austria

Prices

Size	*Prices in Austrian schillings (AS) (or equivalent in US$)*
Full page (255 mm × 178 mm)	AS 5,000
½ page (125 mm × 178 mm or 255 mm × 86 mm)	AS 3,700
¼ (178 mm × 60 mm or 125 mm × 86 mm)	AS 2,500

The price for the publication of announcements of up to five lines under the rubric "Resources available" is AS 1,000. The text is subject to editing.