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CONTENTS

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TO OUR READERS

In recent years, biotechnology has been considered as an essential tool for socio-economic development by an increasing number of developing countries.

Yet, if anything, as the science frontier of the technology is advancing at an ever accelerating pace, commercial entry into modern biotechnology for most developing countries is rapidly moving away.

Globally, biotechnology science has been profoundly influenced by two factors, namely, the drastic reduction of public funds for research and the dominant role of the private sector in biotechnology R&D for health care, agrifood and other industrial applications.

The compound effect of these factors has been that technological advancement has remained stagnant in those areas that have been deemed unattractive in terms of returns on investment.

These are precisely those areas that are of prime importance for developing countries (e.g. orphan crop and infectious disease research) and in which biotechnology can have a profound effect.

Despite this, donor and technical support agencies have been reluctant to redirect part of their investments away from other conventional types of technology assistance towards biotechnology. The reason that is often invoked is the lack of an enabling environment in most developing countries which would translate bioechnology R&D or import products and services into community-level benefits.

However, it is becoming increasingly evident that conventional programmes addressing health care and agricultural productivity needs in the developing world are becoming dependent on biotechnology to enhance their delivery prospects and benefit impacts.

Clearly, in developing countries, biotechnology R&D is not the be all and end all. It needs to be coupled with actions to strengthen adoptive capacity (i.e., introduction of information and other key technologies) and to introduce policy and institutional reforms conducive to public and private investment.

The reason for this is that the ability of developing countries to use biotechnology for public good depends primarily on their capacity to absorb and adapt proprietary technology to their specific needs. Policies with regard to intellectual property protection, increasing scope for intervention and biosafety are essential in generating an enabling environment for the application of biotechnology.

International agencies have an increasing role to play in identifying areas where the interests of the privae sector and the spirations of developing countries are not mutually exclusive and forge public-private partnerships in these areas.

G. Tzotzos
Investment and Technology Promotion Division

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A. SPECIAL ARTICLES

ASSURING QUALITY OF BIOPHARMACEUTICALS: A PREREQUISITE TO START AND STAY IN BUSINESS

by

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Regulations are necessary to ensure consumer protection and safety by providing an efficacious, pure, safe and qualitative pharmaceutical product. On the other hand, the term "quality assurance" has acquired a threatening tone for many emerging economies and companies. Many organizations see regulations on product quality as concealed protective measures that only benefit developed economies and established companies. This is mainly due to the widespread view that ensuring and improving quality in all sectors of industry is normally associated with enormous costs, thereby excluding newcomers with limited resources. This seems particularly true for the field of biopharmaceuticals. In this paper the necessity for stringent regulations to improve and ensure the quality of a pharmaceutical product derived from biotechnology will be outlined in an effort to improve the understanding of quality issues. In this article Good Manufacturing Practice (GMP) concepts are reviewed and practical measures presented. GMP thus applied develops into a business asset, not merely a regulatory hurdle.

Regulations: protectionism or protection

An ever increasing number of national and international regulations have been, and are currently being implemented all over the world. These regulations are not only valid for the countries in which they were issued, but in the case of foreign companies trying to gain access to these markets, also for those companies, irrespective of their location and the economic status of the country. This is particularly true for the pharmaceutical industry, and within this industry for the manufacturing of biopharmaceuticals. Why are regulators so concerned about this special sector of industry, and are these regulations hampering industrial development? The tight regulations in the pharmaceutical industry have become necessary for a number of reasons:

- Adulteration and misbranding;
- Wide distribution;
- The production of new drugs with increasingly complex production technology;
- Potency of (bio)pharmaceuticals;
- Stability of (bio)pharmaceuticals;
- Political concern over possible environmental impacts of biopharmaceutical processes (especially those using recombinant DNA technology) and products.

These points have to be carefully considered to understand the necessity for stringent regulations in the quality of biopharmaceuticals. Most of these points will also apply to both traditional pharmaceuticals (and indeed to many other goods) and biopharmaceuticals.

Adulteration: Adulteration is defined by the statutes of the United States Food and Drug Agency's (FDA) CGMP guidelines (Current Good Manufacturing Practices) as they were put forth under the Federal Food, Drug, and Cosmetic Act:

"A drug or device shall be deemed to be adulterated if it is a drug and the methods used in, or the facilities or controls used for its manufacture, processing, packing or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports or is represented to possess".

The risk of endangering consumers' health by changing the product's quality advertently or inadvertently is the foremost concern of all regulating authorities. Therefore, any change to the process has to be proven to yield an identical product (Kennedy 1995). In the case of modifications to the product characteristics, the resulting new product has to be fully evaluated.

Wide distribution: Due to international commerce an incredible variety of goods is being shipped for use or consumption throughout the world. The consumer purchasing a particular product may be located anywhere from close proximity of the production site, to another country thousands of miles away, with a different language, culture, environment and economic status. Products are being increasingly manufactured, not by diverse manufacturers, but by specialized production sites, in some cases providing supplies to cover large sections of worldwide demand. In the event of defective product quality, a great number of individuals could be affected.

Complex production technology: Biopharmaceuticals are in most cases produced at moderate temperatures and pressures, using biocompatible chemicals, thus enhancing process safety for the operator and environment. But due to the complexity of the metabolic pathways and regulation of living organisms, process parameters have to be carefully adjusted and controlled to ensure batch to batch reproducibility. Small variations in these parameters can lead to modifications in the product. However, not only has the complexity of biosynthesis in the bioreactor to be taken into account, but also the complex steps in downstream processing to remove hazardous impurities from the product. Media used for bioprocessing in many cases provide good growth conditions for contaminating organisms, making aseptic and hygienic processing very important. The validation of the necessary equipment and processes have

become an art in itself and has been the focus of many publications.

Potency: In many cases the potency of traditional biopharmaceuticals has been overestimated by the public, but in the last few years a number of drugs (e.g. immune modulators, substances with hormone-like action, neuroactive substances, etc.) have been produced as biopharmaceuticals that rival or even surpass traditional chemistry-derived drugs. Special care has to be taken to ensure quality with respect to dosing of such potent drugs. Another concern is the carryover of such drugs into subsequent processes in multifunctional bioprocessing plants. This is especially the case if the subsequent product is less potent and has to be administered in comparatively high doses (see also equipment validation).

Stability: Biopharmaceuticals are in many cases less stable than chemically derived products. Therefore packaging, storage, transport and distribution are important issues to be dealt with as regards product quality. Regulatory authorities have undertaken considerable efforts to ensure a proper validation of product stability for biopharmaceuticals.

Environmental impact: Safety aspects have always been an issue and are much discussed in the area of biotechnological production. Pathogenic species, toxins and allergens were considered to be the main risks associated with the use of biological agents. In classical biotechnology only some special cases, such as the production of vaccines with live pathogens were considered to be hazardous, as most of the biological agents used in industrial biotechnology had a long history of safe use. The introduction of genetic engineering has caused much anxiety, with the fear of biological agents having unknown pathogenic or other detrimental traits being unwittingly created and released into the environment. These fears have resulted in the implementation of various regulations (e.g. by the Organization for Economic Cooperation and Development (OECD), the National Institutes for Health (NIH), the European Community (EC)) concerning the application, containment and deliberate release of genetically modified organisms (NIH, 1986), (OECD, 1986), (EC, 1990), (EC, 1990; EC, 1990). Specialized scientific publications, such as the book *Safety in Industrial Microbiology and Biotechnology*, edited by Collins and Beale (Collins and Beale 1990), have recently become available. We are experiencing a new wave of biosafety awareness, and for this reason this section deals with a "new" aspect of bioprocess engineering, although many technological solutions may be more than 10 to 20 years old. In many cases, gene technology has cleared the way for safer products (e.g. vaccines), but as certain dangers cannot be excluded, no major change in public opinion seems to be imminent. This is also true for the views held by people in developing countries. At the same time, developing nations perceive a big chance of benefiting from these technologies, both in agriculture and in the biopharmaceutical industry, with the isolation, characterization and medical application of bioactive substances from, for instance, indigenous plants. In all countries there is now a widely accepted concept for the safe handling of biological agents for contained use based upon:

- Biological containment (gene construct);
- Physical containment;
- Safe working techniques.

Genetic engineers are striving to create different constructs in order to limit the proliferation of biological agents to the defined process areas (e.g. by introducing so-called suicide genes). Bioprocess engineering is now called upon to design new low emission equipment or to test existing equipment for worker and environmental protection.

If microorganisms are pathogenic to a certain species (e.g. human pathogens), risk assessment is relatively easy. Infection and transmission routes are fairly well known and safety measures can therefore be tailored to specific needs. The term environmental risk is a lot more difficult to define and evaluate, as the scenarios become increasingly hypothetical. On the other hand, environmental risk assessment has become one of the central issues for the acceptability of industrial biotechnology using recombinant organisms. The scenario for environmental risks of non-pathogens has been well defined and analyzed by Winkler and Parke (Winkler and Parke 1992) as being dependent on:

- Escape, numbers and routes;
- Survival of transport and arrival in a suitable niche;
- Survival, adaptation and multiplication leading to competitive growth in the niche;
- Survival during famine periods and/or transport to other niches;
- Spread to and growth in many niches;
- Disturbing one or more equilibria;
- Transfer of r-DNA to indigenous strains, causing their increased multiplication.

Although none of the non-pathogen rDNA production strains have shown any adverse effects in the environment, public concern has created a demand for low emission production methods to minimize residual risks. This approach seems to be controversial, but for the next few years at least bioprocessing will have to work with these higher containment levels.

Quality management concepts

Quality systems have to meet the approval of regulatory agencies such as the US Food and Drug Administration (FDA) or the European Agency for the Evaluation of Medicinal Products (EMEA/CPMP), especially if the products are to be marketed in these countries. As mentioned above, companies from developing nations wishing to export their products to these countries will have to abide by their regulations. But even in the case of production for the national markets, it is advisable to create a quality management system that will comply with FDA standards, profiting at the same time from the FDA's long experience in making drugs safe, while at the same time preparing for future market expansion into North American and European markets. A number of excellent reviews and books have been published on the different regulating bodies mentioned above. By far the most frequently cited agency is the FDA, due to the fact that all products sold in the USA have to gain FDA approval and have to meet its quality standards. (For a review of typical FDA policies and philosophies see (Bozzo 1996)).

Three basic terms are very often used in quality management:

Good manufacturing practice (GMP);
Quality control (QC);
Quality assurance (QA).

To date there is still no internationally agreed upon definition of what these terms comprise, how they relate to one another (GMP, especially QC and QA), and how they are to be implemented in practice. However, existing national (e.g. FDA, MCA) and international definitions (EC, World Health Organization (WHO), International Standards Organization (ISO)) suffice to establish Quality Management Systems, which overall meet the spirit of the regulations

worldwide, and which, if implemented with proper care, awareness for quality issues and effort, will satisfy most inspection authorities.

Good manufacturing practice

As good manufacturing practice (GMP) regulations were originally developed to cover preparation of the final dosage form of pharmaceutical products, considerable confusion exists as to how GMP applies to biopharmaceutical production (Fitzpatrick, Ma' Ayan et al., 1990).

In countries where it applies, GMP compliance for the production of pharmaceuticals, cosmetics and foods is a legal requirement, not merely an optional standard. Enforcement is ensured through inspections by government investigators. Although enforcement is practiced in most countries, it is given the most attention by the FDA, which investigates not only within the USA, but as mentioned above, foreign companies wanting to import into the USA.

Good manufacturing practice regulations, or guidelines, are aimed at ensuring quality of the product by assuring the quality of the process. Quality control by product testing is therefore only part of the overall assurance concept. In practice, GMP begins with process research and development (e.g. development reports, approval requirements), proceeds through validation, continues through manufacturing and controls, end-product testing and reaches into the distribution network of the product (Bliem). However, GMP only applies to the manufacture and control of pharmaceuticals; it does not apply to a company's finance and research departments if there is no involvement with manufacturing. GMP applies to research only, if this department is to develop recombinant agents for biotechnology products, or the department develops processes that are to be transferred to manufacturing; here GMP concerns primarily the testing and systematic documentation of the strains, genes or processes.

The difficulties most often encountered in applying GMP regulations involve their interpretation in terms of "nuts and bolts", i.e. reduction to practice. The difficulties are exacerbated on the one hand by the dynamics of regulatory and interpretational change, and on the other hand by the differences in GMP philosophies between countries worldwide. GMP guidelines state what is to be achieved, not how it is to be achieved, although investigators have fairly clear concepts of how, through their investigational experience across the industry. This has led to a set of industry standards, as for clean room quality, water systems, validation practices and other elements.

GMP regulations are but one element of the regulatory framework for approval to market pharmaceuticals. Approval requirements and GMP regulations are interwoven. For example, the above-cited requirement for the testing and documentation of genetic production agents at the research stage is not strictly a GMP requirement, but is required for product approval.

However, it is best assured by way of a quality management system, such as GMP or good laboratory practice. Another area where GMP and approval are closely intertwined is in the changing of processes and equipment. Changes in the process, the product, methods of analysis, facilities or equipment may need registration with the approval authorities. This interwoven texture of GMP and approval requirements adds to the complex nature of GMP.

The GMP guidelines vary in their content structure from country to country; however for the most part the content is very similar and compromises the following elements:

- Organization and personnel;
- Quality assurance/quality control;
- Facilities and equipment;
- Raw materials, product containers;
- Production and process controls;
- Cleaning and hygiene;
- Packaging and labelling;
- Storage and distribution;
- Laboratory testing;
- Documentation and document control;
- Inspections;
- Validation.

This list by and large represents the structural categories that make up today's GMPs.

Compliance to GMP standards has to go hand-in-hand with process development aimed at product quality and productivity. Process improvement is very often seen as being incompatible with GMP compliance, as it requires process modification. If examined more closely, compliance will always involve process improvement, since the process is defined as the overall activities in relation to the product on the one hand (e.g. documentation, control of starting materials, training, environmental monitoring, etc.) (Bhatt 1996), and GMP regulations that require state-of-the-art production and control on the other.

Pitfalls to avoid

Although the technical intricacy in interpreting regulations is the primary difficulty in developing and maintaining a GMP system, the second and third are project, staff and resource management.

Resource management is often overlooked at the beginning of a GMP development programme, and the assumption that GMP development is something secondary to manufacturing development becomes both a resource and management obstacle. Management should be advised that manufacturing development must proceed hand-in-hand with GMP development; that GMP staff must have full management backing otherwise management and regulatory mistakes may result in very expensive and time-consuming exercises in correction programmes involving facility and process retro-engineering.

Quite often facilities are not approved because they are not yet in GMP compliance. This could be because the facility has design flaws, or the procedures are not yet set up, or validation was not complete, or any number of reasons, which are all due to the fact that the GMP development project had not been planned and managed to coincide with the product approval process. The price is generally at least a six-month postponement if the mistake can be corrected in that time. Six months in terms of losses can amount to tens of millions of dollars.

Moving a biopharmaceutical from research to the market is a tedious and expensive procedure. Typical estimates range from 150 to 250 million US dollars. During this phase unnecessary costs can be avoided if the problems most commonly encountered in validation and registration of the product can be avoided. In an excellent series of papers James Akers et al. summarized many of these issues (Akers, McEntire et al., 1994). These include:

- Failure to consult with the regulating authorities at an early stage;
- Inadequate product definition;
- Unrealistic expectations regarding market potentials, costs, time-lines, etc.;
- Development of laboratory-scale processes that cannot be transferred to production scale (see also "keeping it simple" in this article);
- Neglected CGMP issues, such as raw material quality, inadequate pilot facilities for the production of clinical trial material, inadequate hygienic and aseptic equipment design, insufficient in-process controls, poor documentation during process development, insufficient cleaning validation (see also "potency of drugs" in this article) in multi-use pilot plants;
- Inadequate documentation of cell line history;
- Insufficient purification methods derived from laboratory procedures incompatible with scale-up and necessary sanitization procedures;
- Inadequate analytical procedures, such as undefined reference material, non-validatable bioassays, inadequate assay validation (e.g. assay controls and ruggedness), setting product specifications (especially regarding impurities) at the assay limit;
- Limited resources for technology transfer (i.e. validation of procedures during process development) causing insufficient information of QC, production and validation personnel.

Making quality assurance feasible

By avoiding the pitfalls described above, validation and quality assurance become less daunting tasks to perform. In this section of the article a number of very basic principles and examples are outlined without giving an exhaustive list, a task that would surely fill a series of monographs.

Keeping it simple

One of the ways of reducing the cost for quality assurance measures is to keep the production process simple. This seems a trivial statement, but in real life it can be a real challenge. Data from research and development departments are in many cases not as accessible as data from production. Decisions on the final production scheme are very often based on laboratory developments with very little emphasis on simplicity and scalability. The time invested in rethinking and re-engineering the most problematic process steps can turn out to be a major asset for installation, validation and ongoing quality assurance measures.

Setting priorities—risk assessment

In order to develop a feasible validation plan it is of the utmost importance to perform a hazard analysis to identify critical points in the process. A number of methods, such as HAZOP (Hazard and Operability Study) (Kletz, 1992), FMEA (Failure Modes and Effects Analysis), critical points analysis, life cycle assessment, etc. can be used to aid the systematic exploration of the process and implement actions to deal with hazardous consequences. These hazards not only include health hazards to the operator and environmental effects, but also all aspects of product safety and quality. In any case, all activities will have to involve major issues, such as conceptual and detailed design; fabrication and construction; calibration; installation qualification; operational qualification; performance qualification; and process validation.

The standard operating procedure (SOP)

After identifying key procedures, standard operating procedures have to be provided. This formal written system of documents describes in detail all the tasks that have to be performed to ensure a certain goal, such as performance of analytical procedures, product safety, organizational matters, etc. In addition, standard operating procedures have to contain specifications to define the circumstances under which the procedure is deemed successful.

SOPs are just one element in an array of necessary procedures, such as master production procedures, batch production records, analytical procedures, etc.

Records and document control

One of the fundamentals of all quality assurance concepts is meticulously kept records of all activities. Activities that have not been recorded are worthless with respect to regulatory compliance, as the inspecting authorities consider them to be "not performed" unless they are recorded. Organizing documentation structure and maintenance is therefore one of the most important tasks in setting up a QA system and the basis of any validation. Documentation has to be adequate to ensure the traceability of the production history of every batch, including all associated issues, such as raw materials, cleaning procedures, packaging, labelling and distribution.

Validation

Validation is the action of proving that any material, process, procedure, activity, equipment or mechanism used, can, will and does achieve the desired and intended results. This means that sufficient scientifically and technically sound data have to be provided in order to prove that specifications are met, or in other words, the demonstration that what was supposed or intended to happen did in fact happen.

Validating biopharmaceutical production-process steps

Validating a biopharmaceutical process involves steps ranging from design and construction to production. Complete validation of a process can extend from planning an equipment item to its routine inspection within production. The whole cycle of installing and operating a production plant can be split into different tasks:

- Design qualification (DQ), including user requirement specifications and detailed functional specifications used for engineering design and procurement;
- Installation qualification (IQ);
- Operational qualification (OQ) verifying that subsystems perform as intended with model process materials (e.g. water);
- Performance qualification (PQ) of equipment and process (the latter can also be referred to as process qualification or process validation) run with active materials. Once the process has been fully established, three or more batches have to be produced with all parameters recorded and documented;
- Process change control has to be established to ensure that product quality is maintained or optimized after changes have been made to the process.

Facilities

Over the years a number of regulatory requirements for biotechnological plants have been developed, including, for example, requirements for containment measures as well as for equipment systems, such as HVAC (heating, ventilation, air conditioning) systems, water, steam and sterilization systems, material-, equipment-, product- and waste flow, personnel flow and personnel control (Hill and Beatrice, 1989). This is one of the more complex areas of regulatory compliance, as the requirements are rarely laid down in actual engineering terms. Instead, these are subject to interpretation by the authorities, so that the requirements must be based on knowledge of current policies, expectations and issues of the individual regulatory authorities. In other words, one must be fluent in the "language and philosophy" of the individual authorities in order to translate the regulatory guidelines into engineering details for facilities and equipment. Although this is true for all areas of GMP regulation and compliance, it often presents particular difficulties with changes of facilities and major equipment. Two reasons for this predominate: one is that major equipment and facilities are infrequently changed or built, so that individual companies, whether large or small, rarely have the resources to develop and maintain the necessary in-house know-how on current engineering compliance; the other reason is that the interpretations are subject to state-of-the-art technology, and both technology as well as regulatory requirements are constantly in a state of improvement.

Improving facilities to comply with international standards can prove to be very expensive. For companies in developing nations with limited financial means, it is of the utmost importance to set priorities (e.g., improving air quality and wall/floor surfaces in the downstream area first, as processes are normally as well contained as in the fermentation area). In many cases, some problems in facility design can be dealt with by implementing adequate organizational measures and additional safety precautions. By setting clear priorities, the necessary long-term changes in facility design can be done step-by-step, without overburdening the existing budgets.

Equipment

To ensure the safety of the product, manufacturers must show that fermentation was run under aseptic conditions. The art of aseptic design has developed rapidly during the last few years, although the importance of hygienic design is sometimes under estimated. Surface finish, dead legs, alignment of piping and many other criteria are important to maintain a high standard of cleanability and to avoid an accumulation of contaminating material. The necessary technology was basically developed by the food industry and then adapted for bioprocess engineering. Reproducibility of cleaning procedures can be optimized by automatic cleaning-in-place (CIP) systems, without the need to dismantle equipment.

As some confusion has arisen by the use of certain terms, such as aseptic, sterile and cleanability, the European Hygienic Equipment Design Group (EHEDG), has established a number of definitions, as follows:

The design and construction of hygienic equipment class I is based upon some very basic and simple rules, but the problems arising in real world applications should not be underestimated. In many cases (e.g. centrifuges), optimal hygienic design is difficult to achieve without performance loss.

Soil:	Any undesired matter including product residues, whether or not containing undesired micro-organisms
Cleanability:	Suitability to be freed from soil
In-place cleanability:	Suitability to be cleaned without dismantling
Destruction of microorganisms:	Irreversible physical or chemical damage to microorganisms to prevent them from surviving and multiplying
Sterilization:	Removal or destruction of micro-organisms, including all relevant bacterial spores
Steam/hot water sterilization:	Sterilization by saturated steam or water at 120° C for 30 minutes
Hygienic equipment Class I:	Equipment that can be cleaned in-place and freed from relevant microorganisms without dismantling
Hygienic equipment Class II:	Equipment that is cleanable after dismantling and can be freed from relevant microorganisms by steam sterilization or pasteurization after reassembly
Aseptic equipment:	Hygienic equipment that is, in addition, impermeable to micro-organisms

General criteria for hygienic design:

- Product surfaces resistant to product, cleaning, full range of operating pressures and temperatures.
- Product contact surfaces free from crevices.
- Product contact surfaces with roughness of 0.5 μm or better.
- Product contact surfaces either easily accessible for manual cleaning and visual inspection, or validated CIP.
- Avoid condensation on external surfaces of equipment.
- Insulation sealed with stainless steel cladding, preferably fully welded.
- Equipment must be self draining.
- Dead legs must be avoided.
- Dead legs that cannot be avoided have to be positioned correctly to ensure SIP or CIP.
- Equipment and supports either sealed to the building with no gaps or pockets, or adequate clearance to allow for inspection and cleaning.

The validation of cleaning procedures has been focused on in many publications. Particularly in multi-purpose plants the potential carry-over into subsequent products is of major concern. Validation has to ensure that the cleaning procedures are adapted to the equipment and the type of contamination. The hygienic design of fermentation equipment is crucial for cleaning procedures to be successful. In order to assess in-place cleanability, methods have been developed for food-processing equipment (EHEDG, 1992), (Lelieveld, 1985) to test the removability of model contaminants. Validation methods for

the cleaning of fermentation equipment have been reported (Vranch, 1991), (Chisti and Moo Young, 1994).

As mentioned in the introduction, the carry over of drugs into subsequent processes in multifunctional bioprocessing plants has to be carefully considered and particularly so if the subsequent product is less potent and has to be administered in comparatively high doses. The question is how to determine the maximum allowable carryover residue concentration. Calculations can be performed by taking into account such factors as product toxicity or maximum tolerable dose, the maximum dosage of product taken per day, number of dosage units per batch, quantity per batch, and the surface area in common between products (Fourman and Mullen, 1993).

Companies with low financial resources may find it difficult to obtain the necessary funds for expensive up-to-date equipment with optimal hygienic and aseptic design. In many cases, by using common sense and carefully identifying critical parts, the overall performance of equipment with respect to cleanability and sterilizabilty can be dramatically improved with comparatively small changes to the existing equipment. These changes (for instance, reduction of dead legs) can very often be carried out by the company's own workshop, thus reducing costs and at the same time improving the knowledge and understanding of local engineers. Such a building up of expertise is of great importance when decisions have to be taken on subsequent investments, negotiations with equipment manufacturers and the handling of equipment.

Downstream

Purification processes must be validated to prove they are capable of removing impurities to an acceptable level. Special consideration has been given to the capacity of the downstream procedure to remove:

- Components originating from the host cell (e.g. protein, DNA);
- Impurities caused by media components or substances used during downstream processing (nutrients, buffer components, stabilizers, chromatography media, etc.);
- Potential external contamination by adventitious agents (e.g. viruses of mycoplasma in cell cultures or bacterial contaminants) that should not be present throughout the process, but which could contaminate the culture by accident.

Biopharmaceuticals produced from animal cells have to be scrutinized for the possibility of transmission of viruses to patients. Manufacturers have to validate their purification systems to demonstrate inactivation and/or removal of viruses, nucleic acids, mycoplasma and scrapie-like agents (Sito, 1993). These validations are extremely costly because they are time consuming and need considerable expertise in the handling of adventitious agents and analytical procedures. Each step of the purification procedure has to be spiked with model contaminants to evaluate the inactivation or removal capacity of the step if the contaminant is not to be present in the process (e.g. viruses). These spiking tests will be performed on a model scale. Sound scale-up strategies have to be used to guarantee equivalent contaminant clearance on the production scale. A number of approved techniques for virus inactivation/removal have been developed, such as virus inactivation by pH extremes, heat, radiation, chromatography, filtration (Grun, White et al., 1992). However, procedures have to be validated for the specific product and process on hand on a case-by-case basis.

As with fermentation equipment, the cleaning of downstream equipment is of great importance. Since the chromatography media is frequently not steam sterilizable, adequate sanitation procedures have to be developed and validated. (Adner and Sofer, 1994). Sanitation procedures and normal operation are important factors when evaluating chromatography resin reusability and the maximum number of cycles. General criteria can be small ion capacity, total protein capacity, flow versus pressure, particle size distribution, microbial and endotoxin analysis, total organic carbon removed by extreme cleaning solutions, chemical challenge (subjecting the resin to the harshest chemical solution used in the process) (Seely, Wight et al., 1994). Other parameters, such as capacity, selectivity and efficiency can be used in technique-specific tests.

Quality consideration for biopharmaceuticals—product testing

Critical criteria for biologics are:

- Safety;
- Potency;
- Consistency;
- Purity;
- Efficacy.

Final product safety testing must include (Schiff, Moore et al., 1992):

- General safety or abnormal toxicity;
- Sterility;
- Pyrogens;
- Mycoplasma contaminating DNA;
- Viral contaminants (under certain circumstances).

Due to the different composition of biotechnological products (e.g. proteins, polypeptides, polysaccharides, etc.), different approaches to stability studies are often necessary. For biopharmaceuticals consisting of proteins or polypeptides such as cytokines, erythropoeitins, plasminogen activators, blood plasma factors, growth hormones, insulin, monoclonal antibodies and certain types of vaccines, there is a major thrust towards international harmonization of testing procedures, such as storage test conditions, study durations and frequency of testing, release and expiration specifications. The methods used for purity and molecular characterization must be validated to prove that they allow the accurate detection of changes during storage, including subtle changes that reflect the degradation and loss of biological activity (potency) of a product (for example, oxidation, deamidation, aggregation, fragmentation) (Haase, 1995), (Federici, 1994).

Analytical procedures

Analytical procedures have to be tested for accuracy, precision, sensitivity and other statistical parameters, and for the ruggedness of the methods. Validation will have to include the evaluation of matrix effects. Analytical procedures used to evaluate the quality of the final product have highest priority for full and comprehensive validation.

Automated systems

As with all other systems used for the production of pharmaceuticals, automation equipment has to be fully documented and validated. Hardware and software have to be tested for proper performance. As in the case of other system components, installation, operational and performance qualifications have to be performed. Test data have to be documented and evaluated. Systems have to perform within specified limits (performance test) and have to cope

with certain events, such as erroneous operator inputs, sensor failure, etc. (stress test). Software should be reviewed, with the rule of thumb being priority given to software that only has distribution (such as custom process control sequences or algorithms).

Turning the burden into an asset

What are the benefits to be gained from a stringent QA/QC and validation programme? If handled with care, such a programme can help a company to establish an efficient and logical quality management system, covering all activities (for example, management, research, QC laboratories, etc.). This will not only help the company to achieve fast approval for new processes, but will also create an awareness throughout the company of quality issues, and thus boost performance. Also, the definition of clear and measurable objectives helps to streamline activities. This is applicable to both established companies and emerging businesses (Wright, 1996).

An important part of a total quality management system is the quality control and quality assurance of all laboratory operations, including such diverse activities as upstream (e.g. cell banking, strain improvement, inoculum preparation, etc.) or analytics. By following a stringent control programme, laboratory operations can be streamlined. If, for example, analytical equipment is qualified following the classical qualification stages (design qualification,installation qualification, operational qualification, performance qualification), expensive calibration runs may be reduced to the amount necessary. By setting method-specific system suitability criteria (SSC) as part of PQ, the performance of the equipment's critical components can be monitored. This enables early detection of trends towards unacceptable performance, helping to reduce equipment downtime (Freeman, Leng et al., 1995).

For developing country companies with limited financial resources, the clear benefit of implementing stringent QA/QC and validation programmes will be the intensive evaluation of the processes and the identification of critical points. In many cases, major improvements of product quality and safety can be achieved with modest investment into facilities and equipment, mainly by adapting organizational structures and standard operating procedures to eliminate or reduce hazards. Improved consistency of product quality improvement will reduce the amount of rejected batches, thereby boosting productivity. If handled with common sense, and by identifying priorities, A/QC programmes and validation efforts will pay off in the short term, even with limited resources, and will build the foundation for expansion into multinational markets in the long term.

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BIOTECHNOLOGY TRANSFER: A MATTER OF POLICY, NOT TECHNOLOGY

by

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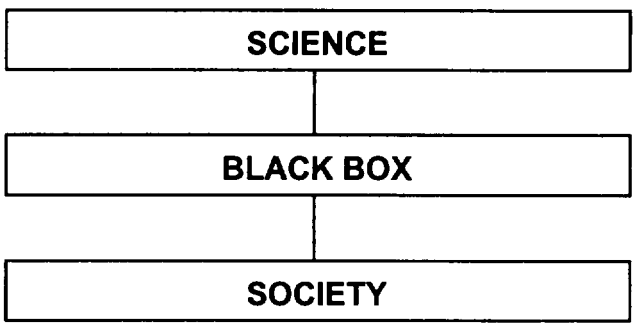
The phenomenal rise to prominence of biotechnology has sparked a sometimes acrimonious debate on how this toolbox can and should be used for the improvement of humanity world-wide, not just for the happy few who happen to have the resources to pay for its techniques and products. One of the many "selling points" of biotechnology has been its image as a diffuse technology, with a wide range of applications in many fields of socio-economic activity and with (relatively) low entry barriers. This perception is caused by the fact that biotechnology, not unlike the software industry for example, is in the first place a knowledge-based industry, much less an infrastructure-based one. To carry the analogy with software further, biotechnology covers such a wide span of levels of sophistication in its applications that virtually any knowledge base, no matter how small (and we will briefly discuss a few examples later in this paper), can serve as a starting point for an industrial sector, if the available resources are used wisely. This should open the way for the rapid establishment of biotechnology applications, and a growing contribution to technology development itself by those developing countries that are richer in well-trained human resources than in capital, of which there are many.

Why is the sector developing so unevenly, and generally much more slowly than expected, especially in developing countries? This article will examine a number of weaknesses in present strategies for the transfer of biotechnology, and through the use of a number of success and failure stories, offer some suggestions for alternative strategies that could lead to improved success rates. The article is meant as a contribution to the debate on a global framework for biotechnology transfer. The options will be very different from one country (or region) to another, they will depend on a wide range of parameters, some potentially under the control of the countries wishing to develop a national policy, and others utterly beyond their control. These parameters vary according to the types of applications chosen for emphasis. The best solution will therefore be quite different from one country to another, and lessons should be learned in terms of successful approaches and strategies, not products.

The international debate on biotechnology transfer has tended to focus more or less randomly on individual components of the policy issue (e.g. biosafety, intellectual property rights). This is due to what is probably the biggest single inhibitor to the integration of technology in global development strategies: the lack of understanding at a decision-making level of the interactions between science, technology, the economy and society in general. Even the most diversified post-industrial nations struggle with this issue. As a result, the highest levels of decision-making tend to see the relation between science and society as in figure 1:



A viable strategy for the use of biotechnology applications as engines for economic development requires a number of basic choices at the level of public policy, regardless of the type of economy in which it is developed, if it is eventually to transform the potential into economic development. Resources are always constrained, and socio-economic priorities are not the same in each region. In industrialized countries, the ease with which medical applications of biotechnology have been introduced contrasts strikingly with the enormous difficulties faced by the introduction of agricultural products. Although the debate is allegedly primarily based on concerns for the environment, the underlying reason may well be that food, unlike health, is not a priority in those countries, although globally, food is still a major priority, and will remain so for the foreseeable future. The strategic choices made in a context of mature economies with a stable and ageing population are therefore very different from those of developing countries.

This, together with other political considerations, has important consequences for the perception of priorities by funding sources. As the priorities of donor countries shift geographically (since the demise of the Soviet Union) and topically (with new emphasis on fields such as biodiversity and conservation), aid programmes have reduced their commitment to the development of long-term training and research efforts, especially in the agricultural sector, but also in the medical sector. This has led to an increasing gap in biotechnology know-how between resource-poor countries and the rest of the world. It is questionable whether the currently available insufficient resources should be spread out between biotechnology and more "traditional" medical and agricultural research, as this may lead to a degradation of the latter. This is a source of concern, as many biotechnology innovations require good "downstream" R&D capacity to reach the economy. (e.g.: no plant genetic engineering effort will ever produce a useful variety without collaboration with a good plant breeding project that can take the new genetic combinations and breed them into locally adapted varieties).

The lack of interest at the policy-making level in the interaction between education, technology development and socio-economic development is one of the most important problems facing biotechnology transfer policies. It leads to disintegrated approaches to the different, related parts of the debate (training, biodiversity protection and utilization, industrial base development, risk assessment and safety regulations). Policy makers in developing countries constantly face the dilemma of choosing between long term solutions through technology and capacity transfer, and short term solutions utilising conventional methods and improvements to their information and management practices.

In the following sections we will briefly touch upon a number of parameters to consider in the development of biotechnology transfer strategies adapted to the particular circumstances and needs of different countries or regions.

Strategies can be designed around:

- MARKETS:
  - Local
  - International
    - South-south (go for growth)
    - South-north (go for size)
- PRODUCT RANGES:
  - Agriculture and/or livestock
  - Food industry
    - Processing
    - Additives
  - Pharmaceuticals
  - Chemical processing
  - Environment (bioremediation, conservation)
- TECHNOLOGY RANGES:
  - Traditional (e.g.)
    - Breeding
    - Fermentation
  - "Modern" (e.g.)
    - Biochemistry
    - Cell biology
    - rDNA technology

Development of long-term ventures, such as the introduction of biotechnology in a national development strategy, requires integrated thinking about this central strategy as well. This is in sharp contrast with existing situations world-wide, where priorities for industrial biotechnology programmes are usually a result of the emergence of a centre of excellence in biotechnology-related research, often linked to the work of a strong personality, but without previous thought to its relevance for local economic development.

Of course, the choice for each particular country, region, or institution will also depend on limiting resources: manpower, financial resources, infrastructure, biological diversity, etc. Thus, part of a long range planning exercise is to find a good fit between the national socio-economic priorities (which can, as stated before, be to promote export industries!) and the existing resources.

Capacity requirements:Choice can be determined by entral need

- Use biotech to improve existing strong sectors

or

- Develop new sectors using newly accessible biological resources (biodiversity)

or

- Use biotech to develop new physical resources, either by developing new species (aquaculture/arid land/ waterlogged land), or by adapting existing species (breeding for stress tolerance)

or

- Develop generic technologies (e.g.)
  - Diagnostics (AB and/or DNA based)
  - Screening technology (biochemical)

or

- Develop biotech around public health priorities
  - Vaccines
  - Screening (epidemiology)

There is scope for regional co-operation between countries with different priority needs. In several developing regions of the world, large differences exist between neighbouring countries in terms of population density, trained manpower availability, food production and productivity. Regional co-operation would seem to be one promising way of ensuring an equitable spread of development around biotechnology in such regions.

The question of competing technologies

In the biotechnology debate, remarkably little attention is paid to the issue of how other technologies could solve some of the big development problems addressed by biotechnology. The spectacular development of information technology and combinatorial chemistry, linked to the most recent developments in rDNA technology, are working towards a major shift in the requirements for natural biodiversity as a source of material for biotechnology to work on. It has been one of the central tenets of the Biodiversity Convention that genetic and organic chemical resources from biodiversity are a key requirement for further development of biotechnology, and therefore constitute both a major potential source of wealth for tropical countries and a priority target for protection. This hypothesis is eroding fast, and the consequences should be carefully considered, as they do not apply equally to all types of biotechnology applications.

Training priorities

- Molecular biologists/biochemists?
- Business and associated? (legal, IPR)
- Downstream strengths? (agro/health/food industry)

The question of competing technologies

- Where are the most dynamic competing technologies interacting with the hopes and aspirations of biotechnology?
  - → Information technology vs. rDNA technology
  - → Combinatorial chemistry vs. secondary metabolites

Common characteristic: high end/ upstream

- Which sectors have least to fear from this?
  - → Food production
  - → First line health care

Common characteristic: close to market sectors of the economy

Attitudes towards intellectual property protection

Possibly the most contentious issue in the international debate on biotechnology is that of ownership rights to living material and its derivatives. While much of this discussion in industrialized countries is on ethical issues, the main issue in the international arena is that of equitable compensation, especially of developing countries, for their contribution to the field. The debate has seemingly gone astray over ideological and philosophical questions. The question is not if or what should be protected, but how. As with any other industry with a high technology component, no entity, be it a country, a corporation or another type of institution, can participate at the cutting edge of a technology if it does not respect the results of the efforts of other entities, and thereby gain legal recognition, respectability and protection for its own work. The question then is not philosophical, but practical: how can developing countries achieve protection for their production of biological resources? One of the key factors missing in most developing countries' training programmes is expertise in IPR. Not surprisingly, countries who do not have access to their own experts in patenting and intellectual rights protection, have a significant handicap at the negotiating table. The best tactic then is usually to say "no" to everything, to avoid giving anything away without proper compensation. It could be that one of the most productive ways to make progress in this area is training of intellectual property rights experts from developing countries.

Consequences of strategic choices for training programmes

Since biotechnology is essentially a knowledge based sector of an economy, a key component of any strategy is definition and implementation of a multidisciplinary training programme. This is at present one of the most neglected parts of the international debate. Amazingly, training strategies generally seem to start from the idea that a biotechnology industry needs highly trained molecular biologists, period. In practice, they are a useful (not an essential!) part of the range of competencies required. More important are engineers, patenting and licensing experts, business analysts, etc.

One of the key policy messages on biotechnology must therefore be that its positive socio-economic effects can only be obtained in the context of a broad range of trained staff. Training for excellence in biotechnology alone will not generate any perceptible economic benefit. This is a particularly important notion to be accepted by the large donors of funding for advanced training of developing country experts. The table below lists some of the fields of expertise required to do more than create finance-starved academic research laboratories in molecular biology.

Capacity requirements

- Legal
- Business
- Engineering
- Human resources
  - Cheap
  - Trained
- Finance
- Transport and communications
- Risk assessment and regulation

The role of international organizations

International organizations, particularly the UN agencies, are in a unique position to evaluate broad strategies for long term industrial development world-wide. In the case of biotechnology, and with special emphasis on developing countries, this is particularly relevant, because of the diffused nature of biotechnology, its pervasiveness across an unequalled diversity of industrial sectors, and its direct impact on human life and the environment.

The criteria for preferring one of these strategies over another are different depending on the situation of each country. This can to some extent be generalized to the level of entire regional blocs. At its most basic level, the choice is between programmes and projects, between a centralized and a diversified approach. Much current thinking about biotechnology appears to take place along similar lines to those used for other types of technologies. It is not obvious that a centralized approach to R&D and industrial development in this area will give the results that a similar approach has given some developing countries in developing a capacity for other complex technologies. The applications of biotechnology do not come in billion dollar chunks, as for example, the mining, or chemical industry, or nuclear capacity. Much of the value is, and is likely to remain, created by a myriad of relatively small incremental value products. There will be exceptions (some drugs), but the reasons why these products carry such huge potential rewards are that they require enormous investments over long periods of time, and that they have a very high risk of failure—in which case the investment is lost.

Whatever the sector chosen for development, and the strategy adopted, the end products will always reach the economy through variations of the following sequence:

Natural resource

➳Basic research

➳Applied research

➳Product development

➳Production

➳Marketing

➳Distribution

Different types of industry require radically different types of approach. The key parameter to consider is where in the process of technology and product development the heaviest investments in human and financial capita are needed.

- For example, in drug development, the most complex parts are basic studies on diseases and clinical testing of potential drugs. Primary screening of molecules is often (relatively) cheap and technologically within easier reach. A country that wishes to stimulate the development of a national capacity in drug development, could adopt a capacity development model starting with primary screening to acquire property on molecules, and access to know-how in advanced screening, testing and clinical trials at a later stage.
- For the use of genetically engineered crop plants, the bulk of costs and risks are in the pre-field stages. Field breeding is much cheaper relatively speaking. Moreover, there are many good breeding programmes already in resource poor countries. Also, no successful crop genetic engineering programme will benefit local farmers unless its products are made available through locally adapted crop varieties. In this context, it is particularly worrying that a number of poor countries are neglecting their small breeding and agricultural research programmes in favour of undirected investments in advanced biotechnology research capacity. This is a good example of how a drive into biotechnology without a proper policy can actually lead to loss of development.

Whatever the field of activity, and the choice of prime actors in the development scheme, the major element for success is a multidisciplinary approach. This has important consequences for the one area in which public initiative is solely responsible: training. Too often, high technology as a tool for development is equated with the production of enough PhDs. In some niche areas (e.g. software development) this may be appropriate. But if the objective is to develop an entire new sector of the economy, with businesses of a kind that did not exist before, a much broader body of expertise is needed.

Moreover, on top of the training policy needed, public authorities face hard choices in other fields: legislation and regulations on safety, IPR capacity development, public information.

Finally, if a national or regional strategy for biotechnology related economic development is to have a chance to succeed, it requires efficient access to financing sources for long term programmes, as much as training and a legal framework.

Basically, strategic choices have to be made along two main axes of thinking:

Technology spectrum

Concentrate efforts in the highest part of the technology range, and go for large projects combining high risk with high potential reward;

▲
▼

Concentrate efforts on producing a broad based industry, moving from relatively low level technology upwards, with many small projects with low risk and low individual potential reward.

Development strategy

Move from "close to market" applications upstream in the development process, developing innovative research capacity after reaching proficiency in manufacturing and product development;

▲
▼

Move downstream from basic technology development through the product development stage towards commercial production.

It is suggested that international organizations would concentrate efforts near the second alternative in terms of the technology spectrum, and near the first alternative in terms of development strategy. This approach seems to offer the best opportunities to build on existing strengths in almost any country. It may also help to resist the temptation to build up unsustainable prestige projects that are insufficiently linked to existing and expected industrial realities.

B. NEWS AND EVENTS

UNIDO news

One of the more recent UNIDO projects that has met with quite considerable success concerns the efforts to offer the *campesinos* in the Chapare region of Bolivia an alternative to the cultivation of coca. The projects comprised a group of 11 activities ranging from a fruit juice processing plant, tea production, essential oil plants, a vinegar production plant, a milk and cheese plant and five small solar dryers for the production of cassava flour and cassava chips. These plants are all operating in good working conditions, their production and management problems have been identified and business and investment plans have been drawn up for each of them to yield profits. All the plants now have a positive cash flow and sales.

In Ghana, meanwhile, a project is being finalized for the use of sorghum in malt and beer processing. The idea is to develop and improve malting and brewing technologies to replace imported barley malt with locally produced sorghum/sorghum malt. The pilot malting plant being set up under the project is presently being installed and will be commissioned shortly.

Another very successful UNIDO-sponsored project that has been going on for some time, has been assistance to Viet Nam's Food Industries Research Institute (FIRI). This project's original objective was to strengthen the capability of the institute in carrying out applied research in bio- and fermentation technology as applied to the food industry in the production of such items as beer, yeasts, fish sauce, food additives, bacterial amylases, glucose from cassava, etc. This was achieved through the provision of direct support services to industry in the design, selection and application of process technologies, as well as in quality control of raw materials and finished products. Naturally, training of technical personnel from industrial plants and units in specific processing technologies, bacteriological, physical and chemical (including instrumental) testing and quality control, product development, product management, etc., was arranged and undertaken in Australia, the United Kingdom, France, Indonesia, Germany and Thailand (in the latter country a study tour had been undertaken to investigate similar relationships as with FIRI, between local industry with research institutes). As a result of the efforts and dedication of the local counterparts, as well as that of the experts and consultants involved, some projects have advanced from the laboratory to the pilot plant or commercialization stage. In fact, one of these (a small brewery) is now so successful that it is marketing its product and even financing some of the research being undertaken at the institute that initially set it up as a spin-off, to the extent that it is being demonstrated as a successful example of joint efforts.

Within the framework of the **Alliance for Africa's Industrialization**, UNIDO's Studies and Research Branch is organizing informal consultations on agro-related industrial development in Africa with a small group of selected experts from Africa and developed countries. These consultations are undertaken in cooperation with the relevant units within UNIDO, in particular the Agro-based Industries Branch, the Engineering and Metallurgical Industries Branch and the Chemical Industries Branch.

These consultations take place within the context of preliminary research being undertaken by UNIDO on agro-related industrial development in Africa. The issue of agro-related industrial development has assumed increased importance in the light of globalization, and of Africa's potential comparative advantages in these industries, which cover both forward and backward linkages. This was fully recognized at the launching of the **Alliance for Africa's Industrialization**, which encompasses—as one of its main pillars—strengthening of agro-industrial development in line with UNIDO's thematic priority on Africa and the least developed countries, specifically linking industry and agriculture.

UNIDO has an extensive programme of assistance to agro-related industrial development in Africa. There is strong justification for further strengthening and supporting these programmes through additional resources, with a focus on both food security and industrial competitiveness.

Agro-related industries account for over half of Africa's manufacturing value added, manufactured exports and employment. Stimulating their growth can make a key contribution towards poverty alleviation, the achievement and maintenance of food security, enhancement of agricultural productivity and the expansion of foreign resource inflows to Africa.

Agro-related industrial development has stalled during the past decade. Investment has fallen. The privatization programme has failed to take off in several countries, and export and foreign financing opportunities remain limited. UNIDO is concerned to make a contribution towards relieving these constraints on socio-economic development in Africa.

The consultations being undertaken will seek to examine the practicability of ideas presented in the research papers and to identify a viable strategy for accelerating the development of agro-related industries in Africa. It will review the existing evidence on performance and constraints on the development of specific branches, focusing on strategic issues of relevance to their development, with a view to identifying viable approaches for structuring UNIDO's contribution towards the further development of key branches of agro-related industry. UNIDO's programme is concerned with developing the type of strategies that can restructure agro-related industries in such a way that it boosts their contribution towards achieving better food security, poverty alleviation and increased agricultural productivity while at the same time increasing foreign resource inflows to the African continent. UNIDO's programme is also expected to facilitate ongoing private, public and multilateral programmes in these areas and serve as a catalyst for their expansion.

Following these consultations, field missions will be undertaken to selected countries to elaborate the approach and scope for assistance, and on the basis of these missions, a major UNIDO-wide initiative covering technical assistance, financing, negotiations, investment and economic research will be developed within the framework of integrated teamwork with all relevant units of the Organization, in view of the overarching nature of agro-industrial development that permeates many of UNIDO's activities—for example, policy issues, small and medium enterprise

development, investment and technology, industrial information, the role of women in industrialization and human resource development.

In addition, the Industrial Sectors and Environment Division implements several biotechnology technical co-operation projects in several countries, including the manufacture of pharmaceuticals and vaccines. One activity of particular relevance is an international convention on *Food Ingredients: New Technologies, Fruits and Vegetables* that will take place in Cuneo (Italy) from 15 to 17 September 1997. The event will consist of the presentation of research papers from industry and from public and private R&D centres in developing and industrialized countries selected by a committee composed of representatives from six Italian and foreign universities, and UNIDO. The convention is being organized and co-sponsored with Allione S.p.A. (Italy), a private company which has also agreed to set up small pilot plants to demonstrate the new technologies being proposed. More than 500 participants from all over the world are expected to attend the convention, coming from industry including multinationals, industrial associations and R&D centres, and from the academic community. The areas of cooperation with the Allione group of companies encompass training and study tours for experts; technical visits for representatives of R&D centres from temperate climate countries with a view to eventual transfer of technology and investment projects—for instance in the production of baby-food in Africa and Asia and the production of non-conventional fruits and vegetables from temperate climates, and tropical products for export; projects for the development of new processed products, particularly from tropical areas; and for the utilization of data banks. A compendium of the innovative technologies selected from developing country R&D centres will also be published.

ICGEB 1997 meetings and courses

Meetings and coursed organized by ICGEB

1-6 September. Trieste, Italy. Practical course "Bioinformatics: Computer Methods in Molecular Biology". Organizer: Sándor Pongor. Requests for information and applications directly to: Ms. Micaela Di Blas, ICGEB, Padriciano 99, 34012 Trieste, Italy. Tel.: +39-40-3757333; Fax: +39-40-226555; Telex: 460396 icgebt i; E-mail: courses@icgeb.trieste.it.

October. Trieste Italy. Symposium "Advances in Medical and Plant Biotechnologies". Requests for information and applications directly to: Ms. Elisabetta Lippolis, ICGEB, Padriciano 99, 34012 Trieste, Italy. Tel.: +39-40-3757332; Fax: +39-40-226555; Telex: 460396 icgebt i; E-mail: courses@icgeb.trieste.it.

20-31 October, Brasilia, Brazil. Course "Transformation Methods and Analysis of Gene Expression in Transgenic Plants". Organizers: Vera T.C. Carneiro and Ana C.M. Brasileiro. Requests for information and applications directly to: Dr. V.T.C. Carneiro, Centro Nacional de Recursos Genéticos e Biotecnologia, CENARGEN, SAIN Parque Rural, Final W/5 Asa Norte, Brasília, Brazil, CEP: 70.770-900. Tel.: +55-61-3403569; Fax: +55-61-3403624; E-mail: course@cenargen.embrapa.br.

3-5 November. New Delhi, India. Workshop "Control of Proliferation of Normal and Cancer Cells". Organizers: Claudio Basilico (NYU Medical Center, NY, USA) and Krishna K. Tewari (ICGEB). Requests for information and applications directly to: Mr. G. Chatterjee, ICGEB, NII Campus, Aruna Asaf Ali Marg, New Delhi, 110067, India. Tel.: +91-11-6167356; Fax: +91-11-6162316; E-mail: chatterj@icgebnd.ernet.in.

10-21 November. New Delhi, India. Practical course "Peptide Vaccines: Immunological Techniques". Organizer: K.V.S. Rao. Requests for information and applications directly to: Mr. G. Chatterjee, ICGEB, NII Campus, Aruna Asaf Ali Marg, New Delhi, 110067, India. Tel.: +91-11-6167356; Fax: +91-11-6162316; E-mail: chatterj@icgebnd.ernet.in.

1-12 December. New Delhi, India. Practical course "Plant Genes: Structure and Transcription". Organizer: Sunil Mukherjee. Requests for information and applications directly to Mr. G. Chatterjee, ICGEB, NII Campus, Aruna Asaf Ali Marg, New Delhi, 110067, India. Tel.: +91-11-6167356; Fax: +91-11-6162316; E-mail: chatterj@icgebnd.ernet.in.

1-5 December, Trieste, Italy. Theoretical course: "Transgenic Organisms: Biological Risk Assessment". Organizer: George Tzotzos (UNIDO, Vienna, Austria). Requests for information and applications directly to: Ms. Micaela Di Blas, ICGEB, Padriciano 99, 34012 Trieste, Italy. Tel.: +39-40-3757333;Fax: +39-40-226555; Tlx.: 460396 icgebt i; E-mail: courses@icgeb.trieste.it.

Meetings and courses sponsored by ICGEB

17-21 August. Budapest, Hungary. Symposium at the 8th European Congress on Biotechnology "Databases in Molecular Biology and Biotechnology". Organizers: Michael Ashburner (University of Cambridge, UK) and Sándor Pongor (ICGEB). Requests for information and applications directly to: Prof. S. Pongor, ICGEB, Protein Structure and Function Group, Padriciano 99, 34012 Trieste, Italy. Tel.: +39-40-3757300; Fax: +39-40-226555; Telex: 460396 icgebt i; E-mail: pongor@icgeb.trieste.it.

7-12 September. Siena, Italy. 16th International Conference "Papillomavirus". Organizer: Piero Tosi (University of Siena, Italy). Requests for information and applications directly to: Prof. P. Tosi, Istituto di Anatomia e Istologia Patologica, Universitá degli Studi di Siena, Via delle Scotte, 53100 Siena, Italy. Tel.: +39-577-285001; Fax: +39-577-263235; E-mail: rettore@unisi.it.

22-26 September. Trieste, Italy. Fifth Trieste Conference on Chemical Evolution "Exobiology: Energy, Matter and Information in the Origin and Evolution of Life in the Universe". Organizers: Julian Chela-Flores (ICTP, Trieste, Italy), IDEA (Caracas, Venezuela), Francois Raulin (LPCE, Paris, France). Requests for information and applications by 30 April to: Trieste Conference on Chemical Evolution—V, ICTP, Office 275, P.O. Box 586, Strada Costiera 11, 34100 Trieste, Italy. Tel.: +39-40-22401; Fax: +39-40-224163; E-mail: smr1009@ictp.trieste.it.

ICGEB, AREA Science Park, Padriciano 99, 34012 Trieste, Italy. Tel.: +39-40-37571; Fax: +39-40-226555; Telex: 460396 icgebt i; http://www.icgeb.trieste.it.

UN and other organizations' news

WHO and UNICEF find vaccines too costly

Officials of the World Health Organization (WHO, Geneva) and the United Nations Children's Fund (UNICEF, New York) have pointedly criticized industry and the biomedical research community over vaccine research and pricing policies in a recent comprehensive report on world-wide immunization efforts. Indeed, the report cites the approval of genetically engineered hepatitis B vaccine in 1986 as signalling "that the days of cheap vaccines were over". But both industry representatives and the two global

health-care organizations agree that disease prevention programmes need to take steps to harness the productive power of commercial biomedicine.

The WHO-UNICEF report, "State of the World's Vaccines and Immunization", lauds recent successful campaigns to deliver vaccines against diseases—including polio, measles, neonatal tetanus, diphtheria, pertussis, tuberculosis, hepatitis B and yellow fever—to the world's children, particularly in developing countries. But the report also warns that, "unless the international community continues to back scientific research and global immunization with adequate resources for new vaccines ... the great promise of molecular biology and genetic engineering may be squandered".

High on the list of global vaccination campaigns are efforts to eradicate polio—a goal that officials expect to meet by the year 2000. But officials are concerned over budget "shortfalls", mainly from decreased donor funding, that now have the managers of this campaign scrambling for the $600-800 million needed for vaccine purchases, personnel, training, research, logistics, establishment of a cold chain to preserve vaccine activity, and development of a global laboratory network. The current full allotment of six childhood vaccines (against polio, diphtheria, pertussis, tetanus, measles and tuberculosis) now costs less than $1 for the vaccines—plus $14 for programme costs.

The hepatitis B vaccine has been a touchstone for the vaccine cost discussion. Unless its price falls below $1 per dose, this vaccine remains out of reach for much of the world.

Pricing is not the only impediment to wider vaccine development and usage. Adequate safeguards for intellectual property rights are also crucial. Strengthening of intellectual property laws in China, for example, made it easier for Merck (Whitehouse Station, NJ) to share some of its hepatitis B vaccine know-how with Chinese collaborators, enabling them to build up domestic vaccine manufacturing capacity.

Another issue pivots on health-care priorities in developing countries. With more than 300 candidate vaccines "in the pipeline", developing countries "need to make resources available at the national level", points out the special adviser for the WHO Global Programme for Vaccines and Immunization. Institutions in such countries need to form "consortia to bring vaccine prices down and make sure these products are widely used". (Extracted from *Nature Biotechnology*, Vol. 14, November 1996)

Global strategy for the prevention and control of AIDS

As one of the six co-sponsors of the joint United Nations Programme on HIV/AIDS, which became operational on 1 January 1996, WHO continues to play a leading role in the world-wide effort to control the AIDS epidemic. The Office of HIV/AIDS and Sexually Transmitted Diseases will coordinate activities within headquarters and with the WHO regional offices, liaise with other institutional partners, and mobilize resources for HIV/AIDS activities.

In particular it will liaise with UNAIDS in order to facilitate the incorporation of UNAIDS-specific policies, norms and strategies into the activities of WHO at global, regional and country levels. The core areas in which WHO will concentrate its activities are:

- Prevention, treatment and case management of sexually transmitted diseases (STD);
- Blood safety;
- Epidemiological surveillance of STD/HIV/AIDS;
- Public health programme management;
- Strengthening the integration of STD/HIV/AIDS-related activities into health-care delivery systems;
- Diagnostics, vaccines and other biologicals;
- Health promotion, advocacy and networking in the health sector and with other agencies.

(Source: *World Health Forum*, Vol. 17, 1996)

Banking a heritage for all the world

A floating foundation built to withstand even the worst earthquakes cradles a priceless collection at the International Rice Research Institute (IRRI) rice in the Philippines. The treasure is IRRI's rice gene bank, officially called the International Rice Genebank (IRG). Here, more than 80,000 samples of rice from 110 countries are maintained and conserved—the world's largest collection for a single crop.

IRG holds the genetic resources of rice in trust. It acquires and conserves rice germ plasm and acts as a conduit for world-wide exchange. The gene bank provides rice seed samples on request. Researchers can obtain materials for rice improvement, and nations use the collection to restore lost rice varieties or to establish their own gene banks.

Cambodia is one country that has benefited from the conserved resources. Because of the political upheavals there during the Pol Pot regime (1975-1978), many farmers lost their traditional rices. When the political situation stabilized, the country restored its rice varieties by asking IRG for samples.

IRG has also helped Malaysia and Mexico establish their own rice gene banks. The gene bank has enabled India to reconstruct 5,000 samples of its so-called Assam rice collection. This collection is especially important because it is a good source of genes for resistance to pests and diseases.

About 95 per cent of the collection consists of varieties of the two species of cultivated rice: *Oryza sativa* (Asian rice) and *Oryza glaberrima* (African rice). Seeds are stored in two facilities. Samples used for exchange and distribution—called the active collection—are kept in a medium-term facility at 1 to 2° C. Samples for posterity—called the base collection—are stored at -20° C, where viability is conserved for up to 100 years. Backup samples are deposited in the USA, at the National Seed Storage Laboratory, Fort Collins, CO.

Managing and conserving genetic resources, however, does not seem to appeal to many people as it is labour intensive and not too exciting. The IRG has trained gene bank managers from several Asian countries but only a few have stayed for any length of time in their positions. (Source: *Chemical and Engineering News*, 7 October 1996)

Establishment of an international network on Geminiviruses: GeminiNet

The International Laboratory for Tropical Agricultural Biotechnology (ILTAB) of the Scripps Research Institute, an ABSP partner working with Egypt in the production of transgenic tomatoes resistant to the tomato yellow leaf curl virus disease (TYLCV-Eg), has launched a new international information network for researchers investigating geminiviruses. Although not a direct product of the ABSP collaboration, the project has stimulated ILTAB scientists to set up the network. GeminiNet will specifically serve the Egyptian colleagues involved in the project as well as the international scientific community involved in the study and control of geminiviruses like TYLCV. The network is comprised of about 100 members with information available in a number of formats, including:

- Gemini SeqDataBase: all the published sequences of geminiviruses are included in two ways: virus per virus and gene by gene under amino-acid and nucleic acid sequences. Alignments of all the sequence comparisons, table of similarity, and phylogenetic trees are provided. There are more than 1,285 accessions.
- Gemini RefDataBase: all the bibliographic references (305) and papers regarding geminiviruses since 1977 have been collected, and there are further plans to collect all the corresponding abstract, to be made available in the network.
- GeminiNet Info: including GeminiNews, a list of officially accepted virus names, a list of GeneBank accessions, and a list of addresses of all the members.

One of the most significant problems in the advancement of research in developing countries is persistent obstacles to the dissemination of the scientific information. Scientists often have difficulty getting access to relevant information, and sometimes, years later, a researcher at work in a developing country will discover that something was already known or done. Geminivirus diseases are in emergence world-wide and many plant and crop diseases are caused by geminiviruses. As a result, the ILTAB team feels it is essential that scientists in Egypt, and around the world, have quick and efficient access to the information available for TYLCV and for all geminivirus diseases. ILTAB researchers acknowledge that activities with the ABSP project helped lead to the development of the network, and have obtained additional support for the initiative from the Rockefeller Foundation and from the French Scientific Research Institute for Development in Cooperation (ORSTOM). (Source: *BioLinks*, Vol. 2, No. 4, 1996)

Biodiversity databases in East Africa

In Nairobi in June, UNEP's Environmental Natural Resource Information Network Programme (ENRIN) hosted a regional workshop on the use of databases to support decision making in biodiversity conservation in East Africa. The event provided a forum to review progress made by the collaborating institutions of the region in developing biodiversity databases in East Africa. The information needs of decision makers were also identified. Furthermore, plans for developing a regional biodiversity database in East Africa were discussed during the workshop. This event was convened under the project Institutional Support for the Protection of East African Biodiversity financed by the GEF. (Source: *Our Planet*, Vol. 8, No.4, 1996)

UNEP's information clearing-house

In response to numerous queries on environmental standards and guidelines for potentially polluting industrial wastes, the Industry and Environment Office of UNEP has set up an in-house database called Industry & Environment Emission Standards and Guidelines Information Clearing-house. Since the creation of the Clearing-house, three compendiums covering a range of industrial sectors have been published to provide helpful information to governments, industries, international organizations, non-governmental organizations (NGOs), trade unions, research institutes and individuals. The compendiums are the following:

Textile Industry Effluent Discharge Standards, Industry & Environment Emission Standards & Guidelines Information Clearing-house, volume I, UNEP, 1996.

Pulp & Paper Industry Effluent Discharge Standards, Industry & Environment Emission Standards & Guidelines Information Clearing-house, volume II, UNEP, 1996.

Iron & Steel Industry Air Emission Standards, Industry & Environment Emission Standards & Guidelines Information Clearing-house, volume IIIa, UNEP, 1996. (Source: *Our Planet*, Vol. 8, No. 4, 1996)

Food and Agriculture Organization sabbatical programme under way

The Food and Agriculture Organization of the United Nations (FAO) hopes to engage academic personnel on sabbatical leave from universities to carry out agricultural research or related assignments in areas of mutual benefit to both parties. In an effort to increase cooperation between FAO and individual academic and research institutions, FAO's Director-General, Jacques Diouf, has introduced a new initiative to attract visiting academicians to work with FAO during periods of sabbatical leave. The visiting professionals would undertake overseas assignments, not exceeding one year, that not only fit their own backgrounds, but which are also relevant to the priority programmes of the FAO (e.g., animal production and health, pesticide management, agricultural marketing, nutrition, aquaculture, forest resource management, sustainable development, etc.). As in a usual sabbatical leave, the sponsoring university would pay salary and any other allowances of the visiting professional. FAO, besides providing the office/work environment and overheads, will also cover travel costs, provide United Nations travel documents and pay the visiting fellow a subsistence allowance of $2,500 per month.

Further information regarding this programme can be obtained by contacting Mr. Charles Riemenschneider, Director, FAO Liaison Office for North America, 1001 22nd Street, N.W., Washington, DC 20437. Tel.: (202) 653-2400/1; Fax: (202) 653-5760. E-mail: (C.Riemenschneider—FAO@cgnet.com). (Source: *BioLinks*, Vol. 2, No. 4, 1996)

Ethical issues

European bioethics convention is finally adopted by CoE

The world's first legally binding international rules on genetics were finally adopted by representatives of the 40-nation Council of Europe (CoE) in Strasbourg on 19 November 1996 and will come into force once they have been ratified by five countries.

After five years of drafting, the European Convention on Bioethics is likely to be opened for signature in January.

In the final discussions, government representatives rejected many of the more restrictive amendments sought by the CoE Parliamentary Assembly in September.

The Convention's Chapter IV deals specifically with the human genome in the following four articles:

- Article 11 (Non-discrimination): Any form of discrimination against a person on the grounds of his or her genetic heritage is prohibited.
- Article 12 (Predictive genetic tests): Tests which are predictive of genetic diseases or which serve either to identify the subject as a carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease may be performed only for health purposes or for scientific research linked to health purposes, and subject to appropriate genetic counselling.
- Article 13 (Interventions on the human genome): An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to

introduce any modification in the genome of any descendants.

- Article 14 (Non-selection of sex): The use of techniques of medically assisted procreation shall not be allowed for the purpose of choosing a future child's sex, except where serious hereditary sex-related disease is to be avoided.

Articles 11 and 12 have been hailed as implying prohibition on genetic screening for the purposes of insurance or employment, although government representatives refused to back the Parliament Assembly on inclusion of further provisions forbidding the communication of screening results, even with the consent of the person concerned.

Article 13 is seen as a reinforcement of research moratoriums on germ-line therapies.

As for Article 14, where the parliamentarians wanted an outright ban on sex selection, governments have opted for the wording suggested by the Convention's drafting committee which provides scope for couples to resort to *in vitro* techniques to avoid risks that their child would suffer from an inherited complaint.

Other sections of the Convention, such as those on scientific research and confidentiality of data, will have general application across the spectrum of pharmaceutical and medical studies. (Source: *Biotechnology Business News*, 2 December 1996)

US Bioethics Commission meets, outlines agenda

Meeting for the first time in October, members of the US National Bioethics Advisory Commission (NBAC, Washington, DC), took modest steps to shape an agenda to consider over the next few years of regular meetings.

NBAC members appear to be slating several issues of importance to the biotechnology industry for near-term consideration, including the use of human subjects in biomedical research, genetic privacy and related tissue sample usage issues, and possibly gene patenting.

No single issue drew more attention than concerns with the overall operation of institutional review boards (IRBs)—the sprawling, locally operating but federally sanctioned—system for reviewing biomedical research protocols and protecting the rights of human subjects. The US National Institutes of Health (NIH, Bethesda, MD) oversees this system.

Despite a good performance record, there are shortcomings to the IRB system that reflect the way it was established and affect the way it performs. There is no federal statute applicable to such research, meaning current rules do not apply universally. Moreover, the IRB system is far from uniform—a factor that sometimes proves frustrating or worse for investigators conducting multisite clinical trials. (Extracted from *Nature Biotechnology*, Vol. 14, November 1996)

Bioethics group finds "no objection" to human gene patents

A group of ethics advisers to the European Commission in Brussels says that it has found no ethical reason why a human gene should not be patented by its "discoverer" if it can be shown that it has a function with a specific industrial application.

But, in a statement in late September 1996, the group added that it should not be possible to patent the simple knowledge of the structure of a complete or partial gene sequence without identifying its function. Such a patent would not meet the primary requirements of novelty, inventive step and industrial application.

The group was asked by the Commission in April 1996 to consider the ethical implications of patenting material of human origin, as part of a wide consultation process intended to help smooth the passage of a European directive on the patenting of biotechnological inventions. An earlier directive failed to win the vote of the European Parliament in 1995, partly because of ethical concerns. (Extracted from *Nature*, Vol. 383, 3 October 1996)

Regulatory issues

US Food and Drug Administration looking into regulating the Internet

Recognizing that nearly every drug-development company now has a Web site where it disseminates information about its products, the US Food and Drug Administration (FDA, Rockville, MD) says it is going to look into what is being said about therapeutics on the Internet. At present, the agency has "statutory provisions, regulations, and policies concerning advertising and labelling" in traditional media, and it wants to be sure that those same standards are being applied on the Web as well. Under these rules, companies are barred from promoting any unapproved uses of drugs and devices by the FDA. But when advocacy groups post information about a drug being approved overseas or a new unapproved use for a drug and link that information to the manufacturer's Web site, what—if anything—should the drug developer do? The FDA also wants to take up the question of "fair balance". Manufacturers are currently required to provide information about a drug's effectiveness as well as its potential side-effects in any advertisement. (Source: *Nature Biotechnolgy*, Vol. 14, November 1996)

General

EU delays corn decision

Amid increasing public concern over the safety of genetically altered crops, the European Commission has postponed its decision on whether to authorize imports of modified corn from the USA.

Since July, three European Union science committees have been analysing the effects of corn produced by Ciba and Mycogen on human health and the environment. Additional information was recently submitted to the committees.

"We cannot rush science, and we cannot make a decision without it", says European environment commissioner Ritt Bjerregaard. "Any decision needs to be met with confidence by the general public". The issue of genetically modified corn that is fed to cattle is particularly sensitive in Europe following the crisis over "mad cow disease".

Meanwhile, several food retailers have decided not to stock products containing Monsanto's *Roundup Ready* genetically engineered soybeans unless they are separated and labelled differently from traditional soybeans. These include Austrian supermarket chain Meinl, Swiss wholesalers Coop Schweiz and Swiss Migros, and UK frozen food chain Iceland. (Source: *Chemical Week*, 20 November 1996)

Campaign to label genetically modified food

A new campaign has been launched to ensure that genetically modified foodstuffs are labelled, possibly delaying European legislation on the patentability of genetically engineered organisms.

Eurocommerce, an organization for EU retailers and wholesalers, and representatives of the Green Party in the

European Parliament have launched a campaign demanding that consumers be informed of the use of genetically engineered products in foodstuffs.

The trade body is also calling for genetically modified US soybeans, now accounting for 2 per cent of the soybean crop, to be segregated from ordinary ones. However, Monsanto, which produces the genetically engineered crop, said segregation was impractical and unnecessary as the product had been approved as safe by EC regulatory authorities in April 1996.

The campaign could be coming at a bad time for the EC, which is pushing through a draft directive on the patentability of genetically modified organisms. Legislation is expected some time in 1997. The equivalent laws in the USA allow a wide range of patentability but there have been problems in the drafting of the EC legislation already. In particular, the patentability of transgenic animals has met with some opposition in Denmark and the Netherlands. (Source: *European Chemical News*, 14-20 October 1996)

One voice for Euro industry

Europe's two biotechnology industry associations—the Senior Advisory Group Biotechnology and the European Secretariat of the National Bioindustry Associations—have joined forces to form EuropaBio.

The newly united association will represent the interests of more than 500 companies and eight national associations in Europe involved in the biotechnology industry. The national associations are located in Belgium, France, Spain, the Netherlands, Denmark, Italy, Sweden and the UK. Germany, Portugal and Switzerland are currently considering setting up their own national bioindustry associations and decisions about their formal applications for EuropaBio membership are expected in the next few months.

The move builds upon the relationship between the SAGB and ESNBA, which already shared the same Brussels offices and have increasingly formulated joint policy issues affecting the industry.

The SAGB-ESNBA merger echoes the calls for a more united approach on EU biotechnology matters made at the recent European Commission-sponsored meeting in Brussels on *The Future of Biotechnologies in Europe* and has been unanimously welcomed by biotechnology representatives.

For further information on EuropaBio contact: Secretary-General, EuropaBio, Avenue de l'Armée 6, 1040 Brussels, Belgium. Tel.: 32 2 735 0313; Fax: 32 2 735 4960. (Extracted from *Biotechnology Business News*, 9 October 1996)

Industry reacts to EU orphan drug proposals

The pharmaceutical industry is expected to welcome the European Commission's recent initiative on orphan drugs, but to say it does not go far enough.

Most companies and associations have so far produced only preliminary observations, and EuropaBio (the newly merged biotechnology industry association) has formed an initial view but has also set up a special task force to consider the issue in greater depth.

There are at least three areas where improvements can be expected: duration of exclusivity, the population threshold for eligibility and the proposed mutual exclusivity of EU, Japanese and US orphan drug status, i.e. a drug with orphan drug status in Japan or the USA would be automatically ineligible to apply in Europe.

The duration proposed is six years, renewable to 10, but with no certainty that the extension will be obtained. The standard threshold at which eligibility would start is a condition affecting fewer than one person per 1,000, but with strict conditions attached on proving that development costs are unlikely to be recouped, which industry sources fear may be a very difficult hurdle. That requirement would be waived where prevalence is less than one per 25,000 as it is considered unlikely at this level that any drug "could generate excessive profits". (Extracted from *Biotechnology Business News*, 9 October 1996)

Human genome map covering 16,000 genes available on Internet

A map of about one fifth of all human genes is now available on the Internet, giving everyone access to genetic information. Scientists predict the Internet will pick up the pace of research into the genetic basis of inherited diseases. The gene map gives the locations on chromosomes of more than 16,000 genes that have already been analysed. Advances in technologies for finding genes and mapping them has made it possible to draw up a preliminary map in advance of the completion of the Human Genome Project, an international effort to analyse all of the estimated 50,000 to 100,000 human genes by 2005.

The map will be updated frequently, as laboratories around the world sequence new genes.

Scientists predict that the map will cut years off any single genetic search. An investigator seeking a gene in a specific location can simply call up the Web site, type in the markers and in seconds obtain a listing of the candidate genes in the area.

Dr. Francis Collins, director of the NIH's National Center for Human Genome Research (NCHGR), said that a "map of this detail gives disease-gene hunters about a one-in-five chance that the gene they are looking for has already been characterized by this effort".

For the general public, the Internet site has been designed so that a person can look at the DNA and access information on 45 diseases, such as Alzheimer's disease or breast cancer, caused by genetic defects.

Clicking on a picture of a brain scan at chromosome one, for example, will call up a general description of Alzheimer's disease, an 800-number for the Alzheimer's Association and the Alzheimer's Disease Education Referral Center, and a quote from Nancy Reagan. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 4 November 1996)

Monsanto buys Seminis' Asgrow

Monsanto will add to its growing biotechnology division by acquiring the Asgrow Agronomics business of Seminis. The deal is the latest in a long line of acquisitions by Monsanto in the biotechnology field and will complete its genetically altered soybean chain from R&D to seed sale.

Seminis is the subsidiary of Empresas La Moderna (ELM) of Mexico, which has global agricultural interests. Monsanto said the purchase will allow it to accelerate sales in its *Roundup Ready* soybean range for which there is a potentially huge market. The beans are genetically engineered and formulated to be resistant to Monsanto's *Roundup* herbicide.

Monsanto and ELM have also made a technology agreement where Monsanto will be preferred to provide agronomic biotechnology to ELM's fruit and vegetable business. Earlier in 1996, Monsanto pledged $200 million to increase production capacity at its formulation plant, to be spent over the next three years. (Source: *European Chemical News*, 7-13 October 1996)

Enzyme marketing deal

Boehringer Mannheim is to market world-wide enzymes produced by the US biotechnology firm Recombinant BioCatalysis. The deal gives Boehringer Mannheim non-exclusive rights to market enzymes which will be used in synthesizing compounds for pharmaceuticals, agrochemicals and speciality chemicals, among others.

Recombinant BioCatalysis specializes in the discovery of enzymes which come from extreme conditions such as hot springs and undersea vents. This means that they can work at high temperatures. This represents a big advantage for biotcatalysis as reaction rates are higher and contamination problems can be minimized. The company also has a proprietary *DirectEvolution* method for optimization and selection of enzymes towards pre-determined properties. (Source: *European Chemical News*, 14-20 October 1996)

Scientific product sales on world market

Over 60 per cent of world-wide sales of life-science research products occur outside the USA, according to **PhorTech International** (San Carlos, CA. Fax: 415-594-9846). Europe represents 29.7 per cent of the global market for laboratory scientific instruments, or $15.2 billion spent annually. Of this, only 3.5 per cent is spent in the Eastern European countries and Russia, reports PhorTech, which recently published a world-wide directory of life-science distributors.

The single largest market in Europe is Germany (34.2 per cent), followed by France (16.3 per cent), the UK (12.1 per cent), Italy (8.2 per cent), Spain and Portugal (8.1 per cent), Benelux (6.5 per cent), the Nordic countries (5.6 per cent), Switzerland (2.7 per cent), Austria (1.3 per cent), Ireland (0.8 per cent) and Greece (0.6 per cent).

Asia represents approximately 21.9 per cent of the global market for laboratory products, or a market of $11.2 billion. Of this region, Japan accounts for 39.1 per cent, followed by Taiwan (10.7 per cent), Singapore (10.1 per cent), Thailand (7.5 per cent), Malaysia (7.3 per cent), Korea (7.1 per cent), People's Republic of China (6.1 per cent), India (4.5 per cent), Indonesia (3.9 per cent), Pakistan (1.5 per cent), Philippines (1.1 per cent) and Hong Kong (0.7 per cent).

PhorTech notes that Oceania's segment of the laboratory market totals $1.5 billion annually (2.8 per cent of global demand); South America 1.9 per cent (almost $1 billion); the Middle East 1.3 per cent ($650 million); Africa 0.7 per cent ($362 million); and Central America 0.2 per cent ($78 million).

North America accounts for 41.5 per cent of the global market for laboratory products, represented by the USA (which is not included in the directory) 39.5 per cent; Canada 1.7 per cent; and Mexico 0.3 per cent. (Source: *Genetic Engineering News*, 15 October 1996)

Collaborations: bringing a research idea to fruition

Scientists could be forgiven for being overwhelmed by the avalanche of challenges they face at each and every stage of their research. In the early days, it seemed clear what their role was. Today, they collide with the realities of debt and equity financing, while at the same time deciding on the research viability of their project.

Some of the practical questions researchers must ask themselves at the outset of a project are:

- Is this research viable?
- Is the expertise available?
- Do I have an effective business as well as a research plan?
- How long will this project take?
- Where can I obtain adequate and timely financing?
- Who are potential partners for this research?
- What are the risks? What are the benefits?
- What regulatory bodies must I work with?
- What are the responsibilities and with whom do they lie?
- Who owns the rights?
- Will the consumer accept the final product?

Scientists are further frustrated by the need to produce practical results while realizing that only through basic science can applied research be achieved. However, with new biotechnology products now on the market, scientists and industry have obviously found successful ways to work in harmony, and we have begun a history of collaboration.

For more information contact Rosemarie Gallays at 306 975-5571. (Source: *The AgBiotech Bulletin*, October 1996)

PGS-AgrEvo deal

Hoechst Schering AgrEvo's (AgrEvo, Berlin, Germany) $730 million acquisition of PGS International (Amsterdam, the Netherlands) in August 1996 was not only the largest ever acquisition of a privately owned biotechnology company; it also greatly increased the likelihood that other plant and agricultural biotechnology companies could soon be swallowed by major corporations.

Multinational agrochemical companies have been building up their plant biotechnology expertise recently by acquiring plant biotechnology companies.

Plant biotechnology companies have always been the poor relations of biopharmaceutical companies. They have not generated enthusiasm within the investment community. PGS attempted to float its shares on NASDAQ (North American Securities and Dealers Automated Quotation) two years ago—but failed. Its timing was bad, but even if it had succeeded, it would have had a market capitalization of only around $200-250 million. the only profit for investors in plant biotechnology has been in selling their shareholdings in agrochemical, food and seed companies. AgrEvo's $730 million bid for PGS demonstrates that this approach can pay off for patient investors.

AgrEvo, like other agrochemical concerns, believes that its future success—or survival even—will depend on access to patent-protected plant biotechnology, especially in the areas of herbicide tolerance and pest protection. AgrEvo believes the global market for genetically modified plants will be worth $6 billion by 2005 and that the PGS acquisition gives it the technological critical mass to command at least $1 billion of that.

The real target for AgrEvo is probably not the Basta-tolerance technology, but PGS's position in insect-resistance technologies based on the *Bacillus thuringiensis (Bt)* toxin gene. The world's first insect-resistant plant was developed at PGS in 1985. The company received its first broad patent on insect-resistant plants in 1993 and has been steadily reinforcing its patent estate ever since. PGS scientists have identified and patented several *Bt* genes, which encode for proteins toxic to the corn borer, of which the crylAb gene is most widely used by companies developing insect-tolerant varieties. (Extracted from *Nature Biotechnology*, Vol. 14, October 1996)

Tied aid

The history of the industrial world's aid to developing countries is littered with horror stories. Aid that is "tied" accounts for around 40 per cent of donations from OECD countries. Most aid agencies claim that tied aid is a

huge burden to the developing countries which receive it, for if a government is forced to buy equipment, spare parts and the services of consultants or scientists from the donor country, then it cannot shop around for the best price and often ends up paying over the odds.

"Instead of giving money, a tied aid policy gives goods which end up as rust heaps", claims Robert Shaw, a Kenyan economics writer. "In a lot of cases it is not a gift, it is a soft loan. Looked at cynically, tied aid is a disguised way of promoting that country's product. Any embassy or high commission of a major developed country has a strong commercial component—it is there to represent their country's companies. In very big deals that becomes a dominant issue".

A report published recently by the Overseas Development Administration (ODA), *Review of UK Aid Tying Policy*, shows that heavy vehicles and industrial equipment, as well as shovels and agricultural tools, cost recipients more if they are bought from British companies. Some spare parts for vehicles are 30 per cent more expensive if bought from Britain.

The OECD estimates that tying aid increases a developing country's costs by an average of 15 per cent. With tied aid worth $15 billion in 1994, the extra cost to the developing world during that year amounted to some $2 billion. The OECD tried to reduce this burden with its 1992 Helsinki Agreement, which restricts the use of tied aid loans to countries below a certain income threshold. It has been partly successful. The volume of tied aid loans from Spain, for example, fell from around 70 per cent of total bilateral aid in 1994 to 22 per cent in 1995.

Scared of change

Countries are finding ways to bypass the restrictions, such as replacing loans with grants, which are not subject to the agreement. And despite increasingly urgent calls from critics—including the World Bank and many aid agencies—for countries to reduce their commitments to tied aid, there is little apparent enthusiasm for doing so.

The Netherlands and Japan have reduced their commitments to tied aid.

Aid agencies insist that tied aid does little to improve the economies of poor countries and the living standards of their people.

A large proportion of emergency relief aid is also tied, even when it is directed through non-governmental organizations.

Robert Maxwell, chief executive of the King's Fund, an independent health charity based in London, accuses donor countries of sometimes putting their interests before those of the recipients. For example, a donor country may choose equipment for a hospital in Africa on the basis of what its domestic companies can supply, rather than on what the hospital actually needs. Tied aid often leads to poor countries being flooded with equipment which is complicated to maintain and needs expensive spare parts from overseas. One survey found more than 16 different kinds of water pump in use in Kenya, each funded by a different donor nation.

The British Government has frequently stated that tied aid is good for business. But even this assumption is being questioned. The ODA's own report argues that an agreement between countries to untie aid would benefit exports and competition. The ODA's report also says that in the absence of international agreement, the effect of untying British aid would be very small. It goes on to warn that cutting back tied aid unilaterally could reduce public support for Britain's entire aid programme.

Yet enthusiasm for tied aid appears to be waning. Even industry chiefs are slow to leap to its defence. Nevertheless, the ODA insists that since 1977, British companies have won £4 billion of business through tied aid. The main beneficiaries have been construction companies.

There has been some change in the ODA's attitude in recent years. In 1994, the High Court ruled that the use of £234 million from the aid budget to fund the Pergau Dam in Malaysia, linked to £1 billion of arms sales, was illegal. Following this, the ODA's funding priorities have switched away from supporting dam builders and metal bashers, and moved towards consultancies. But some critics believe the new policy is just as flawed. (Extracted from *New Scientist*, 12 October 1996)

Biotechnology impacts drug making

Pharmaceutical and fine chemical production is evolving. At the same time, the drug development process is experiencing growing pains.

Spurred on by massive consolidations, increasing specialization and an overall need for cost containment, manufacturers are learning new ways to both view and solve production challenges.

Outsourcing, advances in biotechnology and new alliances are among the trends reshaping the industry.

The role of biotechnology figures prominently in the order of fine chemical production. "The chemistry of tomorrow will be a combination of biotechnology and chemistry", says Larry Drumm, vice-president of business resources for Bio-Technical Resources, Manitowac, WI.

Mr. Drumm says that bioprocesses may in some cases replace chemical synthesis, allowing changes in feedstock and sometimes producing less hazardous by-products. He adds that while new biotechnology and process tools will help with biotechnology's growth, industry's acceptance of biological alternatives and embracement of the technology is equally important.

To illustrate the success of biotechnology, Mr. Drumm points to the agricultural sector, where 22 biotechnology agricultural products are already on the market, and 25 more are awaiting approval.

Mr. Dreikhorn, manager of chemical technology assessment and acquisition for DowElanco, IN, sees outsourcing as another critical part of development efforts. "Third party sourcing of chemical libraries for screening has been key to our finding novel chemistries for our sourcing efforts", he says.

Zeneca Life Science Molecules, a unit of Zeneca Ltd., also says that biotechnology can complement and improve existing processes with increased industry acceptance.

Biotechnology is not only being used as a tool to complement existing chemical processes, however. It is also providing new business to contract manufacturers. Virtual companies, which are based on core technologies and concentrate specifically on drug development, are changing the development process.

These companies most often have small staffs and infrastructure, usually with limited manufacturing or process capability. Such firms provide new business to operators of pilot plant and contract manufacturing facilities.

Fine chemical companies of all types and sizes are rising to meet the needs of the custom and contract market. Some offer process technology and scale-up services, while others are strict contract manufacturers. In addition to independent contract manufacturers, many large multinational firms also have significant contract business. (Extracted from *Chemcial Marketing Reporter*, 7 October 1996)

Indexing the world's known species— Species 2000

Representatives of 18 taxonomic and species diversity databases met in mid-March 1996 at a United Nations Environment Programme workshop to give the formal go-ahead for the programme "Species 2000" which had been planned by the International Union of Biological Sciences (IUBS), the Committee on Data for Science and Technology (CODATA) and the International Union of Microbiological Societies (IUMS). The programme to provide an index of the world's known species was initiated in March 1996 in Manila, Philippines. The Species 2000 programme will enable users world-wide to verify the scientific name, status and classification of every known species of plant, animal, fungus and micro-organism, of which there are about 1.75 million in the world. The existing global species databases may presently account for some 15-20 per cent of the total. The workshop was organized by the Species 2000 Secretariat at the University of Southampton, UK and hosted by Dr. Rainer Froese and staff of the Fish Base species diversity database at its headquarters in the International Centre for Living Aquatic Resources Management (ICLARM) in Manila.

For further information contact the Species 2000 Secretariat, School of Biological Sciences, University of Southampton, Southampton, SO16 7PX, UK. Tel.: 44-1703 592444; Fax: 44-1703 594434. (Source: *INFOFISH International*, March 1996)

Scientists find "new" life form in sea floor vent

Vying for media space with reports of "Life on Mars", researchers at the Institute for Genomic Research in Gaithersburg, MD, identified an ancient microbe found in a volcanic vent in the Pacific. *Methanoccus jannaschii*—discovered during 1982 dives with Woods Hole Oceanographic Institution's *Alvin* submarine—lives several thousand feet down in temperatures near the boiling point of water. Unlike the now-questionable evidence of ancient life on Mars taken from a meteorite, this deep sea microbe's genetic blueprint has been sequenced and identified as part of the ancient third kingdom of organisms known as Archaea. (Source: *Sea Technology*, September 1996)

African nations sow seeds of hope

Twelve African countries are drawing up a plan to help each other if civil unrest or drought threaten to destroy their crops. Each country will hold stocks of seed that can be used to replenish those of a neighbour struck by disaster.

The move follows the success of the Seeds of Hope programme, which helped to kick-start Rwanda's agriculture after the civil war of 1994 and saved it from losing many of its unique varieties of crop plants.

Ten of the countries—Burundi, Djibouti, Eritrea, Ethiopia, Kenya, Rwanda, Somalia, Sudan, Tanzania and Uganda—are part of the Greater Horn of Africa. At no time between 1979 and 1994 has the region been entirely free of either drought or civil unrest. The other two countries are Madagascar and Zaire. The directors of agricultural research for the 12 nations have formed a group called the Association for Strengthening Agricultural Research in East and Central Africa.

The Association is considering a plan to protect the genetic diversity of crop plants. Unique local varieties of crop species are adapted to often highly—specific conditions and have developed a degree of resistance to local pests and diseases.

During the civil war in Rwanda, in which 800,000 people were killed and millions fled their homes, only about half the prewar population of eight million was able to produce food. The harvest of grain crops such as maize, beans and sorghum, fell by 60 per cent. The country's agricultural research institute, where 55 scientists once worked, had two staff left.

Seeds from Rwanda held in seedbanks in India, Mexico, Colombia, Burundi, Uganda and Kenya were multiplied by planting stored grains and harvesting the next crop. They were delivered to farmers by aid organizations such as World Vision, CARE, the Catholic Relief Service, the World Bank and Swiss Disaster Relief.

One of the biggest needs is for a database of information on where particular seeds are held, and the conditions that suit the different varieties.

The database, which would include maps, should be made available to agricultural organizations and non-governmental organizations in East Africa and overseas.

Most seedbanks hold seed at very low temperatures, but they need to think of cheap and simple alternatives, such as keeping seeds in bottles or drums sealed with paraffin wax. In a civil uprising the first thing that will go will be the power supply, so seeds kept in cold rooms could be useless. Identification of seeds also needs to be standardized. (Source: *New Scientist*, 12 October 1996)

Millenium target hinders leprosy fight

WHO's campaign to eliminate leprosy by the turn of the century is unrealistic, and could discourage spending on urgently needed research, scientists warned at an international conference in New Delhi on the disease.

At the meeting, WHO called on health ministers from some of the worst affected countries to support its goal of "eliminating leprosy as a public health concern by the year 2000", but critics say the date is impractical, because the disease afflicts the remotest parts of some of the world's poorest countries. And they warn that money for research into leprosy is already drying up because funding organizations believe that the threat is disappearing.

There are an estimated 1.3 million people in 60 countries who have leprosy. To eliminate the disease, its prevalence would first have to be brought down to 1 in 10,000, the WHO says. Yet South-East Asia has six times this rate. An effective drug treatment does exist, but logistic problems in poor countries often make it difficult to administer. (Source: *New Scientist*, 19 October 1996)

Superwheat to feed the world

To meet the growing demand for wheat, agricultural researchers must improve yields dramatically throughout the next century, warns a new report. Otherwise a growing world population will convert more unspoilt land to agriculture to avoid going hungry.

The report, from the International Maize and Wheat Improvement Centre in Texcoco, Mexico, sets a goal of increasing wheat yields by an average of 2.5 per cent a year. Demand is growing, says Matt Reynolds, a senior scientist at the centre, as developing countries increasingly turn from rice to wheat.

In the 1960s and 1970s, the "green revolution" boosted crop yields, including those of wheat, by as much as 100 per cent. This was largely due to the development of dwarf wheat varieties which made more effective use of fertilizers and irrigation. The plants were able to support increased grain yields without collapsing.

For the past decade, however, yields have been improving at only 0.5 per cent a year. Reynolds acknowledges that the huge gains of the green revolution will never be repeated.

But by concentrating research in a number of areas, he says, the goal outlined in the new report can be attained.

One such area is the development of wheat varieties with foliage situated to make better use of sunlight. Varieties must be bred for different microclimates and for different sowing regimes, such as broadcasting or drilling in rows. (Source: *New Scientist*, 26 October 1996)

Biologists predict catastrophe from crop-to-weed gene flow

Sorghum, one of the most common crops, can cross-breed with a weed that is the bane of many farmers—johnsongrass—according to a new study. The results have plant biologists worried that this will become a serious problem in the era of genetically engineered plants.

This study is the first in which scientists have shown that these two plants can hybridize spontaneously, the scientists said.

Norm Ellstrand, a professor of genetics at the University of California at Riverside predicts an "ecological or economic catastrophe", as more and more fields are planted with crops that have been genetically engineered to resist herbicides, insects and other stresses of the growing season. While any one transgenic crop poses a miniscule risk, taken together they could cause "a multi-million-dollar problem in ten years", he said.

Ellstrand and biologist Paul E. Arriola, currently at Elmhurst College in Illinois, planted experimental johnsongrass in areas surrounding a field of sorghum, and later looked for genetic evidence of hybridization. They found crop/weed hybrids as far away as 100 metres.

The idea that crops and weeds can hybridize raises the possibility that weeds could gain an advantage if they get some of the DNA from transgenic plants. For example, a gene for herbicide resistance could create a type of johnsongrass that is impossible to control.

Scientists are also discovering, in several studies like Ellstrand's, that crop-to-weed gene flow is more common than was previously believed, and can occur in a variety ofplant species. (Source: *McGraw Hill's Biotechnology Newswatch*, 21 October 1996)

International Marine Biotechnology Conference

The 4th IBMC will be held in southern Italy, starting in Sorrento on 22 September 1997. This very innovative conference has been designed to develop a multidisciplinary, highly interactive programme. IMBC '97 will consist of two phases: phase I will take place in Sorrento from 22 to 25 September and will focus on research presentations and poster sessions—the programme will be based on the abstracts selected after peer review; phase II will consist of a four-day scientific working tour of southern continental Italy, during which there will be daily round-table discussions and interactive sessions with representatives of marine biotechnology industries and research facilities. Phase II has been specifically designed to generate new research collaborations and improve links between academia, industry and government, to identify opportunities where marine biotechnology can contribute to solutions in sustaining marine natural resources, to generate the business development of marine biotechnology industries and to communicate to society in general the role marine biotechnology can play in enhancing the quality of life and the environment.

Members of the scientific, regulatory and business communities interested in the current and future status of marine biotechnology are encouraged to participate. Further information may be obtained from Ms. Donatella Capone, Stazione Zoologica "Anton Dohrn", Villa Comunale, I-80121 Naples, Italy. Tel.: +39-(0) 81-58333215; Fax: +39 (0) 817641355. E-mail: imbc@alpha.szn.it.

XVIIIth International Congress of Genetics

The XVIIIth International Congress of Genetics will be held at the Beijing International Convention Centre, Beijing (China) from 22 to 28 August 1998, sponsored by the International Genetics Federation, the Genetics Society of China and the Chinese Academy of Sciences.

There is an increasing awareness that the growing world population is challenged by shortage of food supply, which particularly manacles the lives of third world nations. However, the theories and techniques of genetics and genetic engineering can provide a positive solution to this global problem. The Congress will therefore emphasize the most recent developments in genetics and its relation to agriculture, medicine, population, resources and the environment. One focus will be education in genetics, with special reference to developing countries. The Congress will consist of plenary sessions, symposia, workshops, poster sessions, grouped into the main divisions, as follows:

1. Genestructure and function;
2. Genomic organization;
3. Developmental genetics and neurogenetics;
4. Population genetics and evolution;
5. Genetics and agriculture;
6. Genetics and medicine;
7. Genetics, environment and society.

A pre-congress meeting will be organized by the Genetics Society of Yunnan Province and the Kunming Institute of Zoology on the specific topic of Genetics and the Conservation of Biodiversity, and will be held in Kunming, Yunnan Province, which is rich in many well-preserved natural resources.

Further information may be obtained from: The Secretariat, XVIIIth International Congress of Genetics, Institute of Genetics, CAS, Datun Road, Andingmenwai, Beijing 100101, China. Tel.: 86-10-64914896; Fax: 86-10-64914896 or 86-10-64913428 (Shou-yl Chen). E-mail: SYCHEN@MiMi.CNC.AC.CN

C. COUNTRY NEWS

Bulgaria

Bulgaria gets Eastern Europe's first gene release body

On 16 August 1996, the Bulgarian National Assembly formally approved the first gene regulatory body in Eastern Europe—the Council for Safe Use of Genetically Modified Higher Plants, part of the Ministry of Agriculture and Food Industry (Sofia). Following the model of regulatory structure set out in the European Union's (EU) "deliberate release" directive (90/220), the Council has full responsibility for permitting releases (both for research and commercial purposes) on behalf of the Ministry and will act as Bulgarias "competent authority".

The Council members are appointed by the Minister of Agriculture and may invite input from foreign experts where necessary.

Bulgaria thus becomes the first Eastern European country to adopt specific regulations for genetically modified organisms (GMOs). The former Soviet bloc nations need to develop technical and trade links in Western Europe. However, organizations in the EU or North America have been unwilling to run field trials anywhere where release regulations corresponding to their own domestic legislation is not in force.

Responding to this kind of dilemma and to pressure from scientific and industrial groups, administrators in Bulgaria prepared draft regulations covering releases of all classes of recombinant microorganisms. None have yet been approved, however, either because there were more pressing legislative matters, or because of political and public concerns that focus on genetically engineered micro-organisms.

When these broader proposals faltered, realists in Bulgaria sought a practical compromise: plant-only rules. Plant biotechnology is relatively highly developed in Bulgaria. Although there have been no releases of genetically modified animals or microorganisms, three research field trials with transgenic plants have taken place since 1991. These all concerned plant varieties developed at the Institute of Genetic Engineering at Kostinbrod: tobacco transformed with the gene that encodes the nucleocapsid of tomato spotted-wilt virus; tobacco resistant to bacterial wild-fire disease (*Pseudomonas syringae* pv. *Tabaci*); and alfalfa transformed with marker genes.

The Council is obliged to answer every notification within 30 days, either indicating approval or setting out additional conditions that need to be met before a release can be approved.

The plant regulations are regarded within Bulgaria as a prelude to the adoption and ratification by the National Assembly of a complete set of GMO regulations. (Source: *Nature Biotechnology*, Vol. 14, October 1996)

Canada

Plant disease forecast based on GIS

A plant disease risk forecasting service which can provide a regional indication of weather conditions and disease progression has been developed by Manitoba Agriculture and several corporate and public partners. Using Geographic Information Systems (GIS) software, the service analyses crop stage, weather, and soil moisture conditions from 50 Environment Canada weather stations to produce maps indicating conditions favourable to the outbreak of plant diseases. (Source: *The AgBiotech Bulletin*, October 1996)

Academic and industrial bioinformatics centre established

A partnership between a Canadian biopharmaceutical company, a hospital and a federal research agency will establish the first academic/industrial centre for the fast-growing area of bioinformatics in Canada. Allelix Biopharmaceuticals Inc., (Mississauga, Ontario) announced that its newly formed subsidiary, Base4 Bioinformatics Inc., will collaborate with the federal National Research Council (NRC) and the Samuel Lunenfeld Research Institute of Mount Sinai Hospital (Toronto).

This first important "node" for bioinformatics research in Canada will be followed by others, according to Allelix.

Base4 uses advanced computer methods to analyse information on the role of genes in normal health and disease and offers its services on a contract basis. The NRC selected Base4 to update its Molecular Biology Database Service (BGDS), a computer database service used extensively by Canadian and international researchers. Base4 will also make MBDS accessible over the World Wide Web and provide a Web-based premium service package using advanced data security methods aimed at pharmaceutical and biotechnology companies.

As the companys first node, the Samuel Lunenfeld Research Institute contributes expertise both in molecular genetics and biological function.

Allelix provided financing for the project, with the hospital taking an equity stake. Details regarding ownership of intellectual property remain to be worked out.

Allelix Biopharmaceuticals is in the early stages of developing glucagon-like peptide (GLP)-2 hormones whose function as a stimulator of intestinal lining growth was recently revealed by Daniel Drucker, M.D., at the University of Toronto's Banting and Best Diabetes Centre. Allelix has applied for broad patent coverage for molecular structure as well as therapeutic uses in treating disorders such as short bowel syndrome, intestinal damage from cancer treatment and Crohn's disease. (Extracted from *Genetic Engineering News*, 15 October 1996)

European Union

Soybean labelling

European food retailers are calling for US soybean producers to separate and label genetically modified (GM) produce in this year's crop.

About 40 per cent of US soybeans are exported to Europe. Up to 60 per cent of food products contain some soya-based ingredients.

EuroCommerce, which represents European retail and wholesale groups, does not believe that US suppliers cannot segregate GM soybeans to allow labelling, arguing that they

are "not willing rather than not able". The association fears consumers will be uneasy about GM material and believes consumers should have the freedom to choose.

The industry also faces opposition from environmental groups such as Greenpeace. It claims that GM crops will increase the amount of chemicals in the environment because farmers will now spray throughout the season.

Greenpeace is also concerned that the long-term effects of releasing GM crops into the environment and the food chain are unknown. (Extracted from *Chemistry and Industry*, 7 October 1996)

New European bio-association

Europe's biotechnology companies now have one voice. The European Secretariat of National Biotechnology Associations (ESNBA) and the Senior Advisory Group Biotechnology (SAGB), which have been sharing premises in Brussels for over a year, have joined forces to become EuropaBio. EuropaBio—the European Association for Bioindustries—brings together both the smaller biotechnology specialist companies of ESNBA and the multinational interests associated with SAGB and now represents over 500 companies and their eight national industry associations. The two priorities of the new association are continued lobbying of European and national politicians and legislators, and the promotion of the bioindustry's image to the public. (Source: *Nature Biotechnology*, Vol. 14, November 1996)

No moves yet on European GMOs rules

Proposed changes to European rules on genetically engineered micro-organisms (GMOs) are still stalled following last week's meeting of the Environment Council.

Irish minister Brendan Howlin, who currently holds the presidency of the Council, has made revising the 1990 directive on contained used of GMOs a priority.

The amendment proposals include new definitions of "micro-organisms" and "contained use"—in laboratories, a risk-assessment approach to identifying how GMOs should be "contained" and administrative requirements which increase relative to the level of risk.

The Council also held broad "orientation debates" on the European Commission's new waste management strategy, drinking water quality—where pesticides limits may be changed, climate change and the "Auto-Oil" proposals on fuel quality and car emissions limits. No decisions were taken. (Source: *European Chemical News*, 21-27 October 1996)

Germany

Association of German biotechnology companies launched

Fifty-five start-up German biotechnology companies launched a national "Association of German Biotechnology Companies". Known as the *Vereinigung deutscher Biotechnologie-Unternehmen* (VBU, Frankfurt, Germany), its declared goals are to eliminate the obstacles to biotechnology growth and to promote its economic potential. The group wants to work to increase a positive public perception of biotechnology and to serve as a central exchange for national and international contacts. Its initial agenda will focus on finding partners to help young entrepreneurs launch new start-up biotechnology businesses. (Source: *Nature Biotechnology*, Vol. 14, November 1996)

Hong Kong

"Superchick"

A four-member research team at Hong Kong University is working to establish genetically the best combination of Chinese and Western chickens to produce a Hong Kong "superchick", while retaining genetic diversity among Chinese native lines in danger of dying out.

Chinese chickens are renowned for taste and texture, but they grow slowly. This has led farmers to crossbreed them indiscriminately with Western breeds that grow faster, says Daniel Chan, head of zoology at the University and the project leader. The Government-funded project aims to set up a gene bank of the many Chinese pure lines.The project will last three years.

Researchers and the Hong Kong Government also hope to stimulate a new export industry in addition to the domestic market of six million consumers of chicken. Breeders and scientists from China are also interested in collaboration. (Source: *Nature*, Vol. 383, 3 October 1996)

India

Biotechnology in India

With 900 million people to feed, the Indian agriculture sector is increasing its interest and activity in biotechnology. The most significant area of investment so far has been in the use of tissue-cultures to develop disease-free plants for the quickly expanding ornamental export market. Nearly 10 million micropropagated plants were exported from India last year, and a capacity for 100 million plants is predicted. Researchers have now developed micropropagation techniques for eucalyptus, bamboo, sandalwood, pomegranate, mango, neem and tamarind.

While basic research in molecular biology is limited to a few institutions in India, applied research is going on at many agricultural universities where transgenic crops, diagnostic systems, and improved vaccines are being studied. Courses in biotechnology are also being offered at many universities.

Partnerships between Indian companies and major international biotechnology firms have resulted in the production of transgenic cow pea, mung bean, and other crops, some of which have been field tested. Biotechnologies for corn, brassicas, silkworms and other plants and animals are also being developed with funding assistance from the national Government and several foundations.

Problems faced by Indian researchers include everything from power outages and the high cost of research journals, to the lack of intellectual property rights for plants and patent enforcements (which result in extreme secrecy within the scientific community.) Contact: C.S. Prakash, Centre for Plant Biotechnology Research, Tuskegee University. E-mail: prakash@acd.tusk.edu. (Source: *The AgBiotech Bulletin*, October 1996)

Israel

Peptide research

A consortium of Israeli drug and software companies and universities will receive US$50 million over five years for the design and development of peptide drugs, the Ministry of Industry and Commerce has announced. According to Shuki Gleitman, the Ministry's chief scientist, "there is a lot of academic knowledge and excellence in this

field in Israel that we want to put on a business track". (Source: *Nature*, Vol. 383, 17 October 1996)

Ecogen Israel gets second approval

Aspire, Ecogen Israel Partnership's (EIP, Jerusalem) second biocontrol product, was approved in August 1996 for use in Israel to control a wide range of post-harvest fungi on citrus fruits and apples. A unique formulation of the naturally occurring yeast, *Candida oleophila*, Aspire received US Environmental Protection Agency (EPA, Washington, DC) approval in February 1995 to prevent rot on harvested citrus fruits and apples. Plans for manufacture of Aspire are not yet finalized, but it is likely that it will be produced both in the US and Israel.

The Aspire product is based on a strain of yeast isolated by Edo Chalutz, deputy director of the Agricultural Research Organization (ARO, Rehovot, Israel) and developed in cooperation with US Department of Agriculture (Washington, DC) researcher Charlie Wilson. It acts by colonizing fruit surfaces—especially wounded tissues—and thereby excludes or inhibits decay pathogens. Formulated as dry, water-dispersible granules, Aspire is sprayed on fruit before waxing. It can be applied in combination with only 5-10 per cent of the dose of chemicals currently used, reducing fruit contamination and reducing the chance of developing resistance.

One of the reasons for the failure of biocontrol products to thrive on the market has been the difficulty in handling them up until now, which is not a problem with Aspire or EIP's first product, AQ10, a naturally occurring fungus (*Ampelomyces quisqualis*) discovered by Hebrew University scientist Abraham Sztejnberg. AQ10, a hyperparasite of all species of powdery mildew on grapes and apples, is still the only biofungicide against powdery mildew. This is its first year of sales, and it is expected to be used primarily by vintners in France and California, where many of its field trials were held. Ecogen recently applied for product registration in France.

Two other biocontrol products are in EIP's pipeline: a bionematocide for the control of root-knot nematodes, which should lower the use of methyl bromide fumigants, increasingly banned due to pernicious soil residues; and a biofungicide to control soil diseases. The first is in early field trials, and the biofungicide is in the planning stage. (Source: *Nature Biotechnology*, Vol. 14, October 1996)

Japan

Transgenic crops receive clearance

Two canola biotechnologies have received important regulatory approvals from the Japanese Ministry of Health and Welfare (MHW).

Japan's MHW has granted safety clearance for food products of canola seed grown from AgrEvo's Liberty Link canola. This clearance follows environmental approval early in June. It applies to Liberty-resistant transgenic varieties from Regina, Saskatchewan-based AgrEvo Canada and from PGS, the plant genetics company recently acquired by AgrEvo. The Liberty Link production system was registered in Canada in 1995.

Japanese regulatory clearance is a major step towards allowing Liberty Link canola to move freely through conventional marketing channels, and trade freely on world markets.

Final safety approval has also been given to Monsanto's *Roundup Ready* canola. Two other Monsanto products, as well as a third product that features Monsanto technology, were also approved. These are NewLeaf potatoes, protected from the Colorado potato beetle; *Roundup Ready* soybeans; and Northrup King's corn, which is protected from the European corn borer by Monsanto's YieldGard technology.

Roundup Ready canola has full regulatory approval in Canada, where it is currently being grown on some 50,000 acres. (Source: *The AgBiotech Bulletin*, October 1996)

Highlights of Bio Japan '96

Bio Japan '96, a joint event organized by the Japan Bioindustry Association (JBA), Japan Health Sciences Foundation (JHSF), and the Society for Techno-innovation of Agriculture, Forestry and Fisheries (STAFF), took place at the Tokyo International Exhibition Center in Ariake, Tokyo, from 24 to 27 July 1996.

With its view open to the twenty-first century, Bio Japan '96 took a closer look at the future development and progress of bioscience, biotechnology and the related industries from a thematic horizon, concentrating on the information functions of organisms and their importance to health, food and the environment. It also provided a platform for promoting research and communicating research results and for reaching a deeper understanding of the bioscience and biotechnology area in general.

Bio Japan '96 comprised a number of sub-events such as an international symposium, an exhibition, an open seminar (lectures, presentations by high school students, and bio-experiment corner), and business partnering, a first-ever attempt at providing a forum for opening up international business opportunities.

In the footsteps of the Bio Japan events of 1986, 1988 and 1992, Prince Hitachi was appointed the Honorary Governor to add to the significance of the event. His Excellency was present at the opening ceremony. (Source: *Japan Bioindustry Letters by JBA*, Vol. 13, No. 3, October 1996)

Malaysia

New categories in R&D funding scheme

The recent review of the Intensification of Research in Priority Areas (IRPA) funding scheme will now see a more "market-oriented" approach to the funding of research projects in the country. While the previous system was categorized into five research sectors (agriculture, applied science and technology, medical, strategic, industry), the new system has nine categories (agro-industry, minerals and energy, manufacturing, services, economic, health, social, environment, science). (Extracted from *Australasian Biotechnology*, Vol. 6, No. 5, October 1996)

United Kingdom

Cuts on threatened species programme

The UK Government has plans to wind down its attempts to promote biodiversity and protect declining bird species. The proposals, contained in an unpublished internal review by the Department of the Environment (DOE), have disappointed conservation scientists.

The section of the report on biodiversity and conservation of the report says that the DOE's biodiversity secretariat, which has an annual budget of only £148,000, "might be scaled down in two years'time". The document

also says that the department may reduce its bird conservation work.

Critics of the proposed cuts argue that the DOE's conservation work is already moving too slowly. As part of Britain's response to the United Nations biodiversity convention, the department has completed 116 "action plans" detailing its efforts to conserve declining species, but still has another 278 to prepare. (Extracted from *New Scientist*, 19 October 1996)

United States of America

US Navy to test DNA malaria vaccine in humans

US Navy researchers are on the verge of Phase I trials of a DNA vaccine for malaria that, if successful, would be the first drug that reliably prevents the disease.

Stephen Hoffmann, director of malaria research at the Naval Research Institute in Rockville, MD, said the "target date" for starting the trial is May 1997. Collaborating on the trials are Vical of San Diego and Pasteur Merieux Connaught.

Initially, Hoffmann said, the vaccine used in the tests will be univalent—it will contain only one gene from the plasmodium parasite that causes malaria, but efficacy trials will use a multivalent vaccine containing several genes.

Malaria causes up to 2 million deaths and between 300 and 500 million new cases of the disease are reported a year, Hoffman told about 350 researchers attending Vaccines 2000, a conference in Toronto (Canada) focusing on the potential for new disease-preventing drugs.

Most of the cases of malaria are in the developing world.

The usual treatment for malaria is chloroquine, which relieves the symptoms of the disease but does not prevent infection. But in many parts of the world, the disease no longer responds to chloroquine.

The World Health Organization is currently testing a vaccine invented by Colombian researcher Manuel Patarroyo, but so far results have been disappointing.

Malaria is a difficult disease to treat because the plasmodium parasite has a complicated life cycle: it is injected into the bloodstream by a bitting mosquito, infects cells in the liver for several days and then attacks and infects red blood cells.

"To understand the vaccine development," Hoffman said, "you have to understand the life cycle". Complicating the issue still further, he said, is the fact that there is no natural sterile immunity to malaria—even a robust immune response would not prevent re-infection.

An "optimal vaccine", Hoffman said, would create immunity to plasmodium at every stage of its life in the body. But the Navy vaccine will target only the liver stage, because only infected liver cells display plasmodium proteins on their surfaces—proteins that can trigger an immune response. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 4 November 1996)

US organic standards exclude biotechnology

The US National Organic Standards Board (NOSB) has voted to prohibit genetically modified organisms from organic production systems. The NOSB was established by the 1990 Farm Bill to create a single national organic foods standard to replace varying state organic accreditation programmes.

The approved motion reads: "The NOSB recommends that the class of genetically engineered organisms and their derivatives be prohibited in organic production and handling systems. Genetically engineered is defined as: made with techniques that alter the molecular or cell biology of an organism by means that are not possible under natural conditions or processes. Genetic engineering includes recombinant DNA, cell fusion, micro- and macro-encapsulation, gene deletion and doubling, introducing a foreign gene, and changing the positions of genes. It shall not include breeding, conjugation, fermentation, hybridization, *in vitro* fertilization, and tissue culture." Contact: R. Harold Ricker, Staff Director, USDA/AMS/TMD, Box 96456, Washington, DC 20090-6456. E-mail at harold_s_ricker@usda.gov. (Source: *AgBiotech*, November 1996)

BIO advocates genetic-testing privacy laws

The recent passage of the Kassebaum-Kennedy law in the USA prohibits insurance companies from denying coverage on the basis of an individual's medical history. Now BIO (Biotechnology Industry Organization, Washington, DC), wants to take this protection one step further—a federal privacy law covering medical information that would include results from diagnostics based on genetic testing. BIO says that only by Congress enacting such a comprehensive bill could the privacy of an individual's medical information be protected uniformly in the US. Otherwise, the Organization claims, individual states may develop inconsistent policies that may jeopardize fair treatment under the law. BIO says that in enacting a federal law, it is important that genetic information be included as part of the medical history protected from the outset. Separating the privacy of genetic information from a patient's general medical history may alow loopholes for discriminatory use. The legislation BIO proposes would not allow the release of any medical information without an individual's written consent. (Source: *Nature Biotechnology*, Vol. 14, November 1996)

FBI forensics tries mtDNA

Although forensics specialists at the US Federal Bureau of Investigation (FBI, Washington, DC) have been studying the utility of mitochondrial (mt) DNA for several years, they recently added judicial weight to this technology by taking some specific results into a Tennessee courtroom. There, mtDNA-based analysis is being used for the first time as evidence in a criminal proceeding—specifically, as part of a rape-and-murder trial.

Mitochondrial DNA offers several potential advantages over cellular DNA when it comes to forensic analyses, experts say. For one, mtDNA is present in several hundreds of copies per cell—a distinct advantage when dealing with scarce forensic samples. According to Paul Debenham, chief executive at University Diagnostics (London), mtDNA analysis is a specialist approach applied largely to compacted tissues with a paucity of usable cells. The analysis of skeletal remains using mtDNA both in forensics and in anthropology is one prime area of application. The US military has been using such DNA analysis to identify the remains of military personnel, and this technology also was used to examine the bones of Czar Nicholas II of Russia.

Another advantage, albeit for addressing very different questions through forensic analysis, is that mtDNA is inherited maternally, meaning that it can prove particularly useful for determining mother-child and sibling-sibling relationships. Conversely, however, the maternal inheritance of mtDNA also means that the technique cannot distinguish the sample of a suspect from that of his or her maternal relations: mother, grandmother, sister, brother, or maternal cousins. Indeed, its linear maternal transmission means that

the number of different types of mtDNA is limited. (Extracted from *Nature Biotechnology*, Vol. 14, October 1996)

Cal Poly starts Environmental Biotechnology Institute

Scientists and researchers at California Polytechnic State University (Cal Poly) have started the Environmental Biotechnology Institute to promote research and education in ways of using bioremediation and other biological processes to clean up pollution.

The Institute will focus on research that could lead to the development of bioremediation approaches to cleaning up areas contaminated by petroleum, metals, pesticides, radioactive elements and other toxic materials and wastes, said an institute official.

The organization's goal will be to conduct research that will lead to novel and useful medications and industrial applications, as well.

The multidisciplinary Institute involves professors and students in Cal Poly's colleges of science and mathematics, engineering and agriculture, as well as graduate and undergraduate students from other universities in the California state system, said the Institute's spokesperson. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 7 October 1996)

D. RESEARCH

Research on human genes

Early-onset diabetes gene linked with late-onset NIDDM

The gene responsible for a rare, dominant, early-onset form of diabetes mellitus, MODY3, may also be linked to late-onset non-insulin-dependent diabetes (NIDDM) in those patients with very low insulin levels.

Eric Lander, of the Whitehead Institute for Biomedical Research in the USA, Leif Groop (Lund University, Sweden), and a US and Finnish team screened more than 4,000 individuals from a population isolate in western Finland, identifying 26 families exhibiting an increased likelihood of NIDDM. An initial genome-wide scan carried out with families analysed together resulted in no significant evidence for linkage. But is has been suggested that NIDDM—which affects over 100 million people world-wide—may be caused by either a primary defect in insulin secretion, or a primary defect in insulin action in others. The Scandinavian populations may more closely fit the model of defective insulin secretion.

The researchers therefore subsequently carried out analyses with families classified according to the mean insulin levels in affected individuals. By this method, the families with the lowest insulin levels showed linkage to chromosome 12, near D12S1349, a region which also contains the gene causing MODY3.

However, unlike families with MODY3, for which the onset of diabetes occurs by the age of 30 years, the onset of diabetes in Finnish patients with low insulin averaged at 58 years.

It is possible that MODY3 and the Finnish gene region (which the researchers termed *NIDDM2*) represent different genes on chromosome 12. But, the authors suggest, they may actually represent different alleles at a single gene, the more severe mutations causing MODY3, and the "milder" mutations resulting in later-onset NIDDM characterized by low insulin secretion.

If so, "this gene could have a much more important role in diabetes than has been suspected", they conclude. (Source: *Biotechnology Business News*, 11 September 1996)

Scientists isolate key human repair gene

Scientists at the UK Imperial Cancer Research Fund (ICRF) have isolated a gene that plays a key role in repairing damage to the cell's DNA caused by carcinogens, such as ultraviolet rays and tobacco.

The repair gene, known as XPF, has been the "missing piece in a jigsaw puzzle of nucleotide excision repair (NER) genes", said ICRF's director of laboratory research, Tomas Lindhal. The isolation of this gene will now enable the definition of the way the body's repair system works and may also have future applications to improve cancer treatments that work by damaging DNA.

NER genes are the body's cellular engineers, which control production of enzymes that act as biological scissors. These enzymes highlight, chop out and repair damage to the strands of the DNA double helix. Without their constant vigilance and action, cells can mutate as they divide—a process that may lead to uncontrolled cell proliferation and cancer.

The isolation of XPF was made possible by the study of a rare disease, called xeroderma pigmentosum (XP), which makes people ultra-sensitive to sunlight and particularly at risk from skin cancer. XP is genetically complex and has six forms that involve severe defects in patients' DNA repair systems. The ICRF researchers isolated the gene and enzyme involved in a rare form, XP-F, of which there are only about a dozen known cases world-wide. (Source: *Biotechnology Business News*, 11 September 1996)

Immune system genes reveal surprises

Scientists analysing the sequence of the longest (685-kb) continuous segment of human DNA published to date have uncovered powerful information about the human immune system that may help doctors prevent autoimmune diseases such as arthritis and multiple sclerosis.

Analysis of the human beta T-cell receptor (TCR) locus comprising a complex family of genes was reported in the 21 June 1996 issue of *Science*. The locus contains a cluster of genes that play a vital role in recognizing foreign viruses, bacteria, and cancer cells and in triggering the body's defence mechanisms to destroy these invaders.

Researchers Lee Rowen and Leroy Hood at the University of Washington, Seattle, and Ben. F. Koop at the University of Victoria, Canada, reported identifying and classifying all related genes at the locus. This information will enable development of tests specific to each individual gene, allowing easier identification of genes involved in autoimmune diseases.

Unexpected findings include identification of genes encoding trypsinogen, an important enzyme for digesting protein-rich food. The discovery raises the possibility that trypsinogens and immune receptors may work in concert. Researchers also confirmed that a piece of the immune receptor gene has been copied and moved from chromosome 7 to chromosome 9, providing evidence of evolutionary transfer of genes.

The researchers attribute their dual achievements—sequencing and analysing the entire TCR locus—to advances in automated DNA sequencing and development of computational tools for sequence assembly and analysis.

Sequences can be analysed in a number of ways. For example, two sequences covering the same chromosomal region in different people can be compared for variations, some of which may correlate with disease susceptibilities. A sequence also can be compared against other sequences in large public databases, for example, gene-coding sequences (cDNAs or ESTs) against genomic sequences, sequences from one species against those in another species, or amino acid sequences against protein motif databases. (Source: *Human Genome News*, July-September 1996)

Inherited high blood cholesterol linked to protein-folding defect

Mutations in the liver cell receptor that binds low-density lipo-protein (LDL) are responsible for familial hypercholesterolaemia (FH), an inherited blood cholesterol disorder that causes atherosclerosis and heart disease. Mutant receptors fail to mop up circulating LDL cholesterol. Stephen C. Blacklow and Peter S. Kim of Howard Hughes

Medical Institute and of Whitehead Institute at Massachusetts Institute of Technology have shown that the LDL-binding domain of the mutant protein neither folds correctly nor binds Ca^{2+}. They also discovered that Ca^{2+} is normally needed for proper folding of this domain. Many of the mutations associated with FH occur in the fifth of seven tandem repeat amino acid sequences that make up the LDL-binding domain. The scientists showed that the wild-type fifth segment normally adopts a discrete conformation *in vitro* in the presence of Ca^{2+} by forming distinct disulphide bonds. The mutant segment, however, folds into a variety of shapes via indiscriminate disulphide bonding. The wild-type segment contains a cluster of acidic amino acids that could coordinate Ca^{2+}, says Kim. These residues frequently are substituted in the mutant peptide, he notes. (Source: *Chemical and Engineering News*, 2 September 1996, p. 22)

Kidney cancer genes traced

Two genes involved in the development of kidney cancer have been isolated by British scientists, paving the way to new tests and treatments. The two genes are responsible for papillary cancer, which makes up one fifth of cases.

The research was carried out by Prof. Colin Cooper and his team, and was discovered after searching through thousands of samples of human genetic code. One of the genes, called PRCC, was previously unknown. The other, TFE3, was known to scientists but not linked to cancer. Both turn on cell division but, when defective, allow the cells to multiply out of control to form a tumour. (Source: *Electronic Telegraph*, Issue 482, 17 September 1996)

Epidemiologists link smoking to p53 damage in lung cancer

Molecular epidemiologists have made a direct link between tobacco smoke and damage to the tumour suppressor p53 that leads to lung cancer, according to a new study.

In a laboratory experiment, investigators exposed cells from the lining of the lung to a carcinogenic chemical from smoke, called BPDE. The mutations occurred in the p53 tumour suppressor. More than 50 per cent of all human cancers are related to a disabled p53 gene, and these mutations are present in about 60 per cent of lung cancers.

Genetic damage caused by BPDE in the cells was the same as the mutations found in malignant tumours from lung cancer patients.

The research was carried out by Gerd P. Pfeifer, an associate professor of molecular biology at the Beckman Research Institute of the City of Hope, Duarte, CA. Pfeifer worked with another research team, led by biochemist Moon-shong Tang at the University of Texas M.D. Anderson Cancer Center in Houston.

To cause the mutations, a form of BP binds to parts of the DNA, forming what scientists call adducts. These adducts occurred at the same spots, called hotspots, where scientists usually find the three p53 mutations in lung cancer. One of these hotspots has been found only in lung cancer, while the other two have also been identified in other forms of cancer.

The research may also give some clues to why some chain-smokers never get cancer. Such people may have a more efficient mechanism for repairing the cellular damage caused by BPDE. (Source: *McGraw Hill's Biotechnology Newswatch*, 4 November 1996)

BRCA2 more common than predicted, but triggers cancer less often

The BRCA2 gene occurs three times more often than scientists originally predicted, but it triggers disease less often than they had feared, according to two studies of Jews of Eastern European ancestry.

Dr. Kenneth Offit, chief of the clinical genetics services at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York City, and a team of researchers from MSKCC predicted that the BRCA2 mutation, known as 6174delT, would be present in about one out of every 333 Ashkenazi Jewish women, those of Eastern European descent.

The researchers based their estimate on the assumption that mutations in both breast cancer genes—BRCA1 and BRCA2—gave women the same risk of getting cancer, Offit said. Instead, they found the gene in about one in 100.

But while the BRCA1 mutation, known as 185delAG, raises the risk of getting the disease 30-fold, the new research shows that women who inherit BRCA2 have only nine times greater chance of getting sick by about age 41.

The research is published in the scientific journal *Nature Genetics*, in which a team of researchers from MSKCC, New York University and the National Institutes of Health analysed blood samples from 1,200 Jewish men and women.

In another study that appears in *Nature Genetics*, researchers from the Baylor College of Medicine in Houston conducted at study of 3,000 Ashkenazi Jewish individuals, and reached similar conclusions. They found that one in 100 had the BRCA1 mutation, while the frequency of the BRCA2 mutation was 1.5 per cent, said Dr. C. Sue Richards, who led the investigation. They also estimate that BRCA2's potential to cause cancer is lower than BRCA1.

There are other mutations in both BRCA1 and BRCA2, as well as other genes under investigation, but so far scientists have observed no strong trends in their prevalence or in their cancer-causing potential.

Breast cancer is inherited in only about 5 to 10 per cent of the general population. Most cases are thought to be sporadic, meaning that there are no known genetic factors that raise a woman's vulnerability to the disease.

In a related development, Myriad Genetics, Inc. said it is nearing introduction of the first comprehensive full-sequence test for mutations in both the BRCA1 and BRCA2 genes, key indicators for susceptibility to breast and ovarian cancer, according to company officials. The company had previously said that it would introduce two separate tests for each of the breast cancer genes.

The test, trade-named BRACAnalysis, will be the first fully-integrated and comprehensive genetic susceptibility analysis for all known and unknown mutations in both the BRCA1 and BRCA2 genes, a Myriad official said. (Extracted from: *McGraw Hill's Biotechnology Newswatch*, 7 October 1996)

New breast cancer protein discovered

Scientists from Garvan's Cancer Research Programme have identified and cloned a new protein thought to be involved in the growth of cancer cells. The protein is called Grb 14, Grb standing for growth factor receptor bound, as it binds to receptors on the cell's surface, which in turn regulate cell division in the body.

Principal researcher on the project, Dr. Roger Daly, said the find was an important one: "Grb 14 could be an important factor in the proliferation of cancer cells as it is involved

in the signalling process that causes cells to grow. Dr. Daly explained that on the surface of all cells are a group of molecules called receptor tyrosine kinases that act as receptors, or receivers, of messages in the form of specific hormones or growth factors. Molecules such as Grb 14 pass the message from the surface of the cell to the cell interior, instructing the cell to divide. High expression of the receptor or Grb 14 may result in signal overload and the unrestrained cell growth, characteristic of cancer. (Source: *Australasian Biotechnology*, Vol. 6, No. 5, October 1996)

Gene stops damage by cancer drugs

How can doctors make drugs as toxic as possible for tumour cells without harming healthy cells? Researchers led by Joseph Rafferty at Manchester's Christie Hospital believe that the key could be to introduce protective genes into bone marrow, which is the tissue most vulnerable to chemotherapy.

Cancer drugs kill tumour cells by attacking their DNA, but they can harm healthy cells too. Bone marrow cells are most susceptible to side-effects because, like cancer cells, they have a high turnover of DNA.

The body's defence against DNA damage is an enzyme called ATase, but this enzyme also protects tumour cells. When doctors try to make chemotherapy more effective by knocking out the ATase with drugs called inactivators, the side-effects soar.

The Manchester team says the answer could be to introduce genes into bone marrow cells that produce mutant ATase resistant to the inactivators. In laboratory experiments, bone marrow cells given these mutant ATase genes survived chemotherapy combined with inactivators.

Rafferty says the retrovirus he has used to carry the mutant gene into the bone marrow cells could be ready for testing on patients in just two or three years. (Source: *New Scientist*, 19 October 1996)

Genes that go with a smoother flow

A smooth blood flow may switch on vital genes in cells lining the blood vessels, and so help prevent narrowed arteries and heart disease.

The fatty plaques that can build up inside arteries and impede blood flow form most often at junctions or bends in the blood vessels. Dan Falb and his team at Millennium Pharmaceuticals, a company in Cambridge, MA, working with researchers at Harvard Medical School simulated the conditions inside an artery, first culturing layers of cells taken from the linings of umbilical cord blood vessels. They then placed a spinning metal cone into the liquid growth medium covering the cells. The cone could generate either a smooth or a turbulent flow, depending on how it was tilted.

The researchers found that several genes produced markedly more RNA—and therefore more protein—when subjected to a smooth flow. These included the genes coding for three enzymes that are important in warding off arterial disease: manganese superoxide dismutase, which mops up the reactive free radicals that can damage artery linings and make fat more likely to accumulate; cyclo-oxygenase-2, which is thought to reduce blood clotting; and endothelial cell nitric oxide synthase, which dilates blood vessels.

Farb and his colleagues plan to investigate whether transgenic animals carrying mutant copies of the apparently protective genes that are more active under conditions of smooth blood flow are unusually susceptible to arterial disease. (Source: *New Scientist*, 5 October 1996)

Fast-forward ageing

Recently, molecular geneticist Gerard Schellenberg and his colleagues at the Veterans Affairs Medical Center in Seattle, WA traced the gene that causes Werner's syndrome to a site on chromosome 8. When they then compared the gene's DNA sequence with those of previously identified genes, they found that it closely matched genes known to code for a class of enzymes called helicases, which unwind the double helix of DNA.

Helicases—of which there are many different types—are crucial components of all living cells. They help repair DNA and enable messenger RNA molecules to ferry genetic instructions from the nucleus, where DNA resides, throughout the cell, where the instructions are biochemically translated into proteins.

Schellenberg and his colleagues do not yet know exactly what role the new helicase plays within the cell. They suspect that the enzyme is not one that is essential to life but is somehow conducive to a long and healthy one. Tests have shown that damaged DNA from people with Werner's does seem capable of repairing itself. Despite this, their DNA seems to accumulate mutations at a higher-than-normal rate.

One possibility, Schellenberg says, is that accumulated DNA damage sooner or later interferes with the cell's ability to divide. That could explain why skin cells from young people with Werner's have such a short shelf life; when cultured, they go through very few cell divisions. In fact, their cells behave in the same way as those of the truly elderly.

Understanding how the gene works, says Schellenberg, could provide insight into normal ageing. It may be that "normal" people carry variants of the gene that influence their life spans or predispose them to an earlier death—a possibility he is now investigating. Studying Werner's, he says, could help pinpoint the mechanism that underlies all diseases of ageing, which appear in part to be due to the cell slowdown that is such a dramatic feature of this disease. (Extracted from: *Discover*, November 1996)

Research on animal genes

Biochemical evidence on BSE-CJD link

The results of a study by John Collinge, at the Prion Disease Group (Imperial College School of Medicine at St. Mary's Hospital, London) provide perhaps the first real biochemical evidence "consistent with the hypothesis that new variant Creuzfield-Jacob disease (CJD) results from bovine spongeform encephalitis (BSE) transmission to humans".

To investigate whether there might be more than one type of naturally occurring prion strain causing human disease, the researchers looked at a wide range of cases of human prion diseases in an attempt to identify patterns of protease-resistant prion protein that might distinguish between any different prion strain types. They also looked at the new variant of CJD to determine whether it could be differentiated by molecular criteria from other forms of CJD.

Western blot analysis of protease-treated (to remove normal prion protein) brain tissue from cases of sporadic and iatrogenic CJD resulted in three distinct prion protein signatures. However, western blots of prion protein from cases of the new variant of CJD gave "a unique and highly consistent appearance", including a characteristic pattern of glycosylation, Collinge et al. report. Moreover, when BSE

was transmitted to experimental mice, a glycoform ratio pattern was seen which was very similar to the pattern observed with the new CJD. Experimental BSE in macaques and naturally acquired BSE in domestic cats also showed a glycosylation pattern identical to the new variant CJD. (Extracted from *Biotechnology Business News*, 13 November 1996)

Antisense fights anxiety in Israeli experiment on nervous rats

Israeli scientists have successfully used antisense genetic therapy to reduce anxiety in a rat. Hagit Cohen, Ph.D., a researcher at Ben Gurion University of the Negev, Beer-Sheva, said the non-toxic oligonucleotide developed by researchers at her institution can be considered for human diseases involved in excess protein expression. She is now seeking industrial collaborators to take the antisense programme further.

The theory of the antisense strand or proteins is that the proteins would bind to the end of the 706-base pair CCK gene, rendering it ineffective in expressing the compound. Cohen said anxiety is associated with overproduction of the protein CCK, known as an anxiogenic and as a panicogenic. The short sequence—5'GCT TGG CGG TTT CCAA CG 3'—was designed to disrupt messenger RNA replication of CCK.

Of the 33 rats used in the experiment, Cohen injected 18 with the antisense oligonucleotide. Another nine rats were injected with a non-sense nucleotide—5'CTA GAT GGG CTT CGC 3'—a non-specific strand. Six rats were not injected and served as controls. All the animals were put in a maze with closed arms, open arms and an open platform.

Those receiving the antisense "spent significantly decreased time in the closed arms of the maze", Cohen found, "and increased time in the open arms". Only a few rats were confident enough to climb up on the platform, which was in plain sight—and only the rats receiving the antisense injection appeared on the platform, she said.

Before the antisense project can proceed among humans, Cohen acknowledged that researchers will have to find a better way of getting the drug into the brain. But, she said her experiments prove the viability of antisense genetic therapy. (Source: *McGraw Hill's Biotechnology Newswatch*, 4 November 1996)

New developments in animal biotech

Scientists at the Dairy and Swine Research Centre at Lennoxville, Quebec, (Canada) are using a new process called microsatellite technology to mark genes responsible for desirable traits such as growth rate and carcass quality. The new probes take just two days to deliver results and provide a greater amount of information. The probes may be used to identify desirable traits in male piglets prior to castration.

Also at Lennoxville, researchers have obtained two breeding rams with a unique genetic mutation that is expressed in offspring. The gene is responsible for a double-muscled lamb leg, with much less fat. The gene was originally discovered in the US, where the breeding stock was obtained. The researchers speculate that the gene may be transferable to other animals.

Colorado State University researchers have produced the first test-tube horse. The technology, which is used in human medicine, promises to aid in establishing pregnancies in mares with reproductive problems or from males with low sperm counts.

USDA scientist Hans Cheng is leading a four-year project to draw a genetic map of the domestic chicken. Genetic mapping produces information useful in the genetic enhancements.

Contact: Hans Cheng, Avian Disease and Oncology Laboratory, ARS, USDA, East Lansing, MI 48823 USA. Tel.: 5171 337-6758; e-mail: hcheng@pilot.msu.edu (Source: *AgBiotech*, November 1996)

Research on plant genes

Enhancing gene expression

Researchers at the University of Guelph (Ontario, Canada) have cloned and sequenced several repetitive DNA sequences from alfalfa, according to the *Green Gene Gazette*. The objective of the project was to discover DNA sequences that would enhance transgene integration. The process involved the identification of an alfalfa sequence with homologies to the transformation booster sequence of petunia which increased petunia transformation rates up to 20-fold.

Contact: University of Guelph Crop Science Department laboratory Web site at http://www.uoguelph.ca (Source: *The AgBiotech Bulletin*, October 1996)

New Oji Paper studies genes for lignin

New Oji Paper of Japan has found a recombinant gene that can change the brown coloration of lignin contained in wood to wine red and has confirmed that the amount of liquor used in bleaching wood-chip pulp to produce paper can be reduced to improve production efficiency.

The recombinant gene was produced in tobacco plants at the firm's forestry resource laboratories in Mie Prefecture.

The lignin in trees is produced from the actions of various enzymes with phenylalanine through photosynthesis with the final reaction involving the CAD enzyme.

The recombinant gene prevents the synthesis of the CAD enzyme so that the lignin is produced by one of the CCR enzymes.

Although New Oji originally sought to prevent the production of lignin, just changing this characteristic will enable it to boost the efficiency of pulp production.

The field trials, which may begin in 1997, may also reveal that eucalyptus growth is faster with the recombinant gene. (Source: *McGraw Hill's Biotechnology Newswatch*, 7 October 1996)

Nihon finds cancer killers in flowers

A research team from Nihon University (Japan) has isolated 21 types of triterpenes that suppress skin cancer, according to mouse studies.

The team extracted substances from 14 plant species, including chrysanthemums, dandelions, cosmos and sunflowers.

Initially, the group was looking for anti-inflammatory effects in inflammation suppression studies on the ears of mice when they isolated the triterpenes.

One week after applying 50 micrograms of the carcinogen DBBA on the backs of the mice, one microgram of the inflammation-inducing agent was applied twice in one week to induce the cancers. Comparison with controls was made by applying two micromols of faradiole and taraxasterol 30 minutes before the application of the inflammatory agent. In the eleventh week, carcinomas began appearing on the untreated mice and by the twentieth week 70 per cent developed cancers.

On the treated mice the cancers began to appear in the thirteenth week and only 20 per cent had developed cancers by the twentieth week, demonstrating the effectiveness of the

triterpene compounds. (Source: *McGraw Hill's Biotechnology Newswatch*, 7 October 1996)

Agracetus teaches cotton new tricks

Scientists at Agracetus (Middleton, WI)—a unit of Monsanto—say they have genetically engineered a cotton plant to change the properties of its fibres.

The researchers inserted genes into the cotton for making the biopolymer hydroxybutyrate (PHB). Analysis of the plants' fibres, says an Agracetus scientist, shows the presence of PHB and improved insulating characteristics compared with conventional cotton.

Despite their success in modifying the cotton fibre, the scientists say the work is at "an early research stage" and still years away from commercialization. For one thing, the biopolymer is produced only in "minuscule quantities" in the fibres. (Source: *Chemical Week*, 20 November 1996)

Green glow tags escapee genes

Tobacco plants that glow under ultraviolet light are helping genetic engineers in the US keep track of genes. By inserting the gene for a fluorescent protein alongside any other genes that they introduce, the researchers hope to provide a practical way to spot whether the engineered plants spread, or whether the genes have "escaped" into other plants.

Neal Stewart and his colleagues in the University of North Carolina at Greensboro armed tobacco plants with a gene derived from jellyfish. The gene manufactures green fluorescent protein (GFP), which glows green when exposed to ultraviolet light. Varieties of the protein have been developed to glow in a range of colours.

Existing methods for keeping track of inserted genes involve taking samples of plant tissue back to the laboratory for lengthy analysis. Stewart believes that the gene for GFP could be the most practical method yet for checking whether genes inserted into crop plants spread. Escaped genes could cause problems, for example, if a gene to make crops resistant to herbicides spread to weeds.

The field tests showed that tobacco plants with the gene are easily distinguishable from those without it. Chlorophyll, the substance that enables plants to photosynthesize, glows red when exposed to ultraviolet, so ordinary plants emit a reddy-pink light. Plants with the jellyfish gene emit a green glow that outshines and masks the red of their chlorophyll. Stewart says that some of the plants carry genes that make a blue variant of the fluorescent protein, and these glow purple through a combination of the blue and red fluorescent light.

Stewart used *Agrobacterium tumefaciens*, a bacterium that naturally transmits genes into plant roots, to transport the jellyfish gene into tobacco plants. A promoter "switch" inserted alongside the gene keeps it turned on throughout the plant, but Stewart says that different promoters could switch it on only in certain parts of the plant. For example in other crops it might be made to work in leaves, but not in edible seeds. Stewart has already introduced the gene into oilseed rape. (Source: *New Scientist*, 12 October 1996)

Risks associated with satellite RNA

RNA plant viruses cause millions of dollars in crop damage world-wide every year. One control method undergoing testing is the introduction of satellite RNA into crops. Introducing satellite RNA, a type of nucleic acid extraneous to the virus genome, can result in reduced levels of viral accumulation and reduced symptoms.

According to a paper in *Nature Biotechnology* (research paper p.1264), however, the presence of satellite RNA can have other consequences in some cases. A single mutation to the sequence of a satellite RNA can cause a worsening of disease symptoms. While this was thought to occur rarely in nature and was thought unlikely in transgenic plants, the new research indicates that deleterious mutants can have a selective advantage over protective satellite RNA. This raises serious doubts about the technology, and suggests that its use be re-evaluated. (Source: *AgBiotech*, November 1996)

Gene makes aspens red

Researchers at Michigan Technological University have discovered a way to make aspen trees—and possibly other commercial species—produce red wood. They happened upon the discovery while a graduate student was working on a project to develop genetic engineering for aspen. Two genes were introduced to alter the lignin content, making the wood easier to pulp. While testing the transgenic saplings, the researcher noted that one of the genes had caused the aspen wood to turn red instead of the usual white. The colour varies from tree to tree—some trees are even spotted red and white. The discovery is expected to add value to aspens as a tree for lumber. The technology (which is available for licensing) may also be transferable to other species of hardwoods.

Contact: Sandy Gayk, Director, MTU Intellectual Properties Office. Tel.: 906/487-3429 or e-mail: sgayk@mtu.edu (Source: *AgBiotech*, November 1996)

Research on viral genes

DNA detectives quiz liver virus that stole our gene

A primitive virus found in the livers of some hepatitis patients is actually part human. The discovery that the virus hijacked a human genetic sequence in its evolutionary past may help explain why our genes are peppered with "junk" DNA.

Human hepatitis delta virus, or HDV, is harmless when on its own, but can cause devastating liver disease when it teams up with the hepatitis B virus. HDV is similar to "viroids"—loops of RNA that infect plants. Viroids have no genes that code for proteins, but borrow proteins from their host to copy their RNA.

Unlike viroids, however, HDV does carry one gene. The precise function of its protein, called HDAg, is unknown, but Robert Brazas and Don Ganem of the University of California, San Francisco used a strain of yeast genetically engineered to grow in a simple medium only if it carries a protein that binds to HDAg.

The scientists then took a library of human genes which are known to produce liver proteins and inserted each gene into a separate yeast cell. Cells that multiplied contained a liver protein that was 24 per cent identical to HDAg. Another 56 per cent of the protein's sequence of amino acids was so similar to that of HDAg that their genes must have shared a common evolutionary history.

The best explanation for this, says Ganem, is that an ancestor of the virus captured the human RNA that is the intermediary between gene and liver protein. (Source: *New Scientist*, 12 October 1996)

Onyx's adenovirus mutant to treat tumours lacking p53

Scientists at Onyx Pharmaceuticals have engineered a mutant human adenovirus that replicates and lyses human

tumour cells deficient in the p53 gene, bringing to mind the possibility that "adenoviruses with host ranges restricted to tumour cells may be useful in treating human cancers".

Many human cancers exhibit deletion or mutation of the p53 tumour suppressor gene, with loss of function of the p53 gene affecting more than 50 per cent of all tumours and representing the most common genetic defect in human malignancies. It is thought that p53 monitors "the integrity of the cellular genome", responding to DNA damage by stopping the cell cycle or initiating programmed cell death (apoptosis).

DNA tumour viruses such as adenoviruses infect quiescent cells and induce the S phase of the cell cycle allowing viral DNA replication to proceed. In human adenoviruses this is mediated largely by the E1A protein, while the E1B gene of the viral genome encodes a protein that binds and inactivates p53. The binding is essential for viral replication, possibly because E1A induces p53-dependent apoptosis, the authors explain.

Given these characteristics of adenoviruses, the Onyx Pharmaceuticals team developed a mutant adenovirus that does not produce the E1B protein, to test the hypothesis that such a mutant would be unable to replicate in normal cells (with functional p53) but would be able to replicate in cells (such as tumour cells) already lacking functional p53.

When this human group-C adenovirus mutant (dl1520) was injected into p53-deficient human cervical carcinomas (in nude mice), a significant reduction in tumour size and complete regression of 60 per cent of the tumours was seen.

The virus is currently being tested in US and UK-based Phase I trials in patients with p53-deficient squamous cell carcinoma of the head and neck. (Source: *Biotechnology Business News*, 13 November 1996)

Crafty virus turns down the heat

At least one virus can have a chilling effect on a mammal's defences against infection, say researchers at the University of Oxford, UK. They have found that vaccinia virus, used to vaccinate people against smallpox, releases a protein that prevents fever.

The high temperature that usually follows viral infection is believed to be a defence mechanism—fever is thought to harm viruses more than the host.

Antonio Alcamí and Geoffrey Smith infected mice with large doses of vaccinia virus, expecting the animals to become feverish. Instead, their body temperatures dropped by up to 1° C.

For many years, immunologists have suspected that fever is triggered by one of a group of signalling molecules called cytokines, which help to organize the body's defences against infection. The Oxford researchers found that their virus made a soluble receptor to the cytokine interleukin-1β. They assumed that the receptor mops up IL-1β circulating in the blood, preventing it from reaching the normal receptors in the mice.

As an additional test of the role of IL-1β in triggering fever, the researchers added antibodies to the cytokine, which prevented fever regardless of which strain of virus was used to infect the mice.

However, the researchers were not able to show that mice lacking fever suffered a more severe infection. Smith says that better evidence of the benefits of fever in fighting infection may come from studying other viruses. Smith also points out that extremely high body temperatures can be dangerous to the host as well as the viruses. (Source: *New Scientist*, 12 October 1996)

Modified chemokine locks out AIDS virus

By chopping the end off a naturally occurring protein known as RANTES, researchers have created a compound that, like its parent, blocks the AIDS virus HIV-1 from infecting certain kinds of white cells. Yet the modified protein does not trigger cellular signals that could lead to undesirable inflammation, report Marco Baggiolini of Theodor Kocher Institute at the University of Bern, Switzerland, and coworkers. RANTES is a member of a family of proteins called chemokines, which are released by immune system cells and are involved in inflammatory responses. Chemokines are one of the hottest areas of AIDS research, because scientists recently have shown that HIV-1 needs access to chemokine receptors on the cell surface to infect the cell. One proposal to fight AIDS is to swamp the system with chemokines, but in addition to blocking the virus, that strategy could trigger inflammation and other unwanted effects. By deleting the first eight amino acids on the N-terminus of RANTES, Baggiolini and coworkers created a protein that locks out HIV without activating the cell's normal response to the chemokine. (Source: *Chemical and Engineering News*, 7 October 1996)

Rare mutation in HIV co-receptor protects against AIDS infection

Inheriting two copies of a genetic mutation for an HIV co-receptor can protect people from getting AIDS, said scientists reporting on the largest study to date explaining why some rare people seem to be shielded from the fatal disease.

Inheriting just one copy of the damaged gene, however, does not appear to prevent AIDS infection, but it may delay progression of the disease for two to three years, the investigators wrote.

The double mutation cripples CKR5, a molecule on immune cells that works together with CD4 to help HIV enter white blood cells, the first line of attack in AIDS infection.

Scientists said that at least one copy of the gene is mutated in about 10 per cent of Caucasian Americans, but it appears much less frequently, in less than 2 per cent, of Black Americans.

CKR5 is one of a class of molecules known as co-receptors—molecular keys that work in concert with the main receptor CD4 to open the cell to HIV-1 infection.

Teams of scientists have been working at breakneck speed to figure out how CKR5 works, and to learn how it can be used as a target for developing new AIDS drugs or other strategies for treatment and prevention, such as gene therapy and bone marrow transplants. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 7 October 1996)

Research on bacterial genes

Phage is culprit for cholera pathogenesis

In a classic piece of microbiological research, American researchers have solved the riddle of how *Vibrio cholerae* is transformed from a benign aquatic bacterium into a deadly killer: phage transfer.

Matthew Waldor and John Mekalanos, of Boston's Harvard Medical School, had been working on a live vaccine for cholera, because killed bacteria or bacterial fragments do not produce long-lasting immunity. But they were worried that attenuated strains of *V. cholerae*—which lack the disease-causing genes—could turn virulent just as naturally-occurring ones do.

Their concern was based on two established facts: virulence in cholera is coded in a discrete "pathogenicity island" of genes on a transposon called the CTX element; and in some other bacteria, such as *Corynebacterium diphtheriae*, it is conferred by bacteriophages that carry pathogenicity genes.

Using a CTX element that had the virulence genes replaced by genes coding for kanamycin resistance, the team showed that the *V. cholerae* strain RV508—which has no CTX element—became resistant to kanamycin if it was incubated in a broth that had previously contained an El Tor strain SM44 that carried the marker. This was possible both *in vivo* and *in vitro*.

In other organisms, transformation is often possible through plasmids and other transmissible elements. Yet the El Tor strain that the pair used contained none of these elements. When they used electron microscopy to examine the broth that had contained SM44, they found it contained filamentous bacteriophages.

The toxin genes are regulated by a gene called *toxR*, which also controls pili production in *V. cholerae*. And Waldor and Mekalanos found that pili also play a key role in virulence. Indeed, pili are factors in both virulence and colonization in other gut pathogens too. In this case, the phage will only infect bacteria that have pili, which seem to act as receptors. They therefore say that strains that do not produce pili are better candidates for a live vaccine. (Source: *Microbiology Europe*, Vol. 4, No. 5, September/October 1996)

Gut bacteria recycle rivals' waste

One person's waste is another's livelihood. And the same rule, it seems, applies in the microbial world: slow-growing strains of a bacterium found in our guts hold their own against faster-growing strains by feeding off their competitors' excreta.

As part of a series of experiments on bacterial evolution, researchers led by Paul Turner of Michigan State University in East Lansing grew hybrids of laboratory strains of *Escherichia coli*. According to classical ecological theory, such an environment should soon become dominated by a single strain.

Instead, two strains settled into an apparently stable coexistence. When Turner looked more closely, he found that the two used very different strategies for survival. Every 24 hours, he took a small sample of the culture and transferred it into a fresh flask of broth rich in glucose. In this new growth medium, one strain initially multiplied quickly, but stopped growing once it had consumed all the glucose. But the other strain continued to grow, albeit slowly.

Through further experiments, Turner showed that the slow-growing strain could only keep growing if the more competitive strain was also present—which indicated that the sluggish strain was feeding off the by-products of its companion's metabolism.

These studies show how easily natural systems can transform simple environments into more complex ones, says Turner. He believes that biologists may have overlooked other examples of "cross-feeding", because most bacterial strains are difficult to tell apart. (Source: *New Scientist*, 12 October 1996)

Achieving high gene expression

Although recombinant technology in plants is becoming commonplace, achieving a high expression of introduced genetic material in target plants remains a challenge, particularly when the goal of the project is a plant "biofactory" for the production of products such as pharmaceuticals. Levels of gene expression are partly a function of the promoter to which the coding region of the gene is fused. Purdue University, (IN) scientist Stan Gelvin has reportedly developed what is being hailed as a "super-promoter" from *Agrobacterium*, which results in substantially improved gene expression over the most popular promoter currently in use, the 35S promoter from cauliflower mosaic virus. (Source: *The AgBiotech Bulletin*, October 1996)

The ebb and flow of resistance

Bacteria overcame an antibiotic by making proteins that block the drug's action. Some of these proteins arise from mutations in genes on the bacterial chromosome, but most are produced from genes on plasmids—circular pieces of DNA that are not attached to the chromosome. The importance of plasmids lies in their ability to shuttle between bacteria of the same or different species. In this way, they transfer resistance between bacteria.

Widespread use of antibiotics has created an environment weighted heavily in favour of bacteria that carry resistance genes. To tip the balance back towards non-resistant bacteria, many microbiologists advocate reducing the frequency with which antibiotics are prescribed. This tactic is supported by research which shows that the more antibiotic bacteria are exposed to, the faster they develop resistance to it.

There is also controversial evidence that if an antibiotic is withdrawn from use, bacteria will eventually lose their resistance to it altogether. If this is confirmed, it could make sense to rest antibiotics periodically to flush out resistance in bacterial populations. Numerous experiments have shown that in the absence of an antibiotic, nonresistant bacteria thrive and resistant strains do less well. The reason for this is unclear, but it seems likely that keeping cells resistant requires energy, which bacteria must borrow from the energy they would normally use in other ways to keep fit.

However, Richard Lenski from Michigan State University in East Lansing says these experiments only look at the first few generations after bacteria have acquired a resistance gene. His studies show that after many generations, bacteria adapt to maximize their competitiveness while keeping their resistance genes in place. If this is confirmed, it could mean that it will become increasingly difficult to wipe out bacterial resistance simply by suspending antibiotic use. Resistance that has emerged in 50 years may take millennia to disappear, says Lenski. (Source: *New Scientist*, 12 October 1996)

New class of antibiotics

A compound that mimics the properties of a natural compound found in sharks could be the basis for a new class of antibiotics.

Researchers at Lehigh University in Pennsylvania have already designed a compound that mimics a steroid called squalamine. Squalamine is thought to protect sharks from bacterial attack. Now they report that this mimic possesses other particularly useful properties.

The compound is an ionophore. Ionophores enhance the ability of certain ions to permeate biological membranes, acting either as ion carriers or by creating ion channels cross the membrane. However, the Lehigh ionophore is unusual because it is choosy about which membranes it picks to help transport ions. It mostly favours negatively charged bilayers over electrically neutral membranes.

This is significant, explains team leader Steven Regen, because the outer layer of a bacteria cell's membrane is

negatively charged, whereas a mammalian cell's is electrically neutral. A drug based on the Lehigh compound would only target bacteria cells and not attack the patient's cells indiscriminately.

A drug based on the squalamine mimic would have a useful advantage over conventional antibiotics, which have to enter the bacteria cell to destroy it. Drug-resistant microorganisms have developed defences to either break down the antibiotic inside the cell, or to remove it from the cell quickly. But a squalamine-like drug would attack from the outside of the cell, so presumably reducing the risk of bacteria developing resistance. (Source: *Chemistry and Industry*, 7 October 1996)

Research instrumentation

Antibody purification service

The Cell and Hybridoma Facility at Iowa State University is offering fast and economical purification of antibodies from a variety of animal species and antibody-rich fluid types. The facility employs a gel system using a recombinant form of Protein G that binds to the Fc region of IgG from a variety of animal species, enhancing the versatility of the system.

Contact: Maslak at 515/294-9837 or Harkins at 515/294-2472. (Source: *AgBiotech*, November 1996)

Software finds genes across species

New software called PROCRUSTES, described in the 20 August 1996 issue of the *Proceedings of the National Academy of Sciences*, can identify with remarkable accuracy human versions of genes found in other life forms. The product of a collaboration between an American and two Russian researchers, PROCRUSTES is considered far more useful than existing techniques if a related pattern is known.

Pavel Pevzner (University of Southern California) and his Russian collaborators, Mikhail S. Gelfand (Russian Academy of Science) and Andrey Mironov (Russian National Centre for Biotechnology), devised a spliced-alignment algorithm and software tool that overcomes formidable obstacles. Human genes, which average about 2000 bp, are broken up into smaller segments called exons. The exons can be separated by millions of bases of noncoding DNA that sometimes mimic the exons.

The technique works best when a "target protein" from the nonhuman sample is available to guide the search. With such guidance, the method's accuracy often approaches 100 per cent, the authors report. The new tool should prove particularly useful for researchers trying to pinpoint elusive human versions of cancer-causing genes already sequenced in mice and other species.

Contact: Pevzner 213/740-2407; e-mail: ppevzner@hto.usc.edu; PROCRUSTES: http://www-hto.usc.edu/software/procrustes/ (Source: *Human Genome News*, July/September 1996)

General

CMV structure solved

The three-dimensional atomic structure of the protease enzyme encoded by the human cyto-megalovirus (CMV) has been solved by several researchers, including a group at Agouron Pharmaceuticals (La Jolla, CA), at a resolution of 2.5 Å. In a collaboration with Japan Tobacco (Osaka, Japan), Agouron plans to use this structure to develop new CMV protease inhibitors. Proposed CMV associated indications that the drug could combat would include preventing restenosis in patients undergoing angioplasty, blocking degeneration of vision in AIDS patients, and impeding organ failure in immunocompromised transplant and cancer patients. (Source: *Nature Biotechnology*, Volume 14, October 1996)

Small molecule controls gene therapy delivery

Control of a therapeutic gene *in vivo* through the delivery of an orally available small molecule drug was reported for the first time by researchers at ARIAD Pharmaceuticals (Cambridge, MA). Mouse cells were engineered with genes to produce human growth hormone (hGH) when a gene switch was thrown by the orally available drug rapamycin. After implanting the cells in mice, the research showed that the amount of hGH circulating in the blood was dose dependent on the amount of rapamycin ingested by the mouse—with clinically relevant levels detectable as long as 24 hours after administration of the drug. The company is planning clinical trials in humans with a non-immunosuppressive analogue of rapamycin to test the system's effectiveness. The major clinical benefit would be the ability to deliver drugs such as hGH in a fashion that mimics the body's own natural secretion of the hormone—increasing its effectiveness. At present, recombinant hGH is administered through an injection. If these trials are successful, ARIAD thinks it will have overcome a major obstacle to the implementation of gene therapy approaches across a broad range of potential indications by being able to control gene dosing at will. These recombinant proteins could include proven biotech drugs such as erythropoeitin, colony-stimulating factors and other cytokines. (Source: *Nature Biotechnology*, Vol. 14, October 1996)

Another microbial genome sequenced

Human Genome Sciences (HGS, Rockville, MD) has completed sequencing the entire genome of *Streptococcus pneumoniae*. Streptococcal pneumonias currently have a 5-7 per cent mortality rate even after anti-infective treatment, and multidrug-resistant strains are on the rise.

The *S. pneumoniae* genome sequence is the latest addition to the expanding portfolio of microbial genomes completed by HGS, including *Staphylococcus aureus* and pathogenic *Escherichia coli*. (Source: *Nature Biotechnology*, Vol. 14, November 1996)

Novel poison found in ants

German researchers have discovered an entirely new type of toxin in the poison glands of an African ant. They believe that it might lead to novel bactericidal or fungicidal compounds.

The toxin, called myrmicarin 430A, is an alkaloid and is one of an arsenal of chemical weapons that the ants use to fight off attacking termites. The ant, *Myrmicaria opaciventris*, smears the toxin and limonene over the body of its prey. Limonene makes the viscous toxin easier to spread, so that it can penetrate the termite's outer shell and immobilize it within a couple of minutes.

Frank Schroeder and his colleagues at the University of Hamburg report that myrmicarin 430A is unusual because its structure is far more complex than other chemical weapons made by insects to kill their prey and attackers.

Strangely for a natural compound, myrmicarin 430A lasts less than an hour when exposed to the air. Schroeder cannot explain why these ants bother to make such complex molecules that last only for a short time, when related species get by with simpler molecules that are easier to

produce. This could be the ants' way of making sure that, under tropical conditions, the toxin exists just long enough to do its job and does not linger in the environment. (Source: *Chemistry & Industry*, 7 October 1996)

Making tolerance permanent

Researchers at the University of Pittsburgh Medical Center (Pittsburgh, PA) have found organ tolerance can be induced in patients if they are treated with immunosuppressants for sufficient periods and then weaned while under careful monitoring. Thomas Starzl and colleagues at the University of Pittsburgh have successfully weaned 23 of 91 long-term (greater than five years) liver graft recipients from immunosuppressants. They decreased the dosages and then treated rejection with pulsed steroids. The technique did not work for everyone (27 patients rejected the organ), but the fact that it can work warrants further investigation. (Extracted from *Nature Biotechnology*, Vol. 14, October 1996)

Spy technology joins the fight against breast cancer

Three top-secret technologies developed by intelligence analysts to spot enemy targets and military activity are to be tested against a different enemy: breast cancer.

The pattern recognition technologies, designed to identify targets in spy-satellite photos and help to guide missiles, will be tested at five medical centres in the US for their ability to pinpoint breast tumours.

Although doctors have tried other pattern-recognition techniques in diagnosing breast cancer, the intelligence algorithms are sometimes twice as accurate.

The clinical trials, coordinated by the University of Pennsylvania, will test three technologies. The first is a neural network that will search for microcalcifications—dense areas of tissue that might be an early tumour—near mammary ducts and blood vessels, in much the same way as it might have hunted for missile batteries near highways. Preliminary tests showed that this technique was at least as accurate as state-of-the-art diagnostic techniques, and only half as likely to produce a false alarm.

A second computer algorithm is designed to align a series of images with unprecedented precision. In breast cancer, a comparison of mammogram images taken at different times should reveal any changes signalling the development of a tumour. This technology was developed to compare spy-satellite pictures, in search of changes such as a build-up of troops.

The third technique allows doctors to create an accurate 3-D image of potential tumours from magnetic resonance images. Doctors already use MRI to produce 3-D images of the breast: multiple images are made before and after the breast is injected with a contrast medium that registers brightly in the image. Tumours, which are rich in blood vessels, are well supplied with the contrast medium, which should make them relatively easy to spot.

In practice, however, it is difficult to compare the "before" and "after" images because the woman may have moved slightly, throwing the images out of alignment. The intelligence technique, designed to compare pictures of a military target taken from different directions, will align the images and identify possible tumours.

If the tests are promising, the Government will seek approval from the US Food and Drug Administration to use the techniques routinely. (Source: *New Scientist*, 12 October 1996)

Archaic overachiever thrives in hostile environments

First discovered almost 20 years ago by Carl Woese and Ralph S. Wolfe (both of University of Illinois, Urbana), the Archaea domain (whose name means "ancient" in Greek) is believed to have separated from true bacteria over 3 billion years ago. Archaea once were thought to live only at extreme environmental conditions of temperature and pressure but now are believed to be far more common and to make up a significant part—perhaps half—of the world's biomass. They are suspected of playing important but still unknown roles in the Earth's ecology, including its carbon and nitrogen cycles.

The single-celled, 1738-gene *M. jannaschii* was isolated from a sample collected in over 8,000 ft of water at the base of a deep-sea thermal vent on the floor of the Pacific Ocean. Thriving at pressures that would crush a conventional submarine, this heat-loving, methane-producing microbe lives without sunlight, oxygen, or organic carbon.

Instead, it uses carbon dioxide, nitrogen, and hydrogen expelled from the thermal vent for its life functions. Analysis of the microbe's genome will provide researchers with valuable information for understanding how organisms can make life's building blocks from inorganic sources and under such extreme conditions.

With its unusual characteristics, *M. jannaschii* has the potential to supply fuel and other ingredients for products from plastics to pharmaceuticals. Commercial interests now have the opportunity to develop such heat-resistant products as detergent additives or stable enzymes for the textile, paper and chemical industries.

Methane (CH_4) causes both ozone production and depletion but with a net production of ozone. This means that more knowledge about bacterial/archaeal methane production could lead to better understanding of global-warming processes.

Some of the following areas may benefit from *M. jannaschii* applications.

- Transportation: Develop "biological" vehicles.
- Energy: Generate large supplies of safe, renewable power.
- Weather: Understand and control methane's contribution to global warming.
- Environmental cleanup: Use biological methods to clean up hazardous waste sites.
- Household use: Manufacture biodegradable detergents and cleaners. (Source: *Human Genome News*, July-September 1996)

Cells line up for a complex future

By training cells to grow in precise patterns, researchers have come one step closer to growing complex tissues such as nerves or blood vessels in the laboratory. Their ideas could also pave the way for living electronic circuits.

Most cells will only grow attached to a surface, so George Whitesides and colleagues at Harvard University generated a pattern of sticky and unsticky surfaces for the cells they were studying. They hoped that the cells would only grow on the sticky surfaces. Using a tiny rubber stamp cast from a silicon chip, the researchers made a repeating pattern of plateaus and valleys in clear plastic. A flat stamp spread the sticky material on the plateaus, and the plastic was dipped in a repellent material to coat the valleys.

Cells encouraged to grow on this terrain unswervingly chose the plateaus, even when the sticky areas were only a single cell wide. If the sticky and repellent materials were swapped, the cells chose the valleys instead.

The potential applications are numerous. For example, nerve cells trained to grow in complex patterns could be linked to conventional electronics to make hybrid circuits. (Source: *New Scientist*, 12 October 1996)

VEGF prevents functional maturation of dendritic cells

Blocking the action of vascular endothelial growth factor (VEGF) may have a role in the therapeutic treatment of tumours by a mechanism additional to the inhibition of tumour vasculature, according to the results of a recent study.

Tumour cells are believed to be able to escape the host's immune system through two mechanisms—the low immunogenicity of tumour cells themselves, and the failure of patients to mount an immune response to even novel tumour antigens, because of defects manifesting in the immune system as a result of factors released by the tumours. This inability to mount an effective antitumour immune response promotes uncontrolled tumour growth and represents a "serious obstacle" to successful immunotherapy against cancer, explains Dmitry Gabrilovich et al., at the University of Texas Southwestern Medical Center (Dallas, TX). Dendritic cells represent the class of antigen-presenting cells (APCs) considered to be most effective in the induction of a primary immune response against antigens, as well as the best potential vehicle for delivering tumour-specific antigens for cancer immunotherapy. The researchers report that VEGF (which is released by most solid-tumour cells and mediates angiogenesis and the development of vasculature to the tumour) inhibits functional maturation of antigen-presenting dendritic cells.

Further analysis identified VEGF isolated from the tumour cell supernatant as a causative factor in the inhibition of dendritic cell maturation. VEGF may therefore impair the correct presentation of antigens necessary for inducing a therapeutic antitumour immune response in cancer patients. However, the authors suggest, the data do not preclude the use of dendritic cells as a vaccine antigen delivery vehicle for immunotherapy, as cells expanded *ex vivo* in the presence of cytokines and in the absence of factors released by tumours are probably fully functional.

The results also suggest blocking VEGF with small molecules or antibodies may represent an approach to improving immune function in patients with tumours. This would not only disrupt the development of a blood supply to the tumours, but could also improve the functional presentation of tumour antigens and consequently "assist in the development of spontaneous or therapeutic immunity against the cancer cells themselves". (Source: *Biotechnology Business News*, 9 October 1996)

E. APPLICATIONS

Pharmaceutical and medical applications

Memory drug shows promise

Small-scale clinical studies at the Karoslinka Institute in Stockholm have found that a new class of molecules called ampakines may be able to enhance memory among the elderly. However, the number of people studied was small, leading to scepticism about the results.

Men aged between 65 and 73 years of age who took the drug performed better in memory tests than those who took placebos. (Source: *European Chemical News*, 2-8 December 1996)

Ginseng cloning opens door to crop improvement

Dr. Zamir Punja of Vancouver's (Canada) Simon Fraser University has become the first scientist in the world to clone North American ginseng in the laboratory. Using a small leaf cutting, Punja has grown ginseng in 12 months rather the usual three-year time-frame. Ginseng is used as a medicine, especially in Asia, and ginseng growing is now worth $50 million annually in British Columbia.

In addition to time savings, cloning opens the door to preserving superior genetic material. Punja's goal is to develop a strain of ginseng that will be resistant to fungal diseases and pests so that crops will not have to be sprayed with chemicals. (Source: *AgBiotech*, November 1996)

A sound investment

Cellulose produced by the bacterium *Acetobacter xylinum* has some unusual physical properties that have already inspired a variety of commercial applications. For example, doctors in the USA are testing it as a medical dressing, attracted by the fact that it is non-adhesive, flexible and transparent.

Bacterial cellulose is also fine, strong and maintains its shape when moulded. Furthermore, it propagates sound at about the same speed as aluminium, with a fraction of the resonance. Sony has been exploiting these properties to produce high quality "biocellulose" headphones. When the company first started production in 1989, these cost £2,500 a pair. Now, with improved fermentation methods, they sell for £200.

In the Philippines, bacterial cellulose soaked in coconut milk and sugar is served as a pudding. But the cellulose itself contains no calories. Could this be the next wonder slimming aid? (Source: *New Scientist*, 19 October 1996)

Blood-clotting drug lays siege to tumours

Drugs that kill tumours by starving them of blood can cure mice and guinea pigs of cancer. The new family of drugs causes clots to form in the blood vessels that feed tumours, which then suffocate and die within days. Other blood vessels remain unaffected.

The results were revealed by Steven King from Peregrine Pharmaceuticals of Princeton, NJ, which developed the drugs. The company hopes to begin testing them in people within 16 months.

Each drug has two key components. First, they each contain a single antibody that binds to substances found only on the surfaces of the blood vessels that supply tumours. Of the antibodies the company tested, the most promising was one that binds to the complex formed when a signalling molecule called vascular endothelial growth factor (VEGF) attaches itself to receptors on the surfaces of blood vessels.

VEGF is important in the formation of blood vessels in embryos. In adults it is normally produced only for functions such as wound healing, but tumours also secrete VEGF to instruct nearby blood vessels to build channels that hook up to the tumour and nourish it. The only sites in the body where the antibody can dock are the receptors occupied by VEGF, so only the blood vessels that supply tumours should be affected. (Source: *New Scientist*, 19 October 1996)

GeneChip points way to simpler test for breast cancer

The past two decades have witnessed an extraordinary advance in scientists' understanding of the genetic control of development and disease, with the help of techniques such as genetic engineering, cloning and sequencing—the ability to decipher the language of the genes written in our three-billion "letter" code.

The GeneChip, a laboratory on a chip made by Affymetrix in Santa Clara (CA), promises to revolutionize genetic diagnostics by accelerating the speed at which new genes that cause disease are identified, providing major advances in medicine.

However, the widespread use of the chip will also accelerate the number of ethical dilemmas to be faced by society as employers and insurance companies discriminate against those at risk of disease, with fears of a genetic underclass.

An increasing number of parents will be confronted with lists of diseases that their unborn children may be likely to inherit, and abuses of genetic information may abound.

Developed by Dr. Stephan Fodor's team at the Silicon Valley company Affymax, the GeneChip is able to conduct genetic analysis by exploiting the way one strand of DNA sticks to another with a complementary genetic code. Dr. Fodor took the technology used to print microchips and instead used it to produce vast arrays of single-stranded DNA for tests.

The power of the technology, now inherited by Affymetrix, derives from the ease and speed with which around 400,000 different genetic sequence combinations can be engineered onto the chip, a piece of glass slightly larger than a thumbnail.

Dr. Fodor's team developed semiconductor fabrication techniques, which work in a way that is analogous to developing a photograph, to lay down huge arrays of short DNA fragments with known sequences, in effect encoding vast amounts of genetic information on the chip.

These sequences are used to "interrogate" a patient's DNA sample, which is fluorescently labelled and washed over the chip. Complementary sequences stick together, revealing their presence under laser light. When there are matching sequences, that part of the area probed in the glass chip glows. By examining the results, scientists will have a diagnostic tool more powerful than anything genetic engineers have yet seen.

The success is already spawning efforts to improve the technology. At present, the arrays are on glass, and the presence of complementary strands is revealed only by the use of an optical scanner. If the DNA sequences on the chip could be read directly by circuitry, the procedure could be cheaper.

That may be possible, in the light of a discovery about the physical properties of DNA made by Dr. Thomas Meade of the California Institute of Technology. Electrons normally struggle to travel along a single strand of DNA. But for the double helix—the mutually entwined complementary strands—he found that electrons could scoot along it with ease, providing an electrical signal to announce when a sequence of interest has been found.

The implications of the device for the individual are awesome: in the not-too-distant future, Affymetrix and its partner Molecular Dynamics hope to develop a hand-held gene reader that could enable a GP to tell us what disease, or diseases, we are going to suffer from before there are any symptoms.

The reason is down to the vast quantities of genetic information that are spilling forth from the Human Genome Project, a world-wide enterprise to map and sequence the human genetic code, which consists of three billion genetic "letters". Hence the grant to Affymetrix of nearly $6 million from the US Government's National Center for Human Genome Research.

The GeneChip can, for example, search for the normal version of a gene, and all the variants where there is a "spelling mistake"; that is, where one of the four basic genetic letters is exchanged for another. Just such a mistake leads to haemophilia, for example.

The ability to screen for vast numbers of gene sequences simultaneously will also allow scientists to attack molecular biology at a new level: we are beginning to find out which of a human being's 100,000 genes are at work in a brain cell, for example. But by using a handful of GeneChips, we can watch the choreography of up to 6,000 genes, seeing how they are switched on and off during a normal cell cycle. "We can start to unravel the cell's circuitry", says Dr. Fodor.

The first commercial application of the GeneChip is a probe designed to help researchers identify mutations in the genetic code of the AIDS virus that cause resistance to anti-viral drugs such as AZT, helping doctors to select the best treatment.

The team is developing a GeneChip to study the p53 gene, which has become a byword for tumours. Whether cancer is found in the liver, skin, the breast, bladder or lung, it probably contains a defective version of the gene. (Source: *Electronic Telegraph*, 6 December 1996)

Safer prenatal gene tests use baby's red cells plucked from mother's blood

Scientists have found a way to separate a baby's cells from its mother's blood, in a method that scientists say may pave the way for safer prenatal diagnosis of genetic defects.

The new method uses magnets and a dye to pluck a baby's red blood cells from a tablespoonful of maternal blood, and could replace current diagnostic techniques, such as aminocentesis and chorionic villus sampling.

In the small study, researchers at the University of California, San Francisco, examined foetal cells from the blood of two pregnant women, one at risk for passing on sickle cell anaemia, the other beta thalassaemia.

In both cases, the diagnosis using the new method matched the result of chorionic villus sampling. The babies were normal, the researchers said.

Although the experiment now must be repeated on more pregnant women to make sure that it works, this research has shown it is possible to pluck one foetal cell from millions of the mother's blood cells. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 4 November 1996)

Shock treatment

Septic shock is one of the biggest problems facing the medical profession, claiming 100,000 lives every year in the USA alone. Sufferers are usually patients in intensive care, recovering from major operations. The condition is caused by a reaction to bacterial lipopolysaccharide (LPS), a substance found in the cell walls of bacteria, which interferes with the immune system and causes a high fever which often proves fatal.

According to Piero Foresta and Vito Ruggiero of Sigma-Tau in Rome, the immune system's reaction starts with the release of tumour necrosis factor (TNF), a protein implicated in several autoimmune diseases including rheumatoid arthritis. Finding a compound that blocks this release, or prevents TNF binding to sites in the body, could therefore stop the septic shock taking hold.

The researchers claim that 6,7-substituted-2-aminotetralines can prevent damage caused by TNF. Their application focuses on 2-amino-6-fluoro-7-methoxytetraline, which is already known to moderate the immune system. Animal tests show that the compound blocks the effects of both TNF and LPS, they claim. Moreover, it has anti-fever and anti-inflammatory properties. (*European patent application 0730861).* Source: *Chemistry & Industry*, 7 October 1996)

Fighting tooth decay with eucalyptus

Japanese researchers have found that eight compounds from eucalyptus fight off the bacteria that cause tooth decay and gum diseases. Extracts of the plant might well become dental drugs for humans.

The bacteria *Streptococcus mutans* and *Streptococcus sobrinus* are thought to cause tooth decay in humans. They form insoluble substances, called plaque, from sugars using an enzyme called glucosyltransferase (GTase). The plaque sticks to the surface of teeth and obstructs the diffusion of organic acids from oral bacteria; the resulting acid build-up leads to tooth decay. Other bacteria, including *Porphyromonas gingivalis*, are thought to cause gum disease.

The researchers from Tokyo University of Pharmacy and Life Sciences and a company called Lotte Central Laboratory made a solution of dried eucalyptus leaves in ethanol. They found that this extract showed "appreciable" anti-bacterial activity against *S. mutans* and *P. gingivalis*, and inhibited the effects of GTase. The team is now carrying out *in vivo* tests. (Source: *Chemistry & Industry*, 7 October 1996)

Edible plant vaccines

The first human clinical trial for an edible, plant-based vaccine could start at the beginning of 1997. A team headed by Charles Arntzen at the Boyce Thompson Institute for Plant Research (BTI, Ithaca, NY) is currently undertaking advanced preclinical research on a vaccine for diarrhoea that consists of raw transgenic potatoes expressing an *Escherichia coli* enterotoxin LT-B subunit gene. If the work

goes as planned, the vaccine could enter clinical trials on 12 volunteers at the Baltimore Vaccine Testing Center (Baltimore, MD) in 1997. The potato vaccine may, however, be beaten to the market by more palatable or technically accessible alternatives.

Arntzen's research and the similar work of Hilary Koprowski's group at Thomas Jefferson University (Philadelphia, PA) on plants that produce rabies and human immunodeficiency virus antigens are directed at producing edible vaccines for developing countries since they are cheap and they eliminate both the need for refrigeration, needles and trained medical staff, and the risks of pathogen-derived vaccines.

The BTI potato vaccine has been shown to stimulate the production of specific antienterotoxin IgG and IgA in mice. The next preclinical hurdle for the vaccine is to show that it can protect mice against challenge with the *E. coli* toxin, or with *E. coli* itself.

Even though the potato vaccine will be the first plant-based vaccine in human trials, it is still really just a model system. (Extracted from *Nature Biotechnology*, Vol. 14, November 1996)

New gene therapy trial for brain tumours

An international clinical trial has begun involving the post-surgical administration of GLI-328 for patients with glioblastoma multiforme, a type of malignant brain tumour, according to officials of Sandoz Pharmaceuticals Corp. The study will be conducted at 40 centres in the United States, Canada and Europe.

Previous studies of GLI-328 have been conducted in patients with recurrent tumours, but this will be the first trial in patients with newly diagnosed glioblastoma, said a Sandoz official. The drug was developed by Genetic Therapy, Inc. (GTI), a company acquired by Sandoz Ltd. in 1995. (Source: *McGraw Hill's Biotechnology Newswatch*, 21 October 1996)

NYBC study shows MMPs dissolve blood clots

New York Blood Center (NYBC) research scientists, led by biochemist Alessandra Bini, have shown that matrix metalloproteinases (MMPs) can dissolve blood clots.

The NYBC team demonstrated that two of the MMP enzymes degrade proteins such as fibrinogen, the soluble protein in the blood that converts to insoluble, clot-forming fibrin. The enzymes also work to dissolve the clots themselves that are made up of a matrix of cross-linked proteins, predominantly fibrin, said an NYBC official.

Bini's research team is part of the Laboratory of Blood Coagulation Biochemistry of the Lindsley F. Kimball Research Institute of the NYBC. (Source: *McGraw Hill's Biotechnology Newswatch*, 21 October 1996)

Immunex recruits patients for study of TNFR-FC for arthritis

Seattle (WA)-based Immunex Corp. has begun recruiting rheumatoid arthritis patients into a pivotal Phase III trial of its anti-arthritis tumour necrosis factor receptor fusion protein (TNFR-FC).

At least two other products aimed at using genetically-engineered drugs to break the rheumatoid arthritis cascade of inflammation and pain were outlined by researchers at the recent meeting of the American College of Rheumatology in Orlando, FLA. Rheumatoid arthritis is caused by a faulty autoimmune response in the body that attacks the joints of the fingers, wrists, knees and hips.

Scott Baumgartner, M.D., a University of Washington researcher in Spokane, studied how TNFR-FC, a genetically-modified protein designed to interfere with the inflammatory cascade causes swelling, pain and stiffness in affected joints in rheumatoid arthritis patients.

He reported a 60 per cent reduction in symptoms after a three-month study among 140 patients who were taking the experimental protein. The patients were divided into four groups, one placebo group and three groups that received different doses of the compound. The patients taking the largest dose received the most benefit. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 4 November 1996)

Intermittent interleukin-2 therapy in HIV

Substantial and sustained increases in CD4 cell counts can be achieved by long-term, intermittent interleukin-2 treatment in patients infected with HIV, according to a report by US scientists.

Following on from previous short-term studies of interleukin-2 therapy in HIV patients, Joseph Kovacs (National Institutes of Health, Bethesda, MD) and a team at the NIH and Chiron (Emeryville, CA), carried out a long-term randomized controlled trial to determine the effects of intermittent interleukin-2 treatment on CD4 counts, in 60 HIV patients with baseline CD4 levels above 200 cells per cubic millimetre.

The results showed that mean CD4 count in patients tolerating interleukin-2 therapy was about double the baseline value one year after the beginning of therapy, and continued administration of the cytokine resulted in sustained increases for over two years. Moreover, administration of interleukin-2 did not lead to any increase in viral load, while toxicity of the treatment was lower than that reported in an earlier study by the authors. (Extracted from *Biotechnology Business News*, 13 November 1996)

A new approach to fighting infection

A new vaccine may provide protection against *Chlamydia* infection, the major cause of infectious blindness and some sexually transmitted diseases, according to US researchers. It is the first example of a vaccine that does not target a protein.

When bacteria infect the body, the immune system responds by producing antibodies. These antibodies are proteins that mould themselves so that they can latch onto protein molecules on the surface of the bacterial cell. This marks the bacteria for destruction by the immune system.

Tests in mice show such a vaccine provides prolonged protection against infection. The vaccine can be injected or given orally. The protein can be encased in a biodegradable polymer which protects it from digestion in the stomach.

The team at Johns Hopkins University used *Chlamydia trachomatis* in their experiments, which affects 700 million people world-wide. However, it will be some time before the vaccine is available for human use. (Extracted from *Chemistry & Industry*, 21 October 1996)

Vaccine stabilizes multiple sclerosis symptoms in study

Connective Therapeutics, Inc. (Palo Alto, CA) reports that results from a pilot trial of T-Cell Receptor (TCR) peptide vaccines for the treatment of multiple sclerosis indicate that patients who responded immunologically to the vaccines experienced stabilization of disease without side-effects during one year of therapy.

A Phase I/II study was conducted by a team of scientists led by Arthur A. Vandenbark, Ph.D., Veterans AffairsMedical Center (Portland, OR) and Oregon Health

Sciences University. The double-blind, placebo-controlled trial involved 23 patients with chronic, progressive MS who were treated for a year with a native or substituted version of a V beta 5.2 TCR peptide vaccine or placebo. Successful peptide vaccination boosted protective T-cells and lowered pathogenic T-cells thought to cause the disease, according to the scientists.

Additional findings in the report, which is published in the October issue of *Nature Medicine*, suggest that regulatory cells elicited by the vaccine not only inhibit their specific target pathogenic T cells, but also inhibit "bystander" pathogenic T cells in the area of inflammation in the nervous system. (Extracted from *Genetic Engineering News*, 15 October 1996)

Livestock applications

Animal vaccine drives out danger bugs

Gastroenteritis and diarrhoea caused by eating meat contaminated with common bacteria may soon be a thing of the past. A new Australian vaccine keeps common strains of salmonella out of cattle and poultry, and it is being developed further to protect cattle against two dangerous strains of *Escherichia coli*.

The vaccine is based on the work of Peter Coloe and his colleagues at the Royal Melbourne Institute of Technology, who have developed mutant strains of *Salmonella typhimurium, S. enteritidis, S. choleraesius* and *S. dublin*.

Coloe's group created the salmonellas by deleting the gene for a key enzyme that normally helps to synthesize a compound essential for the bacterium's growth and reproduction. When administered to animals, the altered bacterium survives for about a week. But before disappearing from the body, it triggers an immune response that primes the animal to fight off further infections.

The vaccine, manufactured by Bioproperties Australia, a biotechnology company in Melbourne, has been tested on 10,000 chickens, 10,000 turkeys and 2,500 dairy cattle in Victoria. Injected into eggs, it makes chicks immune to salmonella. Alternatively it can be given to day-old chicks in their drinking water. Cattle are given two injections of the vaccine no more than 10 days apart, followed by annual boosters. The vaccine has been approved for use throughout Australia in chickens. It should be commercially available early in 1997. (Source: *New Scientist*, 5 October 1996)

Aquaculture growing in importance

Aquaculture has been one of the fastest growing food production systems in the world over the past decade with production increasing at an average rate of 9.4 per cent per year. Food and Agriculture Organization (FAO) statistics show that, between 1984 and 1994, total world aquaculture production more than doubled by weight from 10.4 to 25.5 million tons and tripled by value from US$ 13.1 billion to US$ 39.8 billion.

Aquaculture's contribution to world food supplies is also gaining increasing importance. In 1994, for instance, aquaculture contributed 21.7 per cent of total world fisheries landings of aquatic animals and plants, including 16.9 per cent of total fish and shellfish landings, 14 per cent of total finfish landings, 18.0 per cent of total crustacean landings, 42.7 per cent of total mollusc landings, and 87.8 per cent of total aquatic plant landings.

Aquaculture is currently outpacing livestock meat production in terms of growth by two to four times. Farmed finfish and shellfish food production increased at an average rate of 10.7 per cent per year since 1984 compared with only 2.6 per cent per year for total livestock meat production (191.7 million tons) of slaughtered meat was produced in 1994). Furthermore, in contrast to livestock meat production where the bulk (52 per cent of the total) is still produced within developed countries, over 86.4 per cent of total aquaculture production is produced within developing countries. (Extracted from *INFOFISH International*, April 1996)

Simple test developed for BSE

A new simple test can identify bovine spongiform encephalopathy, or BSE in cattle and Creutzfeldt-Jakob disease (CJD) in humans, scientists at US National Institutes of Health (NIH) and California Institute of Technology report.

The test detects a higher than normal concentration of the 14-3-3 family of proteins in the cerebrospinal fluid that surrounds the spinal cord. Until now, the only ways to make definitive diagnoses of these always fatal diseases were to look at the brain after death, to perform a dangerous brain biopsy, or to use expensive, time-consuming, two-dimensional electrophoresis to identify two proteins called spots 130/131 in the spinal fluid. By sequencing the 130/131 proteins, the researchers found that they belong to the 14-3-3 family. The scientists then developed a one-dimensional test for the 14-3-3 family using Western immunoblot. The test identified 96 per cent of 71 patients with CJD and six out of nine cows with BSE. It is now being modified to make it more sensitive for the detection of BSE. (Source: *Chemical and Engineering News*, 30 September 1996)

Agricultural applications

Transgenic papaya

Two lines of genetically-engineered papaya that are resistant to papaya ringspot virus (PRSV) have been introduced by Cornell University (NY) and the University of Hawaii. It is thought that the new introduction could salvage the $45 million Hawaiian papaya industry, which is being destroyed by the viral disease.

The USDA removed regulatory restrictions on the two new lines in September 1996, making papaya the first transgenic fruit crop to be cleared by the agency for commercial release. Approvals from the FDA and EPA are also required. If all clearances and licensing requirements are met in time, fruit from the new papaya lines could be marketed in 1998. (Source: *AgBiotech*, November 1996)

"Bugs" in transgenic cotton technology

Some farmers in Texas are less than satisfied with the pest resistance claims made for Bollgard transgenic cotton. The cotton, which was genetically engineered by Monsanto to incorporate Bt genes toxic to the cotton bollworm, tobacco budworm, and pink bollworm, is sold by Delta and Pine Land Co. It has been planted extensively across the US south.

While many report good results from the new transgenic cotton, some farmers in the Brazos River Valley of Texas say that Bollgard cotton is not working out as expected. Possible causes for high level of pest infestation are favourable weather conditions and increased planting of corn, the favourite host plant of the bollworm.

The development has resulted in a request from the Union of Concerned Scientists to the US EPA to suspend registration of Bollgard cotton. The Union has stated in the past that the use of Bt genes in cotton could result in insects developing resistance to Bt, which is used as a bioinsecticide.

The Union states that EPA registration was based on the condition that a resistance management strategy would be developed. The possible failure of the cotton to kill the bollworm, at least in some areas, could mean that large numbers of insects survive feeding on the transgenic plants, giving succeeding generations an opportunity to build resistance. Monsanto has said that it will study the situation in detail.

Meanwhile, the Australian National Registration Authority has granted registration for Monsanto's Ingard transgenic Bt-containing cotton. The registration allows Ingard cotton to be planted over 30,000 hectares. The move sparked immediate calls for the withdrawal of the approval pending further testing. (Source: *The AgBiotech Bulletin*, October 1996)

Pharmaceutical potential of flax

A flax extract with medicinal value has been identified by researchers at the AAFC Saskatoon Research Centre, the University of Saskatchewan, and the Victoria Hospital in London, Ontario. Industry partners are being sought for commercial development of the patented extraction process.

The technology can extract secoisolariciresinal diglucoside (SDG) from flaxmeal, which can then be used as an animal feed. The extract has potential in the treatment of diseases including atherosclerosis, lupus nephritis and diabetes. It also has antioxidant properties and is useful in the lowering of blood cholesterol.

Contact: Sandy Bresciani, Agriculture and Agri-Food Canada, Saskatoon. Tel.: 306-975-6420; Fax: 306-975-6419. (Source: *The AgBiotech Bulletin*, October 1996)

Pests genetically engineered for self-destruction

Researchers at the University of California, Riverside and the USDA-ARS in Wapato, Washington are developing a technique called Autocidal Biological Control (ABC). The technique involves the mass release of insect pests genetically engineered to be unable to overwinter. When the mutant insects mate with the normal pest population, the offspring cannot survive cold weather conditions, causing the pest population to crash. The researchers are studying the efficacy of a mutant Notch gene, a gene involved in normal embryonic development. ABC research is currently under way for the pink bollworm and the codling moth.

ABC could be cheaper and less labour-intensive than the currently used Sterile Insect Technique (SIT) which involves the release of insects sterilized by irradiation. The genetically-engineered insects would have only one mutation and be hardier and more capable of mating than insects with multiple mutations from the SIT approach. The ABC would also result in reduced pesticide use. (Source: *The AgBiotech Bulletin*, October 1996)

Pesticidal sugar esters

Orestes Chortyk and fellow researchers at the USDA's Natural Products Utilization Research Unit in Athens, GA, have succeeded in producing synthetic sugar esters which can be used as an environmentally-friendly pesticide. The esters are similar in structure to the natural sugars found in plants of the Nicotiana family which offer a natural protection against whiteflies and other pests. The synthesized sugars have proven to be equally toxic to whiteflies. (Source: *The AgBiotech Bulletin*, October 1996)

Plastid transformation technology

Calgene Inc. of Davis, CA, has announced that it has been granted two US patents involving plastid transformation technology. Plastid transformation allows expression of a foreign protein in the plastids of plant cells. A plant cell contains one nucleus and multiple plastids. Typically, genetically engineered plants contain a low number of gene copies inserted into the nuclear genome. Insertion of a foreign gene into the plastid genome via plastid transformation, on the other hand, can produce up to 10,000 copies of the foreign gene per cell. Thus, there is a great potential for amplifying gene expression using this technology. Furthermore, plastid transformed traits are inherited exclusively from the maternal parent in most plant species and, consequently, there is no possibility for pollen-mediated outcrossing of a genetically engineered plant. (Source: *The AgBiotech Bulletin*, October 1996)

Fungicides could improve fruit flavour

Using natural products to protect fruits, such as strawberries, from harmful mould may also enhance the flavour of the fruit, report scientists in the USA.

The team from the University of Kentucky and Kentucky State University was investigating whether natural volatile compounds could be used as fumigants to control the growth of *Botrytis* mould on strawberries at commercial storage temperatures of 2-4° C. Thomas Hamilton-Kemp of the University of Kentucky points out that the number of synthetic agrochemicals available to strawberry growers is dwindling and none is available commercially to treat ripe fruit. His technique could be used to destroy the mould as the fruit is transported to market.

The researchers found that the fruit metabolized vapours of the fumigant compounds and produced an array of new compounds which were released as vapours. The natural products used as fumigants were alcohols, aldehydes, ketones, esters and hydrocarbons.

The Kentucky team have yet to publish any work on their natural fumigants, but Hamilton-Kemp says results so far are encouraging. Some of the compounds have killed or inhibited the *Botrytis* mould. But the team is working to overcome some lingering problems. (Extracted from *Chemistry and Industry*, 7 October 1996)

Food production and processing

Reaction in baker's yeast

A new biological process could improve the production of single-isomer chiral compounds.

The gene for an enzyme from *Acinetobacter*, which catalyses a reaction known as the Baeyer-Villiger oxidation, has been transferred into baker's yeast by John Stewart from the University of Florida and Margaret Kayser from the University of New Brunswick.

The researchers used the yeast to produce an optically active form of a cyclic ester from a ketone. In many of the reactions tested it was found the yeast produced over 98 per cent of a single enantiomer.

Yeast would be an easy organism for industrial chemists to handle and this breakthrough means that it could be widely applied to biotransformations. (Source: *European Chemical News*, 2-8 December 1996)

Brewing and biotechnology

Australian scientists have identified genes in barley which can control qualities of beer such as haziness. The scientists have identified genes that prevent barley from making tannins, the major cause of haze, and have improved a gene transfer mechanism into barley.

The September issue of *Chemical Engineering* reports on a newly developed process in brewing that uses modified yeast strains to increase alcohol production. Other bio-engineered yeasts are being tested for their ability to eliminate haze and unwanted by-products.

The complete genome of brewer's yeast has been sequenced by collaborators from Canada, Europe, the USA and Japan. This is the most complex organism yet sequenced, and the first eukaryote. The 12-million-base-sequence is six times larger than the first bacterial sequence completed in 1995. The project took seven years and cost US$ 30 million. (Source: *AgBiotech*, November 1996)

PCR-based Salmonella detection

Scientists at Applied Biosystems (Foster City, CA) have developed a polymerase chain reaction (PCR) method of detecting *Salmonella* contaminated food products within 24 hours. Perkin Elmer (Norwalk, CT), the product's manufacturer, anticipates that the new one-step method will completely replace current laboratory methods for identifying *Salmonella* and other food-borne pathogens, which currently require four or more days to perform.

The Centers for Disease Control (Atlanta, GA) estimates that approximately 1000 out of 4 million infected people die of *Salmonella* poisoning each year. The new US Government regulations finally acknowledge contaminated food as a major health hazard. With certain modifications, Perkin Elmer is confident that the procedure can also be applied to detect other menacing food-borne pathogens such as *Escherichia coli* 0157, *Campylobacter*, and *Listeria*. (Source: *Nature Biotechnology*, Vol. 14, November 1996)

Cyclodextrins help to keep juices clear

US researchers have found a way of keeping apple and other fruit juices fresh and clear for weeks.

Apple juice is particularly prone to enzymatic browning, a process that causes discolouration. When the juice is exposed to air during the juice extraction process, certain enzymes are triggered to oxidize the natural juice components, such as phenols, to coloured, bitter-tasting quinones. Kevin Hicks of the US Agricultural Research Service and his team have found that cyclodextrins can block the action of these enzymes. Cyclodextrins are made up of several sugar units joined in a ring and are produced naturally by certain micro-organisms, such as *Bacillus macerans*. Chemists have been investigating the doughnut-shaped molecule for years in the hope of finding novel catalysts and drug delivery agents.

The cyclodextrins mop up the phenolic compounds in the juice faster than the browning enzymes can oxidize them, reports Hicks. His team first used a soluble β-cyclodextrin on juices from Granny Smith apples. They found that at room temperature, the treated juices turned brown after several hours compared with just minutes for untreated juices. The juice stays fresh for two to three weeks at 4° C, Hicks claims.

Hicks' team also experimented with small amounts of β-cyclodextrin bound to an insoluble polymer. They found that the browning is "eliminated forever", says Hicks. And the insoluble residue can be easily removed from the juice.

The researchers reported similar results when using cyclodextrins in pear, white grape and celery juices. They have not yet carried out taste tests, but do not expect any problems. Previous research shows that cyclodextrins do not remove the essential flavour-giving oils from these juices. (Source: *Chemistry and Industry*, 4 November 1996)

Chemical applications

Biological route to nicotinamide

Lonza has announced that a biological process will be used in a 3,000 tons/year nicotinamide plant in Guangzhou, South China.

The plant will use immobilized cells of the bacteria *Rhodococcus rhodochrous*. The technology has been licensed from the Japanese company Nitto Chemicals and the plant is due to come onstream at the end of 1997.

Nitto has used a similar process for some years to produce acrylamide from acrylonitrile at a scale of 20,000 tons/year.

Nicotinamide is used as a vitamin supplement and is normally made by the alkaline hydrolysis of 3-cyano-pyridine. The drawback is that up to 4 per cent of the product can be nicotinic acid.

In contrast, the micro-organisms used in the biological method produce the enzyme nitrile hydratase, which hydrolyzes 3-cyanopryridine to nicotinamide. Using this route, nicotinic acid and other contaminating by-products are not produced.

Lonza first became interested in developing the process in 1993 when it decided to expand vitamin capacity. At the time, the price of 3-cyanopyridine was very high and the process did not seem to be competitive with the methylethyl pyridine route then in use.

However, changes in the price of 3-cyanopryidine and promising experimental results have persuaded the firm to go ahead with the biological route. The process will be run continuously. (Source: *European Chemical News*, 2-8 December 1996)

Industrial microbiology

Biologically derived chemicals find niches

Chemicals derived from renewable agricultural feedstocks are not new to chemists or manufacturers, but pressure from customers and regulators for green alternatives to toxic materials, especially solvents, is driving innovation. While such chemicals are far from competing with commodity chemicals, manufacturers are finding niche markets for them.

Nevertheless, industry's move to biologically derived alternatives has been slow. Less than 10 million tons/year of plant matter other than wood goes into industrial and construction products, compared with 175 million tons of petroleum and coal and 300 million tons of inorganic minerals. Some argue that plant raw materials are no match for oil-based products on a cost or performance basis, yet makers of biologically derived chemicals are finding cases in which that is not true.

For example, Genencor (Rochester, NY), was awarded a $16 million grant lat year from the National Institute of Standards and Technology to develop biocatalysts to make industrial chemicals from renewable resources. Separately, Genencore is also applying its enzyme expertise to develop and commercialize a biological route to produce indigo dye from glucose.

Large manufacturers with agricultural interests, such as Monsanto and DuPont, are actively looking at alternative biological routes to chemical processes. For now, though, commercial applications of biologically derived chemicals are very specific to the product, material and market.

The most conspicuous market for biologically derived chemicals is cleaning solvents, because regulations restrict-

ing many of the commodity solvents have left a wide-open market. High on the list of attractive solvents produced biologically is dimethyl sulphoxide (DMSO).

DMSO competes against well-established polymer cleaners and solvents such as methylene chloride, *n*-methyl pyrrolidone, dimethlyformamide and sulphone. Although the cost of DMSO is comparable to that of solvents of similar strength, making the change to use it in existing chemical processes is "not trivial" and users are reluctant to do it. In a few niche markets, however—primarily the paint stripping market—it is making progress. Growing interest is coming from electronics manufacturers.

Terpenes, produced by a number of companies, are also attractive biologically derived solvents. Lactic acid esters are also promising replacement candidates. Lactic acid esters are non-toxic, biodegradable and easily recoverable through distillation.

Biologically derived chemicals are also making headway in plastics. Because of the size of the plastics market and the cheap supply of petrochemicals, however, chemicals derived from renewable resources are merely causing ripples.

Biologically derived chemicals have also made inroads into paint additives.

Biologically derived enzymes can be used in the pretreatment of pulp to reduce chlorine use by paper manufacturers. Xylanase, an enzyme derived from fungi, reduces the quantity of bleach needed by 15 per cent, and it costs less than chlorine per unit of bleaching power.

The American Soybean Association researchers are looking into replacing polyvinyl chloride (PVC) additive dioctyl phthalate (DOP) with epoxidized soybean oil; however, it costs about 14 per cent/lb more than DOP and makes PVC brittle in high concentrations. The researchers, who say that epoxidized soybean oil does not leach or evaporate from PVC as DOP does, are currently working to overcome its negatives. (Extracted from *Chemical Week*, 18 September 1996)

Energy and environmental applications

Fungi reclaim heavy metals

Swiss researchers have shown that it is possible to use fungi to recover heavy metals from incinerated solid waste. They hope that this will improve the environmental quality of the waste residue, some of which could then be reused in construction materials.

Municipal solid waste is usually incinerated because it reduces the volume (by about 90 per cent) and the chemical reactivity by destroying organic compounds. This process produces a residue called fly ash which can contain several heavy metals such as cadmium, copper, nickel, lead and zinc. Because of its toxicity, most fly ash is immobilized in cement, or deposited in landfills or underground chambers.

There are only a few reports of using fungi to reclaim, or leach, metals from waste, according to the researchers at the Institute of Plant Biology at the University of Zurich. Once fungi starts growing on an organic substance, it produces acids which convert the organic material into a solution. These acids bind onto any heavy metals in the residue and reduce them. The resulting heavy metal ions become trapped in the body of the fungus.

The Zurich researchers used the wood fungus *Aspergillus niger* which tends to overproduce organic acid such as oxalic or gluconic acids. They grew the fungus in the presence of fly ash and found that it removed more than half of the cadmium, zinc, copper and lead in the residue after only one day.

"The advantage of bioleaching is that it is quite selective, while chemical leaching is not selective at all", says team leader Helmut Brandl. He can control the selectivity by using different organisms under different growth conditions.

Brandl is working to refine the process, but he predicts that bioleaching will prove to be cheaper and more energy-efficient than conventional thermal techniques, such as metal evaporation and vitrification where the undesirable elements are stored in glass. (Source: *Chemistry & Industry*, 7 October 1996)

Phytotech's mustard plants clean up lead at industrial waste site

Soil contaminated with lead has been treated for the first time at a Trenton, NJ industrial waste site using phytoremediation, a technique that uses plants to clean up non-hazardous and hazardous solid and liquid wastes, according to officials at Phytotech, a Monmouth Junction, NJ company that is among leading developers of the approach.

The latest demonstration of phytoremediation involved the use of a specially selected cultivar of Indian mustard plants to extract the lead from the soil, according to Phytotech scientist Michael Blaylock.

Blaylock, who presented a paper on the project at the American Chemical Society's symposium on "Emerging Technologies in Hazardous Waste Management", pointed to the significance of the field trial at the Trenton site, classified by state and federal officials as a "brownfield", an abandoned industrial facility and its environs targeted for clean-up for future community or commercial use.

"The results of our studies clearly show the potential of using green plants to clean up soil and water contaminated with heavy metals", he commented. "It should enable us to develop an efficient, cost-effective and environmentally compatible approach to address the brownfields problem throughout the US", Blaylock predicted.

"Clearly, the US and other countries dealing with the tremendous expense of cleaning heavy metals from industrial sites will understand the urgency of developing these new, less expensive approaches", said Burt Ensley, president and chief executive officer of Phytotech.

In the case of the Trenton brownfields project, the phytoremediation approach—called phytoextraction—involves the use of the plants to accumulate the heavy metal contaminants in their roots, stalks and leaves.

The plants are then removed, and with them the metals in a mass of material that is at most 10 per cent and as little as 2 per cent of the mass of the contaminated soil that would otherwise have to be handled.

In other words, instead of dealing with a ton of soil, clean-up requires the removal of 200 to 40 pounds of plant material.

A cost analysis by Phytotech—which has been working with various research institutions including the AgBiotech Center of Rutgers University—suggests the cleanup of one acre of sandy loam soil to a depth of 50 cubic metres will cost $60,000 to $100,000. This compares to at least $400,000 for excavation and storage alone using traditional soil removal methods.

The phytoextraction cost estimates include treatment of hazardous materials, extensive metal analysis during and after the treatment, handling and disposing of metal-containing plant residues, and the growing of several sequential crops.

In addition to the cost advantages, noted the Phytotech analysis, "this method is ecologically preferable, since it reclaims soil at the site, recycling it in a biologically safe state rather than permanently disposing of it by removal to a storage site."

Of 16 plant species studied, Phytotech's main focus has been on *Brassica*—which includes the mustard plant—because it was the best accumulator of lead in shoots. In addition to having the highest metal-accumulating ability, it showed low levels of lead toxicity. It is also a high biomass producer, which means it can extract and store more contaminants from the soil, according to the company's analysis.

The second phytoremediation technique on which Phytotech researchers have been concentrating is called rhizofiltration, and the most promising plant so far has been the sunflower, according to Ensley.

In late February, Phytotech unveiled the results of its field trials using sunflowers to remove radionuclides from uranium contaminated water in a pond at Chernobyl and a US Department of Energy facility in Ashtabula, OH.

At the Chernobly site, Phytotech scientists were able to demonstrate a dramatic reduction in the level of caesium and strontium contamination in a four-to-eight week period.

Similar results were achieved at a site in Ohio, where the researchers were able to treat water with concentrations of uranium as high as 350 parts per billion, reducing the contamination by 95 per cent in the first 24 hours.

As to costs, Phytotech estimates to remove radionuclides from water with sunflowers range from two to six dollars, against standard microfiltration and precipitation processes that currently cost about $80 per thousand gallons. (Source: *McGraw Hill's Biotechnology Newswatch*, 7 October 1996)

Algal biofuel cell

The National Institute for Resources and Environment (NIRE), a branch of the Agency of Industrial Science and Technology (AIST), has developed a prototype biofuel cell using the algal electrochemical process to produce a current.

The biofuel cell is based on an alga that emits high-energy electrons during photosynthesis and respiration. The electrons are emitted from algal cells through the cell membrane, and carried to the anode of the fuel cell, where they are delivered to supply the current. The mediator that transports the electrons is 2-hydroxyl-1,4-naphthoquinone (HNQ). The biofuel cell works with or without light, although the source processes of the power are different. During irradiation, the electromotive force is supplied by photosynthesis. In darkness, the electromotive force comes from respiration, in which the algae metabolize sugar into energy.

The alga used in the prototype is *Synechocystis sp.*, a blue-green alga, which is notably efficient at absorbing sugar and converting it into energy. The prototype biofuel cell was made of 40 mL water, 80 mg HNQ and 50 mg (dry weight) of the alga, and yielded 0.3 mW of power when irradiated. When the culture contains sugar, the output power was doubled to 0.6 mW. With the sugar culture, the fuel cell works irrespective of the absence of light, and the algae multiply.

The output power is now too small to be practicable. However, because photosynthesis is very efficient, it is quite possible to greatly improve the output power. The biofuel cell installed in a spacecraft could provide oxygen and electric power by photosynthesis. Synechocystis sp. may be replaced with another alga decomposing organic materials in waste water, so the modified fuel cell can do two essential tasks: waste water purification and power generation.

Further details from National Institute for Resources and Environment, 16-3, Onogawa, Tsukuba City, Ibaraki Pref. 305. Tel.: +81-298-58-8186; Fax: +81-298-58-8158. (Source: *JETRO*, October 1996)

Bacteria could clean up Cold War chemicals

Incineration is not the only way to get rid of stockpiled chemical weapons, says a report from the US National Academy of Sciences. In some cases, the weapons could be neutralized chemically. The finding will provide ammunition for groups who oppose incineration because they fear emissions from the plants could pose a health hazard.

An NAS committee, asked by the Pentagon to look for alternatives, says that the Army could dispose of 1,791 tons of mustard gas at its Aberdeen Proving Ground in Maryland by mixing it with water at 90° C. The mustard gas would react with the water, leaving breakdown products that could be destroyed by common bacteria.

At a second site, the Newport Chemical Depot in Indiana, the Army could rid itself of about 1,400 tons of the nerve gas VX by mixing it with sodium hydroxide. By-products from this reaction could also be broken down by bacteria.

"There are no technical obstacles to either process, nor are they likely to cost more", says Richard Magee, director of the Center for Environmental Engineering and Science at the New Jersey Institute of Technology in Newark, and chairman of the committee.

The Pentagon is expected to decide whether to accept the academy's recommendation for treatment at Aberdeen and Newport. (Extracted from *New Scientist*, 5 October 1996)

Influences of substrate chemistry and microbial metabolic diversity on the bioremediation of xenobiotic contamination

Bioremediation of organic pollution relies on the microbial potential to use xenobiotic compounds as substrates for their metabolism. Three different aspects of organic pollutants—chemical features, concentration and interactions with other pollutants in mixtures—influence their metabolism by microbes, and have implications in bioremediation. The specific chemistry can determine intrinsic recalcitrance. Mixtures of pollutants prone to interaction and low concentrations of contaminants are common circumstances in contaminated environments and these may result in unusual patterns of substrate utilization. Despite such factors augmenting the recalcitrance exhibited by organic contaminants, many micro-organisms are endowed with metabolic properties enabling them to degrade these compounds. These include the presence of mono- and di-oxygenase enzymes for oxidation of organic compounds, the broad specificity of certain enzyme systems involved in the degradation of natural substrates enabling them to adjust to related xenobiotics, and degradation pathways for many compounds that converge on key intermediates and share subsequent steps, with economy of cellular resources. Bacteria also have the metabolic potential to attack highly halogenated aliphatics which, due to their electrophilic character, must be initiated by reductive rather than oxidative processes. Communities of micro-organisms may have an increased degradative potential as they embody the complementary metabolic steps of different populations. Micro-organisms owe this metabolic versatility to their ability to evolve new metabolic capacity through rapid alteration and exchange of genetic material. This review by E.S.B. Limbert and W.B. Betts discusses the influence of chemical structure of organic pollutants on their environmental fate and the diverse range of microbial characteristics that allow these materials to be biodegraded. (Source: *The Genetic Engineer and Biotechnologist*, Vol. 16, No. 3, 1996)

F. PATENTS AND INTELLECTUAL PROPERTY RIGHTS

Canada accedes to Budapest patent treaty

Canada has joined the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. An amendment to the Canadian Patent Act and Rules came into force on 1 October 1996 designating the international depositories under the authority of the Budapest Treaty as the recognized depositories for patent procedure. Canadian legislation now recognizes the deposition on biological material as part of a patent application.

The Budapest Treaty covers biological materials beyond micro-organisms, such as seeds, DNA, and cell cultures. "A single deposit of biological materials by Canadian inventors, seeking to obtain patent protection in several contracting States, will satisfy the patent deposit requirements of the patent offices of all the member States", says Sheila Batchelor, Canada's Commissioner of Patents.

The deposit of biological materials is necessary to provide a complete and enabling patent description of certain inventions relating to biological materials. Whenever the biological material is not publicly available, deposit with an authorized depository provides the public with access to the material. The initiative also responds to recommendations by Canada's biotechnology community.

Contact: Diane Lafontaine, Canadian Intellectual Property Office (CIPO). Tel.: 819/953-9554; e-mail: lafontaine.diane@ic.gc.ca (Source: *AgBiotech*, November 1996)

US patent office to revise some biotech rules

The US Patent and Trademark Office wishes to streamline rules governing submission of biotechnology patent applications. The proposed changes centre on submission requirements for patent applications that contain amino acid or nucleotide sequence listings. Under the proposed rules, the sequence listing will be presented in an international language-neutral format using numeric identifiers. In addition, the paper sequence listing will become a separately numbered section of the patent application. If these rules go into effect in 1997, it will no longer be necessary to provide sequences that contain fewer than four specifically identified nucleotides or amino acids in computer-readable form. Together, these changes are expected to allow applicants to produce a single-sequence listing that will satisfy filing requirements in all countries. (Source: *Chemical and Engineering News*, 14 October 1996)

Patenting in biotechnology

The techniques of genetic modification allow novel characteristics to be introduced into living organisms, but there is debate over how far resulting modified life forms should be patentable. US law allows patents to be considered for all modified organisms whether they be micro-organisms, plants or (non-human) animals. In Europe, a European Commission proposal for a Directive is under consideration to endorse the availability of such rights in all European Union (EU) countries.

This briefing paper is an update of the briefing paper "Patenting Life" which was published in June 1993. It considers the scientific developments which have led to the possibility of patenting living organisms or their products, and the concerns about it. The patent law, commercial and ethical considerations pertaining to genetic modification of naturally occurring substances, micro-organisms, plants and animals differ considerably and therefore each category is considered independently. The overall aim of this briefing paper is to provide balanced information and to advance the public debate about these topics.

The paper results from the combined contributions of patent experts, scientists, industrialists and environmental and consumer group representatives from throughout Europe.

New forms of life

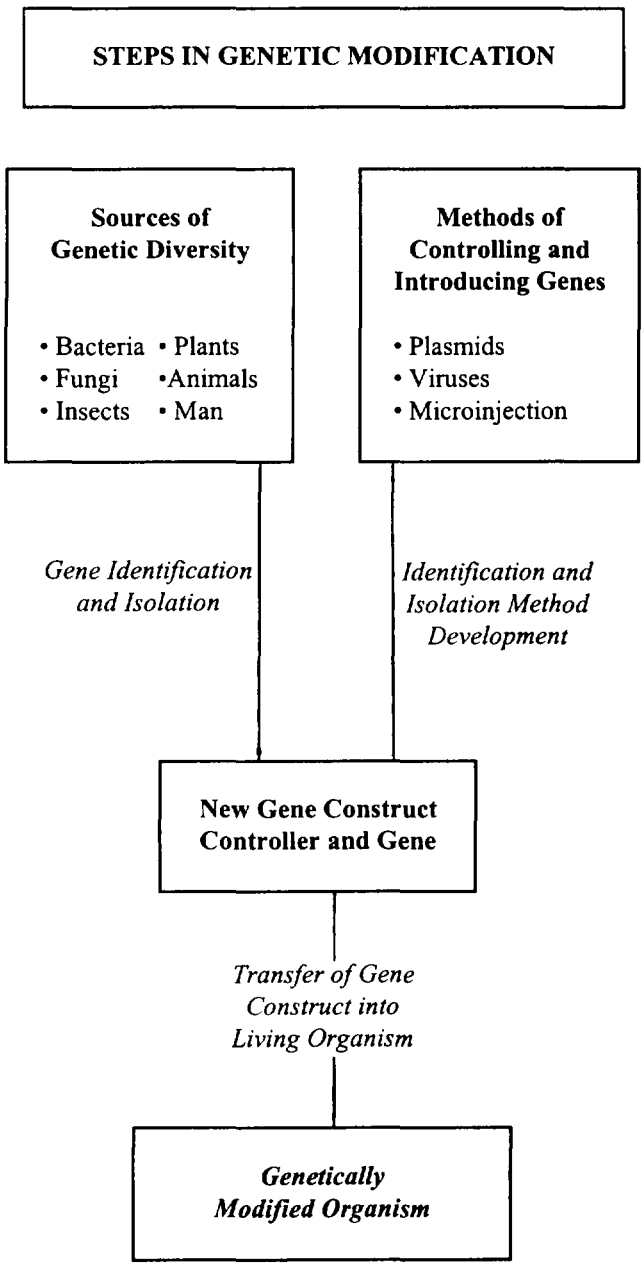
Recombinant DNA technology is the term used for a series of techniques that can be used to modify the basic genetic make-up of a living organism by inserting (or removing) sections of DNA, a molecule that carries hereditary information. Following the first demonstration of these techniques in 1973, their potential to introduce novel characteristics into microbes, plants and animals has been rapidly explored. Initial efforts focused on micro-organisms because of the relative simplicity of their structure, and a number of commercial processes now use micro-organisms which have been genetically "programmed" to produce materials which they would not produce naturally (e.g. drugs such as human insulin, growth hormone and certain enzymes).

With plants, the intentions of the traditional breeder and the genetic engineer are the same—to insert into or modify the genome to introduce a novel trait. The extra power of genetic engineering comes from its ability to control more precisely the introduction of new traits and to introduce genetic material from unrelated species of plants and from organisms other than plants. Genetically modified plants include varieties with traits such as resistance to herbicides, pests or diseases, enhanced nutritive content and new shade of flower colouring.

Genetic modification of farm animals and fish is still largely at the experimental stage. The aims of research include infection resistance and increasing growth rate. A method for producing pharmaceutical products via farm animals' milk is at an advanced stage of development. The first patented genetically modified animal, which is available for medical research, is a mouse which is genetically predisposed to cancer—for use in testing new drugs or chemicals for carcinogenicity.

The use of recombinant DNA methods in relation to human diseases caused by gene defects (e.g. cystic fibrosis) is at present concentrated on diagnostic applications but therapeutic applications are also under investigation. The first attempt to modify human body cells in a patient, using the gene transfer technique (somatic gene therapy) was made in the US in 1984. Bone marrow cells which were unable to produce an enzyme essential to the immune system were removed from the patient, modified to include the gene for the missing enzyme and replaced. This attempt failed, but in 1990 a similar method was successfully used to modify white blood cells genetically. Since then more than 100 clinical protocols involving gene therapy have been recommended and clinical trials are under way in many

countries. More radical and controversial is the proposal for germ line gene therapy. Such manipulation would change the genetic make-up of the eggs or sperm produced by an individual and would be carried on to future generations. The general opinion in Europe about germ line gene therapy is at present strongly negative.



Innovations such as these are clearly industrially significant and potentially valuable to society. Biotechnology companies consider legal protection for these innovations to be essential, as evidenced by the multimillion dollar settlements negotiated in successful patent infringement suits. They therefore insist that there should be no discrimination against legal protection in this field as compared with what is available in other technologies. Patent protection gives the opportunity to the innovator to earn a commercial return on the heavy investment in this research and therefore to fuel the ongoing research necessary for further improvement in e.g. health care and human and animal nutrition.

Patents

Patent laws, like trade mark and copyright laws, are an important area of intellectual property protection legislation. In the case of patent laws, they provide protection of inventions demonstrating the key characteristics of novelty, non-obviousness, utility and sufficient disclosure. The grant of a patent confers a civil right on the patent owner to prevent others from exploiting what is claimed in the patent, excluding use for scientific research purposes. It does not permit the patent owner to exploit his own invention (*e.g.* a patent owner must comply with national regulations regarding the use of the invention), nor does it confer any right of ownership of patented materials. Patenting in the EU can take place either through national patent offices or through the European Patent Office (EPO) in Munich which affords protection in all, or any selection of, States party to the European Patent Convention (EPC).[1] Practice in the US and Japan is also of considerable relevance to EU inventors and companies, since the US often provides the largest single market for products developed in the EU; equally the patent protection available to a US or Japanese company in its home market affects it ability to compete in other markets.

Attempts to harmonize patent law and practice internationally have not yet fully succeeded. For example, at present the US allows a one-year grace period between an inventor's publication and the deadline for filing a US patent application. In contrast, any public disclosure of an invention before filing any application is usually fatal to the prospects of protection in European countries. Again, the US settles disputes over priority as between rival claimants for the same invention by comparing actual dates of invention, whereas, in other countries, whoever has the earlier effective patent application date will usually prevail. Therefore patents encourage secrecy up to the point of filing but ensure publication of the information after the granting of a patent, and thus making it available for research purposes.

Another difference is that in US patent law the term "invention" means invention or discovery. In European law "discovery" is distinguished from "invention" and is unpatentable. The distinction is not easy to define. A discovery involves new knowledge, whereas an invention is a practical application of knowledge. For example: the elucidation by Crick and Watson of the double helix structure of DNA was an unpatentable discovery, whereas later exploitation of this to produce DNA artificially and to produce new forms of DNA have given rise to many patents.

Naturally-occurring substances, present as components of complex mixtures of natural origin, can in principle be patented where they are isolated from their natural surrounding, identified, and made available for the first time and a process is developed for producing them so that they can be put to a useful purpose. This applies to inanimate substances as well as to living materials. In appropriate circumstances, such substances are not ruled out as mere discoveries but are considered as invention by the EPO and other legal authorities.

Micro-organism patents are now routinely granted by the US, European and Japanese Patent Offices. Although a US patent had been granted in 1873 to Pasteur for "*yeast free from germs of disease as an article of manufacture*", the US courts later held that the "*discovery of some of the handiwork of nature*" was unpatentable. In the Chakrabarty case in 1980 the US Supreme Court decided that a micro-organism was not precluded from patentability solely because it was alive. Thus a Pseudomonas bacterium manipulated to contain more than one plasmid controlling the breakdown of hydrocarbons (therefore more useful in dispersing oil slicks than the

natural organism containing only one such plasmid) was "*a new bacterium with markedly different characteristics from any found in nature*" and hence not nature's handiwork but that of the inventor. The "*product of nature*" objection therefore failed and the modified organism was held patentable. This decision was influential in most other industrially developed countries and the issue is now settled in law.

Plant patents are also obtainable in the US, Europe and Japan. The US Plant Patent Act of 1930 is restricted to asexually propagated plants and over 6,500 of such plant patents have been granted (mostly for rose and fruit trees). In the Hibberd case (1985), following the principle established in the Chakrabarty case, it was decided that normal US "utility" patents could be granted for other types of plant e.g. genetically modified plants.

In Europe, patent law was originally considered unsuitable for protecting new plant varieties developed by traditional breeding methods. Special national laws of plant breeder's rights, which are also called Plant Variety Rights (PVR), were therefore established in the 1960s in some countries as well as the International Union for the Protection of New Varieties of Plants (UPOV, 1961). To avoid legal confusion, patent law in Europe subsequently excluded plant varieties from patentability e.g. EPC Article 53 (b) which excludes patents for "*plant and animal varieties*" as such and "*essentially biological processes for the production*" of plants and animals. The UPOV Convention was revised in 1991 and now does not prevent dual protection by PVR or patents. This revision awaits ratification by Member States and is therefore not yet in force.

Plant breeder's rights have been highly successful in their own sphere. However, legal experts now generally recognize that patent law is better suited to the protection of recombinant methods for producing transgenic plants and the resulting products. Patents of this type, claiming methods and products *per se*, have been granted by the EPO.

Animal breeds produced by traditional methods have no legal system for their protection comparable to plant breeder's rights. Based on the micro-organism and plant patent precedents, the US Commissioner of Patents declared in 1987 that US patents would be granted for "*non-naturally occurring non-human multicellular living organisms including animals*". The first transgenic animal patent was issued in 1988 to Harvard University with claims covering the "oncomouse", one in which an oncogene has been introduced to make the animal more susceptible to cancer and therefore more sensitive in testing possible carcinogens. After initial reluctance by the EPO to grant the corresponding European patent (and a successful appeal to the Appeals Board), the European patent was issued. This is now under formal opposition by anti-vivisection and animal rights groups. More than 300 patent applications for transgenic animals have been filed but so far few have been granted (3 in the EPO; 6 in the US Patent Office).

Gene patents are available in all fields of biotechnology. For recombinant DNA inventions, the patent will claim the nucleotide sequence coding for the protein expression product, vectors e.g. plasmids containing this sequence, micro-organisms or higher organisms transformed with the sequence, and in appropriate cases the expression product itself (normally only if the product is new *per se*). Corresponding process technology will also be claimed. The patentability of DNA sequences of unknown function is dubious and controversial. The Human Genome Organization accepts that patents should be granted for full length genes but is against patenting fragmentary cDNA sequences having no established utility.

The debate about patents in biotechnology

The industries that utilize biotechnology are convinced that intellectual property protection should be obtainable for the inventions that stem from research and which have commercial potential. Biotechnology research workers in academic institutions increasingly share this view because of their need for research funding which is in part conditional on patentability. A serious challenge to this assumption has come from a number of interest groups concerned variously with matters of ecology, animal welfare and rights, moral issues and the interests of small farmers and the developing countries. Some of these groups have formally opposed specific European patents and demanded their revocation. For many such groups "patenting" life is considered unethical in principle. The opposition extends also to possible structural change in the agricultural industry which might stem from biotechnology and especially from the acquisition by the larger corporations of legal rights on the advances that are being made.

Legal and moral issues: A legally permissible ground of objection is that genes are naturally occurring entities and that the methods for transferring them to plants or animals are well-known and straightforward. This is a challenge to the inventiveness content of the particular patent at issue; it is an argument that industrial competitors will sometimes use against each other's patents but so far it has not achieved a high success rate. The argument also lies at the heart of the moral objections many with religious beliefs have to patenting genes. They regard claims of invention, instead of discovery, tantamount to claiming to be God.

Some feel that patenting living things changes the relationship between humanity and the rest of nature. This is particularly sensitive as regards animals, where patents are seen as conferring "ownership", thereby undermining the animal's right to independence of being and relegating it to the status of a mere object. However, plants and animals are owned by the farmers who produce them and use them as agricultural commodities. All such owners, whether of patented or unpatented organisms, are bound to respect animal welfare legislation.

The opposers can raise the morality issue where the patent law allows, as in Europe under EPC Article 53(a) which forbids patents for inventions "*the publication or exploitation of which is contrary to 'ordre public'* (public order) *or to morality*". The morality objection is being currently used against the European oncomouse patent. To programme an animal genetically for certain death in laboratory experiments is morally repugnant to these opposing groups and they feel in conscience bound to protest. Animals have, however, long been used as disease models. The response of the patent authorities may depend on whether, in the light of general public acceptance of the use of test animals in research to find cures for serious human diseases, the use of the oncomouse would be generally condemned.

The objection to animal suffering may also apply to the genetic modification of farm animals. One early experiment to insert a growth hormone gene into a pig in order to increase growth rate succeeded but caused severe unforeseen side-effects including arthritis. Animal welfare groups argue that patents will encourage more research on animal genetic modification, which they oppose on grounds of possible suffering and of principle. Intended to prevent undue suffering, legislation requires the granting of animal

experimentation licences and full disclosure of the experimentation.

EXAMPLES OF US & EPC PATENTS ON ORGANISMS AND GENES

	Patent number
Isolated gene coding for enzyme involved in penicillin biosynthesis.	US 4,885,251
Isolated gene coding for human erythropoietin, a hormone stimulating growth of red blood cells.	US 4,703,008 EP 148,605
Recombinant plasmids and transformed micro-organisms expressing precursor of the enzyme chymosin (rennin).	EP 077,109
Pseudomonas with multiple plasmids for degrading hydrocarbons (Chakrabarty, see text)	US 4,259,444
Insecticidal *Bacillus thuringiensis* strain	EP 178,151
Pesticidal (trypsin inhibitor) gene transfer from cowpea to cereals	US 5,306,863
Plant gene/promoter	EP 122,791
Maize seed and plant enriched in tryptophan (Hibberd)	US 4,581,847
Oncomouse (Harvard, see text)	US 4,736,866 EP 169,672
Immunodeficient mouse for study of auto-immune disease	US 5,175,384
Expressing pharmaceuticals in milk of farm animals	US 5,322,775
Herbicide resistance plants	EP 242,236

Freedoms for breeders and farmers are seen by some groups as threatened by patents on transgenic plants and animals. Under PVR, breeders previously enjoyed the so-called "breeder's privilege" or "research exemption" which gave them the freedom not only to use protected plant varieties in their breeding programmes but also to commercialize the further varieties developed therefrom (often only "cosmetically" different from the original) without any royalty payment to the owner of the initial variety. The UPOV Convention as revised in 1991 now expands the scope of the right of the initial variety breeder to include what are termed "essentially derived varieties" (both the terms "essentially derived" and "variety" are defined). This expansion of the right is not automatic but depends on member States amending their national PVR legislation in conformity with UPOV 1991.

Freedom to research and to commercialize: The freedom to research is safeguarded equally under both patent law and PVR law. But the freedom to commercialize the resulting products of research depends on whether or not they infringe the patent claims or are "essentially derived" under PVR law. A strengthened UPOV-type protection would therefore go part of the way towards the strong protection given by patents. Neither system is a threat to the free use of existing germ plasm since these rights can in no sense monopolize known material as such. Again, until the UPOV revision is taken up in national laws, farmers legitimately sowing seed of a protected variety are legally free to save part of the seed from the first crop of plants for sowing on their own farms to produce a second and subsequent crops (the "farmer's privilege"). Recognizing that the current scale of use of farm-saved seed thus deprives the breeder of significant royalty income, the strengthened right under the 1991 version of UPOV would hake this subject to authorization of the breeder. However, Contracting States can "*re-introduce*" this freedom under their national legislation "*within reasonable limits and subject to the safeguarding of the legitimate interests of the breeder*".

International developments

(1) The United Nations Convention on Biological Diversity, enacted in June 1992 and entering into force in December 1993, has been ratified by 157 States to August 1996. It aims to ensure conservation of biological diversity, sustainable use of genetic resources, and the fair and equitable sharing of the benefits from their utilization.

Genetic resources have in the past been declared "*a common heritage of mankind to be preserved, and to be freely available to all, for use for the benefit of present and future generations*". However, in this Convention, Article 15 now recognizes the sovereign rights of States over their natural resources, their authority to determine access thereto, and the need for access to be subject to prior informed consent and on mutually agreed terms. In return for providing access to its genetic resources, a donor country should benefit through any of three mechanisms:

- Participation in research, Article 15 (6),
- Sharing in the results of research and proceeds of commercial exploitation, Article 15 (7), and
- Access to and transfer of derived technology, Article 16 (1).

The Convention recognizes a legitimate role for intellectual property in achieving these objectives.

(2) The Uruguay Round of the General Agreement on Tariffs and Trade (GATT) created a subsidiary Agreement on Trade Related Aspects of Intellectual Property Issues (TRIPS). Any country ratifying GATT accepts the obligation to establish minimum standards of intellectual property. Patents are to be available in all fields of technology except where exploitation of the invention must be prevented to protect "*ordre public*", human, animal or plant life or health or to avoid serious prejudice to the environment.

TRIPS allows Members to provide exclusions from patentability similar to those found in the EPC (see above) but they must provide for "*the protection of plant varieties either by patents or by an effective* sui generis *system or by any combination thereof*". (A *sui generis* system is one devised for its own special purpose.)

EC Directive on protection of biotechnological inventions

The proposed draft of an EU Directive on the Legal Protection of Biotechnological Inventions was originally published in 1988. After several years of debate, a version of this proposal was agreed by a joint committee of the European Parliament (EP), the European Council and the European Commission but was voted down in plenary session of the European Parliament in March 1995. The European Commission published a revised proposal in December 1995. The Directive aims at harmony in the EU between national patent laws and the EPC, and a uniform legal interpretation on some points of special relevance to living systems.

The Directive is addressed to patent issues relating to "biological material", which is defined in Article 2 as any material containing genetic information and capable of self-reproducing or of being reproduced in a biological system. This must therefore cover living matter, viruses, genes and other types of DNA and RNA. Although Article 3 excludes patents on the human body and its elements in their natural state, elements isolated from the body or otherwise produced by a technical process can be patented if they are capable of industrial application. Article 4 provides that no invention is to be refused patent protection for the sole reason that biological material is involved. This principle has been confirmed for many years in patenting jurisprudence in the major industrial countries. Article 4 provides specifically for the patentability of plants and animals and parts of these except for "plant and animal varieties".

Natural products which have biological utility can qualify for patent production in certain circumstances (usually as the purified material). Article 8 of the Directive confirms that patents for these products should not be ruled out in principle as mere "discoveries". Thus the presence of a product as part of a pre-existing material is not alone a sufficient ground for refusing a patent for it.

By Article 9, inventions are not patentable where their exploitation would be contrary to "*ordre public*" or morality. The EPC and laws of most member States already contain a similar exclusion e.g. in EPC Article 53 (a) mentioned above. However, Article 9 goes on to specify particular examples which for this reason cannot be patented. Paraphrasing the actual text, these include (a) methods of human germline gene therapy[2] and (b) any genetic modification of animals which causes suffering disproportionate to the likely benefit to man or animal.

Article 10 confirms that a patent on a biological material (or a process for producing it) covers the first and all subsequent generations of material obtained by multiplication or propagation provided the crucial characteristics of the original are retained. Patent rights in a product normally become exhausted when the product is marketed by the patent owner or a licensee. However, for a product which can be multiplied biologically, the purchaser can obviously propagate the purchased product for the purpose implied in the sale, but Article 12 forbids the resulting material being used in further cycles of multiplication or propagation. Article 13 provides an important exception to this rule, allowing farmers to re-sow seed saved from the first crop. This "farmer's privilege" in patent law is to be limited, however, in order to be in line with the corresponding provision in the EU regulation on an EU plant breeder's right. The new EU plant breeder's right provides for a royalty payment on farm-saved seed which is "*sensibly lower*" than that for bought-in certified seed. Animal farmers are also free to breed from the patented animal for renewal of their own stock.

Article 14 covers the situation in which a third party has bred a new plant variety from a patented transgenic plant and has obtained a plant breeder's right for it. If, to exploit the variety, the breeder needs a licence from the patent holder but has been refused one, a compulsory licence must be granted, "*subject to payment of an appropriate royalty*". This is dependent on the proviso that the new variety constitutes "*significant technical progress*" and the licence is "*dictated by the public interest*". Article 14 is objected to by the agrobiotechnology industry because it detracts from the patent right in an unprecedented way.

General reactions to the revised proposal have been mixed. For example, the Legal Affairs Committee of the EP has raised a number of questions, the European Alliance of Genetic Support Groups are in favour while Greenpeace has expressed a negative opinion. The first plenary EP vote will probably be in 1997. The European Commission's proposal envisages member States implementing the Directive by 1 January 2000 at the latest.

Notes

[1] All EU countries, Switzerland, Liechtenstein and Monaco can be covered by a single application.

[2] Such methods are already excluded in EPC and European national laws.

Information

For further information concerning Briefing Papers and other publications and activities of the European Federation of Biotechnology, Task Group on Public Perceptions of Biotechnology, contact:

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(EFB, Briefing Paper No. 1, September 1996)

G. BOOKS, JOURNALS, REVIEWS AND BIOINFORMATICS

FDA guideline on harmonization

The US Food and Drug Administration has published a final guideline—"Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products". It is intended to provide guidance to applicants regarding the type of stability studies that should be provided in support of marketing applications for biotechnological/biological products.

The guideline was prepared under the auspices of the International Conference on Harmonization (ICH) of Technical Requirement for Registration of Pharmaceuticals for Human Use. ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed among three regions: the European Union, Japan and the USA.

This guidance applies to well-characterized proteins and polypeptides, their derivatives and products of which they are components, and which are isolated from tissues, body fluids, cell cultures or produced using recombinant deoxyribonucleic acid (rDNA) technology.

Copies of the guideline (Docket No. 93D 0139) are available from the Division of Communications Management (HFD-210), Center for Drug Evaluation and Research, FDA, 7500 Standish Place, Rockville, MD 20855, USA. Tel.: 1-301/402-4996.

Biotechnology industry in Saskatoon profiled

The Saskatoon Regional Economic Development Authority has published a 1996/97 directory of bio-technology companies and support agencies in Saskatoon.

Nineteen companies and 28 public support agencies are profiled, including key contacts, current activities, major achievements, sales/revenue/personnel figures, facilities, alliances, and collaborations sought. The charge for the directory is $20.00.

Contact: Saskatoon Regional Economic Development Authority (SREDA), 345 Third Avenue South, Saskatoon, Saskatchewan, Canada S7K 1M6. Tel.: 306/664-0720; 306/244-5033.

Draft US xenotransplantation guidelines available

The US Department of Health and Human Services has proposed a set of guidelines for xenotransplantation aimed at reducing risks without impeding innovation. Xenotransplantation is the transplantation of animal tissues into humans. Interest in xenotransplantation results from the limited availability of human tissues and organs for transplants, coupled with recent advances in biotechnology that make the practice more effective.

Contact: To view the guidelines, connect with the Web site of the US Food and Drug Administration at http://www.fda.gov.

Intellectual Property, Technology Transfer and Genetic Resources: An OECD survey of current practices and policies

The effort to conserve the biological diversity of the planet involves complex issues. As a permanent, world-wide commitment to this effort, the 1992 Convention on Biological Diversity highlights the links between access to genetic resources, equitable sharing of any economic benefits, transfer of the technology needed to derive such benefits, and intellectual property. It also underlines the principle of national sovereignty over indigenous genetic resources.

Intellectual Property, Technology Transfer and Genetic Resources surveys the issues addressed in the Convention, both cataloguing current practices and policies in OECD countries and clarifying linkages between these issues and their potentially conflicting objectives.

Genetic resources—plant, animal, microbial or other—are fundamental to agriculture and its products (food and non-food), are the source of many pharmaceutical products, and are used in the fermentation industries, old and new. As science and technology advance, enabling man to read and even re-write the genetic information at the core of living organisms, issues of intellectual property come to the fore.

Genetic resources underlie debates over the distinction between the discovery of natural substances, including genes, and the innovative and expensive work required to develop useful new products and services; and over the attribution of credit (intellectual and economic) between the supplier of genetic material and the supplier of the science and technology which can add value to it. In pharmaceuticals, attention is switching to the use of combinatorial chemistry and high throughput screening techniques, creating a synthetic biodiversity as a basis for new products.

There is long-standing disagreement, too, about the patentability of living materials. The argument continues today, and features in the World Trade Organization's 1994 agreement on Trade-Related Intellectual Property (TRIPS). The biotechnology-related provisions of TRIPS will be reviewed in 1999.

Genetic resources raises, also, the question of international rules of management of the world's seed collections, built up over many years in national and international seedbanks and breeders' collections. Rules to define their management have been under discussion for several years in the UN Food and Agriculture Organization, in particular through the International Undertaking on Plant Genetic Resources for Food and Agriculture.

Prepared by the OECD Working Party on Biotechnology with the help of two distinguished experts on intellectual property, the report summarizes and analyses elements of the debate in order to contribute to the continuing international discussions and negotiations on these matters.

Intellectual Property, Technology Transfer and Genetic Resources: An OECD Survey of Current Practices and Policies, 86 pages, OECD, Paris 1996, FF80; US$16; DM23. ISBN 92-64-15328-4 (93 96 05 1) (Source: *OECD News Release*, Autumn 1996)

Genetically Modified Foods: Safety Aspects

Editors: Karl-Heinz Engel, Gary R. Takeoka, Roy Teranishi

This book presents concepts and principles underlying the safety assessment of foods and food ingredients produced via recombinant DNA techniques. Issues of antibiotic resistance and potentially increased allergenicity are addressed. The book discusses recent progress and the current state-of-the-art in the application of genetic engineering in

the production of foods. Applications which have entered or are about to enter the market are considered. The official viewpoints of government representatives from the USA, Europe and Japan are included in a discussion of a framework for regulatory oversight of genetically modified foods, developed from a symposium sponsored by the Division of Agriculture and Food Chemistry, at the 208th National Meeting of the American Chemical Society, in Washington, D.C.

Bibliographic data: Clothbound, 256 pages; illustrated, indexed, 6x9 inches; ISBN 0-8412-3320-9.

Price: US & Export: $74.95

Contact: American Chemical Society, 1155 Sixteenth Street, NW, Washington, D.C. 20036. Tel.: 202-872-4600. Telex: 440159 ACS PUI; Cable: JIECHEM.

Plant Cell, Tissue and Organ Culture

Editors: O.L. Gamborg and G.C.Phillips

This book is as much lab and instruction manual as an extensive information resource. The editors indicate that it was designed with researchers in developing countries in mind. The book is designed with the possibility of being used as the principal text for a complete course in plant biotechnology. Tips on data presentation, precautions and suggestions for solving the most frequently encountered problems and study questions for testing comprehension accompany each chapter. Complete descriptions of materials, procedures and expected results are coupled with trouble-shooting hints. Very complete appendices provide material which is often found only in one or more additional reference books. Attention has been given to making the book easy to follow and use.

Bibliographic data: Soft cover, 350 pages; 84 illustrations; ISBN 3-540-58068-9.

Price: US$ 89.00

Contact: Springer Verlag, 333 Meadowlands Parkway, Secaucus, NJ 07096 USA. Tel.: 800-777-4643. Fax: 201-348-4505. e-mail: orders@springer ny.com

European Crop Biotechnology—A Strategic Review and Directory

Biobridge Publications have published a two volume directory on crop biotechnology in Europe. Volume 1 contains a review of the European seed market and an assessment of the international competitiveness of the EU in this sector. The second volume is a Directory of 2,000 crop biotechnology projects.

The report is available from: Biobridge Publications, 45 St. Barnabas Road, Cambridge CB1 2BX, UK. Tel: +44 1223 566850; Fax: +44 1223 566851. It costs £695 for commercial companies, and £395 for non-profit organizations. Volume 2 is also available at £395 and £245 respectively.

Saving biological diversity

The loss of the world's biological diversity, and the economic and ecological consequences of that loss are now widely recognized as an environmental matter of urgent global concern. The importance of conserving diverse biological resources and using them sustainably led to the rapid ratification of the Convention on Biological Diversity, one of three international environmental treaties signed at the United Nations "Earth Summit" in 1992. With the biodiversity Convention in place, international attention is increasingly focused on the practical implementation of strategies for the conservation and sustainable use of biological diversity. The Convention identifies incentive measures as a specific mechanism to help guide national-level actions and to promote the conservation and sustainability goals expressed in the Convention.

The OECD, through its Expert Group on Economic Aspects of Biodiversity has examined how policy can guide human action towards the conservation and sustainable use of biodiversity, with a particular focus on the use of incentive measures. This report provides the main findings of that examination. It has been prepared by the Expert Group with contributions from David Pearce and Dominic Moran, Centre for Social and Economic Research on the Global Environment, University College, London, and contributions from the World Conservation Monitoring Centre, Cambridge, United Kingdom.

ISBN 92-64-14807-8. Copies may be obtained from OECD Publications, 2 rue André-Pascal, 75775 Paris 16, France or from main sales outlets of OECD publications.

Agricultural Biotechnology and the Environment. Science, policy, and social issues

by Sheldon Krimsky and Roger P. Wrubel. Published by the University of Illinois Press, Urbana and Chicago.

Two decades after new biological methods for recombining hereditary material in living organisms were introduced into science and industry, it now seems clear that biotechnology has a secure place among major technological breakthroughs of the twentieth century. Although the industry is still young, there is sufficient evidence for its future growth in pharmaceuticals, diagnostics, and food production.

When historians consider the last quarter of this century, they will note that the discovery and commercial applications of biotechnology did not come without some social resistance and public scepticism. Initially, scientists called attention to potential hazards when gene splicing was first reported in the literature (Krimsky 1982). As the concerns over laboratory hazards waned, public attention was directed towards the technology, the manufacturing and agricultural processes, and the consumer products that resulted from biotechnology. The din of controversy spread over a broad spectrum of issues, including patenting of life, human genetic engineering, genetic screening and identification, the release of genetically modified organisms into the environment, and the production of genetically engineered food, plants and animals.

As these controversies rise and fall, inevitably the questions will be: What was all the fuss about biotechnology? Is applied genetics so different from other technologies? Have industrial nations created higher standards for the adoption of genetic technologies beyond those required for past technological innovations? Or perhaps we are naive in thinking that contemporary societies have selected biotechnology for special treatment. Nuclear and chemical technologies have certainly been met with a formidable degree of public opposition. Even computer technologies have their detractors. There is a notable difference, however. With biotechnology, the public's scrutiny has come at the early stages of innovation, before the technologies are online and before products are marketed. One cannot say the same about the introduction of nuclear and chemical technologies.

Nevertheless, countless thousands of innovations in products and technological processes are introduced into manufacturing plants and the consumer market annually, with citizens having little or no awareness of the changes. Perhaps we are more likely to take note of new technologies when we use them directly and when they offer a new function or a replacement for an old one.

This book examines the directions of research and development for the first generation of agricultural products

and generic product categories arising from the applications of new tools in genetic engineering. The authors are interested in why certain paths of innovation were preferred over others and which factors shaped the direction of new biotechnology products. What, for example, has been the impact of regulation or lack thereof in the investment strategy for agricultural biotechnology products? What has been the outgrowth of social and environmental concerns resulting from the choices of new technologies?

In this study, the authors have sought to answer whether current trends in agricultural biotechnology are likely to promote safer insecticides, promote sustainable agriculture, create more biodiversity, or reduce dependency on fossil fuel and chemically intensive farming.

There is also a focus on the public reception to the first generation of biotechnology products. To what extent does the progress of innovation match the public's expectation? What are the sources of public apprehension? How deep are society's ideological divisions over biotechnology?

This book is organized around generic product types such as disease-resistant crops and transgenic animals. Each chapter provides a systematic overview of scientific developments. Some chapters include interview data from leading-edge biotechnology companies on the state of the art in product development. The technical analysis of research and product development leads to consideration of other contextual issues, such as the anticipated economic benefits, environmental effects, public perceptions, and the social ethical implications associated with the research agenda.

Chapter 1 explores the issue of change in agricultural biotechnology through a general discussion of technological innovation and diffusion in agriculture. The innovation pathways in biotechnology are fashioned by a superposition of government policies, technological maturation, technology transfer mechanisms, regulations and incentives, and social values. The significance of these factors is sorted out through specific cases.

Chapters 2-5 examine the science and social issues associated with transgenic crops; each chapter focuses on a generic class of products and research programmes. Chapters 6-8 address transgenic microorganisms in three agricultural applications: insecticidal, nitrogen-fixing, and frost-inhibiting bacteria. Chapters 9 and 10 discuss transgenic animals, the former examining current science, ethics, and social considerations and the latter human health and animal safety issues. Chapters 2-10 focus on topical applications of biotechnology. The chapters begin with a scientific overview, followed by a discussion of new developments, economic impacts, social and political responses, environmental implications, and ethical considerations. Although these divisions are useful for purposes of analysis, they should not be mistaken for the actual form or chronology of social and scientific controversy where many factors are at work concurrently at the time the technology is being introduced and evaluated by the scientific community, by government, by the media, or by the broader public.

Chapter 11 and the Conclusion are devoted to an interpretation of the current state of development in agricultural biotechnology. Chapter 11 re-examines the early expectations of biotechnology in terms of a set of myths and anti-myths. The Conclusion looks more closely at the impact that biotechnology is having on the system of food production and examines alternative social interpretations of the place of biotechnology in the future of agriculture.

ISBN 0-252-02164-9. Price: $47.50 Hardbacked, $18.95 Paperback. Available from University of Illinois Press, 1325 South Oak Street, Champaign, IL 61820, USA.

Japan Web site

The Department of Foreign Affairs and International Trade (DFAIT) has launched a Website on Japan. *Ni-Ka Online: Canada's Internet Window on Japan* offers market studies and background on various issues relevant to business people and others wanting practical information on the country.

Contact: Ni-Ka Online at http://www.dfait-maeci.gc.ca/english/geo/japan/index.htm

ABSP jumps on the World Wide Web: http:// www.isp.msu.edu/ABSP/

The ABSP Project's newly-developed pages on the World Wide Web were among the first files to be placed on the new International Studies and Programs (ISP) server which was installed at Michigan State University. The APSB Web presence is aimed at the distribution of general information on the project's goals and activities, as well as related areas in biotechnology, regulatory policy, and international development.

The new pages feature a special section where ABSP publications such as Bio*Link* and workshop proceedings can be downloaded in portable document format or PDF. These electronic files can be viewed on PCs, Macintoshes or Unix-based computers. Each new ABSP publication and each new issue of Bio*Link* will be available on ABSP*web*.

Hypertext links or "hotlinks" connect ABSP*web* to the Web sites and Web pages of collaborating partners in the public and private sector, in the US and in other countries. Also featured is a collection of links in biosafety, intellectual property, biotechnology, agriculture, international development, and more.

Soon available will be a "clickable" map of the ABSP management structure, which will give visitors to ABSP*web* access to a detailed overview of the project and its partnerships across the USA and the world.

US biotech information on-line

BT Catalyst from the North Carolina Biotechnology Center reports that the Institute for Biotechnology Information (IBI) has launched a new service on the World Wide Web that provides information on more than 1,300 US biotechnology-related companies and 11,000 strategic industry actions.

The service, called IBInternet, allows subscribers access to IBI's proprietary databases, which track company activities in the biotechnology industry and are updated on a weekly basis. A free phone directory of biotechnology firms is also available at the Web site.

IBI has also created IBInformation, a comprehensive package combining IBInternet with IBI's desk reference, *Biotechnology Guide USA*, and *Strategic Developments in Biotechnology*, a monthly periodical on strategic industry activities.

Contact: IBInternet at http://www.biotechinfo.com.

Biotechnology internet address book available

Genetic Engineering News has just published the **Biotechnology Internet Address Book**, which contains E-Mail addresses and Websites for over 900 companies. The Address Book is 8½ x 3¾ inches, and can fit easily into a breast pocket.

The **GEN Biotechnology Internet Address Book** is $49.95 in the US and Canada, and $60 overseas, shipped by air.

To order copies, call 1-800-6-5432378, or E-Mail to liebert@pipeline.com.

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TECHMART AFRICA '97

Grand Bay, Mauritius
24 – 26 November 1997

INTERNATIONAL BUSINESS FORUM

Organized jointly by the Government of Mauritius, UNIDO (United Nations Industrial Development Organization), SMIDO (Small and Medium Industries Development Organization) and COMESA (Common Market for Eastern and Southern Africa), TECHMART AFRICA '97 is an International Business Forum to promote direct contacts between investment and technology seekers from Egypt, Ethiopia, Ghana, Kenya, Mauritius, Namibia, Uganda, Zambia and Zimbabwe, and investors and technology suppliers from developed and developing countries. TECHMART AFRICA '97 will support private small and medium enterprises in forging technology and joint venture partnerships in the manufacturing, agro-based and agro-related industrial sectors.

Technology acquisition and joint venture partnership discussions between foreign and African coumpanies will take place during the TECHMART, and individual business meetings will be arranged on the basis of indication of interest on the technology and joint venture proposals. Technology seekers from African countries will meet foreign technology suppliers and arrangements will be made to display technologies using sample products, drawings, process flow diagrams, etc.

For further information, please contact:

- Director, Technology Services, Investment and Technology Promotion Division, UNIDO, P.O. Box 300, A-1400 Vienna, Austria. Tel: (43-1) 21131-3693, Fax: (43-1) 21131-6809, E-mail: opadickakudi@unido.org
- Director, Small and Medium Industries Development Organization (SMIDO), Industrial Zone, Royal Road, Coromandel, Republic of Mauritius. Tel: (230) 233-50 30 or 57 12/3/4; Fax: (230) 233-55 45; e-mail: smido@bow.intnet.mu
- Acting Director, Industry, Energy and Environment Division, Common Market for Eastern and Southern Africa (COMESA), Lotti House, Cairo Road, P.O. Box 30051, 10101 Lusaka, Zambia. Tel: (260) 1-229 726/32; Fax: (260) 1-225 107 or 227 318; Telex: ZA 40127; e-mail: comesa@comesa.zm

TECHNOLOGY AND INVESTMENT OPPORTUNITIES

SELECTED INVESTMENT/TECHNOLOGY REQUESTS

MUSHROOM PRODUCTION
A company located in Kabale, Uganda, already producing 200 tons per year of fresh mushrooms (*Pleurotus* spp.) for export and the local market and 20 tons of spawn per year, would like to expand diversification and production to satisfy the present market and enter new markets in other COMESA countries. The benefits of this project are income generation for rural women, non-traditional agricultural export and improved low-cost nutrition.
Preferred mode of cooperation: Joint venture, licensing, equipment supply, technical and marketing advice
(For further information, please contact: Mrs. Enid Rwakatungu, Gloca Investments Ltd., P.O. Box 714, Kabale, Uganda. Tel: 256-486-22331; Fax: 256-486-23200)

MANUFACTURE OF CROWN BOTTLE CORKS FOR BEVERAGES
A company located in Jinja, Uganda, already producing 222 million corks per annum is seeking assistance in improving product quality and quantity to meet international standards (ISO 9002 certification), especially consultancy in JIT, KANBAN and streamlining of present inspection procedures.
Preferred mode of cooperation: Technology transfer, licensing, equipment supply.
(For further information, please contact: Mr. A. N. Poduval, Crown Corks (1994) Ltd., P.O. Box 54, Jinja, Uganda. Tel: +256-43-30032; Fax: (043) 30040/21675; Telex: 64223 KAKIRA UG; e-mail: KSW@starcom.co.ug or: *cpd@imul.com)*

TEA BLENDING AND PROCESSING
A small but expanding blending and packaging enterprise in Kabale, Uganda, is seeking assistance to improve quality and processing, including modern machinery and equipment, technology to maintain weights and volumes. The aim is to supply local markets and export.
Preferred mode of cooperation: Licensing, turnkey agreement, know-how, equipment purchase.
(For further information, please contact: Mr. Alfred Jones K. Kanyamunyu, Managing Director, Akas Enterprises, P.O. Box. 317, Kabale, Uganda. Fax: 256-486-23742)

GARMENT PRODUCTION
A small-scale garment producer in Kabale, Uganda, is seeking assistance in improving quality, variety and quantity of items with a view to expansion. The provision of up-to-date equipment will enable the company to meet local demand and provide employment opportunities.
Preferred mode of cooperation: Know-how, licensing, equipment supply, technical assistance.
(For further information, please contact: I.M. Mbaruka, District Health Inspector, P.O. Box 181, Kabale, Uganda. Tel: 256-0486-24078/22512)

KNITWEAR
A knitwear manufacturer in Kabale, Uganda is seeking assistance in meeting increasing demand for products. The company produces knitwear for school and departmental uniforms, ladies', gentlemen's and children's fashionwear and is increasing its export orders to neighbouring countries. The company is seeking assistance in improving and maintaining quality, standards and improving manufacturing efficiency.
Preferred mode of cooperation: Know-how, licensing, equipment supply.
(For further information, please contact: Mrs. Peace Sabiiti, Managing Director, P.O. Box 928, Kabale, Uganda. Tel: (0486) 23590)

SELECTION OF PRELIMINARY REQUESTS FOR BRAZIL TECHMART (Belo Horizonte, December 1997)

RICE PACKAGING: Electronic technology for rice processing and packaging with capacity to segregate defective grains.

COFFEE PRODUCTION: Coffee grinding and roasting technology, production control methods.

TISSUE CULTURE: Technology for recovery of degraded areas; utilization of native vegetables through tissue culture.

DAIRY PRODUCTS: Technology for new dairy products.

EFFLUENT TREATMENT: Biotechnologies for industrial effluent treatment.

VACCINES: Genetic engineering technology for vaccine production.

CLINICAL ANALYSIS PRODUCTS: technology for new clinical analysis products, urinalysis strips, biochemical reaction readers in dry chemistry and corresponding kits.

SAUSAGE PRODUCTION: Technology for sausage production.

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BRAZIL TECHMART '97

Belo Horizonte (Minas Gerais) Brazil
1 – 3 December 1997

INTERNATIONAL BUSINESS FORUM

Organized jointly by UNIDO (United Nations Industrial Development Organization) and the Federation of Industries of the State of Minas Gerais (FIEMG), BRAZIL TECHMART '97 aims to promote and support the formation of technological and joint venture partnerships between and among enterprises from Brazil, particularly the state of Minas Gerais, and from other parts of the world, paricularly Austria, Italy, Slovenia and the Republic of Korea. By putting into focus the technological needs as well as the strengths of enterprises in the Brazilian metal-mechanic, agro-processing and biotechnology sectors, the event aims at forging strategic business partnerships that will promote the competitiveness and growth of these three sectors.

Over 70 Brazilian enterprises seeking technological solutions for company growth and competitiveness will be present at BRAZIL TECHMART '97, as well as trade associations, chambers of commerce, manufacturers associations, research institutes, government organizations, technology transfer agents, development banks and venture capitalists

For further information, please contact:

- Director, Technology Services, Investment and Technology Promotion Division, UNIDO, P.O. Box 300, A-1400 Vienna, Austria. Tel: (43-1) 21131-3693, Fax: (43-1) 21131-6809, E-mail: opadickakudi@unido.org
- The National Project Coordinator, Brazil Techmart '97 Minas Gerais, FIEMG (Industrial Federation of the State of Minas Gerais), Av. Do Contorno 4520 - 10th floor, CEP 30110-090 Belo Horizonte, Minas Gerais, Brazil. Tel: (0055-31) 229 6645/229 6565; Fax: (0055-31) 239 4636; e-mail: fiemg@fiemg.com.br