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Genetic Engineering and Bio-technology Monitor

Issue No. 44 1997/V

This issue carries a special article by professor [illegible], on the subject of Bioremediation and the application of biotechnology for the clean-up of oil spills and industrial pollutants.

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A. NEWS AND EVENTS

UNIDO News

Symposium on Food Fermentation Technology

The Symposium, which was held from 7 to 19 December 1993, was organized in collaboration with the African Agency for Biotechnology, African Regional Centre for Technology (ARCT) and Institute of Food Technology (ITA), Dakar (Senegal), as part of the first meeting of the AFRISTECH, the theme of which was valorization of research, technological innovation and economic development.

The participants presented papers and discussed the state-of-the-art developments in food fermentation technologies with special reference to lactic acid fermentation, cassava fermentation and mushroom cultivation and proposed far-reaching recommendations to expand research and development in these areas and commercialization of products developed in the African region.

Among the recommendations on lactic acid fermentation technology were exploration of the possibilities of forming a food technology network in the region; promotion of R&D in culture collection, their characterization and supply to laboratories of the region. The participants also called for an extension to Africa of the UNIDO-Korea project, which led to the development of a low-cost, nutritious beverage called "Risogurt".

Cassava being a staple food of many African countries, the participants endorsed the need for R&D in African institutions to bring about stress-resistant varieties with negligible cyanide content. One of the recommendations was the enrichment of the cassava-based products with protein fortification by fermentation, starch production and commercialization through small and medium enterprises in Africa. Noting the promotional activities of UNIDO such as the design of pilot plant with mechanization facilities in the processing of cassava to gari, the Group recommended expansion of the activity to other African countries and to include training of women in the processing technology.

Barring two or three countries, mushroom cultivation is still in its infancy in Africa. The potential and need for widespread cultivation in the region was emphasized by the participants as mushrooms serve as a source of high quality protein, minerals and vitamins and even have considerable medicinal value. The feasibility of growing mushrooms with waste substrates adds an environmental dimension to the project. The Group suggested formation of a mushroom network with links to international centres engaged currently in extensive cultivation. The need for organizing training workshops in popularizing the art of mushroom cultivation was emphasized at the meeting.

Among the collaborative agreements that emerged from the meeting were: 1. formation of a food fermentation network including Africa, Asia and Latin America; 2. Korean University-ITA, Dakar collaboration to produce Risogurt-like fermented beverages using indigenously available cereals; 3. formation of a mushroom network including centres engaged in cultivation in Africa such as Uganda and Nigeria with more advanced centres existing in Hong Kong and Thailand.

UN and other organizations' news

Organization for Economic Cooperation and Development (OECD)

Biotechnology, agriculture and food

Four years' work by 15 authors (14 European), and review by wider expert groups, have led to a 219-page report on the above topic. The report is published, in English and French editions, by the Organization for Economic Cooperation and Development. Its production involved extensive cooperation with industrial companies, and Governments, and was financially supported by the Commission of the European Communities under the BRIDGE Concertation Action.

The report's aim is "to review the important facets of agro-food biotechnology in a form that, although comprehensive and scientifically up-to-date, should also be accessible to an interested lay public and to policy-makers". Looking ahead, it emphasizes that "the technologies currently on the market are only a part, and not a very large one, of what is technically already possible. They are an even smaller fraction of the numerous options which could be made available in the next 10 to 15 years".

The 17 page "overview and policy conclusions" ends with the following seven points:

1. Biotechnology can be applied to all plants, animals and micro-organisms for food and non-food uses, thus affording the opportunity profoundly to improve the quality and efficiency of agricultural production;

2. New agricultural and food biotechnologies are extensions of traditional genetic modification practised in animal and plant breeding throughout civilization, but further progress depends upon support of the basic sciences from which they have sprung;

INTERNATIONAL CENTRE FOR GENETIC ENGINEERING AND BIOTECHNOLOGY

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MEETINGS and COURSES

• 1994 •

Title	*Dates/Location*	*Organizer(s)*
MOLECULAR MECHANISMS OF GENE EXPRESSION Symposium	5-7 January Santiago, Chile	Jorge Allende, Chile
Apply directly to Dr. J. Allende, Department of Biochemistry, Faculty of Medicine, University of Chile, Casilla 70086, Santiago 7, CHILE Tel & Fax: +56-2-737632.		
BACTERIAL GENETICS Theoretical/Practical Course	14-25 March Trieste, Italy	Carlo Bruschi, ICGEB
RNA STRUCTURE AND FUNCTION Theoretical Course	28-31 March Trieste, Italy	Glauco Tocchini-Valentini, Italy
BIOTECHNOLOGY AND FOOD Workshop	10-23 April Awka, Nigeria	Nduka Okafor, Nigeria
Apply directly to: Dr. N. Okafor, FADIB, P. O. Box 1457, Enugu, NIGERIA. Tel: +234-42-339360, Fax: +234-42-332059, Tlx: 51445, 51300 sezen, 51208 trade		
OPEN QUESTIONS IN MOLECULAR EVOLUTION Workshop	18-23 April Guanacaste, Costa Rica	Giorgio Bernardi, France Gabriel Macaya, Costa Rica
Apply directly to: Dr. G. Macaya, University of Costa Rica, Ciudad Universitaria "Rodrigo Facio", San Jose, COSTA RICA. Tel: +506-246749, Fax: +506-346363		
YEAST MOLECULAR GENETICS Theoretical/Practical Course	18-29 April Trieste, Italy	Carlo Bruschi, ICGEB
BIOTECHNOLOGY AND AGRICULTURE IMPROVEMENT IN DEVELOPING COUNTRIES Theoretical Course	21 May-3 June Marrakech, Morocco	Zaid Abdelouahhab, Morocco Oihabi Abdellah, Morocco
Apply directly to: Dr. Z. Abdelouahhab, Department of Biology, Faculty of Sciences, B. P. S 15 Marrakech, MOROCCO. Tel: +212-4-434649, Fax: +212-4-436765		
EMERGING BIOTECHNOLOGIES AND INDUSTRIAL OPPORTUNITIES ICGEB Inaugural Conference	June, tentative Trieste, Italy	Francisco Baralle, ICGEB George Tzotzos, ICGEB
BIOINFORMATICS: COMPUTER METHODS IN MOLECULAR BIOLOGY Practical Course	13-22 July Trieste, Italy	Sándor Pongor, ICGEB
MEDICAL GENETICS IN DEVELOPING COUNTRIES Theoretical Course	21-26 August Beijing, China	Giovanni Romeo, Italy Qin Xinhua, China
Apply directly to: Ms. C. Cogorno, Laboratory of Molecular Genetics, G. Gaslini Institute, 16148 Genova, ITALY. Tel: +39-10-5636370, Fax: +39-10-391254		
ENVIRONMENTAL APPLICATIONS OF BIOTECHNOLOGY: SCIENTIFIC RISK ASSESSMENT METHODOLOGIES Theoretical Course	19-23 September Trieste, Italy	Gilbert Howe, UK George Tzotzos, ICGEB
INSECTICIDAL ENDOTOXINS Practical Course	25 October-12 November New Delhi, India	Raj Bhatnagar, ICGEB
Apply directly to Mr. G. Chatterjee, ICGEB, Nil Campus, Aruna Asaf Ali Marg, New Delhi 110067, INDIA Tel +91-11-6867356, Fax +91-11-6862316, Tlx: 3173286		
PLANT TRANSFORMATION Practical Course (co-sponsored by the Rockefeller Foundation)	22 November-10 December New Delhi, India	Swapan Datta, ICGEB
Apply directly to Mr. G. Chatterjee, ICGEB, Nil Campus, Aruna Asaf Ali Marg, New Delhi 110067, INDIA Tel +91-11-6867356, Fax +91-11-6862316, Tlx: 3173286		
PLANT MOLECULAR BIOLOGY AND BIOTECHNOLOGY International Symposium	14-17 December New Delhi, India	Krishna Tewari, ICGEB
Apply directly to Mr. G. Chatterjee, ICGEB, Nil Campus, Aruna Asaf Ali Marg, New Delhi 110067, INDIA Tel +91-11-6867356, Fax +91-11-6862316, Tlx: 3173286		

General Information and Trieste Meetings/Courses

Ms. Diana Viti, ICGEB, Padriciano 99, 34012 Trieste, Italy
Telephone +39-40-3757333, Fax: +39-40-226555, Telex 460396 icgebt i, Email: viti@icgeb.trieste.it

3. During the next few decades, agricultural and food biotechnologies can make a vital contribution to global economic and social welfare for a rapidly expanding human population;

4. Biotechnology has the capacity to limit the damaging environmental consequences of some agricultural practices, deforestation and climatic change;

5. Contrary to earlier negative predictions, the diffusion of agricultural and food biotechnologies in the OECD area in the next 10 years will be a gradual process without major, destabilizing impacts on social structure or employment;

6. Public perceptions of biotechnology and safety issues remain potent sources of industrial uncertainty and must be addressed by improved communication among governments, scientists, industry, the media and the public;

7. Agro-food biotechnology could make a crucial contribution to the health and prosperity of the Third World, and it is therefore in the economic interest of both OECD and developing countries to devise, in concert, policies on research, intellectual property, safety, etc., that will enable the latter to build up their biotechnology capability.

The report, priced at FF 185, is available from: OECD publications, 2, rue André Pascal, 75775 Paris Cédex 16; or national distributors. (Source: *EBIS*, Vol. 2, No. 4, 1992)

Safety considerations for biotechnology 1992

This report has been published as a follow-up to the 1986 publication "Recombinant DNA Safety Considerations", which set out the first international safety guidelines for biotechnology applications in industry, agriculture and the environment. This second "blue book" prepared by the Group of National Experts on Safety in Biotechnology, considers the further development of biotechnology into industrial production and field experimentation. The 1986 report defined "Good Industrial Large Scale Practice" (GILSP) for fermentation-derived biotechnology products. This report defines "Good Developmental Principles" (GDP) for the design of safe small-scale field research using plants and micro-organisms with newly introduced traits.

Details: OECD, Publication Service, 2, rue Andre Pascal, F-75775 Paris Cédex 16. (Source: *EBIS*, Vol. 2, No. 3, 1992)

The International Institute of Biological Control (IIBC) (an Institute of CAB International)

IIBC is a non-profit organization dedicated to research, training and information provision in the field of biological pest control. For over 60 years, IIBC specialists have assisted scientists in the developing and developed world with finding solutions to serious exotic pest problems and, more recently with developing practical alternatives to chemical pesticides, including biological pesticides and integrated pest management (IPM) packages.

IIBC presently operates from stations in Trinidad, U.K, Switzerland, Kenya, Pakistan and Malaysia. IIBC's work is supported largely by grants and contracts, and the Institute presently undertakes some 30 projects annually for the benefit of over 50 countries world-wide.

IIBC provides information on biological control through various publications, including *Biocontrol News and Information*, and will answer queries from anywhere in the world. In addition, IIBC organizes training courses in biological control for particular pest problems or crop systems. IIBC experts are available to undertake consultancies on temperate and tropical problems in biological control of insects, weeds and other organisms, and to help plan project proposals to sponsors.

From its stations around the world, and its international quarantine centre in U.K, IIBC provides an efficient and reliable service in the exploration, identification and provision of exotic biological control agents, with appropriate training in technical skills and quarantine procedures.

For further details of the work of IIBC please contact: International Institute of Biological Control, Silwood Park, Buckhurst Road, Ascot, Berks SL5 7TA. Tel.: (0344) 872999; Fax: (0344) 872901.

UNESCO short-term fellowship programme in biotechnology

Objective

The UNESCO Short-Term Fellowship Programme in Biotechnology is designed to stimulate and facilitate research and training in plant and aquatic biotechnology and related environmental biotechnologies. Through this scheme scientists, particularly from the developing countries are encouraged to carry out research at well-established scientific centres to learn to use techniques that are normally not accessible to them in their own country. Fellowships are not awarded for

attending scientific meetings or training courses or to meet t[illegible] costs of bench fees levied by some host institutes.

A candidate to be eligible for a UNESCO short-term fellowship in biotechnology has to:

1. Be already engaged in research in biotechnology;

2. Upon termination of the fellowship return back to the country of residence so that the knowledge acquired is put to beneficial use in local research and training programmes;

3. Provide evidence that the theoretical and practical knowledge or training acquired at the host laboratory will be beneficial to the candidate's on-going research programmes.

Applications submitted *must be accompanied by* a letter of recommendation from someone familiar with the candidate's work *and a letter of acceptance from the host institute* (i.e. the institute that has accepted the candidate for work during the period supported by the UNESCO short-term fellowship in biotechnology).

It is the responsibility of the host institute to obtain full particulars from the candidate on matters concerning the candidate's technical qualifications and training needs.

This letter of acceptance must indicate that the host institute confirms its willingness to provide the relevant training facilities required by the candidate in the chosen field of specialization.

It is normally expected that the institute of origin or the host institute will contribute to defray the rest of the expenses incurred by the fellowship holder.

Terms of tenure

A fellowship will be awarded to scientists wishing to spend 1-3 months in a scientific laboratory abroad. It will consist of a lump sum designed to cover, either partially or fully, an economic air/railway ticket; or a modest monthly subsistence allowance; or both. The lump sum provided will not exceed US$ 4,000 and will be made available through a letter of agreement between UNESCO and the host institution on behalf of the candidate. Coverage for life and accident or health insurance are the personal responsibility of the individual or the host institute.

Deadlines for the submission of applications

All applications must be made on the UNESCO/BAC application form (see attachment) and should be received by 30 June or 30 December of the calendar year. Applications should be sent to: UNESCO Short-Term Fellowships in Biotechnology, Biotechnology Action Council, Division of basic Sciences, UNESCO, 1, rue Miollis, 75015 Paris, France. Tel.: (33-1) 45-68-38-83, 45-68-41-82; Telex: UNESCO A 270602 F; Fax: (33-1) 43-06-11-22, 45-67-16-90.

Review of applications

The following criteria will be used for evaluation of applications and selection of successful candidates:

(a) Scientific excellence of the applicant;

(b) Scientific relevance of the proposed project to the objectives of the Fellowship Programme;

(c) Relevance of the host institute's degree of specialization to the candidate's proposed field of research or training;

(d) Age of the applicant (preference will be given to scientists below 40 years of age);

(e) Geographical distribution (preference will be given to candidates from developing countries);

(f) Regional cooperation;

(g) Emphasis on least developed countries;

(h) Cooperation with other United Nations agencies.

Reports and publications

On termination of the fellowship the awardee is required to submit a report, not exceeding 500 words, on the work accomplished to the Biotechnology Action Council. It should be endorsed by the applicant's supervisor at the host institute.

Publication resulting from the stay abroad must clearly acknowledge the award of the UNESCO Short-Term Fellowship in Biotechnology. A reprint must be sent to the UNESCO Short-Term Fellowship Committee for Biotechnology for future reference.

Long-term ecological impacts on GMOS examined

The Council of Europe, based in Strasbourg, has a Steering Committee for the Conservation and Management of the Environment and Natural Habitats (CDPE). This Committee set up a group of specialists on the ecological impacts of gene technology. The group was responsible for a report on the "potential

ecological impacts of the contained used and deliberate release of genetically modified organisms". Further information on programmes and activities may be obtained from Piet Schenkelaars, P.O. Box 38, NL-2250 AA Voorschoten, The Netherlands. Tel.: (31)71-611298; Fax: (3)71-617791. (Source: *EBIS*, Vol. 3, No. 2, 1993)

General

Malaria

Wars, not philanthropy, have produced most of the world's malaria drugs. Until the 1940s there was only quinine. The Second World War spawned two new drugs and the Viet Nam war two more. Now the arsenal for treatment has all but run out, overtaken by the rapid spread of drug-resistant malaria parasites, and the pharmaceuticals industry, seeing little profit in a market confined to poor countries, has all but abandoned the disease.

Scientists not known for their immoderate views are calling the situation desperate. World-wide, the number of cases of the disease is rising, with a dramatic increase in the past two years. Some 280 million people are infected with malaria parasites and at least 110 million develop the disease each year. There are no licensed vaccines to protect against malaria. The WHO abandoned a programme to eradicate the disease by insecticide spraying as long ago as 1969. Drug-resistant parasites, which first appeared in Latin America and South-East Asia simultaneously in the early 1960s, now affect almost every country where the disease is endemic. In parts of Thailand, for example, half the cases of malaria are resistant to treatment with mefloquine, a drug that was licensed only in 1985. Chloroquine, long the favourite, is now all but useless in many countries.

How is it that malaria, once eliminated or largely controlled for 90 per cent of the world's population, now threatens more than 40 per cent of us? The reasons are many: poverty; the increased movement of people in search of work or land, or to escape war; the spread of drug-resistant parasites; a lack of political commitment; and the failure to use existing tools to stop a controllable, and largely preventable, disease.

Malaria is caused by four species of protozoan parasites of the genus *Plasmodium*. The most common is *Plasmodium vivax*, but the one that kills people, and is spreading rapidly, is *Plasmodium falciparum*. The parasites are transmitted by about 30 different species of *Anopheles* mosquitoes and, once in the bloodstream, can overwhelm people within hours, causing coma or damaging the kidneys or lungs. Many of the basic mechanisms of the disease are still a puzzle.

In most of sub-Saharan Africa, malaria has always claimed staggering numbers of lives and debilitated even more. In the villages of the Gambia, for example, one child in 20 under the age of five dies from malaria and the death rate may be even higher elsewhere. No one knows how much, if at all, the disease affects the development of children who survive. Most African countries are now poorer than ever, and malaria is just one of a growing list of problems.

Africa carries the greatest burden of disease, but it is the fast-developing countries of Asia and Latin America that have seen the most dramatic changes. Increasingly, people with no immunity to malaria are moving into malarial regions in search of an income. In Viet Nam, people are beginning to log and clear forest regions where they are exposed to malaria for the first time. In the Thai town of Borai, near the Cambodian border, thousands of Thais and immigrants from Myanmar flock in, searching for work in the gem mines. Some 10,000 cases of the disease are recorded every month among the miners in this town alone.

In Brazil's Amazon Basin, meanwhile, the gold rush has brought thousands of new cases of malaria each year as prospectors enter the forest. In addition, World Bank policies have brought increasing mechanization, and hence unemployment, to the farms in the South of Brazil. So farmers have been moved north, into the forest, to clear land and grow cash crops - and there they encounter malaria head on.

These are simply the latest developments in a long struggle with the disease. Back in 1955, the WHO adopted a policy to eradicate malaria world-wide. But in 1969 the WHO decided it was impossible to eradicate malaria, and resolved instead to "control" the disease. The official WHO version of events is that the eradication policy had failed because it was unrealistically simplistic: mosquitoes developed resistance to insecticides; the programme had failed to take account of social differences; too much money was spent on eradication at the expense of research; and so on.

The unofficial view is different. Certainly, funding from donor countries dropped sharply when the policy was abandoned. The debate is still heated. Although pesticides such as the pyrethroids have been developed that are safer, more effective and cheaper to use than DDT, the WHO has never again considered the possibility of global eradication.

With eradication off the agenda, what are the prospects for local control and treatment? On the drugs side, the picture is bleak with rare exceptions. Wellcome, Hoffmann-La Roche and SmithKline Beecham, the companies most heavily involved in the

past, are fast running down their work on antimalarials. There is no money in tropical diseases because, by and large, those who are affected cannot afford medicines.

New therapies are not going to emerge unless some international initiative is put together. Many scientists would think first of the kind of work done by the Walter Reed Army Institute of Research in Maryland. The US Army has the biggest programme for screening potential antimalarial compounds in the world - the WRAIR was stimulated by the Viet Nam war to develop mefloquine and halofantrine, and was one of the key players in developing chloroquine and primaquine after the Second World War. But the budget for the Experimental Therapeutics Division at the WRAIR has dropped for six years in succession. The US Department of Defense spent $2.4 million on malaria drug research in 1986; in 1990 the figure was down to $1.7 million.

With even the US military under pressure, what hope is there of an international initiative against malaria? The WHO is beset by financial problems of its own, but is under pressure to come up with ideas. So far, nothing clear-cut has emerged.

The WHO's special research programme on tropical diseases now has a product development unit to help scientists and companies with drugs. But the unit has only three staff, and malaria is only one of the diseases it is meant to cover. The WHO may be able to coordinate certain stages of drug development, such as organizing trials, but in terms of making the drugs available to developing countries is ultimately absolutely dependent on the pharmaceuticals companies. The military cutbacks make it imperative that the WHO fosters basic research into malaria. If new antimalarial drugs are to reach the marketplace, basic research institutes must be funded to do much of the expensive and speculative initial work for companies, and clinical trials if necessary.

So far, the basic research has a long way to go. The mechanisms of drug resistance in *P.falciparum* are proving difficult to unravel, although there are signs of progress. Eighteen months ago, Thomas Wellems at the National Institutes of Health in the US mapped a gene for chloroquine resistance in *P. falciparum* (*New Scientist*, Science, 6 April 1991). A few months later, another team demonstrated how the drug may work (*New Scientist*, Science, 11 January). These discoveries are first steps on the way to learning how to outwit the parasite's resistance to chloroquine, though they do not offer instant solutions.

Even if there were enough curative drugs, they alone would not be the answer. Vaccines for malaria are urgently needed, too. While no single vaccine is expected to solve all problems, scientists hope that a combination of approaches will succeed. Vaccines against malaria need to overcome a series of obstacles. First, the parasite goes through different life stages, each of which look different to the immune system. A second difficulty is that the proteins on the surface of the parasite change readily in response to selection pressure from the immune system. A vaccine that puts the parasite under severe pressure might hasten the selection of new mutants, some scientists fear.

There are three main approaches: blocking the parasite as it enters the human bloodstream, in its sporozoite form; blocking the parasite after it has emerged from its initial incubation in liver cells, in its merozoite form; and using a so-called "altruistic" vaccine that would block transmission by immunizing against the parasite during its sexually reproductive stage in the mosquito. This vaccine would not protect individual recipients, but could help to stop the spread of malaria. It would probably be combined with treatment for the individual.

Many scientists have focused on sporozoite proteins as a basis for experimental vaccines. An antisporozoite vaccine should, theoretically, prevent the development of mature parasites, and also block transmission. But vaccines based solely on proteins from the surface of the sporozoite or on whole sporozoites inactivated by radiation have so far produced mixed results in animal and human studies. Vaccines against sporozoites would not protect from merozoites, for example in donated blood.

Several teams are working on blocking the parasite's next developmental stage, the merozoite. This would not prevent infection completely, but it would limit it, making disease unlikely. Scientists are working on merozoite antigens that could be the basis of future vaccines. Manuel Patarroyo from the National University of Colombia, Bogotá, has tested a synthetic peptide vaccine, based on three merozoite protein segments and one segment from the sporozoite protein, on some 20,000 people. Patarroyo's early trials were criticized for lacking controls, but controlled trials have now been completed and the results are expected to be published soon.

In August 1992, the Tanzanian Government, the Swiss Tropical Institute and scientists from Madrid and London began a large controlled field trial in Ifakara, Tanzania to test Patarroyo's vaccine. The final results of the trial, which is partly funded by the WHO, will not be known until mid-1994. Another group at the WRAIR is working with Patarroyo to test a copy of his vaccine in the US and possibly also in Thailand next year.

Other scientists working on merozoite proteins include Tony Holder and his colleagues at the National Institute for Medical Research in London. Holder's group has succeeded in making a merozoite surface protein, designated MSP-1, in genetically engineered bacteria. The merozoite seems to use this protein to invade red cells; used as a vaccine, the team believes it

could stimulate antibodies that block the parasite out of the cells.

A team led by Robin Anders at the Walter and Eliza Hall Institute of Research in Melbourne, Australia, is working on another merozoite surface protein, MSA-2, combining it with a sporozoite protein to make a vaccine. Anders and his colleagues are collaborating with Hoffmann-La Roche and another company, Saramane, in the first phase of human trials of this vaccine. At this stage the trials seek only to measure the safety of the vaccine and the kind of immune response it stimulates.

David Kaslow and his colleagues at the NIH are almost ready to test an altruistic vaccine for safety in humans. The vaccine, shown to be successful in animals, is based on a genetically engineered protein from the ookinete stage of the parasite. It produces antibodies in the blood which block the transmission of the parasite in mosquitoes. This approach has several advantages. For example, the protein produces a strong immune response but, because it acts on a stage of the parasite that is never inside the human host, it should not put any selection pressure on the parasite to develop resistance.

All these vaccines are aimed at the parasite. Another approach is to attack the symptoms with an "anti-disease" vaccine. This approach is suggested by Kamini Mendis at the University of Colombo, Sri Lanka, and by John Playfair in London. A long-standing puzzle is that not everyone infected with malaria parasites becomes ill. Mendis and Richard Carter of the University of Edinburgh have found that people in the acute stage of malaria, known as the paroxysm, produce high levels of a messenger protein called TNF or tumour necrosis factor, which is associated with fevers. At the same time, the body produces other messenger proteins, as yet unidentified, which Carter simply calls "complementary factors". Together with TNF, these complementary factors kill parasites, at least in the laboratory. The surge in TNF and these factors is short-lived, and coincides with the paroxysm.

Next, the team looked at people in regions where malaria is endemic. Individuals with a degree of immunity to the parasite tended to show much less severe paroxysmal symptoms. When the team examined the blood of people with mild symptoms, they found a surge in TNF, but not in the complementary factors. Carter speculates that people with mild symptoms may have developed antibodies to the proteins on the parasite that trigger the production of complementary factors - antibodies that could be helping to prevent the worst symptoms.

Clearly, the key questions for research are to discover exactly how the parasites cause disease and how to protect against them. Some of the most important answers to these questions are coming from the MRC laboratories in the Gambia, headed by Brian Greenwood. One eagerly awaited study is a comparison of no less than 300 pairs of twins, designed to unravel the roles of genes and environment in malaria. For reasons that are still not known, children in Africa suffer more from cerebral malaria than their counterparts elsewhere. But individuals within a population fare very differently when exposed to malaria.

Annette Jepson, who heads the Gambian study, has monitored 40 monozygotic twins and 260 dizygotic pairs. She is looking at a number of factors, including the levels of parasites in their blood.

Researchers are also looking for genetic clues in adult twins, to see if inherited differences of the immune system play a part. In 1991, Adrian Hill and others from the Institute of Molecular Medicine in Oxford joined the MRC's project in the Gambia to study how proteins of the immune system known as HLA (or MHC) antigens help in the defence against malaria. The HLA antigens are vital for presenting foreign matter to the T-cells of the immune system, and are encoded by genes that vary greatly from person to person. Only identical twins have the same set of HOL genes.

Scientists have long speculated that variability in the HLA sequence might be part of the reason why some people are more susceptible to diseases than others. The first hard evidence for this came when Hill and his colleagues showed that two HLA genes common in West Africans were linked with protection from severe malaria (*New Scientist*, 23 February 1991). The team has gone on to identify a protein from the malaria parasite that is offered to T-cells by an HLA antigen encoded by one of these genes. The antigen produces a strong response from killer T-cells and could help, the researchers hope, to form a future vaccine.

Another unanswered question is what determines the infectiousness of the parasite. Chris Drakeley, working at the MRC's field station in Farafenni, upriver in the Gambia, has constructed a model to mimic what happens when mosquitoes feed on blood. He analyses blood samples to see what antibodies and T-cells they make in response to gametocyte proteins in red cells. Such antibodies and T-cells could influence whether mosquitoes become infected or not when they bite people.

These immunological studies may be good science, but for the foreseeable future people at risk of malaria must settle for a simpler solution - the humble bed net, soaked once per year in pyrethroid insecticide and placed properly over the bed at night. Until last year, there was no firm evidence that the nets worked. But then Greenwood, Pedro Alonso and others in the Gambia showed that treated bed nets could cut the death rate from malaria by as much as 70 per cent - a

staggering difference in survival from a measure that costs only 30p per season and that requires little in the way of specialized training. Working with the Gambian Government and the WHO, the MRC researchers have now helped to set up a national bed-net programme. The aim is to give 400 entire villages in the Gambia insecticide-treated bed nets within two years. Because of the success of the trial, bed net studies are now being extended to other countries.

One of the strange findings from the Gambian trial was that the bed nets appeared to prevent more deaths than could be accounted for by malaria alone. This raises the question of whether malaria parasites weaken their host's immunity to other diseases, and whether protection from malaria means protection from other infections too.

Whatever the answer, treated bed nets will be of more use in the short term than some other methods being dreamed up by scientists, which have a certain aura of Star Wars. For example, there are teams attempting to design genetically engineered mosquitos as biological controls to prevent the spread of parasites. Others are hoping for "designer" drugs that will circumvent the current problems of resistance. Neither solution will be ready tomorrow - or even in five years' time. Some scientists say it will take another world war to bring us the malaria drugs we need, and they are only half joking. (Source: *New Scientist*, 31 October 1992)

Malaria - beating retreat?

For 40 years the World Health Organization (WHO) has tried to control malaria by attacking the mosquitoes that carried it. Large tracts of inhabited land were sprayed with insecticides, first DDT, then the safer pyrethroids. Swarms of sterilized male mosquitoes were released, in the hope that the foe would fizzle out in reproductive frustration. Stagnant African pools were stocked with fish that had a taste for things mosquitoid, and mosquito-killing fungi were encouraged in Iran. None of it worked that well, so the strategy has been changed.

Every year over 100 million people get ill from malaria; more than 1 million die. Most live in poor countries, but 10,000 cases were diagnosed from Europe last year. The parasites that cause the disease, of which the worst is *Plasmodium falciparum*, get into the blood by the kind graces of female mosquitoes and then invade liver cells. After a fortnight's incubation, the cells rupture, releasing more parasites which then breed in the blood. In the case of *falciparum*, the subsequent illness often leads to delirium and coma.

For decades, WHO's specialists hoped that, with good control of mosquitoes, malaria could be eradicated. But malaria, with its intermediate hosts and complicated life cycle, proved far more resilient than diseases such as smallpox, which was transmitted directly from man to man before it was wiped out. Now, faced with the brutal fact that, despite years of effort, malaria has not been eradicated and is not likely to be soon, WHO is doing a U-turn. Its new strategy on malaria, formally launched at a meeting of health ministers in Amsterdam on 26 October 1992, is directed at people, not mosquitoes. It gets back to fundamentals: try not to let the mosquitoes bite you; if they do, get treatment fast. This is a wrenching decision for WHO, because it means a complete change in philosophy: large-scale prevention is taking second place to individual cures, much harder to fit into the purview of an international organization.

Part of the reason for the change is the fact that both the mosquitoes and the parasites were able to develop resistance to the chemicals used against them. Another factor is that the drug companies have neglected malaria research; it is hard to make a profit out of poor countries. Even the familiar courses of chloroquine and other prophylactic drugs are no longer as effective as they were - though they are still recommended for travellers, because, even when they fail to prevent infection, they can mitigate its effects.

On the bright side, scientists hope that their long and arduous search for a vaccine may be given new impetus by genetic engineering. However, immune responses to parasites are complicated and mysterious, so a vaccine is not likely in the short term. That is why WHO recommends a return to cheap and easy basics: long sleeves, trousers and skirts, especially at or after sunset; and mosquito nets, preferably dipped in insecticides, such as a home-made decoction of the pyrethrum plant *Chrysanthemum cinerariaefolium*. If you have fever, get treatment - quinine, as likely as not, but there are also more complicated and sophisticated combinations of drugs available. And modern practitioners have (with WHO encouragement) rediscovered the usefulness of artemisin, extracted from the leaves and flowers of *Artemesia annus*, or sweet wormwood. The Chinese have been using it for at least 2,000 years - without any changes in strategy. (Source: *The Economist*, 31 October 1992)

Resistance is not futile

Those who doubt the power of natural selection to fit creatures to their environments should study the case of *Anopheles v Homo sapiens*. The mosquito which carries the malarial parasite has been under constant and coordinated assault since 1955, when the World Health Organization declared war on it. Although the resistance with which this assault was met is not the only reason for WHO's abandonment of the tactic, it was an important one. How was it that the mosquitoes achieved this extraordinary victory?

The chemicals used to kill the mosquitoes and biting flies which spread diseases around tropical (and some not-so-tropical) climes are almost all nerve poisons. Such poisons, be they DDT or modern pyrethroids, work

by sticking to proteins on the nerve cells' outer membranes, thereby either blocking their action or forcing them to send meaningless repetitive messages.

Different types of mosquito have evolved different ways of coping with this assault on their nerves. Insects are made up of tens of thousands of proteins, but only seven have ever been seen to change in such a way as to produce resistance to the nerve poisons. Three are proteins on the surfaces of the nerve cells; the others are enzymes that go around mopping up the chopping up stray and unwanted molecules. Changes to the nerve-cell proteins make them less susceptible to interference; changes to the enzymes improve their ability to chop.

The changes made have to be subtle - small enough not to affect the way the molecules work, but large enough to have the desired effect on the poison. For each protein, only a few changes have both properties. But natural selection is able to find them again and again. Nearly 50 species of *Anopheles* have acquired at least one mutation that confers resistance. Some seem to have mutations in the genes that describe all seven proteins.

Other mosquitoes have eschewed subtlety and gone for the steam-roller. *Culex* is a widespread group of mosquitoes, with bites more painful than those of Anopheles but rarely - except when they carry elephantiasis - as serious. Resistant strains of *Culex* have many copies of the genes for the mopping-up enzymes, rather than improving the enzymes' ability to chop. More genes means more enzymes; in a resistant strain of *Culex*, up to 10 per cent of the working proteins may be mopping up, whereas in *Anopheles* the number is never larger than 0.01 per cent. Force of numbers does the trick.

As if this chemical chicanery were not enough, there are indications that the insects' behaviour may evolve as well. After a good meal, female mosquitoes like to rest for a while, and the nearest wall is as good a place as any - unless it is covered with insecticide. These days, it often is; spraying walls has been a favourite tactic of most mosquito-control programmes. In some places the mosquitoes seem to have grown wise to this. Females fly farther than they used to after dinner, reaching the security of unsprayed bushes before they settle down to digest their meal. (Source: *The Economist*, 31 October 1992)

World declaration on malaria control

The World Declaration on the control of malaria was adopted by the World Health Organization (WHO) at its conference on malaria held in Amsterdam in October 1992. The new global malaria-control strategy is intended to encourage action not only in those countries affected by the disease but also in malaria-free countries. The Declaration aims to reduce morbidity as well as social and economic losses by applying four universal criteria that emphasize the importance of providing early diagnosis and treatment; the planning and implementation of selective and sustainable preventive measures; the detection, containment, or prevention of epidemics; and the strengthening of affected countries' capacity to deal with the problem through research. (Extracted from *European Microbiology*, January/February 1993)

Cystic fibrosis trials approved

Just three years after an international team of researchers isolated the gene associated with cystic fibrosis, CF is about to become the first major inherited illness to be treated with human gene therapy. The US National Institutes of Health's Recombinant DNA Advisory Committee approved three CF clinical trials at its 3-4 December meeting. In two of the studies, researchers will attempt to put the normal gene into cells that line the lungs of CF patients; a third, more conservative, study will put the CF gene into nasal epithelial cells, testing the treatment before going into the lung.

CF, the most common lethal hereditary disease in the United States, afflicts some 25,000 Americans, and 50,000 cases have been reported world-wide. The gene defect disrupts mucus production in the lungs, causing chronic infections and death, and the digestive tract is also affected. Median survival is 29 years in the United States.

The trials will make the first use of a new gene transfer vector made from defective adenovirus, a virus associated with upper respiratory infections and pneumonia. All previous gene transfer trials in humans, 37 in all, have used mouse retroviruses. The trials must still get final approval from the Director of NIH and the Food and Drug Administration. The Michigan study is scheduled to start in early 1993, with others following. (Source: *Science*, Vol. 258, 11 December 1992)

Why divorce runs in families

Divorce has now joined the growing list of human behaviour - ranging from personality traits to specific habits like TV-watching - that twin researchers have discovered to be significantly influenced by genes. The findings are from a study by University of Minnesota psychologists Matt McGue and David T. Lykken, based on a survey of more than 1,500 twin pairs, their parents, and their spouses' parents.

The researchers already knew that divorce tends to run in families, but by comparing information from identical twins with those from fraternal twins (who share 50 per cent of the same genes), the researchers were able to calculate that divorce is about 52 per cent heritable, leaving non-genetic factors with about half the blame. The study showed that the likelihood of divorce

goes up nearly sixfold for an identical twin whose co-twin is divorced, but increases less than twofold for fraternal twins whose co-twins are divorced (the same rate as for those whose parents are divorced).

The researchers explain that such a propensity is mediated through a variety of traits and behaviours that have been shown to be heritable - relating to personal values, individual capacity for happiness, job stability, neuroticism, impulsivity, and sexual behaviours. (Extracted from *Science*, Vol. 258, 11 December 1992)

The new age of DNA

Consummating a strange and wonderful marriage between science and art, the twisted coils of DNA are winding their way into popular culture.

In bookstores of San Francisco, exotic music composed from the resonating frequencies of various genes is all the rage. A New York company is developing wind chimes tuned precisely to the atomic vibrations of DNA, while in France, pens charged with DNA-laced ink offer writers and artists the cachet of signatures that can be authenticated by the forensic technique of DNA fingerprinting.

The surest sign that DNA has entered the zeitgeist is a California company's plan to sell cards bearing the likenesses of celebrities, each impregnated with a cloned smidgen of the personage's genetic material.

Many molecular biologists are shocked to learn that the commercialization of genetic technology has taken such twists, but perhaps they should not be too surprised. Computers led to computer games as well as spreadsheets and holography hatched light-diffracting postcards and key chains. It was inevitable that deoxyribonucleic acid too would sometime diffuse from the laboratory to the streets. (Extracted from *International Herald Tribune*, 9 September 1992)

If biological diversity has a price, who sets it and who should benefit

A one-year old agreement between Merck & Co. Inc., and a group of Costa Rican scientists coupling economic development with the preservation of biodiversity in Costa Rica has raised the question of who owns a nation's biological wealth. The agreement, which gives the world's largest pharmaceutical company the right to search for new medicines among the plants, insects and micro-organisms collected from Costa Rica's protected forests, is seen either as a novel way to finance biodiversity or as an unconscionable sellout of the country's environmental heritage.

The arrangement has inspired a US legislator to propose an international aid programme to help non-profit organizations within Latin America and the Caribbean to obtain the necessary scientific knowledge and commercial sophistication to enter into agreements such as that between Merck and the Instituto Nacional de Biodiversidad de Costa Rica (INBio). At the same time, the Costa Rican legislature is expected to vote soon on a bill that would provide increased public scrutiny and a larger share of the proceeds from such arrangements. The legislation has been revised to meet the concerns of drug companies planning to emulate Merck as well as the private research organizations that would receive royalties from the sale of any products developed from indigenous samples.

The agreement between Merck and INBio treats genetic resources as a natural resource not unlike copper or timber. If that idea is accepted, says Jack Kloppenburg, a rural sociologist at the University of Wisconsin, the question of whether to pay developing nations for access to biological resources becomes instead a matter of "who pays, and how much?"

The environmental organizations do not oppose the commercialization of Costa Rica's natural resources and acknowledge the value of INBio's decade-long effort to create a biological inventory of the country's estimated 500,000 species. They believe, however, that the Costa Rican people should know what biological resources are being sold on their behalf and at what price. Anna Sittenfeld, INBio's director for biodiversity prospecting, says that INBio decided not to divulge such information to prevent organizations in other countries from learning how much Merck was paying per sample and offering Merck the same deal for less than it was paying InBio.

The Merck-INBio agreement, praised by such organizations as the World Resources Institute, the US National Academy of Sciences and the Royal Society in Britain, has become a model for the world because it was the first well-publicized deal to involve a developing nation and a multinational company. But critics argue that what may work in Costa Rica, which has a stable democratic government and where one-quarter of the land area has been set aside for the purposes of conservation, may not work so well in other Latin American countries. (Source: *Nature*, Vol. 359, 15 October 1992)

A fifty-year plan for biodiversity surveys

In the wake of the recently completed "Earth Summit" in Rio de Janeiro, it should be evident why biological systematics, hitherto regarded as "little science", is badly in need of growing large - and soon. The roughly 1.4 million species of living organisms known to date are probably fewer than 15 per cent of the actual number and by some estimates could be fewer than 2 per cent. The Linnaean shortfall reaches from supposedly well-known groups to the most obscure.

Progress toward an overall knowledge of the Earth's prodigious biodiversity over the past 250 years

has been very slow. Close attention to this problem might be postponed for the delectation of future generations, except for two compelling circumstances. On the positive side, biodiversity represents a potential source of wealth in the form of new crops, pharmaceuticals, petroleum substitutes, and other products. If used wisely, wild species will also continue to provide essential services to the ecosystem, fro n the maintenance of hydrologic cycles to the nitrification of soils. On the negative side, biodiversity is disappearing at a rapid rate, primarily due to habitat destruction. Tropical deforestation alone is reducing species in these biomes by half a per cent per year, as estimated by the conservative models of island biogeography. This figure is likely to be boosted many times when the impact of pollution and exotic species is determined and factored in. Coral reefs, the marine equivalent of rain forests in magnitude of diversity, are also in increasing trouble.

There is growing recognition of the need for a crash program me to map biodiversity in order to plan its conservation and practical use. With up to a fifth or more of the species of all groups likely to disappear over the next 30 years, as human population doubles in the warmer parts of the world, we are clearly faced with a dilemma.

Some systematists have urged the initiation of a global biodiversity survey, aimed at the ultimate full identification and biogeography of all species. Others, noting the shortage of personnel funds, and above all, time, see the only realistic hope to lie in overall inventories of those groups that are relatively well known now, including flowering plants, vertebrates, butterflies and a few others. In order to accomplish this second objective as quickly as possible, it would be necessary to survey transects across broad geographic areas and to examine a number of carefully selected sites in great detail. A reasonable number of specialists is available to begin this task, and with adequate funding it could be completed in a decade. The results would reveal a great deal about patterns of endemism, including the existence of hot spots, those parts of the world believed to contain the largest numbers of endangered species. They could be applied directly to problems of economic development, land use, science, and conservation. Meanwhile, adequate numbers of specialists could be trained and supported to deal with all of the remaining groups of organisms. The aim would be to gain a reasonably accurate idea of the representation of these groups on Earth while attempting complete inventories of all the global biota over the course of the next 50 years. As most of the tropical rain forests of the world are likely to be reduced to less than 10 per cent of their original extent during this half-century, adequate planning is of the essence. The results from inventories should be organized in such a way as to apply directly to the development of new crops, sustainable land use, conservation, and the enhancement of allied disciplines of science.

In order to propel systematics into its larger role forecordained by the biodiversity crisis, its practitioners need to formulate an explicitly stated mission with a timetable and cost estimate. In the approach outlined above, the 50-year period could be viewed as a series of successive 10-year plans. As each decade approaches an end, progress to that point could be assessed and new directions for the next decade identified.

Momentum in the enterprise will result in economies of scale. Costs per species will fall as new methods for collecting and distributing specimens are invented and procedures for storing and accessing information improved. Costs are moreover not simply additive when higher taxa are added, but instead fall off on a per-species basis. For example, entomologists could collect nematodes on the insects they gather while identifying these hosts for the nematologists and vice versa. Multiple groups can be collected by mass sampling of entire habitats and then distributed to systematists specializing in individual taxa.

The results of inventorying, as opposed to the costs, are not just additive but multiplicative. As networks of expertise and monographing grow, ecologists, population biologists, biochemists, and others will be drawn into the enterprise. It is also inevitable that genome descriptions similar to those now planned for the human species and *Drosophila* will feed into the database. Molecular biology is destined to fuse with systematics.

Applied systematics can develop collaterally with basic studies, as is being demonstrated by the organization of the Instituto Nacional de Biodiversidad (INBio) in Costa Rica. Chemical prospecting, the search for new natural products, is readily added to the collection of inventories. So is screening for species and gene complexes of special merit in agriculture, forestry, and land reclamation.

Fully 80 per cent of the Earth's terrestrial biodiversity is likely to occur in the tropics where only a few groups of organisms can be described as reasonably well known at present. Aside from the roughly 170,000 flowering plants and 30,000 vertebrates, only about 250,000 species of all groups appear to have been described thus far. With estimates of the remainder ranging from 8 million to 100 million, one can readily appreciate the magnitude of the task at hand, and the fact that the few hundred systematists available are woefully inadequate to complete the task while most of the species are still in existence. We require, in fact, a wholly new approach to this great problem in order to be able to provide even an outline of the nature and occurrence of these species.

Abdus Salam has estimated that some 6 per cent of the world's scientists and engineers live in developing countries, with a rapidly increasing share of 77 per cent

of the world's population, 15 per cent of the world's wealth (by gross national product), and perhaps 20 per cent of the world's industrial energy. A net sum amounting to tens of billions of dollars flows annually from these countries to the rich industrial parts of the world. These relations must be taken into account if our common objective is to chart the outlines of global biodiversity, use it for humanity's benefit, understand it scientifically, and preserve an intelligently selected sample of it for the future.

We believe that the best strategy for approaching this task is the implementation of national biological surveys throughout the world, conceived like INBio, and set up as management strategies for each nation's biodiversity. Such operations will expedite the increased understanding, efficient use (assisted by biotechnology transfer), and conservation, both in nature and ex situ, of as many organisms as possible. They will allow people of every nation to see themselves as benefiting from their own biodiversity, while preserving it for their own purposes. (Source: Extracted from an article prepared by P.H. Raven and E.O. Wilson, which appeared in *Science*, Vol. 258, 13 November 1992)

ASTM, NIST workshop on biotechnology

Standardization needs in biotechnology is the subject of a workshop held in April, sponsored by the US National Institute of Standards and Technology (NIST) in coordination with ASTM Committee E-48 on Biotechnology.

More than 20 ASTM standards have been developed in the biotechnology field and more than 100 are targeted for development during the next few years. The NIST ASTM workshop served as a forum for industry, universities and Government to discuss standards of mutual interest, as well as an opportunity to update industry participants on NIST and ASTM activities and facilitate regulatory compliance. Participants helped to identify and prioritize needs for consensus, voluntary standards and programmes to develop technology.

The workshop included an overview of Committee E-48, NIST and the Advanced Technology Program. Topics considered included: test methods for detecting HIV and other disease-producing organisms; recombinant organism containment practices during manufacturing; intentional release practices for biologically active products; validation of computer control to meet Food and Drug Administration and cGMP requirements; converting biomass to fuels; standard practices to design biopharmaceutical facilities, design practices for bioremediation/kill tanks. (Source: *ASTM Standardization News*, March 1993)

IBM seeks bigger biotech role

International Business Machine's (IBM) "Biotech Expo" demonstrated how information technology can be applied by small and intermediate biotechnology companies in molecular modelling simulation, NMR-structure determination and 3D visualization. Software and systems vendors also showed aids to data management, statistical analysis, clinical case reports and manufacturing and marketing controls. The show featured a call by the Food and Drug Administration for more CANDAs, Computer Assisted New Drug Applications.

The size of the market that IBM foresees for computerizing biotechnology can be surmised from an estimate of equipment and service sales by all vendors for just one phase of biopharmaceutical production - molecular modelling. Richard Taylor, an information technology specialists at Arthur D. Little, technology and management consultants, Cambridge, Mass. reported in ADL's "PRISM" review last year that sales of computer equipment and contract R&D for molecular modelling "is forecast to reach $1.2 billion by 1995, up from $450 million in 1990 and could reach close to $2 billion by the year 2000. (Source: *McGraw Hill's Biotechnology Newswatch*, 1 March 1993)

Governmental stimulation policies in Latin America

The creation of national biotechnology programmes was a first step in defining policies for the development of (modern) biotechnology capabilities in almost all Latin American countries. With these programmes, governments aimed to coordinate R&D institutions and projects, to stimulate linkages to industry, to channel international cooperation and, in some cases, to finance projects. Brazil and Argentina established such programmes as early as 1981-1982. Venezuela and Colombia followed in 1986, Uruguay in 1987. Argentina, Brazil, Chile and Uruguay developed postgraduate training programmes in biology, with an emphasis on biotechnology, during the period 1983-1989. A fairly large number of scholarships were granted to train people locally and abroad; Argentina granted 100 external scholarships in 1983-1985, Brazil 3,401 internal scholarships and Chile 458.

The set up of special biotechnology R&D institutes has been taken a step further by Cuba, Mexico, Brazil and Argentina. In 1982, the Centre for Genetic Engineering and Biotechnology research was created at the National Autonomous University of Mexico. Argentina established a Genetic Engineering and Biotechnology Research Centre (CEINGEBI) within its National Scientific Research Council system.

Argentina, Brazil and Chile also defined a third policy emphasizing the introduction of biotechnology within applied research organizations (national agricultural research institutes or agricultural or engineering university departments). The biotechnology stimulation programmes in these countries are relatively more important than in countries with a more academic orientated research policy.

Brazil and Argentina stand out as the only countries which have created specialized research centres within their national agricultural research institutes. However, only in the case of Cuba, R&D has clearly been subordinated to ambitious industrial and commercial biotechnology goals. In Chile and Uruguay companies were encouraged by fiscal policy to enter the biotechnology sector. In Brazil, not only the national Government, but also national banks, federal states and other national institutions have financed commercial biotechnology activities. (Source: *Biotechnology and Development Monitor*, No. 14, March 1993)

"Greening" of trade key to healthy global environment

World trade - growing far faster than the global economy itself - is an engine that currently accelerates the environmental degradation caused by unsustainable economic activity. But it also has the power to pull the world onto an environmentally sustainable track - if environmental protection is included in the evolving rules of international trade, according to Costly Tradeoffs: Reconciling Trade and the Environment, a new study by the Worldwatch Institute, a policy research organization based in Washington, D.C.

World merchandise trade totalled $3.5 trillion in 1991, nearly a fifth of world output. It has grown eleven-fold since 1950, while economic output rose five-fold over the same period. Trade in services and foreign direct investment are also climbing rapidly.

Costly Tradeoffs documents a growing number of short-term clashes between protecting the environment and promoting free trade. Yet the report rejects the view that these aims are incompatible.

"The interests of trade and of environmental protection ultimately coincide", says Senior Researcher Hilary F. French, author of the report. "The world trading system requires a healthy natural resource base. And an environmentally sustainable global economy depends on some of the benefits of freer trade."

"A 'Green Round' of the General Agreement on Tariffs and Trade (GATT) is a high priority", according to French, "as are efforts through the proposed North American Free Trade Agreement (NAFTA) and in the European Community (EC) to step up environmental reforms".

Key recommendations of Costly Tradeoffs include making prices reflect the full environmental costs of production (such as energy use, resource depletion and waste generation); strengthening enforcement of existing environmental laws; tightening and standardizing environmental laws so that countries cannot reap a comparative advantage in pollution; and providing financial and technical assistance to help poorer countries meet stepped up environmental obligations.

The report cites a number of cases where trade now fuels unsustainable economic activity, including depletion of natural resources, and the creation of pollution havens where enforcement of environmental laws is lax.

- Fish account for half of Iceland's export earnings. But overfishing is endangering the future prosperity of the industry.

- Malaysia alone supplies over 60 per cent of world tropical timber exports, which nets the country $1.5 billion in foreign exchange. But the trade is rapidly decimating forests in the state of Sarawak, homeland to the Penan.

- Somalian exports of sheep, goats, and cattle have increased ten-fold since 1955, contributing to the breakdown of the traditional, more ecologically-sensitive nomadic system of livestock rearing.

- Only 35 per cent of the US companies based in the "maquiladoras" zone along the US Mexican border are believed to comply with Mexican toxic waste laws.

"By spurring increased transport and economic growth, trade can lead to increased pollution - in the absence of internalizing of environmental costs and other policy reforms", says Costly Tradeoffs. If NAFTA is implemented, the US Government predicts that more than 12 million trucks per year - nearly seven times the present volume - could be crossing the border in both directions by the end of the decade. Under Europe's single market, economic growth is expected to boost sulphur dioxide emissions by 8 to 9 per cent and nitrogen oxides emissions by 12 to 14 per cent by the year 2010 without mitigating measures.

In addition, current rules of trade can allow tough national and international environmental laws to be attacked as "non-tariff barriers."

A September 1991 GATT panel ruled that portions of the US Marine Mammal Protection Act were at odds with the GATT agreement after Mexico challenged them. The law prohibits US sales of tuna caught in a way that kills large numbers of dolphins.

The GATT ruling raised concerns that a number of national laws - and several international environmental agreements could be jeopardized. These treaties include the Montreal Protocol on ozone depletion and the Basel Convention on hazardous waste exports, which employ trade measures as carrots and sticks.

Costly Trade-Offs documents a growing number of environmental trade disputes. For instance, the Association of Southeast Asian Nations has complained that an Austrian law requiring tropical timber to be labelled as such violates GATT, and the European Community has levelled similar charges against the US "gas guzzler tax" and fuel economy standards.

"But despite the dangers, trade can also be a partner in the effort to develop a sustainable global economy", notes French. Foreign competition has spurred a spate of environmental innovations including improved auto efficiency, more water-conserving toilets, and more effective pollution control devices. Japan, the United States, and Europe collectively exported $20 billion worth of pollution control devices in 1990 - about 10 per cent of total world production. In 1992, producers exported $200 million worth of photovoltaic solar cells - more than half of world production. Foreign investment also helps distribute environmentally friendly technologies - ranging from compact fluorescent light bulbs to cleaner paper-making processes.

An added benefit of freeing trade is that it can produce income that could be used in part for environmental protection. Today, trade barriers to agricultural commodities alone cost developing countries $100 billion annually.

"Perhaps the most important environmental benefit from trade is its potential to spur the development of stronger environmental laws worldwide", notes French. "In both the EC and the NAFTA, Governments are increasingly concluding that economic integration calls for some political integration - coordinated lawmaking and enforcement procedures, for example", says French.

The European Community has passed hundreds of common minimum environmental standards on products and processes. A side agreement to be negotiated under the NAFTA will create a new North American Commission on the Environment that may have the power to penalize lax enforcement of environmental laws as a trade violation.

"Trade is neither inherently good nor bad", concludes Costly Tradeoffs. "But how it is conducted is now a matter of deep concern - and an unprecedented opportunity. Trade can either contribute to the process of sustainable development, or undermine it. Given the rapidly accelerating destruction of the earth's natural resource base, there is no question what the choice must be." (News *Release* issued by the WorldWatch Institute, Washington DC, USA, 27 March 1993)

Biological diversity

Once biological diversity has commercial value, it is more likely to be worth conserving. Heeding this economic advice, conservationists have scoured the world for markets into which they can sell products from the wild.

These markets are risky allies, according to a report by *TRAFFIC International*, which monitors trade in wildlife from its headquarters in Cambridge, England. The report highlights the boom in the consumption of medicinal plants taking place in Europe. It goes on to argue that as a result some plants are being dangerously overcollected.

For example, *TRAFFIC* has established that Germany is by far Europe's largest market for medicinal plants, but has no figures to show how fast demand is growing, or how it divides between drug companies which want to use natural ingredients in medicines or study and synthesize them, and herbalists selling traditional remedies.

The report argues that the demand for medicinal plants will grow, and not just in developing countries, which rely heavily on traditional remedies. In Europe, EC legislation is now setting standards for herbal medicines. Some of this demand can be met by horticulture, but herbalists and hypochondriacs seem to think that plants harvested in the wild are more effective. Although large drug companies generally grow their own, many medicinal plants traded in Europe are plucked from the wild.

Developing countries are waking up to the fact that their plants are valuable. The Indian Government has banned the export of wild medicinal plants. A few drug companies are drawing up contracts with developing countries to prospect for useful plants and pay royalties on their finds. (Source: *The Economist*, 26 June 1993)

Unique approaches to new - and old - markets

Almost everyone agrees on the merits of sustainable development, which the 1992 Rio Summit defined as "meeting the needs of the present without compromising the ability of future generations to meet their own needs". But "there is a huge range of debate on the exact meaning of sustainable agriculture" and the impact it will have on the agrochemical industry.

The debate over agricultural sustainability is better understood as two debates: one focuses on reducing

environmental impact in developed countries; the other usually centres first on increasing productivity to feed the population, then on protecting the environment in developing countries.

Although some companies say their only role in creating "sustainable agriculture" is to continue developing highly specific, lower volume products, others see it as a far-reaching idea that, amid declining pesticide demand in major markets, is defining new opportunities, particularly in developing countries. North America, Western Europe and Japan account for 65 per cent of the $25 billion year world-wide pesticide market. In a "radical shift" major chemical industries could start to target the specific needs of developing countries to boost their productivity in their agro-economic systems. Sustainable agriculture need not mean that yields will go down, just that they will be obtained in a different way. Because of overuse and improper mixing, the efficiency of fertilizers is decreasing in Asia, Latin America and Africa, with a similar trend in pesticides. Companies could find a profitable role in working alongside existing training programmes - like those run by FAO and GIFAP, the world pesticide producers association - to help farmers switch to more sophisticated products. Companies can play more of a role by delivering better products and more services in developing countries.

In developed countries the sustainability debate centres on better soil management, reducing pesticide and fertilizer inputs through new technologies, and the overall merits of conventional farming versus more extensive systems - at the extreme, organic farming, which in the European Community is gaining popularity but still represents less than 1 per cent of total farmland.

Often the most vocal critics of current farming practices, organic proponents like Patrick Holden, director of the British Organic Farmers Association, charge that "conventional farming is, in the long term, unsustainable". He says that in the UK alone water authorities are spending £1 billion year ($1.5 billion) to remove pesticides and nitrates from the water. "This is a social cost of agriculture that isn't yet applied to the polluter", he says.

Although these claims are not proved, they strike a chord with some European consumers and politicians, particularly in Germany, where conversion to organic farming is subsidized.

In the United States, organic practices are being driven more by market needs than by regulations. Thanks largely to clothing companies marketing environmentally friendly apparel, for example, organically grown cotton acreage has jumped from practically zero in 1988 to 14,000 acres in 1992 and 39,200 acres this year - a small but growing niche.

To develop strategies to halt erosion of land, there is a move towards conservation - or reduced - tillage, which also reduces run-off.

US companies are working to fit their older products into sustainable practices, largely by petitioning a willing Environmental Protection Agency for label changes that direct growers to use smaller amounts, keep them away from surface or well water, and time application more selectively.

Sustainable agriculture is a tough goal by any definition, but agro-chemical companies could play a key role in achieving it by developing new, sustainable markets in developing countries. (Extracted from *Chemical Week*, 17 November 1993)

16th International Congress of Biochemistry and Molecular Biology

The 16th International Congress of Biochemistry and Molecular Biology will be held at New Delhi (India) from 19 to 22 September 1994 at the Hotel Ashok.

The scientific programmes will cover traditional areas of biochemistry and molecular biology, while emphasizing topics of interest to the developing countries. Subjects to be covered are:

- Molecular biology
- Developmental biology
- Biomolecular structure
- Biotechnology applications
- Molecular basis of disease processes
- Immunochemistry and immunogenetics
- Protein structure, function and regulation
- Nutrition, clinical biochemistry
- Endocrinology and reproduction
- Neurochemistry
- Membrane biology
- Biochemical education

An exhibition is arranged to be held alongside the Congress, affording an opportunity for delegates to discuss their needs directly with the manufacturers of scientific equipment and peripherals.

Abstracts and posters are also invited, however, further information regarding deadlines, forms and full details of the Congress programme should be obtained from Dr. N. Appaji Rao, Secretary General, XVI IUBMB Congress, Department of Biochemistry, Indian Institute of Science, Bangalore 560 012, India.

Satellite meetings are planned before and after the Congress at different cities in India, providing an opportunity for Congress participants to attend smaller more specialized symposia. Further information about these meetings may be obtained directly from the convenors of the individual meetings.

I. *Asian Conference on Transcription*
25-27 September 1994, Bangalore, India

Convenor: G. Padmanaban
Department of Biochemistry
Indian Institute of Science
Bangalore 560 012, India
Tel.: 91 80 344411 Ext. 2540
Fax: 91 80 341814

II. *Molecular Mechanisms of Enzyme Action*
24-26 September 1994, Bangalore, India

Convenor: H.S. Savithri
Department of Biochemistry
Indian Institute of Science
Bangalore 560 012, India
Tel.: 91 80 344411 Ext. 2310
Fax: 91 80 341814

III. *Cholinesterases*
24-28 September 1994, Madras, India

Convenors:
A.S. Balasubramanian
Neurochemistry Laboratory
Department of Neurological Sciences
Christian Medical College & Hospital
Vellore 632 004, India
Tel.: 91 416 22102 Ext. 2018
Fax: 91 416 25035

B.P. Doctor
Division of Biochemistry
Walter Reed Army Inst. of Research
Walter Reed Army Medical Center
Washington, D.C. 20307-5100, USA
Tel.: 1-202-576-3001
Fax: 1-202-576-1304

IV. *Laboratory Animals Resource Development, Experimentation and Welfare - Which Way to Go?*
13-15 September 1994, Hyderabad, India

Convenor: M.S. Bamji
National Institute of Nutrition, ICMR
Jamai-Osmania P.O.
Hyderabad 500 007, India
Tel.: 91 842 868920
Fax: 91 842 868083

V. *Plant Biotechnology Application*
16-18 September 1994, Hyderabad, India

Convenor: G.M. Reddy
Department of Genetics
Osmania University
Hyderabad 500 007, India
Tel.: 91 842 868951 Ext. 375
Fax: 91 842 869020

VI. *Genetic Rearrangements & their Biological Significance*
15-17 September 1994, Bombay, India

Convenor: S.K. Mahajan
Molecular Biology and Agriculture Division
Bhabha Atomic Research Centre, Trombay
Bombay 400 085, India
Tel.: 91 22 5514447; Fax: 91 22 556-0750

VII. *Free Radicals in Biology*
14-17 September 1994, Chandigarh, India

Convenors:
N.K. Ganguli
Post-Graduate Institute of Medical Education and Research
Chandigarh 160 012, India
Tel.: 91 172 540403; Fax: 91 172 540403

C.M. Gupta
Institute of Microbia Technology
Sector 39-A
Chandigarh 160 014, India
Tel.: 91 172 44 285

S. Chatterjee
Department of Pediatrics
The Johns Hopkins Hospital
The Children's Medical & Surgical Centre 604
600 N. Wolfe Street
Baltimore, MD 21205, USA
Tel.: 1 410 955-3197; Fax: 1 410 955 1276

VIII. *Molecular Basis of Ageing*
24-26 September 1994, Bhuvaneshwar, India

Convenor: M.S. Kanungo
Department of Zoology
Banaras Hindu University
Varanasi 221 005, India
Tel.: 91 542 310291 Ext. 354
Fax: 91 542 312059

IX. *Biochemical Education (Workshop)*
23-25 September 1994, Aligarh, India

Convenors:
A.M. Siddiqi
Department of Biochemistry
Aligarh Muslim University
Aligarh 202 002, India
Tel.: 91 571 25 741

F. Vella
Department of Biochemistry
University of Saskatchewan
Saskatoon, Canada S7N OWO
Tel.: 1 306 966 4359
Fax: 1 306 966 8718

4th Pacific Rim Biotechnology Conference
Melbourne, Australia, 6-9 February 1995

The 4th Pacific Rim Biotechnology Conference will be held in Melbourne, 6-9 February 1995 conjoint with the 12th Australian Biotechnology Conference, and is contiguous with the specialized meetings at Lorne, Victoria on protein structure and molecular biology.

The aim of the successful international series of meetings has been to establish regional networks, to develop more meaningful cooperation and to provide a forum for the recognition of opportunities in both the technology and business of biotechnology for the benefit of the peoples of this region and beyond.

The Conference will explore and highlight the latest advances and important breakthroughs in all areas of research, precommercial evaluation and commercial development of biotechnology as it impacts on all Pacific Rim countries. Included in the thematic oral and poster sessions will be detailed presentations on:

- Biotechnology Developments and Initiatives in the Pacific Rim
- Natural Resource Utilization
- Agricultural and Food Biotechnology
- Marine Biotechnology, Aquaculture
- Plant Biotechnology, Biopesticides
- Health Care, Biopharmaceuticals and Vaccines
- Cell Biology, Microbial Physiology, Biodiversity
- Genetic Engineering, Gene Transfer, Protein Expression
- Genomic Structure, DNA Sequencing
- Environmental Biotechnology and Bioremediation
- Process Development and Optimization
- Fermentation and Cell Culture; Downstream Processing
- Analytical Biotechnology, New Instrumentation
- Commercialization Experiences and Opportunities
- Regulatory Affairs and Intellectual Property Issues
- Finance, Marketing, Government Policies
- Risk Assessment, Safety, Public Perceptions
- Education, Technology Transfer

Contributions to the Conference proceedings are invited in any area of biotechnology activity, and particularly those outlined above. Any person wishing to submit an abstract should contact the Conference Secretariat for detailed information and registration form. The deadline for the receipt of abstracts is **31 August 1994**. Contributors will be notified shortly thereafter of the acceptance of their paper, and whether a poster or oral presentation is required. The deadline for early registration will be **31 October 1994**.

All accepted contributions will be published in the Conference Proceedings which will be made available to all registrants. Acceptance of papers is conditional upon at least one author registering and being present at the Conference.

English will be the official conference language.

For further information contact:

Dr. Ian Prince (Conference Chairman)
Dept. Chemical Engineering
Monash University, Clayton, VIC. 3168
Australia
Tel.: +61 3 905 3449; Fax: 61 3 905 5686
email: ian.prince@ce eng.monash.edu.au

Mrs. Barbara Arnold (Conference Secretary)
Australian Biotechnology Association Ltd.
P.O. Box 4, Gardenvale, VIC. 3185
Australia
Tel.: 61 3 596 8879; Fax: 61 3 596 8874

B. COUNTRY NEWS

Canada

National Research Council (NRC) strategic assessment of the biotechnology programme

This English/French publication is the final report of the review committee set up in 1990 to assess Canada's $60 million commitment to biotechnology. The authors note that "biotechnology has not grown as quickly as expected", but remain confident that the potential remains for influence on many industrial sectors.

Of Canada's 250 biotech-involved firms, only 27 per cent operate in health care (contrasting with the United States); a substantial number related to agriculture, forestry and aquaculture.

Critical issues mentioned by the report are a lack of investment capital, the regulatory environment, and intense competition. It notes concerns about "fragmentation of public sector efforts ... inadequate linkages with industry to identify commercial priorities and opportunities", advocating better coordination and focused efforts.

The report makes a series of 10 recommendations, culminating in the need to develop a five-year strategic plan. The authors emphasize level funding and better focusing; a review of options for the Biotechnology Pilot Plant at Montreal; and "research projects which can contribute to decreasing the negative impact of regulations on the competitiveness of Canadian biotechnology".

For copies of the report, contact Dr. Alain Albagli, Head of International Affairs, at NRC, Ottawa, Canada K1A OR6; Tel.: (1)613-993 7362; Fax: (1)613-952 9907. (Source: *EBIS*, Vol. 3, No. 2, 1993)

European Community

Political agreement on biotechnology

Chaired by Belgian's Minister of Foreign Trade and European Affairs, Robert Urbain, the Internal Market Council completed its work on 15 December 1993. Amongst others, it approved its "common positions" on biotechnological inventions. The Council agreed, by qualified majority, to a political agreement on its "common position" on this proposal, which aims at harmonizing the conditions for issuing licences for biotechnological inventions and certain related provisions. The directive includes strict criteria for patents on procedures and methods interfering in the bodily integrality of man or animals. The most difficult discussion, however, concerned questions of ethics: Spain and Luxembourg both voted against (because of ethical objections), as well as Denmark, which recently finalized decisions in this connection at national level. As it stands at the moment, the directive should be transposed into national legislation by Member States by 1996, at the latest. The Council has charged Coreper with pursuing work with a view to officially adopting the common position in the near future. (Extracted from *TEXTLINE database*, 18 December 1993)

Global perspective 2010: The case of biotechnology

The final report prepared for the EC-FAST programme (with co-sponsorship from the concertation action of the BRIDGE programme) by the Science Policy Research Unit of the University of Sussex, UK, aims to identify the factors that will promote the application of biotechnology to important global problems confronting the world in 20 years' time. The 77-page report contains the following chapters:

- Present and future trends in the applications of biotechnology;
- The role of the private and public sectors in the development of biotechnology;
- Regulations;
- Intellectual property rights (IPR);
- Regional development of biotechnology.

The report recommends that the developing countries adopt IPR for biotechnology products and processes to encourage the licensing of foreign technology, foreign investment and diffusion of knowledge. The report also suggests that international organizations contract industry in the first world to apply biotechnology to resolve specific developing country problems. Finally, it recommends that national Governments in the first world commit funding to support R&D on biotechnology for the environment.

Further information is available from The Editor, *EBIS*, Rue de la Loi 200, B-1049 Brussels, Belgium. (Source: *EBIS*, Vol. 3, No. 2, 1993)

Documentation centre set up at Joint Research Centre

A documentation centre, BIOSAFE, has been set up at the Community's Joint Research Centre, Ispra (Italy) to serve the competent authorities for the implementation of EC Directives 90/219 and 90/220. This will collect documents relating to biotechnology safety and regulations. The Centre will produce a regular bulletin containing, among other things, a list of the collected documents. The first issue was published in November 1992. Copies of documents not subject to copyright may be ordered. There is no charge to the competent authorities for this service but a charge of 10 ECU for each 50 pages copied will be made for all other interested parties.

Details: G. Van den Eede, BIOSAFE T.P. 634, Joint Research Centre, Institute for Systems Engineering and Informatics, I-21020 Ispra (VA). Tel.: (39)332-785239; Fax: (39)332-785483. (Source: *EBIS*, Vol. 3, No. 2 (1993))

France

Rhône-Poulenc's Bio Avenir Programme results reported

After 18 months of cooperation between Rhône-Poulenc and public-sector research teams, the first made-to-order products - herbicides and fungicides - are now being tested. Medical products should come next.

The Bio Avenir research programme was launched by Rhône-Poulenc in 1991. Significant advances have already been reported in the four principal sectors under study: human health, agriculture, biochemistry and methodology. These advances have been the subject of some 50 scientific announcements and 25 patent applications.

About half of all the research is in the health sector. Of the three major areas covered - atherosclerosis, cancer and neural degenerative disorders - the greatest progress has been made in the latter (Alzheimer's disease, Parkinson's disease), with new prospects for genetic therapy opening up.

In the agricultural sector, one of the objectives is to develop new, specifically-targeted fungicides and herbicides that will be effective in small, non-toxic doses. INRA (National Institute of Agronomic Research) is collaborating with CNRS (National Scientific Research Center) and Rhône-Poulenc in this venture. The partners have identified several enzymes essential to the growth of weeds and mushrooms and developed herbicides and fungicides that are now being evaluated. Botanical gene splicing has also yielded encouraging results. In fact, the discovery of a "co-suppression" phenomenon that allows expression of a particular gene to be inhibited offers numerous potential applications, such as for stopping certain metabolic processes.

Finally, methodological studies are under way with development of animal models of human pathologies and of the intestinal and blood-brain barriers. In that connection, the joint CEA (Atomic Energy Commission) Rhône-Poulenc laboratory is working to improve the [somatic] transport of radioactive materials (medications, insecticides, etc.) by creating natural or artificial "vehicles" for them. One of the first results from this research programme is the development of an anti-cancer medicament.

This cooperative venture between an industrial enterprise, university research teams and joint laboratories (CNRS, INRA, CEA) has already mobilized 350 scientists, including 200 from Rhône-Poulenc and 80 doctoral students. (Extracted from *Industries et Techniques*, 2 July 1993)

CEA presents fungal heavy-metal water decontamination

From micro-organisms fond of heavy metals, to biological molecules with healing powers and natural fibres that protect seedlings, Bioexpo '93 has been a good show.

Bioexpo offers everything, from a bioadhesive that replaces stitches, to lichens used to detect air pollution, and including a diagnostic kit for marine toxins. The biotechnology fair this year was held under the triple sign of health, agriculture and the environment.

On the environment side, the Atomic Energy Commission (CEA) presented its work on the decontamination of water polluted with heavy metals, using fungal fermentation residues. Certain mushrooms (or other organisms such as bacteria, algae and yeasts) can trap metallic ions in water solutions. CEA researchers are assessing the effect of fibrous mushrooms (*Rhizopus*, *Penicillium*, *Aspergillus* and *Mucor*) on cadmium, zinc, nickel, lead and silver. In practice, the fungal biomass obtained through industrial fermentation is placed in contact with the metallic solution in an agitated suspension or in a column. The biomass can absorb from 15 to 40 mg of cadmium, 13 to 50 mg of zinc and 15 to 25 mg of nickel per gram of dry matter. For example, 1 kg of *Mucor* or *Rhizopus* in powder form with a pH stabilized at 7, can completely purify 5,000 litres of water containing 10 mg l of zinc. Under the "Reward" programme of the European Community Commission, tests are being conducted now on effluents containing zinc in a 150-litre pilot line developed by Bertin.

In quite another area, the Clar company emphasized the exploitation of bovine *colostrum*, a mix of lactate secretions and blood serum components. This agricultural co-product is very rich in proteins, particularly immunoglobins, which play a protective role against infections. The *colostrum* also contains anti-microbe factors. It is used in biotechnology for cell culture and for human and animal food. Cosmetics also rely on its growth factors and its polyunsaturated fatty acids. Clar has perfected the preparation process for a product derived from *colostrum* and which is said to be useful as a foetal calf serum substitute in animal cell culture. This product will be marketed by the end of 1993.

Plants and animals, sentries of the environment

Are "natural" indicators of environmental pollution anachronisms or just the opposite, the coming thing? The question does not even arise for Marie-Agnes Letrouit from Pierre and Marie Curie University where she studies lichens as indicators of air pollution. Thanks to species sensitive to sulphur dioxide, it is possible to map acid pollution at various levels (plant, city, region). The property of lichens to accumulate various elements makes it possible to study fluorine, lead or radioactive pollution. Lichen analysis also can detect the presence of nitrogen pollution. Jean-Louis Riviere, at Inra, is studying "witness" animals as markers for assessing risks associated with discharges. He cites the sewer rat which is, according to him, an exceptional model for evaluating the impact of a polluted site on health, since this species lives in cities and proliferates in urban peripheries. (Extracted from *Industries et Techniques*, 2 July 1993)

Germany

Amendment of the German Genetic Engineering Law (GenTG)

The German Genetic Engineering Law, which came into force on 1 July 1990, has been under review for several months. Industry and scientists argue that the "insurmountable bureaucratic burdens have to be overcome" for the development of a competitive German biotechnology industry. They are also very concerned that the law has been interpreted in different ways in the different *Lander*. Furthermore, the European Commission has requested the German Government to make the necessary changes to correctly implement the

EC Directives 90/219/EEC and 90/220/EEC on the contained use and deliberate release of GMOs. As a consequence, the Ministry of Health issued a draft proposal for a revision of the law on 17 March 1993. The initial *Bundestag* resolution called for much wider amendments (including the corresponding EC-Directives) but the present draft appears to be in line with the existing EC Directives. A first discussion with different interest groups was organized in the middle of April 1993. Both the *Bundestag* and the *Bundesrat* will probably debate the new law for the first time before the summer break.

The main proposed amendments include:

1. Production plants for work with group 1 (no risk) organisms will require to be notified only. The time-limit of 90 days will be dropped.

2. Time-limits for research work with micro-organisms in group 1 (no risk) and group 2 (low risk) will be shortened by 30 days. The obligatory participation of ZKBS will be dropped in certain cases.

3. Further continuing work with organisms in higher safety classes (groups 2, 3 and 4) will require notification (the time-limit of 90 days will be dropped).

4. Public hearings for the authorization of a production plant in lower safety classes (groups 1 and 2) will be dropped, and construction of the plant can be started before the permit is received.

5. The possibility of introducing simplified procedures as foreseen in the EC Directive 90/220 will be included. A public hearing in those cases will not be necessary.

Recently, several consumer and environmental organizations such as the *Deutsche Naturschutz Ring* (German Environmental Society) and the *BUND* (Friends of the Earth) have agreed on a common position on the revision of the Gene Law. Their main demands are:

1. The purpose of the law should be limited to the protection of human health and the environment and should not include the promotion of genetic engineering.

2. Inactivation of all GMOs and the DNA in all industrial plants and laboratories.

3. Public participation must take place for all commercial plants at every safety level.

4. The authorization procedure must be kept transparent.

5. Products placed on the market containing or consisting of GMOs should be labelled.

6. A general product liability for the producer should be established.

(Source: *EBIS*, Vol. 3, No. 2, 1993)

Italy

Ecogen wins Italian approval

Ecogen (Langhorne, PA) says its marketing partner Roussel Uclaf (Paris) has received approval from the Italian Ministry to sell three of Ecogen's *Bacillus thuringiensis* biopesticides. Roussel Uclaf expected to begin marketing the products in Italy. The biopesticides are already sold in the United States, Mexico and some Asian countries. (Source: *Chemical Week*, 26 May 1993)

Activities to promote R&D programmes and services in the bioinformatics field

The need to set up research centres and provide biotechnology-relevant information in less developed regions, such as the Italian *Mezzogiorno*, has spurred TECNOPOLIS CSATA to start a feasibility study on setting up a Bioinformatics Centre within TECNOPOLIS Scientific Park in Bari. This study has been carried out in cooperation with the *Centro Nazionale delle Ricerche* (CNR - national research council - Bari area). The main implications of the study concern the opportunity of offering services in "molecular" form both to research centres and to the firms involved in the biotechnology and bioinformatics markets.

Three major objectives have been formulated:

- Provision of information on research and development (in close cooperation with other national and foreign research centres),

- Services to industry (information, quality of production, technology and computer science);

- Specialized training.

Details: TECNOPOLIS, Anna Maria Annicchiarico, P.O. Box 775, I-70010 Valenzano/Bari. Tel.: (39)80-8770321; Fax: (39)80-651868. (Source: *EBIS*, Vol. 3, No. 2, 1993)

Hungary

Biotechnology research and development in Hungary at a glance

ORGANIZATION	MAJOR FOCUS	MAJOR TECHNIQUES	EXAMPLE PROJECT
NATIONAL ACADEMY OF SCIENCES INSTITUTES			
Plant Protection Institute, Dept. of Biotechnology (Budapest)	Biological control of plant disease	Cell and tissue culture, rDNA (*A. tumefacians*)	Horizontal disease resistance in potato
Biological Research Center (Szeged)	Basic and applied research related to agriculture, food industry, pharmaceuticals	Tissue culture protoplast fusion monoclonal antibody, rDNA (various methods)	Maize virus resistance, via protoplast fusion. Production of restriction edonucleases and modification enzymes
Cereal Research Institute (Szeged)	Improvement of wheat, maize, sunflower, rape, and rice	Cell and tissue culture protoplast fusion, rDNA (various methods)	Development of double haploid wheat
Veterinary Medical Research Institute (Budapest)	Mostly basic research on etiology, pathogenesis, diagnosis and prevention of infectious diseases of farm animals, poultry and fish	Monoclonal antibody	Bovine adeno and herpes viruses; classification and analysis
Agricultural Research Institute Department of Cell Biology Department of Genetics (Martonvasar)	Primarily applied research on improvement of wheat and maize	Cell and tissue culture, rDNA (particle gun) technique	Application of haploid in wheat breeding
MINISTRY SUPPORTED RESEARCH			
Agricultural Biotechnology Center (Godollo)	Plant and animal science, molecular genetics, biochemistry and protein research	Cell and tissue culture protoplast fusion, monoclonal antibody, rDNA (particle gun among other methods)	Transformation of rice and wheat using particle gun; improvement of *in vitro* culture and plant regeneration in *Capsicum*
Institute for Animal Breeding and Nutrition (Herceghalom)	Improvement of farm species (sheep, cattle, swine)	*In vitro* fertilization, embryo transfer	Application of cytogenetics to cattle breeding
Central Research Institute for Food Science (Budapest)	Food science and technology	Cell and tissue culture, rDNA	Amylase production via genetic manipulation of *Aspergillus*

UNIVERSITY RESEARCH			
Technical University, Dept. of Engineering Biochemical (Budapest)	Engineering aspects of biotechnology	Fermentation scale-up, immobilized enzyme systems	Research of the active center of amylase
Research Institute of the University of Veterinary Science (Ullo)	Animal husbandry: horse, cattle, sheep, rabbit, pig	Embryo transfer, rDNA	Transgenic animals
STATE-OWNED FIRMS PURSUING PRIVATIZATION			
Institute for Drug Research, Ltd. (Budapest)	Human pharmaceutical research	rDNA	Development of an expression system for recombinant hirudin in *Saccharomyces*
Trigon	Human pharmaceuticals	Monoclonal antibody	Diagnostic kits for determination of human fibronectin concentration
NEW ENTERPRISES			
Diagnosticum, Ltd.	Broad line of immunology products for humans, animals	Monoclonal antibody	Osteocalcin detection
Kaali Institute, Ltd.	Private medical clinic	*In vitro* fertilization	*In vitro* fertilization

(Source: *Bio/Technology*, Vol. 10, November 1992)

Japan

Research news from NIBH

National Institute of Bioscience and Human Technology researchers have developed a water treatment for efficient removal of phosphoric acid from water. According to the team, the technology is based on a recently discovered *coccus* bacterium that can dissociate phosphoric acid in waste water. Another team has developed a way to alter alpha-amylase function, by substituting various amino acids for tyrosine in the active site of the alpha-amylase enzyme. They converted it to an enzyme that catalyzes the hydrolysis of starch into different products and hope to synthesize specific polysaccharides, such as oligosaccharides, for food additive development.

Further research at the National Institute of Bioscience and Human Technology is aimed at developing an anti-cancer agent that contains the metal, osmium. According to experiments, the osmium component inhibits cancer cell proliferation by affecting the cellular electron transmission system, a different mechanism than that of the existing metal-based anti-cancer agent, cisplatin, which contains platinum and acts by inhibiting DNA synthesis. (Source: *Genetic Engineering News*, 26 December 1993)

Research institute to demonstration test bioremediation

The Japan Research Institute and eight firms including general contractors and environmental equipment makers will jointly conduct a demonstration test on bioremediation environmental restoration technology making use of micro-organisms. Its purifying effect on soil and ground water will be ascertained in a small-scale plant set up at a site in Chiba Prefecture polluted with organic chlorine-based compounds such as trichloroethylene. The technology can restore an environment quickly without generation of secondary pollution, and its economics have been praised in the United States and elsewhere. Through the demonstration test, the companies will accelerate transfer of the technology to Japanese firms.

"Methane bacteria" (methane monoxynase), an enzyme utilized when methane is supplied, is known to convert organic chlorine-based compounds such as trichloroethylene to low molecular weight. The converted compounds can be rendered harmless by the action of other micro-organisms. Bioremediation is a technology for the restoration of polluted environments involving activation of "methane bacteria". The Japan Research Institute formed the "Bioremediation Consortium" in July 1991 with the Ebara Research

Institute, Organo, Kumiai Gumi, Takenaka Komuten, NKK, Kanto Kensetsu, Sumitomo Metal Mining and Dowa Mining, and has worked to apply the technology in Japan with the help of specialists such as the (Redmond-based) US venture startup Ecoba.

The distribution of pollution and the soil status at the site where the present demonstration test will be held were ascertained through three borings in July and October 1992 and March 1993, with the help of the Chiba Prefecture Geologic Environment Laboratory. Soil samples were also sent to Ecoba, where screening of two strains of methane bacteria has been successful. Successful purification of 5 ppm pollution to 80 ppb is reportedly anticipated.

System desigr will begin in the United States. Plans call for drilling wells tens of metres deep, dissolving methane in ground water to a several ppm concentration, and activating the methane bacteria. Three American technicians will be retained for installation of the plant. Operation is anticipated in January 1994. An initial operation of six months is anticipated.

Plans also exist for future test demonstrations to be conducted at multiple polluted sights outside Chiba Prefecture, since the circumstances in soil pollution vary widely. The Consortium would like to make bioremediation an industry by 1994. (Source: *Kagaku Kogyo Nippo*, 21 April 1993)

The Netherlands

Threatened lab closure reprieve

A decision to close one of the Netherlands most important research institutes, the Institute of Applied Radiobiology and Immunology (IARI), has been postponed following a government decision to look for another solution. The postponement, precipitated by a major outcry from Dutch scientists, gives hope that the institute and its world-renowned primate centre have a chance of reprieve.

Problems started when the recession-hit Government asked the Netherlands' organization for applied research, the TNO, to generate more of its own income from industrial contracts; overall state funding for TNO's 25 institutes was reduced slightly in real terms during 1992, but much steeper cuts have been proposed for 1993. The TNO board of directors targeted ITRI for reorganization because it was running at a severe financial loss. But the scientific community has been quick to defend the institute, which specializes in diseases such as AIDS and malaria; concerted pressure has forced the Government to look again at its plans. (Extracted from, *Nature*, Vol. 360, 3 December 1992)

Plant industrial platform

A plant industrial platform (PIP) was established in 1992 by some 20 companies involved in plant technology. So far, 17 companies have joined PIP - and the first edition of the *Plant Industrial Platform Newsletter* is now available. The participating companies come from: Belgium: ICI Seeds/SES, Monsanto Europe; France: Biochem SA, LVMH Recherche, Pioneer Hi-Bred SARL, RAGT SA, Rhône-Poulenc Agrochemie; Germany: Planta Pflantzenggenetik Biotech GmbH; Italy: Peto Italiana SRL; The Netherlands: Florigene BV, Keygene NV, Royal Sluis BV, RZ Biofleur CV, VanderHave Research, Zaadunie BV; United Kingdom: ICI Seeds, Nickerson Biocem Ltd. Membership of PIP is open to any European company - and is not limited to the European Community. Details from: Dr. G. E. de Vries, ProBio Products, Meerweg 6, The Netherlands, 9625 PJ Overschild. (Source: *Biotechnology Bulletin*, February 1993)

Biotechnology in the Netherlands - the network approach

The Dutch Ministry of Economic Affairs Project Team Biotechnology and the Netherlands Society for Biotechnology have produced a comprehensive directory of biotechnology in the Netherlands.

It includes detailed information on government and semi-government organizations, research and development institutions, professional and social organizations, public interest groups, etc., information sources and international organizations. Companies are not included, but a useful "directory of directories" of companies is provided.

The loose-leaf report (in English) is available at price Dfl. 65 from: Ministry of Economic Affairs, Project Team Biotechnology, 2500 EC The Hague. Tel.: (31)703798911; Fax: (31)703474081. (Source: *EBIS*, Vol. 3, No. 2 (1993))

Philippines

Commercializable products at BIOTECH

The National Institute of Biotechnology and Applied Microbiology (BIOTECH) is a research and development facility of the University of the Philippines at Los Baños established in 1979. Currently it is regarded as the most important biotech institution in the Philippines. BIOTECH is mandated to develop technologies for goods and services that are cheap alternatives to conventional products, safe to the environment and make use of locally available materials. Although being a public organization, BIOTECH has attempted to commercialize its research results ever since it was established. BIOTECH has developed several technologies that are nearing their final stage or are available for dissemination and commercialization.

- *Hemosep-WC*: A vaccine protecting ruminants like cattle, water buffaloes, goats and sheep against haemorrhagic septicaemia and other forms of pneumonic pasteurellosis. According to BIOTECH, the product gives complete and effective protection, remains stable and effective for two years if stored under refrigerated conditions, and does not cause adverse effects like allergic or anaphylactic reactions;

- *Ectomycorrhiza*: (in tablet or pellet form) a naturally-occurring soil fungus, which maintains a beneficial association with plant roots. The product is a cheaper and an effective alternative to chemical fertilizers. It increases the absorption of essential nutrients and water, thus improving soil aggregation, and acts as a biological deterrent against some pathogenic organisms while producing growth promoting hormones to increase plant and crop yield;

- *Nitro Plus*: A biofertilizer for legumes. This legume inoculant is an effective and cheap substitute for chemical nitrogen fertilizer. It also increases crop yield, conserves soil nitrogen, is environmentally safe, and is easy to apply. Nitro Plus is currently sold in packets of 200 and 500. Clients include soya bean farmers that participate in a national commercialization programme, and pasture land owners. Opportunities are favourable for the product because an increasing number of farmers are going into legume production;

- Another biofertilizer presently being tested is *BIO-N*, an inoculant in powder form containing bacteria that enhance growth, development and yield of rice and maize. It also sustains the nitrogen requirement of plants. BIO-N is relatively easy to apply and environmentally safe.

Contact: Mariechel J. Navarro, Extension Specialist, BIOTECH-UPLB, College, Laguana 4031, The Philippines. Fax: (+63) 2 94 2721. (Source: *Biotechnology and Development Monitor*, No. 14, March 1993)

The Russian Federation

Biotech plants come under control of new Russian company

Under the moribund Soviet economic system, biotechnology plants across the Union of Soviet Socialist Republics were controlled by a single all-powerful Moscow-based ministry, the Ministry of the Medical Industry. Following the collapse of the Soviet Union a new company, Inprobit, has emerged, which now runs a significant part of the biotechnology industry in Russia and the other republics.

Inprobit, which is based in Moscow and managed by its President Mikhail Mikhailovich Sobolev, incorporates about 70 factories, institutes, and other organizations (50 of which are located within the Russian Federation), and it possesses a workforce of more than 60,000. Its enterprises are engaged in the manufacture of a wide variety of microbiological products, including vitamins, antibiotics, enzymes, plant cell biomass, and single cell protein.

Inprobit can be contacted at Ulitsa Novyi Arbat 29, korpus 4, Moscow, GSP-2, 121883, Russia. Tel: +7 095 2913 732; Fax: +7 095 2913 807; Telex: 207 533 BIKHIM. (Source: *European Microbiology*, January/February 1993)

Sweden

Biotechnology advisory commission

Hoping to help keep developing countries from becoming a uncontrolled testing ground for genetically engineered agricultural organisms, the Stockholm Environment Institute has formed a biotechnology advisory commission to assist countries in evaluating such organisms.

Institute director Michael J. Chadwick noted that some companies have "actually almost given free," some genetically engineered organisms to developing countries as a way to test them in the field.

The commission headed by Dr. S. Ramachandran, will work primarily with the countries' Governments to review proposals and consider legal and economic issues connected with genetically engineered organisms, such as whether using them would force small farmers out of business.

The programme has been promoted to developing countries through the United Nations International Development Association (UNIDA) and the International Service for the Acquisition of Agri-Biotech Applications at Cornell University. (Source: *McGraw Hill's Biotechnology Newswatch*, 1 February 1993)

Genetic engineering - A challenge

The Swedish Government in 1990 authorized the Ministry of Justice to set up a Parliament Committee on genetic engineering (Genteknikberedningen). Its report, "Genetic Engineering - A challenge" was delivered in September 1992. A 25-page summary in English has been published, and can be ordered from the address below.

The report gives basic information about the nature and use of genetic engineering, noting scientific opinion that it is not the method itself that can lead to risks, but the organism and the result of the modification. The report describes the evolution and present rules relating to various aspects, including ethical, e.g. in public health or in research on fertilized eggs.

The uncertainties of GMO field releases are emphasized, the Committee taking the view that the assessment of risks should be part of the ethical analysis, since "it is ethically false to base a decision on poor foundations if the decision can be postponed until the foundations have improved. It is also ethically unacceptable to assert that the foundations for a decision are better than they are".

The Committee treats carefully the ethical questions relating to the use of genetic engineering, emphasizing human rights to modify nature, but also the "doctrine of nature conservation" and the need for moral responsibility.

EC Directives 90/219 (contained use of GMMs) and 90/220 (field release of GMOs) are carefully reviewed, with reference to possible Swedish membership of the EC; although they refrain from proposals in these respects.

There is no reference to the EC's April '91 communication, but the report emphasizes regulation by the laws that currently include provisions on organisms and products in the respective fields, and sees no need "for a so-called umbrella law, i.e. a law with common rules to be applied to the entire area of genetic engineering".

Intellectual property issues are competently reviewed, with attention to international developments, and no changes proposed to Swedish law. But the Committee expresses the view that "in international negotiations concerning the protection of biotechnological inventions..., Sweden should actively promote the argument that only use-linked product protection should be given for genes and micro-organisms taken from nature".

The booklet can be ordered from: Allmänna Förlaget, Kundtjänst, 10647 Stockholm; Tel.: (46)87399630; Fax: (46)87399548. (Source: *EBIS*, Vol. 3, No. 1, 1993)

United Kingdom

BIA moves towards ethical dialogue

Just as the first products of biotechnology are moving from the laboratory into the market place, biotechnologists must also emerge and explain to the world what they are doing. Otherwise, there is a danger that through ignorance and misunderstanding the general public may reject the efforts of the biotechnology community.

Organizations such as the BioIndustry Association (BIA) exist to promote constructive dialogue amongst the various stakeholders such as government bodies, public interest groups, the general public or even the sector itself.

Already the BIA has an open dialogue with a number of government departments on subjects such as environmental regulation, through to funding the science base. But BIA members have signalled their interest in increasing the dialogue with environmental pressure groups, according to a survey conducted on behalf of the BIA by SustainAbility Ltd. Two-thirds of respondents reported that environmental issues are already an important consideration for business, while another fifth said they expected such issues to become so in the coming years. Furthermore, 88 per cent of BIA members polled said that they saw value in dialogue with environmental groups. This gives the Association the mandate to be able to talk with such organizations. As such, the BIA has a tremendous opportunity to promote open and constructive dialogue between the various stakeholders, government, companies both large and small, environmental campaigners and the general public.

Indeed, consumer reactions to biotechnology are now beginning to be measured. The London based Food Safety Advisory Centre revealed that during October 1992 almost 1 in 20 (4.9 per cent) calls it received concerned genetic engineering. A straw poll of callers to the centre threw up some interesting answers concerning biotechnology and its application by the food sector. Most people (80 per cent of sample) did not believe they get enough information about biotechnology and only 28 per cent were able to describe what the term meant. Despite this level of ignorance, 84 per cent of those questionned said they believed that foods produced using recombinant DNA technology should be clearly labelled as such. Many callers (44 per cent) were concerned that food biotechnology would lead to products that were less safe, while 44 per cent were unsure if it would make a difference. Only 12 per cent believed biotechnology could lead to safer foods.

It was for these reasons that the BIA took the opportunity to use its inaugural annual meeting to open up the ethical debate about biotechnology and its applications. The BIA is keen to engage in constructive debate and discussion with all those showing an interest in biotechnology. It does not claim to have the monopoly on this subject, but wishes to hear and understand the views of others as well as to have the opportunity of explaining what the Association is doing. Speakers and delegates representing all strands of opinion took part in a lively and informative meeting. Academics and industrialists outlined the successes so far and the potential of technologies, such as gene therapy,

still to be realized. But the meeting also gave leading environmentalists such as Jonathan Porritt an opportunity to voice their concerns while the Archbishop of York, Dr. John Hapgood, himself a biochemist, considered the ethics of the sector.

Interestingly, the major worry for many environmentalists is not biotechnology *per se*, but how it might be used by the multinationals. The issues of agbiotech are now being considered as a possible topic for the second BIA annual meeting. There is as yet no consensus internationally about how to deal with the campaigns of biotechnology's opponents. Some Association representatives do not believe debating with opponents is a constructive use of time, although clearly many British companies welcome such dialogue. Nevertheless, there was general agreement that associations should contribute to a database of support materials, detailing publications and programmes that exist that may be used to promote a more positive image of biotechnology.

International Roundtable

Delegates representing the largest biotechnology associations in the world, accounting for more than 2,800 companies at an international roundtable of biotechnology trade associations hosted by the BIA prior to their annual meeting, agreed that there are grounds for closer cooperation and information exchange between the various groups. In a bid to improve international dialogue the representatives agreed to establish an electronic information exchange network "to provide more immediate responses to relevant issues". During the two days of discussion the representatives discovered that among the associations present there was a wealth of experience and information that was untapped. So rather than each association reinventing the wheel it was decided that all groups should inform the others of the information and resources they possess that would be of mutual benefit. During the discussions it emerged that most countries suffer shortages of key personnel, particularly experienced staff in downstream processing and management. Only the Japanese delegation reported no problems. European representatives noted the importance of programmes such as BEMET and all delegates agreed to exchange information they had on education and training. (Source: *Biotechnology Bulletin*, January 1993)

New regulations on contained use of GMOs laid before Parliament

New regulations governing the contained use of genetically modified organisms (GMOs) were laid before Parliament on 23 December 1992 by the Employment Minister, Patrick McLoughlin. The regulations, which came into force on 1 February 1993, are the result of extensive consultation and implement a European Council Directive (90/219/EEC, of 23 April 1990). Under the regulations, there will for the first time be a consent procedure for work involving GMOs, as well as provisions for both the human health and environmental protection aspects of such activity. The main requirements on persons carrying out GMO work will be to:

- Notify the Health and Safety Executive (HSE) of an intention to carry out the work and, in certain higher risk cases, await consent;
- Classify operations, and the organisms used, according to a prescribed scheme;
- Carry out a risk assessment;
- Adopt controls, including suitable containment measures;
- Draw up emergency plans; and
- Notify the HSE of accidents involving GMOs.

Other provisions deal with the disclosure to the public of information given to the HSE by notifiers. Certain information on activities requiring consent will be placed on a public register, but safeguards for the protection of particularly sensitive information have been included. A document giving practical advice on how to comply with the new regulations will be published shortly by the HSE and will be available from HMSO. The new legislation - the Genetically Modified Organisms (Contained Use) Regulations 1992 - replaces and builds on the Genetic Manipulation Regulations 1989. Unlike existing legislation, the new regulations will not cover the deliberate release of GMOs into the environment. Instead, this aspect will be covered by a parallel set of new regulations, implementing another EC directive, shortly to be laid before Parliament by the Government under the Environmental Protection Act, 1990. Copies of *The Genetically Modified Organisms* (Contained Use) *Regulations 1992*, SI 1992, No. 3217 (ISBN 0-11-025332-1) are priced at £4 and are available from Her Majesty's Stationary Office, London, UK. (Source: *Biotechnology Bulletin*, January 1993)

Biotechnology controls

The Royal Commission on Environmental Pollution (RCEP) has sent its views to the Department of the Environment on the Government's revised proposals for regulations on the use and release of genetically modified organisms (GMOs).

The Commission notes that, in a number of respects, these draft regulations reflect its previous recommendations. However, it repeats two of its earlier recommendations, which are both aimed at strengthening the safeguards for GMO releases.

First, it argues that the legal responsibility for a release should be placed on a specified individual. Second, it suggests that full information should be available to the Secretary of State about the relevant experience of such persons, preferably through the keeping of a register or record of people competent to carry out releases of GMOs. Details from: Royal Commission on Environmental Pollution, Room 653, Church House, Great Smith Street, London SW1P 3BZ or on 071 276 2128. Fax: 071 276 2098. (Source: *Biotechnology Bulletin*, November 1992)

European Bioinformatics Institute

The UK has submitted its bid to host one of Europe's most important scientific facilities, the European Bioinformatics Institute (EBI). The EBI will provide a computerized library of information about human and animal genes to researchers across Europe. It will be an outstation of the European Molecular Biology Laboratory (EMBL), which is based in Heidelberg, Germany.

The site proposed by the bid, which is strongly supported by the Government and has been drawn up by the Medical Research Council (MRC) and The Wellcome Trust, is on the outskirts of Cambridge. Details from: Medical Research Council, 20 Park Crescent, London W1N 4AL. (Source: *Biotechnology Bulletin*, February 1993)

United States of America

Biotechnology Information Center

The Biotechnology Information Center is one of 11 information centres at the National Agricultural Library located in Beltsville, Maryland. The Biotechnology Information Center provides access to a variety of information services and publications covering many aspects of agricultural biotechnology. Specific topics include theory and techniques of genetic engineering, plant and animal genetics, monoclonal antibodies, single-cell proteins, food processing, biomass applications and risk assessment and bioethics. The Center's staff is familiar with concepts and techniques used in biotechnology and can guide library users in securing biotechnology information for business, research and study. In addition, the Center can perform brief, complementary searches of the AGRICOLA database on specific biotechnology topics or conduct an exhaustive search of most major databases on a cost recovery basis. The Center can also refer patrons to organizations or experts in the field of agricultural biotechnology and furnish users with Quick Bibliographies or Special Reference Briefs on a variety of topics such as "Genetic Engineering for Crop Plant Improvement", "Ti-Plasmid and Other Plant Gene Vectors", "Biotechnology and Bioremediation", "Public Perception", "Risk Assessment", "Legislation and Regulation of Biotechnology", and "Biotechnology and Bioethics."

The National Agricultural Library, located in Beltsville, Maryland, USA, is the foremost agricultural library in the world. The library acquires books, journals, maps, audio-visuals, oral histories, and microcomputer software related to the field of agriculture. The library also produces the "Bibliography of Agriculture" and the AGRICOLA database. Tours of NAL are available by appointment. For further information concerning the services and activities of the center, contact: Dr. Susan McCarthy, Biotechnology Information Center, National Agricultural Library, Room 1402, 10301 Baltimore Blvd., Beltsville, MD 20705-2351 USA. Tel.: (301) 504-5947 or (301) 504-6875. Fax: (301) 504-7098; TTY: (301) 504-6856. Internet: Biotech @ nalusda.gov. (Source: *BioLink*, Vol. 1, No. 2, 1993)

US-AID mission perspectives

Funding approaches

The Agency for International Development (AID) is a complex and highly decentralized organization giving support and assistance to developing countries in a number of ways. Central ("core") funding, through the regional and central bureaux, located in Washington, D.C. provide financial support to projects which are globally or regionally focused. ABSP (Agricultural Biotechnology for Sustainable Productivity) is such a project and receives its funding from the Office of Agriculture, Bureau for Research and Development. Regional focus in ABSP, by virtue of the core award is in Asia, Africa, and Latin America.

Individual AID offices ("missions"), located in each country retain a separate budget and portfolio of activities. Additionally, missions may access centrally-funded projects, such as ABSP, through a process informally called a "buy-in", which involves a transfer of mission funds into a centrally-located project's account. Buy-ins are designed to accomplish the specific initiatives mandated by the project in accord with the interests of the missions and their respective countries.

To date, ABSP has been enthusiastically received by various AID missions and developing country national programmes. A number of activities have recently been initiated whereby additional countries, which were not designated for inclusion in ABSP under the core award, are being included through mission buy-ins. The details of specific mission-funded projects will be highlighted in future issues of this newsletter; however, at this point, it may be of greater interest to look at possible reasons for this early, active response to the project.

Recently, many AID foreign assistance programmes have begun to effect a more active involvement on the part of private sector entities in the US and its client countries. This involvement has particular benefit for programmes in biotechnology,

since much of the technology is based in the private sector. Conversely, traditional support for basic agricultural research in the public sector, which has long been the foundation of AID agricultural assistance programmes is currently receiving less emphasis.

Many recent AID initiatives in agriculture have been in agribusiness as opposed to research. Despite the change in focus, the agency and its clients have a continuing interest in realizing the full scientific and institutional benefit of past investments in agricultural research. ABSP has the capability to assist in that realization in a number of ways.

First, biotechnology is a cross-cutting science with orientation in both basic research and product development. ABSP is geared directly towards product development with discretionary funds in the budget allocated as seed money for commercial product development of promising research results.

Second, the project fosters direct linkages between the public and private sectors; for example, the core award includes financial support for the US university community (Michigan State, Texas A&M, Cornell) as well as the private sector (DNA Plant Technology). Involvement of developing country institutions also includes a variety of public groups (KARI in Kenya, CRIFC in Indonesia) and the private sector (Agribiotechnologia de Costa Rica). ABSP capabilities in facilitating diverse linkages are further exemplified in its role as sponsor of memberships in the Association of Biotechnology Companies (ABC). ABC is one of two primary biotechnology trade associations in the US and has as its members companies, universities and research institutions throughout the world.

Third, ABSP is attractive to developing countries seeking to move into the biotechnology arena but unable to access technology that is quickly becoming more proprietary and "privatized". Private sector linkages have been established in ABSP from its initiation, so involvement with the project gives developing country programmes direct access, which can serve to drive reform within their own research system.

Finally, ABSP fosters an integrated approach to the promotion of biotechnology in developing countries by supporting human resource development in technical and policy areas, such as intellectual property and biosafety, which may have a direct impact on the success and adoption of the technology. By supporting consultants and developing country interns in these areas, ABSP hopes to establish a policy environment which encourages the growth and commercial potential of biotechnology. This support is important to developing country programmes which recognize that increased capability in these areas is critical to the success of fledgling biotechnology programmes.

In summary, biotechnology is a growing industry in the USA, which evolved from support to public sector research institutions. Through careful management and an integrated approach, support provided to developing countries can effect a similar transition with mutual benefits to the US and its client countries. ABSP appeals to AID missions because it seeks to effectively link agricultural research investments to the growth of a new agro-industry. (Source: *BioLink*, Vol. 1, No. 1, 1992)

Biotechnology, biologics, and environmental protection

The Animal and Plant Health Inspection Service (APHIS), Biotechnology, Biologics, and Environmental Protection (BBEP) is represented on the Technical Advisory Group of the Agricultural Biotechnology for Sustainable Productivity project to provide scientific, technical, and regulatory advice on matters related to biosafety, environmental safety, and the exportation and importation of genetically engineered organisms.

The US Department of Agriculture (USDA) regulates the products of biotechnology on a case-by-case basis under its existing statutory mandate. USDA's broad authority to protect plant and animal health is applicable to the regulation of plants, micro-organisms and veterinary biological products developed through biotechnological processes. The USDA agency with a major responsibility for regulating these products is APHIS.

Animal and Plant Health Inspection Service (APHIS) regulates the environmental release of certain genetically engineered plants and micro-organisms through the use of a permit process. To date, APHIS has issued nearly 350 permits for such environmental releases. APHIS also uses a permit process to ensure that the importation and interstate movement of certain plants and micro-organisms and all veterinary biological products does not pose a risk to plant and animal health and the environment.

Biotechnology, Biologics, and Environmental Protection (BBEP) coordinates biotechnology regulatory policy for the APHIS and with other USDA regulatory agencies, acts as liaison with public and private organizations on biotechnology regulatory matters, issues permits for the movement and release of genetically engineered organisms and commercial licenses for veterinary biological products; ensures that APHIS programmes comply with the applicable environmental laws; prepares and reviews comprehensive environmental risk analysis and environmental assessments; acts as the agency's primary contact on environmental issues; provides internal policies and procedures for pesticide registration; provides quality assurance/quality control for the agency's laboratories and plant method centers, and environmental monitoring including chemical analysis for pesticide residues.

The regulatory programme, the APHIS, BBEP regulatory programme for the products of biotechnology promotes the transfer of the technology to the marketplace by concentrating on safety and environmental issues, as well as timeliness, in field test and product reviews. As a regulatory agency, APHIS has a balancing role. On one hand, the regulations should be informative, rational and scientifically based, avoiding regulatory uncertainty that can slow down new product development, discourage investment in biotechnology, and lead to the complete abandonment of the technology. Biotechnology regulations should act as a catalyst for safe technology transfer.

APHIS has been looking at the global impact of biotechnology regulatory activities, and has played a leading role in the international harmonization of regulatory policy. Regarding biotechnology regulation, APHIS is committed to the following goals: to develop a balanced regulatory framework; to assure that the regulatory structure is scientifically based; to maintain a regulatory structure based on risk, not process; and to have a harmonized regulatory structure at both national and international levels to protect agriculture and the environment, while facilitating safe technology transfer. (Source: *BioLink*, Vol. 1, No. 1, 1992)

The ICI relationship

US-AID and ICI Seeds have entered into a collaborative agreement, through a contract with Michigan State University, as part of AID's Agricultural Biotechnology for Sustainable Productivity (ABSP) project. ICI will develop, through genetic engineering, insect-resistant tropical corn for Indonesia. The immediate goals of the three-year AID ICI collaboration are: (a) to produce commercially-important insect resistant germplasm for Indonesia; and (b) to train a team of Indonesian scientists in the genetic engineering-enabling technology. In the longer term, it is hoped that commercialization of the germplasm can be achieved through partnership with a private company in Indonesia.

ABSP represents an opportunity for ICI Seeds to address a target, in a developing country, in circumstances of shared cost and, as a consequence, lowered commercial risk. There is clearly synergy between the goals of AID and ICI Seeds in the development of a market for tropical corn in Indonesia. Recent advances in genetic engineering in corn have made possible the conferring of resistance to Asian Corn Borer, a serious insect pest in much of the corn growing areas of Indonesia, by transforming commercial lines with insect control protein genes isolated from *Bacillus thuringiensis* (Bt).

ICI Seeds is currently engaged in research aimed at introducing insect resistance into its US corn hybrids through genetic engineering. A team of researchers, dedicated to this project, covers a range of disciplines including molecular and cell biology, molecular screening, laboratory and field-based entomology, and plant breeding. In addition, ICI Seeds has acquired substantial experience in working with federal regulators on the development of a viable strategy for field testing transgenic crops. Currently ICI Seeds is conducting a second field trial of transgenic corn in Iowa and is involved in trials of other transgenic crops in other states. ICI Seeds is playing an active role on a variety of fronts involving the integration of biotechnology and agriculture and plans to pass on that experience to its Indonesian collaborators.

ICI Seeds and US-AID have identified an important target for biotechnology in Indonesia. The outcome of a successful project could be an improvement in corn yields of up to 40 per cent. The stability of yield would also be enhanced and, therefore, bring about a significant improvement in the reliability of the corn crop's contribution to the food supply in Indonesia. (Source: *BioLink*, Vol. 1, No. 1, 1992)

New centre for ethics and applied biology

A leading immunology researcher is funding a centre dealing with ethical questions raised by biotechnology. Edwards S. Golub, Ph.D. established the Pacific Center for Ethics and Applied Biology in 1992.

The Center's first event will be a workshop on teaching bioethics, in June in Bar Harbor, Maine, aimed at teachers who are responsible for communicating ethical principles to young scientists and will focus on how to deal with misconduct, including sloppy science, conflicts of interest, university-industry relations, and the social responsibilities of scientists. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 1 February 1993)

ABC and IBA expected to merge

In what is billed as a major development for the US biotechnology industry, its two trade associations are expected to merge. The Industrial Biotechnology Association (IBA) represents 143 biotechnology firms, including heavyweights such as Biogen and Genentech, whereas the Association of Biotechnology Companies (ABC), represents 320 smaller firms. Commentators note that the two organizations have promoted similar views around "99.9 per cent of the time".

The new Biotechnology Industry Organization will combine the 150 member companies of Industrial Biotechnology Association and the 340 member firms of Association of Biotechnology Companies.

Officials say the combined group will represent more than 90 per cent of the industry's $5.9 billion in product sales and a majority of the 79,000 jobs directly in the biotechnology industry.

Membership in the new Organization will include more than 300 of the core biotechnology firms in the US as well as 60 biotechnology centres, scores of suppliers and support organizations, state and local affiliates, university research centers and members in 27 countries.

The action was subject to ratification by the membership of both organizations at the annual meetings in spring 1993. Administrative details will be addressed when the merger is completed and BIO officially comes into existence. (Source: *Biotechnology Bulletin* and *Chemical Marketing Reporter*, 18 January 1993)

Approval sought for food additive gene

Calgene Inc. is asking the US Food and Drug Administration to approve kan(r), a selectable marker gene, as a processing aid under food additive provisions of the Federal Food, Drug and Cosmetic Act. The request follows a petition from November 1990 asking FDA for permission to use the gene in genetically-engineered plants.

The Department of Agriculture decided in October 1992 that it would no longer regulate Calgene's Flavr Savr tomato, which contains the kan(r) gene. The tomato can now be grown and sold without USDA's permission, however, the FDA is still reviewing the firm's August 1991 request to approve the tomato as a food.

The US government's policy towards bioengineered foods has touched off protests throughout the country, including a petition by 1,500 gourmet chefs and threats to boycott bioengineered foods.

Meanwhile, DNA Technology Corporation says a team of DNAP and Dupont scientists have demonstrated the use of a patented plant-based selectable marker gene called acetolactate synthase, which is found in all plant-based food and has been isolated by the team. (Extracted from *Chemical Marketing Reporter*, 18 January 1993)

US Army asked to widen vaccine tests

Leading AIDS researchers formally asked the US Army in December 1992 to use a $20 million windfall to test several competing AIDS vaccines, not just the one its own researchers are investigating. Congress approved the money in October for a large-scale trial of gp160, a protein from the coat of HIV, as a therapeutic vaccine to treat people infected with the virus.

Congress added the money to the army's budget, but gave the National Institutes of Health a chance to veto the trial. Officials at the NIH were infuriated by what they saw as political meddling in scientific decisions, but decided not to block the trial, because the $20 million would revert to the treasury. Instead, they are trying to persuade the army to expand the trial to include several other experimental vaccines.

Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases, reviewed data from preliminary trials with several products that have been proposed as therapeutic vaccines, including gp160. All the data tell the same story, says Fauci. The candidate vaccines are relatively safe and stimulate some immune responses, but there is no evidence that any of them reduces the level of HIV in the blood, or significantly benefits patients in the long term. However, the only convincing evidence will be if patients live longer, and that data will not be available until 1996 or later. (Source: *New Scientist*, 5 December 1992)

Biotechnology soared and fell in a roller-coaster 12 months

A report by stock market analysts on the past year in US biotechnology reflects the mixed fortunes of an industry in which most companies are still losing money despite improving financial indicators. The availability and cost of new capital and an unpredictable regulatory environment continue to be a concern.

The report* points out that in the year ending June 1992 the industry raised more than US$ 3 billion in public equity, exceeding the total for the entire decade of the 1980s. In January, Amgen Inc. of Thousand Oaks, California, became the first biotechnology company to be included in the *Fortune* 500 business list, with sales of $645 million in 1991, largely from its first two products, Epogen and Neupogen. Other companies were not so fortunate. It was also a year in which, despite an increase of 29 per cent in revenues for public companies (to $4.5 billion), four out of five publicly held companies lost money and do not expect to make a profit before the middle of the decade.

Increasingly, companies are trying to accelerate commercialization and spread their risk. By acquiring licences for late-stage technologies from other companies and by exchanging products, companies are generating revenues in the short-term and improving their chances of survival. Through acquisitions, partnerships and strategic alliances, they are acquiring manufacturing capabilities and sales forces to produce and distribute their own lines.

The past year saw little change in the demographics of the industry; smaller-sized companies still predominate, with 76 per cent of companies having 50 or fewer employees. There have been double-digit

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* *Biotech 93 Accelerating Commercialization*: Ernst & Young's Seventh Annual Report on the Biotech Industry (Ernst & Young, San Francisco, California, 1992)

percentage increases in both the number of companies and numbers of employees, to 1,231 and 79,000 respectively. As in the past few years, when the industry is broken down by market sector, the survey found that more companies are specializing in human health care than all other market segments combined.

Agricultural biotechnology has in the past been the poor relation of the human health care segment. However, two recent developments on the regulatory front could pave the way for agricultural biotechnology. In May, the FDA announced that foods developed using genetic engineering pose no new or special safety risks to the consumer and should be subject to the same standards of regulation as other foods, and in November 1992, the US Department of Agriculture announced plans to ease regulation of US field tests of genetically engineered crops. The report adds that optimism must be tempered by a need to inform the public about the safety and benefits of genetically engineered agricultural products. (Extracted from *Nature*, Vol. 360, 19 November 1992)

Crop genetics gets biopesticide okay

Crop Genetics International (Columbia, MD) has received the Environmental Protection Agency's go-ahead for its Spod-X bioinsecticide based on an insect virus. DuPont has a strategic alliance with Crop Genetics for virus-based bioinsecticides and provides funding to Crop Genetics to develop production techniques. The alliance also covers field testing and world-wide marketing. The EPA approval is the first for such a virus-based product in 10 years, but major pesticide makers, including Sandoz, American Cyanamid and FMC, have increasingly shown interest in virus-based insecticides as an alternative to chemical products. Crop Genetics must complete an additional study before commercialization but says it expects to begin selling the biopesticide by 1994. The firm has two other virus-based products waiting EPA approval. (Source: *Chemical Week*, 26 May 1993)

C. RESEARCH

Research on human genes

Familial Alzheimer's linked to chromosome 14 gene

The Human Genome Project is now providing researchers with a wealth of new "markers" for mapping the chromosomal locations of disease genes that show more variation, and can therefore provide more information about inheritance patterns, than the old ones. A team led by Gerard Schellenberg of the University of Washington School of Medicine in Seattle reports locating on chromosome 14 a genetic defect linked to an inherited form of Alzheimer's that develops unusually early, at about 45 years of age. Their finding is buttressed by unpublished results from two additional groups that have found linkage between early onset, familial Alzheimer's and a chromosome 14 gene.

None of these groups has yet pinned down the identify of the chromosome 14 gene, but once they do, having the gene should lead them to the biochemical defect that gives rise to the brain degeneration in the affected families. And finding that mechanism, they hope, will point the way to understanding the molecular mechanisms underlying all Alzheimer's cases.

But while the researchers have narrowed down the location of the chromosome 14 gene, they are still a long way from actually finding the gene. They now have to sort through 10 million base pairs of DNA, which may contain hundreds of genes. It will be worth the effort, though, especially if it resolves the vexing β-amyloid question as researchers hope.

The researchers will be looking to see whether the protein encoded by the chromosome 14 gene can be connected to APP synthesis or processing. Also, there are a couple of candidate genes in the region containing the gene that might fit the bill. One is the *fos* gene, which makes a transcription factor that might increase the activity of the APP gene, thereby making more of the protein. Another encodes a heat shock protein that might be involved in the cell's protein-processing pathways. But even if the chromosome 14 gene has nothing at all to do with β-amyloid formation, it should nevertheless provide some clue to Alzheimer's. It is also clear that the gene will not be the last to be linked to familial Alzheimer's. The disease in a group of US families with hereditary Alzheimer's, who are known as the "Volga Germans" because they are descended from Germans who settled along the Volga River in the 18th century, shows no linkage to either chromosome 14 or 21 - nor for that matter, Schellenberg says, to chromosome 19, the site of a gene that has been linked to some cases of late onset Alzheimer's, occurring after the age of 60.

That indicates that at least four genes can cause the disease. When they are all isolated, researchers should have a wealth of clues to Alzheimer's etiology and as the number of genes increases, the disease's genetic heterogeneity, far from being the obstacle it was once thought to be, may well turn out to be a major boon for researchers. (Extracted from *Science*, Vol. 258, 23 October 1992)

Geneticists put finger on key factor in Alzheimer's

A year of rapid development in the understanding of Alzheimer's disease has been capped with the discovery of the cause and mechanism of one form of the condition. Scientists in the US have shown that a genetic defect carried by some Alzheimer's sufferers

stimulates cells to generate abnormally large amounts of amyloid, the protein that congests the brains of people with the disorder.

The research provides the strongest evidence yet that amyloid is the critical agent in all types of Alzheimer's disease. It may also provide a new diagnostic test.

Teams under Dennis Selkoe at Harvard Medical School and Ivan Lieberburg from Athena Neurosciences, a company based in San Francisco, focused their efforts on members of a Swedish family who carry genetic defects on chromosome 21. The mutations affect a stretch of DNA that codes for the amyloid precursor protein, which surrounds the amyloid molecule.

The researchers transferred the gene for the Swedish precursor protein into human cells. These cultures produced between six and eight times as much amyloid as normal cells.

The researchers are working with doctors in Sweden to measure the concentrations of amyloids in the cerebrospinal fluid of affected people. In future, such measurements may yield an early diagnostic test, because deposits of amyloid build up years before dementia sets in. The picture emerging is one in which a variety of environmental factors and genetic or chromosonal defects leads to a build-up of amyloid in the brain which, in certain circumstances, damages the brain cells and leads to dementia.

Selkoe draws an analogy between the role played by amyloid in Alzheimer's and the relationship between cholesterol and coronary heart disease. Too much cholesterol may be the result of a variety of genetic mutations or environmental factors such as a diet rich in meat. However, individuals with high levels of blood cholesterol may live to a ripe old age, while people with low levels can die young, of heart disease. The same riddles that apply to cholesterol have also to be worked out for amyloid, says Selkoe. (Source: *New Scientist*, 19/26 December 1993)

Athena scientists find 'key' Alzheimer's peptide, discovery may lead to test

Athena Neurosciences researchers have successfully measured a key component of Alzheimer's disease in spinal fluid and blood, a discovery they say may lead to a test for the disease within a few years.

The company hopes to use the finding to identify people at risk for developing Alzheimer's to follow the progress of patients and, eventually, to develop a treatment for the disease.

The elusive material isolated by the researchers is a tiny protein called beta-peptide that accumulates at the centre of a web of dead or dying cells in the brains of Alzheimer's patients. Researchers have been confounded as to its source.

Athena began a collaboration with San Diego company Hybritech Inc. in July to fashion a monoclonal antibody that could detect minute amounts of beta-peptide.

Using the Mab, the group not only isolated small amounts of a soluble form of beta-peptide from spinal fluid, but also measured it in blood. Athena found it in healthy people as well as those with degenerative mental disorders.

The Athena group collaborated with researchers at Harvard Medical School and Brigham and Women's Hospital in Boston. In a separate study, scientists at Brigham and Women's Hospital found that normal brain cells grown in culture also produced the beta-peptide.

The findings suggest that beta-peptide normally circulates in the body but it can collect over time and become toxic, just as cholesterol build-up can damage blood vessels. If true, then a high measure of beta peptide would be a good indicator that telltale Alzheimer's plaques were forming in the brain, according to the researchers.

However, other specialists in the field cautioned that the research does not show how the beta-peptide found in body fluids contributes to Alzheimer's. The molecule the Athena researchers found was slightly different from the material that collects in the brains of patients.

The Athena team is preparing to begin clinical tests to see if the beta-peptide would help diagnose Alzheimer's. Other groups are working on diagnostic tests for Alzheimer's that would indirectly measure the presence of the disease. (Source: *McGraw Hill's Biotechnology Newswatch*, 5 October 1992)

Mutations point to sudden death risk

Two missense mutations in a gene producing a major protein involved in the contraction of heart muscle have been discovered by Texas cardiologists, the first step toward identifying people who are at risk for sudden death.

The new findings involve individuals with familiar hypertrophic cardiomyopathy, a disorder marked by ventricular hypertrophy, or enlargement. The course of the disease is variable, but it is the most common cause of sudden cardiac death in people under the age of 35, said Ali Marian, an assistant professor of medicine/cardiology at Baylor College of Medicine, Houston, a member of the Texas team.

The group found a missense mutation in exon 13 of the large beta myosin heavy chain gene and in

exon 23 of the same gene, said Marian. Myosin is a major contractile protein of the heart. Marian said that the mutation in exon 13 is characterized by a high risk of sudden death - almost 9 of 15 affected individuals in one family died in their thirties, and no one lived beyond age 50. In contrast, the exon 23 mutation is benign, with members of a family with the mutation living well into their sixties.

Marian said the myosin gene was first identified in 1989 by a group from Harvard, and since then the Baylor group and an NIH group have found families with a defect in the gene. There are more genes responsible for the congenital disease, but they have not yet been identified. It is also not yet understood how the defects in the myosin gene lead to sudden death, Marian said. The next step in research will be to clone the gene and express it in a transgenic animal model, he said. (Source: *McGraw Hill's Biotechnology Newswatch*, 21 December 1992)

Research on animal genes

Porcine stress syndrome gene

Pig breeders look set to eradicate the gene for stress from their herds. The Pig Improvement Company based in Abingdon, Oxfordshire, using a genetic test developed by scientists at the University of Toronto, has succeeded in removing the gene for porcine stress syndrome from its basic breeding herds and anticipates offering pig farmers a choice of PSS-free or PSS-carrier lines by 1995.

PSS is a source of considerable economic loss to the pig industry because it leads to sudden death of pigs subjected to stress, during transport or mating for example, and to poor meat quality.

Before the development of the new test, called the HAL 1843 halothane test, only pigs carrying two copies of the defective gene could be identified, and then only when they fortuitously reacted adversely during studies on the effects of the anaesthetic halothane. It is these pigs that suffer PSS.

Pigs with only one copy of the defective gene, known as carriers and unaffected by PSS, could not be distinguished from those free of the defect. Consequently, carriers passed the gene on to their progeny, thereby preventing its elimination through conventional breeding programmes. The new test enables scientists to identify the number of PSS genes in any pig. Carriers are not only free from PSS but also have an enhanced feed conversion performance, producing more pork per kilogram of food than pigs completely lacking the defect. Therefore, it was important to develop breeding lines with known genetic backgrounds. (Extracted from *Financial Times*, 29 October 1992)

Conservationists DNA-test rare parrots, hoping to get more birds in hand

In an effort to save a rare parrot from extinction, conservationists are turning to the genetic technology crime fighters use to solve rapes and murders.

The scientists are applying DNA tests to a case of avian incest which has undermined breeding programmes of the endangered Puerto Rican parrot (*Amazona vittata*).

Once numbering in the millions, Puerto Rican parrots were devastated when Europeans colonized the West Indies and destroyed the birds' habitat. By 1975, the population had dwindled to about 13 of the small green and blue parrots, said biologist M. Kelly Brock, of the Amazonia Department of the National Zoological Park in Washington, D.C.

Diligent breeding programmes and protection under the Endangered Species Act boosted their numbers to about 50 wild birds. Then Hurricane Hugo halved the population. Today, there are about 30 birds living wild in the Luqillo Mountains in the north-eastern part of Puerto Rico and 75 in captivity, Brock estimated. They have proven to be difficult to breed, with the wild birds producing just about 1.6 offspring per year before Hugo. She is awaiting updates on offspring produced since the storm.

Efforts to breed the Puerto Rican parrot in captivity were less successful than researchers predicted. Brock, who was in charge of the programme, first thought that management was at fault. But, after renovating the aviary, consulting with parrot breeders, changing diet and exploring artificial incubation and insemination, the scientists tripled the number of pairs producing fertile eggs, but the hatchlings died in the nest. "We began to think that maybe we had a breeding problem", recalled Brock.

She suspected that poor results were caused by inbreeding. "The population had bottlenecked so severely that even though they (the founders) came from different nests, they still could be related". But she had no way to test the hypothesis through conventional means.

Brock decided to try DNA fingerprinting, moving the research to Queen's University in Kingston, in Ontario, Canada, where she worked with Bradley N. White, a McMaster University biologist whose laboratory has conducted forensic tests for Canadian law enforcement agencies.

Brock analysed genetic samples from captive populations of the Hispaniolan parrots and captive and wild populations of the Puerto Rican parrot.

DNA revealed that the Hispaniolan parrots were unrelated. Among the Puerto Rican parrots, the tests showed that even though the founder birds, those used to establish a captive breeding line, were collected from different locations, the birds were in fact second-degree relatives. In human terms, that is like pairing grandparents with offspring, uncles with nieces and half siblings with one another. "The difference in fecundity was due to inbreeding", Brock said. Her research appears in the December edition of the *Proceedings of the National Academy of Sciences*. Her work "could be used to find males and females that are more genetically compatible", said Brock.

Other groups have explored the use of biotechnology in attempts to rescue vanishing species but, said Brock, "to my dismay, it has not caught on", because the technology is new and conservationists are not yet comfortable using it. As for the Puerto Rican parrots, she has recommended that the US Fish and Wildlife Service try the technology, but to date, no programme has started based on the work. "It is up to them now to implement it", she said. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 7 December 1992)

Research on plant genes

r-DNA rice resists stripe virus

By inserting the gene that expresses a viral coat protein, scientists have engineered rice that resists rice stripe virus (RSV), a serious yield reducing-disease.

Teams at the Plantech Research Institute, Yokohama, and the National Institute of Agro-Environmental Sciences, Tsukuba, introduced the gene via electroporation of protoplasts into two japonica rice strains. Transformed plants showed high levels of resistance to RSV infection and the trait was passed on to subsequent generations. Fertile transformed japonica rice plants were selected by using the hygromycin B-resistance marker gene. The scientists said that this report represents the first use of coat-protein mediated resistance to protect cereal crops against viral disease, an approach that has been widely used in tobacco. (Source: *McGraw Hill's Biotechnology Newswatch*, 19 October 1992)

AFRC Institute of Arable Crops uses PCR in work on crop plant nutrient uptake

Molecular biological techniques are used increasingly in studies of ion transport into roots, intracellular compartmentation and nitrate metabolism. Good progress has been made by scientists at the Institute of Arable Crops in their attempts to clone genes for plant membrane transporters. The use of the polymerase chain reaction (PCR) process to clone plant transport genes depends on the identification of conserved amino acid sequences in families of membrane transporters from other organisms. Brian Forde and his colleagues at the Rothamsted Experimental Station have successfully applied PCR to clone three barley cDNA sequences representing members of a group of ATP-dependent permeases that have not previously been identified in plants.

Two of the cloned cDNA fragments encode amino acid sequences that are homologous to the human P-glycoprotein, a 170 kDA membrane protein responsible for the multi-drug resistance in tumours. The function and cellular location of the barley P-glycoprotein homologue is not known. Once full-length cDNA clones are obtained, the researchers will use *Xenopus* oocytes to determine the transport function and properties of the encoded protein. Details from: Brian Forde, Rothamsted Experimental Station, AFRC Institute of Arable Crops Research, Harpenden, Herts. AL5 2JQ (Source: *Biotechnology Bulletin*, September 1992)

Research on bacterial genes

Bacterial anticancer agent

A new strain of bacteria from southern Africa's bushveld is providing a source of compounds that offer a potential treatment for cancer. The bacteria, which were isolated from the soil, produce altromycines as biochemical by-products. Laboratory tests revealed that these altromycins are between 6 and 200 times more potent than adriamycin, the commonly used anticancer drug. Although they are also very toxic, it is hoped that their anticancer properties will be shown at concentrations where the side effects will be acceptable. The mechanism of action of the altromycins is unknown, but the *Journal of Antibiotics* reports that it may be different from that of other anticancer drugs, thus making them suitable for use in drug "cocktails". (Source: *European Microbiology*, January/February 1993)

Exploring new strategies to fight drug-resistant microbes

"Bacteria are cleverer than men", so writes Columbia University physician Harold Neu, an antibiotics expert, on the growing crisis in antibiotic-resistant bacteria. Doctors in other hospitals and clinics around the world are also losing the battle against an onslaught of new drug-resistant bacterial infections, including staph, pneumonia, strep, tuberculosis, dysentery, and other diseases that are costly and difficult, if not impossible, to treat. Close behind are viruses - such as AIDS, herpes, cytomegalovirus, and influenza - and other microbes, including pathogenic fungi and the malaria parasite, that are becoming resistant to new drugs. It all adds up to one frightening conclusion, an epidemic of microbial resistance.

As doctors use up their arsenal of familiar antibiotics one by one, it is clear that they will have to

find new ways to combat these pernicious microbes. Infectious disease experts have proposed a strategy to fight the emerging resistance on three different fronts: in research laboratories, scientists will need to study these deadly bugs to find ways to design better drugs "rationally" that will disarm them longer. In hospitals and clinics, doctors will have to learn to prescribe antimicrobials more selectively, so as to prevent the spread of resistance from one type of bacteria to another, and also improve sanitation so they do not spread resistant strains from patient to patient. And, in the community, world-wide surveillance systems should be put in place to detect new resistant strains early enough so that they can be contained before they spread.

But despite the threat, experts warn that neither the drug companies nor the federal granting agencies are mobilizing to the extent needed to combat the new drug-resistant bugs. Until the 1980s, drug companies were active in developing new antimicrobials, so that if a pathogen became resistant to one, there was always another that would work, but figures from the US Food and Drug Administration confirm that only five new antimicrobials were approved last year, and two the year before. The main reason for the lack of interest is probably economics. With the possible exception of the *Tuberculosis bacillus*, most drug-resistant bacteria are still a bigger problem for developing nations than for developed countries like the United States, where doctors can still usually find at least one antibiotic that will work - even though the patient's health may deteriorate and his bills escalate as doctors search for an effective drug. Since it costs about $200 million to bring a drug to market, a company cannot expect to make a profit on a drug that will be needed mainly by citizens of developing nations who cannot afford the new drugs.

Still, some dire emergencies have spurred the research funding agencies to action. The emergence of a strain of *Tuberculosis bacillus* resistant to one or more drugs - identified in 36 states in 1991, including New York, where it accounted for 42 per cent of hospitalized TB cases - has helped NIAID win more funding for TB research, albeit only a $200,000 increase Miscellaneousin the proposed budget for 1993. And the World Health Organization recently initiated a new TB programme that includes $4.3 million for disease control and about $2 million for research this year. This new wave of interest in TB seems to be paying off already: in August, a team of British and French researchers announced that they had discovered one cause of drug-resistance in the TB bacillus.

The problem is that bacteria, even of different species, can exchange genetic material, including the genes for antibiotic resistance. So if one bacterial species becomes resistant to a broad spectrum antibiotic, it can transfer that resistance to other bacteria as well. The more exposure different bacteria get to different antimicrobials, the more likely they will evolve a new defence against it.

The early identification of reservoirs of drug-resistant strains of microbes will also be critical for trying to contain the spread of the organisms. That will take global surveillance programmes, some of which are already being put in place, such as the WHONET programme from the Microbiology and Immunology Support Services of the World Health Organization.

WHONET's goal, says its coordinator, Thomas O'Brien of Harvard Medical School, is to link a minimum of several hundred microbiology laboratories around the world so that information about drug-resistant strains of bacteria and viruses identified in any particular laboratory could be shared rapidly. Although this four-year-old computer network is operating on a shoestring budget of $3,500 a year and volunteer labour, it already has linked two dozen laboratories in South and Central America and a dozen in Asia, including China.

Luciferase gene in biosensors

McGill University microbiologist Michael DuBow is developing genetically modified strains of *Escherichia coli* that glow when challenged with aluminium and other metals. Using a technique developed in the mid-1980s, DuBow and graduate students Lina Guzzo and Scott Briscoe randomly inserted the gene that codes for luciferase *(lux)* into *E. coli* and created a library of about 3,000 clones. They exposed the clones to aluminium and found that one began to luminesce at a rate higher than the others. It turned out that aluminium - as well as some other metals - was able to increase transcription of a gene that codes for flagellin, a protein important to bacteria motility. The *lux* gene was inserted in the flagellin gene, so it too switched on in the presence of metal ions.

Armed with batches of *E. coli* that express the *lux* genes, DuBow is constructing *E. coli* biosensors that he hopes will be able to detect metals in the environment. Similar efforts are afoot elsewhere. Georges Belfort, director of the bioseparations research centre at Rensselaer Polytechnic Institute, and graduate student Lia Tescione are developing an *E. coli* system that contains a gene sensitive to mercury. (Source: *Science*, Vol. 258, 9 October 1992)

Lethal genes could spark life in business of bioengineered microbes

A Danish firm with a time-released cell-killing gene is aiming to put some life back into businesses using bioengineered microbes.

GX BioSystems ApS of Copenhagen, Denmark, has developed a "containment system" based on a gene that expresses proteins deadly to both gram negative and gram positive bacteria, including *E. coli, Pseudomonas, Enterobacter, Cyanobacter, Salmonella, B. subtillis* and *B. thuringiensis* (Bt.), said James W. Sharpe, president of the US subsidiary in Langhorne, Pennsylvania.

Top ten drug-resistant microbes

	Microbes	Diseases caused	Drugs resisted
1.	*Enterobacteriaceae*	bacteremia, pneumonia, urinary tract, surgical wound infections	Aminoglycosides, Beta-Lactam antibiotics, Chloramphenicol, Trimethoprim
2.	*Enterococcus*	bacteremias, urinary tract, surgical wound infections	Aminoglycosides, Beta-Lactams, Erythromycin, Vancomycin
3.	*Haemophilus influenzae*	epiglotitis, meningitis, otitis media, pneumonia, sinusitis	Beta-Lactams, Chloramphenicol, Tetracycline, Trimethoprim
4.	*Mycobacterium tuberculosis*	tuberculosis	Aminoglycosides, Ethambutol, Isoniazid, Pyrazinamide, Rifampin
5.	*Neisseria gonorrhoeae*	gonorrhea	Beta-Lactams, Spectinomycin, Tetracycline
6.	*Plasmodium falciparum*	malaria	Chloroquine
7.	*Pseudomonas aeruginosa*	bacteremia, pneumonia, urinary tract infections	Aminoglycosides, Beta-Lactams, Chloramphenicol, Ciprofloxacin, Tetracycline, Sulfonamides
8.	*Shigella dysenteriae*	severe diarrhea	Ampicillin, Trimethoprim-Sulfamethoxazole, Chloramphenicol, Tetracycline
9.	*Staphylococcus aureus*	bacteremia, pneumonias, surgical wound infections	Chloramphenicol, Ciprofloxacin, Clindamycin, Erythromycin, Beta-Lactams, Rifampin, Tetracycline, Trimethoprim
10.	*Streptococcus pneumoniae*	meningitis, pneumonia	Aminoglycosides, Chloramphenicol, Erythromycin, Penicillin

(Extracted from *Science*, Vol. 257, 21 August 1992)

Carried into the bacterial genome on a transposon, the host-killing (HOK) gene expresses a 50-amino acid protein that perforates the cell's inner wall and kills it. GXB hooked the HOK gene to a time- or function-dependent promoter system, essentially putting a time bomb into the bacteria. By inserting more than one, GXB hopes to be able to avoid the problem of microbial resistance, Sharpe said. In a population of one million, one microbe may survive the initial HOK system, he said. When a second lethal gene is inserted the survival rate drops to one in 10^{10}.

Sharpe said that the technology could offer a way to get live organisms out of the environment after they have finished their job, whether it is cleaning a toxic spill or killing potato beetles. World-wide government environmental agencies have been hesitant to approve trials of bioengineered microbes because of the fear that living microbes will linger and reproduce out of control.

Without a method of ridding the ecosystem of gene-altered microbes, work in technologies that centred on the release of such organisms slowed.

GXB hopes to be able to test its containment system, which has also been referred to as a "suicide gene", in a Netherlands-based field trial of a bioengineered live organism designed to fight a potato pest known in Europe as the "leatherneck", said Sharpe. GXB is collaborating with scientists at the Dutch Institute for Soil Fertility Research (ISFR). (Source: *Biotechnology Newswatch*, 19 October 1992)

Miscellaneous

Nitrogen fixation in tropical cropping systems

The realization that there was no detailed synthesis of the research on nitrogen fixation relevant to

agriculture in the tropics, inspired the authors of *Nitrogen fixation in tropical cropping systems*.

The book provides an overview of the micro-organisms able to fix atmospheric nitrogen and how these interact with their host plants.

The authors conclude that in the long term it is clear that biological nitrogen fixation, with its ability to capture an inexhaustible nutrient resource, must play a fundamental role in agriculture. A 54-page bibliography and detailed indexes complete their task: providing a thorough appraisal of the potential benefits of biological nitrogen fixation to tropical agriculture.

Nitrogen fixation in tropical cropping systems by Ken E. Giller and Kate J. Wilson (1991), CAB International, Wallingford, Oxfordshire OX10 8DE, UK. 313 p. ISBN 0 85198 671 4. Price: UK£30.00. (Extracted from *Biotechnology and Development Monitor* No. 12, September 1992)

How to have your cake and eat it

A new class of "sugar mimics" has been found by chemists in the US. Unlike familiar artificial sweeteners, these compounds behave like sugars in cooking and baking. They are not fattening and may be used in "diet" products instead of sugar.

Mansur Yalpani and his colleagues at the NutraSweet Company in Mount Prospect, Illinois, believe their non-ionic polyhydroxylic compounds will not be broken down in the gut, so none of their energy will be absorbed by the body.

Although sugar mimics are better known in their guise as artificial sweeteners in diet foods, sugars have many other functions besides imparting taste. They lower the freezing point of a food to keep it liquid at room temperature, and they act as bulking agents. Sugars also delay the gelatinisation of starches during baking; a starch might gel at 65° C without sucrose but at 93° C with it. Such a delay allows a cake to achieve the proper volume and texture.

Yalpani says that his polyhydroxylic compounds will be useful as "sugar macro-nutrient substitutes"(MNSs), a more general term for sugar mimics that act as bulking agents. Such compounds could replace sugar to make very low-calorie cakes, biscuits, frozen desserts and confectionery. These foods generally contain between 30 and 95 per cent sugar, so they have a high calorific value. (Source: *New Scientist*, 7 November 1992)

Molecule of the year

A decade ago, nitric oxide (NO) was just another toxic molecule, one of a lengthy list of environmental pollutants found in unsavoury haunts such as cigarette smoke and smog. Destroyer of ozone, suspected carcinogen, and precursor of acid rain, this gas had a bad reputation.

But over the past five years, diverse lines of evidence have converged to show that this sometime poison is a fundamental player in the everyday business of the human body. In 1992, NO was ushered into the pantheon of messenger molecules with a fanfare of hundreds of research papers. This year scientists probed NO's activities in the brain, arteries, immune system, liver, pancreas, uterus, peripheral nerves, and lungs. They found that the molecule is essential to activities that range from digestion and blood pressure regulation to antimicrobial defence. In the brain, nitric oxide may be a long-sought mystery molecule that aids in learning and remembering. Yet early wariness concerning the power of NO was not ill-founded: this year the molecule's derivatives were found to damage DNA in human cells, and it is implicated in nerve damage left by strokes.

NO wonder. Not to be confused with its cousin, laughing gas or nitrous oxide (N_2O), nitric oxide is the smallest, lightest molecule - and the first gas - known to act as a biological messenger in mammals. The molecule has one unpaired electron, making it a free radical that avidly reacts with other molecules. In the presence of oxygen, NO may vanish a few seconds after it forms, although its life span in the human body is unknown.

In 1992, scientists probed the reasons behind these multiple personalities. One significant clue: the biochemistry of nitric oxide manufacture. Cells rely on various forms of an unusual enzyme called NO synthase (NOS) to do the job, and a single cell may have two kinds of enzyme - constitutive and inducible - that produce NO for different roles. Constitutive enzymes are ever-present citizens of the cell, always available to make brief puffs of NO for delicate tasks like neurotransmission. In contrast, inducible enzymes are goaded into action more slowly by other cellular messengers. But over a period of days they can produce at least 1,000 times more NO for cellular defence. In 1992, scientists cloned the genes for a string of these enzymatic forms, including constitutive NOS from human and bovine endothelial cells, and inducible NOS from mouse macrophages and human liver cells.

Understanding this unusual enzyme is crucial to designing drugs to turn NO on and off. Biochemists discovered that one such molecular helper is heme, the iron-containing compound that carries oxygen and makes blood red. Since heme is a known electron acceptor, the new knowledge gives biochemists a start on figuring out how the enzyme works. Clinical applications of NO knowledge bloomed in several directions at once, but much effort focused on nitric oxide's role as the body's own blood pressure police. In blood vessels, NO is released by endothelial cells on the inside of the vessel wall, migrates to nearby muscle cells,

and relaxes them. This dilates the vessel and lowers blood pressure.

Understanding this process opens the door to a host of new drugs. Indeed, faults in the NO system may be the guilty parties in some familiar cardiovascular diseases, possibly even essential hypertension and atherosclerosis. In 1992, scientists raced to develop a new class of chemicals that can release NO more controllably and successfully tested them in cell cultures and in mammals. In a handful of extreme cases in 1992, physicians have used NO inhibitors to save lives due to septic shock, bringing several patients' blood pressure out of the danger zone in a few minutes. Phase I clinical trials were begun to test NO inhibitors as an adjunct to interleukin-2 (Il-2) therapy for stubborn cancers of the skin and kidney. Il-2 rouses the immune system but also triggers a dangerous flood of nitric oxide; physician-scientists hope NO inhibitors will keep blood pressure up while Il-2 helps kill the cancers. (Extracted from *Science*, Vol. 258, 18 December 1992)

Catalytic antibodies re-route reactions

Scientists at Scripps Research Institute (La Jolla, California) report the use of a precisely designed antibody to catalyze an otherwise kinetically disfavoured chemical reaction. If extended to other chemical reactions, say the researchers, the technology could make it possible to control the outcome of many novel organic reactions. The Scripps scientists used the antibodies to catalyze the ring closure of an epoxy-alcohol to form a tetrahydropyran, violating formal rules for such a reaction. The catalytic antibodies work by acting on the transition state to re-route the chemical reaction pathway from the kinetically favoured route to an otherwise disfavoured reaction pathway. Previously, catalytic antibodies - developed in the mid-1980s - have been used to catalyze such standard organic reactions as ester hydrolysis, the Diels-Alder reaction, and amide bond formation. (Source: *Chemical Week*, 10 February 1993)

A bloody story

A team of scientists led by David Wu of the University of Rochester has built a bioreactor that makes bone marrow and blood cells on demand.

The bioreactor consists of a spongy material (usually a polycarbonate plastic) and a small amount of bovine collagen to encourage initial cell growth. As the reactor is perfused with nutrient medium, bone marrow cells begin to grow in clusters around the holes in the spongy material.

The cells grow in clumps similar to those in the body, unlike cells grown in flasks, which lie in just two dimensions, explains Wu. Harvesting is simple: most of the cells can simply be shaken from the sponge.

This is not the first bioreactor to produce blood cells - another, developed by a Californian company called Advanced Tissue Growth, uses nylon mesh instead of a sponge. However, Wu believes his reactor is a more accurate reflection of nature.

Wu says his group's artificial bone marrow contains most of the stages and types of cells found in natural marrow. And he believes the reactor appears to preserve the stem cells, "the mother of all blood cells".

Medical applications for the bioreactor's products could include transplants of bone marrow for leukaemia patients. At present, about a quart of bone marrow must be painfully harvested from a donor for each transplant. Other uses could be blood transfusions, and treating blood disorders like haemophilia. (Source: *Chemistry & Industry*, 19 April 1993)

Researchers synthesize inorganic double helix

Scientists at the NEC Research Institute (Princeton, New Jersey), Syracuse University, and the University of New Orleans have synthesized an inorganic material with the double helex structure of organic genetic material, DNA. The crystal, a chiral vanadium phosphate, contains intertwined spirals of vanadium, oxygen, and phosphorus. The researchers see applications in electronic materials, as a catalyst, and as a shape-selective absorption medium. (Source: *Chemical Week*, 31 March 1993)

D. APPLICATIONS

Pharmaceutical and medical applications

Recombinant DNA to treat classic haemophilia

The US Food and Drug Administration has cleared for licensing the first recombinant DNA-derived clotting factor for use in persons with haemophilia A. The synthetic version of the clotting factor known as factor VIII, is intended for the prevention and control of excessive bleeding and for people with haemophilia A who require surgery.

The clotting factor is manufactured under a shared agreement between Genetics Institute Inc., Cambridge, Massachusetts, and Baxter Healthcare Corporation, Glendale, California, Genetics Institute will make the bulk product, and Baxter will manufacture the final dosage form, which will be sold under the trade name Recombinate.

Prior to the approval of Recombinate, patients have had to rely on factor VIII concentrates made from human plasma. To obtain sufficient quantities of factor VIII, plasma pools of thousands were used.

In the past, some factor VIII made from such pools transmitted hepatitis and AIDS viruses to patients, but all anti-haemophilic factors currently licensed in the US are now manufactured in ways that are believed to eliminate the risk of transmission of these viruses.

Recombinate is produced by Chinese hamster ovary cells that have been modified by recombinant DNA techniques to introduce and express the gene for human factor VIII. It is highly purified by several steps involving biotechnology processes.

Studies of Recombinate were performed both in persons who had been exposed previously to clotting factor concentrates or other blood products and those who had not. FDA says the trials demonstrated "pharmacokinetic equivalence" to plasma-derived factor VIII and showed that Recombinate is safe and effective when used in persons with haemophilia A. (Source: *Chemical Marketing Reporter*, 21 December 1992)

Drug for Haemophiliacs

The US Food and Drug Administration (FDA) has approved a recombinant version of factor VIII, the blood protein used to treat the most common form of haemophilia. The new product, recombinant anti-haemophilic factor (Recombinate), holds a number of advantages over plasma-derived preparations, and safety is only one. The new drug can be used preventively, thereby improving the quality of life for haemophiliacs.

Recombinate is the fruit of a 10-year research effort at Genetics Institute of Cambridge, Massachusetts. The company, along with Baxter Healthcare Corp., Scripps Research Institute, and Rhône-Poulenc Rorer Inc., is embroiled in a patent dispute over rights to the process of purifying Recombinate. Another version of recombinant factor VIII, from Miles Inc., awaits FDA approval. (Extracted from *Science*, Vol. 259, 1 January 1993)

Degradable coating makes most of antibody implant

Encasing monoclonal antibodies in a coating of polymer could make them far more effective against conditions such as cancer, says a team of polymer engineers in the US. The researchers have packaged the drugs in tiny polymer capsules which could be implanted directly into diseased tissue, where the drug would leach out locally over several days. Monoclonal antibodies are normally injected into the blood stream and often do not reach a high enough concentration in the diseased tissue.

Biotechnologists have isolated natural monoclonal antibodies and manufactured artificial versions which should bind to and destroy diseased cells and ignore healthy ones. In practice, however, results have been disappointing. Only about twice the amount of monoclonal antibodies accumulate in diseased tissue such as tumours, compared with the amount absorbed in healthy tissue.

A team led by Mark Saltzman at Johns Hopkins University in Baltimore, Maryland, has developed two types of polymer into which they bind monoclonal antibodies. The drug then leaches out at a regular rate when capsules of the polymer are implanted in body tissue. But the investigators stress that it will be many years before the technique can be used in people.

One type of polymer, called poly-(ethylene-co-vinyl acetate), is not biodegradable and could be used in inserts that are removed once all the drug has dispersed. The other type is a polyanhydride polymer made by combining stearic acid and sebacic acid, and is biodegradable. It slowly decays in tissues as it releases the antibody.

Saltzman's team has injected mice and rats with capsules of monoclonal antibodies, and hope to test them soon against various forms of cancer, including brain cancer.

The disc-shaped capsules, which are 3 millimeters in diameter, "stay wherever you inject them or implant them", he says. "They are physically too big to move anywhere, and are surrounded by cells, so they slowly degrade and release the antibodies." Almost all the antibodies carried in the capsules accumulate in the target tissue.

Most of the research on animals has so far been on using the capsules for passive immunization against sexually transmitted diseases and diseases such as cholera. Treatments for cancers are even further away, Saltzman says. New types of dual-function capsules may be needed which release some antibodies locally to fight a primary tumour while others enter the bloodstream to seek out and destroy secondary tumours. (Source: *New Scientist*, 12 December 1992)

Rheumatoid arthritis treatments make headway, but not yet ready for market

Companies racing to develop the first effective treatment against rheumatoid arthritis are starting to see benefits of some of the strategies, but the market has proven hard to crack. The only options currently available to rheumatoid arthritis sufferers are anti-inflammatory drugs designed to reduce pain after the body's immune system has started to damage joints. Biotechnology companies are attempting to provide a more effective approach by intervening at an early stage in the inflammatory cascade, seeking to prevent lymphocytes from attacking collagen in the joints in the first place.

Among recent developments are:

- An open-label Phase I study of Burroughs Wellcome's anti-CDw52 humanized monoclonal antibody, CAMPATH-1H. The product is in Phase I/II trials in 75 patients in 10 centres in the US, UK, Canada and Holland;

- Phase II clinical trials, Synergen, Inc., Boulder, Colorado, for 100 rheumatoid arthritis patients with its interleukin-1 receptor antagonist, Antril, at 22 sites in the US.

- Phase II clinical trials of Centocor's chimeric antibody against CD4, Centara. Phase I clinical trials of Immunex's IL-1 soluble receptor at the Multipurpose Arthritis Center of Northwestern University Medical School, with 15 to 25 patients enrolled in each of two studies;

- Phase II trials for the fusion-toxin molecule DAB486 IL-2 of Seragen, Inc. with 50 patients at two clinical centres. Seragen has initiated also Phase I/II trials with a smaller molecule, DAB389 IL-2, with 30 to 50 patients at five centres. DAB486 IL-2 is a diphtheria toxin fused at the gene level to an IL-2-targeting ligand, which attaches to and destroys T lymphocytes expressing high-affinity IL-2 receptors. These are the T-cells that attack collagen fibre in joints;

- Farthest along of any biotech treatment for rheumatoid arthritis, but still in regulatory limbo, is Xoma's CD5 Plus, a monoclonal antibody that is linked with the toxin ricin and targeted against CD5, an antigen expressed on T lymphocytes and also on some B-cells.

Other approaches to treating rheumatoid arthritis are nearing clinical trials. IDEC Pharmaceuticals Corp., La Jolla, California, and SmithKline Beecham announced they have entered into a product development and marketing agreement aimed at the commercialization of therapeutic products based on IDEC's "primatized" anti-CD4 antibodies, with their initial focus being rheumatoid arthritis. As part of its "antigen recognition programme," Cytel Corp., San Diego, is developing CY 727, a peptide blocker of MHC receptors on antigen-presenting macrophages and B-cells associated with rheumatoid arthritis, in collaboration with the Swiss pharmaceutical company Sandoz Corp. Clinical trials are expected to begin in late 1992 or early 1993. Genta Inc., San Diego, California, is exploring antisense molecules to the block messenger RNA that codes for IL-1 receptor alpha and beta proteins. (Extracted from *McGraw Hills's Biotechnology Newswatch*, 16 November 1992)

Cholera vaccine field trial

A field trial on a live oral cholera vaccine is expected in 1993. The vaccine, CVD 103/HGR, has been developed by Myron Levine, James Kaper, and colleagues at the University of Maryland, Baltimore, USA. The field trials are to be conducted in Jakarta, Indonesia, in collaboration with the vaccine's manufacturers (Swiss Serum and Vaccine Institute, Berne, Switzerland), researchers in Jakarta, and the World Health Organization (WHO).

Preliminary studies on volunteers have shown that only a single dose of the vaccine is required for protection, as opposed to the two to three doses required for the killed oral vaccine the WHO is also interested in.

One study has shown that the viable numbers of *Vibrio cholerae* in water can be reduced to safe levels by exposing water in glass bottles to sunlight. This is most effective at 2,000 meters above sea level, but sufficient sterilization below that level can be obtained by holding the water in plastic bottles. If this is combined with the results of a further study from Bangladesh, which showed that after visiting the toilet, hands can be sterilized by washing with a mixture of sterile water and earth or ash, it would seem that the disease can be brought under control. (Extracted from *European Microbiology*, January/February 1992)

Tobacco produces hepatitis antigens; vaccines to go into bananas next

The banana, long touted as a good source of potassium, may be able to provide immunity to hepatitis. Scientists at the Institute of Biosciences and Technology at Texas A&M University in Houston have taken the first step towards the banana vaccine by creating transgenic tobacco plants that express hepatitis B surface antigens (HBsAg).

The antigens, which current tests are showing to be nearly identical to those derived from human serum and recombinant yeast, could be used as a vaccine against the viral disease.

Charles J. Arntzen, the molecular biologist leading a 10-scientist team, said that he is working on a vaccine lettuce that produces the antigen. He and his colleagues plan to start feeding leaves containing HBsAg to test subjects and expect to have an idea by February whether the salad can protect animals against disease.

In the long-term, Arntzen hopes to get the edible vaccine into bananas, which he views as the best package for distribution in the third world. Last week, he traveled to Honduras to examine various

types of bananas as candidates for genetic transformation.

These fruits may be the way to make vaccines affordable in developing countries, Arntzen said.

Since he has "a strong desire to find a way to deliver this technology to the third world", Arntzen is interested in attracting cooperation and funding for his research through groups such as the World Health Organization. On the commercial side, the studies have been conducted in collaboration with Hugh Mason and Dominic Man-Kit Lam of AgriStar Inc. (Source: *McGraw Hill's Biotechnology Newswatch*, 21 December 1992)

Transgenic belladonna fights motion sickness

Scientists at Kyoto University have developed a transgenic form of *Atropa belladonna*, a medicinal plant that contains two motion-sickness drugs - scopolamine and hyoscyamine, tropane alkaloids that act on the parasympathetic nervous system.

Although both compounds have medicinal qualities, scopolamine is more effective, and the commercial demand for it is ten-fold higher than it is for hyoscyamine. Unfortunately, the belladonna plant produces far more hyoscyamine than scopolamine.

The team at Kyoto hopes to be able to change that by insertion of a gene coding for an enzyme, called hyoscyamine 6beta-hydroxylase (H6H), that seems to boost scopolamine production. By inserting the H6H gene into a strain of belladonna, they found that the "change in the alkaloid composition in transgenic belladonna was remarkably efficient: scopolamine was almost the only alkaloid present in the aerial parts." They also said that one copy of the transgene was enough to create an all-scopolamine chemotype in the leaf. The scientists said that although belladonna was used as the transgenic host, the insertion of the H6H gene could be extended to other species. (Source: *McGraw Hill's Biotechnology Newswatch*, 21 December 1992)

Mollusc throws light on disease

A rare shellfish, *Pholas dactylus*, which glows when disturbed is poised to join the medical battle against AIDS, cancer and heart disease. Doctors Jan and Robert Knight of Knight Scientific have been working on the luminescent mollusc for over 14 years and have developed ways of obtaining commercial quantities of the luminescent substance, which they call *Pholasin*, for use in the diagnosis and management of diseases. They have developed tests to monitor the progress of a range of human diseases, including heart disease, arthritis, asthma and shock associated with surgery, burns or accidents that have complications involving the lungs. Pholasin glows when it comes into contact with certain substances released by white blood cells. One of these, a so-called long-lived oxidant, is detected by no other luminescent probe. Such substances are important as they are normally used by white blood cells in their job of destroying bacteria and viruses in our bodies.

Although the substance had been isolated, purified and characterized, the main problem in terms of commercialization has been the rarity of the mollusc. Now the work on cloning the mollusc's genes is close to success and promises an additional benefit: the opportunity to use them as "reporters" or DNA probes in other genetic investigations. In the short term, however, commercial quantities of Pholasin are likely to be obtained through piddock farming. The piddock is a bivalve something like a clam, which lives in holes in rocks it bores itself. Well known in Roman times, the piddock was mentioned by Pliny the Elder, who wrote of "people who ate Pholads, their hands and mouths glowing in the dark". Details from: Doctors Jan or Robert Knight, Knight Scientific Ltd., The Laboratory, 18 Western College Road, Plymouth PL4 7AG, UK. (Source: *Biotechnology Bulletin*, February 1993)

Agricultural applications

How to grow oil in the Persian Gulf

Saudi Arabia spends $1.2 billion a year importing cooking oil, but has just taken the first step towards cooking oil independence, setting an agricultural milestone in the process.

Halophyte Enterprises, a company in Tucson, Arizona, set up to commercialize technology developed at the nearby University of Arizona's Environmental Research Laboratory (ERL), has sent a team to Jubail, Saudi Arabia where it is planting *Salicornia bigelovii*. The seeds of this salt marsh plant yield not only edible oil but even protein meal for animal feed. Halophyte says that "this 300-hectare farm, a joint venture with the Saudi partner, will be the first commercial [crop] in the world to be irrigated with seawater."

The project, code-named "Operation Desert Bloom", is unfolding on the Persian Gulf coast about 100 kilometres north of Jubail. Desert Bloom's strategic plan derives from 15 years of studying halophytes, plants that are extremely salt tolerant. It turns out that as many as 1,500 plant species are capable of living on salt water, but *Salicornia* showed special commercial mettle during field tests in Mexico using seawater from the Gulf of California.

A consultant in Saudi Arabia predicts that the next revolution in agriculture is going to be seawater-based irrigation. He believes not only that the project will prove economically profitable, but that the strategy could also help control global warning by covering barren coastal desert with food crops that would soak up

carbon dioxide. (Source: *Science*, Vol. 258, p. 1574, 4 December 1992)

Corn vaccine

Crop Genetics (Hanover, MD) says that recent field trials of its biotech corn insecticide demonstrate results superior to those of conventional chemical products. The company says the biopesticide reduced damage from corn borers by more than 80 per cent in one corn variety and more than 60 per cent in another. The technology involves a vaccine system using a naturally occurring micro-organism that is genetically engineered to produce a bioinsecticide aimed at protecting the crop during the entire growing season. Crop Genetics, which has already done five years of field-testing of the biopesticide, plans to conduct further multisite field trials in 1993 and, if all goes well, file for Environmental Protection Agency approval. (Source: *Chemical Week*, 18 November 1992)

Self-defence for grapes and tomatoes?

Biotechnology companies have already begun to insert extra defence genes into crop plants, and researchers and farmers are already immunizing crops with live pests or diseases on a commercial scale. For example, Richard Karban of the University of California at Davis has developed a way to protect some of California's vineyards against the Pacific spider mite, a pest which can cause severe and widespread damage. Early in the season, he and his colleagues infect vineyards with a less damaging spider mite and this induces resistance in the vines to the Pacific spider mite. The research has attracted much interest from grape growers, says Karban, although so far only growers with chronic infestations of the mite have resorted to the technique.

Immunization techniques which rely on live pests or diseases, however, are unlikely to become commonplace; for it is difficult to produce, distribute and apply living organisms to crops. There is also the risk of a "vaccination" turning into a pest or disease problem in its own right. To work commercially, an immunization technique must be something farmers are already equipped to handle, such as spraying. In line with this, some research groups are working on chemical sprays which induce immunity.

Spraying plants with salicylic acid induces immunity but is unlikely to find commercial application. The main problem is that healthy plants metabolize the compound so quickly that the immunity would probably be short lived and confined to leaves hit by the spray.

Researchers at Ciba-Geigy, however, have come up with what could be a solution. They have identified a synthetic compound which can mimic the immunizing effects of salicylic acid, called methyl-2, 6-dichloro-isonicotinic acid (INA). Plants sprayed with INA activate the same SAR genes as plants sprayed with salicylic acid. INA has a molecular shape similar to that of salicylic acid but, perhaps because INA is not a natural compound, plants metabolize it more slowly. The result is that INA sprayed onto a leaf is transported through the plant and can induce immunity in unsprayed leaves. Farmers could spray chemicals such as INA onto their crop at the first sign of disease.

One of the first immunizing chemicals on sale may be used to protect tomato plants. An Italian company called Implantec, initially plans to target Italian tomato growers whose crops are presently suffering from a severe outbreak of a disease caused by the cucumber mosaic virus. The virus is spread by aphids, infects a wide range of plants and in tomatoes reduces leaflets to threads. New treatments against viruses are particularly useful because conventional pesticides cannot treat viral diseases. Instead farmers have to kill the insects which spread them.

Farmers and gardeners could also make their own immunizing sprays. Spraying cucumber seedlings with an extract of rhubarb leaves induces immunity to anthracnose. The immunity, for reasons that are still unclear, is triggered by oxalate from the rhubarb leaves. Most other organic acids have no such effect.

In theory, spraying plants with systemin, jasmonic acid or methyl jasmonate would also induce immunity to pests. As with salicylic acid, however, the effects would probably be short-lived because plants can quickly metabolize these compounds. No one has yet reported a synthetic substitute.

Another route to immunization against predators may be to continually expose plants to methyl jasmonate vapour. Methyl jasmonate is so potent that evaporation from a drop of the compound placed near to a tomato plant is sufficient to induce the plant to make proteinase inhibitors. Gardeners could already be using methyl jasmonate without knowing it. Various *Artemisia* species have high levels of methyl jasmonate in their leaves and have long found favour as companion plants that supposedly protect their neighbours against pests. Researchers have discovered that simply placing an *Artemisia* next to a tomato plant causes the tomato plant to synthesize defensive proteins.

An alternative to using live organisms or chemicals is to genetically engineer immunity into crops. Several companies are already using this technique. Their approach is simple. First you identify a gene which confers protection against pests or diseases; then you insert extra copies of the gene into crop plants, ensuring that the genes remain permanently switched on once inside the plant.

For example, Mogen International, based in Leiden in the Netherlands, has collaborated with researchers at the Dutch Universities of Leiden and

Wageningen to isolate the genes for plant enzymes that degrade fungal cell walls. Mogen has licensed the genes to another Dutch company, which plans to use them to develop potatoes that are resistant to fungal diseases. The company has strengthened its position in fungal resistance technology through an exclusive licensing agreement with the US company DNA Plant Technology (DNAP). Under the agreement, Mogen has obtained a world-wide exclusive licence to DNAP patents for transgenic plants expressing chitinase and having disease-resistant qualities, especially fungal resistance. Mogen says it intends to commercialize the patent by sub-licensing it, with its own technologies and patents, to the seed and agri-food industries.

The company is already developing fungal resistant vegetables with Upjohn subsidiary Asgrow and is working with the Dutch seed company Bejo and starch company Avebe on other crops. In return, DNAP received rights to Mogen's binary vector system for genetically transforming broad-leaved crops.

Meanwhile, the Agricultural Genetics Company (AGC), based in Cambridge, UK, is trying to develop plants with extra resistance to pests. One of its main projects involves a gene that encodes a proteinase inhibitor isolated from cow pea plants, which can make plants resistant to several major insect pests. AGC has licensed the gene to a number of other companies who hope to insert it into the genomes of crops such as maize, cotton, potato and tomato. As part of a project funded by the British Government's Overseas Development Administration, AGC is also collaborating with the International Potato Institute in Lima, Peru, to insert the gene into sweet potatoes and into varieties of potato grown by subsistence farmers in developing countries.

The disadvantage of introducing a single resistance gene into a crop is that new strains of pests and diseases which can overcome the resistance may appear very rapidly. For example, if all the potato plants in a field were protected by the same proteinase inhibitor gene then there would be intense selection pressure for tolerant pests to evolve. To alleviate this problem, researchers are considering inserting "cassettes" containing several defence genes. Pests or diseases which evolved resistance to one gene in the cassette would still have to confront the other genes.

On a different tack, other researchers are attempting to boost plant immunization and alarm signals by increasing levels of salicylic acid or systemin. Enhancing such signals, the argument goes, would force plants to switch on an array of defence genes, which in turn would provide "natural" resistance to a broad range of pests and diseases. Biologists at Rutgers University are searching for the genes involved in the synthesis and degradation of salicylic acid in plants. Similarly, a team at Washington State University has introduced extra genes for the systemin precursor into tomato plants. Their hope is that plants capable of producing systemin continually will have higher levels of proteinase inhibitors. (Source: *New Scientist*, 9 January 1993 and *European Chemical News*, 18 January 1993 and 1 February 1993)

Biocooker turns coffee dregs to soil enhancer

Gold Corp. of Osaka has developed equipment that converts coffee bean dregs to a soil conditioner. The equipment, trade-named "biocooker", is used in combination with the firm's fermentation agent, "G-016". Coffee bean dregs contain cellulose, starch, lipids and other nutrients. G-016 contains various strains of nutrient-fermenting microbes. When the dregs are combined with G-016 and placed in the biocooker, they are converted to a soil conditioner within 24 hours. (Source: *McGraw Hill's Biotechnology Newswatch*, 18 January 1993)

Cure for leaf rust

A lasting cure against "leaf rust" - a mould that attacks plants, particularly cereal grasses - has been discovered, reports the International Maize and Wheat Improvement Center, Mexico City, Mexico. A Brazilian-grown wheat plant has been found to have a natural defence against leaf rust. This strain has been crossed with higher-yielding wheat varieties to produce a hybrid that has been found to provide good rust-resistance over a 12-year experimental period. The researchers identified a gene in the Brazilian plant, which keeps the disease at such a low level that the mould does not have the incentive to mutate. (Extracted from *European Microbiology*, January/February 1993)

Field trials of transgenic corn

Ciba Seeds (Basel, Switzerland) has applied to the US Environmental Protection Agency for permission to grow more than 10 acres of its transgenic, insect-resistant corn. Ciba has introduced a gene derived from *Bacillus thuringiensis* into the corn to protect it against corn borer larvae. The development work has been carried out at the firm's agricultural biotechnology research unit in Research Triangle Park, N.C. Trials already completed in France and the USA indicate resistance to corn borer. Ciba cancelled trials in Switzerland following strong opposition and the lack of a legal permitting framework. (Source: *Chemical Week*, 10 February 1993)

Industrial microbiology

Plastic from plants

Dr. Alexander Steinbüchel, a microbiologist at the University of Gottingen, says that plastic made from plants is no longer a utopian dream. "Using merely sunlight and the carbon dioxide contained in the air, cultivated plants such as potatoes or rape seed will one day be able to produce polyesters that resemble

conventional plastics". The scientist managed to isolate a particular genetic root of selected bacteria. This induces crop plants to produce polyester in their cells. In addition, the micro-organisms can even convert the lactose contained in whey into polyester. The scientists are setting great hopes on such biological conjuring tricks, since, unlike plastics based on mineral oil, biopolymers do not fill rubbish tips or release carbon dioxide into the atmosphere when burned. Instead they can be turned into compost just like garden waste: bacteria and fungi break the polymers down into carbon dioxide and water. Since the bioplastics can be shaped under heat, they can be processed into vessels, foil and fibres using conventional techniques. Another possible use is as packaging material, and in the foreseeable future they could well be utilized in medicine too. In operations involving broken bones they could be employed as supports which would then totally disintegrate after a time. Secondary operations, which at present are necessary in such cases of complex bone fractures, would then be superfluous. (Source: *Scala*, July/August 1992)

New acetic acid process

A biological process to make acetic acid from waste whey left from cheese processing has been developed by Shang-Tian Yang of Ohio State University (Colombus). The whey is first used by bacteria to produce lactic acid. A second bacterium then converts this to acetic acid. If dolomitic lime is added during the second step, the deicer calcium-magnesium acetate (CMA) is formed. The deicer is now 50 times more expensive than salt, but the new, cheap process for acetic acid could make CMA more affordable. The cost of acetic acid made by the new process is 50 per cent of its conventional cost. In addition, the process would help the dairy industry dispose of 28 billion pounds/year of waste whey. (Extracted from: *Science News*, 18 July 1992)

Recombinant *E. coli* synthesis dye from glucose

Researchers at US biotechnology companies Amgen and Envirogen have reported the development of a recombinant *E. coli* that can directly synthesis indigo dye from glucose. They have modified no less than nine genes in the bacterium, to produce a multi-enzyme pathway for the synthesis. The scientists claim the whole cell catalysis by a recombinant *E. coli* represents a novel and environmentally acceptable approach to the synthesis of high-value specialty chemicals. (Source: *European Chemical News*, 29 March 1993)

Energy and environmental applications

Horse manure for sewage disposal

Steaming horse manure has yielded treasure that could solve Europe's mounting problems of sewage disposal. European countries have agreed to stop dumping sewage at sea by 1998, but the alternatives - spreading raw sludge on agricultural land or incinerating it - are expensive and could pose environmental risks.

John Pirt of Pirtferm, a company formed by the Department of Life Sciences at King's College London, has identified hitherto unknown bacteria in the horse manure that destroy sewage sludge at the unexpectedly high temperature of 80° C. He has incorporated the bacteria into a prototype system which destroys all the solids in sewage sludge. At the end of the process only treated water remains.

Pirt's system destroys the sludge in four major stages. The key is two cultures of bacteria which provide "food" for one another in successive stages of the process. The switch that turns one culture off and the other on is temperature.

In the first stage, the high temperature bacteria consume 55 per cent of the organic material in the sludge, converting it to carbon dioxide and vegetable matter (biomass). The process of oxidation generates heat, but the process is kept at 80° C by draining off excess heat. Pirt says that it provides enough heat to generate 4 kilowatts of electric power per cubic meter of sludge.

In the second stage, the mixture is piped to a chamber where the contents are cooled to around 37° C. This deactivates the caldoactive bacteria, and a second culture gets to work. The second culture consumes the biomass created by the caldoactive bacteria, reducing the organic content by another 5 per cent.

The final two stages repeat the cycle, first raising the temperature to 80° C in the penultimate chamber and lowering it back to 37° C in the final one. In the third stage, the caldoactive bacteria destroy a further quarter of the original organic material. The remaining 15 per cent is obliterated in the final stage. The contents pass to a settling tank where clear water is siphoned off and any mineral solids are recycled.

Pirt says that the system would work out 40 per cent cheaper than incineration. The system could be erected at sewage works, eliminating the need for costly transport to incineration works. Also, the heat of combustion could provide a cheap source of local electricity. Carbon dioxide could be piped to greenhouses for horticulture.

An important advantage, says Pirt, is that the minerals become concentrated in the residual solids, enabling extraction of heavy metals such as cadmium and mercury, which could pose environmental problems in sludge spread on agricultural land.

The most interesting thing says Pirt, was finding such heat-tolerant bacteria in ordinary horse compost. Biotechnologists only expect to find such bacteria in

unusual environments, such as the hot geysers of Iceland or the hot springs of Yellowstone National Park in the USA. (Source: *New Scientist*, 2 January 1992)

Soapberries promise better mussel control

Biologists at the University of Toledo in Ohio have found that the African soapberry (*Phytolacca dodecandra*) contains compounds that kill zebra mussels, and they hope ultimately to combat the infestations throughout North America's Great Lakes with crude extracts from imported berries.

Ships from Europe accidentally dumped the mussels in the Great Lakes when they emptied ballast there in the mid-1980s. Since then, the mussels (*Dreissena polymorpha*) have spread out of control.

The compounds in the soapberries are called *lemmatoxins* after Aklilu Lemma, an Ethiopian parasitologist. He discovered 25 years ago that extracts from soapberries kill the snails which spread schistosomiasis.

When Lemma visited Toledo, he showed in an experimeat that the extract of the crushed berries could kill zebra mussels as well.

Since then, Harold Lee and colleagues at the department of biology have been evaluating the mussel-killing potential of the berries. In 1992 he ran field tests in which he flushed water from Lake Erie through a pipe infested with the mussels. He found that steady addition of the berry extract takes just four to eight hours to kill the mussels, so continuous treatment of the water intake pipes would be unnecessary.

Moreover, he says, the berry extract takes just two days to biodegrade in water at room temperature, and is only mildly toxic. Chlorine, the chemical used at present to disinfest the pipes, takes several days to act and is highly toxic.

While Lee works on the methodology for applying lemmatoxins, Legesse Wolde-Yohannes of the Institute of Pathobiology in Addis Ababa, Ethiopia, is refining techniques for harvesting the berries. Already, he and colleagues have found a strain of berry that is especially rich in lemmatoxins. (Extracted from *New Scientist*, 7 November 1992)

Clean-up pressures fuel bioremediation

Biological treatment of waste is not a new concept. Bacteria and yeasts capable of consuming waste products have been used for decades in waste water and sewage treatment. Similarly, microbes are now routinely used to treat emergency spills of oils and chemical solvents.

But the transfer of bioremediation and biotreatment into a mainline environmental technology has been painfully slow. As the history of industrial and municipal abuse of the environment emerges, the need to clean up contaminated land becomes more pressing.

Bioremediation is now proving a popular and politically acceptable option in both Germany and in the clean-up of so-called "Superfund" sites in the US. In Germany, bioremediation was responsible for cleaning up 500,000 tons of contaminated soil in 1991 and is being used in 45 projects of the US Environmental Protection Agency's Superfund programme.

More research is desperately needed to make bioremediation a practical, cost-effective answer to the hazardous waste problem, according to a report by the American Academy of Microbiology, Washington, D.C.

The 24-page report, *Scientific Foundations of Bioremediation: Current Status and Future Needs*, puts the price tag for hazardous waste remediation and site restoration in the USA alone at $1.7 trillion in the next 30 years, but for bioremediation to become the treatment of choice, research must start now to solve some of the drawbacks to using the new technology. These include: unpredictability of bioremediation in the field; a void in the understanding of how to combine molecular biology with existing engineering practices; complexity of sites and contaminants, and the need for a realistic economic assessment of the technology. The study calls for significant supplemental and continued funding to fully develop the technology behind bioremediation.

Identifying a bacteria with the enzymes to digest the pollutants is one challenge, being able to develop it so that it operates at industrial scale is much tougher. Research is "still at the laboratory scale, although the long-term outlook is promising", a Bayer spokesman commented.

According to Professor Jürgen Klein, director of the DMT Institute of Environmental Chemistry in Essen, not only is bioremediation more publicly acceptable, it is also cheaper than conventional clean-up processes.

Although bioremediation was first used two decades ago to treat oil spills at US tankfarms, support by the Dutch and German Governments has allowed European scientists to overtake the US in research and application.

Indeed, last year the German research ministry made bioremediation a top priority in the development of environmental engineering techniques. It has earmarked DM 50 million to support R&D projects through 1992-1997.

A key demonstration site is an abandoned waste dump at Eppelheim, near Karlsruhe contaminated with mixed municipal and industrial chemicals. According to Ortwin Meyer, professor of microbiology at the University of Bayreuth and technical adviser on the

project, this industrial-scale demonstration is the first of its kind in the world. It should be completed by the end of this year. (Extracted from *European Chemical News* 15 February 1993 and *McGraw Hill's Biotechnology Newswatch*, 1 February 1993)

UK rejects biodiesel on cost

Biodiesel derived from oil-seed rape is one of the least economically attractive renewable sources of energy, according to a damning report by the UK Department of Trade and Industry. The report concludes that a subsidy of around 15 pence litre (22 cents) would be required for biodiesel to be commercially viable in the UK.

The report comes on top of a recent study released by Germany's federal environmental office which also concluded that there are cheaper and more effective ways of reducing emissions of greenhouse gases than subsidizing the cultivation of rapeseed.

Biofuels are not competitive in energy terms at current oil prices and with existing production systems, concludes a French government-commissioned report made public last week.

The report - by Renault honorary president Raymond Levy - adds a further dampener to the prospects of commercializing biofuels in Europe.

Development of biofuels could only serve to alleviate the shock of CAP measures on farmers - a political solution requiring subsidies, Levy concludes. However, he concedes biofuels could have a future in the longer term if production techniques are improved and oil prices rise. The least costly measure for the taxpayer and the most technically acceptable is the addition of rapeseed ester to diesel oil, Levy concludes.

Despite the findings, companies such as Italian Novamont - backed by the politically strong European farming lobby - are expected to continue with plans to commercialize biodiesel in Europe. Novamont has been conducting trials of its *Diesel-Bi* rapeseed ester fuel across Europe, including use on public buses in Reading, UK. (Extracted from *European Chemical News*, 15 and 22 February 1993)

E. PATENTS AND INTELLECTUAL PROPERTY RIGHTS

Grants patent on AMRAD's novel protein expression system

AMRAD Corporation Limited announced that the European Patent Office published on 26 August 1992 the notification of the grant to AMRAD of a patent covering its unique protein expression technology for producing Glutathione-S-transferase (GST) fusion proteins and recombinant DNA molecules containing GST. The unique technology relates to the development of a series of plasmid cloning vectors referred to as the pGEX vectors. The pGEX vectors were developed in 1987 by Dr. Donald Smith, while undertaking research into a vaccine for Schistomoniasis at the Walter and Eliza Hall Institute of Medical Research, Melbourne. The vectors feature the GST gene from *Schistosoma japonicum* which forms an affinity site on the protein products of genes inserted into a multiple cloning site. Because GST has a strong affinity for glutathione the recombinant fusion proteins can be easily recovered from bacterial lysates by affinity chromatography. As such the pGEX vectors are ideally suited for producing in *E. coli* large amounts of GST fusion protein which is usually soluble, and which, because of the ease of purification, retain biological activity. (Extracted from *Australasian Biotechnology*, Vol. 2, No. 6, December 1992)

Patents directive lurches ahead

A controversial directive covering biotechnology patents has narrowly passed its first reading in the European Parliament. However, the directive did not win approval without parliamentary amendments to the European Commission's proposal, and some of the changes are likely to have major implications for the biotechnology sector.

Parliamentarians want the directive to say that "discoveries" may not be considered as "inventions", and that the human body - or parts of it - are not patentable. However, the MEPs do note that inventions involving genetic modification of human beings, relating to the treatment of disease, should be patentable unless they affect human dignity.

The European Parliament also wants to block patents where unnatural processes for the production or modification of animals cause them unnecessary suffering or physical harm.

By a massive majority, MEPs voted to maintain farmers' right to use seeds harvested on their own farms, even if the seeds originally purchased are covered by a patent. The Parliament is urging that the current proposal should not affect existing treaties on intellectual property.

European legislation is a notoriously long-winded affair, and final adoption of the directive is not expected until the end of 1993, at the earliest. (Source: *Chemistry and Industry*, 7 December 1992)

Licence pact worries US industry

The international treaty intended to protect biological diversity does not protect intellectual property such as patents and licensing rights and, consequently,

the US biotechnology industry continues to oppose signature of the accord, says an industry official.

President Bush refused to sign the biodiversity treaty at the Earth Summit in Rio de Janiero in June after major US industry associations argued it could threaten American leadership in the fledgling biotechnology industry. The aim of the treaty is to ensure that countries curb the destruction of species, habitats and ecosystems.

The Industrial Biotechnology Association opposes the accord because it would subject American biotechnology companies to compulsory licensing, saying the industry's opposition stems from an article of the treaty that would give countries where discoveries are made by US firms easier access to the resulting technology and some of the profits. It notes that most of the negotiators who devised the biodiversity pact at the Rio Summit were from developing countries, "80 per cent of whom want to get their hands on our technology".

Environmentalists maintain that third world countries need financial encouragement to protect resources such as jungles and forests, which often contain untested plant and animal species.

A senior scientist with Environmental Defense Fund says the treaty could require the US and other developed nations to accept the principle that when a gene is used from an organism found in another country, that country is entitled to compensation. "It gives developing countries incentive to protect their biological diversity, including plants and animals in rain forests."

Gareth Porter of the Environment and Energy Study Institute says the treaty does in fact provide for "adequate and effective protection of intellectual property rights". He also maintains the pact does not require the transfer of technology from industrialized countries to the developing world, but only recommends it.

He says technology transfer has been a key component of several major international treaties negotiated in recent years, including the Montreal Protocol on substances that deplete the ozone layer and the climate change convention. (Extracted from *Chemical Marketing Reporter*, 28 December 1992)

PTO issues r-DNA animal patents

The US Patent and Trademark Office, ending what had seemed to be a moratorium on animal patents, issued patents on three transgenic mice on 29 December 1992.

The three inventors had waited as much as five years for legal protection of their animal creations.

Harvard Medical School - the recipient of the first animal patent ever - collected a second patent for a mouse strain that develops large prostate glands. The mice should provide clues to new drugs to treat enlarged prostate glands, a common disorder in older American men.

GenPharm, Inc. in Mountain View, California, won a patent for a mouse that fails to develop a mature immune system. The company is using a family of mice strains with similar traits to study treatments for AIDS, rheumatoid arthritis and transplant rejection.

Ohio University gained a patent for a transgenic mouse that makes its own human beta interferon, a protein that fights viral infections.

The new patents apply specifically to mice, rather than extending to any species altered in the same way, according to patent officials. The agency is currently considering 185 applications. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 4 January 1993)

EP opposes "oncomouse" patent

Members of the European Parliament have voted to ban the patenting of animals. The MEPs voted overwhelmingly in support of an "urgency" motion, tabled by Green Party members, which called on the European Patent Office to withdraw the so-called "oncomouse" patent awarded to Harvard College as "patents on life are immoral and so contravene the European Patent Convention". The motion won the support of 178 MEPs, while 19 voted against and 27 abstained.

MEPs want the EPO to revoke the oncomouse patent and not "respond favourably to any further applications for animal patents until the legal uncertainties have been clarified". Furthermore, the Parliament has called on the Commission and Council to support this position through EC legislation. With this vote, MEPs have joined the ranks of a broad coalition of consumer groups, farming organizations and animal welfare/rights groups in opposing biotech patents. (Source: *European Chemical News*, 22 February 1993)

F. BIOINFORMATICS

The Bioremediation Report

The Bioremediation Report has been available since 1992 and is the first specialist monthly journal to describe the current US scene in bioremediation, with emphasis on technology and business. It offers not an extract from a monthly review of bioremediation but market trends, interviews, the latest findings and products, and comments from a company that is itself

active in the field. The Bioremediation Report, published by COGNIS Inc., gives you a practice-related insight into the latest developments and offers information on where bioremediation is among the clean-up options. Regular features include:

- Profiles of companies successful in applying bioremediation;
- Articles on technologies that are proving themselves in the field;
- A calendar of forthcoming meetings, courses and symposia;
- Summaries of recent developments in business and technologies.

CGNET offers extensive services

CGNET Services International was founded in 1983, with the goal of improving the effectiveness of researchers in developing countries. The primary vehicle for this effort has been the "CGNET", a communication network, which interconnects a group of international research organizations via electronic mail and data transfer. Over the past few years, CGNET's services have expanded beyond the original electronic mail service to include provision of computer equipment and software, and development of custom software for gene banks.

CGNET offers two different types of electronic mail service: single mailboxes for organizations with small volumes of communication, and "desk-to-desk" electronic mail for organizations with local area networks and a high volume of communication. Both types of service include electronic mail, fax and telex capabilities, and both provide CGNET clients with mail gateways to academic networks such as INTERNET and commercial networks such as CompuServe and MCImail. Other services available on the CGNET include news clipping services and database searches. By means of the network's telex, fax, and cable service, CGNET users can easily communicate with others who do not have access to e-mail. A CGNET user can send a fax or telex over the e-mail network, with a simple code that marks it for delivery by means other than e-mail. Similarly, each mailbox on the network can receive telexes sent from locations without access to electronic mail.

The CGNET interconnects over 300 research locations in 60 countries. Most of the world's international agricultural research centres are CGNET members. A number of official development organizations are also CGNET members, including the World Bank, the US Agency for International Development, the Food and Agriculture Organization of the United Nations, CAB International, and the Australian Centre for International Agricultural Research (ACIAR). Non-governmental institutions using the CGNET include the Ford, Rockefeller, and Winrock Foundations; Foster Parents PLAN International; and the Futures Group. Several United States universities are also CGNET members, including Cornell, Oregon State University, Purdue, the University of Arkansas, the University of Hawaii, the University of Minnesota, and the University of Nebraska.

Internet and Bitnet users can send e-mail messages to CGNET members by using the addressing USERNAME@CGNET.COM where "USERNAME" is generally an institute's acronym (e.g. CIAT, CIP, CIMMYT, IBPGR). Internet users with Anonymous FTP capability can pick up a copy of the CGNET user directory from CGNET.COM with organization usernames and individual usernames.

New services

In response to requests from its network users, CGNET broadened its range of services in 1987 to include supplying specialized information equipment and software. CGNET Services now provides computer systems, local area networking equipment and installation, and communications devices ranging from modems to satellite earth stations. From time to time, CGNET Services also contracts to develop database systems for managing germplasm collections and bibliographies. Most recently, CGNET agreed to help bring scientific databases to users in developing countries. To do so, CGNET has become a distributor of a large number of commercially-produced scientific databases on CD-ROM.

Everyone can join the CGNET. Membership is not restricted to research institutes or non-profit organizations. Further information is available from Kris Kerrigan, Network Coordinator, CGNET, 1024 Hamilton Court, Menlo Park, CA 94025, USA. (Source: *BioLink*, Vol. 1, No. 1, 1992)

UK Biotechnology Handbook

The UK Biotechnology Handbook '93 provides full page profiles of almost 700 organizations involved in biotechnology including universities, venture capital providers and government agencies as well as over 500 companies. Many companies reported growth in staff numbers and sales over the last year, despite the recession and over 115 new entries are included. The industry remains one where rapid change is also seen, with many mergers, takeovers, personnel changes and restructurings also recorded. The fourth edition of this key reference book also includes ten in-depth review articles by eminent authors dealing with such topics as environmental regulations, the UK diagnostics industry, biodiversity, reaching the US market, European coordination and recent British public offerings. The articles are topical and informative and provide a source of information complementary to the directory listings. The UK Biotechnology Handbook is produced by the

BioIndustry Association (BIA) and BioCommerce Data. Price $210 plus postage.

For further details contact: BioCommerce Data Ltd., Prudential Buildings, 95 High Street, Slough, SL1 1DH, England, UK. Tel.: +44(0)753 511 777. Fax: +44(0)753 512 239.

For further details on membership of the BIA, contact: Louis Da Gama, BioIndustry Association, 1 Queen Anne's Gate, London SW1H 9BT, England, United Kingdom. Tel.: +44(0)71 957 4600. Fax: +44 (0) 71 957 4644.

Patent law in biotechnology, chemical and pharmaceuticals

Macmillan Press announce the publication of this new book, an addition to their increasingly strong biotechnology and pharmaceuticals lists. The book is written for the scientist, patent lawyer or business executive involved in biotechnology or chemical patenting, and could be an invaluable resource. Starting with US case law, it traces the evolution of patent law as it relates to these specialized technologies and discusses hundreds of cases in detail.

In addition to the cases cited, *Patent Law in Biotechnology, Chemical and Pharmaceuticals* includes 75 case reports, each focusing on a substantive patent issue, prepared specifically for the non-specialist.

Special consideration has been given for those who wish to use the book to conduct a search of the patent literature. It contains a very detailed table of contents, a listing of the main cases cited in the book and an extensive index.

The author of the book, Harold C. Wegner, is Professor of Law and Director of the Intellectual Property Law Program at the George Washington University National Law Centre, Washington D.C., USA.

Patent Law in Biotechnology, Chemical and Pharmaceuticals is available in hardback at £85 from Globe Book Services, the Macmillan Press Ltd., Houndmills, Basingstoke RG21 2XS, UK.

BioCommerce Directory updated and new document delivery service

BioCommerce Abstracts and directory (File CELL on Data-Star and File 286 on Dialog) is an extensive source of company news and financial information as well as scientific and market data about the commercial applications of biotechnology. The directory portion of the file is at present undergoing an extensive update with over 450 of the 1900+ entries on-line revised in August and September 1992. Further amendments are continuing and all of the UK entries will be verified and updated between October and December, prior to the publication of the UK Biotechnology Handbook '93 in January 1993.

Each directory entry gives a detailed organization profile, senior individuals to contact with their job titles, full address/telephone/telex/fax details and controlled indexing terms covering 50 aspects of biotechnology. The 84,000+ abstracts in this file use a unique multicitation approach, whereby several magazine or newspaper articles all covering the same event are combined with a single abstract, making it an extremely cost-effective database to search and removing the need for any manual deduping of results.

The producers have also recently launched a document delivery service providing copyright cleared copies of most of the articles cited in this database, many of which come from low circulation newsletters not often held by academic or national libraries. A same-day fax service is available as well as normal postal delivery. For further details and a request form to use, or information about the hard copy and floppy disk versions of the abstracts in this database, contact: BioCommerce Data Ltd., Prudential Buildings, 95 High Street, Slough, Berkshire, SL1 1DH, UK. Tel.: +44 753 511777. Fax: +44 753 512239.

Handbook on Injectable Drugs
by Lawrence A. Trissel

Macmillan announce the publication of the seventh edition of this trusted reference book.

Handbook on Injectable Drugs is more thorough and complete than ever before and includes monographs on over 270 injectable drugs, including 50 investigational drugs; 30 new monographs; 10 drugs which are only available outside the US; hundreds of updates; over 1,500 published references and more than 200 new references.

Every monograph included contains important information on products, preparation, administration, dosage, stability and compatibility. The concise listings and carefully organized charts make it easy to find information required.

Lawrence A. Trissel is the Director of Investigational Pharmaceutical Services, Division of Pharmacy, at the University of Texas, M. D. Anderson Cancer Centre, Houston. He has been compiling, updating and expanding editions of this book since 1975.

Handbook on Injectable Drugs is available from Globe Book Services, the Macmillan Press Ltd., Houndmills, Basingstoke RG21 2XS, UK, priced at £79.

Growing Diversity: Genetic resources and local food security
Edited by David Cooper, Renée Vellvé and Henk Hobbelink

The decision to produce a book reflecting grassroots experiences in genetic resources conservation and improvement was made jointly by several workers from NGOs active in the field in November 1989. A survey of some 50 development agencies, both official and from the voluntary sector, had shown that, while they considered genetic resources to be a very important aspect of development work, they lacked the concrete and practical information on how to incorporate genetic resources activities into the projects they support. This book is meant to be a first step towards filling the information gap. Hopefully it will stimulate greater discussion with the aim of strengthening local conservation activities in the South.

Most of the contributors to the book are directly involved in grassroots activities with urgent and daily responsibilities to the communities with which they work.

The contents of the book reads as follows:

1. Why farmer-based conservation and improvement of plant genetic resources? GRAIN
2. Community plant genetic resources management: experiences in South East Asia, René Salazar
3. Sowing community seed banks in Indonesia, Didi Soetomo
4. An integrated NGO approach in Thailand, Day-Cha Siripatra and Witoon Lianchamroon
5. Women and biological diversity: lessons from the Indian Himalaya, Vandana Shiva and Irene Dankelman
6. Promoting traditional trees and food crops in Kenya, Kihika Kiambi and Monica Opole
7. Zimbabwean farmers as the starting point, Andrew Mushita
8. Ethiopia: a genebank working with farmers, Melaku Worede
9. Developing local seed production in Mozambique, Andrea Gaifami
10. Grassroots conservation efforts in Latin America, Camila Montecinos and Miguel Altieri
11. Promoting local conservation in Ecuador, Miges Baumann
12. Towards a folk revolution, Pat Roy Mooney
13. Facing the challenges of grassroots conservation, Camila Montecinos.

The project was initiated and coordinated by Genetic Resources Action International (GRAIN) in cooperation with Centro Internazionale Crocevia.

This book is meant to put an untold story on paper, and spread the impetus of further creativity, strength, cooperation and action. No contributor tries to give a blueprint on how things should work or what is the best model to promote conservation and breeding at the grassroots level. Rather, each talks about his or her work and the world they are up against, points out the constraints and raises an infinite number of questions and possibilities. In editing these papers, GRAIN has tried to leave intact each author's style of expression while focusing on the clarity of the message.

Further details available from Intermediate Technology Publications, 103/105 Southampton Row, London WC1B 4HH, UK.

CAB International publications on biological control

The following titles are available from CAB International:

Biological Control of Locusts and Grasshoppers, edited by C. Prior and C. Lomer of the International Institute of Biological Control (March 1992). Price £34.

Biological Control of Weeds - A World Catalogue of Agents and their Target Weeds (third edition), edited by M. H. Julien of the CSIRO Division of Entomology, Australia (January 1992). Price £18.50.

Biological Control of Plant Parasitic Nematodes by G. R. Stirling of the Plant Pathology Branch, Queensland Department of Primary Industries, Australia (September 1991). Price £38.50.

Biological Control of Soil-Borne Pathogens, edited by D. Hornby of Rothamsted Experimental Station, UK and assisted by R. James Cook (USA), Y. Henis (Israel), Wen-hsiung Ko (USA), A. D. Rovira (Australia), B. Schippers (Netherlands) and P. R. Scott (UK) (May 1990). Price £55.

Readers may also be interested in a quarterly journal prepared by the International Institute of Biological Control - Biocontrol News and Information - published to meet the biocontrol information requirements of research organizations, universities, pest control centres, chemical companies and the world's aid organizations. About 2,800 summaries of the world's research literature are published each year. These are selected from over 2,500 journal articles, plus books, conferences and reports. News items cover editorials,

announcements, books, conference reports and forthcoming meetings. Each issue has mini-reviews of the literature on topical subjects, with an author and subject index. The abstracts section is available on floppy disk. Annual subscription is £97. Further details may be obtained from:

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CAB International, Wallingford, Oxon OX10 8DE, United Kingdom. Telephone: (0491) 32111, Telex: 847964 (COMAGG G), Fax: (0491) 33508

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CAB International, 845 North Park Avenue, Tucson, Arizona 85719, USA. Telephone: 800/528-4841 or 602/621-7897, Fax: 602/621-3816

Asia
CAB International, P.O. Box 11872, 50760 Kuala Lumpur, Malaysia. Telephone: (03) 255 2922, Telex: 28031 (MA CABI), Fax: (03) 255 1888

Caribbean and Latin America
CAB International, Gordon Street, Curepe, Trinidad and Tobago. Telephone: 809 662 4173, Telex: 24438 (CARIRI), Fax: 809 663 2859

Directory on Biotechnology Companies in Canada 1993

Now available from Contact International Inc., the 1993 company directory includes 467 companies involved in Canadian biotechnology, with over 650 industrial sector listings and 447 pages of Canadian biotechnology details. There are full page company profiles, as well as a service section covering the finance, legal aspects, regulatory issues, consultants, suppliers, and journals. Areas covered are: agriculture, aquaculture, cosmetics, energy, environment, fermentation, food and beverage, forestry, health care, horticulture and mining. Price $175, including shipping and applicable taxes, and may be ordered from Contact International Inc., 358 Delrex Boulevard, Georgetown, Ontario, Canada L7G 4H4.

Directory on Canadian Clinical Diagnostics 1993 - Survey and Company Directory

This industry and market overview describes over 550 companies active in Canadian clinical diagnostics and provides detailed profiles on over 180 Canadian-based companies. Areas covered are clinical chemistry, haematology, virology, microbiology, radio-immuno assay, non-isotopic immuno assay, cytology/histology, urine/blood test strips, home diagnostics, pregnancy kits, immunology, serology, tissue culture and DNA probes. Price: $175, including shipping and applicable taxes. The book may be ordered from Contact International Inc., 358 Delrex Boulevard, Georgetown, Ontario, Canada L7G 4H4.

Playing God

Described as a "genetic playground" for IBM PCs and compatibles, SimLife is a software toy that challenges players to build and maintain a viable ecosystem despite declining species diversity, delicate food chains, and disasters - both natural and otherwise. Players are free to populate their worlds with plants and animals from an extensive library of flora and fauna.

The program requires at least a 16-MHz 80386 computer with a VGA monitor, a hard drive, 2 megabytes of RAM (twice that is recommended), a mouse, and DOS 3.1 or higher. Supported sound systems include Adlib, Roland MT-32, SoundBlaster, and SoundMaster.

SimLife includes a tutorial, on-line help, a 208-page manual that expands on the concepts of genetics, ecology, and evolution introduced in the game. It is priced at US$ 69.95. Contact: Maxis, 2 Theatre Square, Suite 230, Orinda, Calif. 94563-3346; 510-254-9700; Fax: 510-253-3736. (Source: *IEEE Spectrum*, March 1993)

OECD publishes reports on crop breeding methods, safety principles for transgenic crops, and the field research to date

The OECD Group of National Experts on Safety in Biotechnology has worked to update and develop the principles for safe development of genetically modified organisms (GMOs), as first set out in the 1986 "Blue Book" (used throughout the world as an authoritative guide). The results of this work on crop plants are now appearing in three new reports.

The first report, entitled "**Field Releases of Transgenic Plants, 1986-1992 - an Analysis**", gives a coherent picture of the 1,180 experimental releases of GMOs that have taken place since 1986, when Belgian researchers first brought genetically tagged tobacco plants from laboratory or greenhouse into an open field. Subsequent trials have been made in 15 OECD member countries, for 30 different crop hosts (oilseed rape, potato, tobacco, etc.) and for 10 categories of traits (such as herbicide resistance, virus resistance, etc.). The report concludes that "there have been no surprises in the behaviour of the transgenic plants in relation to what might be expected from the characteristics of the host and the nature of the genetic insert". Some disappointments (the desired effect inadequate); no surprises. From a safety angle, "no news is good news"; but much remains to be learned.

The second report is entitled "**Traditional Crop Breeding Practices: an Historical Review to Serve as a Baseline for Assessing the Role of Modern Biotechnology**". In it, 17 major crops of world-wide importance and their parent species, prime targets for

genetic modification projects, have been studied for their important characteristics, physiology, toxicology and environmental behaviour. A group of eminent experts from all over the world, each an authority in his field of plant breeding, contributed to this overview. This is however by no means a book for specialists on plant breeding; it is written for the layman. It provides insight into how crops were derived from their wild origins, and what goals have been sought in order to make use of their special features. This background information about the nature of crop plant breeding is relevant to the consideration of proper biosafety measures, discussed in the third report, as the precision breeding methods of transgenesis are now applied in many places and in many crops, including maize and rice, as detailed in the report on field releases.

The third report is about safety, risk assessment and risk management. It is entitled "**Safety Considerations for Biotechnology: Scale-up of Crop Plants**". The term "scale-up" is used to describe the continuum of R&D at increasing scale, from field test up to general commercial use. Most effects of new traits, on appearance or behaviour of crop plants, will be recognized during preliminary evaluations in small-scale field tests; but some, including some related to safety, may become apparent only on scale-up. The knowledge gained with crop plants developed by traditional breeding methods, together with the ever-growing experience of plants developed by Recombinant DNA methods (transgenic plants), can be applied to address the safety issues of scale-up. The concept of "familiarity" can be used to identify hazards, determine the magnitude of risk, and indicate appropriate methods of management.

The report on scale-up safety includes as preamble the "General Principles for Safety in Biotechnology", released in 1993 by the OECD as a separate document. These recognize in particular that the safety of an organism is independent of the process of genetic modification *per se*. It is the characteristics of the organism, including new traits (however introduced), the environment and the application that determine the (likelihood of) risk of the introduction of new organisms.

For further information, please contact Mark Cantley, Biotechnology Unit, OECD Directorate for Science, Technology and Industry (Tel.: (33 1) 45 24 93 31; Fax (33 1) 45 24 97 67).

"Field Releases of Transgenic Plants, 1986-1992 - an Analysis", 40 pages, OECD, Paris (1993). France only: FF50. All other countries: FF 65; US$ 12; DM 19. ISBN 92-64-14046-8 (93 93 07 1).

"Traditional Crop Breeding Practices: an Historical Review to Serve as a Baseline for Assessing the Role of Modern Biotechnology", 236 pages, OECD, Paris (1993). France only: FF 270. All other countries: FF 335; US$60; DM 100. ISBN 92-64-14047-6 (93 93 06 1).

"Safety Considerations for Biotechnology: Scale-up of Crop Plants", 40 pages, OECD, Paris (1993). France only: FF 50. All other countries: FF 65; US$12; DM 19. ISBN 92-64-14044-1 (93 93 08 1).

Available from the OECD Publications distributors.

Ecological risks of releasing genetically modified organisms into the natural environment

At the request of the Norwegian Directorate for Nature Management a committee of experts was established to identify the relationship between modern biotechnology and the environment. In this 57-page report the emphasis is placed on the possible outcome of deliberately or unintentionally releasing genetically modified organisms. Possible risks and potential ecological impacts of undertaking such releases are assessed. The report also recommends the research and development required before proper environmental risk assessments can be adequately provided. The committee concludes that risk assessments should follow the internationally established practice where each case is assessed individually (case by case) using a stepwise procedure (step by step) based on the worst possible scenario. The report appears to ignore the large amount of research relating to risk assessment of GMOs and to the 1,000 or so release experiments that have been safely carried out to date, world-wide.

Details: J. Husby, Executive Officer, Directorate for Nature Management, Tuerg. 2, N-7005 Trondheim. Tel.: (47)7-580500; Fax: (47)7-915433.

The Indigenous Fermented Foods of the Sudan: A Study in African Food and Nutrition

Hamid A. Dirar, Faculty of Agriculture, University of Khartoum, Sudan

Recent decades have witnessed increased interest in the foods of Africa, spurred on by the recurrent famines that have plagued the continent. It is now recognized that helping people to use their own knowledge of indigenous foods and agriculture provides better prospects for long-term sustainability than imposing solutions from outside. Yet to date there has been little documented information about the foods that are utilized by the poor of Africa, and particularly how these foods are preserved in a hostile environment for later use.

The author has collected, assembled and characterized the indigenous fermented foods of the Sudan and other parts of Africa. This is truly a monumental achievement. He has discovered and

described over 90 fermented foods for the Sudan alone. The knowledge of these foods has resided in the minds of countless Sudanese women who learned the production of these foods from their mothers and grandmothers. If Dr. Dirar had not collected this information now, much of this knowledge would soon have been lost.

Furthermore, he has collected detailed information regarding the foods that starving people depend upon to survive under the most severe conditions. These include among others roots, leaves, caterpillars, frogs, locusts, bones, hides and even heifer urine, all of which are fermented, sun dried and preserved for times of food shortage.

This book is a unique compilation of both the general literature on Africa's fermented foods and beverages and of original research conducted by the author in Sudan. Information was gathered from elderly rural women who traditionally hand down such knowledge from generation to generation. With increased urbanization and dislocation of family structures, there is a danger that such knowledge might otherwise be lost for ever. The various foods are considered in terms of their role in the struggle for survival and in the social fabric of rural Sudan, as well as from the perspectives of nutrition and food microbiology. The book is a major contribution to this literature, of interest to all concerned with food science, human nutrition and rural development. Price: US$100. ISBN 0 85198 858.

CAB INTERNATIONAL

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Caribbean:	Gordon Street, Curepe, Trinidad and Tobago.

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Food Security and Food Inventories in Developing Countries, edited by P. Berck and D. Bigman, 1993. 400 pages; ISBN 0 85198 810 5.

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Agricultural and Food Marketing in Developing Countries: Selected Readings, edited by J. Abbott, 1993. 432 pages; ISBN 0 85198 804 0.

Research with Farmers: Lessons from Ethiopia, edited by S. Franzel and H. van Houten, 1992. 320 pages; ISBN 0 85198 814 8.

Europe Culture Collections: Microbial Diversity in Safe Hands

This 48-page booklet has been produced by the European Culture Collections Organisation, ECCO, a 10-year-old body bringing together the major service collections.

The advance of biotechnology imposes pressures on the collections to provide additional services (rapid identification, patents, deposits, databases and computer searches, industrial contracts), and ECCO facilitates collaboration and the exchange of ideas and information.

The booklet gives details of the Information Centre for European Culture Collections, ICECC, which has received co-finance from successive Community biotechnology R&D programmes. Also described here (and also EC co-financed) are the Microbial Information Network Europe, MINE, which is creating a centralized and integrated database on bacteria, fungi and yeasts, and MSDN, the Microbial Strain Data Network, an international information and communications network for microbiologists and biotechnologists.

Details of these and other matters, including descriptions of the holdings and services of all the member collections are also provided, with full addresses and numbers.

This valuable reference work is available free from ECCO, Mascheroder Weg, 1b, D-3300 Braunschweig, Germany. Tel.: (49)531-618.715; Fax: (49)531-618.718; Teletex 531.104; E-mail Telecom Gold/Dialcom 10075: DB 10274.

G. SPECIAL ARTICLE

Bioremediation: The Application of Biotechnology for the Clean-up of Oil Spills and Industrial Pollutants

by

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Biotechnology and Environmental Quality

In the face of the increasing severity of environmental damage evidenced during this century, there has been a growing awareness on the part of the public and governments that actions are needed to

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maintain and restore environmental quality. While waste minimization and recycling programmes have been instituted in many industries and by public authorities to help conserve resources and protect the environment against the release of wastes and pollutants, new technologies are needed for the treatment of wastes and pollutants to aid in sustaining development and environmental quality. The accelerated development of biotechnology during the last decade presents new possibilities for dealing with both the current and emerging problems of environmental contamination by oil spills and releases of industrial chemicals.

Biotechnology is one of several competing technologies for the maintenance of environmental quality and must be viewed within the larger spectrum of scientific and engineering disciplines. However, the importance of biotechnology within this overall context has increased significantly within the past five years and will continue to increase. This is, in part, due to the exceptionally rapid advances of knowledge, the low environmental impact and cost-effectiveness of using biological as opposed to physical-chemical treatments, and also to problems associated with non-biological treatments, such as the production of gaseous pollutants by incineration. The advantages of bioremediation over other technologies for environmental clean-up are reduced cost, reduced risk of exposure to harmful chemicals and minimal environmental impact.

Biotechnology has provided solutions to deal with environmental problems. When the disposal of wastes into rivers threatened human health and the well-being of aquatic life, wastewater treatment facilities were developed during the nineteenth century as one of the first applications of biotechnology for the maintenance and restoration of environmental quality, and this treatment has been of great benefit to humankind. Since that time there have been only minor changes in the fundamental designs of the original sewage treatment plans and the way organisms are used, and there are significant numbers of failures of these facilities to meet performance criteria. A particular problem occurs when industrial chemicals enter wastewater treatments that are not specifically designed to cope with those chemicals. Biotechnological processes will continue to play a central role in the treatment of municipal, industrial and agricultural wastes. In the treatment of aqueous and gaseous effluents, biotechnological processes can be regarded as established technologies based on a history of traditional performance of reducing the biochemical oxygen demand (BOD) of the effluent.

Emerging threats to the environment, such as the atmospheric changes that potentially pose a threat of global climate change, the loss of trees and forests due to atmospheric pollutants, and the formation of deserts, are also appropriate for potential biotechnology treatments. Biopolymers, synthetic fuels and other biological alternatives to chemical processes present opportunities for economic and environmental benefit through biotechnology. Biotechnology has the capacity for contributing to sustainable development.

Bioremediation: An Overview

Bioremediation emerged in the 1990s as an important approach for the clean-up of oil spills and numerous industrial pollutants. Bioremediation uses micro-organisms to degrade polluting substances to non-toxic end-products, such as carbon dioxide and microbial biomass that can be accommodated by the environment without causing further environmental damage. It is a "green solution" to environmental pollution that relies upon natural processes to remove and detoxify polluting materials. In essence, bioremediation simply speeds up natural degradation process.

In most cases, bioremediation relies upon naturally occurring micro-organisms that are indigenous to the contaminated site. Often, the degradative activities of indigenous micro-organisms are limited by environmental factors such as the availability of molecular oxygen, phosphates and fixed forms of nitrogen that can be used to support microbial growth. By overcoming environmental limitations, such as by tilling soils to improve aeration or adding fertilizers to overcome nitrogen and phosphate limitations, the activities of indigenous micro-organisms can be stimulated, and the rates of pollutant degradation accelerated. In cases where there is inadequate genetic diversity within the microbial community to effect the degradation of specific pollutants, seed cultures can be added to initiate the degradative process. Seed cultures may be undefined mixtures of micro-organisms, such as occur in manures, or may be very specific cultures of micro-organisms with defined metabolic capacities, including genetically modified micro-organisms.

Treatment of Wastes and Industrial Chemicals in Bioreactors

Liquid wastes are produced by human activities as domestic sewage by various agricultural and industrial operations.[1] In order to maintain water quality, these wastes often are treated in bioreactors before being released to the environment. Contemporary liquid waste treatment facilities aim at reducing the biological oxygen demand (BOD) associated with the organic compounds within the waste. The aim of most liquid waste treatments is a total reduction of degradable compounds that would otherwise cause excessive oxygen consumption in the receiving water bodies. General liquid waste treatment facilities do not target specific classes of compounds.

The introduction of industrial chemicals into sewage treatment facilities and other waste treatment facilities has caused problems because many industrial chemicals are not degraded in traditional waste treatment

facilities and escape as pollutants into the environment. Failure of a chemical waste biodegradation system may be due to unfavourable environmental conditions, to the absence of appropriate micro-organisms with the necessary catabolic pathways, or to both. Biotechnological processes can, in many cases, overcome the limitations of waste treatment facilities and prevent chemical pollutants from entering the environment.

There are a variety of conventional liquid waste treatment facilities, including activated sludge, trickling filter, and rotating biological contactor units. Each of these waste treatments is aerobic, and oxygen is supplied to foster microbial degradation. The inocula for these facilities come from the microbial communities that naturally develop during the degradation of the waste. For example, an activated sludge portion of the microbial biomass produced during the treatment of a prior batch of waste is used to inoculate an incoming new batch of waste. In the trickling filter and biological rotating contactor systems, a biofilm develops that actively degrades the compound in the waste.

Even commonly used treatment systems such as activated sludge occasionally fail to perform adequately. The development of effective wastewater treatment demonstrates the need for coupling fundamental microbiological studies with engineering principles to develop effective systems. More effective waste treatment systems would contribute to pollution prevention. In the wastewater treatment systems, anaerobic systems are now playing a role alongside traditional aerobic ones. Similar systems for industrial pollutants would make significant contributions to pollution prevention.

Some organic compounds are readily degraded, whereas others are totally undegradable by micro-organisms (recalcitrant) at the current time. Many xenobiotic (synthetic - not naturally occurring) pollutants, such as DDT, are halocarbons that have proven recalcitrant to microbial attack. Important groups of halocarbons include halocarbon propellants, solvents and refrigerants, certain organochlorine insecticides, polychlorinated or polybrominated biphenyls and triphenyls, chlorodibenzodioxins and chlorodivenzofurans. In some cases, compounds once thought to be recalcitrant have later been found to be biodegradable. Until very recently, for example, PCBs (polychlorinated biphenyls) and TCE (trichloroethylene) were thought to be undegradable, but these compounds are now known to be biodegraded.

Because industrial waste often escapes degradation by the generalized communities of liquid waste treatment systems, special steps can be taken to design waste treatment facilities for industrial compounds. Sequential batch reactors can be used with each reactor aimed at degrading specific compounds in the industrial waste. Adapted microbial communities are used in each separate reactor so as to accomplish this task. By separating waste streams, micro-organisms grow on the specific compounds in each. Compounds such as azo dyes, which are widely used in the textile industry, can be degraded using such bioreactors.

Some compounds are degraded by co-metabolism where micro-organisms growing on one substrate gratuitously attack another compound. Supplying the necessary co-substrate can result in effective degradation of the target compound. Co-metabolic tetrachloroethylene degradation, for example, has been demonstrated for methanogenic bacterial consortium growing on acetate in an anaerobic reactor. Extensive aerobic degradation of trichloroethylene, a widely distributed halocarbon pollutant, by a methane-utilizing microbial consortium has been demonstrated. The low specificity of methane mono-oxygenase allows the conversion of TCE to TCE epoxide, which subsequently spontaneously hydrolyzes to polar (formic acid, glyoxylic acid) products utilizable by micro-organisms. *Methylococcus capsulatus* has been reported to convert chloro- and bromomethane to formaldehyde, dichloromethane to CO, and trichloro-methane to CO_2 while growing on methane.

The environmental conditions within bioreactors can be altered to favour the degradation of particular compounds. Many modern waste treatment facilities permit varying the oxygen concentration. Oxygen can be substituted for air, as in the UNOX wastewater treatment system developed by Union Carbide. This system achieves higher biological oxidation rates per unit in volume than are achieved when air is used for aeration. The deep shaft process of ICI uses air injection and pressure to similarly achieve elevated oxidation rates for organic compounds. In other cases, anaerobic zones are included that favour the anaerobic degradation of specific compounds. In this manner, industrial wastes can be treated to prevent the release of organic contaminants into the environment where they can cause environmental harm.

The capability of alternating between aerobic and anaerobic conditions can be very important for the degradation of halogenated compounds such as PCBs. Anaerobic dehalogenation (reductive dehalogenation) removes the halides from such compounds, forming compounds that can then be degraded under aerobic conditions. In the case of PCBs, the higher molecular weight congemers - those PCBs that are highly substituted with chlorine substituents - are attacked under anaerobic conditions to form light congemers - those PCBs that have only a few chloride substituents. The lower weight PCB congemers are attacked under aerobic conditions. Thus, extensive degradation of complex mixtures of PCBs can be achieved by first incubating anaerobically and then aerobically. Similar degradation of other highly chlorinated molecules can likewise be achieved in this way.

Waste treatment systems can also be used to remove inorganic compounds. For example, phosphates can be removed, and thus eutrophication can be prevented. When certain bacteria are grown under anoxic (free of air) conditions, they accumulate poly-β-hydroxybutyrate. If these same bacteria with the accumulated poly-β-hydroxybutyrate are subsequently grown under aerobic conditions, they will take up large amounts of phosphate and incorporate it into polyphosphate, thereby removing it from the wastewater. Several biological phosphorous removal systems have been designed incorporating the removal of phosphate into activated sludge treatment systems. These involve alternating anoxic and aerobic cycles.

While waste treatment systems are best used to degrade organic compounds or to sequester inorganic compounds prior to release into the environment, bioreactors can also be used for the treatment of contaminated soils and waters. Soils, sediments, and waters can be transferred to reactors where environmental conditions and microbial communities can be controlled to optimize the degradation of the contaminating compounds. Some bioreactors can be transported to contaminated sites, minimizing the costs of transferring large amounts of contaminated materials from the site to the bioreactor. The conditions within the reactor can be adjusted to favour the degradation of particular compounds.

In Situ Bioremediation

In situ biodegradation is a natural process which has been going on since the first microbes and excess organic matter were both present in the soil.[2] At its most fundamental, biodegradation is a recycling process essential for the proper maintenance of the carbon and nitrogen cycles in nature. *In situ* biodegradation can be applied to hazardous wastes, and techniques for detecting and enhancing natural *in situ* bioremediation have been developed.

The majority of the novel pollution problems with organic compounds involve chemicals that are xenobiotic, that is, compounds synthesized by humans that have no close natural counterparts. Xenobiotic chemicals include pesticides, plastics and other synthetic compounds that may persist because micro-organisms lack the catabolic pathways to degrade them. Given sufficient time, it is assumed that micro-organisms will evolve the capacity to degrade such compounds. To short-circuit the evolutionary time required for the development of such organisms, it is possible to carry out genetic engineering, or to culture organisms in ways that favour major evolutionary changes.

With regard to pollutants that enter the environment, *in situ* methods are likely to prove most cost-effective. However, these *in situ* bioremediation treatments face the problem of identifying limiting factors and delivering appropriately active micro-organisms to the pollutant which, in turn, must be bioavailable. Much work needs to be done on integrated systems that couple engineering and non-biological aspects of pollutant remediation in the emerging field of bioremediation. In some cases, consortia of micro-organisms will be needed and methods for maintaining the appropriate balance of populations within such consortia have yet to be developed.

Site specificity and the inability to predict and monitor performance have limited the acceptance of biotechnological solutions by engineers and managers charged with the responsibility of deciding on appropriate environmental remediation solutions. Improvements in biotechnological processes for treating environmental contamination should increase the uses of bioremediation in the near future. The majority of current problems of contamination and pollution at specific sites can be treated by microbiological processes based on indigenous organisms.

Currently, several hundred sites are being considered for bioremediation or are actually being treated using this technology. Most of these sites are contaminated with hydrocarbons from creosote or fuel spillages. Some have chlorinated hydrocarbon contaminants such as TCEs and PCBs. The degradation of these compounds prevents contamination of neighbouring waters and this often is the aim of *in situ* bioremediation. Slow degradation of complex polynuclear aromatics often makes this a long process.

Two major engineering approaches to the design of *in situ* bioremediation have been developed. The first can be applied to shallow contaminated groundwater systems and the saturated zones of soils. Water from a well is used to create a depression in the saturated zone. The water is supplemented with nutrients and an electron acceptor (e.g. oxygen or nitrate) and returned to the aquifer, near the source of the contamination. The groundwater provides nutrients and water to the indigenous bacteria in the contaminated unsaturated soil. The groundwater is drawn into the saturated zone, where it passes over the contaminated regions of the soils, providing nutrients needed for microbial degradation. In such treatment, studies are performed to determine which nutrients are limiting natural *in situ* biodegradation and what concentrations must be supplied for *in situ* bioremediation.

The second approach for *in situ* bioremediation, called *bioventing*, involves treating unsaturated soils. In this approach, air is forced into the vadose zone at a relatively slow rate. Water is returned to the soils along with nutrients via a sprinkler system. Horizontal pipes below the zone of contamination capture the added water and help draw the air into the aquifer.

Biodegradation of non-growth supporting pollutants is a significant process that must be considered

in engineering design and the subsequent application of bioremediation technology for specific pollutants. For example, TCE is a widely distributed subsurface contaminant of groundwater that is degraded by mono-oxygenase and dioxygenase enzymes, which are induced by substrates that are structurally unrelated to TCE. There is a wide range of micro-organisms which possess the ability to synthesize oxygenases that degrade TCE. These include organisms that can grow with methane, phenol, toluene and ammonia. By supplying methane, it is possible to stimulate the methanogenic bacteria which degrade chlorinated solvents such as TCE by co-metabolism. Thus, methanotrophic bacteria show some promise for bioremediation of halocarbon-contaminated aquifers.

Bioremediation of Oil Spills

Early work on the microbial utilization of petroleum hydrocarbons was ducted in the 1950s and 1960s when petroleum was viewed as an inexpensive carbon source and single cell protein (microbial biomass) was considered as a possible solution to the perceived impending world food shortage for the predicted global population explosion. Applied studies focused on optimizing microbial growth on low-middle molecular weight hydrocarbons, and basic research studies elucidated the metabolic pathways of alkane, cycloalkane and aromatic hydrocarbon utilization. These studies showed that the microbial degradation of hydrocarbons produced cell biomass and carbon dioxide. They also indicated that the greater the complexity of the hydrocarbon structure, that is, the higher number of methyl branched substituents or condensed aromatic rings, the slower the rates of degradation and the greater the likelihood of accumulating partially oxidized intermediary metabolites.

The wreck of the tanker Torrey Canyon in 1969 focused environmental concern on the fate of hydrocarbon pollutants in the oceans, and research interest quickly shifted to examining the biodegradation of oil under real environmental conditions. These studies revealed that hydrocarbon-degrading micro-organisms are ubiquitously distributed in the environment, and that the rates of hydrocarbon biodegradation are limited by abiotic environmental factors; low levels of phosphate and fixed forms of nitrogen in marine environments limit rates of hydrocarbon degradation, and molecular oxygen is required for rapid hydrocarbon biodegradation. The persistence of petroleum pollutants depends on the quantity and quality of the hydrocarbon mixture and on the properties of the affected ecosystem. In one environment, petroleum hydrocarbons can persist almost indefinitely, whereas under another set of conditions, the same hydrocarbons can be completely biodegraded within a few hours or days.

Studies on the natural fate of hydrocarbons in the environment formed the basis for bioremediation, the biotechnological process in which the rates of hydrocarbon biodegradation are accelerated by overcoming the rate limiting factors in order to remove contaminating pollutants. Bioremediation most often uses micro-organisms and their biodegradative capacity to remove pollutants.[3] The end-products of effective bioremediation, such as water and carbon dioxide, are non-toxic and can be accommodated without harm to the environment and living organisms. Using bioremediation to remove pollutants is inexpensive as compared to physical methods for decontaminating the environment that are extraordinarily expensive. While many current technologies call for moving large quantities of toxic waste-contaminated soil to incinerators, bioremediation can be performed on site and requires simple equipment that is readily available. Bioremediation, though, is not the solution for all environmental pollution problems. Like other technologies, bioremediation has limitations as to the materials that can be treated, conditions at the treatment site, and the time that is available for the treatment.

The two approaches taken for the bioremediation of petroleum pollutants are the addition of micro-organisms (seeding) that are able to degrade hydrocarbons and the modification of the environment, for example, by adding fertilizers or by aerating the contaminated site.

Because hydrocarbondegrading bacteria and fungi are widely distributed in marine, freshwater and soil habitats, adding seed cultures has proven less promising for treating oil spills than adding fertilizers and ensuring adequate aeration. Nevertheless, many companies are developing and/or marketing hydrocarbon-degrading seed cultures. Most micro-organisms considered for seeding are obtained by enrichment cultures from previously contaminated sites. Some of these seed cultures may be useful for treating heavy oils that contain hydrocarbons that are relatively resistant to degradation, but seed cultures are likely to be of little benefit for the treatment of the bulk of petroleum contaminants.

The initial steps in the biodegradation of hydrocarbons by bacteria and fungi involve the oxidation of the substrate by oxygenases for which molecular oxygen is required. Conditions of oxygen limitation normally do not exist in the upper levels of the water column in marine and freshwater environments. Low concentration of oxygen, however, is often a critical rate limiting factor for the biodegradation of hydrocarboas in soils and aquifers. In surface soils, oxygenation is best assured by providing adequate drainage and by tilling the soils. This can be accomplished with simple farm equipment. When hydrocarbons have migrated into subsurface soils and if they have contaminated aquifers, oxygen can be provided by forced aeration or through the addition of stabilized peroxides that slowly decompose and release molecular oxygen.

Since micro-organisms require nitrogen, phosphorus and other mineral nutrients for incorporation

into biomass, the availability of these within the area of hydrocarbon degradation is critical. Various types of fertilizers can be applied, including oleophilic fertilizers, such as Inipol EAP22 produced by Elf Equitaine, that are designed to concentrate the nutrients at the oil-water interface where hydrocarbon biodegradation occurs. *In situ* bioremediation of aquifers is a relatively new and promising technique that is limited by finding engineering solutions for distributing mineral nutrients and oxidants in aquifers to permit the full potential of micro-organisms for the biodegradation of polluting hydrocarbons to be realized.

Because there is no definition of how clean is clean following an oil spill, regulatory uncertainty necessarily occurs regarding acceptable performance criteria for bioremediation. For bioremediation to become an effective technology, there must be agreement on performance criteria. Surrogate test organisms for risk-based ecological effects testing are needed and standardized tests are necessary to verify claims about commercial cultures for oil spill bioremediation. Contingency plans must be made prior to a spill that include consideration of regional differences. While the use of genetically engineered micro-organisms for oil spill bioremediation is blocked by regulation, this is not a major problem since the use of such organisms is not scientifically supported as necessary. Bioremediation of oil pollutants can be achieved for the most part by environmental modification - nutrient and oxygen supplementation - and through the actions of naturally occurring micro-organisms.

The Exxon Valdez spill in Prince William Sound, Alaska, formed the basis for a major study on bioremediation and the largest application of this emerging technology. Oleophilic and slow release fertilizers were tested and subsequently used to treat hundreds of miles of contaminated shorelines. Results from the use of fertilizer solutions unequivocally demonstrate that oil biodegradation rates in Prince William Sound were limited by the availability of nitrogen and phosphorous, and that the clean appearance of rock surfaces following fertilizer bioremediation treatment was directly caused by biodegradation. Rates of stimulation by bioremediation with fertilizers typically was about 3-5 times natural rates of oil biodegradation. Greater stimulation might be achieved by higher levels of nutrient addition, but this could risk ecological side-effects such as toxicity to marine life and eutrophication with associated algal blooms. The addition of fertilizers caused no eutrophication, no acute toxicity to sensitive marine test species, and did not cause the release of undegraded oil residues from the beaches. The success of the bioremediation programme in Prince William Sound has set the stage for the consideration of bioremediation as a key component in any clean-up strategy developed for future oil spills.

Role of Genetically Engineered Micro-organisms in Bioremediation

The potential application of recombinant organisms to the environment raises questions relative to risk and regulation.[4] In this regard, methods are clearly needed for monitoring the survival and spread of such organisms; additional research is necessary concerning how to insure the survival of introduced organisms in communities in ways that preclude their untoward effects in nontarget systems.

The absence of a catabolic pathway for xenobiotic compound is no longer an absolute obstacle to finding or engineering micro-organisms that can degrade a specific compound. Searching for mutant strains can be extended by using recombinant DNA technology to more rapidly evolve organisms with greater catabolic capacities. Recent advances in molecular biology allow the regulation of gene expression and the substrate specificity of enzymes to be altered. The expression of catabolic genes - genes that code for the enzymes that degrade organic compounds - is often closely regulated, and degradative activity in the environment can be adversely affected by presence of repressors or the absence of inducers. This can be overcome by replacement or modification of the endogenous promotor(s) so that gene expression is not dependent on the presence of specific compounds or environmental factors. Most often genetic engineering of environmental applications relies upon altering the expression of genes already present among the indigenous microbial populations. Depending upon circumstances, constitutive expression or activation of degradative genes in response to temperature, chemicals or specific environmental factors can be obtained. Under the appropriate conditions, these alterations can significantly enhance the degradation potential of micro-organisms resulting in a more effective process at lower cost.

A hydrocarbon-degrading pseudomonad was engineered for its ability to degrade petroleum hydrocarbons. It was the organism that the Supreme Court of the United States in a landmark decision ruled could be patented. This engineered micro-organism has not been used in the bioremediation of oil spills. It degrades low molecular weight hydrocarbons, but does not degrade the higher molecular weight hydrocarbons that occur as persistent contaminants following oil spills. It has not been used in the bioremediation of oil spills.

Given the current regulatory framework for the deliberate release of genetically engineered micro-organisms, it is unlikely that any such organism would gain the necessary regulatory approval in time to be of much use in treating an oil spill. Such organisms, however, could be useful in enclosed oily waste treatment systems, perhaps replacing current disposal methods in which oily wastes

are spread over surface soils and allowed to degrade in a process called "land farming" or "land-treatment".

Future Research Needs

One of the commonly cited problems for bioremediation, especially when introducing micro-organisms is considered, is the lack of knowledge about microbial community interactions. Research is needed on the factors that control the survival and functioning of micro-organisms within complex communities. At present it is not possible to know whether or not an introduced organism will survive, persist, or function. This lack of knowledge limits the ability to predict the outcome of biological waste and pollutant treatment systems. It also raises concerns about the potential long term impacts of introducing organisms. Some researchers feel it is almost impossible to introduce organisms with novel traits, particularly those that over-express degradative capacities, and to have those micro-organisms survive long enough to be of environmental benefit. Others feel that steps must be taken to ensure that introduced micro-organisms can be recalled, particularly if they are genetically modified; it is possible to engineer suicide functions into genetically modified micro-organisms and this has been proposed as a safety measure.

There is a clear need for performance standards against which the success of bioremediation can be measured. The development of biosensor detection systems could contribute to monitoring system performance as well as serving for other pollutant monitoring. Currently, there is no definition of how low a level of a pollutant can safely remain in the environment, nor how quickly specific pollutants must be eliminated as environmental contaminants. This makes it difficult to evaluate when bioremediation should be employed and when alternate treatments are appropriate.

The Organization for Economic Cooperation and Development (OECD) is in the process of developing a report on the state-of-the-art of biotechnology for a clean environment that covers a very broad range of topics. Both long-standing traditional applications of biological systems for waste treatment and modern approaches for pollution, remediation and minimization are to be considered in this report. The report should serve as a broad guidance document for Governments. Research areas will be identified, particularly where there are bottlenecks to employing biotechnological solutions to environmental problems.

The American Academy of Microbiology examined the scientific foundations of bioremediation and issued a report in 1992 on the current status and future needs. The report states that a major problem in the development of bioremediation technology is the lack of field sites that are well-characterized with respect to contaminants, geohydrology, and geochemistry; such sites are urgently needed for understanding the natural events that are taking place and also for the transfer of technology developed in the laboratory to field conditions. An integrated interdisciplinary approach is essential for the application and verification of bioremediation, and this can only be achieved under environmental conditions. Although some sites may already exist, their openness and flexibility of use is unlikely to support more than a few efforts in the bioremediation community. Predictability of process performance cannot be made with a high level of confidence. In some cases, predictability is limited by the lack of biological information, in other cases by lack of accurate parameter estimation and availability of appropriate models. There is a need to orient aspects of bioremediation research to modern biotechnically integrated science and engineering effort using defined field demonstration sites as vehicles for integration. There is a need for realistic economic analyses of costs and cost saving in the use of bioremediation, as compared to other systems for hazardous waste management, and to promote research, development and demonstration of the next generation technology. Given the magnitude of the cost of hazardous waste management and the potential savings bioremediation may create, it can be anticipated that there will be greater investment in environmental biotechnology and the use of bioremediation.

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