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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

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Genetic Engineering and Biotechnology Monitor

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Dear Reader,

The first quarter of 1986 has been quite busy as far as the preparation for the establishment of the International Centre for Genetic Engineering and Biotechnology (ICGEB) are concerned. The Preparatory Committee of the ICGEB has established a speedy procedure for the selection process of the Director and the Heads of the two components which will be completed before the end of June, before the next meeting of the Committee. A number of advertisements appeared in the major scientific journals for applications to the post of the Director and the response has been very gratifying, confirming the enthusiasm of the international scientific community for the ICGEB. In the next issue of the Monitor we shall hopefully be able to inform you of the names of the first Director of the ICGEB and the two Heads of components at Trieste (Italy) and New Delhi (India).

A specialized workshop on biotechnology and industrial commodities was held at Trieste during March 1986 which was intended to give a sharper focus to the research areas which the Trieste component might address. The workshop was notable for the high quality of the papers presented and the enthusiasm of the many distinguished scientists present. You will find a report on this workshop in this issue.

Progress has also been made regarding the development of safety guidelines relating to biotechnology research and industrial processes. An informal UNIDO/WHO/UNEP working group considered the matter and agreed on a further programme of work. The report prepared by the UNIDO consultant Mr. Karny was well received and a short report of this workshop is also in this issue of the Monitor.

We are grateful for the continued encouragement of our readers and their numerous letters of appreciation. We are continuously trying to improve the Monitor; however we are now in the dilemma of having to face increasing printing costs on the one hand and budgetary constraints on the other. We hope to overcome this situation by limiting the number of copies printed for each issue. We would therefore greatly appreciate it if those readers who are not particularly interested in receiving the Monitor on a regular basis were to drop us a line to this effect. This would also permit us to bring the mailing list up to date.

K. Venkataraman
Special Technical Adviser
Development and Transfer of Technology,
Department for Industrial Promotion,
Consultations and Technology

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

A. POLICY, NEWS AND OTHER EVENTS

UNIDO News

Informal UNIDO/WHO/UNEP Working Group on Biotechnology Safety, Vienna, 27-29 January 1986

While UNIDO for reasons of its mandate has an interest in industrial safety practices, it is also aware of the concerns that the World Health Organization (WHO) has in this area as they relate to health and safety. Particular note has been made of the publication Laboratory Biosafety Manual with its guidelines pertaining to laboratory practices, transfer and shipping of specimens, guide to biosafety equipment, etc., and the report by WHO's Regional Office for Europe "Health Impact of Biotechnology". Interests of the two organizations on this important subject led to the establishment in 1982 of continuous communications between UNIDO and WHO's programme on Safety Measures in Microbiology. During the spring of 1985 it was decided between the two organizations to constitute an informal working group and begin a systematic study on whether a set of biosafety rules and practices could and should be elaborated, the application of which could be recommended to all countries.

In May 1985 UNIDO became acquainted with the interest that the United Nations Environment Programme (UNEP) has in the topics of bio-wastes disposal and the deliberate release of genetically engineered organisms into the environment. In view of the obvious overlap of interest, UNEP was informed of the planned UNIDO/WHO working group and asked if it would be interested to partake in its activities. The response was positive and after consultations between UNIDO and WHO, it was decided among the three organizations to constitute an informal UNIDO/WHO/UNEP working group to consider all facets of biotechnology safety pertaining to research institutions, industry and environment, and decided to hold the first meeting at UNIDO headquarters during 27-29 January 1986. The objectives of the meeting were:

(i) To review existing safety practices as they apply to biotechnology R+D and industry;

(ii) To review existing safety rules and regulations that serve to manage biotechnology R+D institutions and bioscience-based industry;

(iii) To review existing practices that attempt to ensure the safety of releasing genetically engineered organisms into the environment;

(iv) As a result of the foregoing, to consider what elements are required for a set of minimal guidelines useful to the managers of the International Centre for Genetic Engineering and Biotechnology (ICGEB) and to R+D institutions, especially in the developing countries;

(v) Similar to (iv), to consider what elements are required for a set of minimal guidelines useful to developing countries that may wish to regulate bioscience-based industry and industry that utilizes, or will utilize, biotechnology;

(vi) To determine if guidelines should be formulated that seek to assure safe practices when genetically engineered organisms are, or will be, released into the environment;

(vii) To indicate further activities for each member of the working group and to prepare for the working group's next session.

In the early autumn of 1985, UNIDO engaged the services of a consultant to prepare a comprehensive study containing: (1) an overview of existing safety practices and regulations that serve to manage biotechnology R+D and industry; (2) an overview of prevalent practices as to the control over releasing genetically engineered organisms into the environment; and (3) recommendations of activities that the informal working group or the ICGEB could undertake with respect to biotechnology safety. This study, "An International Approach to Biotechnology Safety" was circulated to members of the working group in early January 1986 and was also available at the first meeting. The general organization of the study split genetic engineering into three categories: laboratory research; large-scale operations, which included biowastes; and environmental applications of genetically engineered organisms. For each category the current views of experts on the risks and various regulatory mechanisms for addressing those risks are discussed and common principles in the regulatory mechanisms identified. While individual countries were considering the safety issues raised by genetic engineering, it was considered appropriate for international organizations to address these issues from an international perspective because the technology will have worldwide impacts. Certain advantages from international bodies addressing the safety issues of genetic engineering were noted, the major advantage being the harmonization of regulation. In addition, a costly duplication of effort in risk assessment and guideline development could be avoided. This would be especially valuable for countries with limited resources, which would be better off directing those resources toward local genetic engineering efforts.

The following activities were proposed for the ICGEB or the Informal Working Group:

(1) Act as a forum for information exchange and debate;

(2) Study potential risks and make findings regarding actual hazards or areas where additional research is needed;

(3) Develop risk assessment methodology;

(4) Conduct risk assessment;

(5) Develop safety guidelines for the various categories of applications of genetically engineered organisms;

(6) Assist other countries, especially less developed countries, in adapting the guidelines to their own special needs; and

(7) Train scientists, technicians, workers, and other support staff to handle genetically engineered organisms safely.

During the preparatory work for the ICGEB, the matter of safe laboratory practices, especially as they pertain to research on genetically engineered micro-organisms, became a matter of concern to UNIDO. As several countries offered to host the ICGEB and/or its affiliated centres, it became clear that national rules or guidelines that were aimed at ensuring safe laboratory practices varied from almost no control to control measures akin to the US or UK guidelines. As the time grows ever shorter before research begins at both ICGEB components and at its affiliates, the matter of drawing up and applying adequate and uniform safety rules and practices throughout the ICGEB system takes on an air of urgency. Further, since research at the

ICGEB and its affiliates is to be of an applied nature, and since products and processes will ensue as soon as practicable, there is also a need to consider safety rules and practices as they may be applicable to bioscience-based industry (and to industry which will utilize the advanced biotechnology techniques).

The representative from WHO Headquarters presented his Organization's view on biosafety, particularly as they touch on the manufacture of vaccines and biologicals. He noted that recent advances in molecular biology have prompted the WHO to assess them in reference to public health applications. Primary considerations have been infectious diseases. As a result, new or expanded initiatives have been established within WHO's Division of Communicable Diseases. These include:

(a) WHO Programme for Vaccine Development (see list of documents);

(b) New rapid diagnostic techniques;

(c) Transfer of vaccine production technology to developing countries.

With these initiatives there is the commitment of the Organization to assure the safety of the product, the safety of the biotechnology industry worker, and the safety of the community from possible hazardous discharges from the industry.

WHO is called on by its constitution "... to develop, establish and promote international standards with respect to ... biological ... products". Accordingly, WHO sets international biological standards and provides relevant information to national health authorities so that national standards, calibrated in international units, can be established. Through this process WHO seeks to assure that vaccines and other biological products developed through its programmes, and others, offered through international trade will be safe for use by the general public.

To meet the worker and community safety requirements, WHO's Seventh General Programme of Work calls for the provision of safety guidelines for biotechnology organizations producing vaccines and biological products. Accordingly draft biosafety guidelines are being considered for laboratories and industries engaged in the manufacture or preparation of vaccines and biologicals, where:

1. The process uses organisms or cells that contain foreign DNA inserted by the recombinant DNA technique;

2. The volume of culture, medium or tissue is larger than 10 litres. This definition includes the use of continuous culture where the volume of the culture vessel or of the spent culture is greater than 10 litres; and

3. The work is carried out within contained facilities.

While the proposed guidelines are primarily directed towards fermentation technology, the containment specifications and other practices may be used as a basis to derive similar containment standards for other technologies. The guidelines apply only to minimum practices and physical containment.

Existing national guidelines for large-scale production of vaccines and biological products are serving as the basis of the WHO effort. However, development of the WHO guidelines is currently in abeyance to ascertain if similar guidelines being developed by the OECD or under discussion with UNIDO and UNEP would serve WHO's needs.

The WHO representative from the Regional Office for Europe explained that the Environmental Health Office of WHO, Regional Office for Europe, includes in its work the impacts of air, food, water, housing waste, and occupational environments on health. Its work covers both chemical and physical safety. Biosafety has been given special consideration, especially as it pertains to food, water waste and housing. Due to the great interests of the member States of the Region on safety aspects and possible adverse impact on human health of new developments in biotechnology, a working group on Health Impact of Biotechnology was organized in Dublin, Ireland during 1982. The Regional Office of WHO/EURO is especially concentrating its attention on the possible adverse human health impact of the manipulation of genetic material in the laboratory, the industrial and environmental applications of biotechnology, including those posed by biological waste.

The Environmental Health Service of WHO/EURO has also a strong interest in any research programmes covering health impact assessments of the developments in biotechnology, although it does not include in its programmes any technological development or assessment of biotechnology systems or products. The latter of these is part of the Regional Programme on Appropriate Technology for Health under its activities on biosafety, which has in the past also been working with some aspects of safety of biotechnology.

The views of UNEP were expressed by the following points:

(a) Although biotechnology with its advanced techniques of genetic engineering could generate considerable rewards for humanity, the transfer of genetically manipulated organisms (micro-organisms, plants, animals, cell lines and hybridomas) from the carefully controlled laboratory bench and factory where they have been produced to the environment for agricultural, industrial or other benefits is gathering scientific, public and political concerns as man, animal, plant and other ecosystem populations will be exposed to uncommonly large numbers of such organisms. In fact, the critical area in terms of safety issues concerns will be the environment.

(b) The fact that no single health incident has been reported since the commencement of recombinant DNA in the last decade could be attributed mainly to the guidelines developed at that time. They led to strict control on the types of experiments to be conducted and specified containment procedures. In fact, as none of the postulated dangers has materialized, guidelines developed by many agencies are now being relaxed.

(c) Relative to safety considerations associated with laboratory-scale and large-scale industrial applications little attention was paid to environmental and agricultural applications of genetically manipulated organisms. There is a need for adequate safety measures, guidelines and regulatory actions for the production, field testing and release of genetically manipulated micro-organisms into the environment. In fact, as such organisms will be engineered mainly to spread and perform their desired function in the environment (uncontained applications) they will interact with the ecosystem and potential risks that may be associated with their release will thus have to be evaluated.

(d) A methodology for assessing any potential risk in releasing genetically manipulated organisms

(including those produced by conventional methods) into the environment (as compared to laboratory and industrial scales) needs to be developed, so that properly designed uniform guidelines consistent with the level of anticipated risk may be developed.

(e) At present the scientific basis for risk assessment involves: (i) hazard identification; (ii) dose-response assessment; (iii) exposure assessment; followed by (iv) risk characterization. Once the risk is characterized alternative regulatory actions may then be evaluated for selection (risk management). In case of environmental applications of genetically manipulated organisms, quantitative risk assessment following the above-mentioned approach will be rather difficult for many reasons, such as:

(i) Lack of sufficient and reliable data;

(ii) Lack of data on long-term effects;

(iii) Relatively small size of researchers and workers engaged in this field making assessment insignificant;

(iv) Risks likely to be associated with the release of a given organism will differ from one case to the other;

(v) Difficulty in predicting the fate and effects of released organisms;

(vi) Secrecy associated with recombinant DNA technology;

(vii) Absence of monitoring procedures.

(f) Ecological analysis of the likely consequences of releasing genetically manipulated organisms into the environment is lacking and is needed on a case-by-case basis.

(g) The first initial step towards the qualitative (rather than quantitative) assessment of potential risks associated with the release of genetically manipulated organisms into the environment would be to conduct a detailed study on the successful and/or unsuccessful introduction of alien organisms into the environment (e.g. bio-insecticides, bio-fertilizers, new plant varieties, etc.), with the aim of developing conjectural prediction methods. The results of such a survey would provide a data base for follow-up activities, particularly with regard to the development of risk assessment methodology and, hence, safety guidelines.

The following recommendations were accepted by the Informal Working Group:

(i) A project will be undertaken to develop minimal guidelines for laboratory and industrial scale facilities. In so doing, various national guidelines and guidelines and/or principles proposed by international organizations will be collected and abstracted, with explanations as to why guidelines differ, in order to prepare a first draft of model guidelines. The draft will be discussed and finalized at a workshop of experts in different disciplines and perspectives on the issue of safety, especially in developing countries. UNIDO will be the lead agency in carrying out this project, with equal input from UNEP and WHO.

(ii) A project will be undertaken to assess whether biowastes from large-scale industrial practices where genetically engineered organisms are used may pose hazards to man or the environment.

(iii) UNEP, in co-operation with UNIDO, will prepare a study on the successful and unsuccessful release of genetically manipulated organisms (micro-organisms, plants, animals, insects, etc. manipulated by conventional or advanced techniques) into the environment (e.g. application of bio-insecticides, bio-fertilizers, etc.).

(iv) UNEP will sponsor a round-table discussion on the subject in association with the International Conference on Microbial Ecology to be held in August 1986 in Yugoslavia.

(v) If circumstances allow, UNEP would undertake, in collaboration with its Law Unit, a survey of environmental protection acts already existing in developing and developed countries and the status of their implementation.

(vi) The Working Group agrees that it would be helpful to assess or determine the awareness of biosafety or laboratory safety, particularly in developing countries. The WHO in the past few years has published the WHO Laboratory Biosafety Manual and conducts several biosafety "Train the Trainer" courses. The WHO therefore will survey the impact of these efforts.

(vii) It was agreed that a review of existing biotechnology legal requirements on a global basis is required. WHO agreed to attempt such a review through information compiled by its Health Legislation Unit. Information regarding national laws, rules or regulations pertaining to biotechnology, including aspects of the technology relating to worker health and safety and environmental protection will be gathered and compiled on a country-by-country basis.

(viii) WHO has established four biosafety collaborating centres at institutions with expertise in biosafety training, research, and consultation. Their services are made available to member States. These centres are located at CDC, Atlanta, USA; National Institute of Health (NIH), Bethesda, USA; Laboratory Center for Disease Control (LCDC), Ottawa, Canada; and Fairfield Hospital, Melbourne, Australia. The LCDC and NIH have specific expertise in industrial applications of biotechnology. Other institutions with expertise are the National Institute of Virology, Pune, India; NIH, Tokyo, Japan; and the National Bacteriology Laboratory, Stockholm, Sweden. It is suggested that it would be possible to "twin" these institutions with designated affiliated centres of the ICGEB for development of expertise in biotechnology safety programmes for developing countries. A project to do so will be designed.

All the foregoing recommendations are to be implemented by the time of the second meeting of the Informal Working Group, in November 1986.

ICGEB Workshop on Biotechnology and Industrial Commodities

The ICGEB Workshop on Biotechnology and Industrial Commodities was held at Trieste from 3-7 March 1986 at the International Centre for Theoretical Physics. Its objectives were:

(a) To make recommendations for the Trieste components of the ICGEB that will serve to provide a sharper definition to the research needs in specified areas of industrial biotechnology, particularly those germane to the needs of developing countries; and

(b) To identify experts who could recommend candidates for the ICGEB staff positions in the five areas or who could even be candidates themselves.

In reviewing the state-of-the-art of biotechnology and its implications for industry the

workshop was organized into the following five scientific sessions:

(1) Enzymes, including protein engineering;

(2) Pharmaceuticals;

(3) Vaccines, hormones and other synthetic polypeptides;

(4) Bioprocessing; and

(5) Polysaccharides and hydrocarbon microbiology.

Research at the Centre can be conducted in what is described below as three major areas of biotechnology:

(1) Biocatalysis - the fundamental study of enzyme structure and function using advanced techniques of genetic and protein engineering. By understanding these relationships, new and modified enzymatic activities can be analysed and explored in terms of production of useful products and development of unique processes.

(2) Biomaterials - studies the utilization of raw materials, the production of specific low molecular weight metabolites as well as biopolymers of industrial and medical importance. Such materials might include proteins, polysaccharides with unique properties, new drugs, vaccines, hormones, antitumour agents, antimetabolites and antibiotics, herbicides and pesticides, commodity and specialty chemicals, etc.

(3) Bioprocessing - includes research and development related to upstream processing of raw materials, monitoring and analysing information on conversion rates, yields, and productivity, and downstream processing of products by a variety of techniques available for purification and concentration of biologically active molecules. This research will facilitate the practical application of discoveries emerging from areas (1) and (2) above.

Members of the staff may work in one or more of these areas while addressing specific problems in health care, agriculture, energy or commodities.

There is a very large number of specific projects that can have a positive impact in the developing world. Therefore, projects will have to be carefully and realistically selected because of the limited resources that the Centre has at present. Projects will have to be tailored to country and regional needs. Relative effects on manpower training should be taken into account when projects are chosen.

The following is a list of possible projects demonstrating the type of research activities that relate to the application areas. These projects are envisioned for the Trieste component of the ICGEB. Most possess a multidisciplinary character, involving several of both the research and application areas. They are not listed in order of priority. Perhaps only one or two such projects could be undertaken as the Centre becomes operational.

(a) *Vaccine development:* Target diseases could include parasites (malaria, trypanosomiasis, amoebiasis, schistosomiasis, leishmaniasis, filariasis, etc.), viruses (measles, yellow fever, Lassa fever, rotaviruses and other enteric viruses), fungi (candidiasis) and bacteria (tuberculosis, cholera, leprosy, typhoid fever). Research could pertain to the isolation and culture of pathogens, cloning and identification of antigens, purification and testing of potential vaccine preparations under laboratory conditions; biochemical and immunological studies; antigen preparation (e.g. with live carriers such as vaccinia virus); the induction of humoral and cellular immunity; and the development of adjuvants.

(b) Screening for new pharmacological activities: Efforts should be made to apply modern biochemical and genetic techniques to devise simple, sensitive and selective screens for isolation of drugs against parasites, bacteria and fungi of medical importance in developing countries. Examples include screens for agents affecting ornithine decarboxylase, 7,8-dihydropteroate synthase, nucleic acid metabolism, microtubule formation and nerve function. Other screens would include inhibition of binding of infectious-agent-derived molecules to cell receptors. Such assays could be carried out at the ICGEB and/or at affiliated institutes in order to screen locally available microbial broths and plant extracts.

(c) Diagnostics: Development of immunodiagnostics and DNA/RNA diagnostics for infectious, genetic and neoplastic diseases with high incidence in developing countries. Work should include production and screening of monoclonal antibodies, antigen characterization, development of suitable DNA or RNA probes and optimization of assay conditions.

(d) Biochemistry for rational design of drugs against pathogens: Projects may be set up to discover or investigate already discovered key metabolic pathways or functions of disease-causing organisms. Examples of recent discoveries which might be a starting point for further research in this area are:

Malaria:

- The thymidylate kinase-dihydrofolate reductase double-enzyme,
- Glutathione reductase,
- Synthesis of purine nucleotides.

Trypanosomiasis:

- Attachment of variable surface glycoproteins to the membrane,
- Ornithine decarboxylase,
- Recognition of site of attachment (fibronectin) in the host.

(e) Novel pesticides: Research could be aimed at the development of biologically-produced compounds (e.g. insecticides, herbicides) and appropriate delivery systems for their use. For example, agents can be developed for use against insects associated with human and animal disease and for controlling pests limiting crop production, such as weeds, insects, fungi and viruses.

(f) Bioconversion of biomass: Research could be undertaken to improve the utilization of biomass (plant materials, agro-residues) through optimization of existing processes and the exploration of new approaches, such as the development of thermophilic and recombinant organisms, the use of non-aqueous media and of extreme pH conditions in order to produce commodity and specialty chemicals, feeds, etc.

(g) Food fermentation technology: Research could be undertaken to design and develop, in collaboration with outside organizations,

small-scale, low-maintenance fermentors with suitable instrumentation for use in rural areas of developing countries with the aim of processing fermented beverages and foodstuffs. Special efforts may be made to improve traditional products of food fermentation by the use of advanced biotechnologies in order to improve nutritional values and reduce toxic by-products.

(h) Fermentations using chemically simple feedstocks: Research could be undertaken to develop processes using local resources as feedstocks for the production of endogenous and cloned enzymes, amino acids or other metabolites, starting with pure substrates such as methanol, ethanol, and glycerol in chemically-defined media. Suitable organisms include streptomycetes, nocardiae, Candida yeasts and methylotrophic bacteria.

(i) Enzyme improvement and utilization: Industrial biocatalysis is of great future importance to the third world. It provides the means for adding value to the specific natural resources available locally, thereby providing numerous products for both domestic consumption and export. A project may be initiated which is aimed at isolating novel enzymes, or at improving existing ones by protein engineering; these enzymes should be selected from those useful in food production, health care, specialty chemicals or for the utilization of locally available simple foodstocks for energy purposes.

(j) Single cell proteins (SCP): SCP for human and animal feed could be developed using abundantly available local resources such as natural gas, appropriate cellulosic substances and agricultural wastes as substrates. New strains could be searched for or high producing strains selected. Research could also be initiated to increase yields and/or improve the nutritional quality of SCP organisms by improving fermentation techniques, designing efficient biocatalysts, improving downstream processing techniques and genetically engineered SCP organisms to improve metabolic characteristics, etc.

(k) Biological polymers: There is a growing need in developing countries either to replace or supplement conventional, mainly petroleum-based materials (polymers, detergents, construction materials, plastics, etc.), with renewable biological ones. Research efforts should be conducted to chemically modify natural polymers (starch, proteins, cellulose) in order to achieve the desired physical properties to obtain new materials and to extensively study their structure/function relationships.

(l) Enhanced oil recovery: Research could be directed at the development of a microbial polysaccharide that would have pseudoplasticity, salt-tolerance, viscosity and pH stability similar to xanthan gum, yet have a much greater thermal stability. The unique properties such compounds impart to their aqueous dispersions at low concentrations, such as their ability to form gels and films with special permeabilities, would make this type of hydrocolloid very useful as a water mobility control agent in secondary and tertiary recovery operations. This in turn would lead to an enhanced production of petroleum. Oil-well acidising operations would also benefit from the availability of an acid-stable pseudoplastic biopolymer.

(m) Novel microbial polysaccharides: In view of the yet untapped diversity of microbial life forms, it is clear that many unusual and potentially useful microbial polysaccharides remain to be discovered and developed. A research programme could be undertaken to isolate strains capable of utilizing local resources as feedstocks to produce non-toxic microbial bio-surfactants for use in drugs and cosmetic formulations as well as in clean-up operations of oil pollution. Polymeric bio-emulsifiers can also be used to stabilize heavy oil-in-water emulsions for oil transportation and for generating new fuels. Many such products are formed constitutively in fermentations. Production of microbial biopolymers by straightforward fermentation technology is applicable to developing countries where inexpensive carbohydrate substrates are available.

(n) Soil conditioners: Research could be aimed at the development of technology for on-farm production of polysaccharide-producing blue-green algae (cyanobacteria) or green/red algae to provide soil conditioners and water-retention aids for use in arid and semi-arid regions. Similar technology is proving successful in parts of the western USA. Nitrogen-fixing cyanobacteria would be the preferred agents, but green/red algae could also be used since both are autotrophic, photosynthetic organisms.

(o) Bio-adhesion: Adhesion of micro-organisms to surfaces by means of secreted polysaccharides is a basic mechanism of biofouling, microbial pathogenesis, and most microbially promoted spoilage. Research on the polysaccharides involved may lead to solutions to these problems as well as to the development of useful new polysaccharides and proteins.

In order to establish and maintain a research facility of the highest scientific standards, certain basic capabilities are required to support all aspects of the scientific programmes to be undertaken at the ICGEB. Depending on the choice of projects, these could include the following:

Molecular biology: Studies with nucleic acids (genetic engineering, sequencing, synthesis), host-vector systems, cloning and expression in prokaryotes and eukaryotes.

Chemistry: Protein purification, enzymology, protein sequence determination, peptide synthesis, physical chemistry of biological molecules and natural product isolation, structure and synthesis.

Biochemical engineering: Bioreactor design, fermentation, product recovery and purification.

Microbiology: Studies of micro-organisms, genetics, physiology, the development of novel screening methods, and culture maintenance.

Cell biology: Eukaryotic cell culture, immunology, including antibody production and culture maintenance.

Informatics: Computing and programming as applied to the analysis of structure and function of biological molecules, computerized control of instrumentation, data base access and communication facilities.

The foregoing list of skills and capabilities should not be taken as a proposal for departmental organization, which should be the prerogative of the Director.

It is recommended that the Trieste component of the ICGEB include computer facilities consisting of a central mainframe computer plus workstations in each laboratory consisting of PCs or slave terminals interfaced with the mainframe. Such facilities are considered essential to handle the expected volume of scientific computations, word processing, access

to data banks and administrative data processing. It is further recommended that the ICGEB establish a computer network linking affiliated centres and other appropriate institutions in order to facilitate communications. It is also advisable that the Trieste component be allowed to utilize the excellent computational facilities of the nearby ICTP and a direct linkage should be considered.

The recommended fermentation capacity to support the research and training programmes of the ICGEB should initially consist of five 20 litre fermenters with suitable instrumentation in addition to a number of smaller units (2-10 litre capacity). This configuration will provide the fermentation capacity needed for research and development of new processes and for training in fermentation technology. In addition, the Trieste laboratories of the ICGEB should consider installing a 250 litre fermentation facility, including downstream processing equipment.

It is recommended that during the early years of operation, the Centre should not establish technologically complex and expensive operations, such as a large-scale pilot plant (e.g. 1,000-5,000 litres), X-ray crystallography, or computer graphics. However, it is urged that collaboration with other institutions be initiated in order to provide access to such facilities.

It is understood that the ICGEB Trieste component will include a full complement of general support services and facilities, such as a machine shop, an electronics laboratory, a glassblowing facility, a comprehensive scientific and technical library, and animal facilities.

It should be noted that outstanding scientific facilities and manpower are located in the Trieste area that could contribute to the scientific activities of the ICGEB. For example, there is the University of Trieste, the International Centre for Theoretical Physics (ICTP) and the International School of Advanced Studies.

The ICGEB should maintain contact with the committee charged with the construction of synchrotron facilities in the Trieste area to ensure that the ICGEB can utilize the bright X-ray source for protein crystallography when it becomes available in three to five years.

Training should be an integral part of the research functions of the Centre. The ICGEB staff should include individuals with outstanding competence and motivation to provide training in modern biotechnology and biochemical engineering.

Except in special circumstances, trainees will be expected to have a PhD or equivalent degree before coming to the ICGEB. Trainees should be encouraged to spend periods of up to two years at the Centre to work on all aspects of the projects. Trainees should bring their needs and priorities to the Centre and should be encouraged to maintain a relationship with the ICGEB on return to their home country.

In addition, the Centre should provide short, intensive training through workshops and short courses in specific areas. It is noted that an association with various international organisations may facilitate the planning and funding of such courses.

The training programme should have multiple components, as indicated in the work programme. These include:

(1) Seminars by distinguished scientists visiting the Centre;

(2) Workshops or short courses (duration - several days to four weeks) to teach specific techniques or subject areas of biotechnology. These courses would be given by the permanent or visiting staff;

(3) Research fellowships of one to two years to enable visiting fellows to work on major research projects;

(4) An annual international symposium on biotechnology.

Training opportunities should be provided as described above in the areas of:

- Molecular biology
- Chemistry
- Microbiology
- Cell biology
- Biochemical engineering
- Informatics

It was felt desirable to offer seminars or short courses concerning the commercial and economic context in which biotechnology will affect the developing countries.

A list of documents presented at this workshop may be found in the section marked "Bio-informatics" in this Monitor.

UN and other organizations' news

Second session of the Committee of Experts on Biotechnology Inventions and Industrial Property, Geneva, 3-7 February 1986

This session was convened by the Director General of the World Intellectual Property Organization, WIPO, as part of the 1986/87 programme of the International (Paris) Union for the Protection of Industrial Property.

Discussions were based on a report prepared by the International Bureau of WIPO, entitled "Industrial Property Protection of Biotechnological Inventions". The Committee of Experts considered the report in detail, starting with Parts III and IV, which contain a description of the existing situation. Subsequently, Part II, which deals with possibilities for improvement of the existing situation, was considered. The Committee suggested to the International Bureau of WIPO that it continue its study of the question of industrial property protection of biotechnological inventions, taking into account the views expressed during the session, in preparation for the next session of the Committee of Experts to be held in 1987.

In preparation for the next session, the International Bureau would carry out a study of the existing situation with respect to the legal protection of biotechnological inventions in each field of biotechnology where different forms of protection may be available (process, product and use protection in the field of plants, animals and micro-organisms, and in other areas of biotechnology). This study should include, for the various areas mentioned above, an analysis of the existing possibilities of protection, or lack of protection, by patents and/or by plant or animal variety rights, a comparative analysis of protection of plant varieties under the UPOV Convention, and any patent protection which existed or which could be established for that area. This would include an analysis of questions such as exhaustion of patent rights and dependence of an invention on another invention. The study of the International Bureau would, naturally, take into account any further developments in the field of industrial property protection of biotechnological inventions of which

it is informed before the next session of the Committee of Experts (new legislation or jurisprudence, or new administrative practices).

With respect to the system of deposit of micro-organisms under the Budapest Treaty, the Committee of Experts suggested to the International Bureau that the questions raised in the WIPO report, and the comments made by the Committee of Experts, should be submitted to the Assembly of the Budapest Union which could meet in an extraordinary session during the first half of 1987. The Assembly of the Budapest Union could, in particular, consider how far it would be feasible and desirable to establish clear principles as to what could be deposited as micro-organism. Once the Assembly had reached a conclusion on that question, it would have to be examined whether such a conclusion required an amendment in the Regulations under the Budapest Treaty or whether an agreed statement of the Assembly would be sufficient in order to ensure the desired clarification.

Regulatory issues

OECD initiates new biotechnology guidelines

Last December, after several years of debate, the ad hoc Working Group on Biotechnology of the Organization for Economic Co-operation and Development (OECD, Paris) drafted international guidelines for use of the technology in industry, agriculture and the environment. The Working Group's suggestions are presently being evaluated by the Committee for Scientific and Technology Policy, the approving body that oversees OECD policies. If they are adopted by the OECD, the guidelines will be the first international agreement on the regulation of biotechnology since the Asilomar conference a decade ago. At that meeting, 60 high-level government representatives agreed on the strict research controls that are still observed in most recombinant-DNA laboratories around the world.

Last October the OECD released a report detailing its position on intellectual property rights, specifically relating to biotechnology patent laws in OECD's member nations.

The OECD guidelines proposed in December focus on the use of recombinant-DNA techniques in large-scale industrial, agricultural and environmental applications. They specify the kinds of altered microbes and plants that might pose hazards to human health, either in the workplace or outside, and to the environment. Also covered are specific methods for dealing with such organisms, including physical containment facilities for those presenting high levels of risk.

The proposed guidelines attempt to reconcile European and Japanese wishes for strict controls on industrial applications of biotechnology, together with the US industry's desire for comparatively more relaxed ones.

The final version of the document adopts the US Food and Drug Administration's (FDA) guidelines for a more relaxed risk-assessment framework. However, the safety guidelines also contain the suggestions of the Dutch delegation on methods of containing micro-organisms. At the same time, it takes into account US objections to having rigid levels by not going to the extent of specifying the exact containment levels that should be followed.
(Extracted from Chemical Engineering, 17 February 1986)

Europe considers field test regulations

Regulatory authorities in the United Kingdom and Federal Republic of Germany are considering the possible problems associated with biotechnology field tests. The European Economic Commission is also planning to bring forward proposals to regulate the field testing of gene-spliced organisms later this year. The first release of gene-spliced organisms into the UK environment is now being planned by researchers at the Institute of Virology at Oxford. The Oxford team proposes to spray a pine forest with a modified pine beauty virus which attacks caterpillars.

Meanwhile, the FRG Federal Ministry for Research and Technology has withdrawn its subsidies for the Heidelberg-based venture capital firm, Gen-bio-tec as the company allegedly failed to inform the Government of its experiments to manipulate bacteria to produce anticoagulants.

Under the 1978 federal safety guidelines for biotechnology, firms must report all gene tests to the central commission for biological safety. Until now, co-operation has been voluntary but the Ministry is seeking tougher proposals and new safety guidelines. (Extracted from European Chemical News, 17 March 1986)

Uniform guidelines, according to EPA Panel

A set of uniform guidelines for protecting the public and the environment against the potential dangers of genetically altered pesticides and other products of the biotechnology industry have been proposed by a panel of leading scientists who are helping US Environmental Protection Agency devise a strategy for regulating the release of genetically altered organisms into the environment.

EPA is one of four Federal regulatory agencies which are building a framework for controlling the products of biotechnology, a fledgling industry that is just starting to move out of the laboratory and into the commercial market.

Without established guidelines, EPA has been forced to review new product proposals on a case-by-case basis. It approved the first deliberate release of a genetically engineered organism last year - bacteria designed to prevent frost damage on strawberry blossoms.

Although EPA said the field test would be safe, environmentalists are challenging the experiment in court, and it has been temporarily shelved. (Extracted from Chemical Marketing Reporter, 10 February 1986)

New setback for gene testing

The first outdoor test of genetically engineered organisms took place secretly and was illegal.

The US Environmental Protection Agency (EPA) suspended a permit it had granted last November to Advanced Genetics Sciences (AGS) to test a bacterial "pesticide" on strawberry plants in a field in California. The EPA says the company actually tested the bacteria on about 45 dormant fruit trees contained in pots on the rooftop of its laboratory in February 1985. It later submitted falsified reports that indicated that the test took place in a greenhouse. The company also failed to report cankers that appeared on some of the trees.

According to AGS, the experiments in question involved injecting 20 ml of a solution with a low concentration of the altered bacteria into the branches of 45 trees of 6 different species. The trees stand on the asphalt-covered roof of AGS's Oakland headquarters. The roof is surrounded by a 3-foot-high wall, but otherwise is exposed to the environment. The trees were inoculated to test for

any pathogenicity from the bacteria. After the test the inoculated branches were removed and sterilized.

The biotechnology company, based in Oakland, California, was the first to receive a permit to test genetically engineered organisms outside the laboratory. During 1985, AGS tested two types of bacteria, Pseudomonas fluorescens and Pseudomonas syringae, on various types of plants in greenhouses. The altered bacteria were tailor-made to ward off the effects of frost on strawberries, and were to become a commercial product called "Frostban".

The decision granting AGS permission to be the first to test genetically altered organisms in the field generated objections from some environmental activists and the local community where the bacteria were to be sprayed, but the EPA stuck with its assessment. AGS was to start work this spring. The EPA's investigators in San Francisco had "assumed" that the firm was testing the altered bacterium inside a greenhouse, but company scientists had never claimed that was the case.

The Government has suspended but not revoked the licence, and fined AGS $20,000, the maximum penalty possible. AGS must now start from scratch again, performing new indoor tests and reporting the results to the EPA. AGS has 20 days to appeal. But it is more likely to repeat the experiment indoors and submit the results by the beginning of May, as requested by the EPA. The delay will mean that the experiment will not take place in the open until at least next winter.

People in Monterey County, California, where the ice-minus strain was to have been tested on a strawberry patch, welcomed the EPA's action. Residents became alarmed when they discovered that the altered bacterium was to have been sprayed within 20 metres of homes. Scientists say the bacterium is quite innocuous because it is the same as a naturally-occurring mutant. A further potential complication is a lawsuit brought by the Foundation for Economic Trends, headed by Jeremy Rifkin, that asks for an injunction blocking the trial. (Extracted from Nature, Vol. 320, 6 March 1986 and New Scientist, 3 April 1986)

Genetic release test

The US company Monsanto has decided to make public a lot more information about a genetically engineered microbe it wants to test outdoors as a pesticide. The company wants to analyse bacteria that have been altered to protect corn plants against black cutworm. Nearly a year ago the firm sought approval from EPA to conduct its experiment and, in the process, submitted data concerning the modified bacteria and the test, claiming the information was proprietary. Monsanto has agreed to make public virtually all the information it has submitted to the agency. Up until now, all the company has said about the experiment is that scientists have isolated a gene from Bacillus thuringiensis that codes for the production of toxin lethal to cutworm. The gene has been spliced into Pseudomonas fluorescens, a microbe commonly found on the roots of corn plants. When cutworm attacks corn roots, it eats the bacteria and dies.

In its application, the company describes the genetic engineering methods it used to alter the soil microbes and the technique it used to ensure that the toxin gene is not transferred to another microbial species. Specifically, the company inactivated the transposase to prevent the movement of the transposon, which carries the toxin gene. The company conducted toxicity assays on several species, including fish, aquatic insects, mosquitoes, laboratory mice, earthworms, and quail, and found no untoward effects. About the only information that was struck from the documents concerns the company's method of coating the P. fluorescens to the corn seed.

Although the company originally asked to perform the experiment at locations in Texas, Illinois, and Missouri, it now has limited its request to test only at its Missouri farm in St. Charles. The company proposes to plant 26,000 corn seeds on a 1-acre plot. (extracted from Science, Vol. 231, 7 March 1986)

General

Gene repository to be established

A collection of cloned human genes, DNA probes, and human chromosome specific libraries will be established by the American Type Culture Collection in Rockville, Md., under a contract from the National Institute of Child Health & Human Development. The collection is intended to serve as the major resource centre for distribution of DNA probes and cloned genes, which ATCC notes are proliferating rapidly. A computerized database of complete background information also will be developed and will be designed for on-line use. (Source: Chemical and Engineering News, 27 January 1986)

Biopolymers research centre established

A Center for Biopolymers at Interfaces has been established at the University of Utah, Salt Lake City. The new organization has received $75,000 from the State of Utah for its first year of operation and so far has signed up five industrial sponsors. Research at the centre will be on industrially relevant problems and will focus on areas such as the biocompatibility of polymers for use in artificial organs, spectroscopic and chromatographic characterization of macromolecules adsorbed on surfaces, effects of immobilization on the kinetics of enzymes, and conformational changes associated with immunoglobulin binding. Grants from the centre will be used to support graduate students, post-doctoral fellows, and visiting scientists, and to purchase instrumentation. Principal researchers will be members of the University of Utah faculty. (Source: Chemical and Engineering News, 10 March 1986)

Mixed results for biotech firms

Profits for biotechnology companies still appear to be elusive. Although Genentech moved further into the black, Biogen continues to post losses.

Genentech has reported a fourth quarter profit of $2.2 million and a net income of $5.5 million for the fiscal year 1985, compared with $2.7 million in the previous year. The company has the advantage that it is now generating product-derived revenues. Revenues rose to $25.9 million in 1985, compared with $18.1 million in 1984.

The award of orphan drug status for Protopin, Genentech's gene-spliced human growth hormone, should strengthen the firm's future in this field. The company has completed gamma interferon cancer trials in the US, Europe and Japan, and additional trials are now under way to evaluate the protein as an antiviral agent.

Meanwhile, Biogen NV's fourth quarter net loss widened to $6.5 million from $2.2 million a year

earlier as revenue fell to $4.2 million from $9.4 million in the previous year. The biotechnology company's net loss for the year also increased to $19.1 million from $13.1 million, with revenues falling to $21.4 million from $31.4 million the previous year.

By the start of 1987, the company hopes to turn round the losses to profit. The first commercial product is likely to be alpha interferon. Licensed to Schering-Plough, the protein has recently received a letter of approvability from the UK authorities. (Source: European Chemical News, 24 February 1986)

B. COUNTRY NEWS

Austria

Toxin against Verroa mite

Austrian scientists at the Joanneum Research Society in Graz have found a fungal toxin to attack the bee-killing Verroa mite. The toxin, extracted from Beauveria bassiana, kills the mite very quickly without producing the undesirable side-effects of conventional pesticides used to control the pest. (Source: European Chemical News, 31 March 1986)

Belgium

New biotechnology company formed

Flanders will soon have a third biotechnology company: Innogenetics, which will join PGS [Plant Genetic Systems] and Biogent. Innogenetics' management will be entrusted to E. Tambuyzer, an adviser at Innovi. Scientific management will be handled by A. Van Heuverswijn, former director of Biogent. The financial backer is the Marien Laboratory in Zwijnaarde. Innogenetics will specialize in medical and veterinary diagnostic kits based on the use of monoclonal antibodies. The new company will not be a licensee but will develop its own products. The first products are expected to be marketed in two years. (Source: Industrie Magazine, October 1985)

Canada

Support for biotechnology urged

In its first annual report the Canadian National Biotechnology Advisory Committee (NBAC) warns the federal Government that it must strengthen intellectual property rights, promote technology transfer and improve tax incentives. The NBAC said that much of Canada's domestic resource-based industry, such as mining and forestry, has been reluctant to apply biotechnology. In particular, the Committee stresses that low industry awareness and insufficient spending on biotechnology R&D, even by drugs and chemicals firms, compounded by gaps in Government policy and co-ordination are not conducive to the development of biotechnology activities. The report suggests a change to the tax system to encourage long-term financial support and allow deductions for technology licensing deals. Furthermore, financial assistance schemes should be extended to keep pace with the increasing number of biotechnology start-up firms requiring federal funds. (Extracted from European Chemical News, 27 January 1986)

China

Joint venture with China

China has a surprisingly small number of dairy cattle, 500,000 compared with perhaps 100 times that number of beef cattle. International Embryos has formed a joint venture with the Chinese Government to exploit embryo transfer techniques. A key objective of the Jinan International Embryos Centre, to be based in the province of Guangzhou, will be to increase the number of dairy cows in Guangzhou from 40,000 to about 500,00 within five years. (Source: Biotechnology Bulletin, Vol. 4, No. 12, January 1986)

Costa Rica

Joint venture to convert banana waste

Faced with finding an alternative to throwing 140,000 tons of sub-standard bananas in the ocean every year, Costa Rica has decided to try fermenting the waste to a high-value animal feed. Late last year, the Institut Français de Recherche Scientifique pour le Développement en Coopération (ORSTOM) in Paris signed an agreement with the Centro de Investigationes de Technologica Alimentaria (CITA) at San José to use the French institute's solid-substrate conversion technology on bananas that are too low in quality to export.

The bananas are dried to 10 per cent water content and then treated with a strain of Aspergillus niger, a non-toxic filamentous fungi with high amylase activity. After three days, this yields flour with some 20 per cent protein content. The French group tried a pilot project in Martinique, but it encountered difficulties as electricity is scarce and expensive on the island and banana production is relatively low compared to Costa Rica. (Source: McGraw-Hill's Biotechnology Newswatch, 3 March 1986)

Denmark

Restrictions on experiments

The Danish parliament recently stopped giving permits for new genetically engineered-plant experiments until it has had an opportunity to debate new rules for such projects. The Environmental Ministry is expected to present a bill on the subject to the legislature by early April 1986.

This new parliamentary slow-down does not affect the status of applications by Novo Industri AS and Nordisk Gentofte to produce insulin from yeast or bacteria, but parliament declared that Denmark needs something more than general environmental regulations for the biotechnology industry. (Source: McGraw-Hill's Biotechnology Newswatch, 17 February 1986)

Danish company to build insulin unit

Novo Industri, the Danish drugs and enzymes outfit, has obtained environmental approval from the committee for technology and environmental matters of the Danish county of Western Zealand for a new fermentation facility in Kalundborg. The new plant will be used for the production of human insulin using gene-spliced baker's yeast cells.

Two new buildings are already under construction and a third existing building will be installed with new equipment for the process. Fears concerning the use of gene-spliced organisms and extensive lobbying from environmental activists had held up the projects's approval and the company was required to reveal details of environmental risk and impact assessments before approval could be granted. The approval now means that Novo can start installing process equipment. Nevertheless, production of the biosynthetic human insulin is unlikely to begin until 1987. (Extracted from European Chemical News, 23-30 December 1985)

European Economic Community

Funds assigned to biotechnology

The European Economic Community is proposing to spend Ecu 10.35 billion ($10 billion) on research and development in a five-year period as of 1987. The plan, if approved, calls on the twelve member states to provide Ecu 9 billion for research projects with a Community dimension and an additional Ecu 1.35 billion for a reserve fund.

Industrial competitiveness will provide the focal point for the new five-year plan, which will overlap and eventually replace the current Ecu 3.75 billion programme. Research in areas such as biotechnology, new materials and new areas such as marine science and technology are to be given priority. Emphasis on improved competitiveness will increase from the current 35 per cent share of funds to more than 60 per cent.

On the other hand, research concerned with energy programmes will fall in priority, only winning 20 per cent support as opposed to the current 47 per cent share. However, this fall in emphasis does not represent a reduction in cash terms. The research plan does not represent a formal proposal, though one is expected by July. Commission officials see the current plan as a skeleton which will be filled out with firmer proposals in the next few months.

Research spending from all sources within the Community will probably exceed Ecu 414 billion in the same five-year period the Commission predicts. Nevertheless, competitivity has declined against both Japan and the US in the past decade. The US is expected to spend a total of $1,000 billion on research and development in the next five years. (Source: European Chemical News, 17 March 1986)

Federal Republic of Germany

Proposed safety guidelines

Growing public pressure has persuaded the German government to take a firmer stand than it had previously intended on the regulation of genetic engineering research. In particular, it has proposed that new regulations should be legally binding on all industrial experiments, rather than remain voluntary as they are at present. A revised version of the current safety guidelines will be introduced within a few weeks. Although more liberal than the current guidelines, their application would no longer be formally restricted to publicly funded research. The current guidelines are closely modelled on those developed by the US National Institutes of Health and have remained essentially unchanged since they were introduced in 1978.

The action has been partially prompted by the news that a small Heidelberg-based firm, Gen-Bio-Tec, had been carrying out experiments on the use of bacteria to produce blood-clotting factor without formally notifying the Federal Ministry of Research and Technology's Committee for Biological Safety. The Gen-Bio-Tec incident was the principal trigger of a sharp attack on the Government's handling of genetic engineering research during a debate in the Bundestag. The Government was accused of promoting the rapid development of a new technology before adequate control procedures had been put in place.

Until recently, public debate on genetic engineering has been relatively muted in the Federal Republic of Germany compared to the United States. The Government has had little difficulty in meeting concerns about safety by adopting guidelines closely modelled on those developed by the National Institutes of Health.

The new guidelines are expected to be modelled closely on those currently under discussion within the Organization for Economic Co-operation and Development, which draw heavily on current practice in the United States. (Extracted from Science, Vol. 232, 4 April 1986)

Industrial association supports biotechnology

Biotechnology in the Federal Republic of Germany is to be given a boost by the chemical industry association (Vereinigte Chemische Industrien) (VCI). The Federal Republic of Germany's chemical industry is pledging a total of DM 15 million ($6.1 million) for the next three years to support biotechnology research. The fund, to be administered by the VCI, will contribute DM 12 million to the German Ministry for Science and Technology - more than half the DM 20 million budget. The association is to make an additional DM 3 million available for projects conducted by small firms working in collaboration with the national biotechnology centre at Braunschweig. (Source: European Chemical News, 27 January 1986)

Governmental programme in applied biology and biotechnology

The Federal Republic of Germany's federal Government has recently published its governmental programme for applied biology and biotechnology as a framework programme for the support of research activities in biology and biotechnology.

The objectives laid down in the programme are: (1) encouragement of scientific and technical peak performances; (2) improvement of innovation conditions; (3) R&D support in sectors of public interest; (4) technology assessment; (5) improvement of conditions for young scientists; and (6) support of international co-operation.

The programme at first defines the opportunities and status of biology and biotechnology. Then governmental measures are applied to the different sectors as shown in figures of budgetary planning for 1986.

In total, the federal Government plans to spend about US$70 million in 1986 for applied biology and biotechnological research. This figure is planned to increase to $110 million by 1989 in accordance with the objectives of the new programme.

Apart from the federal Government, other public sources are financing biotechnology in the Federal Republic of Germany. By the end of 1984, a total of 682 research projects in genetic engineering were being carried out in 61 institutions with grants of about $25 million. (Extracted from European Science News, March 1986)

Finland

Company focuses on plant varieties

The Finnish company Kemira has started testing a species of willow that has been cloned for faster growth and hardiness. Willow is a significant source of biomass energy in Finland and the company hopes its new biotechnology division will have a hardy, fast-growing variety of willow on the market within a few years.

Biotechnology is expected to be a major growth area for the Finnish chemicals group, but the company is not expecting the new sector to yield products until the next decade. Before establishing its own biotechnology arm last year, Kemira had signed research agreements with Calgene, the US-based biotechnology firm, to develop pesticide-resistant crops. The biotechnology division is to concentrate its efforts in three particular fields. In addition to improving plant protection and growth the firm is hoping to develop the horticultural efforts of Kemira's Hortus Oy. Cloning techniques are currently being applied to produce new varieties of ornamental plants such as begonias. (Source: European Chemical News, 31 March 1986)

France

Social security refunds on blood detection kits

The cost of AIDS blood detection kits marketed in France will be refunded by the social security providing it is a test which uses the antigen technology developed by Diagnostic Pasteur, the joint subsidiary of Institut Pasteur and Sanofi. Thus other tests sold on the French market are excluded. Institut Pasteur is in litigation with the US National Institutes of Health over its AIDS diagnostic patent in the US. (Source: European Chemical News, 31 March 1986)

Ireland

Swedish company to build drug unit

Ferments, the Swedish biotechnology group, is to set up a plant in Ireland to produce a new drug for treating arterial thrombosis. The new enzyme preparation, Brinase, was developed by the Swedish Foundation for Applied Research in Medicine (FARM) who has agreed to set up a joint venture with Ferments to produce Brinase in Ireland.

Further research work will also be carried out in Ireland. Negotiations are under way to enter a joint venture with an Irish laboratory for clinical pharmacology, to carry out the laboratory work required for the clinical studies. (Source: European Chemical News, 24 February 1986)

Israel

Centre for Biotechnology, Tel-Aviv University

The Centre for Biotechnology, Tel-Aviv University, Israel, was founded in 1982 by Professor Ephraim Katzir-Katchalski, who is also the director.

Although the centre has been in existence for only four years the scientific staff has made important contributions in biotechnology research in several areas such as the immobilization of cells and enzymes; the use of cytometry and cell sorting for bacterial identifications, tumor immunology, etc.; cellulose degradation; thermophilic methane and ethanol fermentation; and microcarriers for culturing mammalian cells. Prof. Katzir-Katchalski has a patent pending on a reagent for the specific identification of enzymes and isoenzymes in clinical specimens with monoclonal antibodies. A current research and development project supported by the Israel Council for R&D is the influence of monoclonal antibodies on the activity, conformation, and stability of an enzyme. (Extracted from European Science News, 40-3, 1986)

Italy

Italy to co-ordinate and subsidize its biotechnology efforts

Farmitalia-Carlo Erba SpA, the largest Italian pharmaceutical enterprise, will use a bioengineering procedure for the first time involving a procedure to manufacture calcitonin which was developed jointly by Unigene Laboratories, Fairfield, New Jersey and Lark SpA of Milan (Italy).

Up to now, economic production of calcitonin has been hampered by the difficulty of amidizing its precursor product. By genetic engineering techniques Unigene and Lark succeeded in growing bacteria which produced a precursor product so pure that the end product obtained therefrom requires no further purification. This end product can be obtained in one step by enzymatic amidization.

Farmitalia would like to increase the availability of this hormone, whose world market is currently estimated at over US$200 million. The pharmaceutical enterprise sees this as an opportunity to reduce hospital costs caused by geriatric osteoporosis, the most important application area of the drug. In Italy alone these costs amount to 150 billion lira annually.

Since a pure process innovation is involved and the end product is already known, tedious clinical testing will be obviated. Farmitalia therefore expects to be able to offer the product on the market within two years.

In the mean time Unigene is researching the next step in order to obtain a bacterium by genetic engineering, enabling the production of the hormone in one step, that is including the amidization. It may then apply the procedure to other rare human hormones, such as gastrin and oxycotin.

Farmitalia is also collaborating with the American research firm Cytogen Corp. of Princeton, New Jersey, in the area of monoclonal antibodies and their application to diagnostics.

Other industrial enterprises who carry on research and development in this field are Sclavo SpA (protein chemistry, recombinant DNA, hybridoma technology, molecular biology and molecular immunology), the Gruppo Lepetit SpA (genetic engineering and monoclonal antibodies) and Sorin Biomedica SpA (protein chemistry, monoclonal antibodies, and immobilization of enzymes).

Another enterprise is joining the above list, namely the Industrie Farmaceutiche Menarini of Florence. After a phase of one-sided technology transfer from the British Life Science Research, the pharmaceutical enterprise intends to carry on its own bioengineering research. For its bioengineering research, it is expanding its research centre in Pomezia, south of Rome. In 1979 it acquired there the Centro di Ricerca Farmaceutica which was constructed by several small and medium pharmaceutical enterprises as a joint research facility. This was expanded and two years ago, with an investment of 32 billion lira, it was supplemented with a toxicological research centre, which also performs studies for third parties. It currently employs 147 scientists, 38 of these from abroad. The construction of a bioengineering research centre, representing an investment of 28 billion lira is under way.

For this reason, the lion's share of Menarini's research expenditure during 1984-88 is assigned to bioengineering, amounting to 200-250 billion lira. The firm wishes to continue collaborating with Life Science Research as well as with American and Japanese partners.

Menarini is working on the production of B-interferon, tissue plasminogen activator and calcitonin. In its tPA development, Menarini is co-operating with Crea.

Sclavo, the pharmaceutical enterprise of the government-owned EniChem SpA, is not only carrying on bioengineering research in the above-mentioned areas, but is also involved in fermentation, in the production of monoclonal antibodies, in cell cultures, and in gene expression.

The Dow subsidiary Lepetit, just like the Genetic Institute of the National Research Council (CNR) in Pavia, is involved in the production of urokinase which the firm hopes to market in two to three years.

Sorin Biomedica, which belongs to the Fiat conglomerate, specializes in the production of artificial organs, mainly the heart, as well as diagnostic systems. The enterprise, in collaboration with the "Biogen NV", has also developed a diagnostic system for hepatitis B. Together with Farmitalia and Sclavo, Sorin Biomedica participates in the Tecnobiomedica, a company for applied research founded by the Government's special credit institute IMI.

Further enterprises carrying on bioengineering research are: Recordati SpA (monoclonal antibodies), the international Ares-Serono group with its Instituto di Ricerca Cesare Serono (genetic engineering), the Soc. Prodotti Antibiotici SpA, a subsidiary of the American G. D. Searle & Co. (immobilization of enzymes), and the Government's ENI group whose research company, the EniRicerche SpA also does research in protein chemistry and plant-cell cultures. Its predecessor firm, the Assoreni, received the first Italian genetic engineering patent three years ago for protein production by means of soil bacteria. The EniChem Agricoltura SpA, a specialty company for fertilizers and pesticides, wishes to co-operate with the Federconsorzo, an umbrella organization of agricultural societies, to spend 20-25 billion lira over the next three years on bioengineering research concerning plant growth and plant protection products.

As the examples show, the Italian lag does not concern so much the engagement of industry but co-ordination based on specific objectives and the corresponding financial subsidies by the State. The Government has recognized this and several months ago founded the National Board for Bioengineering (Comitato Nazionale di Biotecnologie, CNB) whose objectives are the application of bioengineering methods in the pharmaceutical industry and in agriculture; collaboration both on an international level as well as with the International Centre for Genetic Engineering and Biotechnology at Triest, and the special funding of interdisciplinary projects. EEC countries will be the primary co-operation partners, but one of the first specific results was the conclusion of a contract between the Italian Ministry of Health and the American Food and Drug Administration (FDA). This provides for a regular exchange of information concerning research, production, and the registration of new drugs obtained by bioengineering methods, and concerning bioengineering process technology.

Research is expected to be co-ordinated between industrial enterprises, universities and public and private research institutes such as the National Research Council (CNR), the National Society for Alternative Energies (ENEA), the Milan Cancer Research Institute, the Pharmacological Research Institute, Instituto Negri, and the Grain Research Institute Casaccia.

In the educational area, Verona University is preparing to introduce a course of studies for bioengineering and is striving to erect a scientific park according to the American pattern. A feasibility study is currently being carried out. Priority is to be given to applications in the areas of nutrition, agriculture and pharmaceuticals, especially to immuno-diagnostics and monoclonal antibodies. In the pharmacological area it was hoped to be able to profit from enterprises resident in the region, especially Glaxo on Verona and Fidia in Abano Terme, whose research centres on neurology.

After taking inventory of the FAST, the Association of Technical-Scientific Societies, 86 research groups in Italy were active in the area of genetic engineering in 1983, 22 were occupied with monoclonal antibodies, 11 with protein chemistry, 10 each with plant-cell cultures and enzymes and three with the chemistry of oligonucleotides. (Extracted from Chemische Industrie, October 1985)

Japan

Ministry proposes more support for life sciences programme

Japan's Ministry of International Trade and Industry (MITI) is urging the Government to support a Yen 610 billion ($3.4 billion) life sciences programme.

Details of the proposed project have not yet been established but it will mean further research into human health, photosynthesis and biotechnology. More importantly, MITI hopes that it will gain significant international support.

Half the resources for the scheme are expected to be provided by Japanese firms and the Japanese Government, with the remainder being supplied by other developed countries. Given enough support, Japan contends that the scheme could become as important as Europe's EUREKA programme in terms of international research co-operation.

Opposition to the proppoeal is reported to be intense among top Japanese civil servants, making an early introduction for the scheme unlikely. Project supporters are hoping that the Prime Minister will introduce the idea during the annual summit for industrial democracies in May. (Source: European Chemical News, 31 March 1986)

Firms link on protein engineering R&D

Mitsubishi Chemical Industries (Japan) will jointly develop enzyme-based drugs and bioreactors with Takeda Chemical Industries, Kyowa Hakko, Toray Industries and Toa Nenryo Kogyo (all Japan) in 1986-92. The research will seek to establish relationships between the structure and function of enzymes, hormones and other proteins, allowing development of new proteins. The companies expect the State-backed research and development project to be completed by February 1986. The new protein engineering institute is likely to be capitalized at Yen 30 billion ($15 million), which will be spent on the protein project over an eight-year period. The

five partners are seeking other participants including about 10 computer and instrument manufacturers.

In addition, an approach has been made to the Japan key technology centre, a non-profit organization which is controlled by both the Ministry of Posts and Telecommunications and the Ministry of International Trade and Industry (MITI).

The research would require the use of X-ray analysis, nuclear magnetic resonance, electron microscopy and computer-aided graphics, and will thus require co-operation with foreign and domestic equipment firms. Mitsubishi Chemical Industries is currently seeking other participants in the project, which may include ICI (UK). (Extracted from European Chemical News, 23-30 December 1985)

Company moves to diversify

Mitsubishi Chemical Industries is accelerating its move to diversify into lucrative functional product lines. It has targeted biotechnology, electronics materials and novel industrial materials for specific effort in the next five years.

These products are expected to comprise 33 per cent of total sales at that time compared with the current level of 22 per cent.

Biotechnology and pharmaceuticals will probably account for about two-thirds of the planned increase. Despite this strong emphasis on the life sciences, the company expects it will take some time before the division will make an impact on the firm's profit position. The company has plans to file applications soon for two new drugs, one for treating senile dementia and hepato-protectant, with the Japanese Ministry of Health and Welfare. (Source: European Chemical News, 17 March 1986)

Five firms start TPA trials

Mitsubishi Chemical Industries Ltd., and Kyowa Hakko Kogyo Co. Ltd., both of Tokyo, are beginning clinical trials of recombinant tissue plasminogen activator (TPA), which they obtained in bulk from Genentech, Inc., San Francisco, California. Asahi Chemical Industries Co. Ltd., of Osaka and Kyowa launched human trials of natural TPA from cultured renal cells in late 1984 and entered Phase II studies in December of last year. Toyobo Co. Ltd., Tokyo, announced that it will begin Phase I trials with gene-spliced TPA manufactured by Integrated Genetics, Inc., Framingham, Mass. Toyobo has also scaled up production of recombinant TPA in animal cells to the several-hundred-litre level at its recently completed Shiga Research Laboratories. Daiichi Seiyaku, Tokyo, will market the TPA for Toyobo. (Source: McGraw-Hill's Biotechnology Newswatch, 3 March 1986)

Japan screens donated blood

Japan's Health and Welfare Ministry has hastened to implement a programme to screen a large proportion of the nation's blood donors, and an emergency grant has been awarded to develop new diagnostic tests for AIDS. These developments come close on the heels of approval of the import of an AIDS antibody test kit manufactured by Abbot Laboratories of the United States and confirmation of three more cases of AIDS in Japan, bringing the total to fourteen.

Japan's Red Cross will test the blood of one million donors in Tokyo and Osaka over a period of one year from 17 February, thereby screening more than 10 per cent of the 8 million expected donations. As recently as November, the Health and Welfare Ministry had stated that mandatory screening of blood donors for AIDS was unnecessary and that the estimated cost, Y10,000 million (about £38 million), was prohibitively high, but increased media coverage made it more urgent to allay public concern.

The Red Cross will use an enzyme-linked immunosorbent assay (ELISA) antibody test kit supplied by Dynabbot, the Japanese subsidiary of Abbot Laboratories, for the block screening programme. It was announced last week, however, that an emergency grant of Y40 million has been awarded by Japan's Science and Technology Agency to two research teams at the Health and Welfare Ministry's Health and Medical Affairs Bureau and the National Institute of Health to develop more reliable AIDS tests. (Extracted from Nature, Vol. 319, 20 February 1986)

Biotechnology budget up 15 per cent

For the third year in a row, Japan has increased its overall budget allocations for biotechnology. In each area other than biotechnology, government departments were held to a "negative ceiling". Expenditures for life-science projects in six ministries will exceed Y42 billion ($210 million) for the fiscal year 1986 - up 15 per cent from last year. The biological water-recycling programme at the Ministry of International Trade and Industry (MITI) received the largest increase in funds, with allocations up Y1 billion ($5 million) from last year. The Ministry of Agriculture, Forestry and Fisheries (MAFF) started three new projects: MAFF will research biological controls for environmental improvement in-house (Y95 million), while working with private industry to develop new fertilizers (Y26 million) and analyse genes in agricultural plants and animals (Y43 million).

Selected budget items for fiscal years 1985 and 1986 are compared in Table 1 (see page 37). Expansion of biotechnology into new agencies, and rearrangement of line items, account for differences from the previously published 1985 budget. (Source: McGraw-Hill's Biotechnology Newswatch, 17 February 1986)

Biochip project

The Ministry of International Trade and Industry (MITI) is starting a 10-year "biochip project" through its Exploratory Research for Advanced Technology Programme (ERATO). The 8-10 billion yen project aims to involve industry, academia, and government in researching information processing mechanisms in lower animal nervous systems, examining biochemical reactions in biological organic materials, and establishing production and processing technology for organized molecular complexes and membranes. (Source: Bio/Technology, Vol. 4, February 1986)

New developments

Takeda Chemical Industries (Japan) has developed a combined gamma interferon-interleukin-2 compound by means of genetic engineering of a coliform bacterium's genes. Kyowa Hakko (Japan) and Tokyo University's Ocean Laboratory have jointly developed an rDNA process to mass produce eel growth hormone, which may be used in eel farming if future developments are successful. Japanese Chemical Technological Laboratory has also developed an rDNA process to produce lysozyme, a human enzyme, in yeast. The Japanese use lysozyme as treatment for the common cold. (Source: SCRIP, 15 January 1986)

Sankyo (Tokyo), a leader in pharmaceuticals, has produced a recombinant elastase which may aid in the prevention and cure of arteriosclerosis. The company transfected the DNA of pig-elastase into both Escherichia coli and cultured monkey cells. The elastase thus produced is identical in structure and efficacy to the natural elastase. (Source: Bio/Technology, Vol. 4, February 1986)

Nikken Chemicals, a specialist in ethical medicines, and the Japanese National Food Research Institute of the Ministry of Agriculture, Forestry and Fisheries (MAFF) have developed a new sugar alcohol-producing yeast. Reportedly, this is the first time sugar alcohol has been made by fermentation, versus the traditional chemical reaction. Nikken hopes to export erithritol produced by fermentation next year, while it is researching a more economical bioreactor. (Source: Bio/Technology, Vol. 4, February 1986)

Sweden

Biotechnology research and development in Sweden

In Sweden, R&D in the field of biotechnology is financed by different foundations and by industry itself.

Only a few large companies like Pharmacia and the Swedish Sugar Company are active in basic research. Most basic research work is carried out at universities. The Swedish National Board for Technical Development is funding research projects in areas like molecular biology, fermentation and enzyme research as well as down-stream processing. The annual budget is about $2.9 million. Other funders of basic research more or less related to biotechnology are the Medical Research Council, the Cancer Fund, and the Swedish National Science Research Council.

Applied research in biotechnology is mainly financed by the companies active in this field. The Swedish National Board for Technical Development is funding risk projects with companies at a 50:50 basis totalling about $1.5 million per year.

Thus far, the different funding agencies have operated very independently but now a National Committee for Biotechnology is being established. Members of this committee will be representatives from funding agencies and from industry. Its purpose is to co-ordinate the support of R&D and to work out a national policy. (Source: European Science Notes, March 1986)

Growth hormone produced with DNA technique approved in Sweden

A growth hormone produced by means of genetic engineering by the Swedish State-owned pharmaceutical company KabiVitrum AB has been approved for use as a drug by the Drugs Department of the Swedish Board of Health and Welfare. Called Somatonorm, the new preparation is a 100 per cent pure product, which precludes all risks of transmission of infectious agents, KabiVitrum says.

The approval means that some 200 Swedish children can again receive adequate treatment for their growth hormone deficiency after the suspension last spring of treatment with growth hormone extracted from human pituitary glands. This was due to suspicions that an American preparation transmitted infectious agents.

Somatonorm has undergone clinical trials in several countries on more than 400 patients and has already been approved by the registration authorities in the United Kingdom, Belgium and Switzerland. The American equivalent of Somatonorm has recently been approved in the USA. (Source: The Swedish-International Press Bureau, January 1986)

"Gene Assembler" new tool for study and production of genetic structures

The Swedish pharmaceutical company Pharmacia has introduced a new gene machine, the Pharmacia Gene Assembler, produced by the company's Molecular Biology Division. It is the first such machine to be produced in Europe and, according to the manufacturer, is simpler in design, easier to use and considerably less expensive than competitive models already on the market.

Intended primarily for university and industrial researchers studying and developing genetic structures and functions, the machine can be used to manufacture synthetic genes in a matter of a few hours. It can also be used for the diagnosis of diseases involving genetic defects by producing "gene" probes.

The machine consists of a modular assembly of components, a simple supply system and automatic synthesis monitoring. The actual synthesis takes place in two columns filled with Pharmacia's Mono Beads.

With the aid of the electronic control system in the machine's microprocessor, a chemical process takes place in the columns, enabling the nucleotides to be joined in a pre-programmed sequence to form the genes or pieces of genes desired.

Used together with the company's FPLC purification system, the Gene Assembler can thus both synthesize and purify the material, a feature said to be unmatched by other gene machines. (Source: The Swedish-International Press Bureau, January 1986)

United Kingdom

Plant gene "tool kit"

The British Government's Agricultural and Food Research Council (AFRC) has outlined some advances in agricultural technology to be included in its corporate plan for the next five years. The Council says its scientists "have a greater variety of exceedingly powerful research techniques than they have ever had". Its problem is developing them as the Government's spending on agricultural research declines.

Biotechnology offers many prospects for agricultural research. For example scientists at the universities of Durham and Warwick, working with the John Innes Institute and the Plant Breeding Institute near Cambridge, are working on a "plant gene tool-kit" which will enable breeders to identify and isolate particular genes in plants. Of particular interest are those that control desirable characteristics such as resistance to diseases and growth at low temperatures and in dry soils.

The British programme is looking for vectors that will carry genes into wheat, barley, rape and pea. Another part of the tool kit will be techniques of inserting desired genes into protoplasts (cells with their cell walls removed). Some plants, such as petunias, are relatively easy to grow from protoplasts, but important agricultural plants, especially cereals, are not. Much of the work will involve formulating standard conditions for regenerating crops. (Extracted from New Scientist, 20 March 1986)

Research funding

The UK Department of Trade and Industry has provided a £1 million grant to help launch BIOTRANS, a unique association between the Laboratory of the Government Chemist (LGC) in London and the University of Kent (Canterbury), which will focus on biological transformations. Originally established to provide analytical services for Government departments and public bodies, the LGC now makes its expertise available to industry too.

BIOTRANS will embrace feasibility studies, R&D contracts and joint programmes, and small-scale enzyme preparation. The work will be carried out at both the LGC (which set up a Biotechnology Research Group in 1982) and the Biological Laboratory in Canterbury. Chris Knowles, professor of microbial biochemistry, will head the university team.

For the University of Kent, the launch of BIOTRANS represents the second of two recent developments that have advanced its reputation considerably as one of the most aggressive forces behind British biotechnology. Against stiff competition, the Kent Research and Development Centre also attracted the new Porton International subsidiary, LRB Bioprocessing (LRBB), to its complex now being constructed alongside the university's main science laboratories.

In association with other members of the Porton International group, LRB's services cover the discovery, design, and optimisation of bioprocesses; production capability; and the design and provision of process plants.

Governmental sponsorship of biotechnological innovation in industry is still in the build-up phase. From roughly $14.5 million spent annually by the Department of Trade and Industry in direct support of research and development in and for industry only $3 million per year is allocated to biotechnology. A Biotechnology Unit has been established for the management of this sponsorship at the Laboratory of the Government Chemist, London, UK.

The Biotechnology Unit has identified four key areas of biotechnology of strategic importance and is devoting an increasing proportion of its resources and efforts to them. The four areas are: (1) enzymes, production and use; (2) diagnostics including biosensors; (3) agricultural biotechnology; and (4) process plant and instrumentation.

Basic research in the UK is funded in universities by the University Grants Commission and the Research Councils and in public sector research institutes by government departments and Research Councils. The Research Councils alone had a commitment of basic research in the biosciences of about $3.3 million in 1983-1984.

Only in the Science and Engineering Research Council (SERC) has a dedicated Biotechnology Directorate been formed. This Directorate seeks industrial advice in the award of research grants to universities, advocates joint funding of projects with industry, and aims in consultation between academics and industrialists to direct support into strategically important areas. These areas include: (1) immobilized cells and enzymes; (2) plant genetics and biochemistry; (3) a large-scale growth of mammalian and plant cells; (4) fermentation technology; (5) microbial physiology; (6) new reactor design; (7) new concepts in downstream processing; and (8) sensors and bioelectronics. (Source: Bio/Technology, Vol. 4, March 1986 and European Science News, March 1986)

Approval for first British virus release experiment

In advance of the expected publication at the end of March of the British guidelines for the release of genetically engineered organisms into the environment, approval has been given for the first such release experiments. The experiments, which will involve the release of slightly engineered versions of viruses that are used in the biological control of pests, are said to have been a useful first exercise for the Advisory Committee on Genetic Manipulation (ACGM) that has produced the guidelines and awaits their approval by the Health and Safety Commission.

The guidelines are intended to evolve on a case-by-case basis. It will not be compulsory either to notify ACGM of planned releases or to heed their advice, but the expectation is that nobody will risk bypassing the voluntary procedures. Drawn up by a sub-committee, the guidelines will put the initial onus on the experimenter to show that adequate safety tests have been, or will be, carried out in advance of release and that there are adequate plans to monitor the release and to abort the experiment if it proves necessary.

What may well be the first release experiment in the United Kingdom will combine a very minor piece of genetic engineering with a major project in biological control. The problem is that of the damage brought about by the moth Panolis flammea on the lodgepole pine trees planted in great numbers in the hills of Scotland by the Forestry Commission.

In many areas of Britain the caterpillar stage of the moth is subject to natural control by a baculovirus that infects and kills it. But the virus is not present in the lodgepole pine plantations and so is being introduced: this year several hundred hectares will be sprayed with virus in a full-scale trial of the technique.

The Natural Environmental Research Council's Institute of Virology in Oxford has plans to improve the effectiveness of the virus by engineering its genes. As a first step in the direction of releasing altered viruses, workers at the institute have engineered a very small change into the virus and are now busy testing its stability and biological activity in the laboratory. The change is carefully designed not to affect the proteins produced by the virus and is meant merely to serve as a marker by which the virus can be distinguished from its parent. The first release experiments could take place this summer. Dr. David Bishop, director of the institute, has already gained approval in principle for release of the virus from ACGM and the Ministry of Agriculture, Food and Fisheries as well as support from the Forestry Commission and the Nature Conservation Council.

The prediction is that the slightly altered virus will behave just like its natural parent, but the variation will serve as a marker to help test the prediction. If all goes well, the next stage will be to engineer into the virus some self-destruct mechanism for use in conjunction with any of the major modifications that might be tried in the future - such as the introduction of a gene for a caterpillar-killing toxin. (Extracted from Nature, Vol. 320, 6 March 1986)

United States of America

EPA urged to increase biotechnology research

A scientific advisory panel to the Environmental Protection Agency has recommended that the agency establish a biotechnology research programme "larger and broader" than its current

$5.7 million/year effort. The panel believes that would enable the agency to make more accurate predictions about a genetically engineered organism's survivability, growth, genetic transfer, dispersal, and likely environmental and health effects, and to find ways to contain and possibly destroy harmful organisms. (Source: Chemical Week, 12 February 1986)

Institute of Medicine launches assessment of AIDS programmes

The US National Academy of Sciences and the Institute of Medicine have begun a major assessment of national strategies to combat acquired immune deficiency syndrome (AIDS). The study, which is being funded by a consortium of foundations, has been put on a fast track. A report is due in six months.

A stellar cast has been assembled to conduct the study. It will be carried out by two panels and the effort will be co-ordinated by a steering committee. One panel will examine national research efforts, looking in particular at whether the resources being devoted to AIDS research are adequate and whether sufficient numbers of researchers are being drawn into the field. The panel will also look at possible barriers to participation by private industry in areas such as vaccine development and drug therapy.

The second panel will look at the public health aspects of AIDS, including evidence on the spread of the disease in industrialized and developing countries, the cost and effectiveness of various treatment programmes, and the impact of education and public health efforts.

The steering committee will report directly to the councils of the Academy and the Institute of Medicine, which both approved the effort. The study was initiated in part by recommendations made during a day-long meeting on AIDS sponsored last fall by the Institute. (Source: Science, Vol. 231, 28 March 1986)

FDA approves two AIDS kits

The Food and Drug Administration (FDA) has approved two diagnostic tests for antibodies to the virus that causes acquired immune deficiency syndrome (AIDS) bringing to seven the number of licensed tests on the US market. One of the new tests, based on the AIDS virus discovered at France's Pasteur Institute, is manufactured by Bristol-Myers' subsidiary Genetec Systems (Seattle). The US formally denied charges by the Pasteur Institute alleging a breach of contract for commercializing a virus that had been loaned by Pasteur to National Cancer Institute (NCI) researchers for research purposes only. The virus is included in Pasteur's patent application for a diagnostic test on acquired immune deficiency syndrome (AIDS). In a response to Pasteur's suit, the US contends that the complaint does not actually charge that NCI scientists commercialized the specific virus loaned to them, and that similar viruses or "trade secrets" could not be considered part of the "contract" that NCI researchers signed. (Extracted from Chemical Week, 5 March 1986)

Poultry vaccine joint venture

Immunogenetics, a Vineland, New Jersey-based diagnostics firm, has formed a joint venture with an Indian agricultural company for the production and sale of poultry vaccines in India. Subject to approval from the Indian Government, the deal will make Kegg Farms of New Delhi the sole licensee for the technology in India and various African countries. (Source: European Chemical News, 17 March 1986)

Mérieux, State of New York fund virogenetics to develop poly-vaccines

Since 1982 the State of New York had been looking for seed money to commercialize its genetically engineered vaccine technology and has received an initial $4 million commitment from the Institut Mérieux, Lyon, France. The money will go to revive Virogenetics, Inc., a former "corporate shell" for the New York Department of Health. The new biotechnology firm at Albany will develop the vaccinia-virus, cloned-multiple-antigen technology invented by Enzo Paoletti and colleagues at the Wadsworth Center for Laboratories and Research, also in Albany.

Institut Mérieux will own 51 per cent of the company, and Health Research, Inc. (HRI), the non-profit corporation that administers research funding for the New York State Health Department, will hold the balance. In addition to the renewable, three-year agreement for vaccines, Mérieux will also receive worldwide royalties to other undisclosed products being developed in the Health Department's laboratories. The Institut, the State, through HRI, and the inventors will share the proceeds from the vaccine products. A US patent [on the polyvalent vaccinia-based vaccine] is expected to be issued this year. The vaccinia virus was the basis for the once-ubiquitous smallpox vaccine. Recently Paoletti's group spliced antigens for herpes, hepatitis and influenza into the virus - thus creating a multiple-threat prophylactic in a single vaccine. Such a "one shot" vaccine is ideally suited to vaccination programmes in developing countries and in veterinary protocols where multiple inoculations are not always feasible or economical. (Extracted from McGraw-Hill's Biotechnology Newswatch, 3 March 1986)

Yugoslavia

Biotechnology plans in Serbia

The Council of the Community for Mutual Co-operation in Planning and Business Operation of Organizations in the Field of Genetic Engineering, at a meeting held in the Economic Chamber of Serbia, supported the proposal for a project on research and development of new biotechnical processes based on the results of genetic engineering carried out at the School of Technology and Metallurgy at Belgrade University.

This research, to be carried out over the next five years, will aim at developing new biocatalysts, several new types of bioreactors, specific methods and devices for separation of products from biological processes, the development of instruments for controlling bioprocesses, and the development of fundamental chemical-engineering knowledge to design such processes. (Extracted from Privredni Pregled, 18 December 1985)

C. RESEARCH

Research on human genes

Regulatory protein isolated

Genentech and the Salk Institute have jointly isolated and characterized inhibin, a regulatory protein of the human reproductive system. Inhibin selectively blocks production of follicle-stimulating hormone (FSH). Unlike other substances

that block FSH, inhibin does not block production of luteinizing hormone. The discovery could provide the basis for the first hormone-based male contraceptive and could be useful in developing female contraceptives with fewer side effects. (Extracted from Chemical and Engineering News, 23 December 1985)

Diagnosis for arteriosclerosis

A monoclonal antibody for the diagnosis and treatment of human arteriosclerosis has been developed by Tokyo University researchers from an antigen found in rabbits with chronic arteriosclerosis. Arteriosclerosis is currently diagnosed by measuring the amount of lipids metabolized by the liver. The new antibody detected the antigen in rabbit blood. The antigen consists of a glycoprotein found only in rabbits with arteriosclerosis. (Extracted from Japan Economic Journal, 28 December 1985)

Synthetic peptide produces hepatitis antibodies

Antibodies to a synthetic peptide corresponding to a small portion of a hepatitis B virus envelope protein neutralize live hepatitis B virus, according to scientists at the New York Blood Center and California Institute of Technology. The research suggests that a simple peptide could form the basis for a more effective and less expensive vaccine against hepatitis B than those now available.

The researchers were led by A. Robert Neurath of the blood centre and Stephen B. H. Kent of Caltech's division of biology. The discovery is an outgrowth of several years of research on the immune response to hepatitis B virus. The findings were published in the March issue of Vaccine.

Most efforts to develop a hepatitis B vaccine have focused on what is known as the S protein of the virus. Until recently, the S protein, which contains 226 amino acids, was thought to be the sole constituent of the hepatitis B virus envelope.

However, the gene that codes for the hepatitis B envelope protein contains an open reading frame of 1,200 nucleotides, sufficient to code for a protein containing 400 amino acids. Over the past three years, researchers have discovered that, in fact, there are three envelope proteins: the S protein, an M protein that contains an additional 55 amino acids, and an L protein that contains all 400 possible amino acids. The "extra" 55 amino acids in the M protein are called preS2; the additional 119 amino acids in the L protein are called preS1. The two regions are known collectively as preS.

Hepatitis B vaccines based solely on the S protein, such as the currently available Heptavax vaccine produced by Merck, Sharp & Dohme, are effective for about 85 per cent of the general population. However such vaccines are much less effective for newborn infants. In regions where the disease is endemic, a common route of transmission of hepatitis B is from mother to newborn, so a vaccine effective in newborns is important if hepatitis is eventually to be eliminated. There is evidence that vaccines containing the preS region are significantly more effective in newborns as well as evidence that the preS region enhances the immune response to the S protein.

The research also holds promise for vaccines made by chemical synthesis of peptides or recombinant DNA production of peptides rather than by inactivation of live virus.

Tests have to be done in the only creature, apart from a human, that can be infected by hepatitis B: the chimpanzee.

Eventually, the production of either genetically engineered or synthetic vaccines will do away with the need for regular tests on animals. But, ironically, the effectiveness of the synthetic preS vaccine has just been tested on chimpanzees in the Liberian Institute for Biomedical Research in West Africa.

Antibodies produced in response to the preS protein were added to a suspension of live virus and injected into healthy animals who neither developed hepatitis nor became carriers, showing that the virus is inactivated. Tests of the vaccine itself and clinical trials in humans will come soon. Kent believes that the final version of the vaccine will not even need to be as big as the full preS protein. A couple of sequences of six amino acids might do, plus, perhaps, one fragment of the main S protein. (Extracted from Chemical and Engineering News, 3 March 1986 and New Scientist, 6 March 1986)

Leprosy research

One of the biggest obstacles to eradicating leprosy is accumulating sufficient quantities of the bacterium to work with and since it refuses to grow in culture in the laboratory, researchers have been hard put to invent a test for leprosy, let alone to develop a vaccine. The discovery in 1972 that armadillos can develop leprosy eased the scientists' frustration. The World Health Organization (WHO) maintains several armadillo colonies, but they are expensive to run. When they are infected, it takes two years before they accumulate a useful amount of the slow-growing bacterium. Even then, only about three-fifths of those infected develop the disease.

The armadillos have, nevertheless, made it possible to develop the first leprosy vaccine. It has been tried in Venezuela, where 60,000 leprosy contacts have been vaccinated. The disease can take five to ten years to develop, so the lasting effectiveness of the vaccine has yet to be demonstrated. The difficulty with leprosy is that the people most at risk are those whose immune system responds in the wrong manner. Patients suffering from lepromatous leprosy, the most virulent version of the disease, produce large amounts of anti-leprosy antibody yet do not activate the white blood cells needed to destroy the bacteria.

Some hope comes from a test which measures the response of cells to leprosy. People who do not respond in the test are more likely to get the disease. Researchers have found that if people who respond negatively are vaccinated they subsequently respond positively. Better still, the vaccine appears to have a therapeutic effect. When it is given to patients with lepromatous leprosy, it galvanises the scavenger cells which, in most people, engulf and digest the bacteria.

Encouraged by these results, the WHO and the British Leprosy Relief Association have launched a trial of the vaccine in Malawi. The trial is being linked to a large epidemiological survey which scientists hope will help solve the mystery of how the disease spreads.

Even if the present vaccine is effective, leprosy bacteria extracted from armadillos would not be sufficient for a global vaccination campaign. Scientists still hope to find relatives of the

leprosy bacterium that will grow in culture. BCG is one candidate; India has another which it plans to test this year.

The eventual solution is likely to come from biotechnology. In 1985, Dr. Richard Young and his colleagues at the Massachusetts Institute of Technology reported they had transferred all the 5,000 genes of the leprosy bacterium into E. coli. There they can be made easily in large quantities. The MIT team's approach was to cut the DNA of the leprosy bacterium at random and slot the individual pieces into a virus that infects E. coli. The E. coli can then be grown as individual clones of cells, each containing a different piece of leprosy DNA. Some of these clones will make leprosy proteins.

The next job is to identify those proteins which could form the basis of a vaccine. Dr. Young has already found five that are recognized by anti-leprosy antibodies. One may also be able to stimulate the white blood cells that are crucial for protection. (Extracted from The Economist, 15 February 1986)

Leukemia genes

Genes for β_1 interferon and for a cellular proto-oncogene are among those repositioned on chromosomes of patients with acute monocytic leukemia. Hybridization techniques showed that the interferon genes, normally clustered on human chromosome 9, were split: the a gene cluster remained on chromosome 9, while the β_1 gene was translocated to chromosome 11. The c-ets-1 proto-oncogene, normally found on chromosome 11, was found on chromosome 9. Exactly how these genes in their new locations participate in the malignant transformation of acute monocytic leukemia is not known. There is speculation that when the oncogene is translocated near the interferon cluster, regulatory sequences that activate the interferon genes may also activate the oncogene. Although proliferation of monocytic cells is not likely to represent overactive genes of the interferon system (since this system typically produces antiproliferative effects), proliferation could occur if the activated oncogene stimulates an alternative pathway that generates tumor cells. (Source: Science, 17 January 1986)

Progress on a vaccine for Epstein-Barr virus

The apparent contribution of certain viruses to cancer development has given new impetus to efforts to produce vaccines that will prevent viral infections. At a recent meeting on "Viruses and Cancers", which was held on 8 to 10 January on the island of Martinique, M. A. Epstein described the progress of his group at the University of Bristol School of Medicine toward developing a vaccine for the Epstein-Barr virus (EBV), which has been linked to two human cancers. One of them, Burkitt's lymphoma, is relatively rare. Most of the 5,000 to 10,000 annual cases occur in the malarial regions of Africa. Nevertheless, in those regions it is the most common childhood malignancy. The other cancer, nasopharyngeal carcinoma, is much more widely distributed. There are at least 50,000 cases worldwide every year, according to WHO estimates, occurring mainly in Southeast Asia, southern China, northern Africa, and among the Eskimos.

Because of the possibility that EBV DNA may be carcinogenic even if the virus is killed or attenuated, making a vaccine from the complete viral particle would be unwise. Epstein and his colleagues have chosen to use instead a large glycoprotein from the outer membrane of the virus. The glycoprotein has a molecular weight of 340,000 and is designated gp340. People who have been infected naturally by EBV make antibodies to gp340 that can neutralize the virus. Moreover, Marek's disease virus is, like EBV, a herpes virus and causes a lymphoma in chickens. Other investigators have shown that vaccination with the gp340 equivalent from Marek's disease virus prevents the birds from getting the lymphoma.

Epstein and his colleagues have now tested two different gp340-bearing membrane preparations in cottontop tamarins, a species of New World monkey that ordinarily develops a malignant lymphoma within a few weeks after infection by EBV. One of the preparations consisted simply of membranes taken from infected cells, which would not be suitable for human use because they might be contaminated with whole viral particles. The other consisted of the artificial membranes called liposomes that had been impregnated with purified gp340. Both preparations elicited antibodies against gp340 in the immunized animals, which were subsequently challenged with EBV doses sufficient to cause lymphomas in 100 per cent of the control animals. The result showed "that the vaccine is capable of protecting the animals against a massive dose of tumor-inducing virus".

For a human vaccine to be practical, there must be a reliable source of large quantities of pure gp340. The recent cloning of the gp340 gene by Michael Mackett's group at the Patterson Laboratory in Manchester, England, could provide a potential source of the protein by allowing it to be produced in bacterial or other cells.

Meanwhile, Mackett and his colleagues have inserted the gp340 gene into the vaccinia virus genome, thereby making a hybrid virus that might be used to immunize against EBV. Vaccinia virus has been safely administered for many years as a vaccine for smallpox. The Epstein group is beginning trials to determine whether the gp340-vaccinia hybrid can elicit protective immunity to EBV in animals.

Epstein says that it is difficult to predict when testing of an EBV vaccine in humans could begin, but estimates that it might be in as little as a year or two. The first step, he suggests, would be to determine in a few previously uninfected volunteers whether the test vaccine elicits the production of virus-neutralizing antibodies.

Although EBV infections in the developing countries occur in the first year or two of life, in the developed nations individuals usually do not get infected before adolescence or early adulthood. Under these conditions EBV does not appear to dispose to cancer but can cause infectious mononucleosis, which is temporarily debilitating but is not life-threatening. If the vaccine proves capable of eliciting neutralizing antibodies in the volunteers, then the next step might be to determine whether it prevents mononucleosis, Epstein says. If it also passes that test, then a clinical trial could be carried out in one of the African areas where Burkitt's lymphoma is a problem. (Extracted from Science, Vol. 231, 28 February 1986)

Key protein in vision not found in cone cells

A protein called transducin that plays an essential role in the response of retinal rod cells to light may not exist in cone cells, according to researchers at the National Institutes of Health. The finding suggests that rods (which are sensitive to very low levels of light) and cones (which are responsible for colour vision at higher light levels) may use different mechanisms for converting light into nerve impulses. Gerald B. Grunwald,

Peter Gierschik, Marshall Nirenberg, and Allen Spiegel studied the distribution of one of the three subunits of transducin in chicken retina by immunochemical techniques. Although they found the protein subunit in rod cells, they were unable to detect it in cones. That suggests that cones require many fewer transducin molecules than rods, that transducin in cones is not sensitive to the experimental technique used by the researchers, or that rods and cones operate with quite different mechanisms. (Source: Chemical and Engineering News, 17 February 1986)

A monoclonal that reverses organ rejection

Results of a study have shown that a monoclonal antibody is more effective in preventing organ rejection in kidney transplant patients than is conventional steroid therapy. Use of the monoclonal - OKT3, produced by Ortho Pharmaceutical - in fighting tissue rejection is currently under review by the Food and Drug Administration. OKT3 recognizes a specific subset of T-cell lymphocytes that normally bind to foreign proteins in the body and play a role in rejection of tissue transplants. Researchers found that OKT3 reversed acute rejection in 94 per cent of kidney transplant patients, compared with 75 per cent for conventional steroid therapy. In addition, patients treated with OKT3 showed a 68 per cent kidney survival rate; only 48 per cent survived when treated with steroids. However, patients develop antibodies against the monoclonals after receiving one treatment, whose effects last only one to two weeks. (Source: Chemical Week, 12 February 1986)

Researchers synthesize key blood glycoprotein

Researchers at California Institute of Technology and Walt Institute of Medical Research, Melbourne, Australia, have used automated chemical synthesis methods to synthesize interleukin-3 (IL-3), a glycoprotein thought to play a key role in regulating production of blood cells and perhaps important in blood-system cancers.

Although IL-3 is in itself an interesting molecule, the synthesis is important primarily because it demonstrates that solid-phase, automated chemical synthesis can be used to produce large protein molecules. IL-3, consisting of 140 amino acid residues, is approximately twice the size of the largest proteins previously synthesized by this method. Besides producing IL-3, the researchers prepared a number of IL-3 analogs and compared their activities with that of IL-3. These studies show that the integrity of IL-3's stable tertiary structure is crucial to the protein's function. Generally, the researchers say, these studies "suggest that important structure-function correlations can be determined with the peptide synthesis approach". (Extracted from Chemical and Engineering News, 6 January 1986)

Cyclosporine

Cyclosporine may suppress T cells in a way similar to the method of activity of human T lymphotropic virus (HTLV), according to research being carried out at the Johns Hopkins University. Cyclosporine and HTLV-I and II all produce a polylobulated (daisy) pattern in T cell nuclei. Binding of the calcium receptor calmodulin may be responsible for the change. T cell proliferation may be hindered by the inhibition of the lymphokine interleukin-2. Preliminary reports that cyclosporine blocked HTLV-III replication in two AIDS patients may be explained by postulating that the drug robs the virus of its primary target or that it somehow blocks viral replication. A better understanding of how cyclosporine works could allow the production of less toxic and more effective drugs. (Extracted from Medical World, 25 November 1985)

AIDS protein made

Genentech, the Californian biotechnology company, last week announced the synthesis in mammalian cells of a recombinant protein that is the favoured candidate for a vaccine against acquired immune deficiency syndrome (AIDS). Although the work marks an "unexpected modest advance" in AIDS research, it may greatly expedite the search for a safeguard against the disease.

The protein, gp120, is part of the envelope of the AIDS virus, HTLV-III or LAV. Although it has been synthesized by several laboratories in bacteria and yeast cells, these systems cannot match the mammalian cell products. Genentech's Chinese hamster ovary (CHO) cells glycosylate and secrete the protein, while microbial cultures must be engineered to do either. Despite the added expenses of maintaining mammalian cultures, Genentech's system may prove more efficient in the long run because it cuts purification costs.

As a vaccine, gp120's efficacy has yet to be proved, and it may be a year or two before monkey trials provide any data relevant to the human response. Any possible vaccine will also have to counter the many variant forms the AIDS virus is known to assume. (Extracted from Nature, Vol. 319, 13 February 1986)

Protein product of AIDS virus is key enzyme

A protein product of the virus that causes AIDS has been purified and identified as reverse transcriptase by Robert C. Gallo of the National Cancer Institute and co-workers. Such enzymes, which synthesize DNA according to instructions encoded in the viral RNA, are a major target of antiviral drugs and vaccines. Using immunoaffinity chromatography, the researchers isolated the enzyme from a group of viral proteins that invoke antibody activity in persons infected with the AIDS virus. The AIDS enzyme is unusual in that reverse transcriptases from other viruses aren't known to generate an immune response, the researchers point out. The amino acid sequence of the N-terminal end of the enzyme exactly matched what was predicted by analysis of the nucleotides of the gene for reverse transcriptase. Now that pure AIDS reverse transcriptase is available, researchers plan to study its molecular interaction with antiviral drugs. (Source: Chemical and Engineering News, 10 March 1986)

Another AIDS protein identified

In the continuing search for clues as to how the AIDS virus produces disease, attention has focused on the activities of viral genes and their products. Besides the characteristic retroviral genes gag, pol, and env, the AIDS virus contains an unusual gene, sor (short open reading frame), positioned in the DNA between pol and env. The sor gene produces a protein that has now been identified and studied in three different systems: the 23,000-dalton protein (p23) was secreted in large amounts by a bacterial expression system, it was identified in a cell line infected with the AIDS virus; and its obligate association with the sor gene was shown, using cloned AIDS proviruses with gene deletions in the sor region. Serologic analyses indicated that the sor gene produces p23 during the normal course of AIDS infection since antibodies to the protein were present in AIDS

patients. (Antibodies were also present in some controls, suggesting that the viral protein may cross-react with proteins unrelated to AIDS.) A role for sor has yet to be found: it proved unnecessary for either the replication of the AIDS virus in a cell line or for the cytopathologic effects of the virus on the cells in which it was growing. (Source: Science, Vol. 231, 28 March 1986)

New AIDS viruses

French and American scientists claimed independently to have discovered new viruses similar to the one that causes AIDS. Both sets of viruses have been found in people from West Africa.

The French discovery was made by Luc Montagnier and his colleagues at the Pasteur Institute in Paris. Montagnier released information about two AIDS patients from West Africa. He said at meetings in Lisbon that their blood did not contain the French group's AIDS virus, which Montagnier calls LAV, in spite of having the disease. Instead, they had a similar virus, which Montagnier has named LAV-2. He says it "is rare and occurs primarily in West Africa", and that it too causes AIDS.

Meanwhile, Max Essex of the Harvard School of Public Health in the US released to journalists details of a new virus similar to HTLV-3.

The new American virus, which Essex calls HTLV-4, seems to have no similarity to the French discovery, however, apart from being West African. It was found in three healthy Senegalese. The interest in the virus is that it is also related to a monkey virus, STLV-3.

It may be the "missing link" to theories that AIDS originated when a virus contracted from monkeys mutated in humans. Essex says differences between the non-pathogenic and pathogenic HTLV viruses may shed some light on how AIDS develops. Neither group has published its data. Both have submitted papers to the American journal Science. (Extracted from New Scientist, 3 April 1986)

Research on plant genes

Herbicide resistant plants

Calgene has developed a strain of tobacco resistant to glyphosate herbicide. Glyphosate, which is rendered inactive when it touches soil, kills any plant by being absorbed through the leaf. It blocks the action of EPSP synthase, an enzyme needed in the production of amino acids phenylalanine and tryptophan. A slightly different form of the enzyme found in a strain of bacteria does not bind glyphosate, and so is not affected by the herbicide. The gene from the resistant bacterium is inserted into a bacterium, Agrobacterium rhizogenes, that naturally infects plants. This bacterium carries a large infectious plasmid, which inserts itself permanently into a plant's DNA. Plants grown from infected cells demonstrated herbicide resistance, especially if they had two or four copies of the gene per cell.

Engineering crops to resist weed killers

Plants that resist herbicides could be a boon to chemical companies; a prototype may soon be field tested

In the near future the US Department of Agriculture is expected to announce its approval of the first outdoor test of a plant that has been genetically engineered to tolerate a herbicide. Although the experiment is modest, it is part of a major race by many biotechnology and chemical companies to redesign the genetic code of seeds and create crop plants that can withstand weed killers.

These new kinds of plants will not be on the market for at least several years, but there is already considerable speculation about their potential economic and environmental impact. Calgene, in its field test, will analyse a non-crop variety of tobacco plant that tolerates glyphosate, and plans to build herbicide tolerance into several other species, such as tomatoes, cotton, and poplar trees, which are important in the paper industry. Calgene's experimental protocol is being examined by USDA with the help of its Recombinant DNA Research Committee, whose members include scientists from USDA and other government agencies. University scientists also reviewed Calgene's plan. The research committee's main concern is that the mutant gene might be sexually transferred between the tobacco and other plants in the vicinity. The possibility is highly unlikely based on past experience with tobacco, one of the most well-studied species in plant breeding, but to eliminate all possibility, Calgene will snip off the plant flower buds before they bloom.

Herbicide-resistant plants may help a farmer reduce expenses indirectly. Although seeds are a small part of total farm costs, a farmer may save money if the new seeds are paired with herbicides that are cheaper because their patents have expired and have to compete with generic versions. But the biggest potential lies with designer seeds matched with new, more efficient proprietary chemicals. Such a combination could reduce the need for tillage, which is done mainly to control weeds, and have a ripple effect in money savings. Less tillage cuts soil erosion and the costs of energy, fertilizer, and water. According to a market analysis by Calgene, the creation of glyphosate-resistant tomatoes could save farmers in California's Central Valley $30 per acre by reducing the expense for mechanical tillage and hand hoeing and other pesticides.

Herbicide-resistant seeds might also help to solve the problem of "carryover," in which the chemical lingers in the soil and is toxic to the next crop to be planted. (Extracted from New Scientist, 26 December 1985, and Science, Vol. 231, 21 March 1986)

Guayule cloning could give high-yielding plant

Tissue culture techniques for cloning guayule have been developed successfully by scientists at the University of California, Irvine. That cloning technology could give plant breeders a new tool for developing high-yielding varieties of the rubber-producing plant. And such varieties, in turn, hold promise for promoting commercial use of guayule.

Guayule has been of interest for some years as a potential new, domestic source of natural rubber. The plant grows in the desert climate of south-west Texas and northern Mexico, and it produces natural rubber that is nearly identical to that from tropical rubber trees. But a major obstacle to speeding commercial development is the need for higher-yielding varieties.

Conventional plant breeding techniques do not work with guayule which is a highly heterozygous plant, an out-crossing species. It is very difficult to breed true varieties, but with the

tissue culture technology, breeders could reproduce large numbers of genetically identical offspring from an individual improved guayule plant.

For cloning to be useful in this way for guayule, research was specifically aimed at developing techniques that could be used with tissue from older plants. Important traits such as drought resistance and rubber yield are often not expressed until plants are mature. In cloning, small pieces of living plants are used to start the growth tissue from intact mature guayule of tissue cultures in vitro. Once established, the cultures produce undifferentiated tissue that can be transferred to another culture medium that induces root growth. The plantlets can then be removed and grown in soil as with normal seedlings. (Extracted from Chemical and Engineering News, 27 January 1986)

Sesame as oilseed crop

Researchers in Israel are set to alter the genetic code of sesame to make it more useful as a crop. Archaeological evidence suggests that sesame is the most ancient oilseed used by people. Sesame could be an important oilseed crop. Its seeds are about 50 per cent oil, rich in a protein that is comparable with chopped beef and casein. Also, sesame oil keeps because it contains sesamol and sesamolin, which act as anti-oxidants. Unlike domesticated cereals or legumes, however, it has remained faithful to its genetic inheritance - it has indeterminate growth and it scatters its seeds. Plant geneticists in Israel have overcome this problem and by the end of this year, they may be able to combine indehiscence - keeping the mature seed capsule closed to prevent loss of seeds - with the determinate habit.

In December 1984, at a meeting of sesame experts in Rome, Dr. Raymond Brigham, of Texas A&M University in Lubbock, reported that the mutated Israeli variety was stable (its genetic constitution and breeding behaviour do not change) under the conditions of the southern US. It is also stable in southern India, where Dr. S. Thanavelu has been growing it at the Tamil Nadu Agricultural University in Vridhachalam. (Extracted from New Scientist, 20 February 1986)

Calgene clones gene for vegetable oil synthesis

Calgene, Inc. announced in early March that it had cloned the gene that encodes acyl carrier protein (ACP) from spinach into a bacterial host. ACP is a key gene in the synthesis of fatty acids stored in seeds as vegetable oil in such major crops as soybean and sunflower. Lloyd Kunimoto, vice president of product development, described the ACP gene as the first plant fatty acid synthesis gene to be cloned, and that "cloning the gene in bacteria is the first important step towards the genetic engineering of an improved gene".

Dr. Vic Knauf, who leads the Calgene vegetable oil synthesis research team, said that many commercial products were dependent on being able to engineer this important gene in recombinant plants. Dr. Knauf also stated, "at least two more plant genes involved in vegetable oil synthesis will be cloned by Calgene this year". The research programme is part of a comprehensive approach by Calgene to improve oilseed crops and to develop new domestic raw material sources for specialty chemicals based on plant fatty acids. Calgene has previously announced the first successful transformation and regeneration of rapeseed, a major worldwide oilseed crop. (Extracted from Company News Release, 3 March 1986)

Breakthrough reported in biotechnology of plants

A team of Stanford University researchers recently reported breaking through a critical biological barrier and brought significantly closer the day when major crops can be custom-designed. The team said it had combined the technology of electricity with that of altering genes to yield a technique that enables ... scientists to move hereditary material more easily f... unrelated species into important food plants. The method is based on a simple biological principle discovered a decade ago: cells in special solutions will develop tiny openings in their walls after being struck by an intense burst of electricity. The openings allow genes to slip easily through and join with the cell's own genetic material. The process of crossing and re-crossing varieties to improve plants is long and expensive. Producing a new corn hybrid, for instance, takes six years or more. The new method could cut the time to two years or less. (Extracted from Int. Herald Tribune, 17 March 1986)

D. APPLICATIONS

Pharmaceutical and medical applications

Chickenpox vaccine

Oka/Merck's experimental varicella chickenpox vaccine could be commercially available in 1986-87. Data will be submitted to the US Food and Drug Administration soon. The Japanese-developed vaccine would probably be administered in combination with measles-mumps-rubella vaccinations given at the age of 15 months. C. E. Johnson of Case Western Reserve University says the vaccine is efficacious even in young children. Chickenpox costs $400 million/year when parents' lost wages are considered. About 17 per cent of young children in the trials develop a mild varicella-like rash from the vaccine, and 21.9 per cent develop a fever over 38°C. Tests to determine the presence of antibodies showed seroconversion in 97.1 per cent of the children. Most children who were seropositive after ... ccination remained seropositive, and children who were seronegative at six weeks remained seronegative at one year. Earlier studies had indicated the possibility of later serocoaversion to the vaccine. (Extracted from Medical World, 25 November 1985)

"Piggyback" vaccine under development at Stanford

A new anti-typhoid vaccine undergoing development at Stanford University may become one of the first "piggyback" vaccines to protect against several diseases.

The new vaccine consists of live typhoid fever bacteria - Salmonella typhi - that have been genetically altered so they do not cause the disease, said Dr. Bruce Stocker, professor of medical microbiology at the Stanford University Medical School, who heads the research team working on the project.

Now the scientists plan to insert supplemental genetic material into the organism to induce immunity against other diseases, including traveller's diarrhea, malaria, schistosomiasis and hepatitis. These studies are supported in part by Praxis Biologics of Rochester, N.Y.

The new anti-typhoid vaccine may soon undergo clinical trials against typhoid fever in Santiago, Chile, where the illness is common. Typhoid fever

is rare in the US but there are about 12 million cases per year worldwide. An existing anti-typhoid vaccine given by injection is only partially effective and causes some adverse reactions. It also requires yearly booster shots to maintain its partial potency.

According to Dr. Stocker, the new anti-typhoid vaccine has already passed initial safety tests in human volunteers at the Vaccine Development Centre of the University of Maryland School of Medicine in Baltimore.

To make the vaccine, the researchers modified the Salmonella bacteria so that the organism required two growth factors, para-aminobenzoic acid and adenine. Both of these substances are unavailable in human tissues. Thus, the live bacteria can be grown in the laboratory but not in human cells and do not cause typhoid fever disease.

Interestingly, however, these modulated bacteria can live in the body for several days and stimulate an immune response. Since the anti-typhoid vaccine bacteria are changed in two ways, this provides a safety net for human use.

"Each mutation by itself would probably make the strain harmless, which means that a strain with both mutations can be guaranteed to be safe," Dr. Stocker explained. Also, the bacteria have been mutated in such a way that they cannot revert to their original genetic form.

As for the new vaccine's "piggyback" potential, several researchers are now testing genetic "accessories", to expand the vaccine's usefulness. Dr. John Clements of Tulane University Medical School has added a gene engineered to protect against the commonest form of traveller's diarrhea, while Dr. Stocker's laboratory is studying the incorporation of an antimalaria gene. Scientists in England are attempting to insert into the modified Salmonella bacteria a gene to protect against schistosomiasis - one of the undeveloped world's most devastating parasitic diseases.

The new anti-typhoid vaccine can be taken by mouth, which will give it a particular advantage in third world countries where medical treatment is often not easily available. According to Dr. Stocker, manufacturing the vaccine can be very economical since harvesting and purification steps are not necessary. The typhoid bacteria in this vaccine will, themselves, make the other immunity-inducing proteins, forming a naturally packaged multiple vaccine.

The first strains of the anti-typhoid vaccine were developed for use in cattle to protect against a bovine disease caused by the Salmonella bacteria. These vaccines are now in clinical animal trials in calves in Sweden and at the University of California Veterinary School in Davis. (Source: Genetic Engineering News, February 1986)

Approval hopes for antiviral

ICN Pharmaceuticals is hopeful that UK approval for its antiviral preparation, Virazole (ribavirin) is not too far away. The Committee on Safety of Medicines has been looking at the company's drug for use in the treatment of respiratory syncytial virus (RSV) in children for sometime now, and approval by the USA's FDA at the end of last year has encouraged ICN.

Described as the first antiviral with a true broad spectrum of activity, ribavirin has been used in other parts of the world for ten years, but the US go-ahead is the first from a Western country. Apart from RSV, the company says ribavirin has considerable potential in the treatment of AIDS, herpes, influenza, hepatitis, measles and also Lassa fever.

The drug is a synthetic nucleoside analogue, whose mode of action is not fully understood. Administration is via a small particle aerosol generator, which has been specially developed to deliver microscopic particles to the lung at a slow rate. Patients are put under an oxygen mask or hood and it takes up to 18 hours to deliver a single dose. Hospitalization is therefore necessary, but the company says it eventually hopes to develop a 'take-home' inhaler. (Extracted from Manufacturing Chemist, March 1986)

Hepatitis vaccines

Merck Sharp & Dohme's genetically engineered hepatitis B vaccine is in the final stages of clinical trials. The project started five years ago in a partnership with the USA genetic engineering company Chiron. The vaccine is made in baker's yeast, using genetic engineering to splice the gene coding for a protein - from the virus' surface antigen - into a yeast cell. This provokes a strong immune response. The yeast cells are then cultured in large fermenters for several days during which time the cells rupture. The surface antigen is then collected and purified. A vital part of the process is a proprietary chemical reaction which assembles the antigenic protein into a circular particle which resembles the natural molecule more closely.

Smith Kline & French is expecting to gain marketing approval in the USA from the FDA for its vaccine in June 1986. Smith Kline & French's vaccine is made in a very similar way, except that it lacks the chemical step which Merck Sharp & Dohme claims makes its vaccine more effective. Smith Kline & French is expecting a European product registration in September 1986. (Source: Manufacturing Chemist, February 1986)

New cholera vaccine will be tested on volunteers

The first human trials of a genetically engineered vaccine for cholera and typhoid are being undertaken in Adelaide, South Australia. The vaccine, which is taken orally, should give lifelong immunity against cholera, which kills millions of people every year.

Professor Derek Rowley from Adelaide University has worked on the vaccine since 1980 and has successfully tested it on animals. He has approval from the South Australian department of health to carry out the human trials, which will take place at a hospital in Adelaide once used to treat infectious diseases.

The tests are expected to involve one-week trials on six volunteers in order to gauge the optimum dose of the vaccine and its effectiveness. If the trials prove positive, the vaccine will be tested in Baltimore, USA, at the end of the year. Volunteers there will be exposed to the disease after immunisation. The final field trials will take place in Bangladesh, probably in 1988, when several hundred thousand people will be given the vaccine.

The vaccine is made by taking genes of the typhoid and cholera bacteria and cloning them inside harmless bacteria. These bacteria then produce the specific antigens which stimulate the human immune system to produce antibodies able to recognize infection by cholera and typhoid.

This vaccine's main advantage over existing ones is that it gives lifelong immunity and is effective against very heavy doses of the disease. Commercially available vaccines give only limited

immunity for up to six months and are not always effective against heavy infection. They also rely on dead bacteria to provide the immunity and produce uncomfortable side effects, such as fevers, caused by toxins associated with parts of the dead bacterial cells. They tend to suppress the body's natural immune system, particularly in the gut where protection is needed most. (Extracted from New Scientist, 20 March 1986)

Malaria vaccine

Hoffman-La Roche, the Swiss-based drugs group, is set to start tests of a malaria vaccine. In co-operation with New York University, researchers have isolated and identified the surface antigens in the sporozoite stages of the parasite. Roche hopes to have a trial vaccine by the spring. Roche scientists are searching for antigens from other parts of the parasitic life cycle to develop a multiple product that gives broader protection. Roche hopes to plan a vaccination infrastructure with the World Health Organization. Meanwhile scientists at Biogen have successfully isolated and produced, through genetic engineering, a number of surface antigens of the parasite's merozoite form. Behringwerke AG will use these in a vaccine intended to interrupt the disease cycle by preventing the malaria merozoites from infecting red blood cells. Before the vaccine can be sold, however, it will need to undergo several years of extensive testing. Even if a sufficiently attractive market for a malaria vaccine exists, it remains to be seen whether a vaccine aimed at just one stage of the parasite's life cycle can halt this complicated disease in its tracks.

Other merozoite proteins are being investigated as vaccines at the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia, and in Sweden at the University of Stockholm. Vaccines based on proteins on the surface of the sporozoite stage of the parasite, the form in which it is passed from the mosquito into the bloodstream, are in an advanced stage of development both at New York University, probably in conjunction with Hoffmann-La Roche, and at the Walter Reed Army Institute of Research in Washington, DC, in conjunction with Smith Kline and French Laboratories. (Extracted from European Chemical News, 20 January 1986, Nature, Vol. 319, 20 February 1986 and Biotechnology Bulletin, Vol. 5, No. 2, March 1986)

Producing vaccines without side-effects

Professor Morein and colleagues of the Faculty of Veterinary Medicine at Sweden's Agricultural University, Uppsala, has developed a new method of producing vaccines.

Up to now successful tests have been made on animals, for instance with vaccines against rabies, the measles virus, even against retrovirus.

An important role in the new vaccine technology is played by a tree found in the jungles of South America, Quillaja saponaria molina. A glycocide, "Quil A" is extracted from the bark of this tree. From previous experience it was noted that it has the capacity to stimulate the immune defence of the body to react more strongly to vaccination. One application of Quil A is as an adjuvant of vaccine against foot-and-mouth disease.

In Professor Morein's method Quil A acts as a kind of skeleton when a vaccine is built up. To this skeleton surface proteins from the vaccine one intends to produce are attached. These proteins affect the body's immune defence, which is stimulated to produce the right kind of antibodies against the virus. Thus the basic idea is as always to activate the body's own defence mechanisms.

With the presence of Quil A the effect produced by the vaccine is up to ten times stronger. This means that the vaccine doses can be kept relatively low, and any side-effects are reduced to an absolute minimum, even eliminated. It is common knowledge that toxic side-effects from certain types of vaccine are sometimes an obstacle to effective vaccination. A case in point is the vaccine commonly used against whooping cough.

Virus from the USA

Researchers at the Bio-Medical Centre, the BMC, in Uppsala are collaborating, inter alia, with the National Cancer Institute in the USA. From there virus is obtained. In Uppsala the virus is disintegrated and the heredity unit is removed to prevent the virus from repricating in the cells of the body. The interesting virus surface proteins are isolated. These proteins are then attached to the Quil A skeleton. What makes these iscoms important is that those on the surface possess proteins that give signals to the immune defence, while they retain within them a substance that boosts the immune defence.

Professor Bror Morein's colleagues in the development of the new method are Stefan Höglund, BMC, Bo Sundqvist, SVA, Uppsala, and Albert Osterhaus, of Bilthoven in Holland. (Extracted from New Swedish Technology)

Interferon to treat cancer approved

The British Department of Health and Social Security's Committee on Safety of Medicines (CSM) has given its approval for the use of alpha interferon to be sold for the treatment of hairy-cell leukaemia, so-called because of the hairy projections from the malignant cell that are used to diagnose the disease. The approval covers three companies - Schering-Plough, Wellcome, and Hoffman-La Roche.

Schering-Plough, the US pharmaceutical group, has announced that its UK subsidiary, Kirby-Warrick Pharmaceuticals Ltd., has been informed by the British Department of Health's Committee on Safety of Medicines that its alpha-2 interferon, Intron A, is approvable for treatment of hairy-cell leukaemia, pending final product labelling approval. The product is licensed from the genetic engineering company, Biogen.

Hairy-cell leukaemia affects a small number of patients - just 2 per cent of all leukaemia sufferers - a thousand or so in the US, some hundreds in the UK each year. It is claimed that the genetically engineered drug has produced "remarkable" results in a high percentage of people with the disease (80 to 90 per cent). Hopes that the drug would be an important cancer therapeutic were shattered two-and-a-half years ago when clinical trials showed it to be ineffective against the most common solid tumour cancers such as lung, colon and breast cancers.

Prior to these findings, Schering-Plough had planned to build a $106 million commercial-scale plant to produce gene-spliced alpha interferon at Brinny, Innishannon in the Republic of Ireland, but the project was subsequently radically revised.

The Irish plant, which is due for completion soon and is currently running acceptance trials, has no fermentation or primary purification capacity but

carries out the final purification and finishing of interferon produced at Schering-Plough's facility at Union, New Jersey. The US unit has sufficient capacity to fulfil demands for the foreseeable future. Intron A is marketed in Ireland for the treatment of hairy-cell leukaemia, multiple myeloma, Kaposi's sarcoma, malignant melanoma and venereal warts. The company has filed for approval in the US for these diseases plus common cold prevention.

The CSM is considering whether to approve the use of Intron in the treatment of multiple myeloma and Kaposi's sarcoma, which is found in patients suffering from AIDS. Alpha interferon may also help to prevent the spread of the common cold - another use that the CSM is considering.

The approval of interferon in Britain so many years after its discovery heralds a new generation of proteins, including beta and gamma interferons as well as other proteins derived from immune cells.

More than 2,500 Cubans have been treated with interferon over the past five years in tests on 16 viral diseases and 9 cancers. For a developing country, Cuba has displayed remarkable alacrity in its use of the drug. Even the health minister, José R. Fernandez, has had alpha interferon to help cure an acute bout of influenza.

Cuba decided to research into interferon partly as the result of an epidemic of dengue fever in 1981, which killed 100 people. Some Cuban doctors believe that interferon helped to save the lives of at least two children suffering from the disease.

Cuban doctors have routinely treated patients suffering from laryngeal papillomatosis, a rare throat cancer, with alpha interferon. About 100 people with this disease have already taken the drug, which the Cubans prepare from human white blood cells.

For 25 children with throat cancer who had been treated with interferon at the time of the surgery (when tumours are removed), about 80 per cent had no relapses 18 months after treatment. The rest had only one relapse. (Extracted from New Scientist, 6 March 1986 and European Chemical News, 3 February 1986)

Interferon used against rhinoviruses

Interferon may be the first drug that can prevent the spread of cold virus infections in humans, according to studies by US and Australian research teams reported in The New England Journal of Medicine. The studies showed that family members who took interferon had 40 per cent fewer attacks of respiratory illness than those who did not. The incidence of respiratory ailments was reduced by over 80 per cent when only colds caused exclusively by rhinoviruses were involved. Over 100 types of rhinoviruses, the major causes of colds, are known, and account for 30-50 per cent of all colds. They are particularly important in outbreaks of colds in the spring and autumn. Interferons are natural antiviral substances. Recently, many types of human interferons have been produced via genetic engineering techniques. Interferons are considered experimental drugs and are not yet available for use by the general public. Schering-Plough, which sponsored the US and Australian studies, is seeking US Food and Drug Administration approval for use of interferon as a treatment for cancer, the common cold and other diseases. It expects to receive approval in about one year.

In independent studies by the University of Virginia School of Medicine and the University of Adelaide (Australia), interferon alpha 2 was given one day/week by nasal spray as soon as a family member developed cold symptoms. The efficacy of the drug was measured by comparing cold infections among families using the drug and those who used a harmless but ineffective nasal spray. The reports are the first indication of the usefulness of interferon in preventing the spread of colds. (Extracted from New York Times, 9 January 1986)

A delivery system for treating brain cancer

Nova Pharmaceutical (New York City) has acquired exclusive worldwide rights to a new drug delivery system for the treatment of brain cancer. The system, developed by the Massachusetts Institute of Technology (Cambridge, Mass.), is a biodegradable polymer that can be implanted in the brain to deliver a slow, timed release of chemotherapeutic drugs or antibodies directly to the tumour site. It is designed to expose the tumour to drug concentrations hundreds of times greater than is possible through conventional routes. Nova is currently working with the Johns Hopkins University School of Medicine (Baltimore) to arrange clinical trials. (Source: Chemical Week, 5 February 1986)

Preliminary results promising for AIDS drug

A short trial of a drug to counter AIDS has produced encouraging results with 19 patients. The drug, azidothymidine (AZT) has been developed by the Wellcome Laboratories in Britain, but scientists are a long way from developing a proven safe drug against AIDS, and still further from developing a vaccine that could protect people from infection by the virus. The trial was conducted in the US by the National Cancer Institute. After using the drug for six weeks, 15 of the 19 patients showed increases in the number of T-lymphocyte cells in their blood. The number of cells becomes seriously depleted in AIDS patients. The group also showed an average gain in weight of 2.2 kilograms, according to the first reports of the trial, published in The Lancet.

The AIDS virus has an RNA genome that is copied into DNA in infected cells by a viral enzyme. AZT blocks this because cells convert the drug to a substance that resembles a normal DNA building block. The viral enzyme can add this substance to the growing DNA chain, but AZT's structure then prevents the addition of further building blocks, thereby interrupting the life cycle of the AIDS virus.

Although AZT, with its ability to terminate DNA synthesis, might have been expected to produce intolerable side effects, they proved to be relatively mild, at least during the short course of this trial. They included headaches and decreases in the white and red blood cell counts of the patients. No patients died of drug-related causes, but one dropped out because of a possible adverse reaction to AZT.

AZT's side effects may have been less severe than had been feared because the enzyme that synthesizes cellular DNA is more resistant to the drug than is the enzyme that synthesizes the viral DNA. Jerome Horwitz of the Michigan Cancer Foundation in Detroit synthesized AZT in the 1960s as a possible cancer drug, but that idea was abandoned when it failed to kill tumour cells.

The results of the current trial also show that AZT is effective when given by mouth, which is important for any drug that might have to be taken for a long time. Moreover, the drug can pass from the bloodstream into the central nervous system. The AIDS virus often infects cells in the brain, and

a drug for treating AIDS would have to be capable of countering its effects there, as well as in the blood lymphocytes.

The endogenous opiate met-enkephalin can improve immune status in AIDS and cancer patients, according to N. P. Plotnikoff of Oral Roberts University (Tulsa, OK) and J. Wybran of Erasme Hospital (Brussels, Belgium). All six patients treated in Tulsa responded with increases in T cell subsets OKT 3, OKT 4, OKT 8 and OKT 11. Two of the patients had AIDS and Kaposi's sarcoma, and one each had lung cancer, hypernephroma, melanoma, and breast cancer. T cells had more interleukin-2 receptors after treatment. The treatment's effects began to decline four days after the second month after treatment ended. In Brussels, six AIDS or AIDS-related complex patients and eight lung cancer patients were treated with met-enkephalin, with similar results to the Tulsa trials. Enhanced natural killer cell activity was also noted, however.

Much longer studies will be needed before one can be sure whether AZT will affect disease progression or survival in AIDS patients.

There will not be a vaccine available for testing on humans before 1988, at the earliest. Its effectiveness will not be clear for several years after that, because of the length of time that the virus can lie dormant in cells.

AZT is the first drug to start "phase two trials" in which its effectiveness on humans is tested, and will soon be ready for "phase three" trials, involving large numbers of people at varying risks of catching AIDS. These trials may last a year and, if they are successful, the US Food and Drug Administration has promised that it will allow a speedy transfer of the drug to the marketplace.

The search for a vaccine depends on the discovery of a substance that will stimulate the production of antibodies to the AIDS virus. The most promising of these antigens so far is gp120, about which more details may be found in the section marked "Research" earlier in this edition of the Monitor. (Extracted from Medical World, 9 December 1985, New Scientist, 20 March 1985 and Science, Vol. 231, 28 March 1986)

Biosensors

Researchers are attempting to develop tiny biosensors that could be placed inside the body to monitor the level of glucose in the bloodstream and relay the information to an electronically controlled insulin pump. Biosensors combine biological, chemical and electronic technology. Problems include making the sensors safe and reliable, since they must be constantly recalibrated. Biosensors were first used outside the body during open heart surgery. Sensors could provide instantaneous, continuous readouts for blood samples, which currently must be sent to the laboratory for analysis.

Diamond Sensor Systems will introduce a system to monitor blood oxygen, carbon dioxide and pH levels in 1986. Biosensors would be placed in the blood that passes through a heart-lung machine during open heart surgery. Cardiovascular Devices is developing a set of sensors that can be inserted into an artery in the wrist via a catheter. Other applications for biosensors include control of the release of drugs into the bloodstream and of the movement of artificial limbs and organs. Non-medical uses include monitoring industrial processes, such as fermentation. One type of biosensor measures the intensity of light transmitted through optical fibres. Another approach involves coating an electrode with a membrane or chemical that produces a current or voltage when exposed to a certain substance. A silicon chip can also be coated with the membrane or chemical to produce a chemical field effect transistor or chemfet. These sensors would be combined with the computer circuitry needed to analyse the data. However, chemfets have been difficult to make. (Extracted from New York Times, 30 January 1986)

New anticoagulant

Biologically active human protein C - an anticoagulant that plays a crucial role in the regulation of blood clotting - has been produced through genetic engineering by Integrated Genetics (Framingham, Mass.). Protein C, normally produced by the liver, helps maintain the delicate balance between clot formation and dissolution. Failure of the first mechanism could result in excessive bleeding after an injury; failure of the second could cause dangerous, blood-damming clots in the circulatory system. The biological activity of the new protein - made by inserting the human gene responsible for it into bacteria - is said to approach that of the natural chemical. It will be used in the treatment of patients with congenital and acquired protein C deficiencies. The latter group includes postsurgical patients and those with liver disease or a deficiency of vitamin K (another chemical that affects clotting). The protein could also be used in conjunction with tissue plasminogen activator - a clot-dissolving enzyme that has been genetically engineered by Integrated Genetics and other biotechnology firms - in treating heart disease. The project is partly funded under Integrated Genetic's cardiovascular products agreement with BASF Corp. Protein C will be marketed worldwide, except in the Far East, by Knoll Pharmaceutical, a BASF subsidiary. Knoll will conduct necessary preclinical and clinical trials. (Extracted from Chemical Week, 15 January 1986 and High Technology, March 1986)

Likely drug for bone calcium-loss disorders

A structurally simple benzothiophene derivative has shown promise in rat tests as a potential treatment for serious bone-related diseases. The compound, thionaphene-2-carboxylic acid (TNCA), has proven to be a potent inhibitor of the breakdown of bone tissue, which causes the release of calcium into the bloodstream. MacroChem Corp. of Woburn, Mass., which is developing the drug, plans to test its effectiveness in cancer patients suffering from hypercalcemia (excessive calcium in the blood). That condition, associated with malignancies of the breast and lung, sometimes kills the patient, rather than the cancer itself, says Carlos Samour, the firm's chairman and scientific director. TNCA also will be tested for effectiveness in the management of osteoporosis and osteoarthritis. Samour says that no fully satisfactory treatment exists for those diseases. (Source: Chemical and Engineering News, 17 February 1986)

Bacteria help to make vitamin C

A new process for making vitamin C (L-ascorbic acid) could soon replace today's lengthy and expensive method, which consists of five complicated chemical steps and one lengthy fermentation stage. The new process involves only one chemical step. The rest of the synthesis takes place in bacteria.

The unique feature of the process is that genes encoding for enzymes that promote two metabolic steps in the synthesis of ascorbic acid were

successfully combined in the same bacterium. The enzymes normally exist in separate organisms.

The host organism, Erwinia, is a harmless bacterium found in plants. It contains an enzyme that oxidises D-glucose into 2,5 di-keto-D-gluconic acid (2,5 DKG). Another bacterium, Corynebacterium, produces 2,5 DKG reductase which converts the 2,5 DKG to 2 keto-L-gluconic acid (2 KLG), the last intermediate in the chemical synthesis of L-ascorbic acid.

The researchers at Genentech embarked on this project after identifying and cloning the gene responsible for the production of the enzyme 2,5 DKG reductase in the Corynebacterium.

The market around the world for L-ascorbic acid is worth $400 million. To exploit it, Genentech and Lubrizol, a chemical company, have formed GLC Associates. Anderson says Genentech is considering developing similar techniques to produce other chemicals that are difficult and expensive to synthesise. A prime target, says Anderson, would be chiral molecules which have the same chemical formulae, but have their molecules arranged as mirror images of each other. Only one form is useful. Natural products like rose oil and caffeine are also good candidates for a similar process, because all the enzymes needed to make these products exist in bacteria.

But before commercialization there are some engineering problems to overcome. Pfizer Chemical, another large chemical company, will work with GLC Associates to scale up the process. (Extracted from New Scientist, 16 January 1986)

DNA fingerprinting

One of the first uses of the technique developed at the University of Leicester by Dr. Alec Jeffreys for telling the genetic identity of individuals by the use of gene probes is likely to be used in the control of immigration into Britain.

The issue is potentially contentious between the British Government and its immigrant population, because of the requirements of the new strict immigration law distinguishing between blood relatives of different affinity. What appears to have happened so far is that the Home Office and the Foreign Office are jointly sponsoring a pilot study at Leicester, but have not yet decided whether to mount an operational scheme for verifying claims of kinship.

The technique has already been used successfully in a number of disputed immigration cases, the first of them on the initiative of a solicitor (attorney) acting for the father of an immigrant boy whose kinship had been disputed. The solicitor had been alerted to the usefulness of the techniques by publicity following the publication of a paper last March. The first analysis proved the claim of kinship, but the Home Office withdrew from the case so that there is as yet no legal precedent in Britain for the use of evidence of this kind.

The use of DNA fingerprinting in immigration cases is likely to be more complicated than in common paternity cases because disputed kinships may centre on suspicions that an adult is seeking to pass off a nephew as a son. Because of the high frequency of common genes among siblings, it is therefore necessary to test for a greater number of restriction polymorphisms. Even so, it should be possible in routine cases to attain a precision of more than 99 per cent in cases of disputed kinship.

The Home Office emphasises that even if the technique is introduced on a regular basis in considering applications for immigration to Britain, this will be offered only on a voluntary basis. (Nothing is said of the fate of those who decline a blood sample.)

Whatever happens to the immigration project, the forensic use of the technique is likely to be widespread. The commercialization of Jeffrey's version of DNA fingerprinting is being exploited by the Lister Institute. (Extracted from Nature, Vol. 319, 19 January 1986)

'Synthetic' skin

A biodegradable dressing for ulcers, burns and other skin lesions is expected to be approved for tests on people within six months. It is applied like a bandage and is said to keep exposed tissue moist while acting as a barrier to bacteria.

Kendall (Boston), an arm of Colgate-Palmolive, has an exclusive option to license the dressing technology worldwide and has conducted animal tests that were extremely favourable. The dressing currently is in pilot-plant production, and Kendall has immediate plans to file with the US Food and Drug Administration for approval to conduct clinical trials.

The dressing is composed of three water-soluble biopolymers: keratin from sheep, chitosan from crab shell and collagen from cow hide. Keratin, the protein that makes skin waterproof, is used in the anionic form of ammonium keratinate. Chitosan, the deacylated form of the glucosaminoglycan chitin, is used as cationic chitosan acetate; while collagen, a fibrous protein in connective tissue, is used as cationic collagen acetate.

When mixed in water, the three biopolymers spontaneously form a water-insoluble, water-swellable solid mass. The initial attraction is believed to be ionic, but close juxtaposition of the biopolymers brings into play a variety of steric-fitting, chemical-bonding and cross-linking mechanisms. The result is a material having properties totally different from those of the individual components.

In its hydrated form (swollen with water), the dressing resembles a paste or putty and can be formed into membrane sheets. The dehydrated version, on the other hand, is a crystallite form of packed microfibrils. In either form, the dressing can be stored at room temperature in urethane bags or aluminum foil after sterilization - preferably, with ultraviolet radiation or ethylene oxide. It can be applied to wounds as a self-annealing paste or as a membrane 1.7 mils. thick.

The dressing can be modified with additives. For one, glycerine acts as a softener and increases flexibility. Other possibilities: antibiotics, antifungals, cells, antibodies, enzymes and pigments.

There are a number of advantages in using the dressing. It adheres to underlying tissue and is elastic. Moreover, it is permeable to oxygen, acts as a bacterial barrier and, while it is absorbent to wound exudates, it does not lose durability. Furthermore, the dressing does not require stripping. In later stages of wound healing it hardens into a protective scab that falls off naturally, without scarring.

Other potential uses for the material are as scar-tissue covering, sutures, sustained-release drug carriers and tube linings in bypass surgery.

It also could be used as a lining in prosthetic implants. (Extracted from Chemical Week, 19 March 1986)

Dental applications

Human tooth enamel could be used to fill tooth cavities, according to M. C. Slavkin of the University of Southern California. One of the four genes that control production of murine tooth enamel has been cloned, and cloning of the analogous human gene is expected soon. Once the remaining three genes are cloned, the product proteins could be mixed to form enamel. (Extracted from Medical World, 25 November 1985)

Repligen signs protein A deal

Repligen Corp. has signed a contract with Applied Immune Sciences (AIS) to supply and exclusively manufacture recombinant protein A.

AIS will use the gene-spliced bacterial cell wall component for therapeutic apheresis devices for blood plasma filtration, a technique which externally removes disease-causing antibodies and immune-complexes from a patient's blood.

In collaboration with Membtek Corp. of Woburn, Massachusetts, AIS has already developed devices with recombinant protein A immobilized on to membranes that allow for optimal binding to antigen-complexed antibodies. Protein A is a cell wall component of the bacterium Staphylococcus aureus which recognizes and binds to most human IgG complexes.

The therapeutic protein A membrane devices will be used to scavenge sufferers' blood without having to remove plasma. In addition to marketing the devices, AIS will use the technique to harvest and study disease-related marker molecules from patients' plasma. AIS will be responsible for seeking pre-market approvals from the FDA in the next six months.

Repligen will also be supplying AIS with other ligands that may be more specific than protein A. (Source: European Chemical News, 3 February 1986)

Immunex in partnership with Kodak

Eastman Kodak Co., Rochester, N.Y. has made another move into biotechnology by forming Immunology Ventures, a partnership with Immunex Corp., to develop lymphokines. The joint venture will work on B-cell growth factors and interleukin-1 manipulation, such as blocking interleukin-1β, which seems to be involved in the onset of such inflammatory autoimmune diseases as rheumatoid arthritis.

In the non-therapeutic area, Immunology Ventures will develop an affinity separation process for recombinant products. Additionally, Kodak and Cetus Corp., Emeryville, Calif., will jointly develop monoclonal-antibody and DNA-probe tests for physicians' offices and clinical laboratories. The diagnostics for common infectious diseases, cancer, pregnancy and fertility are targeted for mid-1987. (Extracted from McGraw Hill's Biotechnology Newswatch, 17 February 1986)

Heart drug venture set up

Sweden's Pharmacia and the California-based biotechnology concern Chiron have set up a joint venture to market human superoxide dismutase (Hsod), a potential heart drug. Hsod is an enzyme that protects tissues from damage when deprived of oxygen, a condition known as ischaemia commonly associated with strokes and organ transplants.

Pharmacia is to pay an undisclosed sum for Chiron's recombinant DNA technology for the cloning of the Hsod gene and related process engineering for the production of the enzyme in gene-spliced yeast cells. Chiron will retain manufacturing rights in the US for Hsod-based products. Pharmacia will also provide its animal-derived superoxide dismutase pharmacology results and the effects on perfusion in particular. Moreover, the Swedish company will provide regulatory and other pre-marketing assistance in the US and abroad. Furthermore, products from the joint venture will be distributed by Pharmacia in the UK, Japan and Scandinavia, although Grunenthal, the West German concern, will be responsible for marketing to customers within the EEC. (Extracted from European Chemical News, 17 February 1986)

Livestock applications

Trypanosomes resistance

Not all animals are equally susceptible to infection by trypanosomes. Many local game animals and certain breeds of cattle, notably the N'Dama of West Africa, are resistant. Researchers are investigating the genetic basis of this resistance and how it might be transferred to other species.

Some flies are resistant, too. In areas where almost all animals carry the trypanosomes, only 10 per cent of the tsetses are infected, and dissection shows that sometimes only 1 in 1,000 has a severe infection. Cross breeding susceptible and refractory strains shows that susceptibility is passed on only by the mother and not by normal inheritance. So Dr. Ian Maudlin looked at the cytoplasm that is passed on from the mother in egg cells. Electron micrographs reveal tiny bacteria resembling Rickettsia in the cytoplasm of tsetses susceptible to infection.

Dr. Ian Maudlin at the Langford Tsetse Laboratory suggests how the infection might increase the chance of trypanosomes becoming established. The rickettsia-like organisms (RLOs) cause the cells lining the gut to secrete more digestive enzymes which might break down complement, a protein produced in the blood of infected animals that is lethal to trypanosomes. Flies that secrete extra enzyme as a result of the bacterial infection inadvertently protect the trypanosomes.

The RLOs seem to be maintained in the fly population in spite of encouraging trypanosomes. The reason may lie in the observation that flies without the RLOs seem to suffer more abortions and dead larvae. This discovery could have important practical applications.

Already, Dr. Maudlin has a strain of susceptible "superflies" that are finding uses in laboratories wanting to grow and study trypanosomes. It might also make it possible to spot populations of potentially dangerous, susceptible flies in the field. In the longer term, refractory flies might be introduced after susceptible strains are eradicated, thus filling the ecological niche and preventing disease-carrying flies returning. Or, cattle might be vaccinated against the RLOs. Feeding flies would suck up antibodies which would attack the RLOs. So, to cure cattle and people of the parasite it may be necessary to cure flies of bacterial infection. (Source: New Scientist, 27 February 1986)

Approval for TK-free pig pseudorabies vaccine

The US Department of Agriculture has approved a gene-deleted pseudorabies vaccine. Novagene Inc., of Houston, Texas, removed the thymidine kinase (TK) gene from the virus that infects swine herds,

causing stillbirths and piglet death, a major problem in certain US states. TechAmerica Group of Elwood, Kansas, has produced the vaccine in their proprietary cell line. Initial field studies were encouraging.

Pseudorabies, a herpesvirus, is particularly lethal among pigs because it integrates into the genome of nerve cells. There it remains latent and difficult to detect until it reverts to an active form and causes periodic epidemics. A killed virus vaccine gives partial protection. A live virus, the Bucharest strain, gives better protection, but then it is effectively impossible to distinguish between pigs with recurrences of the live virus and those infected with a virulent variety. This is undesirable for disease control purposes. (Extracted from McGraw-Hill's Biotechnology Newswatch, 3 March 1986)

Interferon used against equine respiratory infections

Immuno Modulators Laboratories, Inc., (IML), Stafford, Texas, manufactures 'Equiferon', a non-recombinant α-interferon for prevention and treatment of viral respiratory infections in horses. It is a more concentrated formulation of IML's Agriferon-C, which has been sold in Texas since January of last year for protection of shipping fever in cattle.

Until recently Texas had a "unique law" under which the State health department could license the manufacture and use of such products within Texas, without federal approval.

First-year sales of the bovine interferon were $1 million, and the market is growing. IML concentrates on large feedlot owners, with up to 90,000 head, who pay $1.35 per dose. Agriferon-C is sold to veterinarians and the general public (in Texas only) through distributors, although IML provides technical field support directly to the farmers. Equiferon will be marketed solely to veterinarians, through ethical drug distributors.

In one study, 44 deliberately-infected control animals required 11.6 pounds of feed to produce one pound of calf, while 40 animals in the low-dose treatment group took only 8.6 pounds, according to Prof. Joe Cummins, Texas A&M, Amarillo. If the dose is increased the animals become worse. Anorexia is a common side effect. The benefit was apparently significant only in those calves that had less than 104°F fever. Cummins reported his results at the Bovine Practitioners Meeting in Buffalo, N.Y., in November 1985.

IML is asking the US Food and Drug Administration for approval to use interferon on horses and cows. (Source: McGraw-Hill's Biotechnology Newswatch, 3 March 1986)

Joint effort to prevent mastitis amongst dairy cattle

Eastman Chemicals and Molecular Genetics are consolidating their battle against mastitis in dairy herds. The two firms have contracted to develop and market a therapeutic monoclonal antibody to treat the disease.

A similar agreement for vaccine products to prevent *E. coli* mastitis is currently in operation between the Eastman Kodak division and the biotechnology company. Nevertheless, no effective therapeutic treatment is available for the bacterial disease which causes considerable economic loss. (Source: European Chemical News, 31 March 1986)

Hormones to improve animal fertility

Three animal fertility hormones, equine follicle stimulating hormone (eFSH), equine luteinizing hormone (eLH) and porcine follicle stimulating hormone (pFSH) are expected to have significant applications in increasing reproductive efficiency in horses and pigs. They have been produced through genetic engineering by Integrated Genetics (Framingham, Mass.). The equine hormones are to aid in breeding horses, the farm animal with the lowest reproductive efficiency. (Source: Chemical Week, 12 February 1986)

Vaccine for feline leukaemia

Phillips Petroleum and Cambridge Bioscience will jointly produce specific proteins for use in a vaccine for feline leukaemia virus (FeLV), using Phillips' proprietary rDNA technology. FeLV is a contagious retrovirus that causes cancer and immune suppression in cats. The new rDNA vaccine may protect cats from the virus. Under an existing agreement, Phillips will provide Cambridge with a faster, more economical route for producing the FeLV protein. Phillips' rDNA yeast expression method uses methanol-regulated promoters for the production of rDNA proteins. (Extracted from Chemical and Engineering News, 6 January 1986)

Agricultural applications

Cotton insecticide

Ecogen Inc. has signed a $7.2 million contract with PruTech Research and Development Partnership II to fund the US biotechnology company's development and commercialization of biological insecticides against budworm and bollworm, two major cotton crop pests known as the Heliothis complex. Based on genetically engineered improvements of the Heliothis insecticides produced naturally by Bacillus thuringiensis (BT), the new products are targeted to reach market by 1989-90.

Through the use of conjugative and recombinant genetic manipulations of its extensive library of novel BT strains, Ecogen's scientists will increase the BT toxin's potency to the same level as that of synthetic pyrethroids, which currently dominate the cotton pest market, while also lowering BT production costs to a level likely to be competitive with the pyrethroids. (Extracted from Biotechnology Bulletin, Vol. 4, No. 12, January 1986)

Viral insecticide against codling moth

MicroGeneSys, a biotechnology firm based in West Haven, Connecticut, is evaluating a viral insecticide in field trials that could help West Coast fruit farmers. The viral insecticide, Decyde, is being tested for the control of codling moth on apple, pear and walnut. The company infects larvae of the insect with the virus and then processes them into final formulations suitable for application by farmers. (Source: European Chemical News, 31 March 1986)

Monoclonal assays for plant fungal diseases

Developing monoclonal-antibody-based diagnostic kits that detect fungal diseases affecting field crops and horticultural specialities will be the aim of a co-operative effort between Ciba-Geigy and Agri-Diagnostics Associates (Cinnaminson, N.J.), a joint venture of DNA Plant Technology and Koppers. The assays are expected to provide accurate and

rapid diagnosis of significant plant diseases in major crops, making earlier intervention possible. Earlier this month, Agri-Diagnostics signed an exclusive agreement with O. M. Scott & Sons (Marysville, Ohio) to market a line of monoclonal-based diagnostic kits for fungal turfgrass diseases. The kits contain an easy-to-use dipstick format to allow diagnosis of such diseases as Pythium blight, brown patch or dollar spot. (Source: Chemical Week, 5 March 1986)

Encapsulation system

A proprietary encapsulation system which allows delicate somatic embryos to withstand the rigours of handling and field planting has been developed by Plant Genetics Inc. of Davis, California. The GEL-COAT capsule comes in two parts: a gel matrix which contains the components essential to control the germination of the embryo, adjuvants plus - potentially - a wide range of fungicides, herbicides or insecticides; and a protective polymer covering that prevents water loss, and also provides handling characteristics similar to a true seed.

Plant Genetics (PGI) took an early decision not to take the molecular biology route to plant biotechnology, but decided to concentrate on crop improvement by using cell biology rather than molecular biology. The privately-held company, which has filed more than 20 patent applications, has raised in excess of $12 million from venture capital groups and several small Japanese companies - including Kirin Brewery Co., which now owns a third of PGI. While the other Japanese investors are passive, the Kirin deal involved technology transfer agreements and the two companies have been working jointly to develop synthetic seeds.

Plant Genetics Inc. is using molecular biology techniques to identify and improve plant growth promoting rhizobacteria.

The company's existing products include disease-resistant alfalfa and bean-sized potato tubers (microtubers) produced by tissue culture. This approach permits one rare high quality potato to be cloned into thousands of super-specimens. These can be planted without being cut into pieces, as is the usual practice, which makes these potatoes less susceptible to disease attack once in the soil. On the disease-resistance front, too, PGI is working on such diseases and disease vectors as Fusarium wilt, stem nematodes, Phythophthora root rot, aphids and anthracnose. (Biotechnology Bulletin, Vol. 4, No. 12, January 1986)

Pollution curbs will lift biopesticides

The widespread use of agrochemicals has allowed man unprecedented control over pests, and contributed towards today's high agricultural productivity. This is reflected in the fact that Europe is, for the first time, a food exporter and has built up extensive reserves of grain and other produce.

The use of biological agents in the control of agricultural pests has become more popular in recent years, in reaction to the well known problems experienced with chemical pesticides. The possible dangers associated with the production of agrochemicals have been highlighted recently after the inadvertent release of toxic intermediates at Bhopal and elsewhere.

The agrochemical industry has faced a number of difficulties since the introduction and widespread use of synthetic pesticides. Not least of these is the potentially toxic effects on man and the environment, and the rapid development of resistance in the target pest.

Increasing pressures from environmental groups and regulatory agencies have led to the banning of certain chemical pesticides, especially chlorinated hydrocarbons such as DDT. Economic considerations, such as escalating production costs and extensive toxicological testing, together with the potential environmental hazards, have hastened the search for other methods of pest control.

Interest is turning to non-chemical pesticides, such as agrobiologicals. While the specificity of microbial pesticides leads to a small market for individual products, the significantly lower cost of R&D and safety testing has made these products a realistic commercial possibility. Estimated sales of microbial pesticides are $30-40 million/year, the majority of which is Bacillus thuringiensis.

The microbial control of insects is not new. Classical biological control is the introduction of a wholly novel organism into an isolated or new geographical area to control a pest. Ideally, this organism should be host-seeking, host-specific, self-perpetuating and density-dependent.

Unfortunately, the result of introducing organisms into a foreign environment is not always predictable.

Herbicides, fungicides and insecticides have benefited farmers, but they have also hurt them. Pesticides can kill the natural enemies of pests more effectively than they kill the pests themselves and have nasty side effects as well. Up to 10,000 people a year die from pesticide poisoning in the third world alone. Chemical solutions are expensive. Those that come from fossil fuels cost a small fortune to develop. Third world countries spend huge sums subsidising their use. In Egypt, for instance, agrochemical subsidies work out at an annual $5 a head. Recently, the pace of agrochemical invention has slowed, while the evolution of resistance has accelerated. In the 1940s, the United States lost 7 per cent of its agricultural crops to insects. Today, it loses about 13 per cent.

Genes inserted into plants have already made them resistant to caterpillars and viral disease. Genes that make them resistant to fungal, bacterial and nematode disease will soon follow. Eventually farmers will be able to buy resistant seed and grow crops without insecticide or fungicide. This will save the farmer money, reduce his risk of getting cancer and make the crops' safe for his neighbour's honey bees. His wheat plants will automatically poison every aphid that sinks its proboscis into them, while the nettles in the hedgerow will still nourish all those gracious painted-lady butterflies.

The chemical companies in the forefront of this effort are in it for the money. One of the first genes they inserted confers immunity to herbicides, which enables the farmer to spray the growing crop and kill weeds but not crop plants. This, of course, promises to boost the sales and profits of herbicides. But that will soon be balanced by biotechnology firms. One of these companies is developing strains of bacteria to break down agrochemicals in the soil. Others are at work on the diseases of plants and insects, so that deliberate plagues can be spread among weeds and pests.

Failures are certain. So are unforeseen dangers. But the risks are smaller than they are with the two previous tools at the disposal of agricultural science: chemicals and hybridization. To breed a new hybrid plant in the old-fashioned way, you throw together random combinations of genes. To invent an agrochemical, you throw thousands of chemicals at nature in the minuscule

hope of finding one that kills insects or weeds and not human beings. DDT and Agent Orange have been two of the more lethal results of that process.

Biological control as a component of integrated pest management includes the use of biological chemicals. Much interest in the agrochemical industry centres on discovering and characterizing the molecular structure of such active compounds as starting points for new chemical synthesis.

Microbial pesticides differ from biological chemicals in that they contain life micro-organisms. Like chemical pesticides, they must be applied repeatedly, either by inundation (large numbers of organisms applied over a short period of time) or augmentation (supplementing the existing natural population). They have been developed and formulated so that they can be applied directly to crops.

Insect pathogenic micro-organisms have been known for many years and include a variety of bacteria, fungi and viruses. The list of agrobiologicals currently registered for use is small, but is likely to increase over the next few years following the upsurge of interest by companies such as Abbott, Sandoz and Monsanto, and the establishment of new, more specialized companies, like Ecogen, Mycogen and Microbial Resources.

Although over 100 species of bacteria which infect insects have been described, at present there are commercial products based on only two of these. Bacillus thuringiensis (Bt), a sporulating bacterium that produces a toxic crystalline protein, is active against many lepidopterous insects (caterpillars); B. popilliae is active in the control of Japanese beetles and related species.

Two other bacteria, B. sphaericus and B. penetrans are considered promising for the control of mosquitoes and root-knot nematodes, respectively. However, both have only been used experimentally to date.

Although Bt was discovered in the early part of this century and has been available as a commercial product since 1938, the mechanism of its toxic action has only recently begun to be understood. The toxin, in the form of a proteinaceous crystal, is insecticidal after ingestion and subsequent dissolution in the alkaline environment of the mid-gut of susceptible insects. Ion transport is inhibited, leading to a cessation of feeding and eventual death. Analysis of the genes encoding the toxic proteins started in the late 1970s and is now revealing much about the genetic and biochemical properties of this toxin.

The nature and potency of the toxin crystals varies amongst bacterial serotypes. The two commercially available strains are Kurstaki - available from Microbial Resources as Biobit and used in the control of caterpillars, and Bt H-14, marketed as Skeetal, which is an effective destroyer of mosquitoes and blackfly - the insect vectors of malaria and river blindness.

Although microbial pesticides have many attractive properties in environmental terms, their commercialization has, in the past, been impaired by process development and product formulation capabilities. Innovations in biotechnology have allowed companies to improve fermentation, process control and downstream processing.

Together with strain development, these improvements have, over the last few years, reduced costs by at least 30 per cent. Innovative process steps, presently at the large-scale testing stage, should result in further substantial reductions.

Bt, for example, is produced in liquid fermentation and then concentrated and formulated into a variety of liquid and powder forms, formulation being crucial to the commercial success of any product. Microbial Resources has improved both stability and delivery of Bt products. The shelf life of unformulated Bt H-14 is only a few days at 42°C; when it is formulated into Skeetal the shelf life is 15 months at this temperature.

Perhaps more impressive is the formulation of fungal products based on Verticillium, which extends the refrigerated shelf life of these normally temperature-sensitive spores from two weeks to 11 months. In response to current market demands, Microbial Resources is concentrating much of its R&D effort towards improving formulation and process development.

Other companies specializing in agrobiologicals are adopting a slightly different approach. Their efforts are centred on the genetics of potential microbial pesticides and the use of genetic manipulation to provide novel recombinant micro-organisms and plants.

Monsanto has put Bt toxin into a micro-organism native to the rhizosphere where it can multiply as the plant grows, providing continuous protection. Plant Genetic Systems is reported to have killed caterpillars with Bt toxin expressed from a tobacco plant. A third company, Mycogen, has received environmental protection agency approval to test killed pseudomonads as a biological delivery system for Bt toxins.

Fungi have several advantages as microbial pesticides, such as their ability to sporulate on dead host bodies, thereby spreading through the entire population; and their ability to act without being ingested. Although fungi have fairly stringent humidity and temperature needs to be effective, they are showing great promise as economically feasible methods.

In 1981, the first two fungal insecticides were approved for sale in the West: Mycar (Hirsutella thompsonii) from Abbott Laboratories, and Vertalec (Verticillium lecanii), from Microbial Resources. Mycar is used in the control of citrus mite in Florida, while Vertalec is extremely pathogenic to most glasshouse aphids.

In 1983, another Verticillium product, Mycotal, was introduced. This incorporates a smaller spored strain selected for its high infectivity towards an important whitefly pest in glasshouses. Both Verticillium products were developed by the UK glasshouse crops research institute together with the agricultural development and advisory service, and were commercialized following collaboration with Microbial Resources.

Other products based on fungi include Metarhizium anisopliae, successfully commercialized in Brazil for the control of spittle-bug in sugar cane and pastures; Beauveria bassiana, produced in the USSR to control Colorado beetle; and Nomurea rileyii, not commercialized, but researched for many years in collaboration with Abbott Laboratories for use against caterpillar infestation in soya beans.

Although the genetics of fungi used in the pharmaceutical and food industries have been well studied, relatively little is known about fungi in pest control. It is not understood why one strain of an entomopathogen generates a successful epizootic (epidemic killer of a pest population) while another, equally pathogenic strain, does not.

Future development of successful fungal products for insect control rests as much with the

geneticists, biochemists, physiologists and ecologists, as with the fermentation and formulation specialists. Scientists at King's College, London, working with Microbial Resources, are undertaking research which should lead to a better understanding of some of these problems and improve products.

Several products of viral origin also exist. Elcar, although no longer generally available, has been used successfully in the control of cotton pests. Gypchek has been used in the US for the control of gypsy moth. Virox, a product developed by the MRC institute of virology, Oxford, UK, was commercialized in collaboration with Microbial Resources.

This product contains active viral particles of nuclear polyhedrosis virus which attack the larvae of pine sawfly, a chronic defoliator of Scot's pine and Lodgepole pine. Like bacterial products, Virox must be ingested to be effective, but because of the gregarious nature of the larvae, the disease spreads rapidly, leading to a total collapse of the insect population within two to three weeks.

Virox is highly specific to pine sawfly; even closely-related sawfly species are not affected. Furthermore, extensive safety testing carried out by the US forestry service has shown Virox to be completely harmless to non-target wildlife.

The use of Virox in pest control of forests has been successfully demonstrated. Over the last two years, following approval from the UK pesticide safety precaution scheme, the UK forestry commission has co-ordinated the application of Virox to over 6,500 hectares of Scottish pine plantation. Pest mortality was 100 per cent. This product has also received EPA approval for use in the US.

Many more viruses known to be active against insects could be commercialized. However, the present requirements for viruses to be produced in living insects or cell cultures restricts the cost-effective production of many potential viral insecticides. This problem may be overcome by further advances in biotechnology.

It has been widely demonstrated that microbial pesticides can provide realistic alternatives to synthetic chemicals. Over the past few years, new products have been introduced which exploit the ability of bacteria viruses and fungi to selectively attack certain insects, weeds and pathogens; the demand for agrobiologicals is expected to grow rapidly.

Agrobiologicals are attractive in environmental terms, and are less likely to disturb nature's fragile ecological balance. For example, EPA approval has been granted for the use of Skeetal in mosquito control programmes in the wetlands of Florida and Louisiana where agrochemical usage could have caused pollution. The problem of pest resistance to agrochemicals is leading to increased demand for biological methods of pest control. To date, field resistance to microbial pesticides has not developed.

Microbial Resources, in collaboration with scientists from research institutes and universities, is currently undertaking research aimed at improving the identification and characterization of new pest control organisms, as well as extending the understanding of the genetic basis of their pesticidal properties. However, experts suggest that finding (or creating) novel micro-organisms for use as agrobiologicals will be considerably easier than the manufacture, formulation, registration and marketing of these products. (Source: ECN Fertilizers & Agrochemicals Supplement, February 1986 and The Economist, 12 April 1986)

Food production and processing

Lower-cost method to make L-aspartic acid

Japan's Mitsubishi Petrochemical Co. will begin in the fall to make L-aspartic acid by a fermentation technique that uses the micro-organism Brevibacterium flavum. The amino acid is made from fumaric acid and ammonia by an enzymic reaction that can be induced by a number of bacteria. Escherichia coli, the bacterium usually used, has a weak cell structure that must be protected by immobilizing the bacterium on a solid support if the micro-organisms are to be recycled. B. flavum, on the other hand, has a hard cell wall that can withstand repeated centrifugations without the need for expensive immobilization. Thus, Mitsubishi expects its new technology to lower the cost of L-aspartic acid production. Capacity will be 1,000 tons per year. (Source: Chemical & Engineering News, 24 February 1986)

Energy and environmental applications

Anti-pollution microbes

A team of Japanese scientists at the microbiological engineering research laboratory of the Japanese Ministry of International Trade and Industry is perfecting a genetically engineered microbe that can degrade polychlorinated biphenyls (PCBs). A set of four genes capable of breaking down these troublesome pollutants have been isolated by the team, led by K. Yoshikawa, from the simple soil bacterium Pseudomonas. Together the genes produce enzymes which degrade PCBs to chlorobenzoic acid. Individually, the genes are very different, but they are close together on the bacterium's genetic material and so operate under a uniform system of regulation. Three of the genes have already been cloned in Escherichia coli.

The next step is to identify a host organism for the gene system which could degrade the PCBs still further, providing a complete biological depollution system.

A biological system capable of destroying PCBs would be an important breakthrough: the present method of disposal by incineration is costly and inefficient. Moreover, when incinerated, PCBs can generate dioxins, which have been linked with birth defects in humans and livestock. (Source: New Scientist, 6 February 1986)

Green plants to be used to treat sewage

A municipal sewage treatment approach that could substantially reduce capital investment and operating costs by using growing plants to remove water pollutants will be tested in a pilot-scale facility this spring. William J. Jewell, an agricultural engineer at Cornell University, will set up such a system at the Ithaca, N.Y., municipal sewage treatment facility under the sponsorship of the Gas Research Institute in Chicago and the New York State Energy Research & Development Authority. The test facility will operate for two years, handling 10,000 gallons of sewage per day. In it, a thin "film" of wastewater is directed at the roots of plants growing in watertight troughs similar to gutters. No other nutrients are needed to grow the plants, and the plants' extensive root systems filter pollutants from the water as effectively as conventional chemical sewage treatment. Moreover,

the plant-based system could cost half as much as conventional chemical sewage treatment. Jewell has used many common plants in his system, such as cattails, bullrushes, roses, geraniums and cucumbers. (Source: Chemical & Engineering News, 13 January 1986)

Biocatalyst carriers for waste-eating microbes

A pilot test unit to treat hazardous and toxic organic wastes by immobilizing micro-organisms on inorganic biocatalyst carriers is the subject of an agreement between Manville Filtration and Minerals (Forest Hills, N.Y.) and Louisiana State University (LSU). The two will use a skid-mounted pilot unit to detoxify chlorinated hydrocarbons and other compounds in waste streams under operating conditions at industrial sites. The microbe treatment is expected to have lower operating and capital costs than other methods. In its own independent tests, LSU found that immobilized micro-organisms can reduce toxin levels from 100 parts per million (ppm) to 1 ppm or less. Manville biocatalyst carriers are made of rigid, inorganic materials said to have thermal and chemical stability, mechanical strength and microbial resistance. The carriers are said to be easily sterilized. (Source: Chemical Week, 26 February 1986)

Extraction industry applications

Algae recover gold and uranium

Work by scientists at New Mexico State University shows that some species of algae absorb gold and that other types will extract uranium ions from waste water in uranium mills.

Scientists have known for some time that green or blue-green algae can absorb charged atoms (ions) of metals such as lead, zinc, cadmium, copper, mercury and platinum. However, according to the team, led by Dr. Benjamin Greene, at New Mexico State University, some algae, especially the chlorella variety, hang on to gold more tenaciously than to other metals.

In the right conditions of acidity and salt concentration, the algae will release the gold in preference to whatever other metals they have absorbed. Greene's group believes that these characteristics mean that algae could be harnessed to recover gold.

Various chemical groups on the surface of the algae pick up the gold ions in a process known as biosorption. The gold is removed from the algae by adding other chemicals, such as cyanide and thiourea, that attract gold. If the ions are left in the algae, the organisms convert the ions to the neutral metal. According to Greene's team, this trait suggests that algae may play a part in the formation of natural gold deposits.

The groups tested the algae's goldmining talents by passing a dilute solution of gold ions through a column containing algae attached to silica gel. The gold was extracted from the algae by passing a solution of thiourea through the column. (Source: New Scientist, 16 January 1986)

Industrial microbiology

Enzyme demand growth shows signs of slowing down

The worldwide market for industrial enzymes has been assessed at between $150-330 million for food use and over $500 million for bulk use explains W. G. Northcroft of Northcroft & Hay. These figures exclude the use of very pure specific enzymes for medical use and detergent enzymes.

The manufacturers' sales value for enzymes for food purposes is estimated at $260 million, excluding Eastern bloc countries. This total is not particularly large when compared with other biochemical products.

Although the use of enzymes has increased rapidly and there are some exciting developments in the technology for immobilization and production of ever more active and specific enzymes, growth in sales is slowing down. About 16 enzymes account for 99 per cent of all bulk industrial enzymes. The main enzymes groups for food use are probably no more than 10.

Enzymes seldom represent more than 1 per cent of a food product's factory gate cost. Market growth cannot come from increased usage levels, but only from growth in the basic food market sector itself. Sometimes, as is the case of rennet for cheese manufacture, the market growth exceeds the traditional rate of supply of the enzyme and new sources have to be found. Sometimes, as in the case of fructose syrup production, a market takes off allowing totally new technology to be developed (such as immobilized enzymes).

The main world growth in the use of food enzymes has been in starch processing, particularly high fructose corn syrups in the US. These syrups are of relatively minor importance in the EEC due to production quotas. Wine, dairy, brewing and baking uses have shown steady worldwide growth of about 5 per cent/year.

Microbial rennin is particularly interesting because supplies of animal rennin are limited by the demand for veal, which is declining, and other sources have to be found. Undoubtedly in time the performance of the microbial product will be the same as that of rennet, although there is currently a difference in quality, by no means always adverse, for most applications.

The enzyme industry is dominated by the major European producers, Novo and Gist-brocades, and the Bayer subsidiary Miles Laboratories. Nearly half of the world sales of food enzymes are in Europe with the major uses being for starches, glucose syrups (not fructose syrups) and dairy products. (Extracted from European Chemical News, 31 March 1986)

Potential growth areas for enzymes and micro-organisms

Food Sector	Enzymes	Yeasts and micro-organisms
Cereals	Immobilized amyloglucosidase, glucose isomerase	Dried yeast to replace compressed baker's yeast
Dairy	Microbial rennin for cheese	Use of new organisms to extend the range of low fat yoghurts and cheeses
Meat and fish	*	Use of new Pediococci spp to extend the product range
Snack foods	*	*
Confectionery	*	*

Food Sector	Enzymes	Yeasts and micro-organisms
Plants and micro-organisms	Genetically modified organisms to find new cellulases	Use of Fusarium graminearum for mycoprotein production (a new enzyme source)
Texture and flavour	Flavour enhancement	Gums for highly aerated desserts and ice cream
Alcoholic drinks	Standardized wine and beer starter cultures	Genetically engineered yeasts
Soft Drinks	Increasing use of cellulases for fruit juice production	*

* No particularly novel developments, or inappropriate category

Industrial equipment

Biosensor development

Biosensor development worldwide owes much to a decade of research by Dr. Isao Karube and Dr. Shuichi Suzuki at the Tokyo Institute of Technology. Dr. Karube and his group, in co-operation with Seiko Electronic Industries, have built a sensor which can locate pathogens in the blood using a quartz oscillator attached to an antibody.

If the tip of the sensor is put in a solution containing the right pathogen the immune reaction occurs, causing a minute amount of reaction product to stick on the device. The sensor becomes heavier and the frequency of oscillations changes. The change reflects the concentration of the pathogen present. The sensors could, in theory, be built to detect any kind of pathogen, so specific are antibodies. They promise to be cheaper than conventional tests, which use costly radioactive and fluorescent techniques.

Kirin Beer, Japan's leading brewery, and Dr. Karube's team have together developed a biosensor to measure the concentration of alcohol during fermentation. An enzyme, alcohol oxidase, is immobilized on to an acetyl cellulose fluororesin membrane containing pores about half a micron in diameter. When alcohol molecules enter the membrane, the enzyme causes them to react with oxygen, a process called oxidation. Oxygen consumption is detected and converted to an electrical signal in an adjacent platinum electrode. The current generated gives the concentration.

Earlier alcohol sensors were inadequate, because the enzyme reacted with glucose and organic acids (e.g., vinegar) in the fermentation liquid. The new membrane is highly selective, allowing only molecules of vaporized alcohol to penetrate to the enzyme. Durability is the problem. Dr. Karube and his team are looking for a way to extend the life of the sensor beyond the two to three months of their prototype. (Extracted from The Economist, 25 January 1986)

ECM coated dishes reduce the time interval required for prenatal diagnosis

Prenatal diagnosis through amniocentesis represents one of the most important advances yet attained in the prevention of the birth of infants with irreparable genetic disorders. Amniotic fluid samples containing enough viable cells for culture and further cytogenetic and biochemical analysis cannot usually be obtained prior to the sixteenth week of pregnancy. The average culture time necessary to grow a sufficient number of cells for chromosomal analysis is in most instances about 3 weeks. If biochemical studies are necessary, the time needed is in the range of 5 to 7 weeks. It has therefore been the aim of continuous efforts to minimize the time interval between amniocentesis and diagnosis of the cultured cells in order to enable an earlier termination of pregnancy whenever an affected fetus is diagnosed.

A major limitation of conventional tissue culture techniques is that cells, in contrast to the in vivo situation, proliferate in vitro as a collection of individual cells, resting on plastic rather than on a basal lamina or within a tissue matrix.

In a search for an appropriate tissue culture substrate it has been found that cultured endothelial cells secrete on top of the plastic surface large amounts of extracellular matrix (ECM) similar in organization and chemical composition to naturally occurring basal laminas, upon which cells migrate, proliferate, and differentiate in vivo.

Recently it has been shown that cells of various origins, when plated on ECM, undergo dramatic changes in their rates of adhesion, morphological appearance and growth characteristics. These changes were not observed when the same cells were seeded on regular culture dishes, whether coated or not with poly-L-lysine, fibronectin, or each of the collagen types found in the ECM. The ECM does not function merely as an inert structural support, but rather, plays an active role in the control of cell growth and differentiation possibly via modulation of cell shape and orientation, to make it more responsive to physiologically occurring hormones and growth factors.

Because viable human amniotic fluid cells are available only at clonal densities, the provision of optimal culture conditions and particularly of a proper substrate such as ECM is critical for this type of cells as compared to cells seeded at higher densities. Recently it has been demonstrated that plating of human amniotic fluid cells on ECM improves by three to five-fold their plating efficiency and rate of proliferation leading in most cases to a significant reduction, ranging from two to eight days, in the time interval from amniocentesis to the first harvest of cells for chromosomal analysis.

An even greater effect was observed with cells that failed to attach to plastic surfaces and remained floating in the medium. Plating of these cells on ECM induced cell attachment and subsequent proliferation and yielded a sufficient number of colonies for chromosomal analysis. This result might be of critical importance in those cases in which a repeat tap would be indicated because of failure in cell attachment and growth. It was also found that in cases when a second harvest of cells was needed, the cells left on ECM after the first trypsinization yielded colonies ready for karyotyping in less than half the time required for cells maintained on plastic. The ECM induced stimulation of cell attachment and growth was not associated with any chromosomal aberration nor did it interfere with the handling procedure. Cell plating on ECM has been shown to provide a means of reducing the serum requirement of cultured cells. As shown in Fig. 1, human amniotic fluid cells maintained on ECM exhibited a markedly reduced serum requirement while retaining a sufficiently high

growth rate. This may not only reduce the costs of prenatal diagnosis but could minimize the variability in cell growth and serum induced toxicity encountered with different lots of fetal calf serum.

The main clinical advantage to be gained from cell plating on ECM applies to: (a) cases which show a very slow or no cell attachment and proliferation on plastic so that a chromosomal analysis is either not possible or requires an exceedingly long time interval, and (b) for enzymatic studies requiring large quantities of cells.

For further information contact: IBT, International Bio-Technologies Ltd., Kiryat Hadassah, P.O.B. 12000, Jerusalem 91120.

E. PATENTS AND INTELLECTUAL PROPERTY ISSUES

tPA patent dispute

Genentech, the San Francisco-based genetic engineering firm has announced that it plans to file a suit in the UK against Burroughs Wellcome for patent infringement. At stake is Genentech's recently-awarded UK patent on tissue plasminogen activator and the gene-splicing methods for making it.

The British patent office awarded the patent to Genentech at the end of February, prompting Wellcome to apply for revocation. The UK pharmaceutical company did not think the US firm would succeed in its application. So far details of the suit have not been revealed.

Genentech is confident in the strength of its UK patent and claims that the threatened suit demonstrates the firm's determination to defend its research efforts. Genentech already has been awarded patents for Activase in 10 other countries and the product is currently under clinical trials in the US and Europe for blood clotting diseases, and in preclinical tests in Japan. (Extracted from European Chemical News, 10 March 1986)

US drug firms dominate biotechnology patents

Although the small biotechnology companies that started up during the past decade still gain most of the publicity, it is the large, established pharmaceutical companies that continue to dominate biotechnology-related patent activity in the US, according to Omec International, a Washington, DC, consulting firm. Omec's analysis of patents issued in 1985 in the biotechnology field also show 25 corporations broadening their share of the patent picture at the expense of foreign concerns. US universities, too, are gaining an increasing number of patents.

According to Omec, the US Patent and Trademark Office issued a total of 1,078 biotechnology-related patents in 1985, compared with 1,114 in 1984 and 1,018 in 1983. US companies, universities, organizations, or individuals accounted for 640 of them, compared with 663 in 1984 and 562 the year before that. Of the US total, 489 patents went to corporations, well up from 441 a year earlier and 400 in 1983. US universities were awarded 86 of the patents, up from 1983's 68 but below the 95 in 1984. The largest number of patents went to major pharmaceutical houses. Eli Lilly led all firms with 28 last year, followed by Miles Laboratories with 19, Boehringer Mannheim with 14, Merck with 13, and Pfizer with 12. Of 32 firms receiving five or more biotechnology-related patents in 1985, only four were small biotechnology operations. (Extracted from Chemical and Engineering News, 24 February 1986)

Cetus interleukin-2 patent

Cetus Corp. has been awarded a third interleukin-2 patent by the US patent and trademark office. The new patent is the first to cover both highly purified native and analogue forms of gene-spliced interleukin-2.

Cetus is now in a position to prevent others from marketing genetically engineered native analogue forms of interleukin-2. The patent covers a purification technology called reverse phase high-performance liquid chromatography for removing contaminants such as pyrogens and endotoxins. The company is currently the only holder of US patents for interleukin-2 and has several others pending. Cetus is supplying its highly pure analogue form of interleukin-2 for more than thirty human studies in the US currently involving more than 500 patients.

Cetus also has a patent for a hybrid protein of alpha and beta interferon. (Source: European Chemical News, 24 February 1986)

AIDS diagnostic patent

Technogenetics' Italian subsidiary has filed a patent in Italy for a new diagnostic test that will provide an earlier warning for AIDS sufferers. The test detects the presence of immunoglobulin M. Conventional AIDS kits pick up the presence of immunoglobulin G but IgM appears first in AIDS sufferers. (Source: European Chemical News, 10 February 1986)

F. BIO-INFORMATICS

Conference room papers presented at the Workshop on Biotechnology and Industrial Commodities held at Trieste, Italy, 3-7 March 1986:

Number	Title
CRP.1	Proposed Research Programme for ICGEB by Julian E. Davies.
CRP.2	Screening for New Pharmaceuticals by Arnold L. Demain.
CRP.3	Biochemistry, Genetics and Technology of Extremophilic Microorganisms by Angelo Fontana.
CRP.4	Ethanol: Resource Base and Technology by Tarun K. Ghose.
CRP.5	Protein Crystallography and Needs of Developing Countries by Wim. G. J. Hol.
CRP.6	Production of Rotavirus Neutralization Antigen and Other Proteins of Pharmacological Interest by the Use of a SK-Virus Based Shuttle Vector by C. Milanesi.
CRP.7	Algal Slimes as Potential Soil Conditioners in Desert and Semi-Arid Regions by Terence J. Painter.
CRP.8	Recommendations for Research Programmes at the ICGEB in the Fields of: Single Cell Protein, Waste Fermentation, Methylotrophic Bacteria by Hartmut Voelskow.
CRP.9	Use of Oligonucleotide Probes for Diagnostic Purposes by R. Bruce Wallace.
CRP.10	Possible Research Directions to be conducted at the ICGEB by Alexander M. Klibanov.

CRP.11 Protein Engineering a Protein by Anthony Kossiakoff.

CRP.12 Recommendations for a Research Program on Industrially Useful Microbial Polysaccharides by Morey E. Sloaki.

CRP.13 An Update on Penicillin Acylases: Their Genes, Structures, Functions and Commercial Application by Vladimir Glisin.

CRP.14 Research on Development and Use of Enzyme-Based Bioreactors by David A. Jackson.

CRP.15 Research Recommendations: ICGEB by David Gutnick.

CRP.16 Recommendations for Research at the ICGEB in Trieste, Italy, by James H. Mende.

CRP.17 Recommendations by Tarun K. Ghose.

CRP.18 Recommendations for Research at ICGEB by Sidney Pestka.

CRP.19 Recommendations and Suggestions by P. Valenzuela.

CRP.20 Proposed Programme for the Design of Biologically Active Peptides by E. T. Kaiser.

CRP.21 and CRP.21/Rev.1. Draft Report.

Biotechnology: Principles and Applications, edited by I. J. Higgins, D. J. Best and J. Jones of the Cranfield Institute of Technology's Biotechnology Centre. The book contains chapters contributed by specialists on the applications of biotechnology in such fields as medicine, agriculture, food and drink, energy, chemicals and the environment. The 422-page book is priced at £32.50 (cloth) or £16.50 (paper). Details from: Blackwell Scientific Publications, Osney Mead, Oxford OX2 0EL. (Extracted from Biotechnology Bulletin, Vol. 5, No. 2, March 1986)

Genetics in Aquaculture. (Proceedings of an International Symposium held in University College, Galway, Ireland, 20 March - 2 April 1982, edited by N. P. Wilkins, Faculty of Science, National University of Ireland, University College, Galway, and K. M. Gosling, Department of Biology, Regional Technical College, Galway, Ireland and published by Elsevier Science Publications, price approximately $80).

This book is an up-to-date review of all the major aspects of genetics applied to aquaculture, and comprises papers on such topics as population genetics, genetic markers, hybrids and hybridisation, quantitative genetics, inbreeding, sex reversal, cytogenetics and domestication. Progress in these areas is also assessed in the reports of three workshop sessions devoted to genetic research in fishes, molluscs and crustaceans. Each topic is introduced by a major review paper presented by an invited author.

The book provides a broad overview of recent developments in this rapidly expanding field, that will be useful not only to geneticists entering the field but also to aquaculturists, physiologists and others with academic or commercial interest in cultivable aquatic organisms.

NiCIS newsletter launched

Ever since the Report of the Joint Committee (Spinks Committee) on Biotechnology in 1980, the UK Department of Trade and Industry has been concerned to make the unique resources of the National Culture Collections more available to industry. The decision to set up the Microbial Culture Information Services (MiCIS) was taken in June 1984. Subscribers to MiCIS will be able to search the computerised data-base for the source of a known organism; the known properties of a known organism; and for unknown organisms displaying particular combinations of properties.

MiCIS News will be published quarterly and will be sent to those who have expressed an interest in becoming MiCIS subscribers. Details from: Mrs. Geraldine Allinson, Laboratory of the Government Chemist, Cornwall House, Waterloo Road, London SE1 8XY or on 01-211 8834. (Extracted from Biotechnology Bulletin, Vol. 4, No. 12, January 1986)

Computer aided chemistry

Today's computers are the key to designing tomorrow's molecules, according to a new report from Technical Insights Inc. called Computer-Aided Chemistry: New Routes to Tomorrow's Drugs and Chemicals. The report explains how computer graphics not only open the way to understanding basic mechanisms in biological systems, but also allow the tailoring of molecules that control and modulate such mechanisms. Among the existing users covered are: Du Pont, where research work includes computer modelling studies of extended beta-sheet structures found in proteins; G. D. Searle & Co., where scientists are using computer graphics for generation of DNA opened double-strand confirmations for intercalation (docking) studies; and the Institute of Cancer Research, where a comprehensive molecular modelling programme, MOLEC5, is being used for the modeling of anti-cancer drugs. Details of the report, priced at $675.00, from: Technical Insights Inc., P.O. Box 1304, Ft. Lee, NJ 07024, USA.

C. MEETINGS

Conferences, Courses, Meetings

Chemical Aspects of Biotechnology, 5-7 May at the National Bureau of Standards, Gaithersburg, Md. The Gaithersburg Holiday Inn will be the headquarters hotel for the conference. Details: Kathy C. Stang, National Bureau of Standards, A353 Physics Bldg., Gaithersburg, Md. 20899, telephone (301) 921-2255.

13-15 May 1986. Biotech '86 Europe. To be held at Wembley, London. Details from: Nicky Cross, Online ernational, Pinner Green House, Ash Hill Drive, Pinner, Middlesex HA5 2AE, UK. Telephone: 01-868 4466. Telex: 923498 ONLINE G.

13-16 May. 8th Symposium on Biotechnology for Fuels and Chemicals, Gatlinburg, TN. Info: Charles D. Scott, Oak Ridge National Laboratory, P.O. Box X, Oak Ridge, TN 37831.

21 May 1986. Engineering developments in the pharmaceutical and biological industries. This one-day symposium of industrially-based papers will be held at the Excelsior Hotel, Manchester Airport and should be of interest to operational, design and research staff in the process industries. Papers will cover fermentation of recombinant organisms, sterile engineering, robotics in drugs production, microwave drying, building design, measurement of flow properties of pharmaceutical powders. Further details from D. V. Greenwood, Symposium organizer, 45 Hadrian Way, Sandiway, Northwich, Cheshire CW8 2JY, UK; telephone (0606) 888238.

Biotechnology: Perspectives, policies and issues. University of Florida, Gainesville, Florida, 2-4 June 1986. For further information contact: Ms. Lonie Breese, Symposium Co-ordinator, IFAS,

University of Florida, Building 106, Gainesville, Florida 32611. (904/392-7283).

9-12 June 1986. 30th Annual Meeting of the Wind River Conference on Genetic Exchange, Wind River Ranch, Estes Park, Colorado, USA. For further information: Kenneth F. Bott, Department of Microbiology 2318, University of North Carolina Medical School, Chapel Hill, N.C. 27514, USA.

12-14 June 1986. Second international symposium on the role of micro-nutrients in agriculture, Toulouse, Southern France. Details from: ISAMM asbl, 327 Avenue Louise, 1000 Brussels, Belgium or BMS Micro-Nutrients, Frankrijklei 65, 2000 Antwerp, Belgium. Telephone: 03-233 91 92. Telex: 34660.

16-19 June. 3rd International Conference on Biotechnology in the Pulp and Paper Industry. Stockholm, Sweden. Details: K. E. Eriksson, Svenska Traeforskningsinstitutet, Box 5604, S-11486 Stockholm, Sweden.

23-27 June. International Symposium on Immobilized Enzymes and Cells. Waterloo, Ont. Details: The Director, Industrial Biotechnology Centre, University of Waterloo, Waterloo, Ont., Canada N2L 3G1.

7-11 July 1986. Polymer supported reactions in organic chemistry, Jerusalem, Israel. Details from: Organising Committee, A. Warshawsky, Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel 76100. Telephone: (08) 482111. Telex: 361900 WLX IL.

4-7 August 1986. 2nd Asian agriculture, agrotechnology and agribusiness exhibition and conference, Putra World Trade Centre in Kuala Lumpur, Malaysia. Details from: Cahners Exhibitions Ltd., Chatsworth House, 59 London Road, Twickenham TW1 3SZ, UK. Telephone: 01-891 5051. Telex: 936028.

6-12 August 1986. Third international symposium on environmental management for developing countries, Istanbul, Turkey. Details from: Envitek, Beheriye Cad. 56, Kadikoy, Istanbul, Turkey. Telephone: 90-1 336 47 95. Telex: 29585 ETK-TR attn ENVITEK 105.

Conference on tailoring genes for plant improvement: an agricultural perspective, 24-29 August 1986, the University of California, Davis, Davis, California. For further information: Carroll Miller, Dean's Office, College of A&ES, University of California, Davis, California 95616. (916) 752-6435.

25-28 August 1986. 7th Australian Conference on Biotechnology, Melbourne, Australia. For further information: Melbourne University, Melbourne, Australia.

1-5 September 1986. Biotechnology Seminar. Recent trends and developments in biotechnology production methods will be analysed at this seminar under the auspices of the EEC. It will be hosted by the Government of Bulgaria at Varna. Details from: The Industry and Technology Division, United Nations Economic Commission for Europe, Palais des Nations, CH-1211 Geneva 10, Switzerland. Telephone: 022 34 60 11. Telex: 28 96 96.

23-25 September 1986. The British Laboratory Week, Olympia. Further information from: Curtis Steadman & Partners Ltd., The Hub, Bunon Close, Saffron Walden, Essex CB10 1HL, UK.

Advanced Drug Delivery Research Symposium - Site-Specific Drug Delivery, London, UK, 7-8 October 1986. Details may be obtained from Conference Organizers, Mr. R. E. Marshall, Scientific and Technical Services, Room 403, The Pharmaceutical Society of Great Britain, 1 Lambeth High Street, London, SE1 7JN.

9-18 October 1986. Workshop on yeast, filamentous fungus, and Actinomycetes on genetics, genetic engineering and applications in biotechnology, Bangkok, Thailand. For further information: Poonsook Atthasampunna, Bangkok MIRCEN, Thailand Institute of Scientific and Technological Research, 196 Phahonyothin Road, Bangkok 10900, Thailand.

15-16 October 1986. Bio Fair Tokyo '86. Sponsored by Bidec, in co-operation with the Japanese Government. Details from: Secretariat of Bio Fair Tokyo '86, Nippon Press Centre Building, 2-1 Uchisaiwaicho 2-chome, Chiyoda-ku, Tokyo 100, Japan. Telephone: 03 (508) 1213. Telex: (0) 222 9025 JCS J.

5th World Congress on Medical Informatics. 26-30 October 1986, Sheraton Washington Hotel, Washington, D.C. Details: George Washington University Medical Centre, Office of Continuing Medical Education, 2300 K St., NW, Washington, DC 20037, USA. (202) 676-0929.

Table 1

Government allocations for biotechnology	Millions of yen 1985	1986	% increase
Ministry of International Trade and Industry (MITI, Y5.4 billion)			
Biotechnology section of "Next-Generation" project	1 252	1 280	2
Biomass technology development Fuel Alcohol programme	1 247	1 312	5
Organic acid production from petroleum	362	313	-14
Large-scale industrial water recycling - "Aqua-Renaissance 90"	20	1 072	> 260
Biotechnology projects within STA	283	249	-12
Micro-organism depositories	276	511	85
Science, Technology Agency (STA, Y10 billion)			
Technologies promotion	2 000	2 200	10
Cancer, nuclear medicine	298	340	14
Institute Physical, Chemical Research			
Life-science projects	325	325	0
Genetic sciences	842	992	18
Cell depository	316	371	17
Other	244	364	51
Research Development Corporation of Japan	1 370	1 145	-16
National Institute of Radiological Sciences	1 576	2 390	52
Japan Information Centre	562	744	32
Ministry of Agriculture, Forestry and Fisheries (MAFF, Y3.1 billion)			
Plant cell culture	317	445	40
Infrastructure technologies	386	420	9
Gene bank	836	915	9
Food technologies	409	548	9
Livestock breeding	280	530	89
Ministry of Health and Welfare (MHW, Y3.4 billion)			
Infrastructure technologies	-	785	-
10-year anti-cancer programme	1 530	1 576	3
Biological resources	1 019	1 032	1
Ministry of Education (ME, Y20 billion)			
Animal experimentation facilities	1 558	1 605	3
Cancer programmes	8 616	8 944	4
Bioscience facilities	1 862	1 131	-39
Bioscience equipment	1 698	1 729	2
Ministry of Construction			
"Biofocus wastewater treatment"	103	130	26
Ministry of Labour			
Industrialization of bio-workers	-	8	-
TOTALS: million yen	36 600	42 100	15
= (million US dollars)	($183)	($210)	

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

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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 ☐