OCCASION

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

DISCLAIMER

FAIR USE POLICY

CONTACT

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

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

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

EMERGING TECHNOLOGY SERIES

2/1996

Genetic Engineering and Biotechnology

UNITED NATIONS
INDUSTRIAL DEVELOPMENT
ORGANIZATION
Vienna, 1996

EMERGING TECHNOLOGY SERIES:

GENETIC ENGINEERING AND BIOTECHNOLOGY

1996/2

CONTENTS

UNIDO's *Emerging Technology Series: Genetic Engineering and Biotechnology* is established as a mechanism of current awareness to monitor developments in the genetic engineering and biotechnology sector and inform governments, industry and academia, primarily in developing countries.

The publication is issued four times a year and distributed free of charge to readers in developing countries. It is not a formal document and has been reproduced without formal editing.

Compiled and edited: Diana Rhind
Editorial Board: Y. Maruno, V. Podshibyakin; G. Tzotzos;G. Ramsey; B. Sugavanam; Z. Cziser

Published in 1996 by the United Nations Industrial Development Organization (UNIDO)
Vienna International Centre
P.O. Box 300
A-1400 Vienna
Austria

Tel.: (43-1)21131-0
Fax: (43-1)230-7355

Printed in Austria

TO OUR READERS

Since technology is a key factor in socio-economic develoment the global technological scene is dynamic, and because countries are at different levels of industrial and economic development, a variety of promotional measures are called for, which can be applied transectorally and linked to industrial development efforts. At the national level, countries must be helped to find an optimum mix of activities to balance their multifaceted requirements in the field of technology, with a measure of coherence to enable the achievement of concrete results. Technological advances in such fields as informatics, genetic engineering and biotechnology, new materials and marine industrial technologies have become too important in the global scene to be ignored by developing countries. Experience has shown that developing countries need assistance in becoming sensitized to the potential and applications of such technologies and in developing human resource capabilities to handle the inflow of such technologies. The appropriateness of technologies is still a concept of particular relevance to developing countries. However, it needs to be promoted together with the countries in the light of the conditions prevailing in the 1990s and the increasing concern for sustainable development, while facilitating the blending of modern and traditional technologies.

The capacity for the formulation of technology policy activities and for technology management at government, enterprise and institutional levels has become all the more essential with the increasing complexity of technological development and its application. In the changed macroeconomic context, the revitalization of R&D institutions in developing countries becomes paramount if those countries are to recoup their investments in R&D infrastructure. The formulation and management of major promotional projects, such as intercountry technological centres is a means for securing government and national S&T cooperation. One such successful example is the International Centre for Science and High Technology (ICS), located at Trieste (Italy).

UNIDO, with the generous support of the Italian Government established the ICS in 1988 in an endeavour to provide a targeted response to the needs of developing countries for technological innovation, the transfer of appropriate and compatible technology, and the creation of a dynamic technological and managerial culture. The ICS has predominantly oriented its attention and efforts to the fields of pure and applied chemistry; earth, environmental and marine sciences and technologies; high technology and new materials; and the promotion of high technologies applicable to the environment. The ICS carries out action-oriented research, scientific seminars and training courses, study tours and fellowships, and provides consultancy and advisory services. The extensive programme of work for 1996/1997 is well underway, and in the field of biotechnology alone, carries activities that range from bioremediation and phytoremediation; biodiversity prospecting; and the industrial exploitation of indigenous medicinal and aromatic plants. Ancillary work covers decision support systems and environmental impact assessment for industrial development, the monitoring of industrial siting and pollution by remote sensing and *in situ* automated instrumentation, networking and access to technology information, technology monitoring and forecasting, and many others.

In this issue, readers will find mention of a number of other centres that UNIDO has helped to establish, and some more are in the offing. An interesting new one not mentioned will handle hydrogen for energy requirements.

Managing Director
Investment and Technology Promotion Division

CONTENTS

CONTENTS *(continued)*

CONTENTS *(continued)*

TECHNOLOGY AND INVESTMENT OPPORTUNITIES

TECHNOLOGY OFFERS

CULTURE DEVICE FOR DIRECT MICROBIAL CULTURE/COUNT

The culture device has a protruding culture agar medium giving a flat and smooth culture surface of predetermined dimensions. The device is applied directly onto the test surface to obtain a replicate quantitative sample with minimum manipulation. The device may be pliable and flexible and is adaptable for direct sampling of flat, curved and uneven surfaces. A reliable, practical and economical monitoring system for microbiological surveillance. The counts have direct correlation with sanitary quality standard of the test surface. Minimum sampling variation. Results are more accurate than those of conventional methods. One-step technique – simple, quick and straight forward and can be carried out by lay persons with little training.

(For further information, please contactMr. Brian Plagett, Managing Director, Technology Exchange Ltd., Wrest Park, Silsoe, Bedford MK45 4HS, United Kingdom; Tel: +44-1525-860333; Fax: +44-1525-860664)

GENE PROBES DETECTION/ANPLIFICATION ASSAY

A highly sensitive non-radioactive method for the detection of gene probes and monoclonal antibodies. A derivative of this work is an exceptionally sensitive luminometric method for the quantitative determination of alkaline phosphatase using a single put method and commercially available reagents.

(For further information, please contact Mr. Brian Plagett, Managing Director, Technology Exchange Ltd., Wrest Park, Silsoe, Bedford MK45 4HS, United Kingdom; Tel: +44-1525-860333; Fax: +44-1525-860664)

"SIMBIONT" PREPARATION

Biological mycorrhizal formula using fungi. Ecologically clean plant growth stimulator.
Techno-economic advantages: Increases yield capacity of crops by 30 per cent, enlarges leaf surface by up to 25 per cent (e.g. tea and tobacco) and root system by 100 to 200 per cent.
Application areas (uses): Agriculture (seeds, grain, vegetables and fruit).
Environmental aspects: Increases humus content of soil, strengthens disease resistance and is 100 per cent ecologically safe.
Degree of development: Patented: Patent No. 370932 of 6 December 1972 in Russia. Produced under laboratory conditions on an experimental scale. Small lot sale is organized.
Production capacity: Recommended economic scale: 300 litres per year. Unit market price in Russia US$5 per 1 ml.
Inputs: Raw material, utilities, etc.: 3 cubic m of water per 24 hrs. and 350 kwt power per 24 hrs.
Land/building (sq.metres) Indoor: 1,000 Manpower: 15 skilled, 15 unskilled
Project cost (in US$, excluding land, building and labour): US$ 2,000,000 Equipment/Machinery (FOB): US$ 550,000
Terms of Transfer: Joint venture

(For further information, please contact: Mr. Vitaly Koleshnikov, Executive Director, International Foundation of Science, Culture, Economics, 13/7 Prechistenka Street, 119034 Moscow, Russia.)

ASSAY KITS FOR WATER, FOOD, FISH AND SHELLFISH

Two licensable technologies are offered: (1) A portable and user-friendly immunoassay kit to detect cancer-causing toxins (microcystins) in water, fish and algae-based health foods. (2) A patented US Patent No. 5-180665, Canadian Patent No. 2055935) rapid and highly sensitive enzyme assay for diarrhetic shellfish poisoning toxins and microcystins.
Main use: Analysis of drinking and recreational water, food, fish and shellfish for the presence of microcystins and diarrhetic shellfish poisoning toxins.
Main advantages: Rapid, sensitive and cost-effective
Degree of Development: Laboratory or prototype
Know-how available: Yes
Technology is available for license but is covered by patent protection

(For further information contact: Dr. Ram Mehta, President, Prairie Biological Research Ltd., 4290-91A Street Block C, Edmonton AB, T6E 5V2 Canada, Tel: 403-405-3957; Fax: 403-450-3960)

TECHNOLOGY AND INVESMENT OPPORTUNITIES

TECHNOLOGY REQUESTS

VACCINES AND INJECTIONS
Production of vaccines and injectables for veterinary use. Annual demand growth is 30 per cent. Feasibility study available. Project cost US$3 million, of which one-third available locally at Ahmedabad.

Type of cooperation sought: Licence, investment

(For further information, please contact: Mr. S. V. Purohit, Shubh Pharmaceuticals, 360 Sarvodaya Comm. Centre, Ngar G.P.O., Ahmedabad - 1, India; Tel: +91-79-550.1831; Fax: +91-79-663.1831)

ETHYL VANILLIN AND DERIVATIVES
A new project to manufacture 500 tonnes/year of synthetic vanillin from guaiacol, ethyl vanillin from guaethole and guaiacol/guaethole from catechol in Coimbatore District of Tamil Nadu. Project cost US$ 12 million financed through public issue and term loans. About 1,000 tons per year is currently imported at US$ 34/kg and demand growth is 15 per cent per annum. Import duty is 50 per cent, plus 20 per cent counter-veiling duty (CVD).

Type of cooperation sought: Licence, equipment supply.

(For further information, please contact: Mr. Rajiv Nayan, Executive Director, Tamilnadu Industrial Development Corporation Ltd. (TIDCO), 19-A, Rukmini Lakshimpathy Raod, Egmore, Madras 600 008, India; Tel: +91-44-855-3385; Fax: +91-44-855-3729)

CAPSULES AND TABLETS
A new project to manufacture capsules and tablets of pharmaceutical preparations in Rajasthan, Uttar Pradesh/Haryana, near New Delhi, based on GMP buidelines of the World Health Organization. A marketing potential and feasibility study (June 1995) is available and the annual growth in demand is 25 per cent. The project cost is estimated at US$ 0.8 million, of which US$ 0.6 is locally available, plus 4,500 sq. metres of land and 1,500 to 2,000 sq. metres of building.

Type of cooperation sought: Investment, joint venture

(For further information, please contact: Mr. K. K. Bansal, Kay Kay Imports & Exports, Cho Milap Nagar, Uttam Nagar, New Delhi 110 059, India; Tel: +91-11-550.3004/0841; Fax: +91-11-559.6857)

NEEM BASED BIO-PESTICIDES
A new turnkey project in Haryana requires manufacturing process know-how for bio-pesticides based on Neem. Local investment of US$ 0.1 million, plus 4,000 sq. metres land and 900 sq. metres building available.

Type of cooperation sought: Turnkey project, know-how licence

(For further information, please contact: Mr. Anil Kumar, Cobra Chemicals Pvt. Ltd., F-8 Akarshan Bhawan, 23 Ansari Road, Dryaganj, New Delhi, India; Tel: +91-11-327.8808/2150; Fax: +91-11-328.5585)

TAXOL AND TAXANAES
Technology required for the isolation of taxol and other useful faxanes for use by a company based in Nurpur (Himachal) with the facility for extraction and isolation of therapeutic phytochmicals.

Type of cooperation sought: Joint venture

(For further information, please contact: Namiex Chemicals Pvt. Ltd., P.O. Box 4, Dhangu Road, Pathankot 145 001, Punjab, India; Tel: +91-186-26308/20947; Fax: +91-186-23982/20518)

MANUFACTURE OF TEA MACHINERY AND BLACK TEA
Company seeks strategic alliances and joint venture with international companies for technology upgrading and international market access for tea machinery and black tea.

Type of cooperation sought: Investment,licence

(For further information, please contact: Andrew Yule & Co. Ltd., Yule House, 8 Dr. Rajendra Prasad Sarani, Calcutta 700 001, India; Tel: +91-33-242-8210/7722; Fax: +91-33-242-5477/2943/4417)

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

EMERGING TECHNOLOGY SERIES

(incorporating the Technology Trends Series and Industrial Technology Monitors)

If you would like to receive any of the following publications in future, please complete the list below and return to the address indicated. Please note that all publications are available in English only, and are free of charge to readers in developing countries; for readers in developed countries a handling fee of US$ 40 per annum is imposed for Genetic Engineering and Biotechnology; Information Technology and New and Advanced Materials.

For new subscribers only

- ☐ GENETIC ENGINEERING AND BIOTECHNOLOGY (four issues per year)
- ☐ INFORMATION TECHNOLOGY (formerly Microelectronics) (four issues per year)
- ☐ NEW AND ADVANCED MATERIALS (formerly Advances in Materials (four issues per year)
- ☐ MARINE INDUSTRIAL TECHNOLOGY (two issues per year)
- ☐ HIGH-TECHNOLOGY SPIN-OFFS (two issues per year)

Special issues

- ☐ ADVANCED MATERIALS No.1 (Advanced Materials in High Technology and World Class Manufacturing
- ☐ TRENDS IN PARALLEL PROCESSING
- ☐ ENVIRONMENTALLY SOUND MANAGEMENT OF BIOTECHNOLOGY (The Task Managers' Report on Chapter 16 of Agenda 21)

FAMILY NAME AND GIVEN NAMES	
TITLE OR POSITION	
ORGANIZATION OR COMPANY	
STREET AND/OR P.O. BOX NO.	
CITY AND TEL./FAX NO.	
COUNTRY , TEL./FAX NO. AND E-MAIL	

Return to:

UNIDO, Industrial Information Section, P.O. Box 300, A-1400 Vienna, Austria.
Fax: (+43) 1-21131-6843

A. SPECIAL ARTICLE

CURRENT TRENDS IN IMMUNODIAGNOSIS OF HIV INFECTION

by

Bharat S. Parekh, Ph.D.
Division of AIDS/STD/TB Laboratory Research
Centers for Disease Control and Prevention
Atlanta, Georgia 30333

Since the recognition of HIV infection and its worldwide spread, which began in the late 1970s and continues through the 1990s, prevention of HIV infections and AIDS has become the major focus of health agencies around the world. The World Health Organization (WHO) currently estimates that as many as 20 million people are infected with HIV worldwide, with massive new infections occurring in many African and highly-populated Asian countries. Recent WHO/GPA surveillance data suggest geographic expansion of the epidemic in South-East Asia, as observed earlier in Thailand, is also being repeated in Cambodia and Viet Nam. The situation in the Indian subcontinent is already alarming, with estimates of 1.5 to 2 million infections and a continuing rapid spread of the virus. Worldwide, by the year 2000, more than 30 million people could be infected with the virus. Since most afflicted individuals are adults or young adults, the economic and social impact of this epidemic to affected countries could be enormous. Of this, approximately half will be women, most of them of child-bearing age, with the potential to transmit the virus to as many as two to four million children via the perinatal route. Early diagnosis of HIV infection in these individuals can help to provide proper counselling and treatment, and prevent the further spread of HIV.

Need for testing/diagnosis

Testing for HIV infection is important for the safety of blood supply, for surveillance purposes and for medical diagnosis of HIV infection. Testing is essential for the development of guidelines for prevention programmes and antiviral therapies as well as research leading to preventive vaccines. Laboratory diagnosis is also important because it provides uniform criteria for the identification of HIV infection, for which diagnosis based solely upon clinical criteria is usually too complex and imprecise. During the healthy asymptomatic period, which could last for 10 or more years, laboratory diagnosis is essential before any therapy for HIV infection can be initiated.

Ten years ago, the first tests became available in 1985 to detect HIV infection by detecting HIV-specific antibodies present in the blood. Since then, HIV antibody-testing has become an essential tool of public health efforts to stop the epidemic of HIV infection. The importance of testing for blood supply safety can be clearly illustrated by the fact that in the United States of America, during the period between 1978 and 1985, before testing was implemented, approximately 12,000 individuals were infected with HIV due to transfusion of contaminated blood or blood products. After 1985, when the testing of blood supplies became mandatory, only rare cases of transfusion related transmissions have occurred in the USA. Currently, the risk of transmission due to transfusion of contaminated blood is approximately one in 500,000 donations in the USA. In addition to blood bank screening, testing may be recommended in several other situations such as:

(a) To individuals with high-risk behaviours (homosexuals, prostitutes, intravenous drug users);

(b) To those with clinical conditions suggestive of HIV infection;

(c) To recipients of unscreened blood or blood products;

(d) To people with sexually-transmitted diseases;

(e) To pregnant women;

(f) To children born to high-risk women or to women known to be infected with HIV;

(g) To health care workers; and

(h) To those with accidental or occupational exposure to HIV-infected body fluids.

Additional benefits of testing include the opportunity to provide appropriate counselling to promote behaviour change that is necessary to reduce HIV transmission, referral of HIV-positive individuals for medical evaluation and proper treatment and advice to HIV-positive women to reduce perinatal transmission.

Although at present molecular approaches (e.g. polymerase chain reaction [PCR]) are being developed to detect the virus directly, immunologic diagnosis still remains the basis for almost all testing done worldwide. In this review, I will try to bring together incremental developments in immunodiagnosis, including simple and new approaches that are appropriate for developing countries, and address the issues that may be critical in such situations.

Note: This article was written by Bharat S. Parekh in his private capacity. No official support or endorsement by CDC is intended or should be inferred.

Use of trade names is for identification purposes only and does not imply endorsement by the United States Public Health Service or by the United States Department of Health and Human Services.

Basis for diagnostic tests

HIV infection in an individual results in early viraemia followed by elicitation of HIV-specific antibodies (*see figure 1*). Within weeks after infection, IgM antibody response can be detected, which peaks rapidly but is rather short lived. Almost all infected individuals mount a detectable IgG antibody response to the viral proteins within one to three months after infection and sero-negativity beyond six months is not common. Antibodies to viral proteins, especially to envelope glycoproteins, persist for a lifetime. Detection of these virus specific antibodies forms the basis of all immunodiagnostic testing methods. Although these methods do not detect the presence of virus or virus components directly, this indirect approach to HIV diagnosis has been found to be quite reliable, sensitive and specific. Extensive research has been carried out to better characterize the humoral immune response, to evaluate the kinetics of early IgM and IgG antibodies and to map the antigenic epitopes that are important for immunity. The research has resulted in newer tests that are more sensitive and specific than previous versions of tests and are capable of early diagnosis (Roziers et al., 1995).

Methods of testing

Detection of anti-HIV antibodies in the serum or plasma of an individual is considered an indirect but definitive test for the diagnosis of HIV infection. The basic goal of detection of HIV antibodies is accomplished by the use of viral antigens that interact with specific antibodies, if present. The resulting antigen-antibody complexes are further detected directly or, as is more common, indirectly by a variety of means such as a change in colour (soluble or precipitated), aggregation of particles (agglutination), fluorescence or other properties (detection of endpoint). The assays are optimized to favour the formation of antigen-antibody complexes and thus achieve high sensitivity. Different tests, such as enzyme immunoassay, Western blot, dot-blots, various agglutination tests, or immunofluorescence assays, represent similar underlying principles, but with different formats and detection endpoints and have been developed as alternatives or for various testing needs.

A. Screening tests for diagnosis of HIV-1 and HIV-2

Enzyme immunoassay (EIA)

The most widely used assay format is the EIA in which HIV antigens are coated on the surface of microtiter wells (*see figure 2*). Diluted serum or plasma is incubated to allow binding of HIV antibodies to the antigen. The unbound antibodies are then washed off. The bound specific antibodies are then detected by the use of a secondary antibody (for example, goat antibodies to human IgG) conjugated to peroxidase or alkaline phosphatase enzyme followed by the addition of an appropriate colourless substrate that changes its colour when acted upon by the enzyme. The washings that are needed between different additions are usually accomplished by automated washers, while the final change in colour is quantitated by a spectrophotometer (EIA readers). The available automated or semi-automated instrumentation and application to the mass screening as required by the blood banks has made EIAs the preferred assay format. First-generation EIAs used HIV-1 viral lysate as the antigen. Sensitivity and specificity of newer versions are highly improved by the use of purified recombinant viral proteins and synthetic peptides. In addition, there are several variations of basic EIAs, which may include competitive EIAs, antigen-sandwich EIAs (*see figure 2B*) and IgG capture EIAs (*see figure 2C*). In essence, the second- and third-generation EIAs have evolved to narrow the window period, i.e the time between HIV infection and detection of positivity, while at the same time reducing the false positive results. With the discovery of HIV-2, a closely related but distinct virus, tests were developed to detect HIV-2. Subsequently most HIV-1 EIAs were modified to incorporate HIV-2 antigens to reduce the cost and labour of two separate assays. Testing by combination HIV-1/2 EIA may require a modified algorithm, which should be followed in testing of specimens and reporting of results (Holloman et al. 1993).

Particle agglutination test

There are other screening assays, such as the particle agglutination test, that are used as a primary test in some countries. As shown schematically (*see figure 3*), micro-particles (e.g. latex beads) coated with viral antigens are mixed with the test serum. If the specific antibodies are present, the particles are cross-linked due to bivalency of antibodies and thus agglutinate. In tests such as the SERODIA-HIV (Fujirebio, Japan), a widely-used agglutination test in Japan and some parts of Asia, free particles settle down at the bottom of the well forming a tight button with a defined boundary. Antibody cross-linked particles settle much more slowly and cover the whole surface. Other tests using agglutination as the endpoint are RETROCELL HIV-1 (Abbott Laboratories, Illinois, USA), Recombigen (Cambridge Biotech Corp. Massachusetts, USA) and Capillus HIV-1/2 (Cambridge Biotech Corp. Galway, Ireland). Capillus is a simple and rapid test and is discussed further later. Agglutination tests are fairly easy to perform, however interpretation of results may require some skill. For some tests (e.g. SERODIA-HIV) appropriate instrumentation has been developed to automate the procedure and reading of the results.

Although these assays are quite sensitive as primary screening methods, the positive results have to be confirmed by a more specific test (supplemental test).

B. Supplemental tests

It was recognized early on that diagnosis of HIV infection should be confirmed by a second test that is more specific and has a different format and test design. Thus, confirmation of a positive EIA by a second supplemental test, such as Western blot (WB) or immunofluorescence (IFA), became a routine and standard practice for immunodiagnosis of HIV infection.

Western blot (WB) assay and other line immunoassay (LIA)

WB assay is a procedure in which (1) viral proteins are first separated by their molecular weight on a gel by electrophoresis; (2) proteins are subsequently transferred to the surface of a thin membrane, such as nylon or nitrocellulose; (3) cut strips of this membrane are used for the immunoassay using a serum or plasma specimen to detect antibodies to virus proteins (*see figure 4*). Assay steps usually involve specimen incubation, conjugate incubation and a precipitating substrate, separated by washes, all performed on a rocker for optimal binding and reaction. Antibodies to specific viral proteins are visualized as coloured bands. High specificity of the Western blot is

attributable to its ability to identify viral protein-specific antibodies present in a given serum or plasma. Due to the specific locations where viral proteins migrate when separated by electrophoresis, specific and non-specific reactions can be recognized. A positive interpretation on WB usually requires the presence of antibodies to two or more viral specific proteins (*see table 1*). There are some differences in interpretation criteria, depending on the recommending agency or manufacturers of the WB. A positive WB interpretation is usually regarded as a definitive test for HIV infection. If antibodies to viral proteins are present that do not satisfy positive criteria, the results are termed as indeterminate. Such situations can arise if (a) the person is recently infected with HIV and has not yet developed a full complement of antibodies; or (b) the person has non-specific cross-reactive antibodies. A follow-up testing at a later date (three to six months later) can usually clear up such indeterminate test results.

Table 1

Interpretation criteria for positive Western blot

Recommending agency	Presence of antibodies to at least
CDC/ ASTPHLD	Any two of p24, gp41 and gp 120/160
American Red Cross	At least one band from each of the genes coding for: *gag*, *pol* and *ev*.
WHO	Any two *env* bands ± any other viral proteins
In addition, commercial WB test kits may have their interpretive criteria and in some cases intensity reference band.	

As an alternative to WB, which uses purified virus preparation as the antigen source, line immunoassays have been developed using recombinant proteins and/or synthetic peptides, representing different gene products. These proteins or peptides are applied as discrete individual lines on the nitrocellulose or nylon membrane. Strips of antigen-coated membrane are used in an assay to detect antibodies to viral proteins. A number of commercially available tests have used this format (for example RIBA from Chiron Corporation, California, USA; INNOLIA from Inno-Genetics, Belgium; PeptiLAV from Diagnostic Pasteur, France). Some of these tests also incorporate antigens specific for HIV-2 and thus help differentiate between HIV-1 and HIV-2 infection (see below).

Immunofluorescence assay (IFA)

IFA involves the use of inactivated HIV-1/2 infected cells fixed on a glass slide. Cold acetone or an acetone/ether mixture is usually used to remove lipids and fix the cells without destroying the cell morphology. HIV-infected cells express viral proteins in the cytoplasm and on cell membranes and provide antigens for antibody recognition. Adjacent uninfected cells serve as controls. HIV-specific antibodies, if present in a specimen, bind to infected cells and unbound antibodies are removed with repeated washings. Bound antibodies are detected indirectly by the use of a fluorescently tagged secondary antibody (e.g. fluorescein isothiocynate-conjugated anti-human IgG), which can be observed under a fluorescence microscope. Most of the indeterminate results obtained by the WB can be resolved by IFA. IFA requires a fluorescence microscope and well-trained personnel to interpret the fluorescence results. Thus, although it offers an alternative to WB, the test may be appropriate only for laboratories trained in the use of IFA.

With the discovery of HIV-2, the additional need to confirm and type HIV-2 infection was recognized. Although WB assays carried out using HIV-2 virus preparations are available, this supplemental test (and HIV-2 IFA as well) cannot be used to type infections due to a high cross-reactivity between various HIV-1 and HIV-2 proteins. Therefore, the typing of virus infections is usually achieved by other methods (see below).

C. Typing of viral infections

In most areas of the world, and even in West Africa, where HIV-2 prevalence is relatively high, the HIV-1 epidemic has dominated the spread of the virus. If the typing of viral infection is desired following a positive screening test, then appropriate tests should be used. Typing by commercially available WB is not possible due to extensive cross-reactivity between HIV-1 and HIV-2 viral proteins, including envelope glycoproteins. It was observed that oligomeric forms of the transmembrane envelope protein cross-reacted significantly more than the monomeric glycoprotein, presumably due to common conformational epitopes (Parekh et al., 1991). However, transmembrane glycoproteins of both HIV-1 and HIV-2 were found to have immunodominant epitopes which do not cross-react (Gnann et al., 1987); synthetic peptides made from these sequences can be used for typing purposes (*see table 2*).

Table 2

Immunodominant peptide sequences

Virus	Sequence
HIV-1	LGIWGCSGKLICTT
HIV-2	LNSWGCAFRQVCHT

Therefore a WB assay made with HIV-1 viral proteins and HIV-2 typing antigen (immunodominant transmembrane peptide) applied at the bottom of the strip as a line is able to type and confirm HIV-1 or HIV-2 infections (Pau et al., 1993).

Concern with the high cost of commercial WB assays and their inability to type virus infections has resulted in the development of immunoassays that use immunodominant peptides from HIV-1 and HIV-2 applied as discrete lines or spots. Examples of such tests are PeptiLAV (Diagnostic Pasteur, France), Genie 1/2 (Genetic Systems, Washington, USA), INNOLIA (InnoGenetics, Belgium) and Rapid Testing Device (RTD 1/2) (Cambridge Biotech, USA). Some of these tests have been used for typing of virus infections and examining the extent of dual (HIV-1 and HIV-2) infections in dually seroreactive populations in western Africa (George et al., 1992). Such tests can be used as supplemental assays in a diagnostic algorithm replacing a traditional WB. The assays have good sensitivity, but the specificity to type viral infections varies

from about 70 per cent to more than 90 per cent, depending on the test.

Although, typing of viral infections (HIV-1 or -2) is useful for epidemiologic purposes to monitor the spread of the virus through different populations, questions remain about the usefulness of virus typing in those developing countries that have limited resources. Infections with either HIV-1 or HIV-2 results in the development of AIDS and related opportunistic infections, although low pathogenicity of HIV-2 has been well-recognized, with a longer asymptomatic period. If virus typing is desired, the supplemental test capable of confirming and typing HIV infection, instead of WB, should be used to reduce the cost.

Problems with diagnostics

Enzyme immunoassay

Purified virus preparations were the first antigens to be used in EIAs (first-generation tests). However, there were limitations of both sensitivity and specificity. Envelope proteins constitute only a minor proportion (less than 10 per cent) of total viral proteins in the purified virus, although they elicit an early, persistent and major humoral response in infected individuals. Thus, enrichment of envelope proteins was important. Moreover, purified virus preparations usually contain significant amounts of cellular proteins which could not be removed easily without additional loss of viral envelope proteins. These impurities contribute to low specificity. These limitations could be overcome by use of recombinantly expressed purified envelope proteins. Use of such antigens resulted in the development of second-generation tests, which are not only more sensitive but are also more specific. Thus, tests that use appropriate envelope recombinant proteins are usually more sensitive in detecting early seroconverters than those that use whole viral lysate. In addition, the false positive rate is often lower due to the absence of contaminating cellular proteins.

Simultaneously, EIAs using one or more synthetic peptides derived from HIV proteins were also developed as second-generation tests. Synthetic peptides have the advantages of low cost and high stability. Some of these tests are extremely sensitive in detecting early seroconverters and also exhibit high specificity. Moreover, tests based on synthetic peptides can be used to detect HIV infections or typing HIV infection. However, concerns remain due to the limited epitope sequences presented by peptides and the absence of conformational epitopes, which could compromise sensitivity.

An example of this limitation became evident when Group "O" viruses were discovered in individuals from Cameroon. Due to significant sequence differences between "O" and "M" (main) group viruses, assays that use recombinant proteins or synthetic peptides occasionally failed to detect antibodies to group "O" viruses, but viral lysate based assays were successful in detecting group "O" infections (Schable et al., 1995). This high sensitivity of viral lysate based assays appears to be due to high cross-reactivity of GaG antibodies. Since accurate diagnosis and safety of blood supply is of great importance, commercial companies that use recombinant proteins and/or synthetic peptides are modifying their assays to increase their assay sensitivity to detect group "O" viral infections. These modifications, in most instances, involve the incorporation of immunodominant synthetic peptides or recombinant proteins from group "O" viruses as one of the antigens.

Additional problems with EIAs are the need for instrumentation (washers and spectrophotometer) and refrigeration. EIAs are also not suitable as single test units or field testing of specimens. A simple, low technology test would be more appropriate for such applications, especially in developing countries.

Western blot assays

Although Western blot has been a very useful supplemental test for confirmation of HIV infection, there are several drawbacks:

1. Manufacturing of WB strips has been a very labour intensive process, resulting in a high cost, as much as $20 to $50 per test.
2. The interpretation of WB results has always generated considerable debate. Different manufacturers and organizations have relied upon different interpretive criteria, which classifies a given specimen as positive, based upon the presence of a combination of antibodies to specific HIV proteins (*see table 1*).
3. Moreover, interpretation of FDA approved tests in the United States requires comparison of the test strip results with the intensity of a reference band. This adds to the complexity of interpretation to an already complex procedure.
4. Unlike most other tests, WB testing results in a significant number of individuals being classified as indeterminate and who may require additional follow-up testing.

Paediatric HIV infection

HIV infection in infants mainly occurs as a result of perinatal transmission from infected mothers. Although only about 25 per cent of infants acquire HIV infection, all infants born to seropositive women, irrespective of their HIV infection status, test positive on conventional assays due to transplacentally acquired antibodies. Thus, standard serologic tests are unable to diagnose HIV infection in infants at least for 12 to 18 months after birth, until uninfected infants serorevert and lose their maternal antibodies.

New developments in diagnosis

There are new developments appearing constantly in HIV diagnosis. They relate to one or more of the following: improvements in sensitivity and specificity, simplicity and ease of use of the assay, use of an alternative specimen other than serum/plasma, less labour/low cost, and rapidity of the assay. In addition, tests are specifically developed to address the issue of early diagnosis of HIV infection in infants.

Antigens

Almost all new tests use recombinant proteins and/or synthetic peptides. Since antibodies to both envelope and GaG proteins are believed to be important for diagnosis, new recombinant antigens have been developed that incorporate antigenic portions of envelope and GaG into a single molecule. Such chimeric antigens are available for HIV-1 and HIV-2 and are being explored for diagnosis. Use of a single chimeric antigen, instead of two or more individual antigens, eliminates competition for binding and ensures that important antigenic epitopes are bound to the plastic or solid surface in equimolar amounts. Moreover, this would simplify antigen purification, characterization and handling, thus helping to reduce the cost.

Similarly, chimeric synthetic peptides incorporating immunodominant portions of both HIV-1 and HIV-2 into a single peptide are also being investigated for their ability to recognize HIV-1/2 specific antibodies simultaneously (Shah et al., 1996). We have also used various peptide antigens with V3 loop sequences inserted into a mucin backbone for their diagnostic potential (Fontenot et al., 1996). The results suggest that minimum amino acid sequences of epitopes when presented in a manner to achieve the right conformation can have enhanced antigenicity and can act as better antigens. Short peptide sequences derived from the tip of the V3 loop of gp120 were used in immunoassay to determine the prevalence and distribution of two distinct HIV-1 subtypes (clades B and E) in Thailand (Pau et al., 1993). The study provided very valuable epidemiologic information regarding the introduction and movement of two subtypes in the Thai population. These different antigens can be used in EIAs, line-immunoassay or other rapid assays suitable for a variety of testing situations.

Formats

As the focus of the epidemic is shifting from the Western world to Africa and Asia, testing strategies are also changing towards simpler and more inexpensive methods. The developments in testing formats have resulted in assays that are easy to perform and interpret, do not require any instrumentation and cost significantly less than the traditional EIA/WB algorithm. Examples of different formats include self-containing flow-through devices with dots or lines as markers of positivity, capillary enhanced agglutination, dipsticks or other variations (*see figure 4*). It should be stated that although many such tests are being developed, only a few have good sensitivity and specificity. Simplicity and rapid assay formats sometimes result in inadequate performance. To ensure that simplicity in format does not compromise performance in detecting low antibody levels or local HIV variants, it is important that the test is adequately evaluated in the area of its intended use in parallel with EIA/WB, prior to its use in diagnosis or surveillance.

Tests such as HIVCHECK (Ortho Diagnostic Systems, USA), GENIE 1/2 (Genetic Systems, USA), TESTPACK (Abbott, USA), and AccuSpot (Specialty Biosystems, USA) are examples of flow-through devices with one or more antigen spots on the membrane. The devices have absorbent material underneath to retain the liquid. Sequential addition of test serum, conjugate and substrate (few drops each with washes in between) yields coloured spots if the specimens contained virus-specific antibodies. In some tests, antibody binding is detected by the use of gold-conjugated Protein-A or secondary antibody for direct visualization of positive reaction and does not involve enzyme conjugated secondary antibody or substrate. In one version (Insti-1/2, IntraCell Corp., USA), the secondary reagent was coupled to a coloured dye, giving a blue spot. This test was found to be very sensitive, although specificity needed further optimization. Another similar test, SUDS (Murex Corporation, USA), has absorbent material placed radially and is approved by the US Food and Drug Administration (FDA). The flow-through single unit test devices are self-contained, minimizing the risk of exposure to potentially infectious agents; they do not require any equipment to run, are easy to perform and give results within a few minutes.

Another simple and rapid test using a novel format, is Capillus HIV-1/2 (Cambridge Biotech Corp., Ireland). This is based on the principle of agglutination as described before, however agglutination reaction is favoured by the flow of the latex beads through a narrow capillary, as shown by the direction of arrows (*see figure 4*). As the homogeneous latex suspension flows, a positive reaction is accompanied by the appearance of particulate aggregates of latex. This simple test has been found to be quite sensitive and specific and has gained acceptance in some developing countries and African surveillance programmes.

A recent test, SeroStrip-1/2 (Saliva Diagnostic Systems, Singapore), has a unique dipstick format. Gold conjugate is applied as a dried chemical between the two membranes. When placed in the diluted specimen, gold conjugate with IgG antibody is wicked towards the antigen (applied as a line on the middle part of the dipstick). HIV-specific antibody-gold complexes are captured by the antigen, resulting in a red line. In the absence of the specific antibody, the antigen line remains colourless. The upper line provides IgG control by capturing IgG in the sample to ensure specimen adequacy. Again, this test is very simple to perform and in preliminary evaluation has been found to have good sensitivity and specificity.

Another example of a simple test is Immunocomb, developed by the Program for Appropriate Technology in Health (PATH), Seattle, USA. Antigen is applied as spots on a plastic comb (eight notches) with its positions matched to microtiter plate wells. The comb is dipped into the specimen and then the gold conjugate. The test takes 20-25 minutes to run with two incubations of 10 minutes each. With help from PATH, the test is manufactured in several developing countries. Although the test is simple to perform, it generates potentially infectious liquid waste in open containers (during the wash steps between incubations) and was found to be somewhat cumbersome.

Simplicity of test formats often results in rapid test results. This may be quite important in many developing countries for screening of individuals prior to blood donations. Since many blood donations are by relatives of patients and thus are hot transfusions, tests such as these can serve a very important purpose in screening potential donors and to prevent transmission. Testing algorithms that use two different simple tests, instead of conventional EIA and WB algorithms, have been evaluated in various settings and have been found to be very cost-effective, with sensitivity and specificity equivalent to EIA/WB. Although such tests are very attractive for developing countries, relatively high pricing does not allow their widespread use. A few of the tests being evaluated cost significantly less (less than $1.00 per test) and may find widespread use in developing countries.

Alternative specimens

There has been considerable interest in the use of specimens other than serum or plasma for the detection of antibodies to HIV. Alternative specimens include dried blood spot (collected on a filter paper), saliva or oral fluid and urine.

Dried blood spots (DBS)

DBS can be collected on filter paper, with proper training and instructions, and requires a needle stick and a very small amount of blood. Thus, it can be obtained from individuals resistant to venipuncture or from infants. Moreover, DBS has the advantage of ease of shipping and storage. Antibody can be eluted with an elution buffer containing detergents, and detected using modified EIAs and WB. For the last seven years, the US Centers for Disease Control and Prevention (CDC), in collaboration

with participating State Health Laboratories, have successfully used the DBS for large-scale surveillance of childbearing women in the United States to detect HIV infection. (Gwinn et al., 1991). The DBS were collected from newborn infants as part of their metabolic screening programme. One spot was used for anonymous testing of HIV antibodies. Since antibodies in infants represent the mothers' antibody profile, the survey provided valuable epidemiologic and geographic information on HIV infection in child bearing women. More than 5 million infants (and thus women) have been tested so far by EIA (modified and optimized for DBS), with positive results confirmed by a modified WB (miniblot). Although DBS represents a useful alternative specimen, its collection requires some training. Testing has to be accompanied by stringent quality control and assay modifications.

Oral fluid or saliva

Over the last few years, oral fluid (OF) has generated a lot of interest for the detection of HIV-specific antibodies. A number of commercial companies have developed OF collection devices to ensure collection of adequate specimen and preservation of antibodies (OraSure by Epitope, Oregon, USA; Omni-Sal by Saliva Diagnostic Systems, Washington, USA; and Salivette by Sarsdedt, UK). Collection devices usually involve an absorbent pad that is allowed to saturate with saliva in the mouth. The saturated pad is then transferred to a tube containing a buffer with preservatives that include microbial and protease inhibitors. This, coupled with modified and optimized EIA (e.g. GACELISA by Murex Corp., UK) and WB, has permitted the detection of HIV antibody with sensitivity (Granade et al., 1995), comparable to that achieved for testing of serum specimens. Miniature WB (miniblot), used earlier for dried blood spot specimens, was adapted for the confirmation of positive EIA. IgG concentration in the OF varied from <1 μg/ml to more than 100 μg/ml. However, the detection of HIV-specific antibody was not correlated to the level of IgG. Implication of OF collection and testing in developing countries are enormous and represent tremendous advantages over invasive blood collection procedures. This includes low personnel costs, training and equipment, as well as ease of acceptance of non-invasive collection procedures. Moreover, the risk of breakage during collection and transportation is minimized.

Urine

Although urine could be an attractive specimen due to ease of collection, there have been concerns about the stability of the antibodies in the urine and the effects of its low pH. Recently, tests such as Calypte EIA (Calypte Biomedical, Berkeley, CA) have been specifically developed to detect HIV-antibodies in urine. After collection, a urine preservative tablet is added to the sample to stabilize the antibody. The Calypte EIA is reported to have a sensitivity equivalent to plasma or serum. Occasional detection of urine positivity in seronegative individuals has raised important questions on the validity of this test or the origin of positive results. Therefore, although urine can be a very simple and useful specimen for HIV diagnosis, additional parallel work needs to be done on serum and urine to validate the test or tests. Confirmatory assays also need to be developed to eliminate false positive results.

Diagnosis in infants

The need to diagnose HIV infection in children, specially in the first few months after birth, has resulted in the development of many new approaches. This topic is exhaustive and will require a separate review to do it justice. However, I will briefly summarize the new approaches for paediatric diagnosis. Although molecular or virologic methods, such as polymerase chain reaction (PCR) and virus culture, have been used in many studies to diagnose HIV infection and have been found to be quite sensitive and specific in identifying most infected infants within 30-45 days after birth, at present these tests are not commonly available for paediatric diagnosis. In addition to the technical difficulties, specialized facilities, instrumentation and expertise needed, prohibitively high cost will limit their use for diagnosis in most developing countries. Alternative immunologic approaches would therefore be more desirable.

Immunologic approaches to diagnose HIV infections in infants include p24 antigen detection (p24 Ag assay), HIV-specific IgA detection (by IgA-Western blot or IgA-EIA), detection of HIV-specific IgG secreting cells or secreted antibodies (enzyme linked immunospot assay [ELISPOT] and In-vitro Antibody Production [IVAP]), or detection of HIV-specific IgG (by IgG-Capture EIA).

p24 antigen assay

Since free p24 antigen does not apparently cross the placenta, detection of this viral antigen in infants is considered an indication of HIV infection (Palomba et al., 1992). Therefore, p24 Ag assay (EIA format) has gained significant attention as a test for the diagnosis of HIV infection in children. Microwells coated with p24 antibodies are used to capture p24 that may be present in the serum or plasma. Captured p24 is detected by the use of conjugated anti-p24 antibody (antibody sandwich EIA) and an appropriate substrate. A modification of this assay involves disruption of p24 antigen-antibody complexes (immune complex dissociation) with acid or base prior to the assay to increase sensitivity of detection. The assay has been able to detect p24 antigen only in a subset of infected children. In prospective follow-up studies, some infants show a p24 antigen peak followed by a decline. However, this trend is not universal and the detection of p24 antigen is not always consistent. Therefore a negative p24 Ag assay does not rule out infection. Moreover, uninfected infants have occasionally been shown to have detectable p24 antigen, specially during the first few weeks of life, thus lowering the specificity of the assay.

HIV-specific IgA

Although the maternal IgG crosses the placenta, the IgA and IgM do not. Attempts to detect early HIV-IgM in infants have not been very satisfactory, although specific IgA has been found to be useful. In general, overwhelming and competing IgG present in the specimens is first removed by Protein-G Sepharose adsorption, which permits the detection of the HIV-IgA. Virus-specific IgA is detected by IgA-Western blot, as described (Weiblen et al., 1990). The assay is 30-40 per cent sensitive in the first two months after birth, but the sensitivity increases to 70-80 per cent by six months. Although useful, the assay is extremely cumbersome and expensive. As a simple alternative, IgA-capture EIA has been evaluated by us (Parekh et al. 1993) and was found to be quite comparable to the IgA-WB assay. The assay did not require any prior removal of the competing IgG. The IgA-capture EIA had a sensitivity of almost 75-80 per cent and a specificity of 100 per cent at six months of age. Moreover, due to its EIA format, the assay is less complex than the IgA-WB, costs significantly

less and can be performed in a few hours. Thus IgA-capture EIA has a potential utility for diagnosis in infants in developing countries.

ELISPOT and IVAP

ELISPOT uses antigen coated membrane wells and the infants' lymphocytes. HIV-specific antibody secreting cells adhere to the membrane during incubation. Location of HIV-antibody secreting cells is determined by anti-IgG antibody conjugate and an appropriate substrate and can be seen as coloured spots (Nesheim et al., 1992). IVAP involves culturing of lymphocytes *in vitro* to allow secretion of the antibody. The specific antibody is detected by the assay of the supernatant fluid (Amadori et al., 1990). Although both assays have been able to detect HIV infection in infants, there have been reports of lack of specificity during the first two months. Moreover, the assays are somewhat more technical in nature and require separation and culturing of viable lymphocytes.

IgG-Capture EIA

Although conventional EIAs detect maternal antibody present in the uninfected children up to 18 months of age, IgG-capture EIA was negative in these children by six months (Parekh et al., 1993). By this age, almost all immunocompetent infected infants make detectable HIV-IgG as seen by IgG-Capture EIA. Thus, this assay can be used for serologic diagnosis of HIV infection in infants at or after six months of age with a sensitivity of almost 100 per cent (in immunocompetent infants) and a specificity of 100 per cent. Since it takes about six months for the loss of most (>99 per cent) of maternal IgG (half-life = 23 days), the assay cannot be used for diagnosis prior to six months. However, it still represents a great improvement in the capability of diagnosing HIV infection by a simple serologic means, since a conventional EIA would be reliable only after 18 months of age. These assays have thus increased our understanding of the immune response to HIV in infants and have helped to diagnose HIV infection in children.

Conclusions

There have been continuous developments in the immunodiagnosis of HIV infections. A variety of assays in different formats use natural viral proteins, recombinant antigens and/or synthetic peptides. The goal has been to develop assays that are broadly reactive to identify all different HIV variants, detect antibodies soon after infection and thus are highly sensitive. Improvements in the preparation and design of antigens have also improved the specificity of the assays. In fact, immunoassays for HIV diagnosis have led the revolution in the diagnostic industry and have sought to overcome the many challenges that different situations present. Yet there are no simple and inexpensive assays for the detection of HIV antibodies in oral fluid or urine. Ease of specimen collection for oral fluid or urine, coupled with simple, rapid and affordable assays, can have great implications in the diagnosis of HIV infections in developing countries, and ultimately in halting the spread of HIV infection.

References

1. Roziers, B.N.; Sotto, A.; Arnaud, A.; Sarissi, G.; Nasv, O.; and Jourdan, J.: Kinetics of detection of antibodies to HIV-1 and plasma p24 during a severe primary HIV-1 infection. *AIDS*, 1995; **9**:528-529.

2. Holloman, D.L.; Pau, C.-P.; Parekh, B.; et al. Evaluation of testing algorithms following the use of combination HIV-1/HIV-2 EIA for screening purposes. *AIDS Res. Hum. Retro.*, 1993; **9**:147-151.

3. Parekh, B.S.; Pau, C.-P.; Granade, T.C. et al. Oligomeric nature of transmembrane glycoproteins of HIV-2: procedures for their efficient dissociation and preparation of Western blot for diagnosis. *AIDS*, 1991; **5**:1009-1013.

4. Gnann, J.W.; McCormick, J.B.; Mitchell, S.; Nelson, J.A.; Oldstone, M.B.A. Synthetic peptide immunoassay distinguishes HIV-1 and HIV-2 infections. *Science*, 1987; **237**:1346-49.

5. Pau, C.-P.; Holloman; D.L.; Lee-Thomas, S.; Schochetman, S.; George, J.R. A combination immunoblot for the simultaneous detection and differentiation of HIV-1 and HIV-2. *Clin. Diag. Virol.*1993; **1**:201-205.

6. George, J.R.; Ou, C.-Y.; Parekh, B.; Brattegaard, K.; Brown, V.; Boateg, E.; and DeCock, K. Prevalence of HIV-1 and HIV-2 mixed infections in Côte d'Ivoire. *Lancet*, 1992; **340**:337-339.

7. Schable, C.; Zekeng, L.; Pau, C.-P. et al. Sensitivity of United States HIV antibody tests for detection of HIV-1 group O infections. *Lancet*, 1995; **344**:1333-34.

8. Shah, K.; Davis, C.; Wilson, J.; Parekh, B. Chimeric synthetic peptides as antigens for detection of antibodies to HIV-1 and HIV-2. *East Afr. Med. J.*, 1996; in press.

9. Gwinn, M.; Pappaionou, M.; George, J.R. et al. Prevalence of HIV-1 infection in child bearing women in the United States. *J. Am. Med. Assoc.* 1991; **265**:1704-1708.

10. Fontenot, D.J.; VanCott, T.C.; Parekh, B.S. et al. Presentation of HIV V3 loop epitopes for enhanced antigenicity, immunogenicity and diagnostic potential. *AIDS*, 1995; **9**:1121-1129.
11. Pau, C.-P.; Thomas, S.L.; Auwanit, W. et al. Highly specific V3 peptide enzyme immunoassay for serotyping HIV-1 specimens from Thailand. *AIDS*, 1993; 7:337-340.

10. Fontenot, D.J.; VanCott, T.C.; Parekh, B.S. et al. Presentation of HIV V3 loop epitopes for enhanced antigenicity, immunogenicity and diagnostic potential. *AIDS*, 1995; **9**:1121-1129.
11. Pau, C.-P.; Thomas, S.L.; Auwanit, W. et al. Highly specific V3 peptide enzyme immunoassay for serotyping HIV-1 specimens from Thailand. *AIDS*, 1993; 7:337-340.
12. Granade, T.C.; Phillips, S.K.; Parekh, B.S.; Pau, C.-P. and George, J.R. Oral fluid as a specimen for detection and confirmation of antibodies to HIV-1. *Clin. Diag. Lab. Immunol.* 1995; **2**:395-399.
13. Palomba, E.; Gay, V.; Martin, M. et al. Early Diagnosis of human immunodeficiency virus infection in infants by detection of free and complexed p24 antigen. *J. Infect. Dis.* 1992; **165**:394-5.
14. Weiblen, B.; Lee, F.; Cooper E. at al., Early diagnosis of HIV infection in infants by detection of IgA HIV antibodies. *Lancet*, 1990; **1**:988-90.
15. Parekh, B.S.; Shaffer, N.; Coughlin, R. et al. HIV-specific IgA capture enzyme immunoassay for early diagnosis of HIV infection in infants. *Pediatr. Infect. Dis. J.*, 1993; **12**:908-913.
16. Nesheim, S.; Lee, F.; Sawyer, M. et al. Diagnosis of human immunodeficiency virus infection by enzyme-linked immunospot assays in a prospectively followed cohort of infants of human immunodeficiency virus-seropositive women. *Pediatr. Infect. Dis. J.* 1992; **11**:635-9.
17. Amadori, A.; DeRossi, A.; Chieco, B.L. et al. Diagnosis of human immunodeficiency virus infection in infants: in vitro production of virus-specific antibody in lymphocytes. *Pediatr. Infect. Dis. J.* 1990; **9**:26-30.
18. Parekh, B.S.; Shaffer, N.; Coughlin, R. et al. Dynamics of maternal IgG antibody decay and HIV-specific antibody synthesis in infants born to seropositive mothers. *AIDS Res. Hum. Retro.*, 1993; **9**:907-911.

Figure 1
Schematic representation of dynamics of virus load and antibody levels after HIV infection

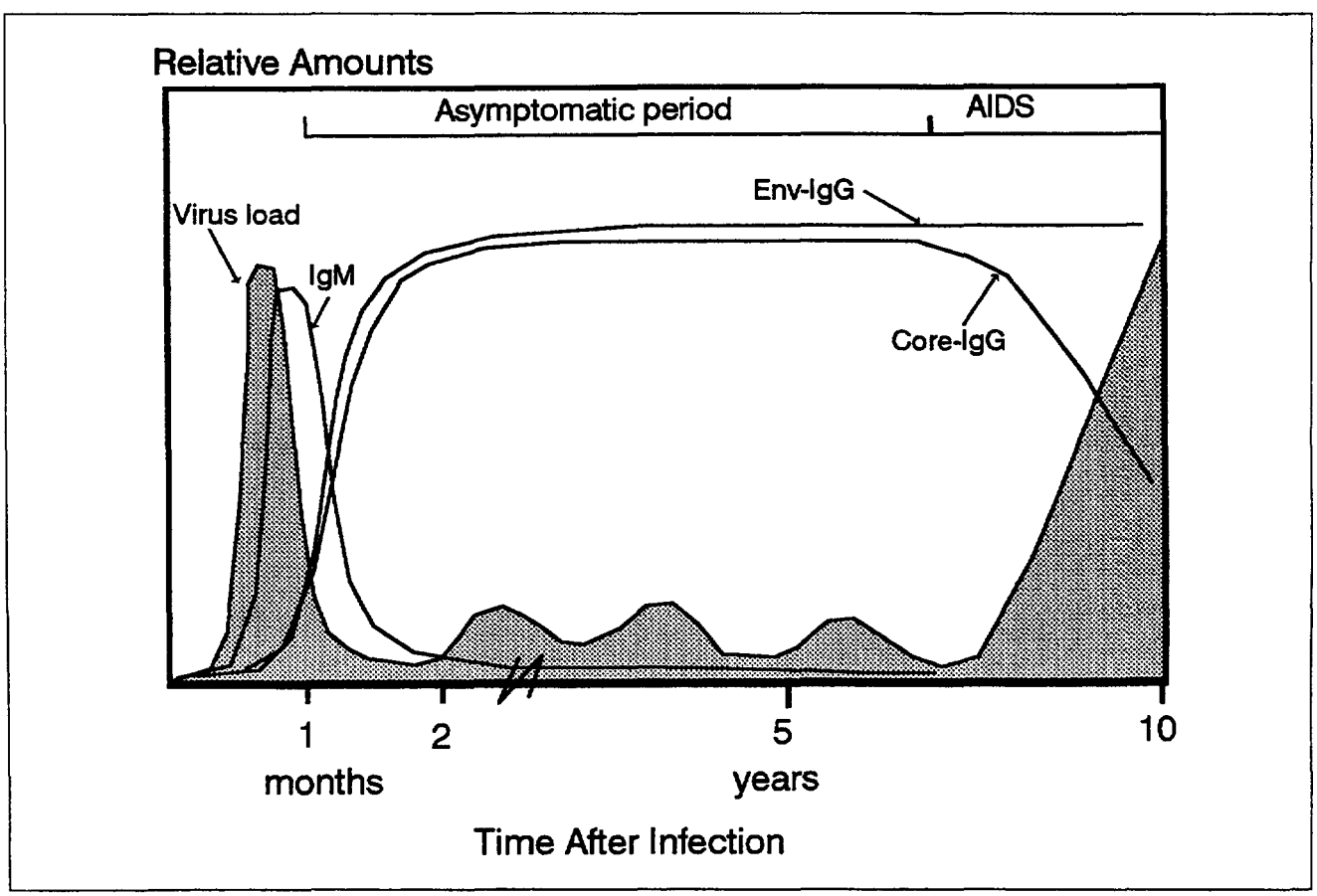


Figure 2
Schematics of enzyme immunoassays. A: conventional indirect EIA; B: antigen sandwich EIA; C: IgG capture EIA

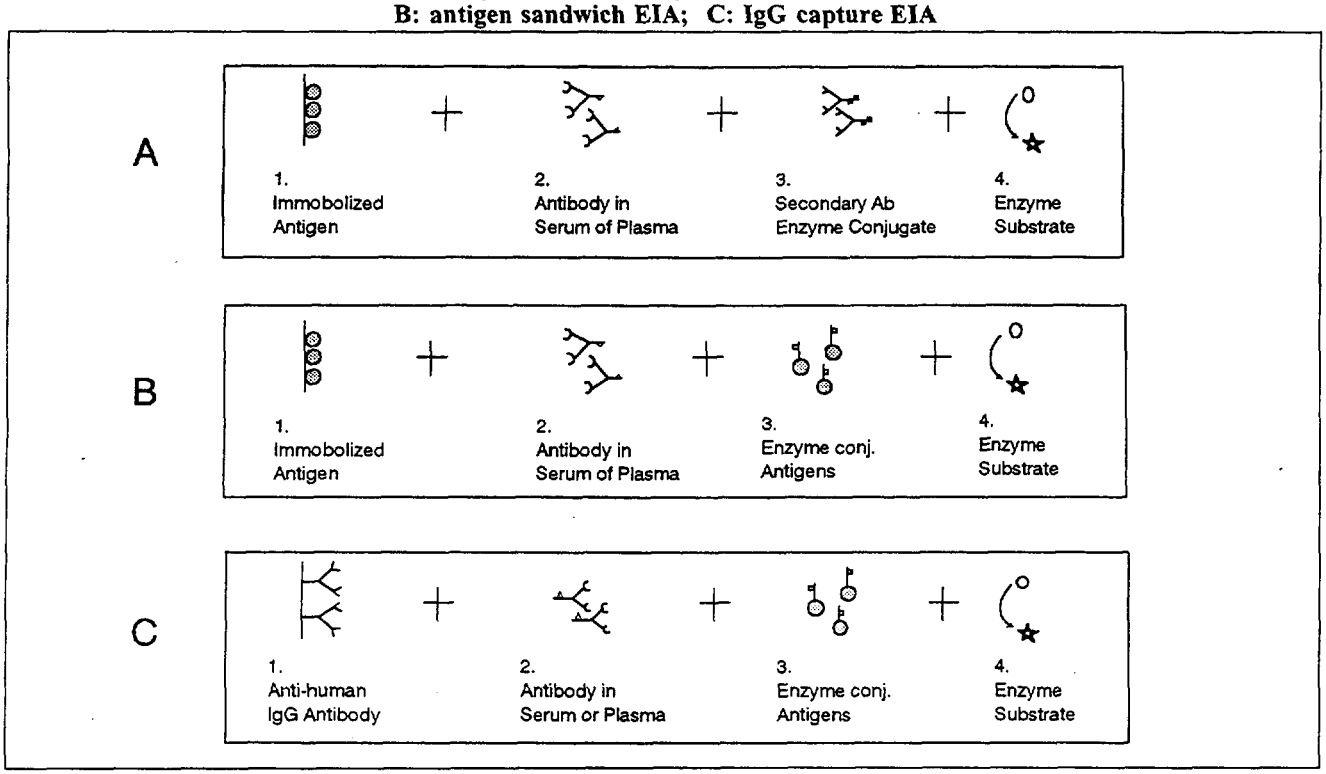


Figure 3
Schematic of agglutination assay

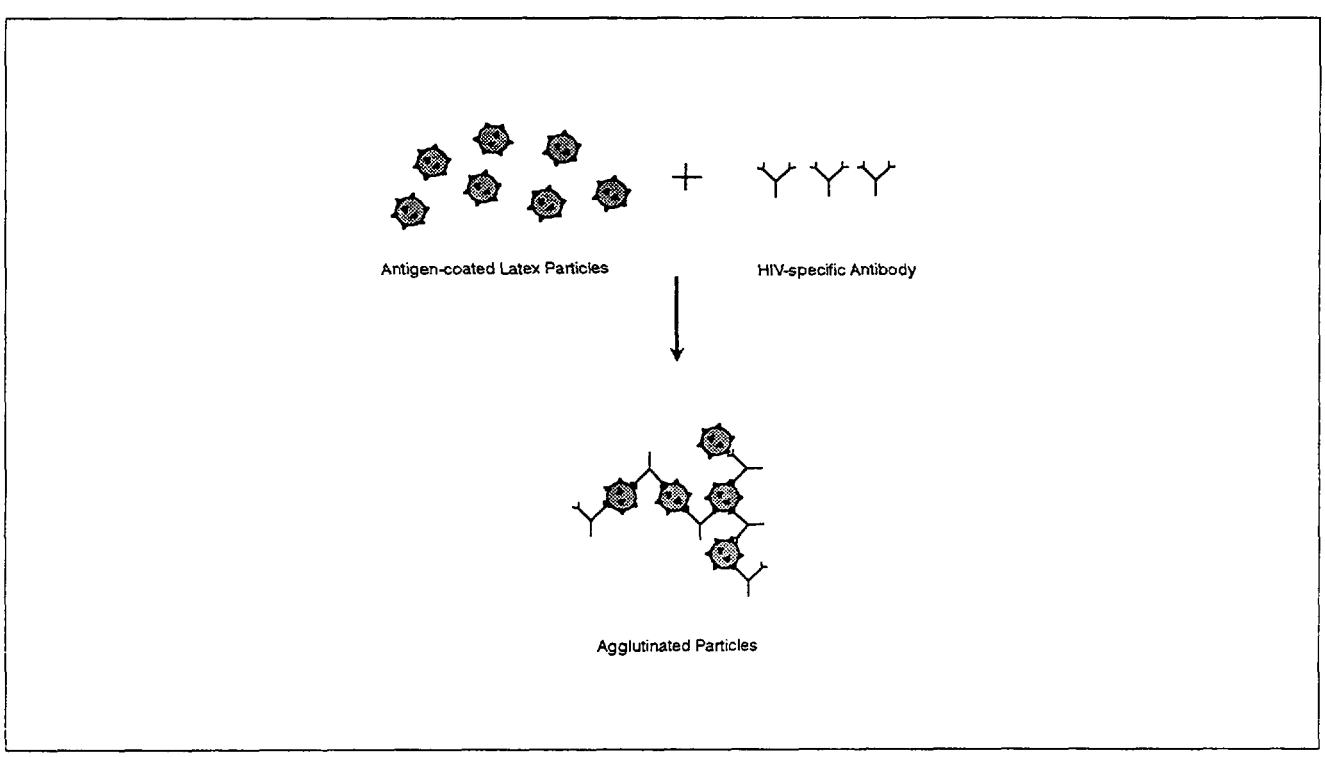


Figure 4
Preparation of Western blot strips (A) and examples of developed strips (B). Strips 1 and 2 represent results from infected individuals, while strip 3 is an indeterminate banding pattern. Strip 4 shows no bands (uninfected individual)

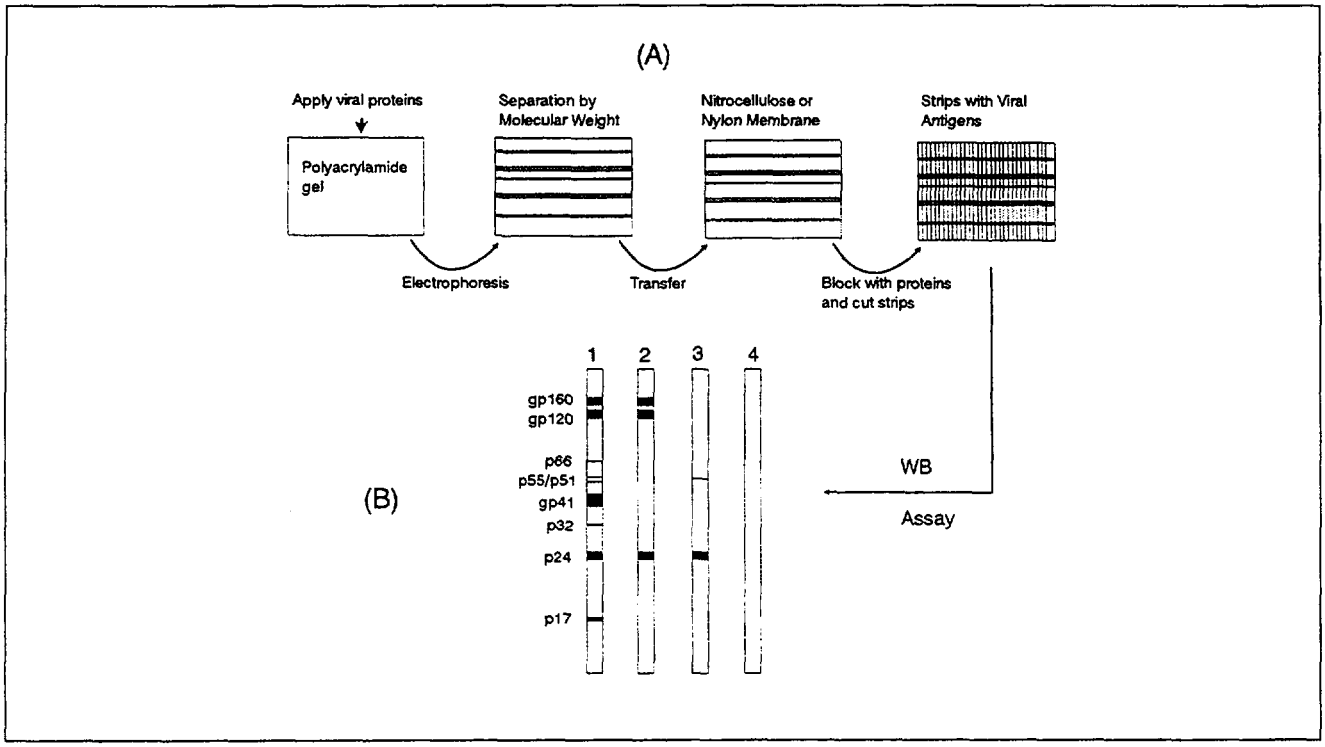
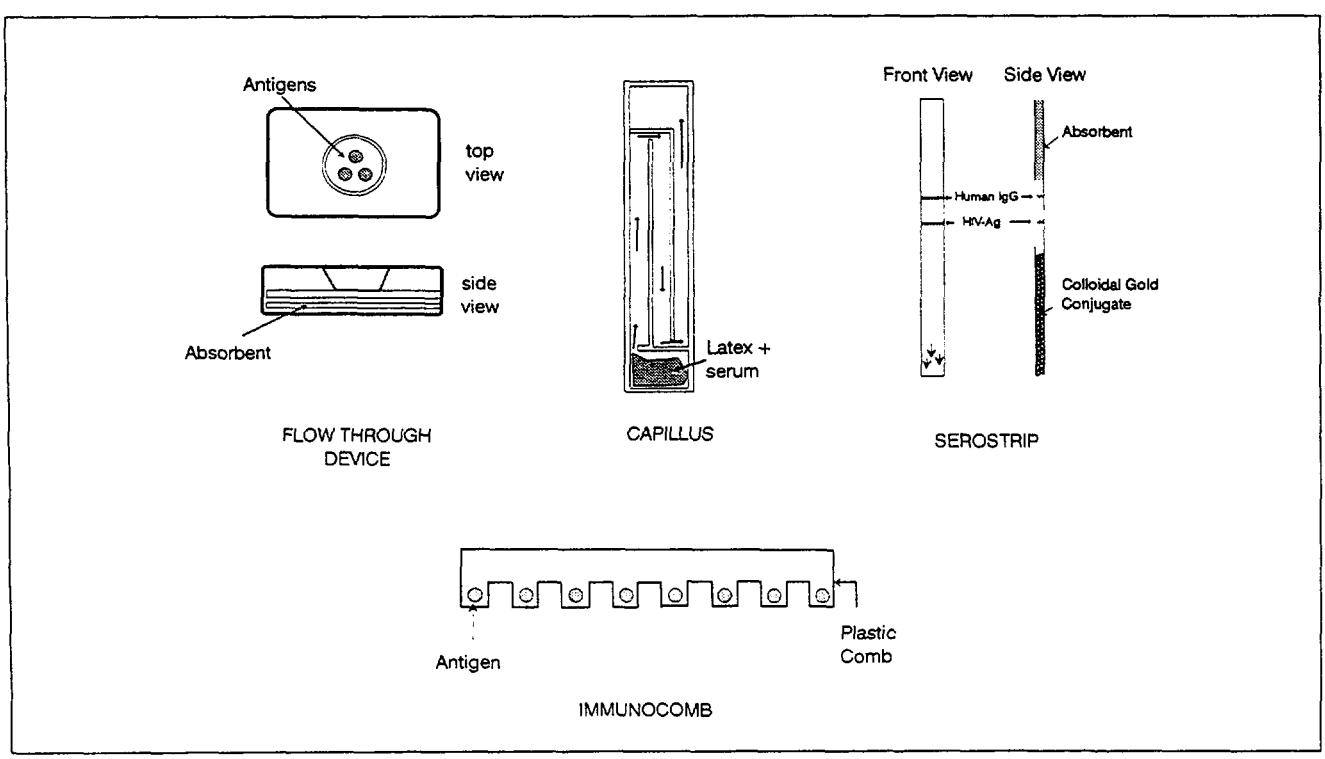


Figure 5
Various simple testing formats



B. NEWS AND EVENTS

UNIDO news

Establishment of the International Centre for Materials Evaluation Technology (ICMET) in Taejon, Republic of Korea

One of the latest achievements of the UNIDO programme in the area of new materials is the establishment of the International Centre for Materials Evaluation Technology (ICMET) on the premises of the Korea Research Institute of Standards and Science (KRISS) in Taejon, the Republic of Korea. The preparatory and pilot activities phase has just started and is planned to be implemented from 1996-1998. The following information about the mission, objectives, functions and the work programme of ICMET will give the opportunity to our readers to know more about this new Institution, which is planned to provide a framework for developing countries to cooperate in this vital area for materials science and engineering.

The mission of the International Centre for Materials Evaluation Technology (ICMET) is to develop international guidelines, codes of practice, standards on testing and characterization for new materials which can be accepted across national boundaries. It is also to bridge the gap between research and development organizations, innovative enterprises and the market place within developing countries to stimulate the diffusion of new materials and processing technologies and their application in materials related sectors of industry.

The objectives of the ICMET is to respond to demands from the developing countries for building up/ strengthening technological capabilities in testing and evaluation of new materials and to act as the focus point for promoting international cooperation in this field.

The ICMET operates under the auspices of the United Nations Industrial Development Organization (UNIDO) and will focus on the following functions.

(a) Awareness building

Gather, monitor and disseminate information from both developing and developed countries in the field of testing and evaluation of new materials, including on-going work of important standards committees and standards issues.

(b) Cooperative R&D

Identify industrially important areas for developing or improving new materials evaluation and characterization techniques through cooperative R&D programmes. Generate validated and widely acceptable techniques which can form the basis for the development of regional and international standards. Intercomparisons of laboratories and development of key reference materials.

(c) Advisory services

Help industry and R&D institutions in the developing countries build up/strengthen their technological capacity in the area of testing and evaluation of new materials. Deliver the service provided by a network of organizations wherever possible.

(d) Training

Make a valuable and sought-after contribution by organizing training programmes which offer practical experience to participants in key and developing fields of materials characterization and evaluation. Provide the scientists and technologists access to state-or-the-art instrumentation and testing facilities which are relevant and important to industry. Place emphasis in seeking industrial views in the design of the courses and making them attractive to participants from industry in developing countries.

(e) Promotion

Promote international/regional cooperation in the field of testing and characterization of new materials in order to eliminate barriers in international trade.

Work programme

ICMET will work in close cooperation with existing research and testing centres and institutions, especially in the Asia and Pacific region at the initial stage.

Taking into consideration the novel nature of the Centre and the complexities of arrangements for international collaboration, the task is planned to be tackled in two phases.

(a) Preparatory and pilot activity phase (1996-1998)

The initial three-year work programme started in January 1996 and includes the following key activities:

(i) Establishment of a Technical Advisory Group and holding three annual meetings to provide guidance for the ICMET, advise on the selection of work programmes and assist in formulating a long-term plan for the operational phase of the Centre;

(ii) Creation of an international network of institutions and individuals dealing with materials evaluation issues in policy-making agencies, professional societies, enterprises, R&D centres and universities;

(iii) Design of appropriate database system and its networking with the existing information system in the area of materials testing and evaluation;

(iv) Organization and conducting of workshops and training courses on specific issues and problems in the area of testing and characterization of new materials;

(v) Formulation of and launching collaborative projects involving intercomparison and validation exercises to demonstrate the basis on which future R&D programmes can be developed and supported;

(vi) Further promotion of the concept and work programme of ICMET;

(vii) Development and approval of a long-term work programme for the next operational phase of the ICMET project.

(b) Operational phase (starting from 1999)

Based on the experience of the pilot activity phase, a fully fledged work programme for ICMET will be put into operation. This is expected to cover all important categories of new materials and an extensive range of activities related to the functions of the Centre. The long-term struc-

ture and administrative arrangements for ICMET will be completed and functioning.

The international dimension of the Centre and the need for its efficient management and innovative methods of work require a kind of pump priming fund that will help the nucleus to grow to a stable size and demonstrate the value of such a cooperative programme. Once this is achieved the Centre should be expected to raise sufficient additional amounts from other sources to carry out its activities.

The Government of the Republic of Korea expressed its interest in hosting the Centre and made the decision to allocate initial funding to start the project. Funds for the Centre's programmes are currently being sought from a range of organizations. These include: international aid and development funding organizations, national government development programmes, non-government aid organizations, organizations sponsoring research, private industry and industrial organizations.

The ICMET provides a unique opportunity for funding organizations to "lever" scarce financial resources. Funding organizations can direct funds towards specific programmes. This ensures that a high ratio of programme funds are effectively applied for maximum benefits of the target communities. Appropriate management procedures ensure a high level of financial accountability.

The Centre also seeks to consolidate funds from a variety of sources to undertake programmes for the benefit of developing countries.

Opportunities now exist, at a number of levels, for participation in the realization of the ICMET concept.

(i) Government organizations, R&D centres and enterprises from both public and private sectors of industry, and funding agencies active in new materials design, development, production and application are invited to submit project proposals and suggestions for areas of cooperation.

(ii) Research, manufacturing, marketing, financing, aid and policy development organizations and trade organizations are invited to make general operational suggestions and specific project recommendations. Discussions focused on identifying joint project opportunities involving the ICMET are also welcome.

(iii) Relevant international organizations are invited to seek formal links with the ICMET. In this manner, as the proposal develops, their additions and participation can be considered from the start.

Correspondence should be addressed to:
Vladimir Kojarnovitch
Technology Service
Investment and Technology Promotion Division
UNIDO, Vienna International Centre
P.O. Box 300, A-1400 Vienna, Austria
Fax.: (0043-1) 21131-6809
Tel.: (0043-1) 21131-3720

Copies of all correspondence and expressions of support should be sent to:
Dr. Gun-Woong Bahng
Materials Evaluation Centre
Korea Research Institute of Standards and Science
P.O. Box 3, Taedok Science Town
Taejon 305-606, Republic of Korea
Fax.: (0082-42) 868-5027
Tel.: (0082-42) 868-5320

The Perth International Centre for Application of Solar Energy (CASE)

Operating under the patronage of the United Nations Industrial Development Organization (UNIDO) the Perth International Centre for Application of Solar Energy (CASE), has as its charter the aim to promote the application of solar energy technology in developing countries. Solar energy encompasses all forms of renewable energy. The Centre is funded by both the government of Western Australia and the Commonwealth Government of Australia and is currently located in the Central Business District of Perth, the capital city of Western Australia.

The Centre aims to undertake a wide range of renewable energy technology-related services, including:

- Carrying out externally funded project definition studies;
- Arranging consultants to carry out feasibility studies;
- Assisting in preparing applications for project financing;
- Organizing contractors to implement projects;
- Managing projects;
- Ensuring local people are trained effectively to operate and maintain renewable energy systems.

CASE is a project oriented organization which draws together expert teams for individual projects. A typical project could include:

- Standalone photovoltaic (PV), wind and mini-hydro systems;
- Hybrid diesel, PV, and wind systems;
- Bio-mass energy systems;
- Solar thermal systems;
- Education and training;
- Technology and skills transfer seminars and workshops.

In collaboration with UNIDO and the recipient country, CASE aims to: define the project, carry out a feasibility study, assist in securing finance and finally to implement the project.

Projects should generally be initiated by an organization in a developing country, which formally requests UNIDO or CASE for assistance. Potential projects may be informally discussed at any time with CASE or UNIDO to ascertain their appropriateness, and will be judged on their own merit.

At the conceptual stage, potential projects may lack definition, scope and specific outcomes. The formulation of this information and the preparation of a project definition document, incorporating a preliminary system proposal and cost estimate is essential before the feasibility study can be carried out. This feasibility study is aimed at the objectives outlines in the project definition document. The study generally includes:

- Analysis of energy requirements and resources;
- Technology and equipment options, cost estimates;
- Economic and financial evaluation; site location studies;
- Analysis of cultural and social issues;
- Environmental considerations;
- Training requirements;
- Preliminary work schedules.

This feasibility study should provide the information required to support a request for project implementation funding. It is expected that where such a study indicates a viable project, the Government of the recipient country will

formally make a request for such funding. CASE and UNIDO assist in the application for national or international funds to implement viable projects. Once funding has been obtained, project implementation can proceed where usually UNIDO or CASE are appointed as project managers. The objective of this project management is to ensure that the project is completed on schedule, within budget limitations and meeting technical specifications. The project ensures that local people are trained in the operation and maintenance of the renewable energy systems so that the system will provide long-term satisfactory operation.

For more information, contact:
Programme Coordinator
Technology Service
UNIDO, Vienna International Centre
P.O. Box 300, A-1400 Vienna, Austria
Fax.: (0043-1) 232156
Tel.: (0043-1) 21131-5158

Managing Director
Perth International Centre for Application of Solar Energy (CASE)
Level 3, 81 St. George's Terrace
Perth, WA 6000
Australia
Fax.: (+619) 321 7497
Tel.: (+619) 321 7600

Establishment of the Mediterranean Centre for Marine Industries in Greece

In spite of the considerable efforts taking place in industrializing countries in scientific research and technology development, the industrial gap between the North and the South continues to widen. The marine sector has significant potential for the South. However, the development of this industry lags behind in terms of access to competitive technology and investment capital. The marine industry and its related technology services is an important economic factor for the Mediterranean region.

Facing this challenge, the United Nations Industrial Development Organization (UNIDO), in cooperation with the Government of Greece (General Secretariat of Research and Technology, Ministry of Industry, Energy and Technology), is now promoting the establishment of a Mediterranean Centre for Marine Industries located in Greece aiming at stimulating the advancement of the marine industries sector in the Mediterranean region, with particular emphasis on North-South cooperation.

The mission of the Mediterranean Centre for Marine Industries is to primarily promote strategic partnerships among Mediterranean countries in marine technology development and commercialization leading to enterprise cooperation between developing and developed countries in the region.

The Centre will undertake activities related to the identification, evaluation and promotion of business development projects. It will assist in the initial phases of joint projects through provision of such services as technology and market assessment, strategy development and project management.

Aiming at increasing industrial activities in the marine sector, the Centre will provide a variety of benefits to its participants, including:

- Acting as a bridge for the transfer of marine technology, encouraging international cooperation and eliminating duplication of efforts;
- Providing information relating to national priorities and business environments, technology and market opportunities, potential partners, funding mechanisms, etc.;
- Improving access to new markets and technologies through promotion of strategic alliances and joint projects between enterprises;
- Promoting the pooling of technology development resources, resulting in an enhanced technology base, shared risks and reduced technology developments costs;
- Provision of a linkage to regional or subregional R&D programmes with implications for the marine industry.

Further details may be obtained from:
Programme Coordinator
Technology Service
UNIDO, Vienna International Centre
P.O. Box 300, A-1400 Vienna, Austria
Fax.: (0043-1) 232156
Tel.: (0043-1) 21131-5158

Establishment of a National Cleaner Production Centre in Prague

The aim is to promote cleaner production to reduce industrial pollution through transfer of technical information and technology to industrial enterprises and environmental management agencies.

At Prague's Koh-I-Noor metal products factory, 80 per cent of production is electroplated, requiring an investment of US$ 800,000 to build a waste water treatment facility to comply with environmental regulations. This would have created a considerable financial burden for the firm, so it turned to the Czech Cleaner Production Centre for assistance.

Launched by UNIDO and the United Nations Environment Programme (UNEP) as part of its National Cleaner Production Centres programme, the Czech Centre organized an eight-month course, in which Koh-I-Noor took part. The course consisted of a series of lectures as well as in-plant training to introduce more efficient methods of pollution control such as recycling of waste material and water-saving measures.

The results have shown increased efficiency in the nickel-plating operation reduced annual water consumption by 8,200 cubic metres, waste water flow by 56 per cent and electricity consumption by 22,000 kilowatts. At the same time, consumption of chemicals dropped by 3,100 kilos and nickel by 980 kilos annually. The reductions meant an overall saving of nearly US$ 500,000 in installing the new treatment plant.

Opportunities for sponsorship of technical cooperation

In this section we intend to highlight some of UNIDO's technical cooperation activities which are of great importance and could have a major impact on developing countries. The majority of the programmes to be highlighted are searching for donors. Should you require further information, please contact the address below:

Programme to eliminate iodine deficiency disorders in China

Problems addressed

Iodine Deficiency Disorders (IDD) are one of the major factors affecting the health of children, women and the elderly in developing countries. Many factors favour

the spread of IDD, resulting in birth defects, miscarriages, infant mortality and brain damage. In the People's Republic of China approximately 450 million people (36 per cent of the population), are known to be affected by IDD.

Programme objectives

IDD can be prevented by simply adding a small amount of iodine to edible salt. The Government of the People's Republic of China has launched, in cooperation with UNICEF, UNDP, WHO and the World Bank, a *Universal Salt Iodization Programme* to eliminate IDD. It aims to produce good and stable quality iodized salt for public consumption. The technique is simple, but necessitates a complete modernization of the salt industry, which in turn requires UNIDO's assistance.

Proposed budgetary requirements

The technical assistance programme developed by UNIDO, for which sponsorship is sought, is divided into three subprogrammes, to be carried out in accordance with the progress of the overall IDD elimination programme, as follows:

(a) Computerized Salt Monitoring System for the IDD Network. Total budget: US$ 676,220;
(b) Technology Transfer Iodization, Quality Control, Packaging, Management Training in the Salt Industry, including ISO 9000. Total budget: US$ 510,760; and
(c) Support to R&D in Salt Technology, Analytical Methods, Packaging, Storage Stability, Training and Market Promotion. Total budget: US$ 1,017,000.

If you are interested in funding this programme kindly contact:

Chief, Coordination of Funds Mobilization Section
Country Programmes and Fund Mobilization Division
UNIDO, P.O. Box 300, A-1400 Vienna, Austria.
Fax: +43 1 21131 6813. E-mail:adegroot@unido.org

UNIDO Manual on technology transfer negotiation

Technology transfer is recognized as a key element to achieving international competitiveness, which firms need to survive the fierce competition of the global marketplace. Nowadays, the challenge is technological superiority and this implies being able to use technology transfer, through its various forms and channels, as a negotiated opportunity for technology absorption, assimilation and innovation.

The search for, choice, evaluation and negotiation of technology by enterprises, technology managers and users is never a simple task. The decision-making process requires information, knowledge and skill, and evaluation tools, standards and parameters. The idea of a manual on technology transfer negotiations was conceived to address these needs, i.e., to make available in one reference material, a comprehensive package of practical information, guiding principles and quantitative approaches to the multifaceted aspects of technology transfer. However, it must be stressed that the preparation of the UNIDO Manual is symbiotic with UNIDO educational activities in technology transfer operations; the two complement each other. In fact, the Manual is the product of a process of sifting through, organizing and making systematic use of the many accumulated training materials and experiences UNIDO has gained in the field of technology transfer operations and in providing advisory services and mediation in technology transfer transactions.

In its present form the Manual comprises nineteen chapters. The chapters are grouped in clusters representing, for the first three clusters, the different stages of the acquisition process. The first cluster runs through the various aspects of the macro-environment and deals with issues such as the role of technology transfer in achieving competitiveness and economic and social growth; the technology market; intellectual property protection; success factors for technology transfer; and the legal environment for technology transfer in developing and developed countries.

The second cluster focuses on matters relating to the search for and choice of technology, i.e., topics related to finding, evaluating and selecting technology, and procuring technology. The third cluster relates to the core issues of the Manual, that is, issues concerning negotiating and contracting. Topics covered comprise basic legal notions, approach to contract drafting, negotiating (techniques and strategy), valuation and methods of payment, training, warranties in technology transfer, types of agreements and general structure of agreements.

A fourth cluster deals with complex forms of technology transfer and comprises chapters on complex industrial projects and strategic partnering,

While initially oriented towards the needs of developing countries, the Manual can actually be used as a reference material by any technology negotiator. One of the purposes is to derive a common understanding of issues by both technology buyers and technology users. Doing so means laying down the groundwork for a lasting and durable relationship, to the advantage of both recipients and suppliers.

Finally, the Manual is an attempt to bring together as many issues as are relevant and critical to technology transfer operations. As a training material, this Manual (eventually its training version) is intended to be a living material; that means, it will grow, expand its coverage and be revised as new developments take place. Today, however, it is one of the most comprehensive bodies of knowledge covering a range of issues which are of relevance throughout the technology transfer and contract negotiation process.

This publication may be ordered from:
Distribution Unit (F-355)
Vienna International Centre
P.O. Box 300, A-1400 Vienna, Austria.
Price US$ 80
Payment through cheque, money order or UNESCO coupon or through the following UNIDO bank account: CA-BV, No. 29-05115 (ref. RB-7310000) Schottengasse 6, A-1010 Vienna, Austria.

Information database keeps decision-making on track

Knowledge may be the driving force of the information age, but what counts most in competitive manufacturing is accurate information and having it available in the right place at the right time. As competitivity and the complexity of modern industry increase, even small firms need more institutional memory and information processing capacity than their senior management can usually muster. So, whether you are a factory manager, an engineer or company information specialist, or a government planner needing quick, reliable and focused information for policy purposes, today's response almost has to be a database: neither the boss's memory nor the filing systems of yesteryear can cope any longer, even where their secretarial support is still affordable.

Some firms design computerized institutional memories from scratch, integrating them with expert systems that also diagnose problems and advise solutions. Depending on the type of information required, others rely on commercial application packages. UNIDO's new Information Resource Management System (IRMS) falls in a third group of specialized systems focusing on a wide variety of data and how industry managers use them.

Developed originally and tested with UNIDO's network of national Industrial and Technological Information Bank (INTIB) focal points in developing countries and economies in transition, the IRMS is now generally available to government departments, industrial companies and institutions as an integrated information processing package. It can be tailored to individual needs of the user organization, and is specially designed to operate in decentralized networks. Thus the same basic package may supply the name of a French-speaking expert on pollution control in the textile dyeing industry at one location, record real-time data for materials balances on a manufacturing process in order to facilitate annual reports on pollutant releases at another, and supply bibliographic information and information sources on technological developments in aluminium can recycling at a third. With the aid of a mailing subsystem, IRMS can also be used to record and index business information such as addresses, telephone and fax numbers etc., and to support office procedures.

Configured particularly to support the activities of information centres and the information needs of small- and medium-size firms, the package handles two major information types—*metadata* for general references (names of institutions, projects, experts and consultants, bibliographic information, meetings, training programmes, and information sources); and *technical data* (technology and process descriptions, environmental audits, case studies). The software basis is UNESCO's Micro-ISIS software, topped up with Pascal programmes that increase user friendliness and guide less experienced users. Menu-driven and featuring pop-up/pull-down sub-menus, the system enables data entry and editing, browsing, searching, display, printing and network functions such as data import and export. A special formatting language allows data to be prepared in a form usable by other software packages such as desktop publishers, expert systems and geographic information systems.

Several levels of validation are built into data entry procedures, thus preventing errors during data collection and storage. Such controls operate at field as well as record level to ensure consistency and correctness of data such as geographic names and the minimum of essential information for each record. Structured queries are automatically formulated with the aid of task tables and mouse-selected keywords. The browse function allows a brief look at the data after sorting according to standard fields. The menus also offer a variety of display formats suitable for different reporting requirements.

Designed for IBM-compatible PCs (386 and above), IRMS comes as a set comprising an installation diskette, user's manual, field specification handbook and a questionnaire for data collection. Price US$ 100. For further information on alternative language versions, postal charges, payment arrangements and availability, contact:

Chief, Industrial Information Section
UNIDO, A-1400 Vienna, Austria
Tel.: (+43 1) 21131 3691; Fax: (+43 1) 21131 6483.

UN and other organizations news

Bioethics Commission to review gene patenting

In October 1995, in an unexpected development, US President Bill Clinton created a national ethics advisory body, the National Bioethics Advisory Commission (NBAC, Washington, DC), to study both research ethics and the management and use of genetic information. Of particular interest to biotechnology companies and researchers is the fact that the Commission's brief encompasses issues about human gene patenting, a subject not contained in earlier proposals for the Commission.

NBAC, a nongovernmental advisory committee of no more than 15 members appointed solely by the President, is expected to be functioning by 31 January 1996. By that time, US federal agencies conducting, supporting, or regulating human subject research (including the departments of defense, energy, and health and human services) will have had to submit to the new Commission a review of their existing agency procedures to protect human research subjects. It is these agencies, too, that are expected to finance the bill of the Commission's estimated $2 million-a-year operating costs.

This is not the first bioethical advisory body either in the USA or abroad. One predecessor was the President's Commission for the Study of Ethical Problems in Medicine, and Biomedical and Behavioral Research, which finished its work in 1983. Current national and international bodies on bioethics include the UK's Nuffield Council on Bioethics (London), the International Bioethics Committee of UNESCO (Paris) and the Group of Advisers (to the European Commission in Brussels) on Ethical Implications of Biotechnology (Brussels, Belgium). (Extracted from *Bio/Technology, Vol. 13*, December 1995)

International Bioethics Committee

Created in 1993, the International Bioethics Committee gathers scientists, philosophers, economists, lawyers and sociologists in providing a forum for transdisciplinary and multicultural questioning concerning the implications of discoveries and technological innovations made in the biological and biomedical sciences. This type of reflection is organized with a view to preparing an international instrument on the human genome to be adopted by the UNESCO General Conference during its 29th session in 1997. (Source: *UNESCO Sources No. 72*, September 1995)

UNESCO centres on biotechnology

If you need evidence that the world has changed since the beginning of this decade, just look at the latest initiatives of the Biotechnology Action Council (BAC) of UNESCO (United Nations Educational, Scientific and Cultural Organization, Paris, France). In the 1980s and before, today's realities from UNESCO—biotechnology training centres for Arab States in Israel, an Asia centre in China, an African centre in South Africa—would have stretched credulity.

Under a new initiative established in 1995, BAC designated a number of existing institutes as regional biotechnology education and training centres: the Agricultural Biotechnology Centre (Godollo, Hungary) for Eastern Europe and the Mediterranean; Bethlehem University (Bethlehem, Israel) for the Arab States; CINVESTAV (Irapuato, Mexico) for Latin America and the Caribbean; Ocean University of Qingdao (Qingdao,

China) for Asia; and the Vegetable and Ornamental Plant Institute (Pretoria, South Africa) for Africa. During 1994-1995, BAC also launched special programmes in plant biotechnology for scientists in South Africa and Palestine.

From September 1991 to June 1995, BAC awarded 223 fellowships, from a pool of nearly 1,000 applicants, to scientists from developing countries. BAC fellowships are awarded twice a year, on a competitive basis, to enable young scientists (up to 40 years old) to spend up to three months in any laboratory in the world. The awardees represented 78 countries and went to host laboratories in 32 countries. Seventy-seven of the awardees were women. (Source: *Bio/Technology, Vol. 13*, November 1995)

Early warning system for plant genetic resources

In an attempt to obtain information on plant genetic resources and halt the loss and further erosion of valuable plant germplasm of food crops, the UN Food and Agriculture Organization (FAO) has established the World Information and Early Warning System on Plant Genetic Resources with a database containing information on about 4.8 million germplasm accessions held in some 1,220 genebanks or botanical gardens.

One of the main purposes of the system is the assessment of plant genetic resources erosion in seed collections as well as in natural stands. The international community would be alerted on all critical situations which are likely to occur in genebanks, field collections and natural habitats due to accidents, natural disasters and changes in the environment. An action may be initiated to prevent or minimize the genetic erosion. FAO and other international organizations successfully provided emergency assistance to genebanks particularly in Eastern Europe, as in Bulgaria, the Czech Republic and Hungary.

To enhance international cooperation to save and use many plant species which could help feed the planet's spiralling population, FAO also announced it will hold a major conference in Leipzig, Germany, in June 1996. FAO is concerned that thousands of little known indigenous plant varieties of interest for food and agriculture could be at risk of being lost by the middle of the next century if appropriate measures to preserve them are not taken.

Today, most of the world's farmed food comes from about 20 crops. Factors such as the substitution of local genotypes by a very small number of uniform modern varieties, colonization of new land and desertification are causing rapid erosion of the genetic base of these crops.

FAO's Fourth International Technical Conference on Plant Genetic Resources will discuss the first Report on the State of the World's Plant Genetic Resources and a costed Plan of Action to promote the conservation and use of plant genetic resources and ensure a better sharing of the benefits between rich and poor nations. The Conference will assist countries to determine their gaps and strengthen their national capabilities for the management of plant genetic resources for food and agriculture. (Source: *Development & Cooperation*, May 1995)

1996 ATCC Workshops/Conferences — May to September 1996

1. Cell Culture & Hybridomas: Quality Control & Cryopreservation Techniques
   1-3 May 1996 and
   11-13 September 1996
2. In Vitro Toxicology: Techniques and Applications
   4-7 June 1996
3. Communication Skills and Technical Writing Workshop For Scientists
   19-21 June 1996
4. Polymerase Chain Reaction (PCR) Applications/Cycle DNA Sequencing
   15-18 July 1996 and 19-22 November 1996
5. Theory and Techniques for Archaeal Research
   29 July-1 August 1996
6. Hybridoma Technology & Monoclonal Antibody Product Development
   6-9 August 1996 and 4-7 November 1996
7. 14th Annual Biotech Patent Forum
   16-17 September 1996
8. Downstream Processing, Recovery and Purification of Proteins
   18-20 September 1996
9. Fermentation Microbiology
   24-27 September 1996
10. Microscopy/Photomicrography
    2-4 October 1996
11. Growth of Animal Viruses
    9-11 October 1996
12. Freezing & Freeze-Drying of Microorganisms
    15-18 October 1996
13. Advanced Recombinant DNA: Techniques & Applications
    11-15 November 1996

For information on ATCC workshops please contact:
ATCC, Workshop Coordinator, 12301 Parklawn Drive, Rockville, Maryland, USA 20852
Telephone: (301) 231-5566 or 1-800-359-7370
Fax: (301) 816-4364
ATCC Internet Address:
http://www.atcc.org/workshops/workshop.html
E-mail: workshops@atcc.org

Biosafety

Biosafety protocol update

Last November in Jakarta, Indonesia, the Convention on Biological Diversity (CBD) set in motion a process for giving the world some legally binding, international regulation of biotechnology. At the second Conference of the parties, the CBD officially adopted terms of reference for a working group to develop a protocol on biosafety "in the field of safe transfer, handling and use of living modified organisms", with a specific focus on trans-boundary movement and including procedures for "advanced informed agreement".[1]

Although the Conference of the parties labelled the biosafety protocol a matter of "urgency", the working group mandated to develop the protocol was merely asked

to "try and complete its work in 1998". The first meeting of the working group is scheduled for 22-26 July 1996, in Aarhus, Denmark. NGOs accredited to the Convention on Biological Diversity can attend.

The Conference of the Parties gave guidelines to the working group, asking that it (a) take into account the principles of the Rio Declaration, in particular the precautionary principle, (b) not exceed the scope of the CBD, (c) not override or duplicate other international legal instruments in this area, (d) provide for a review mechanism, (e) be efficient and effective and seek to minimize unnecessary negative impacts on biotechnology research and development, and (f) not hinder access to and transfer of technology.

Although some of the guidelines seemed unclear and mutually contradictory,[2] even this imperfect call for a protocol represented a major victory for those concerned with the ecological, economic and human health impacts of modern biotechnologies.

Although some have claimed that the US and others object to a protocol because they believe that biotechnology should be regulated on the national level or they believe that there is no need to regulate at all, others counter that such objections simply evidence the influence and needs of powerful biotechnology industry interests. The US, though technically not a member of the Convention on Biological Diversity because the Senate has never ratified the treaty, has consistently blocked moves towards international regulation of biotechnology.

Article 19.3 of the Convention on Biological Diversity, signed at the Earth Summit in Rio de Janeiro in 1992 and now ratified by 120 countries, states:

"The parties shall consider the need for and modalities of a protocol setting out appropriate procedures, including, in particular, advanced informed agreement, in the safe transfer, handling and use of any living modified organism resulting from biotechnology that may have adverse effect on the conservation and sustainable use of biological diversity."

While US resistance to binding international regulation persisted, evidence of ineffective US national regulation surfaced. Two months before the meeting in Jakarta, US agencies that regulate genetic engineering were under attack: Professor David Kronfield, of Virginia Polytechnic Institute and State University, joined others in criticizing the quality of the science and analysis behind the Food and Drug Administration's approval process for rBGH (recombinant bovine growth hormone); the Union of Concerned Scientists and the Environmental Defense Fund published an alert criticizing US Department of Agriculture (USDA) moves to virtually eliminate risk assessment of field trials of transgenic crops; and US Environmental Protection Agency (EPA) scientists, in an attempt to prevent a premature and potentially disastrous release of genetically engineered bacteria, issued a report highly critical of EPA risk assessment procedures.[3]

Further, despite minuscule funding for research on ecological impacts of genetic engineering, by the time of the Convention on Biological Diversity in Jakarta, considerable scientific evidence of ecological problems with the products of genetic engineering had been gathered. For example:

- Scientists in Denmark reported rapid transfer of herbicide tolerance to a weedy (cross-pollinated) relative of a genetically engineered oilseed rape plant.[4]
- Oregon State University scientists, using soil assessment methods different than those used by EPA, discovered reduction of myccorhizal fungi (which are necessary for uptake of nutrients by plants) in soils into which a genetically engineered microorganism previously deemed benign had been introduced.[5]
- And a German scientist at the Institute for Applied Ecology listed publication after publication enumerating modified organisms previously thought to be unable to survive outside the laboratory being found in waste water, in soils, and on the clothes and in the stomachs of research scientists, among other locations.

Although its presence was obvious, the role that industry actually played at Jakarta is not certain. Industry opposition to a biosafety protocol was greater at Jakarta than it had been at previous biosafety meetings. Even so, the Convention on Biological Diversity called for and set the terms of a biosafety protocol. The scope of the protocol was broader than many industrialized countries wanted and the final terms of reference included a mandate protocol opponents objected to: the possibility of provisions concerning liability and socio-economic impacts of genetically modified organisms. Some observers fear that those countries who reluctantly agreed to a protocol have simply postponed their obstruction until the negotiation process.

---

[1] UNEP/CBD/COP/2/CWL.22.

[2] The precautionary principle in the preamble to the Convention on Biological Diversity says, "Where there is threat of significant reduction or loss of biological diversity, lack of scientific certainty should not be used as a reason for postponing measures to avoid or minimize such a threat."

[3] For the Kronfield criticism of FDA, see Christiansen, Andrew, Recombinant Bovine Growth Hormone: Alarming Tests, Unfounded Approval (The Story Behind the Rush To Bring rBGH to Market), *Rural Vermont*, July 1995, 4. For the EPA scientists report, see "Genetic Genie, the Premature Commercial Release of Genetically Engineered Bacteria", September 21, 1995, a *PEER* White Paper prepared by Public Employees for Environmental Responsibility, Washington, DC: The Union of Concerned Scientists action alert, "USDA to Virtually Abandon Oversight of Genetically Engineered Organisms," 29 September 1995 referring to a 22 August 1995 (USDA proposal (*Federal Register* 60:43567-73).

[4] Jorgensen, R.B. and Andersen, B. Spontaneous hybridization between oilseed rape (*Brassica Napus*) and weedy *B. Campestris (Brassicaceae)*: A risk of growing genetically modified oilseed rape. *American Journal of Botany* (1994).

[5] Holmes, Michael T. and Ingham, Elaine R., Department of Botany and Plant Pathology, Oregon State University. Abstract of presentation on *Klebsiella planticola* at the 79th Annual Ecological Society of America meeting, Science and Public Policy, Knoxville, Tennessee, August 1994. Published in *Bulletin of the Ecological Society of America, Volume 75, No. 2.*

(Extracted from *Global Pesticide Campaigner, Vol. 6, No. 1*, March 1996)

Why a biosafety protocol?

"Biosafety" is a phrase that recognizes both the potential for undesirable consequences stemming from new technologies and the need for enforceable measures to prevent (or minimize) those consequences. In the case of genetic engineering of crops, for example, proponents frequently claim that the technology holds the answers to many of the world's problems, particularly hunger. In reality, however, much of the agricultural research carried out is focused on developing herbicide-resistant crops. Further, much of the testing is done by Northern experimenters working in developing countries where oversight and environmental regulations are less stringent than in the North. This "test dumping" leads to the suspicion that those who will receive the benefits of the new technology are not the same as those forced to assume the risks. To ensure that such imbalances do not occur and to ensure that no country ends up with a catastrophe it cannot remediate, activists and scientists from around the world have repeatedly called for an internationally-binding biosafety protocol that encompasses the ecological risks and socio-economic impacts of genetically engineered organisms, as well as risks to human health.

A few of the reasons cited why genetically modified organisms should be regulated under a biosafety protocol are:

- The potential for transgenic crops to become weeds and unwanted plants, to become conduits through which new genes move to wild plants, and to facilitate the creation of new viruses that cause new plant diseases.
- The potential of genetic engineering to contribute to the erosion of agricultural biodiversity by (1) the creation of crops that compete with wild plants and traditional varieties, and (2) the transfer of new crop genes into the more primitive varieties.
- The potential of genetic engineering to upset ecosystems in ways that may not be understood or remediated.
- The potential for negative social and economic impacts in developing countries from the products of genetic engineering. For example, production of substitutes for export crops already has led to loss of livelihoods and export earnings in some countries.
- The lack of capacity in some countries to ensure the safety of genetically modified organisms, to monitor their entry at the border, and to take remedial measures in the event of mishap.
- The existence of a transboundary ecological dimension to genetically engineered organisms. Even where there is no human intent to export, living organisms tend to mutate, multiply and migrate.
- The historical inadequacy of self-regulation and voluntary codes of conduct.
- The lack of predictive ecology where genetic engineering is concerned. Genetic engineering is based on the idea that characteristics of organisms are determined uniquely by stable genes, such that the transfer of genes automatically results in the transfer of the desired characteristics. This genetic determinism fails to take into account the complex interactions among genes that are involved in the development of all characteristics of an organism, and therefore masks our inability to predict the consequences of transferring a gene from one type of organism to another.

(Source: *Global Pesticide Campaigner, Vol. 6, No. 1*, March 1996)

Designing biosafe laboratories

Over 10 per cent of the biotechnology products currently in the pipeline target high-risk infectious agents such as HIV and TB. As this type of drug research ramps up, biopharmaceutical companies are becoming increasingly sensitive to the dangers that accompany handling these agents. Rather than attempt to cobble together a safe environment in an existing laboratory space, architects are called upon to plan new laboratories that integrate basic biosafety principles into their design. More complex than simply adding a few walls to an existing laboratory space, implementing a successful facility requires a well-thought-out team approach: The architect not only works with an engineer, but also the laboratory's director, the researchers involved, and the management staff that will fund the project to assure the laboratory's safety in its actual use and operation. (Source: *Bio/Technology, Vol. 13*, October 1995)

Biosafety aspects of agricultural biotechnology: an international internship programme

In countries where new transgenic crops are ready to be tested in the environment, national and institutional biosafety committees must first conduct a biosafety review of the planned release. It is imperative that scientists and government officials have the information, skills and resources required to appropriately evaluate the biosafety issues inherent in the release of a particular genetically modified organism to the environment. To address these needs, Michigan State University will host a two-week internship programme in the *Biosafety Aspects of Agricultural Biotechnology* from 11 to 24 August 1996.

The internship is designed to give participants a thorough grounding in all aspects of biosafety for environmental release of genetically engineered organisms. It will cover the theory and practice of risk assessment and management in agricultural biotechnology applications. A major component of the programme will provide practical experience in biosafety evaluation through case studies presented to the workshop participants.

Risk assessment case studies will give participants experience in evaluating field release proposals. Example proposals will be presented to the group by a resource person acting as the principal investigator. Workshop members, acting as a biosafety committee, will review each proposal, prepare questions for the principal investigator, analyse the information, and make recommendations on the proposed release. Instructors and participants will then discuss and critique the review process.

Site visits and tours will include locations where field tests are in progress and greenhouse facilities where transgenic crop research is being conducted.

A review session at the end of the programme will provide an opportunity to integrate information from the entire course. Follow-up support will be offered, so participants can serve as effective resource persons in their home countries. (Source: *Bio Link, Vol. 2, No. 2 and 3*, 1995)

Regional biosafety focal point for Southern and Eastern Africa

An African Regional Conference for International Cooperation on Safety in Biotechnology was held in October 1993, to discuss approaches for ensuring safe practices in the conduct of biotechnology. The meeting was organized by the Research Council of Zimbabwe (RCZ) and the Netherlands Ministries for Foreign Affairs and for Housing, Physical Planning and the Environment.

Participants in the meeting were from Botswana, Kenya, Malawi, Mozambique, Namibia, Swaziland, South Africa, Tanzania, Uganda, Zambia and Zimbabwe. It is hoped that Lesotho will become the twelfth member of the network.

At the concluding session of the Conference, participants recommended the establishment of a regional coordinating committee composed of one delegate from each country in the Southern Eastern African (SEA) region, to meet on a regular basis. To facilitate the coordination of network activities, it was suggested that a focal point mechanism be put in place. The participants highlighted the desirability of a regional approach to provide for safety in biotechnology.

Significant progress has been made in implementing the conference recommendations. A Regional Focal Point on Safety in Biotechnology has been established at the Scientific and Industrial Research and Development Centre (SIRDC) in Harare. The office will serve as the secretariat for coordinating network activities.

The network will promote the establishment of coordinated regional cooperation in sharing information on the criteria, procedures and management of issues on safety in biotechnology. It is considered essential that each country in the network establishes a node for biosafety issues. It is recognized that countries of this region are interested in developing a capacity in biotechnology and in exploiting the opportunities that biotechnology offers in agriculture, health and industry. The technology also has aspects of potential harm to health and the environment. As the harmful effects would not recognize national boundaries, it is prudent that the SEA region countries coordinate their safety provisions.

There is now an accumulated global knowledge base on some ways of ensuring safety in biotechnology. By working together, the SEA network countries can harmonize their approaches to the safe conduct of biotechnology and share their experiences to mutual benefit. This cooperation could provide a platform for sharing ideas on the formulation of safety guidelines.

For more information, contact:
Biosafety Network Newsletter
Regional Biosafety Focal Point
Project Officer: Joy Chigogora
P.O. Box 6640
Harare, Zimbabwe
Tel./Fax: 263-4-733796
(Source: *Bio Link, Vol. 2, No. 2 & 3*, 1995)

Development of non-disruptive biomarkers for GMOs

Deliberate release of genetically modified microorganisms (GMOs) for environmental purposes is frequently hampered by public concern over their ecological impact on native systems. The possibility of uncontrolled genetic exchange between the introduced GMOs and the native bacterial population, which could generate undesirable genetic combinations, is the major cause of potential hazards. However, the integrated work of five European laboratories have brought into reality the possibility of monitoring GMO performance *in situ* by the development of genetic and biochemical biomarkers.

The development of at least three surface reporters was established in the first year of the project. These are proteins that become exposed on the surface of the GMO and can be tracked immunologically after introduction into the environment. Various biomarkers have been integrated into regulatory circuits of *Pseudomonas sp.* and employed to monitor non-disruptively the degradation of polychlorobiphenyls (PCBs), halo/alkyl benzoates in soil and rhizosphere microcosms. These markers have either enzymatic, antigenic, or physical properties which permit qualitative measurement of GMO activity in terms of lateral transfer, stability and growth phase.

There is considerable scope for the use of GMOs in both agricultural and environmental research. Further developments within this EU funded project will allow for the effective monitoring of GMOs, while enhancing our understanding of their performance in nature.

For details contact: Phil O'Leary, BioResearch Ireland, Forbairt, Glasnevin, Dublin 9, Ireland (Fax: +353 1 8370176). (Source: *Australasian Biotechnology, Vol. 5, No. 6*, December 1995)

Biosafety protocol on the cards

There is an urgent need to consider an international agreement to regulate the transfer of genetically modified organisms (GMOs) between nations, according to signatories to the United Nations Convention on Biological Diversity. In November 1995 they agreed to start drafting a biosafety protocol which would address trade and accidental releases of GMOs.

The meeting agreed to set up a working group to develop the protocol which would be part of the Biodiversity Convention. It hopes to report in 1998. None of the existing regulations on biotechnology and biodiversity specifically address the transboundary movements of GMOs.

The meeting recognized that significant gaps in knowledge existed about the interaction of GMOs with the environment. It noted that there was a need for further analysis of national and international regulations governing the impact of GMOs on biodiversity.

In 1994, Greenpeace intercepted a Swiss sample of genetically modified rice on route to the Philippines to demonstrate the dangers of unregulated exports and transport. Swiss researchers have now agreed to voluntary safety guidelines on GMO exports.

The International BioIndustry Forum says the outcome is sensible and welcome. Most environmental groups are also satisfied with the result, although Friends of the Earth is calling for legislation on the domestic handling of GMOs as well.

The signatories did not decide on guidelines allowing companies access to other countries' genetic resources or the patenting of traditional knowledge of indigenous peoples, but they agreed to create a new post in the Convention's secretariat to work on issues concerning indigenous peoples, such as land rights and access to genetic resources.

The Biodiversity Convention was signed at the 1992 Rio Earth Summit and has 134 signatories. The secretariat is based in Montreal. (Source: *Chemistry & Industry*, 4 December 1995)

MAFF to investigate bio-crop safety

Japan's Ministry of Agriculture, Forestry and Fisheries (MAFF) has plans to start research aimed at establishing methods of assessing the safety of recombinant plants for food use, including rice and rapeseed. MAFF has already worked out guidelines for the use of bioengineered products belonging to the agriculture, forestry and fishery fields. The Ministry of Health and Welfare is also trying to set up guidelines for genetically engineered foods. These

guidelines are necessary because field tests on recombinant plants are already being conducted.

MAFF also plans to establish technology to ensure the safety of gene-altered plants and look into the possibility that new viruses may develop therein. It will take three years to complete the project and a budget of $700,000 has been earmarked for the initial year. (Source: *McGraw Hill's Biotechnology Newswatch*, 19 February 1996)

Regulatory issues

FDA guidance on human drugs derived from transgenic animals

In late August 1995, the Food and Drug Administration (FDA) issued its first official guidance to biotechnology and pharmaceutical companies planning to manufacture human drugs in genetically engineered animals. The "Points to Consider" document, neither a rule nor a guideline, represents FDA's current thoughts about the issues companies should consider as they produce human drugs in milk and blood of transgenic cows, goats, sheep and other animals. The FDA will regulate most such drugs from transgenic animals as biological products under the Federal Food, Drug and Cosmetic Act and the Public Health Service Act. The guidance also applies to tissues or cells obtained from transgenic animals and used for therapeutic purposes in humans.

According to an Associated Press report (31 August 1995), this action by FDA is likely to accelerate pharmaceutical companies' investment in transgenic animal drug R&D.

Under the FDA guidance, companies are encouraged to voluntarily describe the genetic engineering process, assure consistent production of the drug through several generations of animals, and develop procedures that ensure the safety and purity of the final product. (Extracted from: *The Gene Exchange*, December 1995)

Bioethics Convention runs into more delays

Specialists framing the Bioethics Convention made some progress during three days of debate in Strasbourg (20-22 November 1995), but failed to present a final text. They agreed to meet again in early 1996.

In addition to general guidelines on research, the draft European Bioethics Convention will cover genetic screening and testing.

Council of Europe officials said that if the spring meeting of the steering committee settles outstanding issues, the text will still have to be scrutinized by the Council's Parliamentary Assembly.

Parliamentarians voiced particular concern about provisions on embryo research and "interventions on the incapacitated" in an earlier draft.

Officials foresaw that a final version might be cleared by the Assembly at sittings in either April or June 1996, clearing the way for final approval in September at the latest by the Committee of Ministers, on behalf of the Council's 38 member States.

A further area of controversy, relating to research on human embryos, has already been taken out of the body of the Convention, following an agreement that this should be tackled in a separate protocol. That procedure might allow States opposed to these procedures to ratify the main Convention, while opting out of signing the protocol. (Extracted from *Biotechnology Business News*, 6 December 1995)

General

Drug majors sign biotech firms

The trend for large pharmaceutical companies to link up with specialist biotechnology outfits continues.

Hoechst has announced that its US company, Hoechst Marion Roussel, has acquired two California biotechnology deals in short succession. A gene therapy collaboration deal into AIDS research was agreed with Cell Genesys and one in genomics—the study of the chromosomal order, structure and function of genes—was agreed with two other California companies, Incyte Pharmaceuticals and Lynx Therapeutics.

British Biotech pleased City analysts with its tie-up with drug giant Glaxo Wellcome in a licensing deal for the oral treatment of arthritis BB-2983. Glaxo will fund all development costs and have worldwide exclusive marketing rights. British Biotech will be paid royalties on sales.

Celltech also signed a collaboration deal, this time with Zeneca, in a research deal to develop gelatinase inhibitors to combat cancer.

The terms of the deal mean that Celltech will receive payments depending on the success of the research and royalties on any product developed. Celltech will do the early work and Zeneca will be responsible for clinical development. (Extracted from *Manufacturing Chemist*, November 1995)

Importance of non-medical biotechnology to increase

Although the ratio of non-medical to medical products of biotechnology in the market place is about ten to one, biotechnology is still thought of primarily in a pharmaceutical context, according to a report in the *Washington Post*.

There are more than 300 commercialized agricultural and environmental biotechnology products currently available compared to just 32 biotechnology drugs. Yet non-drug biotechnology products account for less than $1 billion of the $7.7 billion in annual overall biotechnology sales in the United States, reflecting the higher profitability of pharmaceuticals.

However, investment firms are predicting that the non-drug biotechnology will gain in momentum in the next five to ten years, with potential sales estimates ranging from $50 billion to hundreds of billions annually.

Analysts say that biotechnology will allow the food industry to continue the century-old trend of low food prices, increasing productivity and less labour.

Meanwhile, an OECD study predicts that bioremediation could become the largest domain of biotechnology. Bioremediation, the use of biological clean-up and recycling methods to combat pollution, is already the third largest area of biotechnology after health care and agriculture.

Environmental biotechnology is becoming more popular because bioremediation is usually cheaper than traditional physical and chemical remediation methods. OECD anticipates that the market for environmental biotechnologies will grow from current levels of $40 billion to some $75 billion by the end of the decade. (Source: *The AgBiotech Bulletin*, November 1995)

Technology transfer — commercializing genome resources

When the genome project formally began in late 1990, available technologies were not nearly efficient or cheap

enough to accomplish the goals for mapping, sequencing, and managing and analysing data. Now, five years later, a burgeoning body of resources is providing a new base for a wide range of technology industries involving instrumentation, diagnostics, therapeutics, software and DNA chip development, bioengineering and agriculture.

The necessity for large-scale approaches to genome research has pushed technology development towards increasing capacity and decreasing size. Demand for high-throughput DNA sequencing methods, for example, has given rise to gel multiplexing and automated sequence-detection machines and gel readers. A new, multiplexed fluorescence detector for capillary electrophoresis, developed by genome project researchers and licensed in 1995 to the private sector, will form the basis for a new sequencing instrument projected to increase significantly the DNA sequencing rate. Another resource transferred to the private sector in 1995 is a new heat-stable enzyme for replicating DNA that promises to make sequencing faster and more accurate. In September 1995, the "chromosome painting" technology developed by genome project researchers was licensed to a private company that will offer it for disease detection to both the research and clinical communities. The technology is used to detect many chromosomal abnormalities, including Down's syndrome and cancers. Other technology transfer is carried out through software licensing and library distribution.

A US Government-sponsored plan to accelerate pay-offs from genome research is the Tools for DNA Diagnostics component of the Advanced Technology Program, National Institute of Standards and Technology. Funded companies are engaged in such activities as developing diagnostic DNA arrays and adapting fluorescent mapping techniques for analysing human tissues. Other projects focus on applications of DNA "superchip" technology that have high potential for disease diagnosis and treatment, extremely rapid sequencing, and industrial and environmental monitoring.

Cheap, rapid and relatively easy-to-use tools for DNA analysis have increased dramatically the number of disease genes isolated during the past few years, providing the raw material for new strategies to diagnose, prevent and treat disease. Almost 250 gene-derived products are in clinical development, and over 100 companies currently have DNA-based therapies in human clinical trials. Additionally, the top US public biotechnology companies have an estimated 2,000 therapeutics in early developmental stages, including monoclonal antibodies, clotting factors, growth factors and hormones, interleukins and interferons, and a variety of other protein or peptide molecules. Since 1988, more than 100 human gene-therapy or gene-transfer protocols have been approved by the NIH Recombinant DNA Advisory Committee.

Clinical tests to detect disease-associated mutations offer powerful new tools for disease identification and management and are proving to be the most immediate commercial applications of gene discovery. These tests, however, also pose several medical and technical challenges. Key questions in determining whether a gene discovery will translate into a clinically useful diagnostic test include the following: How often does the test pick up disease-linked mutations? Are these mutations associated with disease development? Is the disease treatable or preventable? Does testing reduce medical cost or improve quality of life?

The NIH-DOE Joint ELSI Working Group is addressing some of these issues and has recently launched the Task Force on Genetic Testing to perform a comprehensive, two-year evaluation of the current state of US genetic-testing technologies. The task force will examine safety, accuracy, predictability, quality assurance and counselling strategies for the responsible delivery of genetic tests. (Source: *Human Genome News*, September/December 1995)

European food rules creep forward

After more than 12 months of wrangling, ministers from European Union (EU, Brussels, Belgium) member States have agreed to a form of wording for the European "novel foods" regulation that introduces a requirement to label some—but not all—genetically modified foods. Industry will accept the requirements, albeit reluctantly, on the basis that it can work with one somewhat unsatisfactory set of Europe-wide rules more easily than it can work with 15 sets of national rules. It would, undoubtedly, have preferred a less prescriptive approach.

Environmental groups and some parts of the European Parliament (EP) are expected to continue to push for stricter controls. Food labelling has been a rallying cry for a "rainbow coalition" of political allegiances that includes Greens, liberals and the religious right. The signs are that many of these groups are not happy with the Council's proposed text.

There is also a long-standing division among the Governments of EU member States as to the best way of coping with food labelling. Austria, Denmark, Germany and Sweden have pressed for strict labelling rules, believing consumers should always be informed that a foodstuff has been genetically modified. Other countries argue that it is unfair to stigmatize new foods through systematic labelling. The proposed rules are a compromise, requiring foods to carry labels saying they are genetically engineered only if they differ in a "significant" way from an existing food.

The agreed text has next to go before the EP for a second reading. Since the legislation is being adopted under co-decision-making procedures, members of the EP can veto the directive if a real majority—a majority of all members and not just of those attending a debate—opposes it.

Biotechnology was a victim of one of the most recent occasions on which that happened. The "biotechnology patents" directive failed in the EP in March 1995 largely because it was to be voted on a day when an unusually large number of members were in Strasbourg to vote on enlargement of the EU. European parliamentarians seem particularly keen to introduce labelling requirements for recombinant products by any credible means. (Extracted from *Bio/Technology, Vol. 13*, December 1995)

AIDS prognosis for Asia

Thailand has lessons to offer on the spread of AIDS that are pertinent to the rest of Asia. For the moment, Asia's share of the world's HIV and AIDS infections is small relative to the size of its population. But the number of Asians known to carry HIV has doubled in the past two years. By the end of the decade, it is estimated, Asia will have more new cases than any other region, including Africa.

Thailand has some 800,000 of Asia's 3 million reported HIV cases. According to the United Nations Development Programme (UNDP), India will soon take the lead with an estimated 4 million people infected with the virus by the end of the decade. Myanmar has one of Asia's highest rates of infection and receives tiny amounts of

foreign assistance to attack the problem. A UNDP study of eight Asian countries, among them China, India, Indonesia and Thailand, suggests that rates of GDP have not so far been affected and are unlikely to be in the future. But, alarmed that this view will make politicians complacent, it gives warning of social problems caused by the spread of the disease. In Thailand, which is more advanced in the cycle of AIDS infection than most other Asian countries, economists believe that dealing with these social problems will cost the country $9 billion by the end of the decade.

Thailand's programme for combating AIDS is among the most comprehensive in the developing world, but political leaders appear to be losing interest. The situation in other countries is not encouraging. India's federal programmes for fighting the disease show little result, despite a World Bank loan of $100 million nearly three years ago to promote them. Religious groups are also regarded as obstacles to promoting AIDS education.

New figures from the global AIDS Policy Coalition, a body based at Harvard University, that brings together specialists on AIDS from all parts of the world, are higher and its prognosis grimmer than those of the UN World Health Organisation.

The number of adults becoming infected each year seems to have decreased, at least temporarily, in North America, Oceania and the south-east Mediterranean, says the report. It has reached a plateau in Western Europe, the Caribbean and sub-Saharan Africa. But in recently affected areas, such as South-East and North-East Asia, the number of new infections is rising steeply.

The main news and figures—inevitably, estimates—emerging from the study are that:

- 30.6 million people are now infected with HIV.
- This figure may more than double by the end of the 1990s.
- 4.7 million people became infected with HIV in 1995—13,000 a day. Of these, more than half, 2.5 million, were in South-East Asia, but fewer than 4 per cent in industrialized countries.
- The worst-hit region is Africa, with 19.2 million people now infected, 63 per cent of the world-wide total.
- 9.2 million people have died of AIDS, 7.6 million of them in Africa.
- 1.7 million died of AIDS in 1995.
- And worst of all: 516,000 children were born already HIV-infected in 1995, and 400,000 below the age of 15 developed AIDS.

(Extracted from: *The Economist*, 23 September 1995 and 10 February 1996)

Biodegradable plastics players form trade body

Manufacturers of biodegradable plastics are hoping to increase their influence on planned standards for their products with the foundation of the first international trade body for the sector.

Some 40 firms have expressed interest in joining the International Biodegradable Product Manufacturers Association (IBPMA). A major aim of the new organization is to represent members' views to the international standards organizations, including CEN, which are developing standards for biodegradables.

IBPMA will also play a role in promoting biodegradable products, and representing the industry to government and other bodies. It will work in cooperation with existing national trade bodies for the sector in the US and Japan, but will effectively be the first such organization for European suppliers. (Source: *European Chemical News*, 22-28 January 1996)

Survival picture dims for biotechnology firms, says Ernst & Young study

The survival picture for young US biotechnology firms grew dimmer over the last year, according to Ernst & Young's annual report card.

Nevertheless, according to the authors, certain benchmarks—such as product revenues—are clearly improving, despite the overall gloom in the media and on Wall Street about the future of the industry.

About 36 per cent of public biotechnology companies have enough cash to survive for less than one year, according to the review. Another 25 per cent have only enough to last for about two years, said the report. Overall the survival index for the industry has "declined dramatically" from 25 to 16 months, with the monthly burn rate for the median public company increasing from $665,000 in 1994 to $726,000 in 1995.

And for the first time, the number of biotechnology companies has declined, with public companies dropping from 265 to 260 and all companies dropping from 1,311 to 1,308. The report also said that 19 companies merged or delisted, while 14 went public.

There were only nine new companies started in 1995, down from 42 in 1994 and down from a high of 112 in 1987.

Venture capitalists are looking at later-stage firms, with some compounds in clinical trials, and are also leaning towards firms that have broad-platform or enabling technologies. Seed-stage companies raised $240 million in 1993 and $119 million in 1994, but only $34 million between January and June 1995.

Revenues from products sold by public companies rose by 21 per cent, to $6.8 billion, and revenues for the total industry jumped 18 per cent to $9.3 billion.

The industry raised less capital in 1995, with significantly fewer initial public offerings (from 36 offerings that raised $935 million to 14 offerings that raised a total of $274 million). Private placements dropped by about a third. But capital raised through strategic alliances rose from $1.3 billion to $1.4 billion.

About 494 drugs are in human clinical trials by 158 companies, according to the report, as well as several promising pre-clinical candidates. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 2 October 95)

What's Coming to Market?

An update on commercialization

The following chart summarizes US Federal Department of Agriculture actions on commercialization of genetically engineered agricultural products as of December 1995.

Product	Company	Altered Trait	Purpose	Sources of New Genes	Agency Action[1]	Approved for Sale/Name
Canola (Oilseed rape)	Calgene	Altered oil composition - high lauric acid	Expand use in soap and food products	California bay, turnip rape, bacteria, virus	USDA/Approved FDA/Approved[2] EPA/Not required	1995 Laurical
Corn	Ciba-Geigy	Resistance to corn borer (Bt toxin)	Control insect pests	Corn, bacteria, virus	USDA/Approved FDA/Approved EPA/Approved	1995 Maximizer
Corn	Mycogen	Resistance to corn borer (Bt toxin)	Control insect pests	Corn, bacteria, virus	USDA/Approved FDA/Approved EPA/Approved	1995 NaturGard
Cotton	Calgene/ Rhone Poulenc	Resistance to herbicide bromoxynil	Control weeds	Bacteria, virus	USDA/Approved FDA/Approved EPA/Approved	1995 BXN Cotton
Cotton	Monsanto	Resistance to bollworms and budworm (Bt toxin)	Control insect pests	Bacteria	USDA/Approved FDA/Approved EPA/Approved	1995 Bollgard
Potato	Monsanto	Resistance to Colorado potato beetle (Bt toxin)	Control insect pests	Bacteria	USDA/Approved FDA/Approved EPA/Approved	1995 NewLeaf
Soybean	Monsanto	Resistance to herbicide glyphosate	Control weeds	Petunia, soybean, bacteria, viruses	USDA/Approved FDA/Approved EPA/Approved	1995 Roundup Ready
Squash	Asgrow	Resistance to viruses	Control virus diseases	Viruses	USDA/Approved FDA/Approved EPA/Not required	1995 Freedom II
Tomato	Calgene	Delayed ripening	Enhance fresh market value	Tomato, bacteria, virus	USDA/Approved FDA/Approved EPA/Not required	1994 Flavr-Savr
Tomato	DNA Plant Technology	Delayed ripening	Enhance fresh market value	Tomato, bacteria, virus	USDA/Approved FDA/Approved EPA/Not required	1995 Endless Summer
Tomato	Monsanto	Delayed ripening	Enhance fresh market value	Bacteria	USDA/Approved FDA/Approved EPA/Not required	1995
Tomato	Zeneca/Peto Seed	Thicker skin, altered pectin	Enhance processing value	Tomato, bacteria, virus	USDA/Approved FDA/Approved EPA/Not required	1995
Pseudomonas fluorescens[3]	Mycogen	Toxicity to insects (Bt toxin)	Control insect pests	Bacteria	USDA/Not required FDA/Not required EPA/Approved	Yes M-Peril M-Trak MVP
Vaccinia virus vaccine	Rhone Merieux	Immunity to rabies	Control raccoon rabies epidemics	Rabies virus	USDA/Approved FDA/Not required EPA/Not required	1995 Raboral

Product	Company	Altered Trait	Purpose	Sources of New Genes	Agency Action[1]	Approved for Sale/Name
Canola	Monsanto	Resistance to herbicide glyphosate	Control weeds	NA[4]	USDA[5] FDA/Approved EPA[5]	No
Corn	DeKalb	Resistance to herbicide glufosinate	Control weeds	Bacteria, virus	USDA/Pending FDA[5] EPA[5]	No
Corn	Hoechst/ AgrEvo	Resistance to herbicide glufosinate	Control weeds	Bacteria, virus	USDA/Approved FDA/Approved EPA/Pending	No Liberty Link
Corn	Plant Genetic Systems	Male sterility	Facilitate plant breeding	Bacteria, virus	USDA/Pending FDA[5] EPA[5]	No
Corn	Monsanto	Resistance to corn borer (Bt toxin)	Control insect pests	Bacteria	USDA/Approved FDA[5] EPA/Pending	No
Corn	Sandoz/ Northrup King	Resistance to corn borer (Bt toxin)	Control insect pests	Bacteria	USDA/Pending FDA[5] EPA/Pending	No
Cotton	DuPont	Resistance to herbicide sulfonylurea	Control weeds	Tobacco, bacteria	USDA/Pending FDA[5] EPA[5]	No
Cotton	Monsanto	Resistance to herbicide glyphosate	Control weeds	Arabidopsis, bacteria, virus	USDA/Approved FDA/Approved EPA/Pending	No Roundup Ready
Tomato	Agritope	Altered ripening	NA[4]	NA[4]	USDA/Pending FDA[5] EPA/Not required	No
Rhizobium meliloti	Research Seeds	Enhance nitrogen fixation	Increase yield in alfalfa	Bacteria	USDA/Not required FDA/Not required EPA/Pending	No

Approved for Sale	**Awaiting Approval**

Notes:

[1] Action may respond to either voluntary or required submissions from companies.

[2] FDA approval means that FDA has completed consultations with the company and will allow the product to enter the market once regulatory requirements are met at other agencies. Except for the Calgene tomato approved in 1994, FDA consultations are abbreviated reviews of company safety assessments.

[3] The organism is killed before it is applied in the environment.

[4] Information not available.

[5] Status of consultations, if any, is unknown.

(Source: *The Gene Exchange*, December 1995)

Biodiesel

The Second European Liquid Biofuels Forum will be held in Graz, Austria, on 22-25 September 1996.

Two years after the First European Biofuels Forum, which took place in Tours, France, this year's event will cover feedstocks, conversion technologies, environmental issues and the need for joint industry-government collaboration for greater biofuels use. (Source: *Chemical Marketing Reporter*, 4 March 1996)

C. COUNTRY NEWS

Australia

Gene technology survey

An International Social Science Survey on public perceptions of gene technology has revealed that Australians believe the long-term benefits of genetic engineering were likely to outweigh the risks. The findings complement those released in February 1995 which showed community support for the use of genetic engineering to help achieve desired goals, such as improved health, better foods and developing pest-resistant crops.

The survey found those knowledgeable about the technology were a little more optimistic about its long-term benefits. To gain a broad picture of community feeling, the survey inquired about community concerns about the technology. Results were expressed in the form of a worry scale, from zero (no worry) to 100 (huge worry, terrible and very likely to happen).

The survey also showed that Australians were a worrying lot even when observed risks were quite low.

The survey was undertaken on behalf of the Department of Industry, Science and Technology by the International Social Science Survey (ISSS), Australia, at the Australian National University.

Results are based on more than 1,300 responses from people randomly selected from the electoral roll. This number of responses is more than sufficient to provide a high level of confidence in extrapolating findings to the whole population. (Extracted from *Australasian Biotechnology*, Vol. 5, No. 4, 1995)

Leukaemia inhibitory factor

AMRAD recently announced that the US Patent and Trademark Office has granted AMRAD a further two US patents covering methods for recombinantly producing leukaemia inhibitory factor (LIF) as well as covering the human LIF molecule *per se*.

The molecule LIF was identified, isolated and cloned by researchers at The Walter and Eliza Hall Institute of Medical Research in 1987. LIF is a critical agent in embryology research and in the production of transgenic animals from embryonic stem cells. AMRAD markets LIF either in its pure form or under the name ESGRO™ through its authorized distributors world-wide for these research uses.

AMRAD is currently also undertaking pre-clinical development and testing of LIF as an agent for the treatment of particular tumours in humans, as an agent for treating thrombocytopenia (low platelet counts) as well as a possible agent to treat various neurological diseases. (Extracted from *Australasian Biotechnology*, Vol. 5 No. 6, December 1995)

CSIRO enhances ethanol production

Australia's Commonwealth Scientific and Industrial Research Organization (CSIRO) has developed a process that could mean substantial savings in the production of ethanol.

CSIRO researchers have cloned genes from a livestock fungus, which produces cellulases, which in turn break down fibre.

According to CSIRO, one of the most exciting applications of the technology could be cost-effective ethanol production. If the genes can be inserted into the yeast which produces ethanol, the cost of ethanol production could be significantly lowered. This means that renewable resources, such as wood, could be used to produce the fuel, rather than coal and oil.

The researchers have developed and patented the two new genes from the fungus, *neocallimastix patriciarium*, which is normally found in the front stomach of livestock. (Source: *Biotechnology Business News*, 1 September 1995)

Canada

Asia Pacific Research Network

The Asia Pacific Foundation (APF) of Canada has established a research network to promote collaborative research and enhance links among policy, business and research communities. The network will focus on current issues related to Canada's involvement in APEC and the Asia-Pacific region in general. It seeks participation from all organizations and individuals in Canada involved in strategic and policy research and analysis related to the Asia-Pacific region. There are no registration or other fees associated with the network.

Contact: Mary Chan, Programme Director, Saskatchewan, Asia Pacific Foundation of Canada, Hong Kong Bank Building, 1874 Scarth Street, Regina, SK. S4P 4B3; Tel.: (306) 791-8778, Fax: (306) 359-3778. (Source: *AgBiotech Bulletin*, October 1995)

Technology transfer opportunities at UTI

University Technologies International, Inc. (UTI) of Calgary has the following technology transfer opportunities available:

- A new method for the recombinant expression of protein based on transgenic plants. The system, which developers expect to be cost-effective, is currently being tested with a variety of proteins and peptides.
- A novel oilseed gene promoter that is seed tissue specific and expresses at high levels in developing embryos. This class of promoter is expected to be useful in developing new seed varieties.
- A bio-electric effect anti-biofilm technology based on the discovery that a biofilm's inherent resistance to antimicrobial agents can be completely removed if antibacterial agents are applied to these slime-protected microbial populations within an electric field.
- A technique for assaying microbial populations termed "reverse sample genome probing".
- A new approach to automating assays will allow the evaluation of antibiotic sensitivity of biofilm grown bacteria using simple robotics.
- A new treatment able to significantly reduce intestinal concentrations of pathogens and eliminate clinical signs of infection, allowing significant weight gain in comparison to control animals.

Contact: UTI, HM 382, 3330 Hospital Drive NW, Calgary, AB T2N 4N1; Tel.: (403) 220-3790, Fax: (403) 270-3236. (Source: *AgBiotech Bulletin*, October 1995)

China

Plant biotechnology in China

Zhi-hong Xu, Chinese Academy of Science, Beijing 100864, China

The paper was the author's talk at the 4th Pacific Rim Biotechnology Conference (Melbourne, 6-9 February 1995). Prof. Z.H. Xu is Vice President of the Chinese Academy of Sciences, and as a plant biologist, also is Director of the National Laboratory of Plant Molecular Genetics, Shanghai Institute of Plant Physiology, CAS.

In the face of over 1.2 billion and a net increase of 14-15 million babies per year, how to stably increase agricultural production has been a big challenge for China. Since the 1980s, China has been working out active national programmes for biotechnology development in which agro-biotechnology is one of the priorities. Rapid progress has been made in certain areas of agro-biotechnology. Plant tissue and cell culture have been a traditional dominant field in China. In recent years, some valuable achievements have also been made in plant molecular biology and genetic engineering, especially in plant transformation, virus- and insect-resistance, and quality improvement researches, and their application in agriculture. I hope that this paper can provide the readers with the present general status of plant biotechnology in China, and also show some results, mainly coming from my colleagues working in different institutions under the Chinese Academy of Sciences (CAS).

Micropropagation

Plant regeneration has been achieved in meristem and callus culture of over 700 plant species in China. Such techniques have been extensively used for production of virus-free plants and clonal propagation. Virus-free potatoes are at present cultivated in 25 provinces of China, with the total cultivation area of 670 thousand ha and the yield increased by 3,750 kg/ha. The estimated economic benefit reaches to a hundred million Yuan (RMB) a year (Meng and Yuan, 1993). *Cassava* is an important staple food crop in mountain and poor areas in South China (total cultivation average: 230 thousand ha). Local cultivators have very low yield. Since 1981, scientists in the South China Institute of Botany, CAS, introduced over 80 cassava cultivars by using the *in vitro* culture system, from CIAT, Colombia. After years of regional adaptation trials for screening the best cultivars for local farmers' plantations, a promising high yielding cassava cultivar "Nan Zhi 188" has been released. An improved micropropagation system with reduced cost was established for rural areas. It had an average yield of about 20 t/ha, 30-70 per cent higher than the local ones in the different regions tested (Guo and Liu, 1994; and J.Y. Huo, personal communication). In banana production, test tube plants increased 30-50 per cent more yield than the traditional cultivation method had. The area for growing test tube bananas in several southern provinces already reached 150-200 thousand ha. Many small workshops or companies had already started their business for banana test tube plant production, some of which are joint ventures with companies in Taiwan and other countries or regions. Similar facilities have been set up for clonal propagation of some élite tree or hybrid *Eucalyptus* and *Populus tomentosa*, with a production capacity of about one million each in Guangxi and Hebei respectively. In Guangxi Autonomous Region, the micropropagation technique has been used for accelerating the propagation of new strains or cultivars of sugar-cane selected for breeding research. With the improved procedure for plantlet regeneration, the propagation rate is as high as 3×10^4 times per year, compared to 40 times in conventional vegetative propagation (J.Z. Zeng, 1988; and personal communication).

Meristem culture has also been used to eradicate viruses and other pathogens and for clonal propagation in apple, grape, *Citrus* spp., *Paulownia*, medicinal herbs (e.g. *Rehmannia glutinosa*, etc.) and ornamental plants (e.g. *Gladiolus*, carnation, etc.). It is estimated that the total output of plantlets produced from tissue culture will reach 50 million by 1995 (Meng and Yuan, 1993). Artificial seed techniques have also been developed for *Eucalyptus* by using the minibud system at the Institute of Genetics, CAS, while several pine species are being tested for propagation by using somatic embryos.

The tissue culture technique is very helpful for plant scientists to fully use natural germplasm and protect biodiversity. For example, the genera *Actinidia* has over 60 species, and among them 57 species and 39 varieties have been found in China, according to a comprehensive field survey during 1978-1989. Some species or strains have certain unique characteristics, such as fruit colour, disease resistance and cold tolerance. Scientists at the Botanical Institute, Beijing, have obtained some hybrid plants from five combinations among 19 interspecific crosses and by the embryo rescue technique. A new strain "Ke Zhi No. 1" was screened from the combination of *Actinidia deliciosa* (female) X *A. arguta* (male). It has big, green fruit with no hair, easy-peel, and contains higher levels of vitamin C and sugars (Mu, 1993; and personal communication). *In vitro* propagation techniques have also made it possible to save and protect some of the wild rare plant species (see Loo and Xu, 1986). For example, all wild species of *Camellia* found in China are already maintained in tissue culture.

Another culture and haploid breeding

Since the 1970s, haploid or pollen plants have been obtained from more than 50 species in China, and over 40 species among them were reported for the first time, including wheat, maize, sugar-cane, rubber tree, poplar tree, apple, etc. Important cereals and economic crops (such as rice, wheat, barley, maize and rapeseed) have been given more emphasis. The N6 medium developed by Prof. Chu and colleagues has been widely applied in cereal's anther culture. The frequencies of anther induction and green plant regeneration have been greatly increased. The techniques for the culture of isolated pollen have also been improved. For example, three to four green pollen plants on average could be obtained from pollen of each anther in 17 barley varieties tested, with the highest being 14 plants (Li et al., 1993). There are two new varieties of rapeseed (*Brassica napus*), H165 and H166 with low erucic acid (<1 per cent) and glucosinolates (<30 μmol/g), released from pollen plants by scientists from the Institute of Genetics, CAS in collaboration with Yunnan Academy of Agricultural Sciences. They give an average yield of over 4,000 kg/ha in Yunnan Province, which is 11-22 per cent higher than that of the local variety cultivated. Their cultivated area will reach more than 330 thousand ha. by the year 2000 (Chen et al., 1989; and personal communication). During 1985-1990 alone, seven varieties of rice, wheat and rapeseed were released from those institutes supported by national key projects of biotechnology, with the total cultivated area of about 480,000 ha.

Protoplast culture and genetic manipulation

Up to now, plant regeneration from protoplast culture has been obtained in more than 80 species in China; over 50 species of them were reported for the first time. In the past several years, the successful species have included important crops, e.g. maize (1987), wheat (1989), soybean (1987), *Phaseolus angularis* (1987), *Canavallia ensiformis* (1991), *Vicia faba* (1992), peanut (1993) and some woody species and fruit trees, e.g. *Populus tomentosa* (1990), *Paulownia fortunei* (1991), *Platanus orientalis* (1991), *Morus alba* (1992), Kiwis (1990), longan (1992), etc. Somatic hybrids have been obtained after protoplast fusion and selection, in different combinations, including *Glycine max* + *G. soja, Nicotiana tabacum* + *Solanum nigrum, N. tabacum* + *Lycium barbarum, Solanum tuberosum* + *S. bulbocastanum, Oryza sativa* subsp. *japonica* + *O. officinalis, O. sativa* + *Panicum maximum, Triticum aestivum* + *Haynaldia villosa, Actinidia chinensis* + *A. deliciosa, A. chinensis* + *A. kolomikta* and interspecific or intergenic hybrids of *Citrus*. Transgenic plants have been obtained from protoplasts by DNA direct transformation in rice, wheat, sorghum, soybean, *Brassica* spp., etc. (see Xu, 1995).

***In vitro* production of secondary metabolites from plants**

Successful examples of large-scale culture for secondary metabolite biosynthesis are quite limited: *Lithospermum erythrorhizon* and *Arnebia euchroma* for shikonin derivatives, *Panax gingseng, P. notogingseng, P. quinquefolium* for saponins, and a few other medicinal plants. Recent development of genetic transformation systems of plant cells offered a new approach to *in vitro* production of secondary compounds. Hairy root induction and cultures, by using Ri plasmid, have been reported from a number of medicinal plant species, such as *Artemisia annua* that produces little artemisinin in normal cultured cells, and from *Glycyrrhiza uralensis*. Now, Chinese scientists are also working on large-scale cell cultures of *Taxus* spp. and *A. annua*, for the production of secondary metabolites with medicinal interests. One or two groups of scientists will be engaged in molecular cloning of the key enzymes in plant secondary metabolism.

Plant genetic engineering

TMV resistant tobacco has been obtained by introducing coat protein gene. The transgenic tobacco against both TMV and CMV were also selected out after transfer of both TMV and CMV cp gene or cDNA of CMV satellite RNA. The selected strains show good virus resistance in the field test (Zhou et al. 1995). So far, the total cultivation area has been over 33,000 ha. Transgenic potato plants against viroid PSTV and transgenic tomato against CMV are also in field test. Bt toxin genes from a different *Bacillus thuringiensis* strains have been cloned and transferred into tobacco, cabbage and poplar tree by *Agrobacterium* mediated method. Transgenic wheat lines against army worm have also been obtained. The new designed Bt toxin genes by changing the codon to fit to plant cells in gene expression were completed in three different laboratories and are being tested for their activity. A new type of proteinase inhibitor gene was cloned from *Sagittaria sagittifolia* (Xu et al., 1993), and the inhibitor showed insecticidal activity in *ex planta* testing.

The technique of introducing foreign DNA through pollen tube pathway, developed by Prof. G.Y. Zhou, has been applied to various crops. For example, new strains of *Fusarium* wilt-resistant cotton No. 3118, bred with this technique, are already planted over 26,000 ha with the yield increased by 15 per cent on average.

Particle gun for gene transfer has been used quite extensively for cereal transformation. Preliminary results from Prof. L.C. Li of the Institute of Genetics, CAS in collaboration with China Rice Research Institute, Hangzhou, showed that transgenic rice plants obtained resistance to rice bacterial streak and rice bacterial blight disease by transfer of Cecropin B gene (L.C. Li, personal communication). Some new transformation techniques have been developed. Gene transfer has been successful in ultrasonication treatment in tobacco as well. Recently, it has been found that low energy ion beam treatment can deliver foreign DNA into the cells of mature rice embryos. The regenerated plants from Hm resistant cell lines selected have proved to be transformed by PCR or southern blotting (Yang et al., 1994).

In conclusion, although we still face the many problems most developing countries usually have, e.g. funding problems, shortage of equipment and facilities, continuing brain drain, etc. (see Xu and Chen, 1993), and it seems to take time to establish efficient collaborative links between research and business, molecular biologists and agronomists/plant breeders, plant biotechnology R&D is beginning to flourish in China, and the integration of the molecular biology techniques, plant tissue culture work and crop breeding has already made and will continue to make it more fruitful.

References

Chen, X.Y. and Z.H. Xu, (1995). Present status and prospects *in vitro* production of secondary metabolites from plants in China. An invited article for the 3rd National Symp. of the Botanical Soc. of Korea, titled with "Present status and prospects of *in vitro* production of secondary metabolites" (August 1995)

Chen, Z.H., S.X. Cun, Z.Z., T.H. Zhang, W.B. Li, and L.H. Zhang, (1989). Obtaining new variety of rape by biotechnology. Proc. of the 6th International Congr. of SABRAO, Pages: 505-508.

Guo, J.Y. and Y.Q. Liu, (1994). Rapid propagation of cassava by tissue culture and its application in rural district. Second International Scientific Meeting, Cassava Biotechnology Network (CBNII) (August 1994. Bogor, Indonesia). Page 39.

Li, W.Z., J.K. Jing, G.H. Yao and H. Hu, (1993). The effects of genotype and mannitol pretreatment on high frequency androgenesis in barley. Chinese Sci. Bull. **38**: 151-155.

Loo, S.W. and Z.H. Xu, (1986). Recent advances in plant tissue and cell culture work in China. In: Advances in Science of China, Biology vol. 1. Edited by Cao, T.Q. (Sci. Press, Beijing). Pages: 295-354.

Meng, G.Z. and P. Yuan, (1993). Rapid propagation in China. In: "Adapted Propagation Techniques for Commercial Crops of the Tropics". Proc. of the Southeast Asian Regional Workshop on Propagation Techniques for Commercial Crops of the Tropics. (February 1993. Viet Nam, organized by IFS). Pages: 31-39.

Mu, X.K. (1993). Present status of researches and production of *Actinidia* in China. Proc. of Sino-Japan Biotechnology Symp. Pages: 145-151.

Xu, W.F., W.K. Tao, Z.Z. Gong C.W. Chi, (1993). cDNA and genomic structures of arrowhead proteinase inhibitors. *J. Biochem.* **113**: 153-158

Xu, Z.H. (1995). History and the present of plant protoplast studies. In: Plant Protoplast Culture and Genetic Transformation. Edited by Xu, Z.H. and Z.M. Wei, (*Shanghai Sci. and Tech. Press*, Shanghai) (in press, in Chinese).

Xu, Z.H. and S.Y. Chen, (1993). Agricultural biotechnology in Asian developing countries: Priorities, problems and strategies. In: Proc. of the Intern. Seminar on "Impacts of Biotechnology in Agriculture and Food in Developing Countries" (Madras, 3-4 February, 1992, COSTED/ANBS), Pages: 95-103.

Yang, J.B., J.D. Wu, Y.J. Wu, Z.L. Yu and Z.H. Xu, (1994). Transgenic rice plants obtained by low energy ion beam mediated DNA delivery into cells. *Chinese Sci. Bull.* 39: 1530-1534.

Zeng, J.Z. (1988). Techniques of micropropagation and field cultivation of test tube plants of sugar cane. In: "Tissue Culture of Economic plants". Edited by S.W. Loo and Z.H. Xu (Sci. Press, Beijing). Pages 154-159 (in Chinese).

Zhou, R., Z. Zhang, Q. Wu, R. Fang, K. Mang, Y. Tian and G. Wang, (1995). Large-scale field performance of transgenic tobacco plants resistant to both tobacco mosaic virus and cucumber mosaic virus. Proc. of 3rd International Symp. on the Biosafety Results of Genetic Modified Plants and Microorganisms (13-16 November 1994, Monterey) (in press).

(Source: *Australasian Biotechnology* Vol.5, No. 5, October 1995)

Egypt

Wheat research pays off for Egypt's farmers

Egyptian wheat production is 125 per cent higher than it was in the early 1980s. This dramatic improvement has resulted from a combination of new wheat technology, effective technology transfer and a series of bold reforms by the Government of Egypt to get the market moving.

Now a study by the International Center for Agricultural Research in the Dry Areas (ICARDA) Nile Valley Regional Program (NVRP), in collaboration with the Egyptian national research programme has been made to quantify the benefits of modern wheat research to farmers in Egypt. Concentrating on Sohag and Qena in upper Egypt, the study found that farmers who invested in new packages of wheat technology could see high cash returns on their investment. At 1993 prices, a farmer who shifted from traditional techniques and varieties to an intermediate package of improved varieties and agronomic practices would see marginal rates of return of 404 per cent. Farmers already using such a package who shifted to the full recommended package would see a marginal rate of return of 281 per cent.

In 1992-1993 a team from ICARDA/NRVP and Egypt's Agricultural Research Center (ARC) carried out a survey to see how widely these new packages had been adopted, and to try to quantify the real benefits to farmers. The results were encouraging; 64 per cent of the farmers surveyed in Sohag and Qena had adopted the new varieties, 73 per cent the new planting date, and 77 per cent the recommended irrigation interval. However, other components of the package were a lot less popular—planting method (12 per cent), seed rate (12 per cent), nitrogen fertilizers (7 per cent) and timing of first irrigation (37 per cent).

The report therefore suggests that further socio-economic research is needed to find out why farmers have not adopted certain economic components.

Contact: Mike Robbins, Communiciation, Documentation and Information Services, ICARDA, P.O. Box 5466, Aleppo, Syria. Fax: +963-21 213490, 225105, 551860. Tel.: +963-21 213433, 213477, 235220, 225012, 225112, 225635. Telex: (492) 331 206, 331 208, 331 263 ICARDA SY. Cable: ICARDA Aleppo. (Extracted from *News Release*, October 1995)

Germany

Chaperone research initiative

The German Federal Ministry of Research (BMBF) is investing in a research project into so-called chaperones, which are components of living cells that support the stabilization and formation of proteins. Proteins can only carry out their functions in the organism if they are "folded up" in a particular way. To date, a dozen types of chaperone models in human, animal and bacteria cells have been identified, but little is known about the way they function.

In the BMBF-backed enterprise, the Max-Dellbrück-Centre for Molecular Medicine in Berlin, the University of Halle and the Heidelberg Centre for Molecular Biology will investigate chaperone use.

The three-year project aims to develop standardized testing procedures and researchers hope to discover the basis for an industrial application of chaperones when producing proteins using genetic, biochemical and biophysical methods.

The long-term goal of the project is to develop a "reactor" to shape proteins throughout the production process. (Source: *Biotechnology Business News*, 14 February 1995)

Hamburg sets up genetic testing laboratory

Hamburg has established a municipal laboratory for the supervision of genetic engineering experiments.

Following the lead taken by Bavaria, Baden-Württemburg and Berlin, Hamburg becomes the fourth state to open a laboratory of this kind. It is the first, however, which is suitable to supervise experiments up to the second highest security level (S3), according to the Hamburg authorities. (Extracted from *Biotechnology Business News*, 17 January 1996)

Germany focuses on biotechnology

Germany's Federal Research Ministry plans to help the country's small biotechnology sector to find its place at the "top of the market" in Europe.

The Minister described biotechnology as "one of the key industries for Germany's competitive position in the 21st century". At the same time, he announced a competition among German regions in promoting biotechnology. (Extracted from *European Chemical News*, 23-29 October 1995)

Ireland

Anti-gene technology

Researchers at the National Pharmaceutical Biotechnology Centre are developing a new anti-sense/antigene technology involving "triple-helix" formation. Crucially this new technology can be employed to construct

an anti-gene molecule capable of spanning the entire width of the major groove of the double helix. This approach, while retaining the selectivity of current "triple-helix" strategies, will have superior versatility in controlling gene expression and in targeting reagents or enzymes to specific DNA sites. A commercial partner is sought to assist in the confirmation of this technology and to develop commercial applications.

Further details are available from: Seamus O'Hara, Commercial Manager, National Pharmaceutical Biotechnology Centre, O'Reilly Institute, Trinity College, Dublin 2, Eire. Tel.: +353 1 608 2153; Fax: +353 1 671 5198; E-mail: sohara@mail.tcd.ie (Source: *Irish Biotech News*, January 1996)

New initiative to promote biotechnology for biodiversity

A "Biotechnology for Biodiversity Platform" was launched to promote the flow of information on molecular tools useful in biodiversity measurement. The new organization hopes to attract experts and end-users involved in biodiversity. It is intended to promote understanding of the role of biotechnology in biodiversity conservation.

An important aspect of this initiative is the provision of a service for those wishing to establish relevant technologies in their laboratories.

For details contact: Dr. Tim Roche, NAVBC, Biotechnology Building, University College, Belfield, Dublin 4. Tel.: +353 1 7062814; Fax: + 353 1 2672016; E-mail: timroche@ollamh.ucd.ie (Source: *Irish Biotech News*, January 1996)

Israel

Israel backs scientific collaboration

Scientific collaboration in the Middle East is being actively pursued as the political climate thaws.

At the end of 1995, UNESCO, together with the Hebrew University, inaugurated a joint international school for molecular biology and microbiology. Based at the Hebrew University in Jerusalem, the purpose of the school is to further cooperation between scientists and universities in the Middle East, develop programmes for the training of lecturers and researchers, and establish links between scientists working in molecular biology, medicine, biotechnology and microbiology world-wide.

In the long run, it is hoped that the school will help to enhance the state of health of mankind, the provision of food for both humans and animals, and protect the environment.

The agreement to create the international school was originally signed in April 1995. Its theme is "Science for Peace" and it will involve more than 20 Israeli and Palestinian researchers. Cooperation between Egypt and Jordan is also expected in the future.

The school will join the UNESCO Global Network for Molecular and Cell Biology. Funding is primarily from UNESCO, with the Hebrew University supplying the infrastructure. Other interested agencies and foundations are welcome to pledge their support.

The curriculum for each 10-day session will focus on a major subject such as biotechnology approaches to microbial agents, molecular biological aspects of parasitic microorganisms, and molecular immunology of microbial infections in man and animals. In addition to lectures and workshops, students will be able to join one of the research teams at the Institute of Microbiology for the duration of the session. At present, the budget allows for one or two sessions a year. (Source: *Biotechnology Business News*, 17 January 1996)

Japan

Genome DNA database service planned

The Japan Information Center of Science and Technology (JICST) said that it will start a human genome DNA base sequence information service shortly as part of its effort to develop an advanced biological database to help users retrieve and analyse genetic information such as human genome DNA base sequence information.

This project, initiated by JICST, will be carried out over three years by the Japanese Foundation for Cancer Research and three universities. JICST will contract with more institutions and laboratories during 1996 to expand this project. (Source: *McGraw Hill's Biotechnology Newswatch*, 6 November 1995)

MAFF launches basic research initiative

In 1996, the Japanese Ministry of Agriculture, Forestry and Fisheries (MAFF) will launch a basic research project for the development of new biotechnology-applied technology and industry by requesting budgetary appropriations $21 million.

The project is aimed at carrying out about 20 research themes over three to six years.

The target themes will cover the development of:

- Living organisms producing new materials;
- Multifunctional foodstuffs;
- Living organisms growing under extremely severe conditions;
- New living organisms producing energy; and
- Living organisms useful for making the environment comfortable.

Opinions from outside the Ministry will also be sought regarding the research themes concerned. Research tasks will be commissioned to the Bio-oriented Technology Research Advancement Institution attached to MAFF. (Source: *McGraw Hill's Biotechnology Newswatch*, 2 October 1995)

Biotech panel has draft of plant guidelines

An ad hoc biotechnology committee attached to Japan's Ministry of Health and Welfare has recently worked out a draft for new guidelines for assessing the safety of genetically engineered seed plants, including rapeseed and soybeans, both of which are expected to be imported into Japan.

The drafted guidelines allow supply of the seeds in question as foods if they are identified as being almost the same as natural ones in the light of the stipulations of the guidelines themselves. Needed for the identification are, the guideline claims, data on the hereditary characteristics of the said plants, dietary habits of the humans consuming the foods concerned, constituents of the foods and differences in the use (consumption) of existing and new biotechnology species of the plants.

The ad hoc committee is scheduled to hold hearings soliciting the views of consumers, food producers and importers and submit the draft to the Health and Welfare Minister.

In a related development, Japan's Ministry of Agriculture, Forestry and Fisheries has confirmed that the

corn and rapeseed developed via gene modification by Hoechst Schering AgrEvo K.K. and the carnations produced via genetic engineering by Suntory Ltd. satisfy the Ministry's biotechnology-application guideline—a guideline for utilization of gene-modified products in the fields of agriculture, forestry and fisheries—allowing these plants to undergo tests in a quasi-open environment. Tests in a quasi-open environment have to be conducted to confirm the safety of the plant in question before being cultivated in an ordinary field.

Prior to the latest confirmation by the Ministry, Monsanto Japan and Plant Genetic Systems had already launched tests of gene-modified herbicide resistant rapeseed and soybeans and are likely to be granted safety approval for their use in spring 1996. Hoechst Schering's two crops and Suntory's carnations will soon be put to the test, which will last until autumn 1996. (Source: *McGraw Hill's Biotechnology Newswatch*, 20 November 1995)

Gene therapy guidelines approved

The Committee on Biotechnology of the Central Pharmaceutical Affairs Council has approved guidelines to the quality and safety of drugs for use in gene therapy. The guidelines consist of general provisions, and sections on:

- Manufacturing methods, standards, test methods;
- Stability;
- Preparation design;
- Non-clinical safety tests, tests to support efficacy;
- Pharmacokinetics;
- Manufacturing facilities and equipment for drugs used in gene therapy.

The manufacturing methods are classified as:

- Those using viral vectors;
- Those using non-viral vectors;
- Those with direct introduction of the gene without a vector.

In the section on standards and test methods and preparation design, the establishment of appropriate purity tests for quality assurance and process validation are specified.

In the non-clinical safety tests, conditions must reflect the route of administration of the drug in humans, viral proliferation must not occur, and the possibility of damage to cells or tissue must be explained. (Source: *McGraw Hill's Biotechnology Newswatch*, 4 December 1995)

Malaysia

Commercialization emphasis for new National Biotechnology Directorate (NBD)

Malaysia has recently established the National Biotechnology Directorate (NBD) to promote the development of biotechnology in the country. Elaborating on the functions of NBD, the Government has indicated that it aims to enhance further national capabilities and consolidate R&D efforts for projects that could be commercialized. Essentially, NBD is to organize existing research efforts into an entity which combines optimal use of Malaysia's biotechnology expertise and facilities. NBD will also provide the management infrastructure to commercialize research findings. NBD's management team will be responsible for overseeing and implementing an industry-oriented national biotechnology programme, which will use the facilities of existing research institutions and universities. Initially, NBD will be set up under the Ministry of Science, Technology and Environment and will be fully funded by the Government. However, it is envisaged that Government funding will be phased out gradually once the Directorate becomes fully operational and receives income from the leasing of its common facilities and from fees collected as a result of the commercialization of R&D outputs. Bioprocessing facilities would then be introduced in the second phase of the programme. (Source: *Australasian Biotechnology*, Vol. 5, No. 4, 1995)

New Zealand

Biotechnology designated a key science

Biotechnology is one of six generic technologies identified as underpinning eight key science areas (KSAs) defined in a Discussion Draft of the New Zealand Government's strategy for research, science and technology to the year 2010.

The other generic technologies are materials science and technology; food technology; production and process engineering; information and knowledge engineering; and social research methodologies.

The key science areas are: evaluating the resource potential of New Zealand's exclusive economic zone; characterizing New Zealand's biodiversity; sustainable biological production systems; understanding biological hazards; innovative industrial processing and manufacturing; product development; New Zealand social and cultural dynamics; and information and communications.

The goal of the strategy is to increase overall publicly funded investment in science and technology from below 0.57 per cent of GDP in 1992/1993 to 0.8 per cent by 2010. (Extracted from: *Biotechnology Business News*, 1 September 1995)

Interim assessment group for the field testing or release of GMOs

Field testing or release of genetically modified organisms (GMOs) is covered in a report from the GMO Interim Assessment Group (IAG) at New Zealand's Ministry of the Environment.

The IAG was established by the Minister in 1988 as an interim measure. The background to this establishment was the realization that existing legislation was inadequate for regulating the field testing or release of GMOs, and that new legislation would be some time away. Since its inception, the IAG has received 32 applications involving the use of GMOs outside strictly contained facilities. Of these, 28 were for field trials, glasshouse trials and taste tests, three were for large-scale fermentation of genetically modified *Escherichia coli* bacteria, and one was to transport a GMO within New Zealand. An inquiry relating to the export of GMOs was also received.

Details available from: Dr Abdul Moeed, Chairperson, Minister for Environment, P.O. Box 10-362, Wellington, New Zealand. (Source: *EBIS*, Vol.5, No.1, 1995)

Russia

New professional body set to raise profile of the Russian bioindustry

A major new initiative aimed at giving the Russian Federation's bioindustry its own voice has been launched in Moscow. The Biotechnology Academy is an independent non-governmental organization that seeks to represent the views of the industry, both domestically and internationally. It will embark upon a number of important projects,

including the training of new specialists to draft legislation impacting upon bioindustry, and campaigns to raise public awareness of the potential benefits to be derived from the application of new biotechnological techniques.

It was founded in the summer of 1991 by Russian researchers and industrial managers concerned about the possible collapse of the system responsible for the management of biosciences in the USSR. It was originally based at the Science Production Centre of Medical Biotechnology in Moscow and has recently been transferred to new headquarters at the Institute of Genetics and Selection of Industrial Microorganisms, also in Moscow. The Academy, which publishes the Russian bioindustry's flagship journal *Biotekhnologiya* ("Biotechnology") and the Russian version of the Genetic Engineering and Biotechnology Monitor, is now being recognized and relaunched by its new chief scientific secretary, Vladimir Bundin. One of Bundin's key aims is to strengthen ties between the research and industrial sectors in bioindustry.

Another way in which academic-industrial links are being strengthened is by the Academy expanding its membership base and encouraging institutes, research centres, production facilities and companies to become corporate members. Already, four major R&D centres in Moscow have obtained membership, and Russia's major producer of pharmaceuticals, the State Scientific Centre of Virology and Biotechnology, *Vektor*, is expected to join soon. In an attempt to increase revenue and promote international collaboration, foreign companies are also being encouraged to become members of the Academy.

The Academy is hoping to become involved in the management of international projects aimed at the conversion of military microbiological facilities in the Russian Federation. The Moscow-based International Science & Technology Centre (ISTC), which is funded by the United States and other Western countries, is funding programmes at several institutes with the aim of refocusing their R&D on civilian rather than military applications.

Another key issue that the Academy hopes to address is the lack of specialists in the Russian Federation able to draft and comment upon legislation impacting upon bioindustry, especially regarding the use of genetically modified organisms. Recently a small group from UNIDO modified an unworkable Russian draft law on the use of recombinant techniques and their application in industry. The intention is to create a small department that will recruit 10-20 graduates from Moscow State University and other institutes of higher education for specialist training in law and its application to various aspects of biotechnological research and production. Following completion of a two- to three-year course, the students will be sent abroad for additional training at internationally recognized centres, such as the University of Sheffield's (UK) Institute of Biotechnological Law and Ethics.

The Russian Government is being lobbied to provide funding for new national biotechnology R&D and production programmes that will be administered and coordinated by the Academy.

The long-term aim of the Academy's management is that it should develop into an organization closely resembling European bioindustry associations, with the power to lobby government effectively, project a strong image of Russian bioindustry abroad, and ensure that public awareness of biotechnology is maintained at a high level.

The Biotechnology Academy can be contacted at 1-yi Dorozhnyi proezd 1, 113545 Moscow, Russian Federation, Tel.: + 7 095 315 1229; Fax: + 7 095 315 0501. (Extracted from *Microbiology Europe*, Vol.3 No.6, November/ December 1995)

United Kingdom

Biotechnology opportunities

The UK Department of Trade and Industry has launched the Biotechnology Means Business initiative to help companies, whatever their size or industry, understand and exploit the potential of biotechnology as a key to competitiveness and as a source of new opportunities. It offers information, advice, assistance and technical support to help businesses discover and implement new and better ways of using this versatile technology. Further details from BMB Initiative, Chemicals and Biotechnology Division, DTI, 151 Buckingham Palace Road, London SW1W 9SS. (Source: *Chemistry & Industry*, 4 December 1995)

UK sets up research body

The Biotechnology and Biological Sciences Research Council (BBSCR) has been set up in the UK to be responsible for basic and strategic research in biotechnology. The Council was formed by incorporation of the former Agricultural and Food Research Council with the biotechnology and biological sciences programmes of the former Science and Engineering Research Council. Membership of the Council reflects the academic and industrial communities serviced by the programmes of research. The mission of the new Council is to sustain and promote a broad base of interdisciplinary research and training to help UK industry, commerce and government create wealth and improve the quality of life.

The new body says that its creation recognizes the major contribution to wealth creation in the UK coming from the biology-based industries, including biotechnology, in addition to the contribution made by the fields of pharmaceuticals, agriculture, agrochemicals and food. (Source: *EBIS*, Vol. 5, No. 1, 1995)

Official launch of Northern Ireland biotech centre

The new £1.6 million, IFI-funded Centre for Innovation in Biotechnology was officially launched on 7 November 1995 at an event organized by the Industrial Research and Technology Unit (IRTU), in conjunction with the UK Dept. of Trade and Industry (DTI).

The new Centre is an associate member of the BRI group and brings to the partnership the two universities in the North, the University of Ulster and Queen's University Belfast with its associated research centres in the Department of Agriculture for Northern Ireland. The partnership represents a significant opportunity to raise the profile of biotechnology research in Northern Ireland.

The new centre will be working closely with BRI in early 1996 on the updated version of the Irish Biotechnology Sourcebook to include additional information on the expertise available in Northern Ireland industry and the academic research centres.

For further details of the Centre's activities contact: Dr. Jeremy Carmichael, Tel.: 080 1265 324051; Fax: 080 1265 324906; E-mail: j.carmichael@ulst.ac.uk (Source: *Irish Biotech News*, January 1996)

United States of America

Biotech initiatives at Iowa State University

Iowa State University will be among the first public academic institutions in the United States to establish a Plant Transformation Facility. Maize and soybeans will be the first two crops targeted for transformation research. Ninety per cent of activities at the Iowa facility will serve on-campus users in a fee-based arrangement.

Meanwhile, ISU's Animal Science Department is studying new ways to track the inheritance of economically valuable genes through generations of chickens. One project involving a phenomenon called genomic imprinting may some day help producers to select their chicks' traits long before they hatch.

Contact: ISU Office of Biotechnology, 1210 Molecular Biology Building, Ames, Iowa USA 50011. Tel.: (515) 294-9818; Fax: (515) 294-4629. (Source: *The AgBiotech Bulletin*, January 1996)

Gene therapy trials

Two gene therapy trials have begun in the US, both using deactivated cold viruses to deliver genes. One, at the University of Philadelphia Medical Center, aims to shrink lung tumours, caused by contact with asbestos dust, by bombarding them with a gene that makes them susceptible to an antiviral drug. The other, at Johns Hopkins University Medical School, will test the safety of using viruses to deliver corrected versions of the malfunctioning gene in cystic fibrosis. (Source: *Chemistry & Industry*, 4 December 1995)

US eases biotechnology regulation

The US Food and Drug Administration has introduced a package of reforms aimed at easing restrictions of drugs developed with the use of biotechnology. Biotechnology derived drugs will now be treated similarly to other medicines.

Biotechnology drug companies will no longer be expected to get special licences; the FDA will no longer examine each lot of drugs before it can be sold. Drug approvals will be speeded up, and application forms will be consolidated to reduce paperwork.

The reform of drug restrictions is expected to save US companies hundreds of millions of dollars and accelerate drug introductions. (Source: *The AgBiotech Bulletin*, January 1996)

New horizons for 21st century biotechnology

Biotechnology for the 21st Century: New Horizons is a recent report from the Biotechnology Research Subcommittee, Committee on Fundamental Science, US National Science and Technology Council.

The report identifies three priority areas for biotechnology research.

The first priority is to "expand research and discover, characterize, modify and control the genetics and biochemical products and processes of a broad range of terrestrial and marine organisms for applications in biotechnology".

The second is to "apply the tools of modern biotechnology to problems in agriculture, the environment and manufacturing to facilitate the development of new and improved products, processes and test methods".

The third is to "strengthen and enhance facilities, repositories, databases, reference standards and human resources to ensure the future vitality of the US biotechnology enterprise".

Specific priorities for agricultural biotechnology are to:

- Continue mapping and sequencing of animal/plant/microbial genomes to elucidate gene function and regulation and to facilitate the discovery of new genes as a prelude to gene modification;
- Determine biochemical and genetic control mechanisms of metabolic pathways in animals, plants, and microbes that may lead to products with novel food, pharmaceutical, and industrial uses;
- Extend understanding of the biochemical and molecular basis of growth and development including structural biology of plants and animals;
- Elucidate the molecular basis of interactions of plants and animals with their physical and biological environments, as a basis for improving the organism's well-being; and
- Enhance food safety assurance methodologies, such as rapid tests for identifying chemical and biological contaminants in food and water.

Contact: Copies of the document are available for sale from the US Government Printing Office, Superintendent of Documents, Mail Stop, SSOP, Washington, DC USA 20402-9328. Quote stock number 038-000-00590-1. (Source: *The AgBiotech Bulletin*, January 1996)

Opening the world's largest repository of human cDNA materials

The Institute of Genomic Research (TIGR) and the American Type Culture Collection (ATCC) recently announced the creation of the "TIGR/ATCC Human cDNA Special Collection". This Special Collection will be the largest repository of human cDNA materials in the world, representing the majority of human genes. It will provide scientists with access to biological materials needed to begin a comprehensive exploration of the relationships of human genes to health and disease.

Human cDNA clones from TIGR, a non-profit cDNA research institute in Gaithersburg, MD, will be made available to the world-wide scientific community through the distribution systems provided by ATCC, the world's leading biological materials repository, located in Rockville, MD. Because TIGR and ATCC place high value on the quality of materials distributed, TIGR will confirm the sequence of each clone prior to distribution.

Consistent with current ATCC policy, materials in the TIGR/ATCC Special Collection will be distributed by the ATCC and will include clones available to the scientific community without restriction (including all human cDNA clones previously available from ATCC), clones restricted to not-for-profit institutions and proprietary clones available to users of the Human cDNA Database (HCD) at TIGR or researchers who sign a material transfer agreement. In addition to the clones from TIGR, Human Genome Sciences, Inc. (HGS) has contributed data and clones to HCD, with the clones also to be available as part of the Special Collection. Clones corresponding to more than 160,000 cDNA sequences will be available to the academic community. For certain clones, non-users of HCD may need to execute a material transfer agreement.

For further information: ATCC, Kaye Sloan Breen (Tel.: (301) 816-4378; Fax: (301) 816-4362; TIGR, Damar Hawkins (Tel: (301) 838-0200; Fax: (301) 838-0209).

(Source: *Australasian Biotechnology* Vol. 5, No. 6, December 1995)

Biotechnology regains momentum

Strong signs of recovery are evident in the US biotechnology industry. Product sales in 1995 increased 18 per cent, to $9.3 billion, and are predicted to exceed $10 billion in 1996. Biotechnology stock prices are again on the rise, and several promising products, including the first wave of genetically engineered crops, are expected to hit the market this year.

Human therapeutics are the star performers, growing at 13 per cent/year and accounting for 75 per cent of biotechnology sales. And, according to experts, the drug pipeline looks promising. Ernst & Young (San Francisco) reports that 127 biotechnology drug candidates are in human clinical trials and another 18 are awaiting regulatory approval. Notable products that could soon enter the market include a treatment for multiple sclerosis developed by Biogen (Cambridge, MA) and a growth factor developed by Immunex (Seattle, WA) for treating blood disorders associated with cancer treatments.

Plant biotechnology—long overshadowed by the drug sector—could also become a major commercial force. Several genetically engineered agricultural products gained regulatory approval in 1995 and are scheduled for commercialization in 1996.

Signs from Washington are also encouraging. Positive events in 1995 include progress on reforming procedures of the Food and Drug Administration (FDA) and the Congressional passage of a bill protecting process patents. (Extracted from: *Chemical Week*, 3/10 January 1996)

EPA approves Bt corn and cotton with conditions

The Environmental Protection Agency (EPA) has given the go-ahead for the commercialization of corn and cotton genetically engineered to resist attack by insects. In addition to Bt potato approved last spring, this makes three so-called Bt crops that will be planted in farmers' fields in the next growing season. Because the crops produce their own insect-killing toxins, they are being registered as pesticides under the EPA's federal pesticide law.

The crops all contain genes from a bacterium *Bacillus thuringiensis* (Bt) which allow them to produce toxins that kill insects which feed on the crop. EPA and industry are hailing the new crops as a way to reduce the application of chemical insecticides. Environmental groups and organic farmers on the other hand oppose the approvals because they fear that widespread use of Bt crops will accelerate the development of resistance to Bt.

After heavy criticism for its unconditional approval of Bt potato, the EPA has imposed restrictions on the registrations of Bt corn and cotton that partially address the resistance concern. The conditions require companies to take a number of steps, including developing long-term resistance management plans and undertaking extensive new research. The conditions for Bt cotton include a restriction that farmers plant a certain percentage of their fields with non-Bt cotton. Unfortunately, however, scientists are not sure that the measures contained in the plans are sufficient to prevent resistance. Much more research is needed to determine what will work to avoid resistance resulting from these novel crops. (Source: *The Gene Exchange*, Vol. 6, Nos. 2 and 3, December 1995)

D. RESEARCH

Research on human genes

Cloned gene for rare syndrome hints at common cancer cause

Until recently, only a small number of scientists spent much time studying the extremely rare inherited condition known as Bloom's syndrome, which causes short stature, skin pigmentation, immune defects—and a terrifyingly high risk of cancer early in life. Bloom's is likely to attract a lot more attention since researchers reported the cloning of mutant gene on the long arm of chromosome 15. This gene is apparently unique in that its malfunction can undermine the stability of the entire genome.

With a faulty Bloom's gene, cells undergo so much chromosomal breakage and rearrangement and mutation in other genes that malignancies occur far more often and earlier than in the general population, as if individuals with Bloom's syndrome are born to get cancer—and, unlike some other cancer syndromes, the range of malignancies reflects the entire spectrum of human cancers.

The syndrome is inherited in an autosomal recessive fashion. The discovery is credited to James L. German and Nathan A. Ellis at the New York Blood Center and Joanna Groden of the University of Cincinnati College of Medicine. The finding is so new that the researchers do not yet know precisely the function of the protein encoded by the Bloom's gene. However, they believe it belongs to a family of enzymes, the DNA helicases, that play a crucial role in the duplication of the DNA strand when a cell divides. Specifically, the helicases help uncoil the helical molecule so that each strand can be individually copied.

For reasons not yet clear, Bloom's cells that lack a properly functioning helicase are prone to making all sorts of replication errors, and these errors apparently do not undergo normal repair. Some of the resulting ruination can be seen under a microscope: chromosomes reveal gaps and breaks and rearrangements.

In addition, crossing-over between sister chromatids occurs at a remarkably high rate in Bloom's cells compared to normal cells. The Bloom's phenotype is marked not just by the cancer predisposition. The individuals are normally proportioned but short, rarely reaching five feet. They tend to have narrow faces often disfigured by a reddish, sun-sensitive lesion, and a variety of behavioural manifestations including lowered IQ. The syndrome also causes immune deficiencies that are not well understood. What light the Bloom's discovery may shed on the general process of cancer is not yet clear. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 15 January 1996)

Scientists find large piece of puzzle in melanoma

An important piece in the puzzle of how to cure melanoma has been found by a team from Sequana Therapeutics and the US National Cancer Institute (NCI).

The scientists discovered an inherited cancer-causing alteration in the CDK4 gene.

Melanoma, skin cancer associated with too much exposure to the sun, is the most common cancer in the United States. The disease is also the most curable of cancers when it is caught early. At later stages, after it has spread to other parts of the body, the disease is an aggressive killer.

The study in which the inherited mutation was found examined only two unrelated melanoma families. The mutation was found in 11 melanoma patients in the group while 17 others were unaffected.

Sequana's team believes that the p16 gene is responsible for as much as 50 per cent of melanomas and that the CDK4 gene may account for from 5 to 10 per cent. Sequana is said to be interested in finding "all the genes responsible for melanoma" so they can be used to understand the mechanism of the disease. Another objective is to see if p16 and CDK4 genes can be mutated by exposure to ultraviolet light, which would indicate that they may cause non-hereditary melanoma as well as the inherited form of the disease.

In addition to the two families discussed in the paper, researchers analysed DNA from 29 other families with hereditary melanoma with normal p16 genes. No alterations in CDK4 were found. The results indicate that CDK4 alterations account for somewhere between 1 and 20 per cent of hereditary melanoma cases and that other genes will likely be found to play a role in the development of the disease.

The study was done using samples of DNA provided by NCI, with the alteration identified by Sequana researchers. The results have been published in the January issue of *Nature Genetics*. It appears that only two of the 31 high-risk melanoma families looked at by the NCI-Sequana team had the CDK4 mutation.

In a healthy cell CDK4 binds to a regulatory protein, p16, that controls the normal rate of cell division. Earlier studies have shown that family members who inherit an alteration in the p16 gene have an 80 per cent lifetime risk of melanoma, compared with a one per cent risk in the general population. But p16 alterations account for only a third of the hereditary melanoma cases. So, the NCI-Sequana team looked for alterations in the CDK4 gene, reasoning that normal cell division could be affected as easily by an alteration in that gene as in the p16. The DNA studied was from melanoma families with normal p16 genes.

The scientists found that a mutation in CDK4 effectively eliminates the negative regulation of CDK4 by p16, allowing tumour cells to grow unchecked. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 15 January 1996)

Obesity gene

It seems that every major science journal has a story on the **obesity (ob) gene**. Scientists had demonstrated that the ob gene encodes a protein called leptin that binds to a receptor in the brain. Leptin appears to regulate food intake by signalling fullness.

Rockefeller University and Millennium Pharmaceuticals researchers showed that the mouse diabetes (db) gene and the gene encoding for the leptin receptor are the same gene (*Science*, 1996, **271**, 994). In the 9 February issue of *Cell*, another team from Millennium revealed that the db gene and the gene for the leptin receptor are equivalent.

In *Nature*, researchers from Rockefeller University showed that the diabetes gene encodes the leptin receptor which has six alternative forms. The team suggests that the effects of leptin are controlled by signals that pass through a leptin receptor in the hypothalamus as one form of the gene is highly expressed in this region in the brain (*Nature*, 1996, 379, 632).

Genentech researchers showed that leptin also reduces body fat by a separate mechanism and may have a role in fuel storage and/or energy expenditure (*Proc. Natl Acad. Sci.*, 1996, **93**, 1726). (Source: *Chemistry & Industry*, 19 February 1996)

Gene linked to most breast cancer

A gene that was thought to cause only a small proportion of breast cancers now appears to be at the heart of nearly all of them, researchers report. The finding may lead to new ways to give a prognosis and to treat breast cancer, but there is no immediate action recommended for women who have breast cancer or are concerned about a genetic predisposition to the disease.

Researchers are excited about the finding because it means that the rare forms of breast cancer that run in families no longer appear to be distinct from the most common forms of breast cancer.

The gene in question, known as BRCA-1, was isolated just a year ago. Women who inherited a mutated form of the gene had about a 90 per cent chance of developing breast cancer and about a 60 per cent chance of developing ovarian cancer.

But women with familial breast cancers constitute just 5 per cent of all women with the disease, so the importance of the finding seemed of minor importance for the vast majority of women who might contract breast cancer. When researchers examined cancers from women who did not have a strong family history of the disease, the gene seemed normal.

Dr. Wen-Hwa Lee and his colleagues at the University of Texas at San Antonio have now reported that women with breast and ovarian cancers, but no family history of the disease, have certain abnormalities related to this same gene. The abnormalities have to do with a protein called the BRCA-1 protein. The BRCA-1 gene instructs the cells to make this protein.

Normally, this protein is successfully produced and does its work in the cell nucleus, which contains the genetic material. In the rare familial breast cancers, the gene produces a faulty form of the protein. In the more common forms of breast cancer, the researchers report that the protein is misplaced, found in the wrong part of the cell.

Dr. Lee and his colleagues looked for the BRCA-1 protein in normal cells from various body tissues, including the breast. They also looked in breast and ovarian cancer cells taken from women with newly diagnosed cancer, in cells from women with advanced cancer and in cells from cancers other than those of the breast or ovary.

What they found was that normal cells and cells from other sorts of cancers contained the protein in the nucleus. But the protein was either outside the nucleus or absent altogether in nearly all the breast and ovarian cancer cells they examined.

Dr. Lee said the BRCA-1 protein's structure suggests that its role is to attach itself to genetic material and control the switching on and off of genes. If that is correct, then the misplacement of the protein outside the nucleus could leave a cell without a vital modifier of cell development, leading to malignant growth.

The misplacement of the BRCA-1 protein in cells indicates that the protein, even if properly formed, may not be functioning in most women with breast or ovarian cancers, indicating that it may one day be possible to move the misplaced protein back to where it belongs.

An earlier discovery concerns a special feature of a particular mutation of BRCA-1 known as 185 del-AG. As many as 1 per cent of the descendants of Ashkenazi Jews, those of Eastern and Central European origin, have this particular mutation in their BRCA-1 gene. In effect, this amounts to about 1 per cent of American Jews, because the overwhelming majority of them are of Ashkenazi descent. This is a surprisingly high percentage for a genetic disease, since even quite common genetic diseases are usually found in a very small proportion of the population. (Source: *International Herald Tribune*, 4-5 November and 30 September 1995)

Brain protein seen as key in Huntington's disease

Researchers have identified a protein made in the brain that may cause Huntington's disease, providing for the first time a possible treatment for the debilitating brain disorder, according to a new study.

The protein interacts strongly with a second protein called huntingtin produced by the gene for the disease, suggesting it plays a key role in the degeneration of nerve cells in the brain. It is the first protein ever found that chemically binds to the large huntingtin protein and it appears to selectively kill cells only in the brain.

Huntington's disease affects neurons in the basal ganglia, which control coordination, and in the cortex, the seat of thought, memory and perception. Patients typically have jerky, involuntary movements and progressive dementia.

In 1993, the gene for the disease was identified on chromosome 4, but its function and its target were a mystery. The gene's product, the large huntingtin protein, contains trinucleotide repeats of cytosine-adenine-guanine (CAG), the sequence for the amino acid glutamine. The normal gene codes for about 6 to 35 glutamines in the huntingtin protein, while the mutated gene increases the number to 38 to 100.

The gene's function is still not known, but the mutated huntingtin protein has been found early in development, said Marian DiFaglia, a researcher at Massachusetts General Hospital, who presented new evidence about the distribution of the protein in the brain. A research group at Johns Hopkins Medical School identified a protein, dubbed HAP-1, that bound tightly to the huntingtin protein and so far has only been found in the brain. The protein was found using a yeast two-hybrid system, which revealed that part of the huntingtin protein with the expanded CAG repeats interacted with HAP-1 from rat brains.

In studies of human lymphocytes, the protein bound more tightly to huntingtin protein from patients with the disease than from healthy individuals. Later, the group found a portion of the HAP-1 gene in humans, and showed that its protein also binds to huntingtin. The distribution and concentrations of HAP-1 in the brain is not known, and right now it is mere speculation how the protein could cause the death of brain cells.

DiFaglia's group is exploring how the expansion of CAG repeats affects the brain. They examined post-mortem

brain tissue from 11 adults and 11 children with the disease and from eight control patients using sensitive antisera directed to different regions of the huntingtin protein.

All of the Huntington's patients were heterozygotes. All of the patients who died of the disease had a normal huntingtin protein and an abnormally large protein containing 40 to 150 CAG repeats. The size of the mutant protein was directly proportional to the expanded number of repeat sequences; and children, who suffer the most severe symptoms of the disease, had the largest and most complex mutant proteins.

The mutant protein was found in all brain areas and at the same concentrations as the normal protein, regardless of the size of the CAG repeats.

In other research, Steven Hersch and co-workers at Emory University School of Medicine reported that the huntingtin protein was found in the cytoplasm of neurons and in dendrites using an immunogold antibody tracking assay. University of Strasbourg researchers reported that they found an antibody that selectively recognizes the polyglutamine regions in Huntington's and four other neurodegenerative diseases that are also associated with repeat CAG sequences. (Source: *McGraw Hill's Biotechnology Newswatch*, 20 November 1995)

Cystic fibrosis gene therapy results

The first double-blinded, randomized clinical trial using an adenoviral vector to correct the gene deficiency in cystic fibrosis (CF) patients "did not correct functional defects in nasal epithelium, and local inflammatory responses limited to the dose of adenovirus that could be administered to overcome the inefficiency of gene transfer" according to a report of a study in the 28 September issue of the *New England Journal of Medicine*.

Michael Knowles and Richard Boucher, both professors of medicine, and their colleagues at the University of North Carolina at Chapel Hill found "less than one per cent" of nasal epithelium cells were transfected at the highest doses of the adenoviral vector. No messenger RNA coding for adenoviral-vector CFTR (cystic fibrosis transmembrane conductance regulator) was detected at the lowest doses.

In their study, Knowles and Boucher administered four logarithmically increasing doses of a replication-defective adenovirus serotype 5 vector in a randomized, blinded fashion to the nasal epithelium of 12 CF patients. *In vitro* studies had shown transfection rates as high as 40 per cent, and he estimates a 10 per cent rate probably is needed *in vivo* for a therapeutic effect. Knowles attributes the poor showing in the clinical study to "the sophistication of the surface lining cells of the airways to prevent these adenoviruses from entering... Actually, it turns out that if you scrape off the surface cells, the basal cells that are right down below, which are the proliferative cells, are very receptive to the adenovirus."

Unblinded studies with virtually the same vector given intranasally to three patients by Michael Welsh of Howard Hughes Medical Institute at the University of Iowa had initially shown more positive results and no inflammation. But Ronald Crystal at Cornell University had run into inflammatory problems in unblinded studies of adenoviral vector administered directly to the lungs of three other patients, forcing a temporary halt to the experiments. Six other investigators have won approval from the National Institutes of Health's (NIH) Recombinant-DNA Advisory Committee (RAC) to conduct CF trials, but only two of them have actually treated any patients and neither has published any results.

The lack of positive results from the Knowles-Boucher CF trial fuels a growing disillusionment with gene therapy that has led to a review of the RAC's support of the experiments by an ad hoc committee. (Source: *McGraw Hill's Biotechnology Newswatch*, 2 October 1995)

Human milk kills tumour cells

Swedish scientists have found that a protein in human milk induces cancer cells to die, leaving other cells intact. This could lead to new anti-tumour treatments.

Human milk provides the breast-fed child with nutrients and a range of substances that protect it from respiratory and gastro-intestinal infections. But until now it was not known whether milk contains chemicals that act on cells.

Scientists from the University of Lund were studying how milk affected bacteria in human lung cancer cells when they were surprised to see that the milk killed the cells, but it left alone mature lining tissue cells and cells from solid organs.

On examining the milk, the researchers pinpointed the responsible protein as a form of human α-lactalbumin in the casein fraction of the milk, but only the dimer and trimer species produced the effect. Commercial baby milk and cow's milk also had no effect on the cancer cells.

Although α-lactalbumin is one of the most abundant proteins in human milk, its functions are not clear. The researchers believe that its job could be to restrict specific cell populations in the baby. They speculate that milk not only furnishes the baby with antimicrobial weapons but also polices the cell danger areas, such as cell linings and their defendants, white blood cells.

The key to the process is calcium; during programmed cell death, or apoptosis, Ca^{2+} levels increase rapidly. And α-lactalbumin was not able to trigger apoptosis under calcium-free conditions.

The body relies on apoptosis to eliminate unwanted cells without evoking an inflammatory response. "Since tumour cells are often resistant to normal apoptosis signals, our finding may be important to further elucidation of the pathways that lead to apoptosis in tumour cells" says the team. (Source: *Chemistry & Industry*, 21 August 1995)

Research on animal genes

Salmon soft roe DNA suppresses the proliferation of cells

Scientists in Japan have discovered that salmon soft roe deoxyribonucleic acid (DNA) displays a cheloid prevention effect, or suppresses the proliferation of cells.

In general, DNA is found in the nuclei of cells. Genetic engineering attempts to implant DNA with specific information into cells with the aim of introducing and manifesting specific functions into these cells. High molecular weight DNA retaining the double-strand structure is defined as native DNA.

The research project confirmed that native DNA outside the cells displays a fibroblast cell proliferation suppression effect. DNA outside the cell nucleus is an unstable water-soluble substance, when a calcium chloride aqueous solution is added into an aqueous solution consisting of a mixture of DNA and alginic acid, the DNA is gelled and immobilized. Producing a film of DNA-immobilizing alginic acid gel enables the DNA to be

released gradually to prolong the DNA effect, so applying this to surgical sutures prevents cheloids caused by the excessive proliferation of cells in the process of healing surgical wounds.

In experiments, DNA obtained from salmon soft roe disposed as waste in Hokkaido was added to a culture bed and the proliferation of epithelial cells derived from human dermis and fibroblast was observed. About three hours are required for the commencement of proliferation in an ordinary culture bed, but when DNA is added, the proliferation starts only after about six hours, indicating that fibroblast proliferation is suppressed by about 40 per cent.

For easier handling, the mixed aqueous solution consisting of DNA and alginic acid was gelled and dehydrated to prepare an immobilization film. Culturing with this film showed that the cell proliferation suppression effect is increased, since the DNA is released gradually in the culture bed and decomposition is slowed.

This film only suppresses cell proliferation and does not kill cells. Since alginic acid DNA displays the biodegradation effect, it is usable as a functional polymer for producing biological materials. The research team plans to commercialize salmon soft roe DNA for use as a substance to prevent cheloids caused by the excessive proliferation of fibroblasts. Further details from: Graduate School of Environmental Earth Science, Hokkaido University, Nishi 5 chome, Kita 10 jo, Kita-ku, Sapporo City, Hokkaido 060. Tel.: +81-11-706-2256, Fax: +81-11-747-9780. (Source: *JETRO*, September 1995)

Scientists' work may hasten marketing of transgenic fish

Scientists at the ARS Catfish Genetics Research Unit (Stoneville, Massachussetts) have developed female fish with a male sex genotype. These females produce male and female gynogenetic offspring, thus permitting cross-breeding to occur within and among gynogenetic lines.

As the nascent aquaculture industry proves its economic viability, producing $32.5 billion worth of products world-wide in 1993, researchers are finding ways to improve fish germplasm to make fish farming easier and more profitable. Aquaculture specialists recently discussed these techniques in detail at the annual meeting of the American Association for the Advancement of Science, in Atlanta.

Hormonal manipulations depend on the surprisingly flexible system of sex determination in most fish. After hatching, a male fingerling exposed to oestrogen will become female in appearance, while remaining genetically male. That pseudofemale can even lay eggs that produce viable offspring, despite the pseudofemale's male chromosomes. Female fingerlings can be sex-reversed in the same way through exposure to testosterone, becoming reproductively viable pseudomales.

Scientists can take advantage of that to fulfil one goal of fish farmers: to hatch out all-male groups of fingerlings. Males generally grow faster than females, and single-sex ponds mean that a second generation of fingerlings, or "recruits", is not produced when the stocked fish become sexually mature. Recruits are undesirable because they eat some of the food but will not reach a marketable size by harvest time.

After a series of manipulations, researchers can come up with parent stock that will produce only male fingerlings. While those manipulations involve both genetics and hormones, the male fish that are finally produced are themselves genetically normal and have not been exposed to hormones. These fish should face no regulatory hurdles in getting to market.

The method for producing sexually homogeneous fish was described by Graham C. Mair, Ph.D., at the AAAS meeting. He and his colleagues at the University of Swansea in Wales and at Central Luzon State University in the Phillipines have worked out the procedure for tilapia, a tropical fish that dominates Asian aquaculture. A similar system is being developed for channel catfish by Cheryl A. Goudie, Ph.D. at the Agricultural Research Service's Catfish Genetics Research Unit (Stoneville, MS).

These "homogeneous" populations of males and females are not absolutely pure. In fish, XX and XY chromosomes do not tell the whole story when it comes to sexual differentiation. Other genes and environmental factors can also play a role. But the populations are more than 95 per cent homogeneous; Dr. Mair said researchers were aiming to get that percentage above 99 per cent.

Dr. Mair said that when tilapia XY males were tested by fish farmers in the Phillipines under normal management conditions, the farmers' net return increased by 100 per cent.

"The method is environmentally friendly, and the fish that are eaten are not exposed to hormones", Dr. Mair said. "The method can help get fish up to export size, usually 500 grams or more". (Extracted from *Genetic Engineering News*, 15 May 1995)

Laboratory-grown islet cells reverse insulin-dependent diabetes in mice

University of Florida (Gainesville) scientists have grown insulin-producing tissue generated from individual cells and demonstrated that diabetes can be reversed in mice when this tissue is implanted in them. The tissue was cultured in liquid growth media developed from immature cells isolated from the pancreas of pre-diabetic mice.

The scientists unexpectedly discovered that new pancreatic tissue formed just outside the kidney at the site where the laboratory-grown islet-like structures were surgically implanted. Within this pseudo-pancreas, new islet-like structures developed with a normal blood vessel network, suggesting the tissue was assuming a function in the mice.

Immunologist Ammon Peck said they were first surprised to discover the growth of new pancreatic tissue and to find that islets of Langerhans grew within this tissue, and were surprised again to find that the tissue grown in culture and implanted in the mice was not invaded by T-lymphocytes, which are implicated as the major killers of insulin-producing cells. (Source: *Genetic Engineering News*, July 1995)

Research on plant genes

Fungal resistance in transgenic carrots

Dutch biotechnology company Mogen has developed transgenic carrot plants with a high level of resistance to the fungus known as powdery mildew. Resistance has also been demonstrated in the same variety for three other fungi.

Mogen scientists genetically engineered the carrot plants to permanently express anti-fungal genes isolated from tobacco plants. The results are considered particularly significant as the transgenic varieties show broad spectrum fungal resistance, a feature that is very difficult to achieve with conventional breeding methods.

According to Mogen, crop losses attributable to fungal diseases world-wide are estimated at US$40 billion annually. European sales of fungicides exceed $6 billion annually.

Contact: Arie L. Breure, Managing Director, Mogen International nv, Einsteinweg 97, 2333CB Leiden, The Netherlands. Tel.: 31 (71) 525 8282, Fax: 31 (71) 522 1471. (Source: *The AgBiotech Bulletin*, February 1996)

Genetic resistance in rice

Researchers have succeeded in genetically engineering resistance to leaf blight in rice, a major disease in African and Asian rice crops. This is the first successful effort to achieve built-in disease resistance through genetic engineering in the world's most important food source.

Researchers first discovered a gene that immunizes a wild African variety against the blight, and then transferred it to a crop variety. Field testing will begin this year in the United States, followed by tests in the Phillipines and China next year. (Source: *The AgBiotech Bulletin*, February 1996)

Fireflies light up food bacteria

University of Guelph (Ontario, Canada) researcher Mansel Griffiths has determined that the lux gene, the gene that causes fireflies to glow, can be used in the detection of food-borne pathogens.

The process involves cloning the lux gene into host-specific *bacteriophage* (viruses specific for bacteria). When the phage infect host cells in the pathogenic food bacteria, luminescence is also transferred. The luminescence is detectable with specialized equipment, and can be used as an indicator of the presence of food-borne pathogens.

Patents are currently out on applications of this process to food diagnostics, and commercialization is anticipated in the near future. *Contact: Mansel Griffiths, Food Sciences, University of Guelph. Tel.: (519) 767-5036, ex. 2269* (Source: *The AgBiotech Bulletin*, February 1996)

Research on viral genes

Stanford research findings may change views on AIDS

Stanford (California) University Medical Centre scientists have uncovered drastic shortages of naive T-cells among people infected with HIV. The investigators say their findings could fundamentally change scientists' understanding of how HIV infection progresses and may prompt a rethinking of some proposed treatment strategies based on current dogma.

The researchers measured naive T-cells in blood samples from 346 people. The two new studies, one in children and the other in adults, are the first to link HIV infection with a drop in naive T-cells, according to the team. The reduction showed up in naive versions of both CD4 and CD8 cells.

Until now, scientists had not seen any CD8 killer cell reduction contributing to HIV disease, the researchers noted. The discovery suggests that, contrary to previous assumptions, "AIDS is not a disease primarily of the loss of CD4 helper cells. Instead the disease attacks naive T-cells of all types. Therefore, even CD8 killer cell function is severely compromised", said lead investigator Mario Roederer, an immunologist working with Stanford genetics professors Leonard and Leonore A. Herzenberg.

The researchers found that an infected person's supply of naive T-cells begins to dwindle even before outward signs of illness emerge. By the time a person develops advanced AIDS, naive T-cells have fallen to one-tenth the level seen in healthy individuals. Whereas naive cells represent about 50 per cent of all T-cells in healthy adults, they make up less than 10 per cent in adults with advanced AIDS, Roederer and his co-workers found. A study of HIV-infected children showed a similar loss in naive T-cells. The finding could explain why the immune systems of people with HIV disease cannot keep up with the ever-changing virus and why these patients fall prey to opportunistic infections. It might also explain why some patients with high CD4 counts none the less succumb to disease and, conversely, why some people with low CD4 counts survive for long periods of time.

The results also raise doubts about several treatment strategies currently under study. Many AIDS strategies being developed today, including therapeutic vaccines and some forms of gene therapy, would require the activity of naive T-cells. Such approaches—based on earlier studies indicating that naive T-cells remain stable with the progression of HIV disease—are almost "doomed to failure" in patients whose naive cell counts are actually quite low.

A novel treatment approach would be to find ways to replenish the supply of naive cells. (Source: *Genetic Engineering News*, 15 May 1995)

Research on bacterial genes

Three bacteria chosen for sequencing

The US Department of Energy (DoE) is to provide funding for the sequencing of three bacterial genomes, bringing its total to eight. The DoE chose the three from 15 other contenders and will confirm its selection later. The three microbes were chosen because they were the most likely to produce information useful to industry, medicine and science. Two of the probable selections, *Archaeoglobus fulgidus* and *Thermotoga maritima*, are thermophiles and live at temperatures in excess of 100°C. The DoE, the Department of Defense and the private sector are all looking for stable enzymes to decontaminate high-temperature salty toxic wastes. Heat tolerant enzymes might also convert process wastes to commodities or fine chemicals. Various enzymes from thermophiles might also improve high-temperature industrial processes. *T. maritima* produces xylanase which is used in paper bleaching, and a glucose isomerase from *A. fulgidus* might increase the efficiency of fructose production from glucose by reducing the process from two steps to one.

Craig Venter, director of the Institute for Genomic Research in Gaithersburg, Maryland, plans to sequence *A. fulgidus*. Robert Weiss of the University of Utah Medical Centre hopes to study *T. maritima*.

Several strains of the marine cyanobacterium *Synechococcus* are under consideration as the third selection. They produce haloperoxidases that are potentially valuable in chemical commodity industries such as benzene manufacture because they operate at higher concentrations of hydrogen peroxide than the commonly used enzyme hydrogen peroxidase. They are also found in medical diagnostic kits that use enzyme assays to test for infection such as HIV.

Synechococcus is also a crucial cog in global ecology. The microbe accounts for 10-30 per cent of oxygen

production in the oceans, says Douglas Smith of Genome Therapeutics Corporation, who plans to sequence it.

In addition to funding the three sequences, the DoE plans to broker funding for sequencing *Pseudomonas originosa*, which will be more expensive as it has a larger genome.

The National Institutes of Health are concerned because *P. originosa* is a scourge of hospitals, infecting patients and resisting all known antibiotics. As it also infects animals and plants, the Department of Agriculture might offer support. The microbe degrades aromatic and long chain aliphatic compounds, and thrives in the presence of heavy metals, which should attract the Environmental Protection Agency, the DoE and the National Science Foundation. Some funds may also come from the private sector. (Source: *Chemistry & Industry*, 16 October 1995)

Hitch hiking germs made safe

New treatments for meningitis and pneumonia may arise from research by scientists at New York's Rockefeller University. The team of scientists thinks it has found a way to interrupt the sequence of events needed for pneumonia-causing bacteria to invade cells.

The *Streptococcuspneumoniae* bacterium causessepsis and meningitis, as well as pneumonia, says the team. The bacteria sit on the surfaces of the cells that line the nose and throat. In about 40 per cent of people they cause no ill effects. But when the cells become inflamed, the bacteria enter with devastating results.

The Rockefeller researchers have found that the bacteria hitch hike on the body's own defence mechanism to get inside the cells. The immune system releases compounds known as cytokines in response to any infection or injury, inducing inflammation. The cytokines "activate" the cells so that several proteins appear on their surface. These act as further stimulants to the immune system, the team explains.

One of these proteins, known as the platelet-activating factor (PAF) receptor, instantly retreats inside the cell when anything binds onto it. Unfortunately for the body, the pneumonia bacterium has the same binding sites as PAF. The team has found that as soon as the cell is activated and the PAF receptor appears, the bacterium takes it and is ferried inside the cell, where it can wreak havoc.

But the process can be stopped by treating the cells with PAF receptor antagonists, which attach themselves to the protein even faster than the bacterium and prevent it from binding, says the team. The researchers used two commercially-available PAF receptor antagonists, explains researcher Diana Cundell; both stopped 90 per cent of the bacteria from invading the cells. This suggests that pneumonia and sepsis could be treated with PAF receptor antagonists, Cundell comments.

The researchers are about to start developing drugs based on PAF-receptor antagonists, and are in discussion with several pharmaceutical companies. Because the bacterium is implicated in so many diseases, it is hoped that this treatment could have widespread applications. (Source: *Chemistry & Industry*, 16 October 1995)

Bio-engineered bacteria breaks down trichloroethylene

Professor Kensuke Furukawa's research group at Kyushu University has used genetic engineering to develop a bacteria that can quickly decompose trichloroethylene, a soil pollutant. If trichloroethylene is present in a concentration of 10 parts per million (PPM), the bacteria can completely degrade the soil pollutant in just five hours—a world record. Since the bio-engineered bacteria can also decompose polychlorinated biphenyl (PCB), naphthalene, and other hard-to-treat pollutants, it is a promising candidate for bioremediation, or biological repair of environmental pollution.

Professor Furukawa noticed that the enzyme which decomposes the hard-to-treat substance is composed of a combination of four protein parts. As a result of his studies, he discovered a highly active composite enzyme made of a portion of the enzyme that carries oxygen to toluene and a portion of another enzyme that carries oxygen to biphenyl.

Next he isolated the gene of the "protein parts" and created an artificially connected hybrid gene which he inserted into the bacteria called *Pseudomonas aeruginous.* Before the insertion, the gene of the similar enzyme was eliminated. Therefore, the inserted artificial gene was stabilized in the bacteria.

It was confirmed that many hard-to-decompose molecules, including trichloroethylene, toluene and biphenyl, were quickly decomposed by the new bacteria. Especially noteworthy was the new bacteria's ability to decompose trichloroethylene more rapidly than the current world record holding bacteria.

Trichloroethylene is used by the semiconductor industry as a substitute for chloroflurocarbon-based cleaning agents. However, the substance is a carcinogen which builds up in soil and around high-technology parks, creating problems.

Bioremediation technology entails placing high-performance bacteria that treat a pollutant as a food source in soil so that growth of the bacteria decomposes the pollutant. Since it is a cheap means of treating contaminated soil, the new technology has received considerable attention in many countries, including the United States. The latest achievement by Kysushu University may further stimulate research into designing bacteria for bioremediation. (Source: *Nikkei Sangyo Shimbun*, 9 August 1995)

Research instrumentation

Dual enzyme process

The Dual Enzyme Process is a novel and inexpensive method for the accurate and speedy detection of DNA mutations.

Accurate detection of specific DNA mutations is an essential requirement for the ever-expanding market for diagnostic tools in molecular research. Existing mutation detection methodologies are often cumbersome, non-specific, poorly adaptable to automation and both difficult to use and to optimize. At BioResearch Ireland, a novel solution to the limitations of these technologies has been developed—the "Dual Enzyme Process". Both easy to use and optimize, this method affords accurate detection of a range of DNA mutations at specific gene locations, including point mutations, deletions, insertions and re-arrangements. This method is extremely versatile and has a wide range of applications which include human, animal, bacterial and viral gene diagnosis, PCR product verification and DNA typing, to name but a few. It also has the advantage of being easily adaptable to automation particularly with automated fluorescent fragment analysers.

BioResearch Ireland is seeking strategic partners, with or without automation capabilities, through collaborative licensing agreements for the commercial exploitation of this technology. Contact: Sinéad Canning, BioResearch Ireland, Forbairt, Glasnevin, Dublin 9, Republic of Ireland. Tel.: 353 1 837 0177, Fax: 353 1 837 0176. (Source: *BioResearch Ireland News Release*, 17 October 1995.)

A cloned $5HT_{5A}$ receptor available for use in drug-screening programmes

A cloned receptor for use in assessing the effects of compounds on the nervous system is available from BioResearch Ireland (BRI). This receptor is designed for use in research on neuro-receptors of commercial and therapeutic interest. Such receptors are now commonly used in programmes to screen compounds which have neuro-active drug potential.

The $5HT_{5A}$ receptor cDNA clone available from BRI is for a human receptor belonging to the G-protein coupled 7-transmembrane receptor superfamily. It was developed by the Receptor Cloning Unit in the National Agricultural and Veterinary Biotechnology Centre, one of the five research centres operated by BioResearch Ireland.

The receptor has been cloned into two plasmids for use as follows:

- pBS-h5HTR$_{5A}$: For use in generating an anti-sense probe for Northern blot analysis; RNase protection analysis; or *in situ* hybridization.
- pBK-CMV-h5HTR$_{5A}$: For use in expression studies. This plasmid, containing the clone can be transfected into a suitable cell line (e.g. HEK 293 cells) within which both transient and stable expression of the receptor can be achieved. It is provided in pBluescript SK II + or PBK-CMV and can be released from both plasmids using the restriction enzymes *Cla I* and *Kpn I*.

For further details contact: Phil O'Leary, BioResearch Ireland, Forbairt, Glasnevin, Dublin 9, Ireland. Tel: +353 1 837 0177, Fax: +353 1 837 0176. (Source: *BioResearch Ireland News Release*, 12 October 1995)

Glucagon-like peptide 1 (GLP-1)

It is 12 years since the mammalian preproglucagon molecule was identified, but much research has recently been generated by the realization that GLP-1 is one of the most powerful incretins known.

Proglucagon is differentially processed according to the cell type in which it is expressed. Various molecular forms of GLP-1 have been identified, but GLP-1 [7-36] amide remains as the most powerful incretin candidate. GLP-1 [7-36] amide and GLP-1 [7-37] are the predominant molecular forms detected in the ileal mucosa and both forms have been proposed as potential therapeutic hypoglycaemic agents in cases of non-insulin dependent diabetes mellitus.

Affiniti's Ace1L™ range includes fully characterized antibodies to glucagon, GLP-1 [1-36] amide, GLP-1 [7-36] amide, GLP-2 and glucose-dependent insulinotropic peptide (GIP) which are suitable for use in radioimmunoassay and immunohistochemistry. The cognate peptides are also available.

Each antibody is supplied with a data sheet which details its application and specificity. A leaflet detailing the Ace1L™ range is now available from Affiniti in Exeter. (Source: *Affiniti Press Release*, 8 August 1995)

New kit for immunolocalization studies—the One Kit

Affiniti Research Products Ltd. (Exeter, UK) is now offering an innovative immunochemical detection system known as THE ONE KIT, produced by Sternberger Monoclonals, Inc. (Baltimore, MD, USA). THE ONE KIT offers the convenience of prediluted stable immunoperoxidase reagents for the detection of rabbit, rat and mouse antibodies with unsurpassed staining intensity and almost non-existent "background" effects. Sternberger Monoclonals claim that the use of this "quality-select", high activity peroxidase-antiperoxidase kit results in stronger staining, higher sensitivity and lower background than avidin-biotin, and avoids the non-specific staining frequently observed in CNS tissue with stretavidin. Whether working with rabbit polyclonal antisera, or mouse monoclonals, only THE ONE KIT is needed.

More details are available from Affiniti Research Products Ltd., Mamhead Castle, Mamhead, Exeter, EX6 8HD, UK. Tel.: +44/0 1626 891010, Fax: +44/0 1626 891090, E-mail: (Compuserve) 100337, 1606). (Source: *Press Release*, 21 August 1995)

General

RNA, long seen as genetic errand boy, catching eye of drug designers

Drug designers are beginning to take a closer look at ribonucleic acid, long neglected as the errand boy of its renowned parent, as a target in the fight against cancer and AIDS.

Although the work is only just beginning, the researchers believe that RNA may be a better therapeutic target than DNA because it is more accessible and easily damaged.

Most of the anti-cancer agents now available work by damaging DNA. However, a team at the University of Virginia has recently discovered that bleomycin, which cuts DNA in half, also cleaves all three forms of RNA—transfer, messenger and ribosomal.

The finding is said to open up a whole new avenue for developing new therapeutics because bleomycin's potency is limited by the fact that it must pass through the cellular and nuclear membranes of cancer cells. But if an agent could be developed that only had to pass through the cellular membrane to destroy RNA, it should effectively lead to cell death.

In AIDS research, RNA is also proving to be a tempting target for drug designers. A group led by Anthony Czarnik at Parke-Davis, a subsidiary of Warner-Lambert Co., is studying how to inhibit protein-RNA interactions needed for the replication of HIV in cells.

His group is focusing on transactivation-activation responsive RNA, or TAR, a nucleotide sequence that sits at the 5' end of the HIV-messenger RNA molecule. The TAT protein, which is generated in an earlier part of HIV's life cycle in cells, binds to the 5' end of the molecule, and facilitates the synthesis of full-length HIV RNA.

"If a way could be found to inhibit the binding of the TAT protein, it should dramatically decrease the replication of the HIV virus inside the body", said Czarnik.

Czarnik has reported that his group has now found a class of molecules that "definitely" inhibits the TAT-TAR interaction. They used as a model 31-nucleotide-long pieces of TAR RNA from the larger messenger RNA that

gradually ends up being incorporated into new HIV particles. The RNA pieces are "completely non-infectious", and are bound tightly to the TAT protein, said Czarnik. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 2 October 1995)

Test boosts ageing research

Researchers in California have developed a test to detect cells that may be involved in ageing and cancer.

All normal body cells (but not reproductive or germ cells) pass into an irreversible stage called senescence when they stop growing. Senescent cells are still metabolically active although they change their function. This process is thought to be an underlying cause of ageing and a tumour-suppressing mechanism.

The new technique provides the first evidence that senescent cells exist in living organisms, says team leader Judy Campisi of the Lawrence Berkeley National Laboratory; until now, research has been limited to test tubes. It is also the first time that it has been shown that these cells accumulate with age.

Campisi's team noticed that some senescent cells produce an unusual form of an enzyme called beta-galactosidase; the reason for producing this enzyme is unknown. Younger cells either produce very little or none of this enzyme. The test uses a blue stain to detect the presence of the enzyme; senescent cells turn blue.

Two skin cell types, fibroblasts and keratynocytes, express the enzyme when senescent. Campisi believes that senescent fibroblasts could explain why old skin is thin and contains less collagen. When fibroblasts become senescent, they start producing excessive amounts of the enzyme that degrades collagen.

The new technique should allow scientists to screen for senescence inducing and delaying compounds which may have anti-tumour or anti-ageing properties. It should also help identify genes able to stop cancer cells replicating and isolate genes that trigger premature ageing syndromes. (Source: *Chemistry & Industry*, 2 October 1995)

Defining the role of leukaemia-specific proteins

A project funded by the EU Biotechnology Programme is studying the role of several proteins implicated in the development of leukaemia. These leukaemia-specific proteins are PML, PML/RARα and RARα.

This work was initiated after the researchers discovered that the PML and RARα genes were the chromosome break-points involved in the development of a leukaemia called acute promyelocytic leukaemia (APL). This leukaemia involves a specific chromosome translocation which results in the formation of PML/RARα, a leukaemia-specific protein.

The main aim of this research project is to define the role that the above proteins play in the myeloid differentiation process, i.e. the path that myeloid cells take when differentiating from bone marrow cells to granular leucocytes and finally into specific white cells.

This work also yields an insight as to how genetic defects in the differentiation programme of myeloid lineage cells can contribute to the development of leukaemia.

Major achievements include the identification of several PML/RARα target genes and a PML binding protein. The expression of PML/RARα into haemopoietic precursor cell lines and the definition of its effect on differentiation and survival was also achieved.

From a commercial point of view, a number of cellular and molecular reagents have been developed through this work and will be available to European laboratories once the project is completed. These molecular tools have development potential as diagnostic kits for the diagnosis of acute promyelocytic leukaemia. In addition the knowledge gained on the differentiation of normal and neoplastic myeloid cells will serve to further this research area.

For further information contact: Phil O'Leary, BioResearch Ireland, Forbairt, Glasnevin, Dublin 9, Ireland, Tel.: +353 1 8370177, Fax: +353 1 837 0176. (Source: *BioResearch Ireland News Release*, 19 December 1995)

Curing clots

There is a paradox about the enzyme thrombin: it can both cause and prevent blood clots. Researchers at Gilead Sciences, a Californian biotechnology firm, have now found how to turn off the protein's clot-forming properties, transforming it into a prospective anti-clotting agent.

Thrombin's double life results from its ability to bind to many different proteins. At an injury site, it activates clotting factors and platelets, and converts fibrinogen to fibrin, the insoluble fibre that forms the scaffold for clots.

But it can also bind to a protein called thrombomodulin, found on the lining of blood vessels. This activates a protein-cleaving enzyme known as "protein C", a very powerful anticoagulant. Normally, these two processes operate simultaneously, with the anticoagulant properties slightly more powerful than those associated with clotting.

The Gilead team has traced thrombin's clot-promoting properties to one small section of amino acids. Swapping the glutamic acid residue at position 229 in the protein chain for an alanine drastically weakens thrombin's ability to bind fibrinogen, but does not alter its affinity for thrombomodulin, they claim. This makes thrombin 22 times more powerful as an anticoagulant than as a clot-former. In animal trials, the team reported that the modified protein causes reversible anticoagulation with no sign of clotting.

Moreover, the protein did not increase the bleeding times of wounds which means that, unlike other anti-coagulants, it cannot trigger such problems as strokes. The transformed thrombin could therefore be a very useful new anticoagulant, the researchers conclude. (Source: *Chemistry & Industry*, 4 December 1995)

Antifungal compounds

A commonly used antifungal and antimicrobial agent causes DNA damage when exposed to light, according to a team of German chemists. The team says their findings cast doubt on the safety preparations containing *Omadine*, such as dandruff shampoos. But its damaging properties could also lead to new anti-cancer drugs.

Scientists have known for several years that *Omadine* (*N*-hydroxypyridine-2-thione) releases hydroxyl radicals when irradiated with light. Waldemar Adam and his team at the University of Würzburg thought that the properties of the antifungal compounds could come from these light-generated hydroxyl radicals. They claim to be the first to demonstrate the thiones' direct effect on DNA.

Adam's work shows that *N*-hydroxypyridine-2-thione and its isomer, the 4-thione, modifies the bases in DNA strands by oxidising guanine—they can cut DNA strands in two. The team has yet to publish results of *in vitro* studies which show that the compounds kill mouse and Chinese hamster cells on exposure to light.

Omadine is used in antidandruff shampoos, detergents and toothpaste. (Extracted from *Chemistry & Industry*, 4 December 1995)

Algae used to make EPA

A group at Tokyo University has succeeded in genetically engineering blue algae to manufacture eicosapentaenoic acid (EPA), a fatty acid normally extracted from fish.

Eicosapentaenoic acid is produced by a bacterium living in fish intestines. It is made from relatively simple starting materials, but the process involves a complicated series of chemical reactions. Because laboratory synthesis of EPA is difficult, the material is currently obtained by extraction from such fish as sardines and mackerel.

The researchers first isolated the entire set of genes that code for the enzymes which control production of EPA in bacteria. This gene group was then introduced into algae.

Following these DNA blueprints, the algae produced the enzymes which then choreographed the synthesis of EPA down a multi-step chemical pathway. (Source: *Manufacturing Chemist*, January 1996)

E. APPLICATIONS

Pharmaceutical and medical applications

Medicinal tobacco?

Researchers at Crop Tech Development Corp. in Blacksburg, Virginia have designed a transgenic tobacco plant to express a human enzyme that is useful in the treatment of Gaucher's disease.

Current treatment of the rare genetic disorder involves the use of a drug derived from human placentas. However, thousands of placentas are required to yield sufficient amounts of the drug to treat one patient, making treatment extremely costly.

It is estimated that several years' research are required before the drug produced from the plant will be ready for human trials. (Source: *The AgBiotech Bulletin*, January 1996)

Osteoporosis drugs raise hopes for making bone ailment "thing of the past"

New drugs for osteoporosis—some slowing bone loss and others building bone—will be reaching the market over the next few years and researchers are optimistic they will be able to cut the incidence of the disease dramatically.

Currently, more than one woman in three over the age of 50 suffers osteoporotic fractures caused by weakened bone. Men also suffer from osteoporosis, but in fewer numbers and with a later onset.

The body remodels bone continually, tearing it down and rebuilding, much as the skin is continually made and sloughed off. Like the skin, bone grows thinner with age as the rebuilding process loses ground. Key players in the cycle are bone-destroying cells, called osteolclasts, and bone-building cells, or osteoblasts.

The main approach has been to tackle "expenses"—preventing bone resorption, or breakdown.

Oestrogen and oestrogen-like molecules are perhaps prototypical. In the absence of oestrogen—after menopause, for example—bone resorption gains the upper hand. The obvious solution is to replace the missing hormone. The problem is that oestrogen replacement has side-effects that make it very unpopular with women—headaches, bloating, breast engorgement and, of course, the continuation or resumption of the menstrual cycle. Oestrogen has also been linked to some forms of breast cancer.

Until a few years ago, hormone replacement was almost the only treatment option available to physicians. (The hormone calcitonin is approved for osteoporosis and does increase bone mass, but it must be given by injection, which is unpopular, and its effectiveness appears to diminish over time.)

But a range of new drugs—the aminobisphosphonates or just biphosphonates—is now reaching the market and their promise is exciting.

"The advantage of the bisphosphonates is that they are entirely specific to bone, while other drugs act on every tissue", says Marc Grynpas, a biophysicist at the University of Toronto who is studying the long-term effects of the drugs on bone strength and on body chemistry.

On the other hand, Grynpas says, a drawback of bisphosphonates is that they are not particularly well-absorbed by the body. The skeleton gets perhaps 40 to 50 per cent of injected bisphosphonates and only about half a per cent of oral formulations.

The bisphosphonates are not the only anti-resorptive approach. Eli Lilly Co., of Indianapolis, is in Phase III trials on raloxifene, which was initially developed as an anti-cancer agent. It is one of a group of compounds known as selected oestrogen receptor modulators—they target different receptors differently.

Raloxifene appears to block only gender-specific oestrogen receptors—those found in the uterus and breast—while actually boosting non-specific receptors. The result appears to be an oestrogen-like inhibition of bone resorption, without the side-effects of oestrogen itself.

Meanwhile, Toronto's Allelix Biopharmaceuticals is in the last stages of a year-long search for an industrial partner for Phase III trials of its recombinant parathyroid hormone (rPTH). A spokesman said a deal is likely to be announced in the first two weeks of 1996.

The drug—Allelix calls it ALX1-11—has been in Phase II trials at 18 centres across Canada and the US and so far data show it can add "significant amounts of new bone in osteoporotic patients". (Extracted from *McGraw Hill's Biotechnology Newswatch*, 1 January 1996)

Liver cancer reduced through IFN treatment

The onset of liver cancer appears to be reduced by more than one third through interferon (IFN) treatment of hepatitis, according to Masao Omata, Professor of Internal Medicine II, Faculty of Medicine, University of Tokyo. He stressed the necessity of treatment aimed at eradication of hepatocellular carcinoma from the hepatitis treatment stage. Omata said that at present hepatocellular carcinoma develops in 83 per cent of patients with hepatitis C and 11 per cent of those with hepatitis B.

Based on comparative data between patients with hepatitis treated or not treated with IFN, hepatocellular carcinoma occurs in 2,200 patients per 100,000 of the population in the untreated group. But in the treated group, this figure is reduced to 600 patients. This indicates that IFN treatment of hepatitis inhibits the onset of the cancer.

The five-year survival rate for 500 patients treated for hepatocellular carcinoma over the past three and a half years was 35 per cent. (Source: *McGraw Hill's Biotechnology Newswatch*, 1 January 1996)

Hepatitis B vaccine

The Pasteur Merieux-Merck Sharp & Dohme joint venture expects to launch its recombinant hepatitis B vaccine, *HB Vax-DNA*, in France by the end of the year. Developed by Merck, the drug will be used in school vaccinations in the country in 1996, in a programme dominated so far by SmithKline Beecham's *Engerix. HB Vax-DNA* is the second vaccine to be brought to the market by the joint venture. The first was a measles-mumps-rubella-chicken pox combination. To follow are two vaccines for hepatitis A in 1996, and a vaccine for diphtheria-tetanus-acellular whooping cough and polio. (Source: *European Chemical News*, 27 November-3 December 1995)

Lung cancer vaccine breakthrough

Researchers at Israel's Weizmann Institute of Science have discovered an experimental vaccine that has

demonstrated the ability to protect mice against a form of lung cancer and helped prevent tumour spread in cancer-bearing animal models.

The researchers, led by Gideon Berke of the Institute's Department of Immunology, focused on a tumour-specific antigenic peptide of a particular mouse tumour—Lewis carcinoma—a small fragment of which was isolated and reproduced. They then vaccinated the mice with the peptide and exposed them to cancer cells. Tumours did not develop in the mice exposed to cancer cells, while those with tumours did not suffer a spread or relapse after surgery when vaccinated.

While unlikely to act as a total cure for human cancer, the vaccine could be useful as an adjuvant therapy following surgery or possibly in conjunction with cytokines, interferons or biologically active modifiers. It could also be effective as a prophylactic measure in high-risk families. (Source: *Biotechnology Business News*, 22 November 1995)

Contraceptive vaccine shows promise in controlling cancer

A contraceptive vaccine that shows promise as a way to control an exploding global population may also hold the key to checking the world's cancer epidemic, according to some scientists. But research that can prove whether the vaccine will ultimately work has stalled because of a lack of funding. The vaccine targets human chorionic gonadotrophin (hCG) beta, a hormone that normally has the life-affirming responsibility of protecting a developing foetus from attack by the mother's immune system.

It has been known for years that this hormone, like other substances involved in reproduction, is also produced by tumours. Some scientists hypothesize that it may serve a similar function by protecting a growing tumour from immune attack.

Vaccines targeting this hormone are under investigation by the World Health Organization as a potential method of contraception, initially in the third world. Scientists at Ohio State University have also experimented with the vaccine—which consists of peptide unique to hCG grafted to diphtheria toxoid—in a Phase I study of 23 patients, and had results that were promising enough to earn US Food and Drug Administration (FDA) approval to begin Phase II.

In the Phase I study, scientists observed some very promising events, including antibody production and some tumour responses, including a complete response in one patient with advanced colorectal cancer that had metastasized to the liver, said Vernon Stevens, the director of the division of reproductive biology at Ohio State University in Columbus. Stevens invented the contraceptive vaccine and Ohio State holds patents on the technology which is designed to prompt a human body to reject something it normally would not, said Stevens. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 20 November 1995)

Hyaluronic acid and cancer

Hyal Pharmaceutical Corporation in Canada announced during 1995 that there is strong evidence that hyaluronic acid can prevent a cancer-causing gene from creating tumours.

Hyaluronic acid can prevent the *ras* gene from mutating and starting the generation of tumours, according to Dr. Eva Turley, researcher at the Manitoba Institute of Biology.

Clinical trials with hyaluronic acid are being conducted in the USA and Canada, and are being planned for Australia. (Source: *Australasian Biotechnology*, Vol. 5, No. 6, December 1995)

ATP inhaler could bring cystic fibrosis relief

New insight into how a malfunctioning gene causes cystic fibrosis could lead to an ingenious treatment for the disease, according to US researchers.

Cystic fibrosis sufferers are missing a gene known as CFTR, which controls the formation of a chloride ion channel in the cells lining the lungs and airways.

Using cultured human cells, the team of the medical school at Johns Hopkins University in Baltimore has found that the protein that CFTR encodes excretes a small amount of adenosine triphosphate (ATP), the energy source of cells. Outside the cell, ATP behaves like a hormone, binding to a receptor on the cell surface where it triggers the opening of the second chloride channel. The channel stays shut if there is no ATP. It also controls the sodium channel, although the mechanism of this is not known.

Topping up ATP levels in CF sufferers using an aerosol inhaler could treat the symptoms of the disease. This would activate the second chloride channel and the sodium channel, which would restore the passage of some fluid into the cell linings to thin down the thick mucus; the first chloride channel would still be missing.

However, patients could still end up with infections and inflammation because CFTR appears to control the composition of sugars on the surface of the airway lining. In healthy people, these sugars bar most infections, but in CF they provide very little protection. Researchers are testing to see if this process could also be mediated by ATP.

Genetic therapy techniques aim to implant working copies of CFTR into CF patients. But researchers have not yet found a suitable vehicle to carry CFTR into the airway cells. (Source: *Chemistry & Industry*, 16 October 1995)

New antibodies determine resistant tumour cells in cancer patients

A series of three antibodies for the detection of cancer cells resistant to anti-cancer drugs have been licensed for sale to international distributors. The antibodies are used to identify human tumour cells that do not respond to common chemotherapy drugs. The antibodies were developed at BioResearch Ireland's National Cell and Tissue Culture Centre based in Dublin City University. Certain tumours exhibit resistance to a range of anti-cancer drugs. In treatment of cancer patients, it is important to determine such resistance before the appropriate chemotherapy treatment is chosen. The products are also used by researchers involved in the development of cancer treatments.

The BioResearch Ireland products have been licensed for sale to two international companies specializing in products for this market: Kamiya BioMedical Company, California, USA, and Dainippon Pharmaceuticals Ltd., Osaka, Japan.

Resistance of tumour cells to anti-cancer drug-treatment (i.e. chemotherapy) is a major problem for clinicians. About 50 per cent of patients can be cured by surgery and radiation therapy if their tumours have not spread. Of the remaining 50 per cent, about 10 per cent are curable with chemotherapy. However, the majority of metastatic cancers are not currently curable by chemotherapy or any other kind of therapy.

There are two categories of such cancers: cancers which show no significant response to chemotherapy at any time; and those cancers that initially respond to

chemotherapy but then acquire resistance during the course of therapy.

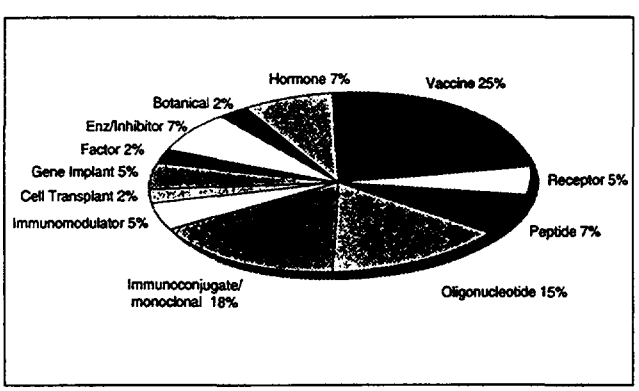
Tumours can sometimes be resistant to one drug; however there are cancer cells that are resistant to a number of anti-cancer drugs. These cells are said to possess multidrug resistance (MDR). This resistance is often due to the drugs being pumped out of the cells before they can have an effect. In deciding which drugs to use for treatment, it is important to determine if the tumour shows resistance to specific drugs or to multiple drugs.

BioResearch Ireland's National Cell and Tissue Culture Centre (NCTCC) has an extensive MDR research programme in progress. A team of over 20 researchers, mainly at post-doctoral level, are involved full time on this programme. The research involves understanding the mechanisms for MDR and finding ways to counteract it. BioResearch Ireland also works in close collaboration with Dublin hospitals on MDR research.

Further details on drug resistance can be obtained from Professor Martin Clynes, National Cell and Tissue Culture Centre, Dublin City University, Glasnevin, Dublin 9. Tel.: +353 1 704 5700; Fax: +353 1 704 5848. (Source: *BioResearch Ireland Press Release*, 1995)

AIDS drugs: A patchwork quilt

The drugs in development for treating AIDS are many and varied. Of 138 antiviral drugs making their way through the pharmaceutical development pipeline, 107 (77 per cent) are targeted to the treatment of AIDS or AIDS-related diseases, according to data from the market researchers, Technical Communications (Lafayette, CA). Vaccines still represent the biggest single slice of the development activity, but oligonucleotides and antibody conjugates also have substantial shares. The complexity of both combination therapies and patterns of viral resistance will increase enormously as the products move through research and clinical development.



(Source: *Biotechnology*, Vol. 13, November 1995)

Studies find two drugs better than one in AIDS treatment

Two new studies have changed the way doctors will treat people infected with the virus that causes AIDS, researchers say.

Before the release of the reports, the European-Australian Delta study and the US AIDS Clinical Trials Group (ACTG) 175 study, the standard of care for those infected with HIV was the single use of the drug AZT. As many as half the patients infected with the virus that causes AIDS are now receiving just AZT. But the studies showed a clear, significant advantage in delaying the onset of AIDS symptoms and death by starting treatment with two drugs, such as AZT and Didanosine (ddI) or AZT and Zalcitabine (ddC).

A panel of scientists from Europe and the United States, while agreeing that new patients diagnosed with infection by human immunodeficiency virus (HIV) should receive combination therapy, said there is still no consensus on when in the course of the disease the use of AZT and other drugs should begin.

Patrick Yeni of Hopital Bichat in Paris, who discussed the Delta study at the European AIDS Clinical Society conference, said the data showed a 38 per cent reduction in the risk of death if patients were taking AZT and a second drug. In the ACTG study, AZT alone was compared to AZT plus ddI and ddC as well as ddI alone. The results showed a significant positive difference for using the combination forms and ddI.

Scott Hammer of Harvard Medical School, Cambridge, MA, who presented the ACTG 175 results to the conference, said physicians have a number of choices now in selecting drugs to be used in conjunction with AZT, in addition to ddI and ddC. He cited the newly approved drug Stavudine (d4T) and the experimental drug 3TC, now in widespread compassionate use protocols in the United States. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 16 October 1995)

TPA leads to complete recoveries in stroke victims treated in three hours

Nearly one third of acute ischemic stroke patients who were given intravenous tissue plasminogen activator (tPA) within three hours of the onset of their symptoms fully recovered all normal functions, according to results of a major clinical trial reported in December 1995. Only 20 per cent of patients on placebo did equally well, and mortality rates for patients getting either tPA or placebo were nearly equal.

Results of the five-year trial, involving 624 patients and nine medical centres across the USA, were reported in the 14 December issue of the *New England Journal of Medicine*. It is "the first unequivocal evidence of the effective treatment of the most common form of stroke", said Zach Hall, director of the National Institute of Neurological Diseases and Stroke (NINDS), which organized and funded the study. The results "signal a new era, in which stroke is recognized as a condition that can be treated", Hall said at a press conference.

Genentech, Inc., which manufactures recombinant tPA under the trade name Activase, immediately announced plans to ask the Food and Drug Administration for permission to add acute ischemic stroke to the drug's approved indications. However, not all stroke victims should get tPA, Hall stressed. About four out of five strokes are ischemic, caused by a blood clot that reduces blood flow to the brain, and the rest are haemorrhagic strokes, caused by bleeding into the brain. Haemorrhagic strokes must be ruled out by a CT (computerized tomographic) brain scan before a patient can be treated with tPA. Not only would tPA not stop the bleeding but it can cause it. In the study, intracerebral haemorrhage occurred in 6.4 per cent of the patients who received tPA, compared with just 0.6 per cent in patients given placebo.

Also, 8 per cent of the tPA treatment group died of brain haemorrhage, compared to just 1 per cent of the placebo group. Nevertheless, after three months, only

17 per cent of the tPA treatment group had died, compared to 20 per cent of patients who had been given placebos.

To benefit patients with acute ischemic strokes, tPA must be given within three hours of the onset of symptoms. Previous studies, such as the European Cooperative Acute Stroke Study (ECASS), have shown no benefit in ischemic stroke patients treated with tPA within six hours of symptom onset. (Extracted from: *McGraw Hill's Biotechnology Newswatch*, December 1995)

The use of radioactive molecules for the diagnosis and treatment of disease

Over twenty million patients world-wide are treated or diagnosed annually using nuclear medicine techniques. This involves the administration of a small amount of a radioactive material, called a radio-pharmaceutical, to the patient. Depending upon the radioactive isotope used and the chemical form in which it is administered, it is possible to target different biological processes or organs in the body for imaging. The patient is imaged using a detection device called a gamma camera, which images the distribution of the radioactive material highlighting functional or anatomical abnormalities in the patient. Nuclear medicine is unique in its ability to give functional as well as anatomical diagnostic information; other imaging technologies such as Magnetic Resonance Imaging (MRI), Computer Tomography (CT) and ultrasound give essentially only anatomical information.

Nuclear medicine started as a spin-off from the nuclear research programmes of the 1940s to 1950s, when it became possible to manufacture commercial amounts of different radioactive isotopes. Since then it has developed into a business worth more than $1.5 billion with more than 10,000 hospitals and clinics world-wide using these diagnostic techniques.

The first radiopharmaceuticals were developed to study overall function, such as kidney or liver function rates or to detect the sites of cancer in bone. However, as the speciality has developed, the real strength of nuclear medicine has been recognized as its ability to diagnose disease at increasingly specific molecular levels compared to CT or MRI. In fact, nuclear medicine has recently been renamed molecular medicine by some proponents because of the ability of the new generation of radiopharmaceuticals to image highly specific molecular processes within the body.

For example, in many neurological disorders there is an up or down regulation of certain structures called neuroreceptors. By developing radioactive molecules which selectively bind to these neuroreceptors, one can obtain information on the distribution and quantity of these receptors in the brain of a living person. This knowledge helps not only to confirm a diagnosis of specific disorders, but also allows follow-up treatment with neurologic drugs in a more precise way. Indeed, it may be possible to predict the correct dose of a drug that should be effective in a patient. Additionally, it may well be possible, using nuclear medicine techniques to more scientifically define neurological disorders such as schizophrenia and Alzheimer's.

Another major area of interest is the ability to accurately locate, delineate and assess areas of inflammation and underlying infection. Patients with post-operative fever, osteomyelitis and those who are immunocompromised may benefit from imaging studies as previously it has not been possible to accurately image such disorders. Together these conditions affect more than ten million patients world-wide.

Over the past two years Resolution Pharmaceuticals has leveraged the strengths of chemistry, biochemistry and pharmacology expertise in Allelix and the radiopharmaceutical expertise of Nordion International—guided and focused by a dedicated and experienced radiopharmaceutical management team. Towards the end of 1995 it is anticipated that the first product, an agent for imaging inflammation, will enter clinical trials and others will follow in the forthcoming years as the company grows. The company strategy is to develop products to Phase II clinical trials and then seek alliances for further development and commercialization. This strategy has been productively employed in Allelix's biopharmaceutical business.

The radiopharamaceutical business is global and Resolution intends within the next five years to become the leading research-based company in this expanding field. It is the intention of Allelix and Nordion, the joint owners of Resolution, that Resolution become a fully independent company and, accordingly, a private equity placement is currently under way. Through Allelix, it will be possible to participate in the development of a valuable asset in Resolution Pharmaceuticals. (Source: *Allelix News Release*, March 1995)

CDP 571 shows therapeutic benefit in Crohn's disease

Celltech Therapeutics has announced that it has successfully completed a Phase II clinical trial of its genetically engineered human antibody CDP 571 in patients with Crohn's disease, a serious inflammatory bowel disorder. A significant reduction in disease activity was observed in patients treated with the drug.

CDP 571 is a genetically engineered human antibody that blocks the action of an important mediator of inflammation, tumour necrosis factor (TNF). It has been developed by Celltech and is licensed to Bayer AG.

Thirty-one patients with active Crohn's disease who did not respond to standard therapy were evaluated in a trial conducted at five UK centres; twenty-one were injected with a single dose (5 mg/kg) of CDP 571 while 10 patients received placebo. Patients were assessed two weeks after treatment, using several different clinical measures of disease activity.

Nine of the treated patients showed complete or near-complete disease remission at two weeks. Only one of the 10 patients in the placebo group achieved remission.

There was a statistically significant improvement in the median Crohn's Disease Activity Index score for the patients in the CDP 571 treated group after two weeks. Similar statistically significant improvements were seen with the other clinical scores.

The infusion of CDP 571 was well tolerated and there were no drug-related adverse events.

These results were achieved in patients who were receiving, but not responding to, the current best therapy.

The beneficial effects were similar in extent to those reported recently in patients with another inflammatory bowel disease, ulcerative colitis, who were treated with CDP 571. This suggests that CDP 571 may have wide utility in treating inflammatory bowel diseases. (Source: *Celltech News Release*, 9 November 1995)

Receptor antagonist introduced

Research Biochemicals International has introduced a serotonin (5-HT) receptor antagonist, p-MPPI.

The high concentrations of 5-HT_{1A} receptors in brain regions, which are associated with mood and anxiety, has

led to much research in this receptor subtype. Until now, research has been hampered by the lack of a selective, high affinity 5-HT_{1A} receptor antagonist.

The company claims that p-MMPI is a potent antagonist of central 5-HT_{1A} receptors. In rats it completely blocks the 8-hydroxy-DPAT-induced inhibition of forskolin-stimulated adenylate cyclase activity.

Also, *in vitro* homogenate binding studies performed in rat hippocampal homogenates using [^{125}I]-p-MPPI have revealed a significant increase in the number of binding sites in the presence of quanyl nucleotides.

A number of cloned 5-HT serotonin receptors, supplied as frozen aliquots, are also available.

Contact: Semat, St. Albans, Herts., UK. Tel.: +44 1727 841414; Fax: +44 1727 843965. (Source: *Manufacturing Chemist*, December 1995)

New developments to design vaccines against mucosally transmitted infectious diseases

Shigella flexneri is a gram-negative bacillus belonging to the Enterobacteriaceae that causes bacillary dysentery, an invasive disease of the human colon. Studies have shown that the initial site of intestinal invasion are lymphoid follicles associated to the colonic mucosa and that the invasins (Ipa proteins) secreted by *S. flexneri* are strong immunogens.

This has prompted an EU funded research project under the Biotechnology Programme to construct live attenuated mutants that can be orally administered and which are protective in animal models of infection.

The aim is to develop orally-delivered vaccine vectors based on rational genetic attenuation of virulence of the invasive enteric pathogen. Gene deletions are introduced to attenuate virulence while reaching a balance between reactogenicity and strong mucosal immunogenecity. This project is now in its final year and several important results have been achieved.

The researchers characterized the molecular and cellular processes of cell and tissue invasion by *S. flexneri* and have identified several new targets for virulence attenuation.

In addition, the genetic systems necessary to construct vaccine strains expressing and secreting stable hybrid proteins have been established. This includes the establishment of genetic constructs to identify gene promoters expressing at high levels intracellularly. The construction of expression cassettes is currently under way. And it was shown that the invasin IpaC is an excellent candidate for construction of stable and properly secreted hybrid proteins. Several constructions are available for testing now.

For information contact: Phil O'Leary, BioResearch Ireland, Forbairt, Glasnevin, Dublin 9, Ireland. Tel.: +353 1 8370177; Fax: +353 1 8370176. (Source: *BioResearch Ireland News Release*, 18 December 1995)

Simple DNA urine test pinpoints very early bladder malignancies

A simple urine test that detects damaged DNA appears to be able to spot bladder cancer at very early stages, and could lead to a routine, inexpensive examination that would dramatically boost the survival rate from the disease.

The screening technique is also being experimented with as a way of spotting very early lung and colon cancers.

In a limited trial, 19 out of 20 cases of bladder cancer were correctly identified using the microsatellite analysis technique developed by a team headed by Dr. David Sidransky of Johns Hopkins University School of Medicine.

In Sidransky's trial, DNA from the urine sediment of 25 patients with suspicious bladder lesions and five controls who showed no evidence of bladder cancer were amplified by PCR. Then, polymorphic alleles were compared at 10 preselected microsatellite loci. Analysis of three additional dinucleotide markers on chromosome 9p21 also confirmed damage in urine-sample DNA.

When the number code in the blind test was broken it was learned that 20 of the 25 patients had confirmed bladder cancer. The microsatellite analysis using 13 markers detected genetic alterations in 19 of the 20 cancer patients.

None of the five patients without signs of cancer showed any microsatellite changes.

To confirm that the altered alleles came from the primary tumour, biopsies of 15 of the 20 cancer patients were performed. All 15 showed that the same microsatellite alterations detected in the urine were present in the tumour. In five of the patients there was not enough of a sample for a biopsy.

Sidransky said that the analysis can detect bladder cancers with a 95 per cent accuracy at a very early stage in the disease, when possibility of a successful treatment and five-year survival is as high as 91 per cent. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 19 February 1996)

Test-tube evolution—selecting novel therapeutics

In recent years, biotechnology has started to invest in techniques that generate novel biomolecules by reproducing Darwinian evolution in the test-tube.

One of the most spectacular successes is phage display technology, the use of bacterial viruses to isolate proteins with potential therapeutic activities. The last five years have seen the inception of several companies pioneering this field and forging corporate partnerships with large bio/pharmaceutical companies keen to access this exciting, proprietary science.

Darwinian evolution selects for desirable traits by ensuring survival of the fittest. In the same way, scientists can "pan" large populations of proteins, such as antibodies, to select activities towards therapeutic targets.

By genetic engineering, harmless bacterial viruses, known as phages, have been turned into carriers for human antibodies. When these populations, or libraries, of antibodies are panned in tubes coated with a target molecule, antibodies which bind the target are captured with their phage carriers. These antibodies can then be multiplied by allowing the phages to replicate in bacteria. After repeated rounds of panning and replication, antibodies that bind the target can be identified and used directly in laboratory tests of cell targeting and neutralization.

Researchers believe that this technology has several advantages over traditional methods of animal immunization to generate therapeutic antibodies. First, the antibodies come from human genes, making them less prone to rejection by the patient's immune system, a serious problem with animal antibodies. Second, candidate antibodies can be identified in days as opposed to the months or years with animal immunization. Third, by using bacterial production, candidates can be rapidly produced and engineered for therapy, for example, by coupling to molecules which exert a toxic effect on the target.

Like many biotechnologies, phage display is gripping science, but has yet to prove its worth in generating useful drugs. However, given the speed at which it is being used to generate molecules against new targets at several firms using phage display, it should not be long before this technology reaches the clinic. (Extracted from: *Biotechnology Business News*, 28 February 1996)

Development of in vitro assays to evaluate the immunotoxicology of drugs and biotechnology-derived products

This very large project is funded under the current Biotechnology Programme. The project is coordinated from Brussels and involves the work of 29 research laboratories from nine European countries.

The programme uses recent advances in molecular immunology and related disciplines to develop *in vitro* assays to assess any adverse immune reactions induced by drugs and medical compounds.

The project focuses on six major areas, namely:

1. Cytokines and growth factors
2. Monoclonal antibodies
3. Drug metabolism
4. Autoimmunity
5. Allergy
6. Immunosuppression.

The project is now coming to a close and considerable successes have been achieved. These include the development of sensitive *in vitro* assays for the detection of compounds inducing the production of cytokines and the development of *in vitro* models for drug-induced allergic reactions. Further information is available on each of the above areas from Phil O'Leary, BioResearch Ireland, Forbairt, Glasnevin, Dublin 9, Ireland. Tel.: +353 1 8370177; Fax: +353 1 8370176. (Source: *BioResearch Ireland News Release*, 30 January 1996)

Agricultural applications

Three new bio-pesticides identified

Three compounds from plants that act as natural pesticides have been identified and patented by Canadian and Thai scientists. Researchers at the Universities of Ottawa, British Columbia, and Chiang Mai in Thailand expect the compounds to have commercial potential because they are effective against pests without harming the environment.

With assistance from the International Development Research Council (IDRC), the researchers screened 300 Thai plant species to obtain the bio-pesticides. Their research included methods of extraction, purification and identification of the active ingredients.

The products have been named *ITK, Stopfeed,* and *Swimtop. ITK (Instantkill)* is effective against corn borers and the larvae of some mosquitoes. *Stopfeed* reduces the appetite of caterpillars that eat rice and cabbage. *Swimtop* is a pesticide against predatory fish that devour shrimp.

Contact: Bernard Philogene, Entomologist, University of Ottawa, Ottawa, Ontario. Tel.: (613) 562-5737; Fax: (613) 562-5103; e-mail bphilog@ uottawa.ca (Source: *The AgBiotech Bulletin*, February 1996)

Fungal resistant carrots

Dutch plant biotechnology firm Mogen has demonstrated resistance in carrots to multiple fungal species, claiming an advance over the single resistance produced with conventional breeding techniques. Recent trials with carrots genetically engineered with genes from the tobacco plant showed resistance to powdery mildew as well as *Cercospora* and two species of *Alternaria.* (Source: *European Chemical News*, 18-31 December 1995)

Approval for insect-resistant cotton

Monsanto has received a long-anticipated US Environment Protection Agency go-ahead for its insect-resistant cotton and expects to fully commercialize the genetically engineered crops for the 1996 growing season. The cotton has already been approved by the US Department of Agriculture and US Food and Drug Administration.

The EPA approval marks another milestone in Monsanto's ambitious build-up of its plant biotechnology business. The company received EPA approval for its insect-resistant potato and herbicide-tolerant soybean in May (Chemical Week, 27 September 1995, p. 25). It is also developing insect-resistant corn as well as cotton, canola and corn tolerant to its Roundup herbicide.

Monsanto plans to initially commercialize the insect-resistant cotton working with Delta and Pine Land, a leading cotton seed company. It also expects to collaborate with Jacob Hartz Seed and Stoneville Pedigreed Seed to market the genetically-engineered cotton. (Source: *Chemical Week*, 8 November 1995)

Biocontrol agent for nematode control of crops

Nematech Co., Ltd. has commercialized *Pasteuria penetrans*, a bacterial parasite of rootknot nematode, as a biological control agent. Rootknot nematodes present in soil damage a wide variety of crops and are a serious problem in the cultivation of vegetables such as tomato, eggplant and cucumber as well as in the production of fruit such as grapes, figs and kiwi.

The biocontrol agent *Pasteuria penetrans* is a parasitic bacterium that suppresses the egg laying of infected females, reducing or eliminating the next generation of nematodes. It is extremely safe and environmentally friendly. It attacks only rootknot and is harmless to man and other organisms present in the environment. It produces highly resistant spores that can be applied like conventional pesticides, but unlike conventional pesticides that have to be repeatedly applied, a single application of *Pasteuria penetrans* is effective for at least five years. Conventional pesticides also damage the ecology of soil, decreasing the numbers of useful microbe nematode biocontrol organisms, so that the rootknot nematode densities recover rapidly and may surpass the original density (resurgence phenomena). Conventional pesticides also cause underground water pollution through soil seepage and may impair the health of those applying these chemicals.

The spores of *Pasteuria penetrans* are highly resistant to a number of pesticides used for control of rootknot nematode and are present in soil, on the surface of nematodes and within the infected female nematodes. The spores are saucer shaped with a diameter of 3-5 microns and can survive for years in soil. After a crop is harvested, the crop roots containing *Pasteuria penetrans* infected nematodes decompose, releasing the bacterium to the surrounding soil. The internal nutrients of infected nematodes are devoured by the bacterium and a single infected nematode can produce 1-2 million spores of *Pasteuria penetrans*. The nematode deprived of nutrients by the bacterium is unable

to lay eggs but lives to maturity. Tens of millions of the bacterium can be present in one litre of soil and this number of spores, although not killing the nematode directly, reduces nematode reproduction to a level that does not cause damage to crops.

The company has developed a technique to suspend the spores of *Pasteuria penetrans* in water for applying as a spray to soil. The technique is much more effective than the previous method used of applying dried crushed root powder to soil. The effect has been fully confirmed through field tests with tomatoes, sweet potato, pumpkins, cucumbers and container figs.

Further details from: Nematech Co., Ltd., Public Relations Dept., 66-2 Horikawa-cho, Sawai-ku, Kawasaki City, Kanagawa Pref. 210. Tel.: +81-44-549-6659; Fax: +81-44-549-6631. (Source: *Jetro*, November 1995)

Tomato time

Zeneca's (London) genetically modified tomatoes have marched a step closer to the UK market. The first crop of the slow-rotting tomatoes, cleared for the UK market in February 1995, has now been harvested and processed into puree by leading grocers J.Sainsbury and Safeway. The puree will be sold as the grocers' house brands and will be labelled as genetically modified; it will be on the shelves early in 1996, though the small harvest will mean only a few stores will be stocked. Zeneca's tomatoes were approved in the US in spring 1995. (Source: *Chemical Week*, 11 October 1995)

Supertrees and supercrops with the help of a robot

A Brisbane company has developed DNA fingerprinting technology to identify supertrees and other superior plant species. ForBio Ltd., a biotechnology company, is already the world's largest forest biotechnology research company.

Professor Teasdale, director of ForBio Ltd., said it is possible using the DNA fingerprints of trees to select for particular traits, such as speedy growth, straightness and lack of knots. "The predictive tool allows us to reject those that do not meet the criteria and to amplify those that are superior", he said.

ForBio has completed genetic maps of a number of plantation trees, following development of new marker technology by DuPont in the United States. "Particularly valuable to forestry is the fact that molecular markers allow us to produce saturated genetic maps. Every position in the plant's genome has a marker on it or somewhere near it, and that means that every valuable gene will have a marker near it. Having now achieved that first stage of a complete genetic map, we can develop correlations between valuable traits and markers".

A robot developed by ForBio allows speedy, large-scale commercial exploitation of those high-value plants selected through ForBio's genetic systems.

For example, the robot can mass-produce up to 4 million plants per year, and one person can operate three such machines. "Through this large-scale production using high-technology cloning we aim to reduce the burden on our native forests, as well as to develop better-value crops", Professor Teasdale said. This robotic mass propagation is vitally important, since nature often takes too long. ForBio is the world's only commercial supplier of robotic equipment and protocols for automation of micropropagation and tissue culture of plants, such as potatoes, vegetables, flowers, ornamentals and sugar cane, as well as forest trees.

Further information: Professor Bob Teasdale, ForBio Ltd., 50 Meiers Rd., Indooroopilly, QLD 4068 (Tel.: (07) 3870 5888). (Source: *Australasian Biotechnology*, Vol. 5, No. 6, December 1995)

Test of toxin-expressing baculovirus successful

The first US field test of a genetically engineered toxin-expressing baculovirus designed as an insecticide has been judged successful by the University of Georgia researchers supervising the experiments. Successful tests had previously been made in controlled environments.

The baculovirus contains a gene encoded for an insect-specific toxin found in scorpions. It killed virtually all of the cotton bollworms and tobacco budworms on the cotton crops to which it was applied, but had no effect on honey bees and other beneficial insects. It was deemed at least as effective as Bt, a widely used biological insecticide. (Source: *The AgBiotech Bulletin*, January 1996)

Natural insecticide discovered

Two potent naturally occurring insecticide compounds, identified as naphthaquinones and effective against insect pests which are showing resistance to many current insecticides, have been isolated from a South American plant.

According to Ian Harvey, chief executive of BTG, a technology transfer company, the breakthrough could be the most important crop protection discovery since the pyrethrins. BTG has applied for patents on the compounds and is discussing their development with several companies.

Researchers at IACR-Rothamsted agricultural research centre have isolated the active compounds from the *Calceolaria andina* plant and found them to be effective against a range of resistant insect strains including the B-biotype of the tobacco whitefly which is devasting crops world-wide.

The new compounds are easy to extract and are present in the plant up to five per cent on a dry weight basis. More active synthetic analogues have been produced.

The five-year project, centred at IACR-Rothamsted, is funded and coordinated by BTG. Other institutions involved are the Royal Botanic Gardens, Kew, the University of Southampton and the University of Chile. (Source: *European Chemical News*, 29 January-4 February 1996)

Biological control: Making a meal of mealybugs

In the mid-1970s an unknown disease began to attack cassava plants in Congo and Zaire. The leaves curled up, the roots shrivelled and the plants died. Since cassava, with its starchy root and protein-packed leaves, is the basic foodstuff of nearly half of sub-Saharan Africa's 500 million people, this was bad news.

The mystery illness was caused by a tiny mealybug—white and 2-3 mm long—which sucked the sap of the plants and at the same time injected a toxin. The plants' defence against this was to curl and thicken, offering the mealybug perfect protection. Free from the need to mate (the species reproduces asexually, like its distant relation the greenfly), a bug snug in a cassava leaf can turn out 300-400 offspring in the course of three months. And because cassava is propagated from cuttings, not seeds, the infestations not only destroy the current food crop but the future one as well.

The Government of Zaire then approached the International Institute of Tropical Agriculture in Ibadan, Nigeria, for help. Hans Herren, then the Institute's director,

judged that it would take years to develop a bug-resistant strain of cassava and the only solution was to track down the origin of the bug and find its natural predator.

Taxonomists at the Natural History Museum in London had declared the bug to be a new species, *Phenacoccus manihoti*. Dr. Herren eventually located his quarry in Paraguay. Within a week he had also tracked down his true target: the predator. A small wasp, also previously unknown to science, keeps the bug in check in its natural habitat by laying its eggs in it.

Dr. Herren introduced the wasps into a trial area in 1981. It was an instant success. The mealybug population in the trial zone dropped by 95 per cent over the course of a year. The wasps also proved to be eager travellers; Dr. Herren found one over 100 km (about 60 miles) from the release site within a year. To speed up the natural process of migration, he devised a method of aerial bombardment, releasing wasps over a target area from a light aircraft.

By 1993, with some 1,000 people trained in biological control methods and the mealybug retreating, Dr. Herren moved on to investigate other biological methods of pest control. He has found possible predators for stem borers in maize, and the mango mealybug. His latest discovery is something that will attack the water hyacinth that is choking Lake Victoria and the Upper Nile. Now he wants to automate the process of delivery. Working from the International Centre of Insect Physiology and Ecology in Nairobi, where he is the director, he is trying to create a system of off-the-shelf biological control. (Extracted from: *The Economist*, 7 October 1995)

More nutritious canola

Researchers at DuPont and the University of Delaware have succeeded in producing transgenic canola and soybean seeds with substantially higher lysine content than is normal in these foods.

The nutritional quality of most grains is limited by a deficiency in the amino acid lysine. Previous attempts to use genetic engineering to increase lysine in these crops had met with little success.

The transgenic canola developed through the project nearly doubled the proportion of lysine in total seed amino acids over standard canola. (Source: *The AgBiotech Bulletin*, October 1995)

Apomixis: new promise for agriculture

Some plant species can reproduce by apomixis, producing daughter plants that are identical clones of the parent from unfertilized seeds. Researchers now hope to harness this quality for plant breeding.

Most of the world's small farmers use low-yield, hardy landraces, selecting the best ears from each crop as seed for the next year—but in many species, the next generation does not reproduce the same high quality. Hybrid seed from the plant breeders, though it does ensure high yields under the right conditions, requires heavy inputs to perform well and produces sterile seed; most farmers cannot afford to buy fertilizer, pesticides and fresh hybrid seed each year.

However, if a certain percentage of apoximis could be introduced into a hardy landrace, yield would be improved without compromising hardiness or sustainability. In the wild, apomictic species are just as polymorphic as sexually-reproducing species, and have the further advantage of reproducing hybrid strains.

ORSTOM has been working on apomixis for 30 years; its early work on Guinea grass revealed that apomixis is governed by a single gene. Since 1986, joint research with EMBRAPA in Brazil has focused on the wholly apomictic forage crop *Bracharia* (work which is now the core of a European project) and on Guinea grass, of which two new varieties have been launched.

In Mexico, ORSTOM and CIMMYT are working to produce apomictic maize by transferring the apomixis gene from a wild *Tripsacum*. Hybrid maize could be produced far more quickly and cheaply with apomictic maize than by existing methods.

Researchers in other countries are focusing on wheat and on *Arabidopsis*, a model plant in modern genetics.

Molecular genetics plays a vital part in this work, from gene maps of crop species and markers that can ascertain the presence or absence of the gene at an early stage, to transposons for isolating the apomixis gene in *Tripsacum*. ORSTOM has initiated an international apomixis research network; this year, with help from the Rockefeller Foundation, a newsletter has been circulated to 300 researchers. In September 1995 ORSTOM and the University of Texas A&M held the first international conference on the question, to further cooperation among apomixis experts and molecular geneticists. (Source: *ORSTOM Actualités*, 1995)

Stripe rust meets challenge

Barley producers in the United States face an unpleasant challenge with the arrival of stripe rust. It is a fungus that has already done enormous damage in South America, where it has wiped out barley crops used for food, as well as for feed and beer.

But the fungus is going to be out of luck in the Pacific North-west, thanks to gene mapping—and strong collaboration between ICARDA's Latin American Regional Programme and Oregon State University (OSU).

Together, ICARDA and OSU researchers have succeeded in producing resistant varieties that will be ready for yield testing in 1996. They have done it by identifying the disease-resistant material in their germplasm, allowing them to breed new resistant lines far more quickly than with the traditional plant breeding methods.

Over the last decade, Dr. Hugo Vivar, the Barley Breeder and Latin American Programme Coordinator for ICARDA—the International Centre for Agricultural Research in the Dry Areas—based in Aleppo, Syria, and has a world-wide mandate for barley improvement.

Dr. Vivar, working out of ICARDA's sister centre, CIMMYT,* near Mexico City, has developed an impressive armoury of barley germplasm which is resistant to biotic stresses—that is, pests and diseases, such as yellow rust. He then worked with national research programmes to exploit this germplasm. This led to the release of tough, productive varieties such as Calicuchima and Shyri in South America.

These are no ordinary crosses, however. Also 10 years ago, Dr. Patrick Hayes, associate professor of Crop and Soil Science at Oregon State University, Corvallis, USA, started to work with the double-haploid technique. This works by isolating one half of the chromosomes and then doubling them with the chemical colchicine, producing a plant that is homozygous—that is, which breeds true to its

* CIMMYT is the Centro Internacional de Mejoramiento de Maiz y Trigo, the CGIAR centre committed to increasing the productivity of maize and wheat in developing countries. (Source: *News Release*, October 1995)

characteristics in every generation. This permits much faster production of true breeding lines. Four years ago, the two teamed up to try and characterize and manipulate multiple disease-resistant germplasm. Now they have used molecular markers to speed up the identification of stripe-rust resistant lines. Of 134 double-haploid lines of Oregon-grown barley, 13 were found to have high resistance to stripe rust. The work took two years, and yield-testing of these disease-resistant lines will start in 1996.

The strategy has been for Dr. Hayes' laboratory to develop doubled-haploid mapping populations from crosses of Dr. Vivar's resistant germplasm with genotypes adapted to the Pacific North-west of the USA. Dr. Vivar's team then conducts extensive tests for disease reaction in central Mexico, while Dr. Hayes' group does molecular marker analysis in order to map the genes and find the sources of resistance. The benefits of this for farmers should be important in the US, but in the developing world it is absolutely crucial. There are real implications for food security.

Barley is also a tremendously important crop in the Middle East and North Africa, and ICARDA is working with national programmes there to stabilize yields by exploiting local sources of resistance—in Ethiopia, for example—and by collaborating with farmers on crop trials.

"Agricultural research is not going to remove all the risk from farming just yet!" says Dr. Vivar. "And if it was, plant breeders would not be able to do it on their own. Still, we are protecting the poor. Barley is mainly used as cattle feed, but is also a staple part of the diet in the mountains of Bolivia, Peru and Ecuador."

Further details from: Mike Robbins, Communication, Documentation and Information Services, ICARDA, P.O. Box 5466, Aleppo, Syria. Fax: +963-21 213490, 225105, 551860. Tel.: +963-21 213433, 213477, 235220, 225012, 225112, 225635. Telex: (492) 331206, 331208, 331263 ICARDA SY. Cable: ICARDA Aleppo. ICARDA

A job for super rice

Spurred by concern about serious food shortages predicted for twenty-first-century Asia, scientists at the International Rice Research Institute (IRRI) in the Philippines have developed the first prototype breeding lines for what they hope will be a high-yielding rice of the future. Gurdev Khush, IRRI's chief plant breeder, says the new plant will increase harvests by as much as 25 per cent when farmers start growing it early in the next century.

IRRI scientists believe the new rice could boost annual yields by 100 million tons. That would reduce the IRRI-projected gap between current production and future demand by about one third.

IRRI scientists believe they have found at least a partial solution by cross-pollinating the highest-yielding varieties IRRI created during the first Green Revolution over several generations totalling five years. Compared with IRRI's existing high-yielding rice varieties, the resulting "super rice" appears far less bushy—each plant consists of only about 10 stems compared with 20 to 25. But all of the stems contain seed pods bearing 200 to 250 grains of rice, while only about 15 stems on other varieties of modern rice carry pods that bear about 100 grains. Thus, a single super rice plant will produce up to 2,500 grains of rice compared with a maximum of 1,500 grains from today's varieties.

According to Khush, the super rice is also a more efficient plant. Thick, dark green, and erect leaves catch more sunlight, boosting per-leaf photosynthesis by 15 per cent. Because the plant makes more grain and less chaff, it produces more food per unit of fertilizer. And fewer excess stems mean farmers can grow plants closer together, increasing paddy yield.

Despite the new strain's promise, some rice specialists are sceptical. They worry that it will perform poorly in less-than-optimal conditions, especially considering that super rice, like earlier high-yielding varieties, requires abundant irrigation to achieve greater yields. (Extracted from *Technology Review*, August/September 1995)

Transgenic crops head to market

Plant biotechnology is emerging as a commercial reality. Genetically engineered cotton and canola seeds reached the market in 1995, and in 1996, a wave of biotechnology crops, including the first insect-resistant cotton, corn and potatoes, as well as herbicide-tolerant soybeans, cotton and canola, are expected to become widely available to farmers.

How the biotechnology crops fare will help define winners and losers in the highly competitive agro-chemical business. The promise, say biotechnology proponents, is that transgenic crops will radically reshape the agro-chemical markets, shifting demand in favour of selected herbicides and slashing the use of chemical insecticides. At the same time, genetically engineered plants, including tomatoes, could produce a new market for value-added produce.

Monsanto predicts plant biotechnology will blossom into a $2 billion/year world-wide business by the year 2000 and a $6 billion/year market by 2005. Consulting Resources (Lexington, MA) puts US sales of plant biotechnology products at slightly over $1 billion by 2005, and predicts sales of genetically engineered foods will reach $400 million/year and non-food biotechnology plant crops will reach $330 million/year.

Whether such rosy scenarios prove correct is uncertain. But companies that have bet heavily on plant biotechnology hope it is payoff time after years of development work and delayed promises.

Monsanto anticipates it will commercialize a half-dozen transgenic crops over the next two years and is looking for profits through the sales of value-added seeds and increased sales of its herbicides, and says it expects the genetically engineered products to be key to the future of its agricultural business.

Still, other agro-chemical producers remain cautious over the promise of biotech.

The crops could prove lucrative for agro-chemical makers because they potentially open up large new applications for the herbicides. Calgene's bromoxynil-resistant cotton, for example, permits the Rhône-Poulenc herbicide—sold as Buctril—to enter the $200 million/year cotton herbicide market. Buctril can be used to control broadleaf weeds after the genetically engineered plants have germinated.

Similarly, AgrEvo expects its genetically engineered crops will allow its glufosinate-based Liberty herbicide to be used for the first time in several large-quantity applications, including on soybeans. AgrEvo's biotechnology canola was commercialized in Canada in 1995, with some 50,000 planted acres, and the company hopes to commercialize Liberty-tolerant corn and soybeans in the US by 1997.

While the herbicide-tolerant crops could redraw marketing lines in the weed-killing business, insect-resistant plants could mean the death of certain conventional insec-

ticides, according to biotechnology proponents. In the summer of 1995, EPA approved the first *Bt*-based pesticide plants, including *Bt*-corn— codeveloped but sold separately by Mycogen and Ciba Seeds—that is resistant to European corn borer, and *Bt*-potatoes developed by Monsanto that are resistant to the Colorado potato beetle.

Indeed, companies say they plan to commercialize a series of insect-resistant crops over the next several years.

Beyond herbicide-tolerant and insect-resistant crops, some agro-chemical producers think they can create new markets by genetically engineering improved qualities and characteristics into crops. (Extracted from *Chemical Week*, 27 September 1995)

Food production and processing

Genes of firefly's glow shedding light on meat safety in Canadian research

A team led by Mansel Griffiths, a food science professor at the University of Guelph, has found a simple, quick and inexpensive way to test meat and poultry products for bacteria, such as salmonella and *E. coli* 0157, using the genes that cause fireflies and some bacteria to glow.

To test for bacteria, Griffiths inserts a lux gene into a bacteriophage that is specific to the microbes for which he is testing. If suspect microbes are present, the phage infects them and transfers the lux gene. The microbes use the gene to produce the enzyme luciferase and begin to glow.

The glow of the microbes can be picked up by a charge-coupled video camera and the intensity of the light gives a reliable estimate of the amount of bacteria present in the sample.

As well as a bacteriophage/lux test for *E. coli* 1057 —which causes the deadly "hamburger disease"—and salmonella, Griffiths has a test for *Staphylococcus aureus* and is working on a test for *Listeria monocytogenes*, which can cause severe blood poisoning and meningitis.

It may be the speed that will be most attractive to the meat and poultry industry; Griffith's phage test system can detect bacteria within three to six hours, depending on the reproduction rate of the microbes themselves.

Current tests can take up to three days—by which time tainted meat could be in stores or being served in fast-food restaurants. (Extracted from: *McGraw Hill's Biotechnology Newswatch*, 4 December 1995)

Industrial microbiology

Hercules uses bioprocess to convert halo-alcohols

A bioprocess developed in Wales to remove unwanted contaminants in the manufacture of *Kymene ULX* used in the paper-making process has been commercialized by Hercules in two plants, one in France and the other in Sweden.

Carbury Herne in the UK and Hercules of Wilmington, DE, USA, are collaborating on the use of biocatalysts to detoxify halo-alcohols, a by-product in a reaction between epichlorohydrin and aqueous solutions of polyaminoamide. The reaction produces polymers which are then used to give extra strength to paper. The halo-alcohol by-products have no value and it is believed they may diffuse through packaging into food and could prove to be carcinogenic. Indeed, Germany, France and the Scandinavian nations enforce regulations on absorbable halogens as part of measures to reduce organo-chlorines.

So far two different strains of bacteria have been developed to degrade the halo-alcohols. These work through a hydrolysis reaction, which effectively restructures the molecule to form an epoxide. Of the two principle forms of halo-alcohol, 1,3 dichloropropan-2-ol (DCP) and 3-chloropropanediol (CPD), DCP is first converted into epichlorohydrin and then into CPD. The CPD is then converted into glycidol, then glycerol, which is finally broken down into carbon dioxide, water and chloride ions. Hercules claims the process reduces the levels of both DCP and CPD by a factor of ten, to below the detectable levels of 1 ppm for DCP and 5 ppm for CPD. (Source: *European Chemical News* , 5-11 February 1996)

Microbial detection kit available

Culture-Check, a simple cost-effective kit for testing cell lines and media components for microbial contamination, is available from American Type Culture Collection (ATCC). The kit is used to differentiate between normal cell debris and impurities due to bacterial and fungal contamination.

Contact: ATCC Sales, 12301 Parklawn Dr., Rockville, MD USA 20852. Tel.: (301) 881-2600; Fax: (301) 816-4361. (Source: *AgBiotech Bulletin*, January 1996)

Corn starch/EVOH overcomes hitch

Researchers at the Massachusetts Institute of Technology (MIT) have developed a biodegradable material combining corn starch and an ethylene vinyl alcohol (EVOH) polymer, to stop the material becoming soft or brittle in changing atmospheric conditions.

A team led by Edwin Thomas of the Department of Materials Science and Engineering has focused on creating a 1 micron-thick surface with the protective properties of pure plastic.

By varying the ratio of the ethylene and vinyl alcohol components in EVOH, properties ranging from non-biodegradable PE to water-soluble, biodegradable PVOH can be obtained.

Since EVOH has a lower molecular weight, surface tension and viscosity than the starch component, it moves up to the surface because it is more attracted to the air interface. Once the product is discarded and shredded, the heavier starch is exposed to the elements.

Meanwhile, an improved grade of Novamont's starch-based biodegradable film, which degrades in 45 days in composting conditions, has met decomposing criteria from the Organic Reclamation and Composting Association. Novamont has also improved the physical properties of its *Mater-Bi* ZF03U film.

These films are designed to perform as standard plastics in industrial applications. An important use is in degradable bags for waste collection. The films and bags are produced by traditional ldPe film blowing and sealing techniques with minor modifications.

Other starch-based biodegradable materials produced by Novamont include a product containing EVOH copolymers, a replacement for PS packaging foams, and a completely natural material for rigid and dimensionally-stable injection moulded items. (Source: *European Chemical News*, 22-28 January 1996)

Novel haem-based catalysts with industrial applications

A research project funded under the EU Biotechnology Programme is investigating novel haem-based catalysts with industrial potential. Haem-enzymes catalyze many indus-

trially important redox processes. Quite often these reactions have many varying control parameters, resulting in a reaction which is difficult to predict.

This project is working towards advancing our understanding of these mechanisms by using a multidisciplinary research approach with the aim of elucidating structure/function relationships of haem-proteins involved in commercially and environmentally important redox processes.

The research undertaken was extensive and resulted in the following achievements:

- Several peroxidases were characterized using both site directed metagenesis and NMR spectroscopy.
- Different haem compounds were prepared with specific microperoxidase activity towards aromatic compounds.
- An analogue compound of manganese peroxidase was synthesized.
- The structure/function relationship of several natural and mutated cytochromes (with new functions) were obtained and their mechanisms of action determined.

These research developments are of interest to a number of industries. The peroxidases in particular have potential applications in the paper-pulp industries and in depollution and detoxification processes. Peroxidases may also be applied to selectively oxidate/hydroxylate organic substrates of commercial interest, particularly in the pharmaceutical and food industries. For more information contact: Phil O'Leary, BioResearch Ireland, Forbairt, Glasnevin, Dublin 9, Ireland. Tel: +353 1 8370177; Fax: +353 1 8370176. (Source: *BioResearch Ireland News Release*, 18 December 1995)

Energy and environmental applications

Biomass ethanol

Corn- and ethylene-based ethanol producers are both keeping a wary eye on emerging biomass technologies that would manufacture the fuel from organic wastes. Biomass is not yet a factor in the commercial market, but it has the potential to become the low-cost technology as its feedstocks would be virtually free.

Swan Biomass Company, a partnership between Amoco Corporation and Stone & Webster Engineering Corporation, is launching a study to see whether manufacturing biomass ethanol could be an economic and environmental means of getting rid of waste rice straw in California's Sacramento Valley. Swan says it can convert crop wastes into ethanol and a variety of by-products. The company's technology is based on research by Amoco, NREL, Iogen Corporation, Purdue University and others.

The study will be conducted at a 1-ton-per-day pilot plant at NREL's facility in Golden, CO. Town officials will then decide whether to build a commercial biomass facility before legislation banning the burning of rice straw is phased in.

Sacramento is home to a second possible rice straw-to-ethanol technology. Ark Energy, in conjunction with the Sacramento Municipal Utility District, is planning a 148.5 megawatt, natural gas-fired cogeneration plant that will use a 12-million-gallon-per-year rice straw-based ethanol facility as its thermal host. (Source: *Chemical Marketing Reporter*, 19 February 1996)

Sulphur-based breakdown of oil

A bacterium discovered on the seafloor in an oxygen free environment can break down crude oil, a task previously considered improbable. The bacterium uses sulphur or sulphates as its conversion medium instead of oxygen. The bacterium, also believed to sour reservoir oils, was discovered by a crew from Woods Hole Oceanographic Institute at 6,000 ft depths. (Source: *Offshore*, January 1996)

Micro-organism decomposes and converts dyes into colourless substances

Professor M. Shoda and his research team at Tokyo Institute of Technology have discovered a micro-organism that decomposes dyes into colourless substances.

Today, dyes are mostly treated by absorption methods, concentration and incineration, but are expensive.

The micro-organism *Geotrichum candidum* is a filamentous fungus isolated from the soil that can decompose and convert 18 different kinds of blue, red, yellow and purple dyes in wide use today into colourless substances in liquid and solid cultures.

This micro-organism prefers a pH of 4-7, and proliferates readily in environments with temperatures of 20-30° C. This fungus can grow under simple nutritional conditions at higher growth rates compared to other well-known micro-organisms claimed to decompose dyes. Even in a super-high concentration of 12 g per litre of dye, the fungus decomposed the dye into colourless substances in about two days. Ordinary microbes are incapable of proliferating in a culture containing about 0.5 g of dye due to its toxic property.

Investigation of the dye-decolorizing mechanism indicated that peroxide enzymes are secreted by the filamentous fungus to decompose the dyes. This fungus secretes several types of oxidation enzymes and can decompose various compounds. It is usable as a bioreactor to decompose waste water or for bioremediation in decomposing dyes in the soil. Further details from: Tokyo Institute of Technology, 4259 Nagatsuda-machi, Midori-ku, Yokohama City, Kanagawa Pref. 226. Tel.: +81-45-924-5274; Fax: +81-45-924-5276. (Source: *JETRO*, November 1995)

Extraction industry applications

Biotechnology in mining industry

A new study on the application of biotechnology to the mining industry has been published. Written by R.W. Lawrence and R. Poulin of the University of British Columbia (Canada) for the National Biotechnology Advisory Committee, the study reviews biotechnology processes in production; summarizes the status of various technologies, indicating the level of their development and commercialization; provides details on required developments, process principles, and patents; and lists a number of technologies that could find new or additional uses in Canada.

The report also analyses the impact of biotechnology on mineral reserves and mine waste as a source of metal extraction, and shows that several biotechnology processes are economically attractive. Regulations, reviews and barriers to the application of biotechnology are considered.

Contact: Order Evaluation of the Potential for Biotechnology in the Canadian Mining Industry from T.J. Patel, CANMET, Intellectual Property and Technical Information Management, 555 Booth Street, Ottawa, Ontario, K1A 0G1. Tel.: (613) 996-9758; Fax: (613) 952-2587. (Source: *AgBiotech*, November 1996)

F. PATENTS AND INTELLECTUAL PROPERTY RIGHTS

Myristate gene patented

Calgene has received a patent on a gene that will allow the commercial development of plant oils rich in the specialty industrial oil myristate. Myristate can be used in applications similar to laurate, which has been previously expressed in a transgenic canola variety developed by Calgene. Calgene has already developed canola plants producing an oil which is more than 40 per cent myristate. The oil can be used in high-quality personal care and cosmetic products, and Calgene reports that myristate canola has all of the benefits of laurate and none of the drawbacks. (Source: *AgBiotech Bulletin*, January 1996)

Setback for modified plant patent

Acting on a complaint brought by Greenpeace, the European Patent Office in Munich has ruled in the final instance that patents on genetically manipulated plants and their seeds are not legally acceptable in the EU.

The case dates back to 1991, when the environmentalist organization brought a suit against patents issued to Plant Genetic Systems and Biogen. While the technical complaints chamber of the Munich patent authority ruled in February 1995 that patents on plants were not lawful, the authority continued to issue patents, according to Greenpeace.

For the chemical industry, the Munich decision will have less impact than for the seeds sector. Agrochemicals producers now file for patents on genes or processes, as well as plants or seeds. The Hoechst-Schering agrochemicals joint venture AgrEvo, for example, has patented a gene which makes maize, oilseed rape, sugar beet or soya resistant to its glufosinate selective herbicide *Basta*. (Source: *European Chemical News*, 1-14 January 1996)

"Oncomouse" trial ends in confusion

The European Patent Office hearing on the Harvard University "Oncomouse" has broken up in confusion. Unexpectedly, the EPO's tribunal called a halt to the proceedings after advising Harvard to redraft its patent claims.

The Harvard mouse is genetically engineered to be susceptible to cancer. It was patented in the US in 1987; the EPO followed suit in 1992. Seventeen European groups, including animal rights campaigners, environmentalists and religious groups, are fighting the patent under a clause in the European Patent Convention, which states that a patent cannot be granted if it is contrary to morality. The opponents argue that "genetically engineering animals to develop a painful, lethal disease is morally unjustifiable".

The EPO said that "it has not yet been able to arrive at a decision to maintain or revoke the patent". Certain points had arisen "on which not all the parties were in a position to comment", it added. The proceedings will continue in writing.

The decision to go to written proceedings is rare, notes an EPO spokesman. The EPO now has to decide which—if any—of the new claims it will accept, and still has to decide whether to revoke or uphold the patent. All the bodies opposing the patent will receive copies of the new claims for comment. The tribunal is likely to take several months to consider their remarks; there is no time- limit on the written process. (Extracted from *Chemistry and Industry*, 4 December 1995)

EU biotechnology patent legislation

Nine months after the European Parliament rejected the proposal on the legal protection of biotechnological inventions, the European Commission has adopted a new version.

The latest text attempts to address the three main concerns that led to the previous draft legislation to be thrown out after seven years in the making, while providing the same level of patent protection:

- A clear distinction is drawn between inventions and discoveries and does not include the words "as such" in relation to parts of the human body in order to remove difficulties of interpretation regarding their patentability.
- Methods of germ-line gene therapy on humans are completely excluded from patentability. The exclusion applies to methods that could make it possible to alter a future individual's genetic identity in the course of *in vitro* fertilization.
- The new proposal introduces directly into patent law a derogation for farmers in respect of breeding stock. In the interests of greater clarity, express provision is made for farmers to use part of their breeding stock for the purpose of replenishing stock numbers.

Clear European patent legislation is urgently needed because the current patent law was drafted 30 years ago "at a time when the scope offered by biotech could not be imagined", according to the Commission. "All the discussions that took place regarding the initial proposal in 1988 confirmed the need for the Member States' laws to be harmonized, in order to avoid a proliferation of divergent legislation and case-law that would threaten both to fragment the single market and to take insufficient account of the ethical aspects."

The proposal will be submitted officially to the Economic and Social Committee, the European Council and the European Parliament in January 1996. The proposal could finally be adopted by the end of 1997. (Extracted from *Biotechnology Business News*, 19 December 1995)

Specific biotechnology legislation in 1996

Biotechnology will be one of the few industrial sectors to receive specific legislative attention from the European Commission during 1996.

This became clear when the Commission tabled its 1996 work programme in Strasbourg in November 1995, to coincide with state of the Union debate in the European Parliament.

EU activity would involve "operations to enhance competitiveness" of the sector, along with review of the regulatory framework.

As part of Commission support for research and development and innovation, a new initiative is planned to support biotechnology innovation in small businesses.

Further work is promised on extending EU rules on plant-health products to products containing genetically modified organisms.

The Commission is also planning a review of Directive 90/220/EC on deliberate GMO release into the environment. (Source: *Biotechnology Business News*, 22 November 1995)

US Genetic Privacy Act

A Genetic Privacy Act is currently before US legislators. The proposal provides legislation governing collection, analysis, storage and use of DNA cells and the genetic information obtained from them. Under the Act, anyone who collects a DNA sample such as blood, saliva, hair and other tissue for genetic analysis is required to provide specific verbal information and a written notice of rights and assurances before sample collection, obtain written authorization containing required information, restrict access as authorized by the sample source, and abide by the source's instructions regarding maintenance and destruction of DNA samples. The purpose of the Act is that no stranger should have or control identifiable DNA samples or genetic information about an individual unless the source specifically authorizes collection and maintains control of access and dissemination of that information. (Source: *Australasian Biotechnology*, Vol. 5, No. 4, 1995)

Brazil patent law bill gets some fresh air

Good news recently came out of the legislative process which the Brazilian Industrial Property Bill has been undergoing since it was first introduced by the Collor administration in 1991. Approved by the Chamber of Deputies in 1993, since then the Bill has been under discussion in two Senate commissions. Senator Suassuna, rapporteur, got the Constitution and Justice Commission (CCJ) to approve an entirely new version of the Bill in May 1995, pretty much favourable to the NGO positions. And on 7 December the CCJ unanimously voted favourably on amendments proposed by Sen. Suassuna that would further restrict the scope of patents under the law, while at the same time supporting national interests. For biotechnology and life patents, the CCJ's new version of the Bill is fairly restrictive. The whole or parts of plants and animals may not be patented even if they qualify as "inventions", since they are explicitly excluded from the definition of "transgenic micro-organisms", which are the only patentable "living beings". A very important development is that everyone, including the Government Senate representative, has recognized the GATT legality of the Bill's version approved by the CCJ. However, at the same time, the Senate Commission on Economic Affairs (CAE) proposes a version considered to be pro-industry. The final Senate vote is expected some time in 1996. For more information please contact David Hathaway, of AS-PTA, at Rua Princesa Isabel, 318, Nova Friburgo, RJ 28 615, Brazil. E-mail: hathaway@ax.apc.org. (Source: *Seedling*, December 1995)

United States process patent bill passes

The long-awaited Biotechnology Process Patent Protection Act has finally been passed by the United States House of Representatives, six years after it was originally introduced into the Congress. The Bill has already been passed by the Senate, and has been referred to President Clinton for signature. In the United States, as in all of the major industrialized countries, a patent can only be granted in respect of an invention which is novel, non-obvious, and useful. In a 1985 decision of the Court of Appeals of the Federal Circuit, *in re Durden*, it was held that a patent cannot be granted in respect of a process which uses novel starting materials and produces a novel product unless one of the steps of the process itself is novel. Because a very large number of different proteins can be produced using similar genetic engineering steps, this decision greatly limited the patent protection available for biotechnological processes. The new legislation will bring the United States into line with other major countries. The Biotechnology Industry Organization and its predecessors have lobbied extensively to have the Bill passed. (Source: *Australasian Biotechnology*, Vol. 5, No. 6, December 1995)

China joins Budapest Treaty

Where an invention either is a micro-organism or involves the use of a micro-organism and it is not possible to describe the micro-organism fully in writing, the description of the invention in the specification can be supplemented by a deposit of a sample of that micro-organism under the Budapest Treaty. The deposit is made in an International Depositary Authority. As of 1 July 1995, China has joined the Treaty, and therefore it is no longer necessary for applicants for patents in China to make a second deposit with a Depositary Authority in that country. Previously the need to make such a second deposit had caused serious inconvenience and extra costs for applicants for Chinese patents.

Provided that the deposit is made on or before the date of filing of the application in China, or of a PCT application designating China, a deposit in any International Depositary Authority will be accepted by the Chinese Patent Office. The two Depositary Authorities previously recognized by the Chinese Patent Office, the China Centre for Type Culture Collection and the Centre for General Microbiological Culture Collection, became International Depositary Authorities as of 1 July 1995.

This brings the total membership of the Budapest Treaty, as at 1 September 1995, to 35 countries. (Source: *Australasian Biotechnology*, Vol. 5, No. 6, December 1995)

When is a biotechnology invention really an invention?

One of the hardest questions facing researchers—and management—is judging whether a new discovery is patentable. At present, biotechnology patents are sought as an almost automatic reaction to any discovery—long before any real applications are known. Most often the reason for seeking intellectual protection so quickly is the perception that the first to file for an invention—if successful—will gain the upper hand against competitors. While it is true that "pioneering" patents are generally an extremely effective means to protect both the discovery and the inventions' potential market, the risk of having a biotechnology patent application rejected when based only on initial discovery data is very high.

One reason for this is that the dynamic pace of biotechnological innovation has outpaced the ability of the patent laws to interpret fairly what constitutes technological innovation. As a result, patenting biotechnology-derived innovations is ultimately unpredictable, because the unique, evolving nature of these inventions must fit into a comparatively static legal framework. This leaves the ultimate decision about what is patentable in biotechnology up to the courts.

Unfortunately, so far, there has been little discernible consistency in court decisions from which to garner

meaningful guidance in determining the critical biotechnology patent issues. But outlining some of the critical issues for obtaining biotechnology patent protection, and how the courts have ruled on these issues, the article attempts to give inventors an overview of how to answer the question, "When does the improvement of a laboratory procedure, or the modification of a protein, merit seeking patent protection?" Although recent decisions on DNA patents focusing on the invention but not the process are helpful, the absence of a clear, general rule by which all cases can be decided has created a degree of confusion and tension within the field. Indeed, as the technology has progressed, many techniques, such as those involving monoclonal antibodies, have evolved from patentable to unpatentable. Whether this will change in the light of more liberal rulings for DNA remains to be seen.

Recent changes in the patent law highlight the inequity of this uncertainty in the biotechnology arena. Under the June 1995 legislation for the General Agreement on Tariffs and Trade (GATT), patent applications are automatically made public 18 months after filing. Whereas previously the only risk associated with pursuing a patent for an invention that was unlikely to receive approval was the financial cost, now, under the GATT provisions, the end result of unsuccessful filing may be to provide competitors with valuable information for which there is no protection. It is likely that a the combination of inconsistent court rulings and the "unveiling" provisions of GATT will force a reconsideration of biotechnology's practice of filing patents as spontaneous reaction to discovery. (Extracted from *Bio/Technology*, Vol. 13, December 1995)

Court reverses injunction against Novo growth hormone

Denmark-based Novo Nordisk A/S claims a Federal Appeals Court has reversed an injunction issued by a lower court which blocked US sales of the company's genetically engineered growth hormone.

The injunction from June 1995 was the product of a lawsuit brought by Genentech Inc., the leader in the human growth hormone market, alleging patent infringement. Genentech also charged Bio-Technology General, against whom the injunction remains in place.

Novo says it is pleased with the Appeals Court decision to vacate the preliminary injunction. The move clears the way for the company to market its Norditropin human growth hormone in the US. (Source: *Chemical Marketing Reporter*, 4 March 1996)

G. BIOINFORMATICS

Guidelines on genetic diagnosis presented

The Japanese *Journal of Human Genetics* has presented guidelines on genetic diagnosis. Covering a dozen items, the guidelines clarify what needs to be taken into consideration in regard to the benefits of genetic diagnosis and their families. It also explores related social and broader medical issues.

In the guidelines, concern is expressed for a lack of understanding of the implications of a physician's genetic diagnosis. The authors also point out that genetic abnormalities are not necessarily connected to the onset of a condition.

The guidelines recommend the preparation of easily understood explanations that acknowledge the special characteristics of each kind of patient, and repeated efforts to obtain informed consent.

The right of the person who is to be diagnosed not to know the outcome of the diagnosis is to be respected, as well as the right to refuse notification. In addition, out of consideration of cases in which full guarantees for the care of the person to be diagnosed cannot be given, the physician also can refuse to perform a diagnosis.

The guidelines also suggest that people other than the person diagnosed should not be informed of the results.

Also contained in the guidelines are items covering thorough protection of privacy and the obligation to provide periodic post-notification counselling and considerations for providing psychological support.

Global Herbicide Directory

A directory combining technical and marketing data on the world's herbicides is now available.

The *Global Herbicide Directory*, is a 180-page compendium that identifies and provides key information on both experimental and commercial herbicide compounds and products. It offers complete reference to the world's more than 250 active individual herbicide molecules. It also includes a guide to the dollar value of the past, current and future global herbicide market, plus a brief overview of biological herbicides and the emerging technology of herbicides and transgenic crops.

Each compound is listed under its discovery company. Each listing includes technical data such as chemical structure, name, rates of use and target weeds/crops. The market overview includes the global dollar value of all herbicide use, broken down by crop, geography, company and chemical class. It also includes market forecasts into the next decade. (Contact: *AgChem Information Services*, 6705 East 71st Street, Indianapolis, IN, USA 46220. Tel.: (317) 845-0681; Fax: (317) 841-1210)

Fish as Biocontrol Agents in Rice. The potential of common Cyprinus carpio (L.) and Nile tilapia Oreochromis niloticus (L.) by Matthias Halwart

World-wide there is an increasing need for sustainable crop production making efficient use of scarce natural resources.

The integration of fish culture in rice-based farming systems has a long tradition in parts of Asia and, after a period of heavy pesticide use, rice-fish culture is currently regaining importance in the region.

The economic viability of this integrated enterprise has been documented in many studies, however agro-ecological impacts have received little attention.

This book deals with the contribution of two common and widespread fish species to integrated pest management (IPM), particularly the biological control of pests in rice. Weikersheim (Germany) 1994. 169 pp; ill. ISBN: 3-8236-1241-7. Tropical Agroecology; Margraf Verlag, P.O. Box 105, Weikersheim, Germany. (Source: *Gate*, March 1995)

Compendium on biofuels for combustion engines

The application of biologically-derived products as fuels or additives in combustion engines is the subject of *Biofuels*, a soft-back, 185 page book published by the European Commission, Directorate-General XII (Science, Research and Development). The objective of the study, from the Agro-Industrial Research unit, was to collect data pertaining to biofuel research and development, the economic and environmental factors which govern their application and introduction into the marketplace, and finally to give recommendations concerning priorities for future research. This is against a background that biofuels, in the form of biodiesel, or bioethanol, might be considered for future European agriculture.

Hazard analysis in food safety

A users' guide for food safety based on the principle of Application of Hazard Analysis Critical Control Point (HACCP) has been published as part of a Food Linked Agro Industrial Research Programme (FLAIR) sponsored by the European Community. The guide was developed by consumers, scientists and professionals from nine countries, with the objective that it will promote safety in food production through the application of the HACCP system.

The report, which is bilingual in English and French, is available from: Sequal, 191 rue de Vaugirard, Fr-75015 Paris, Tel.: (33 1) 45 66 99 44; Fax: (33 1) 40 56 04 97.

Fact-sheet on biotechnology in foods and drinks available in various languages

A comprehensive fact-sheet on aspects of biotechnology in foods and drinks has been produced by the European Federation of Biotechnology Task Group on Perceptions of Biotechnology. Written with the intelligent layman in mind, this "briefing paper", which covers four pages, is available in French, German, Italian, Spanish and Greek. It has also been published in the specialist press, in the appropriate language, in Poland and the Czech Republic.

The briefing paper runs through the history of the subject, current research on genetically modified crops, impact on genetic diversity, people's views on the ethics involved, a report on opinion poll results, and regulation and labelling. Details: European Federation of Biotechnology, Cambridge Biomedical Consultants, Schuytstraat 12, NL 2517 XE Den Haag, Tel. and Fax: (31) 70 3653857.

ATCC CD-ROM Culture Guides

The American Type Culture Collection (ATCC) now provides their culture databases on CD-ROM. All ATCC's

collections are available on one CD and it includes: Algae and Protozoa, Animal Viruses and Antisera, Bacteria and Bacteriophages, Cell Lines and Hybridomas, Fungi and Yeasts, Plant Viruses and Antisera, and Vectors, Clones, Libraries and Hosts.

The easy-to-use CD-ROM format is cross-platform compatible for DOS, Windows, or Macintosh environments. Search software is included to help you find the right strain to fit your research, industrial or educational needs. To run the software, ATCC recommends a 486 PC with 8 MB RAM or a System 7.0 on a 68020 Macintosh with 4 MB RAM.

The price of the CD is US$145.00. US$7.00 postage is charged for foreign shipments. A new edition will be published each year in January. Further information: ATCC/Marketing, 12301 Parklawn Drive, Rockville, MD 20852, USA (Tel.: (800) 638 6597; Fax: (301) 816 4361; e-mail: mkting@atcc.org).

Vector NTI for Windows and Macintosh — Intelligent Software for Molecular Biology

ATCC, in partnership with InforMax, Inc., announces a new upgraded version of Vector NTI for Windows and the newly available Macintosh version. Vector NTI is an innovative, knowledge-based software product designed to automate many cloning applications. Vector NTI is capable of designing new genetic molecules automatically, utilizing user's specifications for the desired molecule. The software contains over 3,000 rules for genetic engineering designing. The new upgraded version of Vector NTI includes a database of 80 commonly-used vectors, including vectors available from the ATCC, and permits transferring changes to molecules in child-parent trees and visualization of those changes. Additional features include a more powerful and user-friendly sequencer, and the ability to choose any number of best options for new molecule design. All molecules can be analysed to identify sequences for PCR primers, restriction sites, open reading frames, and sequence motifs. The user has complete flexibility in adding new enzymes or motif descriptions. Further information: ATCC/Marketing, 12301 Parklawn Drive, Rockville, MD 20852, USA (Tel.: (800) 638 6597; Fax: (301) 816 4361; e-mail: mkting@atcc.org). (Source: *Australasian Biotechnology, Vol. 5, No. 4*, August 1995)

The impact of biotechnology on the world trade in vegetable oils: three scenarios for developing countries

This is a study by the Department of International Relations of the University of Amsterdam. It starts with a detailed description of the international trade on vegetable oils and related biotechnology developments. It also contains three case studies: the Philippines, Ivory Coast and India. An in-depth research on biotechnology in vegetable oils—which includes the main actors and trends—is used to signal the likely impact of biotechnology on vegetable oils world trade in three different political and economic scenarios: trade protectionism, liberalization and sustainable development. Another study by the same authors, *The impact of biotechnology on the world trade in vegetable oils: Options for technology transfer*, focuses on the Philippines coconut sector as exporter country and on the European Union as international trade policy maker. The study describes the general problems and barriers related to technology transfer and indicates some priorities. P. Commandeur, G.V. Roozendaal, G. Junne, P. Elshof, G. Manicad, G. Ruivenkamp, *The impact of biotechnology on the world trade in vegetable oils* (two draft documents). Order from : University of Amsterdam, Department of International Relations, Oudezijds Achterburgwal 237 1012 DL Amsterdam, The Netherlands. Fax: (31-20) 525 20 86.

Let the Dawn Come - Social Development: Looking Behind the Cliches, 1995.

F. Frayssinet, R. Biswas, S. Mirermbe, F. Chimbindi and I. Ahmed. Journalists from Africa, Asia and Latin America examine the role of NGOs in Third World development from the perspective of recipients of development assistance. 152 pp. £8.95. Panos London, 9 White Lion St., London N1 9PD UK; phone (44-171) 278-1111; fax (44-171) 278-0345; e-mail panoslondon@gn.apc.org.

Special issue highlights fifth anniversary of Human Genome Project

To commemorate the fifth anniversary of the US Human Genome Project, a special issue of *Human Genome News* (*HGN*) has been published (Vol. 7, Nos. 3 & 4 (September-December) about the project's history, progress, impact and future challenges. The 20-page issue provides an overview of progress towards initial short-term goals set out by the Department of Energy and National Institutes of Health in October 1990 and the long-term goal of developing scientific resources and technologies for the DNA-based biology of the twenty-first century.

Single or multiple copies of this issue are available at no cost from the Human Genome Management Information System (HGMIS) at Oak Ridge National Laboratory. This issue and back issues of *HGN* are also available on a searchable World Wide Web site (see contact information below).

HGN, currently sponsored by the genome programmes of NIH and DOE, is produced by HGMIS to facilitate genome research, genetic education, and genome project communication. HGMIS answers questions from researchers and others interested in the genome project via telephone, fax and e-mail. HGMIS also produces the 41-page *DOE Primer on Molecular Genetics* and DOE genome programme reports, which are available via hardcopy and the Website listed below.

HGMIS, initiated in 1989 under sponsorship of the DOE Office of Health and Environmental Research, welcomes comments and suggestions. Contact: Betty Mansfield, Human Genome News, Oak Ridge National Laboratory, 1060 Commerce Park, MS 6480, Oak Ridge, TN 37830, Tel.: (423) 576-6669; Fax: (423) 574-9888; e-mail: *bkq@ornl.gov*. HGMIS World Wide Web URL: *http://www.ornl.gov/TechResources/Human_Genome/homehtml*

Bioceramics, Volume 6

Edited by P. Ducheyne and D. Christiansen, University of Pennsylvania, Philadelphia, USA

Bioceramics, Volume 6 contains 78 papers from the sixth International Symposium on Ceramics in Medicine, held in Philadelphia, USA and offers an extensive account of the leading edge research in this field of bioceramics. The sections are organized in such a way that they reflect the major lines of ceramics research, as well as focus on the critical properties and the mechanistic analyses of the interactions these materials elicit in tissues. The book includes sections on so-called bioinert ceramics. These ceramics such as alumina and zirconia, are chemically very stable materials. They are primarily used in artificial joints and dental implants. Carbon-based ceramics have outstanding blood contact properties, and therefore are the

materials of choice in the construction of heart valves. This volume includes sections covering the current research on the use of bioactive ceramics and glasses as coatings on prostheses to achieve long-lasting fixation of devices.

Chapter headings: Induction of Calcification and Osteogenesis. Fundamentals of Bioactivity. Clinical Results Versus Experimental Data Bioactivity: Interface and Surface Reaction Layers. *In Vitro* and *In Vivo* Effects of Bioactive Materials. Processing-Property Relationships. Ceramic Heart Valves. New Clinical Uses. Bioinert and Wear-Resistant Materials. Composites. Applications of Bioactivity. Bioactive Glasses. Hydroxyapatite Coatings. Bone Cement. Mechanical Aspects of Bioactive Ceramics. 528 pages, ISBN 0-08-042143-1 Hardbound Publication: March 1995, Price: £69.00 (US$110.00)

Bioceramics, Volume 7

Edited by Ö.H. Andersson, R.-P. Happonen, Abo Akademi University, Turku and A. Yli-Urpo, University of Turku, Finland

The primary forum for presentation of new work in the field of bioceramics is the annual International Symposium on Ceramics in Medicine. The chapters of this book represent the proceedings of the seventh meeting in this series, held in Turku, Finland, in July 1994. The conference attracted a multidisciplinary audience from the bioceramic community, including leading academic and industrial scientists, manufacturers and regulators. The volume comprises 69 article.

Chapter headings: Review. Preparation of Bioceramics. Reaction Kinetics and Mechanisms of Bioactive Ceramics. Induction of Bioactivity. Bioactive Ceramics and Tissue Reactions. Hydroxylapaptite Coatings. Bioactive Composites and Cements. Cells and Materials. Bone Induction. Bioinert and Wear-Resistant Materials. Clinical Results. 480 pages, ISBN 0-08-042144-X. Hardbound Publication: March 1995, Price: £90.00 (US$145.00)

Bioceramics, Volume 8

Edited by J. Wilson, L.L. Hench, University of Florida, USA and D. Greenspan, US Biomaterials Corporation, Florida, USA

This work contains the latest research on the increasingly important and wide-ranging role of bioceramics in medicine. Contributions from internationally renowned scientists and researchers reflect the rapid developments occurring in major areas of ceramic materials used in orthopaedic, cardiovascular, dental and other applications.

Bioceramics, Volume 8 is the edited proceedings of the eighth International Symposium on Ceramics in Medicine, held in Florida, USA in November 1995. The symposium provided a valuable forum in which important work in the field of bioceramics was presented.

This up-to-date and comprehensive account of current work in bioceramics will be a vital reference document for academic and industrial researchers in the field, and it will also be of great value to students and lecturers in materials science, medical engineering and clinical implantology. The book contains 115 high-quality photographs, and contains both an author index and a subject index.

Chapter headings and selected papers:

Bone Biology. Bone and its repair (J. Hollinger, B. McAllister). Bone cell responses to artificially produced surface apatite layers (J.D. de Bruijn et al.). Bone induction on the surface of hydroxyapatite ceramics (H. Ohgushi et al.).

Spinal Reconstruction. Biomechanics of the spine—a materials perspective (V.K. Goel).

Orthopaedic Applications. Comparative bone formation in several kinds of bioceramic granules (H. Oonishi et al.). Evaluation of the effect of stress corrosion on zirconia femoral heads (M.G.S. Murray et al). Structural characterization of natural and synthetic bioceramics by photo acoustic—FTR spectroscopy (I. Rehman, W. Bonfield). Active brazing for biomedical applications (E. Lugscheider et al.).

ENT and Maxillofacial. Interactions between the frontal sinusitis-associated pathogen *haemophilus influenzae* and the bioactive glass S53P4 (P. Stoor et al). The importance of adhesion through biological glass to the acustic membrane of TOR Protheses (P. Laudadio et al.).

Dental Applications. Bioceramics in dentistry (K. de Groot, J.G.C. Wolke). Glass ceramics for dental restorations (W. Höland et al.).

Calcium Phosphate Coatings. Structural changes induced during thermal spraying of hydroxyapatite. A comparison of three different spraying methods (J.C. Knowles et al.). Characterization of hydroxyapatite precipitated from different reactants (N. Asaoka et al.). Artificial trachea made of polymers coated with hydroxyapatite (Kazuya Suzuki et al.).

New Directions. Microfracture and acoustic emission in pyrolytic carbon heart valve material (J. Lankford et al.)

Composites. Analysis of surface structures on bioglass®/polyethylene composites *in vitro* (J. Huang et al.). Rapid bone formation by grafting cultured bone in porous hydroxyapatite (T. Yoshikawa et al.). A hydroxyapatite-polymer composite prepared by mimicking bone mineralization (P.J. Li et al.). Preparation of calcium phosphate bioceramics by moulding and sintering (E. Mejdoubi et al.)

Bioactive Glasses. The evaluation of surface structure of bioactive glasses *in vitro* (D.C. Greenspan et al.). Glass for radiotherapy of cancer prepared by phosphorous ion implantation (M. Kawashita et al.).

Subject index. Author index. 552 pages ISBN: 0-08-042677-8 Hardbound Publication: November 1995, Price: £125 (US$ 200)

New resources from CAB International

Two new bibliographies are available on floppy disk from the Centre for Agriculture and Biosciences (CAB). Both contain references to literature published world-wide since 1989 and include user-friendly search software.

The bibliography on biosafety contains 900 entries. Each record has a full bibliographic reference with detailed indexing for accurate searching. Over 95 per cent of records include an informative summary.

The bibliography on Intellectual Property Rights (IPR) in Biodiversity contains 600 references. Subjects include: the impact of the Convention on Biodiversity; the patenting of genes and gene technology; and public attitudes and practical aspects of IPR.

Also, CAB has a new book titled *Genetically Modified Organisms: A Guide to Biosafety.* The book is prepared by the United Nations Industrial Development Organization in cooperation with the International Centre for Genetic Engineering and Biotechnology. Topics include biological risk assessment; public perception of biotechnology; environmental release of GMOs; and safety issues. Contact:

CAB International, 845 North Park Avenue, Tucson, AZ, USA 86719. Tel.: (800) 528-4841; Fax: (602) 621-3816.

Information service covering publicly funded research projects in the EU

An information service covering ongoing and recently completed publicly funded research in the member States of the EU, under the title BIOREP, has three main objectives. These are: to further scientific contacts; to identify trends; and, to assist in the coordination and planning of research projects.

The database contains more than 7,000 projects from over 2,300 laboratories and institutes.

Biotechnology topics include: nucleotide sequences, protein sequences, 3-D structures, European Bioinformatics Network, biomaterials repositories and horizontal services.

Details: Library of the Royal Netherlands Academy of Arts and Sciences (Library KNAW), P.O. Box 41950, NI-1009 DD Amsterdam, e-mail: harrie.lalieu@library.knaw.nl, Tel.: (31 20) 6685511, Fax: (31 20) 6685079. Also available on the World Wide Web: http://www.knaw.nl/www/bibbron.html.

Directory of Australian Biotechnology

A 64-page Directory of Australian biotechnology companies will be produced by the ABA early in 1996. It is planned to also put the entire Directory "on-line" on Internet. The Directory will be produced for release at the International Biotechnology Congress and International Symposium on Yeasts in Sydney in August 1996. The Directory will include full description of all biotechnology companies who are corporate members of the ABA or who become corporate members in 1996.

Collecting Plant Genetic Diversity: Technical Guidelines. Edited by Luigi Guarino, V. Ramanatha Rao, International Plant Genetic Resources Institute, and Robert Reid, Department of Primary Industry, Australia

The case for conserving biodiversity is well established on economic as well as scientific grounds. Biodiversity is essential for sustainable development, adaptation to a changing environment and the continued functioning of the biosphere—indeed to human survival itself. Plant breeders are dependent upon the availability of a large pool of diverse genetic material represented by local races and wild relatives, since in themselves modern crop varieties provide too restricted a gene pool for further breeding. Without the ability to draw from a diverse genetic reservoir, further improvement may not be possible. It is therefore essential that guidance is available on collecting plant germplasm.

In recent years, it has become evident that there is no single publication that provides the prospective collector of germplasm with generic as well as specific and theoretical, as well as practical, information. It was to fill this gap that the International Plant Genetic Resources Institute (IPGRI), together with FAO, IUCN and UNEP, cooperated to produce this book. The volume is a comprehensive reference work and is aimed at both new and experienced collectors as well as those with a general interest in plant genetics, breeding and biodiversity.

748 pages, published April 1995, US$120.00 (ISBN 0-85198-964-0). Contact: CAB International, Headquarters: Wallingford, Oxon OX10 8DE UK, 1230 N. Park Avenue, Tel.: 01491-832111; Fax: 01491-826090; Telex: 847964 (COMAGG G). Distributed in the US by The University of Arizona Press, Tucson AZ 85719, Tel.: 1-800-426-3797; Fax: 520-621-8899, Tel.: 520-621-1441, Wayne Koch.

Chinese Biotechnology Directory 1996

(English edition available)

This second edition has been expanded, updated and revised completely, and contains the most up-to-date and accurate data. It has been divided into three parts, with an index and appendix. The first part covers an overview of China's biotechnology R&D, policy, bioindustry, regulatory environment and information services. The second part lists all government agencies and societies. The third part lists research institutes, university departments and companies. Information is provided on the organization's name, address, telephone/telex/faxnumbers, activities and services offered.

Also available from the same source is the *China Catalogue of Cultures (English Edition)*. Compiled by the China Committee for Culture of Microorganisms (CCCM), this reference contains data on 10,716 strains covering species of cultures, including viruses, bacteriophages, bacteria, actinomycetes, yeasts and filamentous fungi.

Information on prices and ordering is available from: Han Consultants Inc., P.O. Box 71006, Wuhan, Hubei 430071, P.R. China, Tel.: +86-27-783-8532, Fax: +86-27-781-8343.

Canadian Biotechnology Directory 1996

The fully revised and expanded third edition of the *Canadian Biotechnology Directory* is now available. This new edition contains over 1,000 entries and covers all sectors of industry. Price: US$ 149.95. Further details from Contact International Inc., 358 Delrex Blvd, Georgetown, Ontario, Canada L7G 4H4. Tel.: (905) 873-1295; Fax: (905) 873-6133, e-mail: CNTACT@io.org.

Biocomputing

Genetic resources on the Internet

The Internet is a net of computer networks. A universal language known as the IP/TCP (Internet Protocol/Transmission Control Protocol) allows the exchange of information between different kinds of computers. Telephone lines connect the computers, each of which has an address assigned by the Domain Nomenclature System, which is universally recognized. Some of these computers function as "nodes", which means they automatically receive information, assess its origin and destination and instantly select the most suitable place to send it. In this way, information flows from one node to another via the Internet across the planet. Both the nodes and the connections between them make up what is known as "cyberspace".

The Internet (or "Net" for short) is not the product of a single designer, but the result of the extension and expansion of individual communication networks that were set up to enhance the sharing of information between universities and public research centres. The way the system has been set up has two main consequences. The first is the emergence of a decentralized communication system. The second is the sharing of costs. Each node pays for connections to several other nodes which in turn pay to those connecting them to the rest of the Net. As a result, any user may contact a computer in another continent for the same cost of reaching the nearest node.

The flow of information among millions of computers has been made possible not just by the IP/TCP protocols,

but because of the use of server/client architecture. A server is a program on the transmitter computer that standardizes the information in such a way that it can be readily deciphered by its partner program, the client, which could be any one of the millions of computers on the Net that will receive the information.

One of the potential drawbacks of the Internet is that it adds another hole in the fabric linking North and South: an information gap. According to a recent Panos Institute *Media Briefing*, both the lack of reliable (or any!) telephone lines and the higher (relative and absolute) costs of both equipment and Internet providers in the South are at the heart of this gap. Because of this, Internet access is likely to reinforce the existing intellectual elite. At the same time, Internet is providing communities, NGOs, activists and concerned people in the South unprecedented opportunities for political and cultural influence. Internet also has practical advantages: Panos reports that in western Zambia, for example, doctors working in rural hospitals have access to electronic mail, which allows them to get prompt specialist advice from the Lusaka Medical School.

Information can be handled in many ways on the Net. The TELNET service allows the user direct access to a computer, as a temporary terminal (that is: it allows the user to work in that computer). Some nodes store information in servers, offering it to the public. These servers act as relay nodes for users, enabling them to contact other nodes hosting related or specialized information. The Net also allows users to retrieve both files and programs from other computers, through the FTP (File Transfer Protocol) service. Electronic mail services allow users to send a message to as many e-mail addresses as desired, for the same cost as sending it to one. Electronic conference systems, based in the e-mail system, allow people around the world to network on issues of common concern. News groups alow an open access to debates on an almost endless variety of issues.

What do you need to enter the Internet?

The Internet can be reached in several ways. Each method required:

- A computer: Any computer enables entry to the Internet, if it has
- A modem, which is a device allowing computer to use
- A telephone line, through which you can contact an
- Internet provider, which is an organization owning at least one
- Internet node, which may be used as a bridge to access all the Internet.

There are three kinds of Internet providers: commercial companies (i.e. IBM, CompuServe), private organizations (such as the Association for Progressive Communication, or APC), and public networks (which are normally set up to serve governments, universities and research centres). Some of them only offer some of the services, such as e-mail. Two things must be born in mind when choosing a provider: the cost of the telephone call to reach the node—to be paid to the telephone company—and the cost of the Internet connection—which depends on the provider. Normally, providers charge according the amount of time connected to the Net, not for the amount of information that is reached or retrieved.

The best way to access the Internet in your country or region is by getting a connection to a pubic node through a local university or research institute. If that is not possible, try a private organization such as the APC, which will always be cheaper than a commercial provider. Since, as was stated before, the Net is a not a monolithic structure but a web of webs, navigating will be quite bewildering at first. Below we recommend a good introductory manual that has been published for NGO users.

Some places to visit

The *WWW Virtual Library: Biotechnology, General/ Information Sources Including Other Biotechnology Directories*—provides a large list of biotechnology-related Web sites, both public and industry, and many thematic areas related to biotechnology, from commerce to patents to pharmaceutical information. This is a good place to start if you are looking for information from mainstream institutions. At the moment they do not seem to include NGO perspectives (or Web sites). This might, however, change if NGOs asked for their Web sites to be included.
http://www.cato.com/interweb/cato/biotech/bio-info.html.

The Agricultural Biotechnology Centre (Hungary) is a well-connected Web site that you will often come across when navigating in search of biotechnology information. It limits its information to the Centre's activities. Besides that specific information, the interest of the ABC relies on the fact that it is running an experimental newsreader programme allowing access to Bionet conferences.
http://www.abc.hu.

Bio-Online is the (US) Biotechnology Industry Organization's public relations Web page. It is a good place to go and look for general information on the US biotechnology sector: number of companies, number of employees, revenues, sales, patent applications, and so on. The information seems to be updated from time to time (it includes 1994 data). *http:/cns.bio.com/bio/2usbio.html.*

The Biotechnology Information Center (BIC) is a service of the National Agricultural Library of the US Department of Agriculture. Designed as a service to the biotechnology industry, it contains useful research tools such as a thematic bibliography (from the National Agricultural Library's Electronic Bulletin Board System (ALF), a complete BIC publication list, which is updated quite regularly, a list of AgBiotech-related databases (from June 93); a list of (and connections to) Biotech Newsletters (where you can find alternative points of view, such as IATP and RAFI); and multiple connections to other biotechnology sites (both WWW sites and Gophers). Perhaps the most interesting service the BIC provides is the FULL TEXT of all US PATENTS on biotechnology, both for 1994 and 1995. Worth a visit.
http:/www.inform.umd.edu:8080/EdRes/Topic/AgrEnv/Biotech/

The Rural Advancement Foundation International has its own Web site where it is possible to find out what they do and even who they are: ever wondered who was hiding behind "Hope Shand" or "Edward Hammond"? Now you can find their photos on-line, along with RAFI documents. All the *RAFI COMMUNIQUES* from June 1991 are available, although they are not necessarily complete (the table on biopiracy is not there). *RAFI OCCASIONAL PAPERS* are also on line, and RAFI has an ongoing project to include the Spanish version of some of their documents. The main pages introduce the organization and reports on the key issues RAFI is working on (where these lead to RAFI documents). Only a small complaint: there are some difficulties in reading the main pages, because of a lack of

contrast between the background and the writing. *http:/www.charm.net/~rafi/rafihome.html.*

In an unprecedented move towards transparency and open participation, the FAO Plant Genetic Resources (PGR) Department has set up a Web site for the upcoming *International Technical Conference (ITC) on Plant Genetic Resources.* Besides a presentation of the Conference, it includes the country reports that have already been sent to the Secretary of the Conference, and also an outline of both the report on the state of the world's PGR and the Global Plan of Action, which will both be the main outcomes of the ITC. In order to promote debate, electronic conferences (accessible via both e-mail and a Web browser program) have been set up on: Plant Breeding/Improvement, Genetic Diversity/Genetic Erosion, Ex Situ Collections, In Situ Conservation and Crop Improvement, Regeneration and Trading/Education. *http://web.icppgr.fao.org.* (Reprinted courtesy of GRAIN from *Seedling*, December 1995)

Additional biotechnology resources available on the Internet

American Type Culture Collection (ATCC): http://www.atcc.org/
Australian National Genomic Information Service (ANGIS): http://morgan.angis.su.oz.au/
ANU Bioinformatics Service: http://life.anu.edu.au/
DNA Data Bank of Japan: http://www.nig.ac.jp
Enzyme Data Bank: http://expasy.hcuge.ch/sprot/enzyme.-html
European Molecular Biology Laboratory: http://www.embl-heidelberg.de/
GDB Human Genome Database:http://gdbwww.gdb.org/
Medline via Entrez: http://atlas.nlm.nih.gov:5700/entreztopmed.html
Natonal Center for Biotechnology Information (NCBI) — Genbank: http://www.ncbi.nlm.nih.gov/ *or* http://www.ncbi.nlm.nih.gov/Search/Entrez/index.html
Prosite: http://expasy.hcuge.ch/sprot/prosite.html
Prot Web (Johns Hopkins University): http://www.gdb.org/
Protein Data Bank (PDB): http://www.pdb.bnl.gov/
Protein Information Resource (Houston): http://www.bchs.uh.edu/
Restriction Enzyme Database (NEB): http://www.neb.com/rebase/rebase.html
Swiss-Prot — Protein Sequence Database: http://expasy.hcuge.ch/htbin/sprot-search-de/ (Geneva)
The Flybase WWW Server (Indiana University): http://iubio.bio.indiana.edu:80/1/Flybase
Topics in Biological Sciences on the Internet: http://molbio.umn.edu/bionetwork.html
Virtual Laboratory: http://joda.cis.temple.edu/~mandviwa/vlab.html
WFCC World Data Center on Microorganisms: http://www.riken.go.jp/

(Source: *Australasian Biotechnology*, Vol. 5, No. 5, October 1995)

ABA Launches its Web Site

The Austrialian Biotechnology Association (ABA) will be going "on-line" very soon.

The ABA has set up its own Home Page on the World Wide Web and the Internet mode for this will soon be announced.

The new Home Page contains information about the ABA and about publications and conferences. It also contains very useful cross-references to biotechnology-related e-mail addresses and World Wide Web addresses.

The new Home Page contains the full text of all the ABA educational leaflet series, and this facility should be a great boon to school users.

It is initially planned to place the contents page of the journal issue of *Australasian Biotechnology* on the Home Page. (Source: *Australasian Biotechnology*, Vol. 5, No. 4, 1995)

The EBI NetNews Filtering Service

The NetNews Filtering Service tries to provide a simple and efficient way to access the articles published in the science news groups of USENET News. It allows scientists to subscribe specifying a profile of interest, and sends them periodically any new articles published in relation with this profile. The Filtering Service can be accessed through the EMBL Outstation at Hinxton Hall (the EBI) by electronic mail to netnews@embl-ebi.ac.ukor through the World Wide Web at URL http://www.embl-ebi.ac.uk.

Modern researchers need to keep up to date with new advances in their fields of interest. While classic media, like books and journals are very valuable tools, the slow pace at which these publication methods work results often in important delays which can render the information completely outdated by the time it reaches the reader.

For that reason each day more scientists pay attention to electronic media: the efficiency with which they can publish results, get help, engage in technical discussions or even know in advance what is to be published in scientific journals has converted the USENET News into a very popular tool.

In the USENET News, people can arrange in special interest groups devoted to different topics. However, with the increasing popularity of this system, the traffic of information in each of the groups grows constantly, rendering them easily unmanageable. This in turn results in the creation of new groups for the discussion of more specialized topics.

Further details available from help@embl-ebi.ac.uk. (Extracted from *BIOBYTES*, Vol. 3, No. 3 and Vol. 4, No. 1)

Genome Data Base access via WWW

The GDB Web server is available directly at the following URLs:

United States *http://gdbwww.gdb.org/*
Australia *http://morgan.angis.su.oz.au/gdb/docs/gdbhome.html*
France *http://www.infobiogen.fr/gdbwww/*
Germany *http://gdbwww.dkfz-heidelberg.de/*
Israel *http://inherit1.weizmann.ac.il/gdb/docs/gdbhome.html*
Japan *http://gdb.gdbnet.ad.jp/gdb/docs/gdbhome.html*
Netherlands *http://www-gdb.caos.kun.nl/gdb/docs/gdbhome.html*
Sweden *http://gdb.embnet.se:443/gdb/docs/gdbhome.html*
United Kingdom *http://www.hgmp.mrc.ac.uk/gdb/docs/gdbhome.html*

GDB User Support Offices

United States, Baltimore, Maryland, *help@gdb.org*
Australia, Sydney, *bucholtz@angis.su.oz.au*
France, Villejuif, *gdb@infobiogen.fr*
Germany, Heidelberg, *gdb@dkfz-heidelberg.de*
Israel, Rehovot, *lsprilus@weizmann.weizmann.ac.il*
Japan, Tokyo, *mika@gdb.gdbnet.ad.jp*
Netherlands, Nijmegen, *post@caos.caos.kun.nl*
Sweden, Uppsala, *help@gdb.embnet.se*
United Kingdom, Cambridge, *admin@hgmp.mrc.ac.uk*

Biodiversity Information Network List

BIN21 held a meeting at BDT (Base de Dados Tropical) in Campinas, Sao Paulo, Brazil on 17-19 October to discuss the Clearing-House Mechanism under the Convention on Biological Diversity. The document prepared by the Secretariat to the Convention for the COP-2 (Conference of the Parties held in Jakarta, Indonesia in November 1995) on the "Establishment of the Clearing-House Mechanism to Promote and Facilitate Technical and Scientific Cooperation" (UNEP/CBD/COP/2/6) was discussed by the participants.

While agreeing with the broad concepts as laid out in that paper, participants were concerned with the proposed implementation through the Pilot Phase (part 5) as laid out in paragraphs 17-22.

A report was prepared proposing specific actions for the pilot phase, its goals and including the role of BIN21 *vis-à-vis* the Clearing-House Mechanism. This report is available at *http://bdt.org.br/bin21/wks95/chm_doc.html.*

Further information about BIN21 and its participating nodes can be found at the BIN21 Home Page on the Internet at *http://bdt.org.br/bin21/bin21.html.* (Source: *Australasian Biotechnology*, Vol. 5, No. 6, December 1995)

The Human Genome Management Information System (HGMIS)

The Human Genome Management Information System (HGMIS) facilitates genome research and genetics education of the US Department of Energy (DOE) Human Genome Program Task Group. HGMIS staff members use their scientific and literary expertise to communicate with researchers, interested public, and industry representatives person to person and via a newsletter and other printed and electronic publications. HGMIS fosters collaboration and helps to reduce duplication of effort in the genome research community. Educational outreach is expanding in response to the great demand for information about the Human Genome Project—the international effort to characterizethe entire human genome and make human genes accessible for biomedical study.

HGMIS staff answer questions about the genome project and supply general information by telephone, fax, e-mail and mail. Callers have included graduate students, researchers, medical professionals, private companies and individuals interested in different aspects of the project. Biotechnology companies, for example, have contacted HGMIS for background information to identify goods or services potentially useful to genome researchers and the medical community.

HGMIS produces and distributes publications to a broad audience that includes genome project investigators and basic researchers, genetic counsellors and genetic-disease support groups, teachers and students, industry and government representatives, ethicists, science writers and other interested individuals. In addition to the newsletter, over 50,000 document copies have been distributed to requestors. (Multiple copies of HGMIS documents are available for meetings and educational purposes.)

Human Genome News

This 16-page bimonthly newsletter serves a broad audience with technical and general-interest genome articles, meeting reports, national and international project news, informatics and research resources, meeting and training calendars, and funding announcements. In November 1995, subscribers numbered 11,500 in 69 countries. *Human Genome News (HGN)* also serves as a primary information source for other, more discipline-specific publications that extract or reprint information. The newsletter is jointly funded by DOE and the National Institutes of Health (NIH).

DOE Human Genome Program Reports

The *Human Genome 1991-92 Program Report* provides a detailed overview and history of the DOE genome programme, research highlights, abstracts of funded work, and a 41-page primer explaining some basic genome-project science and strategies. The *Human Genome 1993 Program Report* updates the 1991-92 report and provides new information, including abstracts of 60 new or renewed projects. The 1994-95 report is in progress.

DOE Primer

The *Primer on Molecular Genetics* is a popular resource for teachers, genetic counsellors, and eductional organizations and for researchers' educational outreach efforts across the USA. More than 33,000 copies have been distributed in lectures, biology teacher meetings, genetic-counsellor workshops, college classrooms and continuing medical education courses.

DOE Workshop Reports

These reports feature an overview and detailed abstracts of ongoing DOE-funded research presented at biannual DOE contractor-grantee workshops. The meetings are intended to facilitate collaboration, assess the state-of-the-art in genomic research and develop strategies to attain project goals.

Electronic Access

The HGMIS Home Page is available on the World Wide Web at *http://www.ornl.gov/TechResources/Human_Genome/home.html.* This comprehensive text-based WWW server provides access to the primer, DOE programme and workshop reports, issues of *HGN*, textual genome information and links with related databases. DOE programme reports and *HGN* are also available in a searchable format through the Johns Hopkins University computational biology gopher at *gopher.gdb.org* under *Genome Project.* (Source: *News Release*, 1995)

SEPASAL Survey of Economic Plants for Arid and Semi-Arid Lands

Many readers will already be aware of the SEPASAL database (the Survey of Economic Plants for Arid and Semi-Arid Lands). The following is intended to provide an update on recent developments and to introduce the database to those who do not know of it, or have not used its services.

SEPASAL is a major and unique database on useful plants of drylands and is maintained at the Royal Botanic Gardens, Kew. It began in 1981 with funding from OXFAM. More recently, funds have been provided by the Clothworkers' Foundation. The database contains information on approximately 6,000 useful dryland species, excluding major crops. It is widely used by aid agencies, development organizations, governmental and non-governmental organizations and individual research workers and growers. SEPASAL is also used to target species for germplasm collection and storage for research, biodiversity conservation and utilization.

Funding from the Clothworkers' Foundation has enabled the computer software to be extensively upgraded over the last two years. Data fields now available include:

- Scientific name (including synonyms);
- Plant family;
- Vernacular and trade names;
- Plant description;
- Geographical distribution (to country or state level) and status (native or introduced, etc.);
- Distribution map;
- Conservation status;
- Life cycle and regeneration;
- Uses of plants (adopting an international standard classification);
- Use-related properties and chemical analyses;
- Ecological data including climatic tolerances, soil preferences, topography and associated species;
- Physiology;
- Cultivation details, pests and diseases;
- Production;
- Seed sources;
- Colour images.

All the information will be linked to data sources.

The SEPASAL team is now revising the details held on each taxon in the database using extensive information held in manual files and other sources. At the same time, data sources are being attached to items of information. The expanded data sets will enable more accurate assessments of the economic value and potential of individual plant species, and will also allow detailed answers to be provided more easily on a wider range of inquiries than has been possible to date.

Work is currently under way on the *Burseraceae* (which includes the frankincense trees), *Cucurbitaceae* (the cucumber family) and *Ebenaceae* (the ebony family). Legumes, grasses, amaranths and chenopods are among a list of 30 priority groups which will be worked upon initially.

Two other databases are maintained by the Centre for Economic Botany. The Economic Botany Bibliographic Database (EBBD) currently contains citations to more than 150,000 references dealing with plants of economic value (including those of drylands), while the Contracts' Database has records of over 1,000 organizations and projects mostly concerned with drylands.

With Kew's unique resources at its disposal, SEPASAL can help to answer a wide range of inquiries on useful plants of drylands. For example, you may need to know which plants could provide soil cover to prevent erosion in an area which has less than 300 mm of rainfall, or you may want ideas on edible plants that would be suitable for saline soils.

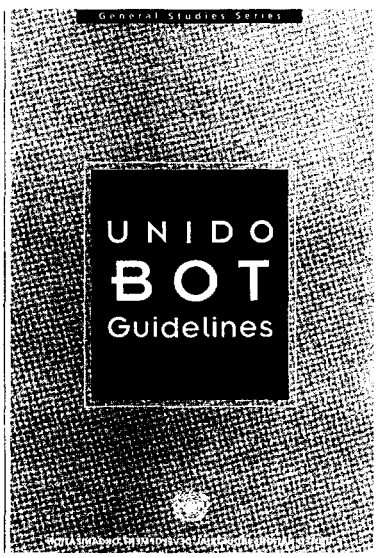
Whatever your inquiry may be, please state clearly what information you would like, and give as much detail as possible, including the reasons for your interest in the subject. General outputs can be provided, such as information on economic plants of a particular region, but these can be lengthy, and it may be more useful to narrow the request down, for example by being more specific about the following:

- The type(s) of plant you are interested in (e.g. tree, shrub or herb, annual or perennial, thorny or unarmed, etc.);
- The environmental parameters that concern you (e.g. soil type, rainfall range, altitude);
- The uses you require of the plants;
- The country or area you are working in;
- Other information you regard as important.

The value of SEPASAL depends on feedback from its users. For example, the team would like to know which families or groups of plants are of interest to you to ensure that priorities match those of the users. You can help the team by completing a short questionnaire form (available from the address below). They also welcome the results of field trials or other research on species of potential value. Please write or e-mail to the address below.

The information SEPASAL provides is free for NGOs involved in development work. Charges are made to commercial inquiries.

Concurrent with improvements to its data sets, SEPASAL is reviewing methods of data dissemination and exchange. The possibilities of releasing CD-ROM versions of SEPASAL or Run-Time Versions of the software are being examined, along with ways of transferring data between databases. The Contacts' Database may be made available on the Internet in the future. More details are available from SEPASAL, Centre for Economic Botany, Royal Botanic Gardens, Kew, Richmond, Surrey TW9 3AE, United Kingdom. Tel.: (44)- (0)181-332-5772/5704; Fax: (44)-(0)181-332-5278, E-mail: sepasal@rbgkew.org.uk.



UNIDO BOT Guidelines

The *Guidelines for Infrastructure Development through Build-Operate-Transfer (BOT) Projects* prepared by UNIDO cover the entire spectrum of financial and legal issues faced by government authorities and project managers in the development of BOT projects, while offering developing countries the basic orientation needed to design effective BOT strategies. The *Guidelines* also provide essential practical information on the structure and procedures of BOT arrangements and are intended to help reduce the time and costs involved in developing and contracting BOT projects.

The *Guidelines* contain chapters on the following subjects: introduction to the BOT concept; phases of a BOT project; economic framework for BOT schemes; the Government's role in providing for successful BOT projects; transfer of technology and capability building through BOT projects; procurement issues and selection of sponsors; financial and economic appraisal of BOT projects; risk identification and management; financial structuring of BOT projects; the contract package; the project agreement; the construction agreement; operation and maintenance contract; transfer of ownership; and factors that determine success.

The *Guidelines for Infrastructure Development through Build-Operate-Transfer (BOT) Projects* (UNIDO, 1996) ID/SER.0/22 are available at US$ 65, plus postage.

Further information and orders:

UNIDO
Documents Unit (F-355)
Vienna International Centre
P.O. Box 300
Vienna A-1400, Austria

In addition, copies may also be ordered from:

Sales Section
United Nations (Room DC2-0853)
New York, N.Y. 10017, USA

Sales Unit
United Nations
Palais des Nations
CH-1211 Geneva, Switzerland