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EMERGING
TECHNOLOGY
SERIES

3/1996

Genetic Engineering and Biotechnology

UNITED NATIONS
INDUSTRIAL DEVELOPMENT
ORGANIZATION
Vienna, 1997

EMERGING TECHNOLOGY SERIES:

GENETIC ENGINEERING AND BIOTECHNOLOGY

1996/3

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

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Published in 1996 by the United Nations Industrial Development Organization (UNIDO)
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A-1400 Vienna
Austria
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TO OUR READERS

In the previous issue of this publication I briefly touched on the aims and activities of the International Centre for Science and High Technology, based in Trieste (Italy). Now I would like to give you news of another centre of excellence that UNIDO has been asked to help set up.

The most recent centre to be initiated is the International Materials Assessment and Application Centre (IMAAC), to be located in Rio de Janeiro in Brazil. IMAAC will assist the developing countries in solving problems of monitoring, assessing and forecasting trends in materials technology by providing them with information on the impact of new materials on industrial and economic development and competitiveness, and by providing information on the potential areas of utilization of the abundant raw and natural material resources they possess for industrial application. The new centre will also assist developing countries through building up and strengthening their technological capacity, including materials policy issues, while taking into consideration environmental and energy saving issues. Materials technology is a key enabling technology for a wide range of industrial sectors that will have a major influence on economic and industrial competitiveness. At this stage, the pilot activity programme has already been started.

Our old friends ICMET (the International Centre for Materials Evaluation Technology) is expanding its activities to include cooperative research projects on testing and evaluation, which will lead to develop new standards in testing methodology.

I am also pleased to inform you that a new investment partnership scheme has very recently come into being, namely a $1000 million window of opportunity for British investment and technology. The new two-year project between UNIDO and NIMTECH (the UK's leading private-sector technology transfer network) represents a major step towards helping private firms in developing countries meet new business partners in the United Kingdom. The project will build on the success of an initial cooperative arrangement between UNIDO and NIMTECH, and aims to sharpen the focus of commercialization of new and emerging technologies to which viable markets (estimated to be worth more than $1000 million) ave been identified. Emphasis so far has been on cleaner production techniques, biotechnology and nanotechnology.

We are also happy to report on the first agreement between UNIDO and the Common Fund for Agricultural Development (CFC), which is expected to generate more than 250,000 jobs by developing new uses for the sisal and henequen industry in Kenya and Tanzania. The project calls for a major revitalization of the industry, focusing on diversification into using sisal and henequen for pulp and paper production. Scheduled for completion at the end of 2001, the project is expected to benefit small landholders and larger farming estates alike.

Another landmark has been the first investors forum for sugar cane linked to a TECHNOCANA '96 sugar fair in Havana, Cuba The forum covered the industry's enormous potential for diversification into new by-products. Some 60 opportunities on offer, such as upgraded mills, sugar cane alternatives, animal feed and yeast, cane derivatives and sugar based fuel production were discussed between project sponsors and their potential foreign partners. The TECHNOCANA gave participants an opportunity to see the progress made by the Cuban sugar industry in equipment maintenance, spare parts R&D and the development for diversification of various industries.

Managing Director
Investment and Technology Promotion Division

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A. SPECIAL ARTICLES

STRATEGY FOR BIOTECHNOLOGY DEVELOPMENT IN ASIA

By K. Venkataraman

Dr. Venkataraman was until recently Managing Director for Investment and Technology Promotion in the United Nations Industrial Development Organization.

General scene

Though Asia is bio-resource rich and most Asian developing countries are aware of it, the scene continues to be one of promise and not much fulfilment. Broadly speaking, the Asian developing countries fall into three categories, in terms of biotechnology development:

1. Countries that have advanced considerably in research capability but not equally so in industrial and commercial application. Examples are China, India, the Republic of Korea and Thailand, although in the Republic of Korea the interest taken by industrial companies with a background in fermentation is significantly high—a feature which is not so visible in India or China.
2. Countries that have some research capability but are still striving to consolidate and strengthen it. Arguably, the examples are Pakistan, the Philippines, Sri Lanka and Viet Nam.
3. Countries that can build up, but do not at present have a research capability, let alone industrial capability, for example, Bangladesh and Nepal.
4. The foregoing classification is not watertight, but serves to illustrate that different countries have different starting points. They all have to go further from their respective starting points and advance their capabilities. Modern biotechnology is science-based. The building up of a research capability (scientific capability would in fact be a more desirable and correct term) is essential, but the building of an industrial capability need not be sequential to it. They should indeed be concurrent and interactive.

The disparities in biotechnology status also provide scope for plenty of intraregional cooperation for sharing and strengthening capabilities. Countries, such as China, India and the Republic of Korea could take the lead. The present scenario also suggests that many countries, after acquiring a basic scientific capability could identify a niche where the strength of each is greatest and in any case avoid stretching too thin.

The reasons for inadequate biotechnology development are several. The attempt in this short paper is not to dwell on them, but to make observations on those aspects which have been relatively neglected and also to make suggestions and proposals of an operational nature.

A strategy and its components

The basic problem of course is that in general most countries do not have a strategy and where they have them, the strategies are limited in scope and lack coherence, synergy and the elements of sustainability and self-generation. Serious attention must be given to what constitutes a national strategy. It includes an important promotional role by Government (which is necessary in this sector), but is not limited to it. A national strategy has to be seen as a partnership and an interaction between the Government, industry, the research community and the public at large, thus requiring a larger perspective than several conventional industry sectors require. Once the initial push is given, biotechnology development must be sustaining and self-generating through the market mechanism. In that sense a strategy is not one which is merely articulated in a document but incorporates in its operation pacing devices, pulls and pressures which take the industry forward. Some operational proposals of this nature are made later on.

It is necessary, however, to highlight some essential but less recognized aspects relating to the four partners. The Government's role is not limited to providing funds for scientific research, or starting an institution focusing sooner or later on the prospect of financial support. A few incentives by themselves do not carry development far. Providing an enabling environment is essential, but it is important to understand what such an environment really comprises. It must include regulations relating to safety and intellectual property, a host of supporting institutions such as for supply of bio-reagents, culture collections, testing facilities and demonstration and pilot plants (the Department of Biotechnology of the Government of India has started several facilities which could also be accessed and used by neighbouring countries, but also market development, entrepreneurship development, venture capital, etc. It is important not only to provide a road, but also a destination. National, institutional and enterprise level goals must be promoted, backed by technology monitoring, forecasting and intelligence.

Industry, however, works not on exhortations but on the prospect of profits, typically short-term. Barring a few exceptions, Indian industry, particularly the large companies, has not taken to biotechnology in a big way. Perhaps perceptions of the wide-ranging scope of biotechnology applications have not developed and some promotional effort in this respect is needed. Even in the developed countries modern biotechnology was first commercially introduced in the pharmaceutical, health care and diagnostic sectors, followed in the last 10 years by agricultural and livestock applications. The food processing sector has received attention first in Japan and more recently in Europe.

It is paradoxical that Asia has bioresources on the one hand and "bioneeds" on the other, but the two have not been matched through acceptable and marketable products. This is partially due to some amount of distraction by the high technology end of applications without looking at what is possible at the other end; for example, processes such as tissue culture and economic opportunities say, in agriculture, mushrooms or environmental technology. Scientific research is often lost in the glare of high technology and contributes less to upgrading conventional products. One of the starting points for biotechnology applications would be to bring to the notice of industry the market opportunities through product information, product and technology profiles and economic and commercial information, backed by technology monitoring, forecasting and intelligence. It is possible to develop/strengthen appropriate mechanisms for this purpose.

Public perceptions and the time needed (and sometimes taken) for regulatory approvals have a role in the development of the market. Typically, a biotechnology application would mean the introduction of a new product; improvement of an existing product; or provision of a more cost-effective solution than a chemical or conventional process. Industry needs to know more and more what biotechnology can offer in this respect.

Joint venture and technology transfer agreements (certainly for proprietary products and processes) are essential but they are not a substitute for local knowledge and endogenous scientific capabilities, which must be recognized as a crucial asset in a joint venture. Partnership with small science-based firms abroad could be less rigid and formal and more rewarding in terms of learning by experience the skills needed to promote such ventures. Contract research by institutions and "research firms" could perform knowledge-intensive services for foreign clients, for example, in the Human Genome project. Computer software skills and bio-science could be combined to provide services such as the development of computer models of biological molecules. Equity participation in science-based firms abroad would also be a good learning experience.

Science-based enterprises need also to be promoted within a country through specific measures. For example, if a scientific researcher finds an economic opportunity in his research and a possible personal stake in it, he will be more prone to make his research application—orient it and pursue it to a positive conclusion.

Cost-effectiveness and competitiveness in biotechnology depend on the equipment and techniques of fermentation and purification. Purification standards, for example in vaccines, are set by developed country firms and institutions and continually "chased" by developing countries. As for fermentation, it is the manufacturing technology in many biotechnology applications and as such is a crucial determinant of the cost. Scientists are generally prone to under-emphasize the importance of fermentation technology. More attention needs to be paid to the design and operation of bio reactors and good manufacturing practices.

A few observations on building scientific and research capabilities will be in order. Limited access to bio-reagents and advanced equipment is a handicap in several countries. Research tools are constantly upgraded in the developed countries so that many steps are leap-frogged and time is saved. Innovative mechanisms for the supply of bio-reagents, leasing of equipment and donation of second generation equipment by developed country institutions could be considered. A system of dispersed tissue culture laboratories could spread out biotechnology research and applications. Short and long-term training in advanced techniques is available through the International Centre for Genetic Engineering and Biotechnology located in Trieste and New Delhi.

Two important points need to be considered in national programmes for building up scientific and research capabilities. When resources are scarce, one has to be wary of building large new institutions, but resort rather to networking and strengthening capabilities available in existing institutions and universities. For example, the National Centre for Genetic Engineering and Biotechnology in Thailand does not undertake research, but networks and supports existing institutions. The second point is that biotechnology applications require not only micro-biologists and molecular biologists but biochemists, fermentation engineers and instrumentation experts on the technical side, and lawyers and financial and marketing experts on the commercial side. The effort should be to create inter-disciplinary "core groups" and "core competencies" rather than institutional monoliths.

Public involvement in biotechnology has several dimensions. The first is public perceptions and reservations about possible risks. Such reservations are particularly held against genetically engineered products. In countries like Germany, initial strong reservations have given place to application-oriented approaches. Another dimension is market acceptance, particularly of agro-products. In Asian countries there is a tradition of fermented foods, which may make acceptance easier. A third dimension is the traditional knowledge about plant species, products and practices. The preservation of biodiversity must include the preservation of such knowledge.

Having considered some aspects of the roles of the four partners in a brief manner, we come to the question of how to pull it all together in a strategy. Dialogues and policy documents are necessary but not sufficient. They could and indeed should be the first step. Networking, pooling and interaction of resources and expertise are essential. Above all, targeting areas where all four partners have a stake can be the prime mover. Self-generating interaction and momentum can be sustained only when there is an economic opportunity and shared benefit.

Missing links in biotechnology application

Biotechnology as an industry involving knowledge-based applications is new to most developing countries. The pace of this industry and its ground rules are set by developed country firms. The acquisition and negotiation of technology itself requires skill and experience and a regular monitoring of the trends in the industry and the technology. The link between it and research and industry is tenuous, even in some developed countries and is distressingly so in most developing countries. Commercialization of biotechnology requires a range of skills, including information, monitoring, contracting, testing and evaluation, patenting, safety protocols, venture capital financing, market surveys, product development and the like. These may be called "soft" skills, which are not only scarce but scattered in different institutions and individuals in most developing countries. Large firms could afford a dedicated department for such work, but small firms and new entrepreneurs lack even the knowledge of the various steps to be taken, let alone information on where to turn for such services and the capacity to coordinate the various steps. A research result, even after it is recognized as useful, remains on the

laboratory bench, because whatever interest the researcher may have in commercializing it, will soon evaporate when he has no clear idea on how to set about the whole matter. Such "soft" skills need to be identified, strengthened, consolidated and networks have to be built to make them available to researchers and small and medium-sized entrepreneurs.

A starting point in forging this missing link would be the establishment of a "clearing house" of biotechnology support services working initially on a referral and advisory basis. It would identify referees in regard to each of the skills, prepare and update directories and promote the strengthening of such skills through training programmes. A researcher or enterprise could approach the "clearing house" for information on specific skills or general advice. A small fee may be charged for services involving more than a routine referral or supply of information. The enquirer would be free to get in direct touch with the referees or may request the "clearing house" to monitor and coordinate the various steps involved in a workable sequence. Such a "clearing house" would be useful both in India and most other developing countries and would accelerate the pace of biotechnology applications. The Asian and Pacific Centre for Technology Transfer (APCTT) could be a suitable venue for such a "clearing house" to serve Asia.

Harnessing biotechnology and biodiversity

Despite ample biodiversity and a keenness to increase biotechnology applications the present situation is characterized by a low level of utilization of the potential of biotechnology. The present situation can be radically improved if biotechnology and biodiversity are harnessed together as a development challenge and an economic opportunity. Approaches to the preservation, prospecting and exploitation of biodiversity must be proactive rather than reactive. Against this background a proposal for a biodiversity revolving fund and related measures is roughly outlined below.

The objective is to achieve an articulated capacity for preserving, exploring, managing and using biodiversity; a capacity that needs to be internal to the country, and to impart dimensional change to the pace of biotechnology applications.

A national effort involving a partnership between industry, research community, Government and the public must be mounted. Such an effort should include the following features:

- The research community will screen, characterize and document, particularly at the molecular level, bioresources through a set of accredited institutions, building upon existing surveys and data, but going substantially beyond them. This will be essentially precompetitive research. At the competitive stage, research institutions may undertake contract research, observing the requisite confidentiality.
- Industrial enterprises (including agriculture as an industry) will subscribe to the precompetitive effort with a membership fee, in return for which they will have full access to the results of the screening and initial technical advice; the fee may be treated as research expenditure eligible for deduction for tax purposes.
- Government as the initiator and prime mover with overall policy and monitoring responsibilities. Patents may be taken by Government where necessary and feasible.
- Participation of local communities is essential, particularly to capture and document traditional knowledge.

A small secretariat could do the coordination, guided by a representative governing council and a smaller executive council.

The aim is to create a revolving fund, although it will take some years to "revolve". The point is that services must be charged and operations run on business lines. Funds will come essentially through membership fees from participating enterprises; fees for services rendered; initial start-up costs from Government; and royalties earned by the Government and rerouted.

Certain supporting and advisory services must be provided for, such as for testing, clinical trials, commercialization, feasibility studies, entrepreneurship training, etc.

What is needed is a detailed examination of the viability and the means of operationalization of the concept, including a survey of information and data that already exist and the means of strengthening such sources thereof; identification of participating institutions; ascertaining the views of industry and enlisting its participation; estimating the cost of operation, sources of funding, and the size of the revolving fund; together with a plan of action and a time schedule.

Those involved in biotechnology development in Asia may be reminded of Robert Frost's lines:

"The woods are lovely, dark and deep
But I have promises to keep
And miles to go before I sleep"

* * * * *

SOME PRELIMINARY THOUGHTS ON BIOTECHNOLOGY IN LDCS

(Kindly supplied by Dr. Michael Dan, Chief Executive Officer at Novopharm Biotech of Canada)

The subject of biotechnology in less developed countries (LDCs) is a particularly challenging topic since it runs counter to the natural flow of economic activity in such countries. Nevertheless, there are certain ironies about biotechnolgy in LDCs that make it appealing.

Economic activities can be broken down into two categories. Capital intensive activities require a comparatively greater proportion of expensive manufacturing equipment, and are more commonly associated with industrialized societies. An example would be the manufacture of automobiles using robotic machinery. Labour intensive activities require a comparatively greater proportion of manual labour. Examples would be the types of hand-made goods that many less developed countries typically export.

The central irony of biotechnology is that although it is a very capital intensive industry, the critical success

factor is entirely in the field of human resources. Another way of stating this is that although biotechnology requires much in the way of infrastructure and capital equipment, the most valuable resource in any biotechnology industry are the scientists and research personnel who comprise that industry.

Economists like to talk about the comparative advantage of nations and how one nation that has a comparative advantage in capital intensive goods can trade with a nation having a comparative advantage in labour intensive goods. My own personal impression of biotechnology is that it is capital intensive in the short run and labour intensive in the long run. Although it takes a certain dedication of resources to establish a biotechnology industry in a country, once it is up and running, it is the people who make up that industry that ultimately determine its success or failure.

In this regard, I believe that biotechnology in less developed countries has a much better chance of success than one might initially believe. Once the proper infrastructure is established, Western-trained scientists could maintain a competitive advantage in the industry for an indefinite period.

So how do we think about biotechnology in a less developed country? On a very superficial level I like to break biotechnology down into two areas: agricultural and medical. Clearly, LDCs have a need for both, and any generalizations I make can be extrapolated to both forms of biotechnology. For purposes of discussion, I would like to break my remarks into three sections: (1) Consumers of Biotechnology, (2) Manufacturing in Biotechnology, (3) R&D in Biotechnology. All three areas are interrelated but can be conceived as independent functions. Further, all three areas can be transplanted to less developed countries individually or in tandem. Clearly, the most value-added approach would be to transfer all three areas to LDCs.

Consumers of biotechnology

People in LDCs can become consumers of Western biotechnology just as easily as they can be consumers of any other Western export products. The constraints on biotechnology are essentially no different than any other Western-based health-care products. The single most important factor impeding transfer of Western-manufactured biotechnology products would be the price of those products. Most companies avoid a policy of discriminatory pricing and therefore price their products for LDCs in about the same range as for Western countries. The purpose of this practice is to prevent activity in the so-called grey market whereby a consumer in the West could purchase lower cost equivalent biotechnology products in an Eastern LDC and then resell them in a Western market at a higher price.

In addition to problems with hard currency, LDCs have difficulty with storage of labile pharmaceutical products as well as distribution systems through various hospitals and pharmacies. Any efforts to make people in LDCs more avid consumers of Western manufactured biotechnology products would only benefit them to the extent that the products can improve their lifestyle beyond its present level. This is no small achievement in itself. However there is very little value added that is retained by the LDC if manufacturing and R&D are not carried out in the local economy.

Manufacturing of biotechnology products in LDCs

There are a number of significant problems facing the prospects of manufacturing biotechnology products in LDCs. The number one issue that comes to mind is patent enforceability. Biotechnology is the most vulnerable industry in the world from an industrial security point of view. An entire research programme—and for that matter an entire commercially successful product—can disappear from a manufacturing site in the form of a small cryotube that can be carried in a pocket or briefcase. If you think this is a joke, just consider the movie Jurassic Park in which the principal villain made off with dinosaur embryos that were stored in an improved liquid nitrogen container disguised as a can of shaving cream.

The principle frustration of American-based biotechnology companies is that they have no mechanism for enforcing their patents in LDCs. Any episodes of patent infringement have to be dealt with by local authorities who do not possess the resources to prosecute these cases adequately. If a system could be established whereby Western Governments would be allowed to collaborate with their counterparts in LDCs to enforce patents, then there would be a very strong incentive to relocate manufacturing facilities to LDCs.

Other barriers to manufacturing in LDCs have to do with general problems facing the installation and maintenance of good manufacturing practices (GMP) facilities in LDCs. This is an ongoing problem due to lack of infrastructure and to a certain extent distribution networks, but is remediable.

Finding the personnel to staff and maintain GMP facilities in LDCs should not be a significant problem. All GMP facilities operate with a system of Standard Operating Procedures (SOPs) and if the local personnel are sufficiently literate to follow a basic instruction manual then they can learn to follow SOPs and perform them to the same standard as Western manufacturing facility personnel.

Biotechnology R&D in LDCs

This is the most exciting of the three areas. When I look at our own staff at our facility in Winnipeg, I see representatives of many nationalities, many of whom come from LDCs. These are Western trained scientists and research technicians who could be just as comfortable performing the same duties in their countries of origin as they are in Winnipeg (Winnipeg being a much more inclement place than the countries from which most people originate).

Scientists and researchers from LDCs are just as bright as their Western counterparts. The main problem is that once many of them come to the West and receive an education, they are reluctant to return to their countries of origin. I believe this problem can be remedied by administering the right kind of incentives which I will elaborate further on.

There is also a need for Western trained entrepreneurial managers in LDCs. I believe there is no shortage of individuals who would welcome a three to five year term in an LDC if the right economic incentives were in place.

The largest problem facing the development of biotechnology R&D in LDCs is the lack of entrepreneurial spirit in these countries, combined with an often crushing bureaucracy. If this cultural attitude could somehow be changed, which I indeed believe is possible, then the floodgates would open and the opportunities would create themselves.

Proposals for developing biotechnology in LDCs

As I mentioned earlier, biotechnology can be developed in LDCs on three fronts: on the consumer front, on the manufacturing front, and on the R&D front. There

is no justification for not developing all three, but this has to be done in a comprehensive fashion. The single most important principle to follow is that biotechnology in LDCs must be brought up to the same standard as biotechnology in the West. There can be no compromise on this approach if the long-term competitive position is to be maintained. Ideally, one would like to see a scenario where a senior biotechnology executive in California is literally flipping a coin to decide if they want to build a new manufacturing plant in the United States or China.

Consumers of biotechnology products in LDCs should be made to pay the same price as their Western counterparts. This refers to individual consumers of biotechnology products. Because such a policy will put the price of biotechnology products out of the reach of individual consumers, we have to construct a way to get around this problem. The best proposal I can determine is that a Government agency becomes the purchaser of biotechnology products at a reduced price and then passes on the savings to consumers who are part of a registered health plan of some kind. The Government agency may ask for a small one to two per cent mark-up to cover its administrative costs, but in principle the prices will remain at Western levels for individual consumers of biotechnology products and far below Western levels for individuals who are covered by a Government health-care plan. This is a way of upholding the principle of Western pricing while undermining it at the same time. It imposes an additional layer between the manufacturing company and the Government approved consumer, as well as imposing the cost of the subsidy onto the biotechnology company. However, with the type of sales volumes that can be generated in LDCs, it should still lead to a profitable situation for both parties.

Manufacturing facilities can and should be established in LDCs. One way to do this would be for local and Western Governments to give tax breaks for a limited number of years to biotechnology companies that build facilities in LDCs. As far as patent protection is concerned, LDCs in Western countries could become signatories of a biotechnology patent treaty that would permit Western countries to collaborate with local authorities as far as enforcement of patent infringement is concerned. This might be viewed as a violation of the sovereignty of LDCs. However, I believe it is a necessary concession that must be made in order to entice Western-based biotechnology companies to locate some of their manufacturing facilities in LDCs. The tax shelter could also be extended to personnel who are Western-trained and choose to relocate in LDCs.

Biotechnology R&D can be promoted in LDCs if there are incentives for citizens of LDCs to obtain a Western scientific education and then return to their countries of origin. Incentives could take the form of income tax breaks for a limited number of years as long as they remain in the employment of the company, or possibly educational subsidies from either the LDC Governments (probably too costly), or the biotechnology companies themselves in exchange for further tax breaks.

* * * * *

POINTS TO CONSIDER IN STARTING A BUSINESS

Kindly provided by Dr. Walter Haeussler, of the Cornell Research Foundation, Cornell Business and Technology Park, 20 Thornwood Drive, Suite 105, Ithaca, NY 14850, USA

This summary is not comprehensive but is intended to stimulate thought when considering starting a new biotechnolgy-based business or for that matter any technology-based business.

Starting a business

A successful start-up business requires the confluence of a number of factors. There must be a technology capable of supporting a new business. Many technologies are great additions to existing product lines or can be sustained as an additional product in a large organization, but they are not the kind of technology that supports a new business which generates a succession of improved or diverging products to sustain a business.

- **There must be a technology champion**

It may be the inventor of the technology, someone who has worked for the inventor or someone who understands the technology niche sufficiently to promote the technology and sustain product development as well as supervise, engineer and manufacture the technology.

- **There must be a management team**

The skills required for inventing product development, the raising of capital, the supervision of manufacturing and the supervision of marketing, are very different skill sets and few people possess them all. Also, even if one person is capable of doing all those things, many of the functions are full-time occupations. One cannot be working on product development, which is usually a full-time job, and at the same time attempt to raise capital which is always a full-time job.

- **There must be adequate financial support**

Financial support as discussed hereinafter, can come from a number of sources, but the message is clear. Most small businesses fail within two years after they are started and the principal cause of failure is that the company is undercapitalized.

- **There must be a window of opportunity**

A technology may be too early or too advanced for the market-place, or there may be a need to develop a market before one can even attempt to sell a product in that market.

If all of the above factors seem to come together, then the possibility of starting a business exists.

Starting a business—first steps—the business plan

The planning process can vary widely between different types of companies, but a number of steps should

probably be included in the process of planning for a start-up company.

- **Identifying the business and industry**

What goods or services are being produced? What are the dominant characteristics and interests of the customers the company is going to serve? Who is the in-country competition, regionally and globally?

- **Make detailed assumptions about future business conditions**

What are the expectations about population, trends, economic growth, taxes, inflation, interest rates, material supplies, transportation availability, governmental policies? Also, how sensitive is the potential market to particular changes in business conditions? Full treatment of these questions would require the use of forecasting and other forms of financial analysis. At the minimum, it is important to think about how changing business conditions can affect the proposed company.

- **Research of the industry**

Information on its historical development and trends in market segments, competitors' strengths and weaknesses, and on relevant Government regulations can be located.

- **Analyse the market**

Information on market size, characteristics and trends can be found in census studies and industry surveys. After looking at the different characteristics and interests of potential customers and grouping them into distinctive market segments, the company should determine what market segment or segments to target. Then buyer preferences need to be assessed, including effects of different price levels and alternative customer service possibilities.

- **Set multi-year goals**

It is helpful to have quantitative benchmarks for such things as sales, market share, profits and customer service levels. Qualitative goals should cover such things as new products development and/or changing or increasing manufacturing capability and location.

- **Develop a strategic plan**

This involves knowing the company's business goals and showing a comprehension of the necessary steps to obtain the company's goals over a period of time.

- **Project business performance over a multi-year period**

The company should develop operating budgets, cash flow budgets and projected income statements and balance sheets. These projected statements are vital when assessing the future profitability, liquidity and solvency of your business and will be a basis for investors to judge, in part, whether to invest. Make sure that the company's financial projections make sense based on the information that has been gathered, and that the investors could gather, and also correspond to the representations in the business plan discussed above.

- **Do alternative analysis**

A major benefit derived from developing an operating plan is the opportunity to use a plan to test the alternative business strategies in order to judge the effectiveness of the tactics the company intends to employ without actually having implemented them. Analyse the company's own projections and economic forecasts to see how sensitive its business proposal is to changes in sales, the cost of sales, inventory management and all the other things that are variables for the business. The company should know the benefits of certain positive actions, for example: payment and collection efforts and cash flow, as well as expected negative or adverse developments, such as delays in putting a product in the market-place, poor sales, or higher interest rates. Spreadsheet software packages can be used on a personal computer to automate the process.

Organization of the business plan

- **Executive summary**

First and foremost, there must be an executive summary. The purpose of the executive summary is to emphasize the strengths and provide a *brief* overview of the new venture. *It must convince busy investors to read further.* It is known that many investors or bankers lose interest in a business strictly because of an inadequate or unappealing executive summary.

Briefly describe the product or service concept. Pinpoint the characteristics that make it unique. Identify the current status of the company, for example, whether the focus is primarily research and development, production or marketing. Discuss the company's goals, strategy and critical success factors. Specify the target market and its size and explain why it is ready for the product. Indicate what share of the market the product will capture and over what period. The company may be creating a new market, or a new process or product for an existing market. Add a brief discussion of any relevant regulatory considerations. Furthermore, the competition should be analysed with an indication of how the company and its rival(s) compare in the market-place, now and in the future.

The relevant qualifications of the key staff and top managers should also be described in the executive summary.

The last topic to address in the executive summary is the reasonableness of the planning. Being realistic is crucial. Three to five year projections of cost revenues, losses and profits should also be considered for inclusion.

The body of the business plan

- **Specific subject areas**

The remainder of the business plan should expand on the subject areas highlighted in the executive summary. The plan should cover these subjects in considerable detail. (a) The business and the relevant industry; (b) management and ownership; (c) marketing strategy; (d) operating and production strategy; (e) the implementation schedule; (f) use of funds and financial data, as well as other topics unique to the business.

- **The description of the business**

The business and its industry should be discussed in non-financial terms, both in historical and future perspectives. The business description section should explain those factors critical to the success of the business.

Critical success factors are not limited to strengths. Critical weaknesses, including dependencies, exposures or other obvious risks that are part of the business environment, should be frankly discussed. They must be protected against, improved on, or made allowance for. Discuss in detail the firms that the company will compete with, their known strengths and weaknesses, and market share. The assessment will show that the company understands and has considered risk before going into business and before requesting investment.

- **Marketing strategy**

The business plan should describe the market segments the company will penetrate. How the company will identify its customers and convince them to invest in its projects or buy its products and how the company will deliver

products to them. A chart comparing the project's or product's capabilities with those of the competition is helpful. Include market studies and trade journal articles where available.

- **Operations or production strategy**

If the company is marketing a self-produced product, describe how and by what methods production will be done internally, and why the production is being done internally. The plan must discuss present and future capacity limitations and, given the marketing strategy set forth, the capital requirements will provide the necessary expansion. Discuss the sources and the availability of critical components, raw materials and labour.

If the company is marketing a product produced, in the most part, externally, briefly explain the processes that will be performed in-house and the value added by these steps.

If the product is a service, such as diagnosis and testing, describe what is unique about the service, or the methods that are used in providing the service. The plans should discuss the methods by which the company will acquire the personnel and equipment to meet its projected income figures and the amount of funds required to provide start-up and expansion.

Start-up and expansion

- **Implementation schedule**

Outline of all the activities required to implement the strategies presented in the other parts of the business plan. Typically, the schedule is a diagram which shows the activities on one axis and time, generally measured in months. On the other axis, indicate decisions, points and the growth of the business when further funds can be committed or delayed. Allow time in the schedule for regulatory testing and approval where appropriate.

- **Management and ownership**

The evaluation of the management team is an important element to be considered. The management team should be briefly introduced, with emphasis on experience and past success. Detailed biographies can be included as exhibits.

Management organizational charts are useful. Where there are obvious management gaps, they should be identified and plans to fill them should be described. Where management structure is limited, identify key consultants and other advisors as a way to offset the apparent weakness of a company.

- **The use of funds**

A detailed explanation of how the business intends to use the funds is required. Generally, with early stage start-up companies, the actual use, timing and amount of money required may only be estimated based upon financial projections or forecasts. The funding may be in stages. Each stage will represent a decision point to measure progress and make necessary changes.

If the business plan involves equity financing, the price basis for ownership, i.e. the cost for a share of stock, should be clearly set forth. The effects of dilution of early investors should be discussed. Plans for eventually "going public", if any, should be described in terms of the business and market conditions that must be achieved before "going public" can be contemplated.

- **Financial section**

Financial data should be represented at least for the expected period of funding and repayment. Early years will need to be more detailed than later years. Projected data should include statements of income and cash flow, as well as balance sheets for all of the periods presented in the business plan. Indicate the cash flow, break-even level of sales and approximately when that will occur. Where an assumption is critical, its effect over a range of possibilities must be presented.

- **Additional information in exhibits**

A business plan should include all information that could or should influence a potential investor's decision. Special matters can be included in separate sections. These can include discussions of patents or trademarks, significant litigation, income tax matters, administrative matters, regulatory matters. Exhibits can be extensive and are necessary to support the narrative summaries. Exhibits will generally include management biographies and production information, market research studies and additional financial detail, advertising material and related news or business articles.

- **The image of the document**

The overall document should project a positive image and demonstrate a desire for success. The image should reflect the company's unique identity or personality. It may be that the company will want to engage public relation advisors or professional business proposal writers for assistance. The advisor cannot generate the raw material that is the heart of the business plan. Only the company can do that.

- **Confidentiality**

The proprietary product or process is the company's competitive advantage. The business plan that is developed will contain proprietary information and the company must ensure that it remains confidential. Limit distribution of the plan to selected investors and control the number of copies which are issued. A statement regarding the confidentiality of the plan may be placed on the cover. Whatever disclaimers are required by regulatory bodies, be they financial or technical, should be included.

The physical space requirements of a biotechnology company

- **Function versus architecture**

A typical biotechnology industry site is potentially a very complex building unit that places heavy demands on electrical, mechanical and plumbing systems. In addition to office space, facilities will contain some or all of the following areas: laboratories (biological, chemical, pharmacological or other application specific units); clean rooms and manufacturing facilities, which may be either full-scale or pilot plant, together with warehouse or storage space.

The building is merely a container for the sub-systems and therefore the architecture of the building is far less important than the contents.

A growing biotechnology company is constantly in a state of change: growing, shrinking and changing to meet the needs of its progress or lack of progress, as well as the actions of the competition and the changing market-place. A well-run biotechnology company is capable of creating and maintaining a costly infrastructure while remaining reasonably flexible.

It is seldom true early on that a custom-built building is either a reality or a useful effort. The multi-year leadtime for planning and construction is longer than the typical early biotechnology company's certain knowledge of their facility requirements, which, in part depends on a regulatory approval process, which may change timeframes or directions.

- **Site selection**

A key to site selection for a biotechnology building is expansion room, so that if there is a need to grow, the company does not have to pack up and completely move. They can either expand the existing building or move into a neighbouring site.

An alternative to physical expansion is outsourcing; for example, the outsourcing of manufacturing needs rather than building manufacturing space. Another alternative is to acquire space that is larger than present needs and sub-lease excess space to third party tenants. This then allows for future expansion into the space initially occupied by tenants.

Clearly, the physical space requirements of any biotechnology company are a substantial consideration of the initial company-formation team and will remain a considerable subject of management effort throughout the life of the company.

Financing the business

During the start-up phase of a business, the company will incur significant costs before the business ever opens its doors and it is very likely that it will face negative cash flows until sufficient revenues are achieved. Until it reaches this level, financing will have to come from sources outside the business.

The process in obtaining financing is chief among the factors critical to success. Once the company has a completed business plan in hand, it is ready to begin looking for and evaluating financing alternatives.

- **Financing alternatives**

In general, there are two types of financing alternatives: equity and debt. Equity financing is most often thought of as the permanent amount of capital invested or placed at risk in a business, generally by the owner, venture capitalists or other individuals.

Most frequently, equity capital is derived from the sale of the company's common stock. Debt financing is normally comprised of funds borrowed from banks or financial institutions or from individuals on a more or less temporary basis. Far more often than not, initial start-up money is usually provided by the owner's personal, including family, resources. Whether that is from savings, money invested by family members or accumulated personal equity which is pledged. While there are exceptions, the person starting the business is almost always required to provide the initial capital to get the business rolling. The likelihood of getting outside financing is almost zero. The organization that has not first demonstrated some willingness to place a significant portion of the founders' personal financial self on the line, will have difficulty in interesting outside investors.

- **Financing sources**

The company will not only have to compete in ordinary business to survive, competition runs beyond the mere ability to generate sales. It extends to competing for financing. The goal must be to secure adequate financing in a sufficient amount at competitive rates, so that the company can operate efficiently, as compared to similar organizations.

Review of sources of equity needs

- **Funds from individuals**

Generally, the most difficult money to raise will be the equity to initially start the business. The most common sources will be the organizer's own funds and those of family members or close business associates.

- **Funds from venture capitalists**

Venture capitalists are institutional risk takers and are generally a collective group of wealthy individuals, Government assisted sources or major financial institutions. Most specialize in one or a few closely related industries. They have formal, established investment evaluation criteria and place emphasis on capital appreciation through rapid growth.

Venture capitalists have traditionally preferred proven growth businesses with the potential to go public in three to five years. The biotechnology industry has been a favourite of venture capitalists in recent years. The possibility of a public stock offering is critical to the venture capitalists since their investments are normally minority positions that would be difficult to liquidate in any other manner. Venture capitalists are looking for an exit strategy to realize the gain on their investments.

- **Funds from Government assisted equity sources**

There are equity sources that combine governmental assistance and private funds. The Government assistance role is to further social and/or economic policy. Thus, availability and policy changes frequently do occur. This assistance can be in the form of either debt or equity investments and may have greater flexibility than those offering only loans. Those equity sources may also provide straight loans or loans with equity incentives.

- **Sources of borrowed funds**

In start-up situations, a personal guarantee of a loan is commonly required for the lack of equity or proven successful earning history for the company. A guarantee serves as both a decrease in the lender's risk and as a proof of the organizer's commitment to his or her business. Accordingly, the organizer must be prepared to provide "personal signature" on most borrowed funds.

The company can borrow from commercial banks, although commercial banks are usually reluctant to fund initial start-ups. It is important that the organizer establish early personal relationships with a banker so that the banker knows the organizer and the company before you seek funds. Government supported borrowing sources are more likely to invest in small business. There may be small business research grants from the Government which will fund a portion of the company's budget, directed to research or product development. In the USA, the SBIR programme is just one such programme.

- **Choosing the form of business**

Even before writing a business plan, one of the first decisions to be made in organizing a new business is the legal form of the organization. It may be a sole proprietorship, i.e. where the organizer personally owns the business. It may be a partnership where the organizer has a legal agreement with several persons to be partners and share the risk and reward, or it may be a corporation which limits liability and has certain tax consequences. The form of the business has an impact on how investors will react with the organizer and also who will recover ultimate profits from the corporation, as well as what sort of tax obligation the organizer may have from a successful business, or how the organizer can write-off the losses from an unsuccessful business.

- **General assistance to the business from Government and NGOs**

One major way in which the company can attract additional investment or make the company more attractive to investors is through the use of Governmental or NGO assistance so that the private investment is leveraged with Government or NGO derived funds. There may also be

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One major way in which the company can attract additional investment or make the company more attractive to investors is through the use of Governmental or NGO assistance so that the private investment is leveraged with Government or NGO derived funds. There may also be

business assistance programmes that will help in resolving red tape difficulties as far as regulatory matters and registration matters are concerned.

Look at training and technical assistance programmes available in-country and throughout the world to train staff, or as a source of staff for your business.

Look to governmental training and manpower programmes to train business people. There are many programmes available in-country and throughout the world that are not broadly advertised and are only discovered when motivated informed people begin exploring possibilities.

Other very important considerations

A number of decisions concerning the start-up company have to be made in the light of governmental issues such as tax compliance, environmental regulation, site location control and general regulatory compliance at multiple levels. Also business insurance is a matter that should not be neglected. Key to the success of a business is the selection of the consulting or advisory groups surrounding the business, such as lawyers, accountants and bankers. Consider placing key advisors on the Board of Directors and the creation of scientific advisory panels or committees.

B. NEWS AND EVENTS

UNIDO News

Investment and Technology Promotion Programme

Introduction

While the flow of investment and technology towards some developing countries has increased sharply in the past decade, large areas of the developing world have been excluded from this trend. This is one of the reasons why global economic disparities are growing and development gaps within regions are increasing. The majority of developing countries have enormous difficulties in attracting investors to potential industrial projects. In many cases, the problem lies with the investment climate in the country concerned and the lack of entrepreneurial acumen available to promote investment and technology projects effectively. Other limiting factors are the absence of institutional support, lack of managerial skills and restricted financial resources. Uneven investment and technology inflows to different regions of the same country are also a matter of concern, particularly in large developing countries such as China and India.

The ability to take advantage of changing technology and new opportunities in today's competitive business environment is crucial for the survival of emerging industries in the developing countries. Enterprises require up-to-date data on market trends and economic conditions as well as technological information covering a broad range of equipment and machinery, raw materials, spare parts, patents, environmental protection, etc. The advances in electronic networking in recent years have revolutionized access to technical and business-related information.

Unfortunately, not all developing countries have the means to capitalize on these advances. The resulting lack of information on opportunities and options available, especially with respect to new technology, is a major obstacle to many developing country industries.

Without a supporting network of institutions, local enterprises in developing countries are severely hampered when it comes to negotiating the conditions and arrangements for controlling foreign investment and technology inflows.

UNIDO's wealth of experience in industrialization, combined with its world-wide network of contacts, make the Organization an ideal partner for assisting developing countries in their investment and technology promotion efforts. While UNIDO is one of several institutions promoting investment to developing countries, it is the only one with a comprehensive background in industrial development, investment promotion and technology transfer.

UNIDO's comparative strengths

UNIDO has responded to changes in industrial realities and support requirements by re-examining and re-focusing its priorities and introducing internal reforms. The Organization's Mission Statement emphasizes UNIDO's role as a catalyst seeking to harness the joint forces of Government and the private sector. The overall aim is to raise living standard through industrial development.

The Organization has radically changed its programmes to adapt to the needs of a globalized trade and investment system and the changing roles of the public and private sectors, so as to assist developing countries in meeting the new global challenges of competitiveness, technological change and sustainable development. It serves as the international community's principal source of industrial information and as a major intermediary and clearing-house for industrial investment and technology transfer.

Reflecting the complexity of industrial development, UNIDO's work programme is a blend of industrial analyses, technical assistance, investment and technology promotion, and human resource development. Drawing on sectoral expertise and first-hand experience in promoting industrialization in developing countries, UNIDO is in a position to provide a wide range of services to guide manufacturers towards profitable and well-founded international partnerships.

The competitive advantage of UNIDO *vis-à-vis* other organizations engaged in similar activities can be summarized as follows:

- UNIDO is able, through an integrated programme, to provide not only inputs related to investment, but also technology- and industrial information-related matters;
- UNIDO is the only organization in the United Nations system that possesses a wealth of industrial sector knowledge. The application of this knowledge is increasingly used in the design and implementation of the overall investment and technology programme;
- UNIDO's investment promotion network, technology centres and information focal points in developing and developed countries constitute a unique investment and technology promotion mechanism;
- UNIDO works directly, at the operational level, with private enterprises, in particular small and medium enterprises (SMEs), providing comprehensive tailor-made services.

Integrating investment promotion with technology transfer

Foreign investment and technology acquisition now take place within liberalized regimes in most developing countries. However, functioning national capacities are essential to reaping the full benefit of investment and technology flows. Neither the national interest, nor the interest of local and foreign partners will be served if investment and technology flows do not result in viable and cost-effective production. It is essential therefore, that international support is provided, in particular to the less advanced among developing countries, in building competitive industrial supply capacities, strengthening investment promotion agencies and establishing partnerships with overseas investors and technology suppliers. Support is also required in fostering technological development and innovation.

UNIDO's integrated investment and technology promotion programme brings together the Government, private companies and national institutions in an interrelated set of activities that enhances the ability to effectively absorb incoming investment and technology.

The primary goal of the programme is to support developing countries in gaining access to foreign investment resources, technology and know-how, and managerial

skills, as well as in upgrading their domestic capabilities in these fields.

An Integrated Programme—United Republic of Tanzania

The Tanzanian project is a textbook example of UNIDO's integrated investment and technology promotion approach. The programme embraces the range of assistance provided by UNIDO, including:

- Advice to the Government on investment policy, including revision of the investment code;
- Preparation of sectoral studies;
- In-service training including the hosting of a delegate in an Investment Promotion Service (IPS) and training of consultants in project preparation to UNIDO standards;
- Identification, formulation, screening of projects;
- Promotion of investment projects with potential foreign partners through IPS offices, publicity and mailing campaigns, consultants in target countries;
- Country presentation tours;
- Organization of an international investment and technology promotion forum (INTECHMART);
- Follow-up of projects with all participants, in particular those who signed letters of intent at the forum;
- Project Completion Facility for the preparation of pre-investment/marketing studies etc., required to ensure positive investment decisions and implementation.

An INTECHMART was organized in Dar-es-Salaam in November 1996. The forum was particularly successful in promoting business partnerships between Tanzania and other developing countries. The results of the forum in the context of South-South cooperation can be summarized as follows:

- 140 participants from developing countries (India, South Africa, Kenya, Lebanon, Middle East and Gulf countries);
- 72 letters of intent with developing country partners, having a total value of US$ 100.53 million;
- 3 direct foreign investment contracts, also with developing country partners, with a total value of US$ 4.79 million;
- 2 letters of intent for Build-Operate-Transfer (BOT) projects with a total value of US$ 443 million;
- 12 technology transfer agreements for a value of US$ 3.42 million.

To achieve these objectives, the integrated investment and technology promotion programme operates at the following three levels:

Policy level

UNIDO can assist a Government in the formulation and assessment of policies and strategies relating to investment promotion, technology development and transfer by:

- Providing assessed information on recent trends in the international arena;
- Conducting a diagnosis of major constraints and problem areas requiring assistance;
- Analysing a country's investment climate;
- Assessing its technology system;
- Providing advice on how to integrate investment and technology strategies and policies.

Institutional level

UNIDO can help a country build up its capacity to identify, formulate, analyse, appraise and promote investment projects by providing assistance in:

- Establishment/strengthening of a National Investment Promotion Agency;
- Establishment/upgrading of a database on investment opportunities and national investors;
- Strengthening the capability of national institutions to conduct pre-investment studies and feasibility studies;
- Establishment of a UNIDO Investment Promotion Service.

UNIDO can also help a country build up its capacity to render technology promotion and management services, by providing assistance in:

- Establishment/strengthening of National Consultancy and Advisory Agencies;
- Strengthening the capabilities of national institutions to:
  - Conduct, on a self-sufficient basis, training programmes for negotiators of technology transfer;
  - Evaluate technology in connection with the acquisition process.

Enterprise level

UNIDO can help entrepreneurs and promoters in a developing country at different stages of the investment and technology cycle by providing assistance in:

- Identification of opportunities for investment and/or technology transfer;
- Formulation/screening of project profiles and proposals;
- Identification of available technology;
- Promotion of proposals/identification of partners;
- Negotiation of investment projects and technology transactions;
- Preparation of pre-investment studies and feasibility studies;
- Identification/mobilization of financial resources.

UNIDO's Integrated Investment and Technology Programmes not only strengthen the capacity of the national counterpart organizations to promote business partnerships involving the transfer of resources from more advanced countries, but also lead to inflows of resources for industrial expansion, modernization and rehabilitation in the framework of investment projects jointly implemented with foreign partners.

With help from Brazil

Transfer of an integrated package of know-how from Brazil for the development of dairy industries in African countries.

Participating countries: Angola, Botswana, Cameroon, Ethiopia, Guinea, Niger, Sierra Leone, United Republic of Tanzania, Zimbabwe.

While the world is ready to give a helping hand to Africa, the advice and assistance of those who have wrestled with the same sort of social and economic difficulties is particularly valuable.

The Institute of Candido Tostes in Brazil is one of the most important research and training centres in Latin America in dairy industries.

Recognizing that the vast experience of the Candido Tostes Institute makes it an ideal partner in South-South cooperation, UNIDO has organized a number of activities that enabled the Brazilian experience to be put to good use in Africa. Nine participants from selected African countries visited the Institute in July 1995 to assess the full potential of Brazil's dairy industry and discuss how best to tackle the problems of the dairy industry in their respective countries. Upon their return home, they finalized their requirements and presented them at a meeting in August 1995 held in Abidjan (Côte d'Ivoire), with the participation of the African Development Bank.

Several Projects discussed at that meeting are now being implemented.

The most significant advantage of such business partnerships is that they entail the direct operational involvement of the foreign investor in the management of industrial enterprises, thereby contributing to development in the following areas:

- Transfer of process technologies;
- Transfer of managerial and organizational know-how, including skills in operational management, marketing and accounting/financial control;
- Employment creation and human resource development;
- Access to non-traditional markets and diversification of exports;
- Development of the national economy through the creation of forward, backward and horizontal linkages.

Investment and technology promotion: main mechanisms and tools

Over the years, UNIDO has built up an array of investment and technology promotion tools and mechanisms. These are described below.

Investment Promotion Network

Initially, this network consisted of Investment Promotion Services (IPS) located in industrially developed countries. As more countries, developed and developing alike, came to recognize the network's benefits, it has been expanding and diversifying. In 1996, IPS were officially opened in Beijing (China) and in Manama (Bahrain), and reopened in Vienna (Austria). In addition, UNIDO has been contacted by Governments/institutions from Egypt, the Philippines, Thailand and Tunisia, to name only a few.

Investment Promotion Network

The Network is a genuine reflection of UNIDO's role as a neutral "honest broker", bringing together partners from different countries.

At present the Network consists of:

- Investment Promotion Services (IPSs) in the following cities/countries:

Athens (Greece)	Paris (France)
Beijing (China)	Tokyo (Japan)
Istanbul (Turkey)	Vienna (Austria)
Manama (Bahrain)	Warsaw (Poland)
Milan (Italy)	Zurich (Switzerland)

- International Centre of Industrial Cooperation in Moscow (Russian Federation)
- Investment Promotion Initiative-Walloon Region (Belgium)
- Investment and Technology Promotion initiative - New Delhi (India)
- NIMTECH, focal point in Manchester (United Kingdom)
- Investment Promotion Unit - Riyadh, Saudi Arabia (to be established shortly)
- Under negotiation - Egypt, Tunisia, the Philippines.

With its expected rapid expansion in developing countries, the Investment Promotion Network, will become an efficient mechanism for promoting investment and transfer of technology among developing countries.

The role of these services is to establish contacts with enterprises of the host country that are interested in business partnerships with foreign partners, to inform these companies about business conditions, potential business partnership opportunities and sectors of interest in the developing countries, and to assist the potential partners to make contact and negotiate agreements for project implementation.

As the Network is expanding to more developing countries it can be increasingly used to promote investment and technology within the framework of South-South cooperation.

IPS Bahrain—the latest to join the network

In April 1996 IPS Bahrain officially opened. Its characteristics are a strong regional and South-South orientation. The opening ceremony was attended by Heads of existing IPSs, and by 37 senior officials and industry leaders from Kuwait, Lebanon, Oman, Qatar, Saudi Arabia and the United Arab Emirates. Clearly, decision makers in the Gulf region were looking to UNIDO and IPS Bahrain as a gateway to overseas technology and managementskills. Decisions to establish similar offices in other countries immediately followed. The next Office is to be established in Saudi Arabia, while negotiations are under way with Kuwait, Oman, Qatar and the United Arab Emirates. Eventually, a regional network will be in place to contribute to economic and technical cooperation among developing countries in the region.

Delegate programme

One or two national investment promotion officers from the recipient country could be placed in selected IPS offices to promote projects among the respective business communities. These "delegates", who may spend from three months to one year in a selected IPS office, will be in a position to establish dialogue with the business community of the respective IPS country as well as with bilateral agencies and financial institutions, to establish a direct link between the entrepreneurs proposing investment projects and investors of the IPS host country, and to provide continuous updates and information to host country institutions and entrepreneurs.

Brazilian delegate in IPS Paris

The placement of a Brazilian delegate in the IPS Paris represents a tangible example of inter-action with the private sector. The delegate, who took up his assignment in March 1995, was financed jointly by the French Government and two private-sector organizations (National Confederation of Brazilian Industry, Brazilian Micro- and Medium Companies Support Service). The delegate's work formed part of a co-operation programme between Brazil and France, which began in 1992.

The delegate arrived with a portfolio of 337 investment projects. During his assignment, 16 projects for cooperation were concluded between Brazilian and French entrepreneurs, and a further three projects reached an operational phase. The delegate concentrated on cooperation in advanced technology. He established linkages between relevant French organizations, such as the Regional Centre for Innovation and Transfer of Technology, the Agency for Environment and Energy Management, and the French Electrical and Electronic Industry Association, and their Brazilian counterparts. Particular emphasis was placed on industrial cooperation in the electronics industry, precision instruments, bio-technology and building materials. Projects of this nature formed 20 per cent of the overall portfolio of projects.

International technology centres

Through its international technology centres, UNIDO assists developing countries in building up their technological strengths, mobilizing international support and promoting commercial application of new and advanced technologies.

Among these centres are:

- *International Centre for Genetic Engineering and Biotechnology (ICGEB)*

Comprising two components located at Trieste, Italy and New Delhi, India, the Centre forms an interactive network with affiliated centres in Member States. ICGEB develops state-of-the-art research of importance to bio-industries in Member States and strengthens the research capabilities of its members through training, collaborative research programmes and advisory services. The Centre is seeking to advance applications of the latest biotechnologies in public health, nutrition, industrial production, environmental protection/remediation and energy saving.

The Centre was established as an international organization in February 1994, and the transfer of assets from UNIDO to ICGEB were effected in December 1995. To maintain close cooperation between UNIDO and ICGEB, a liaison office has been established at UNIDO Headquarters.

- *International Centre for Science and High Technology (ICS)*

The International Centre for Science and High Technology is intended to strengthen the capabilities of developing countries in applying science and technology to the development of the industrial sector, and in particular to promote the transfer of know-how and closer cooperation between enterprises and R&D institutions. The emphasis is on assisting developing countries' industrial enterprises and R&D centres with technology transfer in specialized fields such as lasers, fibre optics and new materials.

- *International Centre for Application of Solar Energy (CASE)*

The International Centre for Application of Solar Energy was established in 1994 with the mandate to promote the application of solar energy technology in developing countries. The Centre is located in Perth, Australia. In collaboration with UNIDO, the Centre provides the following principal services: assistance in preparing applications for project finance; assistance in training to ensure the proper operation and maintenance of renewable energy systems; support to project implementation and management; consultancy services for feasibility work; and externally funded project definition studies. Typical projects involve photo-voltaic, wind, solar thermal and other systems, technology seminars, and other issues. Projects are based on demand from institutions in developing countries formally requesting UNIDO or CASE assistance.

Within a five-year programme for CASE, 1995 was the first full year of operation. The Centre initiated solar energy activities in Indonesia, Malaysia, Thailand and Viet Nam. In addition, an international workshop on solar energy was held at Perth in October 1995.

International Centre for Materials Evaluation Technology (ICMET)

The preparatory pilot phase started in 1996. The Centre is expected to be full operational in 1998. ICMET is presently established on the premises of the Korea Research Institute of Standards and Science in Taejon (Republic of Korea).

A key function of ICMET is to promote international collaboration among developing countries as well as between them and developed countries in materials evaluation technology, thereby assisting the formulation of national/regional/international standards and codes of practice. In addition, ICMET would serve as a training centre offering the exchange of practical experience in the field of testing and evaluation of new materials.

Reliable methods of testing and evaluation of new materials are crucial for successful development and utilization in competitive industrial products. Hence, ICMET will facilitate the development of standards in order to enable a new product to appear on the market in the shortest possible time.

At present, seven developing countries are participating in the ICMET project: China, India, Indonesia, Republic of Korea, Malaysia, Singapore and Thailand.

Preparatory activities and feasibility studies were completed on the potential establishment of three further global technology centres: an international centre for hydrogen technology in Turkey; an international centre for advancement of manufacturing technology in India, and an international centre for materials evaluation technology in the Republic of Korea.

Industrial information

As a global forum for industrial development, UNIDO has helped build knowledge of industry worldwide by monitoring global economic, political and technological developments as they unfold and assessing their quantitative and qualitative impacts on different regions and countries. Similarly, through technical cooperation it has created a unique bank of information and expertise on technology transfer in a variety of sectors.

The Industrial and Technological Information Bank (INTIB) uses its expertise in collecting, storing, retrieving and disseminating information to exploit the comparative advantage of UNIDO and ensure that this knowledge on industrial development is made as widely available, known and used as possible.

Responding to General Conference resolution GC.5/Res.3 "to provide information services to industry to facilitate the widest possible access of developing countries to technological information on industrial subsectors", the promotion of industrial information is part of the seven thematic priorities of UNIDO. The main objective of the programme in 1995 was to develop and enhance the access of Member States to information sources on industrial technologies and investment opportunities; to support INTIB regional, national and sectoral networks—with a focus on strengthening the regional focal points through advisory and inquiry/referral services—and expanding INTIB national focal points into self-sufficient and self-sustainable industrial information networks. A variety of approaches were used, depending on the status of development of a country, the potential of existing institutions and networks, and the need for training, hardware and software.

Regional information programmes for Africa and Arab countries, Asia and the Pacific, Eastern and Central Europe and NIS and Latin America and the Caribbean were formulated to establish and interlink a global integrated information service for industry to facilitate interregional cooperation in building up technology and investment partnerships. For instance:

- In Africa, the regional project to install the INTIB standard database application and to develop the African network in cooperation with ARCT was implemented for 10 African countries. ITMIN (Industry, Technology and Market Information Network)-type projects were developed for selected countries (Ghana, Kenya).
- In Asia and the Pacific, cooperation was strengthened with APCTT as the INTIB regional focal point. The ITMIN project for Sri Lanka was under implementation. Requests for similar projects were received from Indonesia, Thailand and Viet Nam.
- In Eastern Europe and the NIS, a project for upgrading information services in the region to provide industry and business information for SMEs was developed and considered at the regional workshop on industrial and business information services for SMEs at Bratislava, Slovakia.
- In Latin American and the Caribbean, cooperation was established with RITLA to strengthen information services in the region. ITMIN-type projects for Bolivia, Colombia and Peru were developed under trust fund arrangements.

To increase the flow of technology, including environmentally sustainable technologies, to developing countries, a pilot methodology—consistent with the recommendations of the Commission on Sustainable Development—has been developed by INTIB. The methodology provides comparative analyses of industrial process/technology needs, identified through country surveys, with the technology options available (and their vendors). The pilot application of the methodology was implemented in Peru and Thailand.

A variety of tools and services developed by INTIB support the network members to function more effectively. In particular, the International Referral System serves as a rapid and efficient means of identifying and matching different sources of information in response to enquiries from business communities. The core of the system, which is an inventory of all the specialized sources of information in each Member State of UNIDO, was compiled and produced in computerized format as the World Directory of Industrial and Technological Information Sources.

To provide access to new and emerging technologies, including environmentally friendly technologies, the technology monitors on genetic engineering and biotechnology, microelectronics, advances in materials technology, high technology spin-offs and marine industrial technology were redesigned and merged into a more focused emerging technology series that also include the former Technology Trends Series. This will concentrate on technologies of special significance to developing countries, with closer linkage to the work of international centres, such as ICGEB, ICS and CASE, initiated by UNIDO.

To establish world-wide electronic access to UNIDO information resources, the Organization established its presence on the World Wide Web of the Internet in October 1995. Since its introduction, thousands of requests from over 70 countries were serviced. Efforts also continued to improve the connection of the INTIB focal points to the Internet global communications network and knowledge base. In addition to electronic messaging, this includes access to computerized information resources. Training was provided in the use of the Internet and other interactive networks to gain access to business, technology and investment information. The first workshop took place in Moscow in May 1995 for the NIS countries, followed by workshops held in September at Prague for Central and Eastern Europe and at Bogota for Latin America and Caribbean countries; with similar workshops developed for other regions for implementation in 1996 and beyond.

Methodologies and computer software

In the past, UNIDO published several methodological contributions that have helped in the standardization of approaches to investment analysis and in the improvement of the standard of investment projects (for example, the "Manual for the Preparation of Industrial Feasibility Studies", "Guidelines for Project Evaluation", etc.). Recently, following practical experience gained in technical assistance projects, a new publication has been added to this list—"Guidelines for the Development, Negotiation and Contracting of BOT Projects", which is one of the first practical publications to be used by developing country government agencies involved in such infrastructure projects.

The issues related to the negotiation and implementation of the various types of technology and investment partnerships have been the subject of a consistent normative work over the years. In this connection, UNIDO has developed and published a "Manual on Technology Transfer Negotiation" which extensively covers the range of issues that are relevant throughout the technology acquisition process. Other publications are in preparation, such as a manual on "Technology Transfer through Joint Ventures" and a "Guide on the Negotiation and Management of Strategic Business Alliances".

UNIDO has developed a simple application software PROPSPIN (Project Screening and Pre-appraisal Information System) to assist in the formulation and screening of investment projects.

The Databank for Investment Promotion Programme (DIPP) is a database package designed and copyrighted by UNIDO to automate the maintenance and use of information necessary for an investment promotion programme. It integrates information on projects, national investors and foreign partners as well as on the promotion, negotiation and follow-up of projects.

UNIDO also assists in the preparation of feasibility studies. These analyses are based on the internationally accepted UNIDO guidelines for preparing industrial feasibility analyses. This is further strengthened by the UNIDO Computer Model for Feasibility Analysis and Reporting (COMFAR). This software first released in 1982-1983 has been constantly improved over the years. It is now commercialized in its latest version as COMFAR III Expert.

COMFAR III Expert for Windows

The "COMFAR III Expert for Windows" is the new version of COMFAR, which is in use in 126 countries. Owing to high demand, the software and user manuals have recently been translated into French, German, Polish, Portuguese and Spanish. Arabic, Chinese and Russian versions are expected to be prepared in the future. A more user-friendly version of COMFAR, called "COMFAR III Mini Expert", was developed and released in 1996.

UNIDO continuously improves its methodological approaches, adjusts them to the latest developments in information technology and to the needs of the developing countries. Appropriate training programmes are offered for dissemination of the new approaches.

Advisory services

UNIDO provides counselling and impartial advice to Governments, institutions and enterprises on the main aspects related to the investment and technology cycle, with particular regard to the negotiation and implementation phases. UNIDO can assist negotiators in evaluating proposals and selecting suppliers, appraising technological alternatives, preparing tender documents and drafting agreements. It can also advise entrepreneurs on matters relating to the absorption of technology, the application of the ISO 9000 series and the introduction of quality management practices.

Investment and technology related training programmes

The Training Programme on Investment Project Preparation and Appraisal addresses specific issues of investment project appraisal and helps national promoters (private sector and public institutions) in rational investment decision-making. The programme is designed to suit specific target groups of trainees in the developing countries, as well as in countries in transition, and presents applications of the UNIDO methodology to different types of investment projects (new investment, modernization/expansion, industrial restructuring/rehabilitation, privatization). The content of the training and its presentation are based on a solid theoretical basis and on over 15 years of worldwide accumulated experience in investment project appraisal and related training.

The Training Programme on Technology Transfer Negotiations aims at strengthening the capacities of developing countries to evaluate technology in connection with the acquisition process, to increase their awareness of the range of alternatives available to them and to enhance their capability to negotiate and acquire technology. The Programme organizes different types of training based on the specific needs of the target groups concerned.

Implementation strategy

Within the framework of the South-South cooperation, UNIDO can act as a catalyst in identifying and bringing together partners from developing countries, and thereby establishing efficient South-South cooperation schemes. Given the different levels of industrial development in participating countries, such schemes should enable them to match their needs and capacities and maximize benefits.

Triangular project on South-South Cooperation

UNIDO has started implementation of a project within the framework of South-South Cooperation. The purpose of the project is to upgrade the knowledge of experts from Kyrgyzstan in export-oriented investment project identification and promotion, to attract foreign investments into small- and medium-scale enterprises, and to gain access to the international markets. This project will contribute to cooperation among developing countries through the transfer of Philippine investment know-how to Kyrgyzstan, with the financial support of Japan and through attracting Japanese investments into Kyrgyzstan's economy.

Implementation consists of the following phases:

(a) A workshop on Bishkek jointly organized by UNIDO Headquarters, IPS Tokyo and the Philippine Board of Investment, as well as plant visits to Kyrgyzstan enterprises;

(b) Identification and formulation of export-oriented investment projects by Kyrgyzstan and Philippine experts;

(c) A follow-up programme for 1997-1998 will include:

- (i) Promotion of projects identified by the Kyrgyzstan delegate at IPS Tokyo:
- (ii) Investment promotion tour of businessmen to enterprises in Kyrgyzstan;
- (iii) Preparation of feasibility studies for selected projects;
- (iv) Preparation of an investor's Guide to Kyrgyzstan;
- (v) An investment forum to enable potential investors and entrepreneurs to hold face-to-face bilateral negotiations on investment projects.

The countries involved, and UNIDO, could therefore join efforts to develop either integrated investment and technology promotion programmes, or individual projects/services. To get these programmes/projects off the ground, UNIDO will assist its partners—the Government, national institutions and entrepreneurial associations—to conduct a detailed assessment of the country's situation, define an integrated package of services or individual projects to suit their specific requirements, and identify the financial resources required for implementation.

The actual content of such programmes/projects could vary, depending on a number of factors, such as the country's perceived needs, the size of markets and the potential opportunities that exist. The assistance to be provided by UNIDO can only be part of a much bigger effort at the national level.

In order to produce a concrete impact and to achieve sustainability, UNIDO will, from the beginning, mobilize the synergies and cooperation of all the parties concerned, with particular regard to entrepreneurial associations and enterprises.

UNIDO and the Common Fund for Commodities collaborate

The Amsterdam-based financial institution, the Common Fund for Commodities (CFC), has requested UNIDO to carry out a project on sisal and henequen fibres in Kenya and Tanzania. The project's total value is $5.4 million, $3.3 million of which will be implemented by UNIDO. Contributors are CFC, the International Fund for Agricultural Development, the two countries concerned, Belgium and UNIDO.

CFC started operations in 1989 and was created as a key instrument for achieving the objectives of the Integrated Programme for Commodities, which was designed by UNCTAD (UN Conference on Trade and Development). CFC finances, through its First Account, buffer stock operations as well as actions to develop markets and, through its Second Account, projects to improve structural conditions in markets and to enhance the long-term competitiveness of particular commodities. For the Second Account, emphasis is placed on the need of African countries and the least developed countries to diversify their primary commodities on which they depend for export earnings. Activities include modernizing and improving production, distribution and marketing systems, and stabilizing and increasing export earnings, despite the fall in prices of most primary commodities. Another aspect is developing new uses for commodities and uses for by-products that were formerly discarded.

World production of sisal and henequen has stagnated during the last 10 years and is half that of 1970. One reasons is the emergence of synthetic substitutes—polypropylene polymer—as baler twine for harvesting. Consequently, future demand for sisal is expected to be in the form of speciality papers, carpets and animal feed.

UNIDO's technical expertise in manufacturing pulp and paper was the reason why CFC chose the Organization to execute the sisal and henequen project. UNIDO will develop new end-uses for sisal and henequen—especially paper, animal feed and biomass—and a strategy for marketing the final products, and evaluate their sales potential.

"The project is a good example of strengthening the link between industry and agriculture as it includes elements of the whole chain of production, from agricultural studies to processing and marketing the products" says Rosely Viegas Assumpçao, the senior industrial development officer who is handling the project at UNIDO Headquarters. She will be working closely with the Kenya Sisal Board and the Tanzania Sisal Authority in introducing new varieties of sisal, improving production and processing, converting waste and unused plant materials into valuable products, carrying out research and development

and market trials for the new products, disseminating technology and attracting investors.

Although the groundwork will be carried out in Kenya and Tanzania, its results will be disseminated to other sisal- and henequen-producing countries (e.g. Brazil, China, Haiti, Madagascar and the Philippines) in keeping with CFC policy.

Hopes are high that the sisal and henequen project will be the first of a series of projects resulting from co-operation between UNIDO and CFC and the international commodity bodies responsible for specific commodities. Adrie De Groot, Chief of the Coordination of Funds Mobilization Section, says: "Targeted development of projects dealing with processing of agricultural commodities and diversification of end-products should be pursued under the new UNIDO priorities in close co-operation with CFC". Other commodities for which CFC is interested in developing projects with UNIDO—in the order of about $9 million—are cashew, sorghum, timber, abaca and copra (dried coconut). Sisal and henequen may be the first commodities to tie up cooperation between UNIDO and CFC, but they are hopefully not the last to do so.

Today's opportunities—tomorrow's industries

Montreal Protocol. The Executive Committee of the Multilateral Fund for the Implementation of the Montreal Protocol, meeting in May 1996, approved 16 new investment projects worth almost $4.7 million for execution in 11 countries. The aim is to phase out the industrial use of chlorofluorocarbons and other ozone-depleting substances used in refrigerants, foams, solvents, aerosols, halons and nethyl bromide. UNIDO's activities on behalf of the Protocol now cover 160 projects, valued at about $80,038,221, excluding support costs in 41 countries.

Regional Europe. The Netherlands is funding a regional project to establish high-tech business incubation facilities in selected scientific institutes in the Czech Republic, Hungary, Poland and Slovakia, with a view to expanding them into science parks. Later the experience gained could be useful to less developed countries. Project allotment: $1,578,610. US/RER/95/145.

Bulgaria. EMIS, a State-owned company manufacturing water purification equipment, is to start producing more advanced and environmentally friendly water treatment systems using reverse osmosis techniques. By meeting international standards, the quality of the water supplied to the health-care system, the public and the pharmaceutical industry will be improved. Project allotment: $65,000. SI/BUL/96/801.

Gambia. An industrial statistician and a systems analyst are to assist the Ministry of Trade, Industry and Employment survey local manufacturing enterprises, using National Industrial Statistics programme software developed by UNIDO. The data on economic indicators will be a reliable source for policy-making and investment decisions and enable the country to promote its small-scale manufacturing base. Project allotment: $120,000. XA/GAM/96/624.

Kyrgyzstan. Philippine know-how is to be transferred to Kyrgystan in an export-oriented investment-promotion project financed by the Government of Japan. Staff from the Kyrgyz State Commission on Foreign Investments, the Ministries of Finance and Economy, and the National Bank will be trained in identifying, preparing, appraising, screening and promoting investment projects so that a portfolio of 60-70 project profiles can be promoted through the Investment Promotion Service office in Tokyo. An investment promotion tour and forum for Japanese entrepreneurs in Kyrgyzstan are also planned. Project allotment: $100,000. TF/KYR/95/A10.

Mali. Belgium is funding a project to assist women entrepreneurs make their food-processing businesses more efficient and competitive. The project is part of a high-impact programme providing assistance to one of Africa's least developed countries. Project allotment: $1,075,760. US.MLI/96/106.

Mauritania. Following a similar project in Senegal that enabled fish exports to meet the standards of the European Union, good manufacturing practices and hazard-analysis-critical-control-point procedures will be introduced in fish-processing enterprises. Assistance will also be given to the Centre National de Recherches Oceanographiques et des Peches so that it can provide technical support to the enterprises. Project allotment: $177,000. XA/MAU/96/630.

Russian Federation. In phase two of a project to restructure and revitalize industry in the Kalingrad region, funded by Denmark, Finland, Norway and Sweden, a regional strategy will be devised including the creation of a favourable business climate. Programmes for the restructuring of industrial enterprises will be elaborated and industry-related services strengthened. Project allotment: $370,000. TF/RUS/94/001.

UN and other organizations' news

International biotechnology centre opens in Delhi with plea for cash

The final step in establishing the International Centre for Genetic Engineering and Biotechnology (ICGEB) took place in February with the opening of a new building for the Centre's laboratories in New Delhi, after occupying temporary accommodation for the past nine years.

The Centre's other base at Trieste in Italy moved into new laboratories last year.

One major task is still left—ensuring that the Centre will be able to attract the financial support that it needs to run its research programmes.

Until now, the two host countries, Italy and India, backed by donations from international agencies, have met the Centre's expenses of US$ 12 million a year. "Other member countries will have to start paying from 1999", says Arturo Falaschi, the director of ICGEB. "That is the deadline". The Governments of 35 countries have so far ratified agreements with the ICGEB.

ICGEB, with its structure of twin laboratories, was set up in 1986 by the United Nations Industrial Development Organization (UNIDO) to ensure that developing countries are able to share the benefits of biotechnology. This objective has been achieved with about 230 scientists from 28 countries now working at the Centre's two laboratories, and 400 more receiving short-term training each year.

Since February 1994, the Centre has operated independently of UNIDO. Important contributions from the New Delhi laboratory include a new peptide vaccine for hepatitis B, and the isolation of a gene able to impart viral resistance to crops. An inexpensive AIDS diagnostic kit developed at the Centre was put on the market in India last month, and will soon be produced locally in Nigeria, Sudan and Morocco. (Source: *Nature*, Vol. 380, 7 March 1996)

Cancer therapeutic in demand

International pharmaceutical producers are seeking access to a drug developed by the Braunschweig-based German State-owned biotechnology "think tank" GBF, which is believed to have considerable potential as a cancer therapeutic.

GBF holds a German patent for epothilon, a substance related to taxol, but believed to be less toxic. Recent tests in the US have shown the drug, originally developed as a herbicide, is effective against 60 different types of tumours, especially breast and colon cancers.

GBF admits that it initially failed to recognize epothilon's potential in cancer therapy. This was discovered by Merck Sharp & Dohme in its search for less toxic alternatives to taxol. Epothilon has several advantages over taxol. It is water-soluble, eliminating the need to add solvents, which can cause side effects. It also adheres to individual cells longer, increasing its effectiveness.

Although GBF's patent extends only to Germany, it owns the production technology and the bacteria with which it is manufactured. GBF says that it is interested in finding a partner to finance clinical trials. (Source: *European Chemical News*, 3-9 June 1996)

Biosafety issues

The Biodiversity Convention: decisions made at Second Conference of Parties

As a mechanism for the progress being made at the Conference of Parties (COP-1, COP-2) towards a possible biosafety protocol associated with the Biodiversity Convention, COP-2 decided to establish an "open-ended *ad hoc* group", whose membership is open to all interested countries. This Group will meet in Denmark in July 1996, and is charged with endeavouring to complete its work in 1998. COP-2's Decision on Biosafety mentions two important articles[1]. The resulting negotiations will include the following issues:

- All activities related to living modified organisms (LMOs) resulting from modern biotechnology that may have adverse effect on the conservation and sustainable use of biological diversity, including research, development, handling, transfer, use and disposal;
- Transboundary movement of LMOs resulting from modern biotechnology and other transboundary issues, including unintended movement of LMOs resulting from modern biotechnology across national boundaries, and their potential adverse effects;
- The release of LMOs resulting from modern biotechnology in centres of origin and genetic diversity;
- Mechanisms for risk assessment and management;
- Procedure for advance informed agreement;
- Facilitation of exchange of information from all publicly available sources, including local communities;
- Capacity building in all the aspects required for biosafety;
- Implementation mechanisms;
- Definition of terms.

It should be noted that these are issues to be addressed in the negotiations, but whether the eventual Protocol will cover each issue is yet to be decided. Although the focus is to be on transboundary movements of genetically modified organisms and procedures for a system of advance informed agreement, the Group will also consider the inclusion of the following issues:

- Socio-economic considerations;
- Liability and compensation;
- Financial issues.

A number of parties are thought to oppose the inclusion of the latter issues in any protocol.

UNEP'S International Technical Guidelines for Safety in Biotechnology

COP-2's Decision on a biosafety Protocol explicitly mentions the UNEP International Technical Guidelines, and they are therefore likely to be an important ingredient in future Protocol negotiations. The Guidelines arose from an original draft produced by the Netherlands and the United Kingdom Governments.

UNEP held seven regional consultations and a Global consultation on the UNEP Guidelines was held in Cairo, Egypt, from 11-14 December 1995. The Cairo meeting was attended by 1-2 person delegations representing 59 countries, as well as representatives of 6 intergovernmental and non-Government organizations and the Biodiversity Convention Secretariat, and negotiations on the text were rather protracted.

It was agreed by the Cairo meeting that agreement on the guidelines by a meeting of technical experts did not constitute formal Government endorsement, and that Governments should be given the opportunity to examine the guidelines in their final form in order to consider their possible implementation and their possible implications for a Biosafety Protocol.

One particularly important issue was the definition of the term *organisms with novel traits* (ONTs). This was resolved only at the very end of the meeting and only after protracted and intense negotiations, particularly by the US, Japanese and Norwegian delegations. The finally agreed definition for ONTs was:

> *Organisms produced by genetic modification and whose genetic make-up is unlikely to occur in nature. These do not include organisms produced by conventional techniques and traditional breeding.*

This definition is tied to the following agreed definition of *genetic modification:*

> *Modern biotechnology used to alter the genetic material of living cells or organisms in order to make them capable of producing new substances or performing new functions.*

This definition would seem, for example, to include hybridomas used to generate monoclonal antibodies. In

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[1] Namely:
Article 19.4. *Each Contracting Party shall...provide any available information about the use and safety regulations required by that Contracting Party in handling such* [living modified] *organisms, as well as any available information on the potential adverse impact of the specific organisms concerned, to the Contracting Party into which those organisms are to be introduced.* Article 8(g) requires Parties, as far as possible, to *establish or maintain means to regulate, manage or control the risks associated with the use and release of living modified organisms resulting from biotechnology which are likely to have adverse environmental impacts that could affect the conservation and sustainable use of biological diversity, taking also into account the risks to human health.*

Australia, for instance, a working definition of *genetically modified organisms* is:

> *Organisms produced through the use of recombinant DNA technology, and organisms in which the genetic material has been altered in a way that does not occur naturally by spontaneous mutation, mating and/or natural recombination.*

The Guidelines consist of the following sections:

Introduction

Broad background, plus issues and considerations. Includes a statement of common elements and principles derived from relevant national, regional and international instruments, regulations and guidelines.

General principles and considerations

Covers principles and considerations relevant to risk assessment and risk management.

Assessment and management of risks

Key parameters for assessment of risks to human health and the environment. The role of international databases.

Providing for safety: mechanisms at national and regional level

Effective biosafety mechanisms.

Providing for safety: mechanisms at international level using information supply and exchange

Includes exchange of general information; supply of information when the use of novel organisms could affect another country; and supply of information related to transboundary transfer of novel organisms.

Capacity building

The need for building the capacity of countries to implement the guidelines.

Annexes

1. Sources consulted in preparation of these guidelines and other relevant sources.
2. Glossary of terms used in these guidelines.
3. Risk assessment: examples of points to consider, as appropriate.
4. Examples of risk-management measures for controlled applications.
5. Examples of risk-management measures for controlled releases.
6. Databases.
7. Possible mechanisms for providing information to the public.

(Source: *Australasian Biotechnology*, Vol. 6, No. 2, April 1996)

Ethical issues

About-face on Bioethics Convention

In an apparent about-face on the part of the European Commission, research commissioner Edith Cresson has suggested that the European Union is unlikely to sign an eventual European Bioethics Convention on medical research and genetics—although individual member States would be free to proceed with national ratifications.

EU accession to the Convention being drafted by the 39-nation Council of Europe has previously figured in the Commission's published annual work programme.

Ms. Cresson had referred to doubts as to whether the Commission enjoyed powers under EU treaties to commit Member States to the kind of wide-ranging human rights obligations which would be imposed by the Convention.

These uncertainties have grown in recent months, in the light of wider discussions on the supremacy of international law, in the form of conventions, over EU legislation.

The EU's Court of Justice in Luxembourg has warned that if the EU were to accede to the European Convention on Human Rights, this would in effect make the European Court of Human Rights in Strasbourg the court of final appeal on interpretation of EU law.

Further complications would arise if, as seems likely, the Bioethics Convention were to include a mechanism allowing individual signatories to enter reservations against particular provisions or against application of the Convention in particular territories (for example, overseas territories in the case of France). Source: *Biotechnology Business News*, 22 May 1996)

UK ethics report clears xenografts

The UK's main bioethics advisory group has given the green light to xenotransplantation—the transplantation into humans of organs taken from other animals—and endorsed the use of pigs, rather than primates such as chimpanzees and baboons, as the most acceptable source of such organs.

At the same time, the bioethics group points out in a report published in early 1996 that there is still considerable uncertainty about the potential hazards of xenotransplantation.

No clinical trials of the technique should be permitted, it therefore suggests, until the Government has set up a new Advisory Committee on Transplantation, and this committee has given its approval to the proposed trials.

The report has been produced by a ten-member working party set up by the Nuffield Council on Bioethics. It comes at a time of growing interest in xenotransplantation, not only because of the growing gap between the number of patients awaiting transplants and the supply of human organs, but also because of hopes that some of the main scientific hurdles—such as the "hyperacute rejection" of pig organs by humans—may be close to resolution through genetic engineering.

The working group, which was chaired by Albert Weale, professor of Government at the University of Essex, concludes that the development of xenotransplantation "should continue", provided it is subject to "rigorous regulation" to ensure both the protection of potential human recipients and adequate care of the animals involved.

Given both ethical concerns about using primates such as chimpanzees which are widely seen as closer biologically to humans than other animals, and the potential threat of extinction that could result from the wide-scale use of primates for transplant organs, the working group suggests that "non-primate species should be regarded as the source animals of choice". Indeed, it says that the breeding of pigs to supply organs for transplantation "would be ethically justified".

But the working group also concludes that the risks associated with the possible transmission of infectious diseases, including, for example, the spread of currently unknown animal viruses in humans that might be difficult to control, "have not been adequately dealt with". In the light of such uncertainty, it recommends a cautious approach, in particular stating that at present "it would not be ethical to begin clinical trials of xenotransplantation involving human beings".

The group says that standards and mechanisms for monitoring xenograft recipients and for action to be taken in case of disease transmission "should be in place before human trials begin". It suggests that the proposed advisory committee should be responsible both for developing these procedures and ensuring that they are properly applied. But it also admits that the setting up of such a committee is likely to encounter some reluctance from the UK Department of Health. (Source: *Nature, Vol. 380*, 7 March 1996)

Regulatory issues

Japan, Europe move to accept GMOs

Japan's Ministry of Health and Welfare is accepting formal applications for the approval of genetically modified organisms. The Ministry intends to announce approvals for all species (canola, soybeans, corn, potatoes) at one time. As numerous transgenic varieties such as corn and soybeans from the US come into commercial production Japan may not require specific approval of every variety.

Meanwhile, the European Commission has allowed the marketing of genetically modified rapeseed for seed breeding. The rapeseed variety resistant to the herbicide Basta cannot be used for human consumption. However, a majority of member States agreed to the marketing of the variety for breeding purposes without a label stating that it is genetically engineered. The label will simply state that the variety is herbicide resistant. (Source: *The AgBiotech Bulletin*, March 1996)

The Biodiversity Convention Summary of Progress in Negotiations

One of the most significant outcomes of the United Nations Conference on Environment and Development held in Rio de Janeiro in June 1992 was the introduction of the Convention on Biological Diversity (often abbreviated to the Biodiversity Convention). The Convention's aims are, as the name implies, the conservation of biological diversity, the sustainable use of its components and the fair and equitable sharing of benefits arising from the use of genetic resources.

The process of negotiating and implementing international conventions is a complex one which involves a substantial specialist vocabulary. A nation goes through a three-stage process to become a "party" to a convention. Firstly, it becomes a "signatory" to a treaty which indicates a willingness to be bound by the convention and not take actions inconsistent with it. Secondly, the nation demonstrates a readiness to be bound by ratifying, acceding or accepting the provisions of the convention. The final stage involves the despatch of an instrument of ratification, acceptance or approval (i.e. a letter) from the national Government to the convention secretariat stating that the convention is consistent with and/or has been introduced into the domestic law of that country. The convention enters into force after a designated number of countries have reached the last stage. The Biodiversity Convention was signed by a number of countries at the Rio conference and came into force on 29 December 1993. It has now been ratified by more than 130 countries including Australia, but notably not the United States.

Countries which are parties to a convention may also, through a similar three-stage process, have the choice not only of becoming parties to legally binding instruments, known as protocols, that may be subsequently negotiated to give effect to the aims and objectives of the convention.

The need for protocols and the terms of reference for their negotiation are determined at meetings held under the auspices of Conferences of the Parties (COPs), where attendance is not, as the name implies, limited to parties to the convention but includes observers from countries which have not ratified the convention, UN agencies and intergovernmental organizations (such as the OECD) as well as non-governmental organizations (NGOs) lobbying on behalf of interest groups such as the environmental movement and industry. However, participation in official decision-making is restricted to parties to the convention.

Because of the large number of countries involved, countries are grouped in regional blocks in order to make the negotiation process manageable. Australia, for example, is in the "Western Europe and Others Group". Issues are often progressed through small contact groups which consist of nominated members of two or three regional groups. In addition, out of session work is often conducted through so-called Ad Hoc Groups of Experts which are convened to prepare position papers for consideration at COPs.

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(Source: *Australasian Biotechnology*, Vol. 6, No. 2, April 1996)

General

Europe's robust growth catches investors' eyes

Europe's entrepreneurial biotechnology industry is showing robust growth, creating value from what has been considered to be a volatile environment.

A report by consultancy Ernst & Young presented to the European Life Sciences conference in Amsterdam in April, reveals that total revenues from small to medium-sized European bioscience companies grew some 20 per cent in 1995 to $1.48 billion, while spending on research and development increased and net losses declined.

The report forecasts that 1996 will see the acquisition of European biotechnology companies by large pharmaceutical firms. European biotechnology companies were relatively successful in raising funds during 1995, in spite of a slow start to the year when a number of prominent bioscience companies had to unveil disappointing biotechnology news. Figures compiled by Ernst & Young and the Oxford-based newsletter *BioBusiness* confirm that Europe is regaining some of the ground it lost to the US sector in the past decade. Also, the consolidation within the pharmaceutical industry and the emergence of public capital markets for bioscience companies in Europe are expected to close the gap between the US and Europe even faster. (Extracted from *European Chemical News*, 22-28 April 1996)

Cost of producing new drugs

The costs of producing new drugs are escalating and the chances of securing a decent return on research and development investment are dwindling. Lehman Brothers advise collaboration with the biotechnology sector. Lehman Brothers has calculated that $4 billion spent on R&D in 1980 produced sales in 1990 of $105 billion. This is a return on expenditure of 22 per cent per year.

But getting adequate returns is increasingly difficult. A company that spent $29 billion pre-tax in 1994 would need sales of $227 billion in 2004 to achieve a reduced return of 12 per cent. This assumes a market growth of 9 per cent which is unlikely, making the return look equally uncertain.

In the early 1980s, R&D was 5-8 per cent of sales and was rewarded by a market growing at 10 per cent per year. In the early 1990s, R&D is now 15 per cent of sales and must be recouped in a market growing at 5-7 per cent per year.

Companies have two ways to fight against diminishing returns. They can lower the cost of producing new drugs or they can "widen the base of innovation".

However, the cost of churning out new molecules is increasing. Lehman has calculated that it cost $600 million on average in 1995 to get a new molecule to market. This includes the costs of failing compounds, research, infrastructure and personnel. This figure is confirmed by considering that industry spent more than $25 billion on R&D in 1995 and produced about 40 new molecules.

More and more pharmaceutical companies are looking to increase innovation by turning to biotechnology companies. By the next century, about half of the drugs arriving at the market will have come from the biotechnology sector.

Biotechnology companies spend $4 billion on R&D and employ upwards of 35,000 research staff. In comparison, pharmaceutical companies invest $8 billion on research and employ 80,000 staff, but numbers are falling.

A biotechnology company can spend $350 million on in-house R&D to produce a massive return of 90 per cent. Collaborative development cuts the costs to $130 million with royalties of 15 per cent lowering the return to 75 per cent. In contrast, a pharmaceutical company will only achieve a 50 per cent return by spending $440 million on R&D. A similar collaborative development programme with an investment of $265 million achieves a 75 per cent return.

It is not surprising then that pharmaceutical companies are seeking collaborations as the answer to their problems. The advantages are several, including access to innovative technologies and better returns on R&D spending.

The biotechnology companies also stand to gain. They too can receive a superior return on R&D spent, but they can also secure attractive terms for their new products and gain access to faster, more efficient product development and up to 45 per cent of trading profit. In addition, investors are reassured by the partnership of a large company.

This acknowledgement of mutual gain is reflected in the growing number and size of deals in the biotechnology sector. In 1995, there were almost 60 agreements compared with 35 in 1991.

By 1997 the top ten companies will only be producing about six new molecules a year. Only the Japanese are increasing the number of new molecules they produce. However, by 1999, the biotechnology sector will produce 14-24 new molecules per year.

The pharmaceutical industry is faced with increasing productivity without jeopardizing quality. One approach is to participate in more external collaborations with biotechnology companies and academia. Another is to detach the research function from the corporate structure where scientific creativity is stifled and make it semi-autonomous, informal and less bureaucratic. (Source: *Chemistry & Industry*, 18 March 1996)

Technology is the key to future success

The world drugs market is set to change dramatically over the next five years, predicts a report from investment bank Lehman Brothers*. Familiar blockbuster drugs will sink without trace, to be replaced by biotechnology-derived treatments. Major drugs companies will also abandon their appetite for mega-mergers in favour of collaborating with small firms specializing in new technologies.

The report surveys "blockbuster" drugs, classed as those with sales of over $500 million. Generic competition will force most of the changes, it says. Revenues from

*"PharmaPipelines"; contact Judith Bower. Tel.: +44-171-601 0011; e-mail judith bower@gbccmail.lehman.com (Source: *Chemistry & Industry*, 15 January 1996)

gastrointestinal drugs, cardiovascular agents and antibiotics are all set to fall by up to a tenth over the next five years. They will still be the largest drugs sectors, however, each accounting for around 10 per cent of the $101 billion predicted market for blockbusters.

The fastest growing categories will be osteoporosis drugs, antiviral and immune system agents, drugs affecting red blood cells, and cancer treatments. Sales of biotechnology drugs will almost double, from $9.5 billion or 11 per cent of total blockbuster sales in 1994, to $17 billion or 17 per cent of the total in the year 2000. But despite these impressive-sounding projections, the pharmaceutical industry is faced by a paradox, says the report. A strong R&D department no longer guarantees a satisfactory return on sales; but without R&D, there will be no new drugs.

The solution is to reduce even further the cost of developing a new drug. Mergers help, but they do not tackle the whole issue, as "no company—no matter how large—has a monopoly on good ideas". Technology, not size, will be the key to success, it predicts, and with the rate of innovation increasing, the only way for firms to widen their technology base is to collaborate with specialists.

Small companies will supply at least half of the technologies for discovering and developing new drugs in the opening decade of the twenty-first century, the report continues. The advantages are huge: in-house development of a successful product will cost $205 million and achieve about 225 per cent return on sales, but a collaborative project will cost only $40 million, generating a 475 per cent return. Moreover, it adds, collaborative projects can generate new launches about every ten months, instead of four years for in-house R&D.

Bioremediation growth to slow but stay in double digits to the year 2000

The US market for bioremediation products and services will grow at a robust 15.8 per cent from 1995 to the year 2000, when it will achieve revenues of $475 million, according to a new study by FIND/SVP, Inc.

While still dramatic, this rate of expansion represents a slowdown from 19.1 per cent between 1990 and 1995, 75.6 per cent from 1986 to 1990, and almost 42 per cent in the combined period of 1986 to 1995, according to the report, "*The Market for Bioremediation Products and Services*".

In 1995, the bioremediation product and service market broke through the $200 million barrier set in 1994 as revenues jumped 14.0 per cent to $228 million. This year they are projected to exceed the quarter-billion-dollar mark, rising to $265 million by the end of 1996.

As to the portion of this development that represents genetically engineered processes, "There is [said to be] no significant commercial data", said Arthur Mayer, the market research consultant who authored the study for FIND/SVP. Because of regulatory and public concerns of the possible effects of bioengineered organisms on the environment, what little of these products are available are in "closed systems", such as bioreactors.

Based on discussion with bioremediation experts, genetically engineered forms of bioremediation are not expected to undergo any significant commercial development for the next 5 to 10 years.

The growth of bioremediation based on naturally occurring micro-organisms and processes, meanwhile, will continue to depend on Government spending.

One of the biggest markets for bioremediation in the forecast period from 1996 to the year 2000 will be leaking underground storage tanks, which have been contaminated largely by petroleum hydrocarbons, one of the most easily biodegraded compounds, Mayer's study predicts.

In addition, private-party transactions such as real estate transfers and mergers and acquisitions will promote site remediation activity. And State environmental enforcement and remediation activity at the State level "will also increase, encouraged by the new, decentralizing Congress".

The Superfund market, meanwhile, is expected to decline in importance, with fewer sites undergoing remediation as a result of risk-based and future-use cleanup decisions. However, the report notes, "there will be cases where bioremediation's favourable cost profile lands contracts even in the face of declining expenditures".

The results of all these forces will be continued expansion of the bioremediation, but at a rate "substantially lower than it was during the 1980s and early 1990s" states FIND/SVP. Among the decelerating factors will be competition within the industry, from other remediation technologies and the eventual limits of its own technology.

Looking at the competitive trends in the industry, the report sees some deep structural shifts occurring. New types of companies are entering the business and the size of the competitors is changing.

Pharmaceutical companies with their own remediation needs, or an interest in new applications for biotechnology, are beginning to enter the market to compete with the more established hazardous waste management and remediation firms, the study reports. Also, incineration vendors have diversified into bioremediation to minimize the risk of their declining market.

Also, the end-users of bioremediation services—especially oil and chemical companies—have "integrated backwards" into the business or are engaged in cooperative research, the FIND/SVP study notes.

For further information on this report, contact FIND/SVP, Department RGX, 625 Avenue of the Americas, New York, NY 10011-2002; Tel.: 212-645-4500. (Source: *McGraw Hill's Biotechnology Newswatch*, 4 March 1996)

The Basel merger

Ciba (Basel, Switzerland) and Sandoz (Basel) have unveiled plans to merge into the world's largest life science group. The two Swiss companies took the market—and their own employees—by surprise when they announced their intention to conduct what is possibly the world's biggest corporate merger and certainly the largest life sciences merger and create a newly christened entity, Novartis. The deal has been estimated to be worth some $27 billion.

Novartis plans to focus on its core life sciences business: pharmaceuticals, agrochemicals and seeds, and nutrition. It intends to spin off Ciba's speciality chemicals business and the Sandoz construction chemicals operations. Novartis will immediately take top positions in the leading life science markets.

In pharmaceutical sales, it will be the world's second largest company after Glaxo Wellcome (London), but ahead of Merck Sharp & Dohme (Rahway, NJ), Hoechst Marion Roussel (Frankfurt, Germany) and Bristol Myers Squibb (Princeton, NJ).

In crop protection and pest control, the combined firm will be able to build on Ciba's number one position in the world market. In the seeds sector, the combined sales will

create the world's second largest business—after Pioneer Hi-Bred (Des Moines, IL).

Another tier for the new company will be its nutrition business. Novartis will be Europe's largest health-food producer and the number two company in the world medical nutrition market.

The importance of biotechnology expertise to the future of the pharmaceutical industry is reflected in mainstream business commentaries on the Novartis merger, which have focused heavily on the biotechnology relationships between the two companies.

Novartis will also emerge as one of the major players in the development of agricultural biotechnology. The company's seed product line includes high value added varieties in corn, oilseeds, sugar beet, vegetables and flowers. It will have one of the broadest investments in breeding and a substantial germplasm base, as well as one of the largest and most focused biotechnology research commitments. Novartis will be looking to roll out maize resistant to the European corn borer, while continuing to engineer both disease and insect resistance into other crops.

Through equity holdings and research and development collaborations made in the past five years, Novartis will have links with more than 20 biotechnology companies. And it seems unlikely that Novartis will abandon active biopartnering. (Extracted from *Nature Biotechnology*, Volume 14, April 1996)

Japan's DNA industry to reach ten trillion yen by 2010

The DNA Industry Study Group of the Basic Industry Bureau of the Ministry of International Trade and Industry (MITI), chaired by Professor Emeritus Itaru Watanabe of the School of Medicine, Keio University, has compiled its final report.

In this report, the DNA industry is defined as a general term for industries engaged in clarification of biofunctions at the DNA level, and utilization of this knowledge at the industrial level.

The actual fields include:

- DNA diagnosis and characterization of individuals;
- Techniques which mimic life phenomena;
- Utilization of conventional DNA technology such as recombinant technology;
- DNA analysers and processors.

DNA diagnosis is currently used for viral infections, malignant tumours and hereditary diseases mainly in university hospitals, and the market is about 3 billion yen. However, this market should show a major expansion with the development of simpler test methods.

With respect to drugs and medical treatment, it is expected that immunosuppressants and antibody preparations for treatment of cardiovascular diseases and malignant tumours will increase in the future.

According to the Basic Problems Subcommittee of the MITI's Industrial Structure Council, the DNA industry should reach 10 trillion yen by the year 2010. (Source: *McGraw Hill's Biotechnology Newswatch*, 15 April 1996)

Biotechnology investment boom continues

If the upward trend continues, the amount invested in the biotechnology company sector through public stock offerings and private financing in 1996 could break all records. Biotechnology's previous boom year was 1991, when over $4.5 billion of new money went into the sector. The first quarter took 1996 almost halfway to that total, with $1.955 billion raised in initial public offerings (IPOs), secondary public offerings, and venture capital, and other deals.

Perhaps the most consistent trend over the past 12 months has been the steady rise in the value of IPOs. This has increased every quarter since the beginning of 1995.

The rising market for biotechnology companies' stocks seems not to have been anticipated by most companies. The lag between the mid-1995 market recovery and the recent flurry of IPOs suggests that many companies have had to plan their market launch offerings from a standing start.

Mathematicians would urge caution in extrapolating too optimistically. Today's rising curve of investment may continue, or it may be at its peak. What really counts though, is that small corporate biotechnology enterprises already have $2 billion "in the bag" this year. (Extracted from *Nature Biotechnology*, Volume 14, May 1996)

BASF/Mitotix in deal

BASF Pharma has struck a five-year research collaboration deal with US-based biotechnology company Mitotix, aimed at discovering novel anti-cancer drugs.

The two companies will work together on drugs which target human cdc25, enzymes which regulate cell division. BASF has commercialization rights in the US and Europe, while Japanese rights will be jointly owned.

Meanwhile, BASF Bioresearch has bought exclusive rights to the "TET" systems developed by Hermann Bujard at the Heidelberg University centre for molecular biology.

The system allows precise steering of gene expression through dosage of the antibiotic tetracycline. According to BASF it is the "only method that promises a high degree of success" in experiments with animals.

The technology can be used in gene therapy, in research with transgenic animals and new primary cell lines; in the development of screening procedures in biological process technology; and in molecular biological research.

BASF plans not only to use the TET system in its own research, but also intends to develop it in joint R&D pacts with other pharmaceutical producers. (Source: *European Chemical News*, 3-9 June 1996)

Seed banks fall on hard times

A million varieties of agricultural plants are threatened with extinction because the gene banks in which they are stored are badly equipped and poorly funded, says the United Nations Food and Agriculture Organization. The world needs to invest up to $3 billion over the next decade to prevent an "alarming" loss of genetic diversity, warn FAO scientists.

The first comprehensive analysis of the world's crop of genetic resources was presented to scientists and ministers from more than a hundred countries in Rome. A report scheduled to be launched by the FAO, concludes that more than half the world's 1,300 stores for rare strains of cereals, vegetables and fruit are "perhaps incapable at present of performing the basic conservation role of a gene bank".

Some gene banks "are in a state of rapid deterioration", says the report, while many have "poor storage conditions, lack of funds or facilities for regeneration, poor management, or a combination of such factors". About 130 countries lack long-term storage facilities, including one of the world's largest gene banks at the Vavilov Institute of General Genetics in Moscow.

At the US National Seed Storage Laboratory in Colorado there are delays in regenerating a fifth of the samples because of shortages of staff and resources. Germany, India, Brazil, Republic of Korea and Ethiopia also report problems with regeneration, as a result of inadequate funding. If seeds are not germinated and fresh seed collected every 10 years, they can deteriorate.

Many of the world's poorer nations admit to serious problems with their cooling and storage equipment, including Romania, Egypt, Iraq, Viet Nam and a number of African countries.

An FAO Global Action Plan proposes that between $1 billion and $3 billion should be invested over the next decade to upgrade gene banks and enhance genetic conservation on farms. "Action must be taken soon if the material collected in past decades is to be saved", the plan says. It calls for a major international programme "to transform the current diverse, poorly coordinated, often inefficient and frequently redundant efforts into a rational, effective and sustainable system". (Source: *New Scientist*, 27 April 1996)

Monsanto reaps biotechnology benefits

Monsanto's biotechnology division is said to be beginning to reap the benefits from a $1.5 billion R&D investment in biotechnology. 1996 results will be small, but in 1997 there is expected to be an increase in products available, with larger availability in 1998. Monsanto is focusing on products such as insect resistant potatoes and cotton plants, but the danger in pursuing a product which is yet to be consumer tested is enormous.

Bovine somatotropin (BST), which is designed to increase milk production from cows, was Monsanto's first genetically-engineeredproduct, but success has so far failed to materialize because of the public's safety concerns. (Source: *European Chemical News*, 1-7 April 1996)

Global biodiversity assessment

The long-awaited *Global Biodiversity Assessment*, the first global scientific assessment to be carried out on the Earth's biodiversity, was released at the second Conference of the Parties in Jakarta on 14 November 1995. The GBA project originated shortly after the signing of the Convention on Biological Diversity at the Rio Earth Summit in 1992 when the Global Environment Facility (GEF) Technical and Scientific Advisory Panel recommended to UNEP that a global assessment of current knowledge in the broad field of biodiversity be carried out. The GBA is an independent, peer-reviewed scientific analysis of the current issues, theories and views regarding biodiversity.

The massive 1,140 page volume, published in 13 separate chapters complete with executive summaries and extensive references, provides analysis of a broad range of biodiversity issues ranging from characterization and distribution to biotechnology and the influences of humans on the decline of biodiversity. Each chapter also includes relevant graphs, maps, tables and other illustrative material.

The GBA reaffirms that genetic variation within species is the ultimate basis for evolution, the adaptation of wild populations to local environmental conditions, and the development of animal breeds and cultivated crop varieties that have yielded significant direct benefits to humanity.

The loss of biological resources and diversity, the GBA warns, threatens humanity's food supplies, the sources of wood, medicines and energy, and opportunities for recreation and tourism. It also interferes with essential ecological functions such as regulation of water runoff, control of soil erosion, assimilation of wastes, purification of water, and the cycling of carbon and nutrients.

The primary causes underlying the loss of biodiversity are demographic, economic, institutional and technological, according to findings in the GBA. They include:

- Increasing demand for biological resources due to increasing population, economic development and wasteful overconsumption;
- Failure of people to appreciate the consequences of using inappropriate technology;
- Failure of economic markets to recognize the true value of biodiversity or to apply the global values of biodiversity at local levels;
- Institutional failure to regulate the use of biological resources resulting from the growth in urbanization, changes in property rights and shifting cultural attitudes;
- Failure of Government policies to address the overuse of biological resources; and
- Increasing human migration, travel and international trade.

GBA major findings

Biodiversity is the natural biological capital of the Earth and offers important opportunities for all nations, but failure to take immediate action to protect biodiversity will restrict future options.

Humans are the main cause of the increasing loss of biodiversity world-wide and are destroying the Earth's biodiversity at unprecedented rates, with between 5 and 20 per cent of some groups of animal and plant species possibly threatened with extinction in the foreseeable future unless present trends are reversed.

Because of the world-wide loss or conversion of habitat that has already occurred, tens of thousands of species now existing are headed for certain extinction, with no preventive action possible.

The number of species of flowering plants and some animal groups that will become extinct or are *en route* to extinction due to projected tropical forest loss over the next 25-30 years range from 2 to 25 per cent, greatly accelerated from expected rates. Even if endangered species do not become extinct, many of them will lose distinct populations or will suffer severe loss of genetic variability through habitat loss or breakdown.

A wide ranging and flexible approach to conservation planning is needed today, including many more disciplines than is the current case. The involvement of local people in conservation is essential.

Biodiversity management must go far beyond simply establishing isolated nature reserves or setting up agricultural seed banks. Instead, it must be fully integrated into all aspects, including agriculture, socio-economics, and other relevant fields.

Monitoring the changes that are happening to biodiversity is important if appropriate action is to be taken for its conservation and sustainable use.

Summary for policy makers

In addition to the full report, UNEP also released a companionpiece, *Global Biodiversity Assessment: Summary for Policy Makers*, based largely on information from the executive summaries of each chapter of the GBA. The 46-page booklet emphasizes the recommendations that will be of most interest to policy-makers.

The GBA was funded by the GEF, the financial mechanism for the CBD established in 1991 to assist

developing countries in protecting the global environment. GEF-funded activities are implemented by UNEP, the World Bank and UNDP.

For more information, contact: Robert Bisset, Information Officer, Information and Public Affairs, UNEP, Nairobi, Kenya. Tel.: +254-2-62-3084; Fax: +254-2-62-3692; e-mail: robert.bisset@unep.no.

Global Biodiversity Assessment is published by Cambridge University Press. Hardback: 0 521 56403 4 $110.00/£80.00. Paperback: 0 521 56481 6 $44.95/£29.95. *The Global Diversity Assessment Summary for Policy Makers* is also available in paperback: 0521 56480 8 $19.95/£9.95. (Source: *Diversity*, Vol. 12, No. 1, 1996)

First post-NAFTA and UPOV findings on plant breeders' rights released

As the push to create more stringent enforcement of plant breeding rights (PBR) accelerated in the early 1990s—following the ratification of the 1991 Union for the Protection of Plant Varieties (UPOV) and the North American Free Trade Association (NAFTA)—there was considerable debate over whether the new requirements contained in these international agreements would hinder the exchange of improved germplasm among breeders and users around the world.

A new study carried out under the auspices of the University of Amsterdam's Inter-American Institute for Cooperation on Agriculture sees evidence that PBR may, in fact, stimulate access to foreign varieties. But the report—*The Impact of Plant Breeders' Rights in Developing Countries: Debate and Experience in Argentina, Chile, Colombia, Mexico and Uruguay*—also cautions that the new legal protection dictated by the 1991 UPOV Convention may well restrict breeders' opportunities to sell new varieties in certain areas. And while it finds no evidence that PBR under that 1991 agreement currently affects landrace development among poor farmers, the report states that such an impact could not be ruled out in the future.

The study, conducted by Jeroen van Wijk and Walter Jaffé in 1994 and released in October 1995, examines the "expected" effects of PBR in three Latin American countries that have had PBR legislation for a decade or more (Argentina, Chile and Uruguay); one that has only recently enacted it (Colombia); and one (Mexico) that will enact it in 1996 as a result of NAFTA. By the year 2000 all five nations are expected to be members of the 1991 UPOV. The Dutch researchers worked with five local groups examining literature and interviewing 157 persons who represented 131 organizations interested in PBR.

To obtain copies of the report and for additional information, contact: Jeroen van Wijk, University of Amsterdam, CEDLA, Keizersgracht 397, 1016 EK Amsterdam, The Netherlands. Fax: +31-20-625-5127; e-mail: jvwijk@ sara.nl (Source: *Diversity*, Vol. 12, No. 1, 1996)

Report on the state of the World's Plant Genetic Resources

This year FAO published the first (draft) Report on the State of the World's Plant Genetic Resources for Food and Agriculture. The Report is the result of an unprecedented effort to review and assess the state of plant genetic resources in agriculture. It also tries to identify the causes of their erosion and to analyse the areas where action can be taken in order to conserve genetic resources. The Report identifies the intensification of agriculture as the leading cause of genetic erosion. It formally recognizes the role of resource poor farming communities in the conservation and development of biodiversity.

The Report, based on 151 country reports, 12 sub-regional meetings and FAO's World Information and Early Warning System (WIEWS) database, contains a lot of interesting information. It also confirms some of the fears NGOs and farmers have been expressing for a long time. Besides the political issue of who has the control over the accessions, the Report talks about problems related to the security of genebanks, available information on the accessions, the danger of deterioration due to lack of regeneration, and the use of existing accessions.

By the end of the 1970s, there were 54 seed keeping facilities, of which 24 had long-term storage capabilities. After a widespread but largely uncoordinated effort by both countries and the Consultative Group on International Agricultural Research (CGIAR) in the late 1970s and early 1980s to build up a genebank system and to collect existing agricultural biodiversity, the world now has a total of 1,308 national, regional and international germplasm collections, according to the FAO Report. Of these, 397 are maintained under long or medium-term storage conditions, most of the rest being active working collections for use by researchers and plant breeders. For the purpose of conservation, the base collections—held under long or medium-term storage conditions—are the most important ones, as these supposedly contain the unique material for use sometime in the future.

According to FAO, there are a total of about 6.1 million accessions under *ex situ* conditions: 600,000 in the CGIAR system and 5.5 million in national collections and regional genebanks. Some 50 to 65 per cent of the accessions (3-4 million) are in base collections. About 90 per cent are kept under cold storage, while 8 per cent are kept in field banks and less than 1 per cent *in vitro*.

More than 80 per cent of the accessions are held in national banks, and 45 per cent in just 12 countries (Brazil, Canada, China, France, Germany, India, Japan, Korean Republic, Russia, Ukraine, UK and USA).

All these figures might seem overwhelming, and give a sense of security that most of the diversity is stored safely away. FAO itself is quick in denouncing this false sense of security that the big numbers might suggest. A lot of the materials are quickly losing their viability and there is a lot of uncoordinated duplication. Some countries have expensive excess storage space and find it hard to keep up with the growing maintenance costs, while other countries lack proper long-term facilities.

All but six participating States reported having *ex situ* conservation facilities. Some 75 countries have seed storage facilities suitable for medium/long-term storage, but only 35 countries have secure long-term seed storage facilities, if measured according to internationally accepted criteria. To these secure national collections, one would have to add nine of the CGIAR genebanks and four regional genebanks which are in a decent state.

One of the main problems genebanks around the world are facing is regeneration. In order to stay alive, seeds stored in genebanks need to be grown out and harvested—regenerated—once in a while. The frequency of this regeneration depends on the crop. As the FAO report states, if a genebank had to regenerate its collection once every 10 years, one would expect routine regeneration needs to be 10 per cent annually. However, the FAO report

finds the reality quite different: *some 95 per cent of the countries report a far higher level of need.* Of the 95 countries providing information about regeneration activities, at least 71 (together holding nearly three million accessions) "*experience some difficulties in regenerating their collections*".

FAO concludes that almost half (48 per cent of all stored seeds world-wide now need to be regenerated. But its report also warns that some of these "*may already have lost their viability or genetic integrity, or they may be from populations where re-collecting may prove more cost-effective than regeneration*". However, for many of the accessions, re-collecting may prove impossible, because of extinction in the field.

In addition, many countries do not have either the funds, facilities or staff necessary to conduct their needed regeneration activities. Although countries in the South are most affected by this backlog, both the CGIAR genebanks and some countries in the North (such as the USA and Japan) are also affected. Part of the problem comes from the fact that when the genebank system was set up, nobody really took into account the needs and costs of the long-term maintenance of the accessions. One notorious example has been the spread of expensive genebanks in some Asian countries—built with Japanese aid money—several of which are now virtually empty or simply not functioning. The global picture, according to the FAO Plan of Action, is "*a steady deterioration of many facilities and their ability to perform even basic conservation functions*". This is serious language, especially if it comes from an agency that is coordinating a Global System on Plant Genetic Resources, which takes the *ex situ* genebank approach as the starting point.

Duplication of the existing collections is both a problem and a need. The FAO report notes that there is a lot of uncoordinated and unknown duplication amongst the world's stored seeds. One study published in 1987 estimated that only 35 per cent of the stored seeds were unique, the rest being duplicates. This study was based on 2.5 million accessions, and the FAO notes that with the steep rise in the amount of stored seeds world-wide since then, "*it must be assumed that inadverted duplication is now even higher*". It states that this over-duplication is a waste of money and should be minimized.

But on the other hand, duplication of unique accessions and their storage in other genebanks is crucial to ensure their security in the face of unexpected losses (because of fire, earthquakes, war, etc.). Also in this area, the results of the FAO surveys are alarming: only half of the countries provided information on their duplication effort (probably meaning that they do not have a structural approach to duplication). Of the other half that did respond, only 11 countries indicated that their collections (430,000 accessions) were fully duplicated somewhere, 51 countries reported partial duplication, and 10 countries reported no duplication at all.

The security and duplication problems in the current genebank system lead to a situation where genetic erosion in the banks might be higher than that in the field.

The information on the accessions held *ex situ* may be almost as important as the accessions themselves. This information may aid rapid identification of the required accessions and/or characteristics and may help to prevent excessive duplication of efforts, while showing where the gaps are. From a political and equity perspective, information on the origin of the accessions is also relevant. Ease of access to the information may make it easier for both breeders (as is the case) and also farmers (as it should also be) to use the materials.

Yet news from the Report on what we know about the stored seeds is, again, not good:

- Although 37 per cent of national collections and nearly all the CGIAR genebanks accessions have passport data, in most collections these data refer only to the country of origin. Plant breeders often develop their own collections because of the lack of information on collections in the genebanks.
- The rates of characterization and evaluation are also very low. As a result, the accessions of national collections are not fully utilized even by current genebank clients: breeders. The only exceptions to poor characterization seem to be most countries in Europe, East Asia, North America, Ethiopia, India and the Philippines.
- While some genebanks have their collections fully documented, computerized and even put in the Internet (as is the case of the Vavilov Institute and the USA base collections), others have not documented any of their accessions.

These factors clearly limit the use of the accessions stored in the genebanks. Nevertheless, a large number of accessions are exchanged around the world.

After its review of the *ex situ* conservation around the world, FAO makes some proposals to improve the current genebank system. This should be done mainly through rationalization, regional and international collaboration and the filling of the existing gaps, both in the plants covered and in the information on them. These ideas have been further developed in the Global Plan of Action, in the form of priority activities. (Extracted from *Seedling*, June 1996)

How ex situ conservation works

Genebanks are compartmentalized cold storages in which seeds are theoretically kept in controlled conditions of temperature and humidity. The banks work on the principle that dehydrated seeds are capable of remaining viable for long periods of time in cold conditions. Seeds may be kept in long-term storage (from 0 to -18° C), medium-term storage (0 to 10° C), or short-term storage (more than 10° C). Orthodox seeds (those that can be dehydrated) account for most of crops, including all major cereals. But so-called recalcitrant plants have seeds that do not stand up to such a process, as is the case with coconut, avocado, mango and tea. The *ex situ* conservation of these crops and vegetatively propagated plants relies largely on field banks. Recently, *in vitro* conservation techniques have also been used for the conservation of recalcitrant crops. Wild crop relatives and large species (such as trees) are often conserved in botanical gardens.

For *ex situ* conservation a number of seeds have to be collected, because even under the most stringent long-term conservation conditions seeds eventually lose viability and die. Accessions have to be regenerated regularly by planting them out in order to obtain new seed. However, the process of regeneration also results in a loss of genetic diversity, especially if it is done in conditions different from those of the site of origin of the accession. This is because the new environment may result in a different kind of selective pressure.

But even the best conserved accession will be of limited use unless basic information on it is available. Information on accessions is classified in three categories:

- Passport: this includes basic data such as the sampling date and site.
- Characterization: this includes data on taxonomic, environment-independent properties that describe the variety.
- Evaluation: it includes data on agronomic properties of the accession, which are normally closely related to the environment.

(Source: *Seedling*, June 1996)

Fungi species head for oblivion

Fungi are becoming extinct faster than scientists can study them, according to a declaration issued by 85 leading international mycologists at the British Mycological Society's centenary symposium at the University of Sheffield. The declaration expressed deep regret at the continued loss of habitat for fungi around the world and called for action to cut the rate of loss. Of the estimated 1.5 million species of fungi in the world, only 72,000 have been described by scientists. (Source: *Nature*, Vol. 381, 9 May 1996)

Who will pay for HIV's big push?

Answers to key questions about whether some strains of HIV-1 spread more easily than others will come only after a big new push in research, according to a panel of AIDS experts. The answers could change the approach to vaccine design and may help to explain why more heterosexuals have been infected in Africa and Asia than in Europe and North America.

AIDS researchers met early in 1996 in Berlin at the request of the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the German Government after reports that some subtypes of HIV-1 might infect heterosexuals more easily than others. They called for initiatives to set up international facilities to analyse subtypes, standardize laboratory techniques, and build stronger links between virologists and epidemiologists.

However, UNAIDS, with a budget of just $120 million over two years, does not fund basic research and has to hope that others will step in.

There are 10 known genetic subtypes of HIV-1. Subtype B, found mainly in North America and Europe, has received far more attention than the rest and almost all experimental vaccines are based on it. Max Essex at Harvard has shown that in the laboratory, subtype B is much less likely to infect Langerhans cells found in the vagina than two other subtypes, E and C, which are spreading in Thailand, Central Africa and India. In Thailand, epidemiologists have found that subtype E is behaving like some kind of "super-strain", rapidly overtaking B and infecting mainly heterosexuals. Essex has warned that the West may face fresh risks from E and C.

The Berlin group says that "scientifically sound" conclusions cannot be reached without more research. Roy Anderson of the University of Oxford, who chaired the meeting, says that there is contradictory evidence about the spread of B and E, and about who is susceptible to each subtype.

Virologists still do not know how the genetic characteristics of HIV-1 related to its spread, its virulence, or whether immune responses to one subtype protect against another. But the rules for classifying subtypes may have to be rewritten. Francine McCutchan at the Henry Jackson Foundation, near Washington DC, has found "mosaic" viruses with a core from one subtype and an envelope from another. (Source: *New Scientist*, 6 April 1996)

Genetic testing outside research acceptable, says cancer society

The American Society of Clinical Oncology (ASCO) has split with other prominent biomedical research bodies by announcing that genetic testing need not be confined to research settings.

The society, whose 10,000 members are all cancer specialists, says that testing for mutations predisposing to cancer should be made available to selected patients "as part of the preventive oncologic care of families". ASCO says that testing should be performed "to the greatest extent possible" as part of long-term outcome studies. But, it adds, "all individuals at hereditary risk for cancer should have access to appropriate genetic testing".

In contrast, organizations such as the National Advisory Council for Human Genome Research, the American Society of Human Genetics, and the National Breast Cancer Coalition have urged that genetic testing be confined to research settings. Frances Visco, for example, the president of the National Breast Cancer Coalition, says in the same journal that breast cancer advocates needs the medical community to recognize "the need to do less, rather than more". (Source: *Nature*, Vol. 381, 16 May 1996)

More vaccine research urged

Although new viruses such as Ebola, Hanta and Dangue have emerged with alarming regularity in recent years, little is being spent on vaccine research, according to Donald A. Henderson, director of the Smallpox Eradication Campaign at the World Health Organization. Mankind's survival in an increasingly populated and well-travelled world requires that funds be made available rapidly to develop vaccines against emerging viruses. Addressing a meeting at London's Royal Society held on the bicentenary of the first use by Edward Jenner of cowpox as a vaccine against smallpox, Henderson pointed out that vaccines were most needed in poorer countries, but that few national research authorities in the developed world were willing to support medical research which does not directly benefit their own citizens. "Resources are not the problem; it is our priorities that are", he said. (Source: *Nature*, Vol. 381, 16 May 1996)

Rice bodies stick together

Representatives from agricultural research institutes in 10 rice-growing countries in Asia established a Council for Partnership on Rice Research in Asia (CORRA) at a recent meeting at the International Rice Research Institute (IRRI) in Manila, Philippines.

Besides strengthening partnership among rice research institutes and links with other agriculture research institutions, the Council aims to seek support from "donors" and to develop regional approaches for research in rice. (Source: *Nature*, Vol. 381, 16 May 1996)

In the blood

A project to analyse the genotypes of thousands of people whose families are afflicted by inherited diseases is expected to go ahead in the autumn. The National Institutes of Health and Johns Hopkins University in Baltimore will create the Centre for Inherited Disease Research, with the NIH funding it to the tune of $5 million to $10 million a year for the next five years.

The Centre will obtain about 5000 DNA samples a year, analyse them and store the data. Researchers will be able to use the database to study the genetic components of diseases such as alcoholism, autism, breast

cancer and schizophrenia. (Source: *New Scientist*, 1 June 1996)

Stalemate is best humans can achieve in war versus pathogens

The war against infectious disease is going to end in a stalemate, rather than defeat for either humans or pathogens, according to geneticist William Haseltine, of Maryland-based Human Genome Sciences. But as infectious diseases develop antibiotic resistance and make a comeback, that view amounts to optimism.

The complete gene sequence of any pathogen can now be analysed in a matter of weeks, not months, and work is actively under way on several diseases. Knowing the sequence opens the door to novel antibiotics that "attack all the pathways of the pathogen".

The prediction was part of a survey of the state of the science of genetics, which Haseltine said has been remarkably successful using a reductionist approach.

The knowledge already gained has applications for improving crops, developing industrial catalysts and enzymes and finding vaccines against common pathogens as well as gene therapy. But Haseltine called for a programme of synthesis to bridge the gap between the molecular basis of life and the way human beings and other creatures actually behave.

More powerful machinery to carry out the routine work of analysis is on the horizon, creating the "very exciting prospect" of being able to have the sequences of several human beings and to watch as the phenotype changes over time.

Haseltine also called for a "human proteome project" which would aim at understanding and cataloguing all the proteins in the human body, in the same way the genome project seeks to catalogue and understand genes. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 4 March 1996)

Panel calls for overhaul of AIDS research

A long-awaited report by a 118-member panel of scientists and other experts has called for a major revamping of the $1.4 billion AIDS research programme of the US National Institutes of Health (NIH), which it says has been poorly focused and uncoordinated.

The report recommends that NIH scientists be stripped of strategic control over vaccine research, and that funding for AIDS research by non-NIH scientists be doubled. The new money would come in part from work wrongly labelled as AIDS-related. The report also wants drug discovery efforts scaled back, on the grounds that many duplicate the drug industry's work.

At the same time, the report calls for more basic research, especially in immunology, prevention and opportunistic infections. It suggests that a mix of clinical trials be consolidated into a single network, and describes as "critical" the need to actively recruit promising and distinguished scientists to a field that consumes 12 per cent of NIH spending.

The report also says that it is "crucial" for the NIH's Office of AIDS Research (OAR) to keep control over AIDS research at the NIH's 24 institutes and centres and it recommends against establishing a separate AIDS institute at the NIH.

The AIDS Research Programme Evaluation Working Group included 90 scientists, as well as activists and representatives of the biotechnology and pharmaceutical industries.

The conclusions of the working group were unanimously accepted by the advisory council of the OAR, which commissioned the report in late 1994.

The report makes a watershed in AIDS research at NIH, which accounts for 85 per cent of public spending on AIDS research world-wide. While commending past NIH efforts for producing "unprecedented dividends" that have created "the first real chance" of turning AIDS from an inexorably fatal condition into a chronic, manageable disease, it is also highly critical of many aspects of that research.

The overarching theme is the need for better coordination, prioritization and focusing of AIDS research, in which all 24 NIH institutes and centres are involved.

One key recommendation is that the OAR and the institutes develop stricter definitions of AIDS and AIDS-related research.

Another significant recommendation is that the entire AIDS vaccine research effort be restructured, given that vaccine research has "received less funding and attention" than other areas at NIH, and that the spread of HIV worldwide means that it is no longer acceptable. "In many developing nations, vaccines may be the only cost-effective way to prevent transmission", the panel writes.

In particular, it recommends establishing a trans-NIH vaccine research effort as an independent unit within the NIAID. The effort would be directed by an AIDS Vaccine Research Committee (AVRC), chaired by and composed primarily of non-government scientists.

The panel suggests that all AIDS clinical trials be condensed into a single network sponsored primarily by NIAID and overseen by an OAR committee to ensure coordination between the institutes. (Extracted from *Nature*, Vol. 380, 21 March 1996)

HUGO approves ethics code for genomics

Genetics researchers should not offer "undue inducement" to individuals, families and population groups taking part in gene mapping and other related experiments, according to a code of ethics for genomics research approved by the Human Genome Organization (HUGO).

The code does endorse various types of agreement that might be reached in exchange for such participation, ranging from the provision of health care, or "information infrastructures" to "the possible use of a percentage of any royalties for humanitarian purposes".

At the same time, it underlines the importance of obtaining informed consent for such participation "free from coercion by scientific, medical or other authorities". Such consent, it adds, can be "individual, familial or at the level of the communities and populations"—a potentially controversial statement, as it does not require that consent be expressed by an individual participant.

The code was endorsed by the executive council of HUGO, the umbrella organization which loosely oversees both the Human Genome Project (HGP) and the Human Genome Diversity Project (HGDP). It was immediately distributed to members of the organization attending its first full international meeting held at Heidelberg in Germany.

The organization felt it was important to make a statement about ethics that tried to be culturally sensitive, but without giving in to the dictates of any one particular culture.

The working group which drew up the statement says that its recommendations are based on four principles: recognition that the human genome is part of the common heritage of mankind; adherence to international norms of

human rights; respect for the "values, traditions, culture and integrity" of participants; and "acceptanceand upholding of human dignity and freedom".

The sections of the statement likely to attract the most attention, following recent controversy over the implementation of the HGDP, are those dealing with the need to ensure that the informed consent has been obtained from participants, and for the provision of appropriate compensation. (Extracted from *Nature*, Vol. 380, 28 March 1996)

Growth hormones

The disagreement between the European Union and the US over the use of growth hormones in meat has escalated, with the US requesting formal consultations with the World Trade Organization (WTO).

The EU has opted to keep its seven-year-old ban on beef raised using natural and synthetic growth hormones, originally imposed because of health concerns. This is despite the findings of a special conference, convened in December 1995 by agriculture commissioner Franz Fischler, which found no evidence of any risk from hormone use. However, scientists at the meeting called for an update of the available data, much of which are over 10 years old. The effects of hormones on animal health should be studied, they added.

The US allows the use of three natural hormones: testosterone, progesterone and oestradiol, and two synthetic ones: zeranol and trenbolone.

Fischler has cited overproduction and public opinion as reasons to uphold the ban. Hormone use would increase beef production by 10 per cent "in an already overburdened sector", he said, but consumption would fall by 20 per cent because of consumers' unallayed fears.

The European Parliament voted unanimously to uphold the ban. All the Member States' agriculture ministers agreed, except for the UK minister. (Source: *Chemistry & Industry*, 5 February 1996)

Quantitative DNA molecular weight standards kit

American Type Culture Collection (ATCC) announces availability of the ATCC Quantitative DNA Molecular Weight Standards Kit. This kit accurately measures the size and quantity of experimental DNA samples in one simple step. The kit produces 16 standard gel bands which are easily visualized on an agarose gel using ethidium bromide staining. Size standards are generated for four DNA fragment lengths (0.94 kb, 2.06 kb, 3.0 kb and 4.4 kb and quantitation standards at four concentrations of DNA (25 ng/ 5 μl, 50 ng/ 5 μl, 100 ng/ 5 μl and 200 ng/5 μl). Each kit contains sufficient material for 40 assays.

The standards are gel ready, requiring no additional mixing, diluting or sample buffer. The kit, Product No. 60-1001K, is priced at $110.

Further information and requests: ATTC Sales, 12301 Parklawn Dr., Rockville, MD 20852, USA. Tel.: 800 638 6597; Fax: 301 816 4361. (Source: *Australasian Biotechnology*, Vol. 6, No. 2, April 1996)

World Food Summit

A World Food Summit to be held in Rome, Italy, 13-17 November 1996, is expected to be the largest assemblage in history of Heads of State. It has been summoned at the initiative of FAO Director-General Jacques Diouf and will be the first opportunity since the 1974 World Food Conference for Governments to concentrate their attention on food security. The national leaders will seek a global consensus and commitment to implement policies, programmes and strategies that will lead to eradication of hunger world-wide.

For additional information, contact: World Food Summit, FAO, Vialle delle Terme di Caracalla, 00100 Rome, Italy. Tel.: +39-6-5225-3259; Fax: +39-6-5225-5824. (Source: *Diversity*, Vol. 12, No. 1, 1996)

New hope for alternative animal testing

A new toxicity test that measures the electrical resistance of cells could reduce the number of animals used in chemical safety assessments. Current animal tests are expensive, time-consuming and unpopular with the public.

Scientists have used electrochemical measurements before to study the damage caused to living cells by exposure to chemicals. William Miller and Andrew Pasternak at Northwestern University have now devised a model that allows them to continuously measure the toxicity of a chemical, under typical exposure conditions, without killing the test cells.

The Northwestern team used a monolayer of cells cultured on a membrane to provide a model of living tissue. They chose epithelial cells (lining cells) because they are the first line of defence against toxins and their response is crucial in gauging the likely effects of exposure. Other tests using cell cultures measure only metabolic activity or cell viability, the researchers point out.

The fully automated technique involves placing the cultured cell layer between two electrodes and measuring the resistance across it—called the trans-epithelial electrical resistance (TER)—while exposing the cells to a solution containing toxic chemicals. The TER decreases as the chemical changes the cells. The test shows how permeable the tissue model is to ions and electrons, reflecting how small molecules pass across cell membranes.

One advantage of the new system is that it can continuously monitor changes in the cells. For example, when the toxic chemical is removed from the solution, the cells may start to recover and the TER will increase. This is a more accurate model of exposure than current cell culture techniques, which simply monitor cells as they die.

Miller found that the results of his tests on a range of detergents matched those from the Draize eye test.

The new system should work with surfactants, heavy metals and any water-soluble chemical. The team is also testing cell responses to a mixture of chemicals. They point out that the system can use a variety of different cells of specific tissues and organs, such as eyes, skin and lungs. (Source: *Chemistry & Industry*, 3 June 1996)

Turning intellectual property and lab concepts into marketable products

The US biotechnology industry is founded on technology transfer. The Cohen-Boyer patent, licensed broadly on a non-exclusive basis from Stanford and the University of California at San Francisco, transferred the rights to practice recombinant technology for research and commercial purposes. The licensing income is evidence that universities can benefit from technology transfer.

US biotechnology patents (almost 5,000 notices of allowance were sent out by the US Patent Office in 1995) contribute to industry sales, but patent value extends beyond the obvious market exclusivity that is granted. Start-up companies present patent portfolios as part of the valuation when raising private and public funding.

In some cases, distinguished scientists bring companies enhanced credibility along with their founding technology.

Universities and Government laboratories, like the National Institutes for Health, will continue to be a rich resource for technology and scientific expertise for the biotechnology industry, and with Government biomedical research budgets shrinking, universities will increasingly rely on corporate-sponsored research grants. Sponsoring research links an academic investigator to a company early on and the arrangement can be of mutual benefit: scientists receive an infusion of money to continue basic work while companies gain access to key technologies plus scientific guidance from people who have devoted decades to the study of fundamental biological concepts.

When technology transfer generates a blockbuster product, companies profit from sales and universities are paid up-front fees (they may also receive a sustainable royalty income that is recycled back to inventors and laboratories.

The Bayh-Dole Act essentially established a uniform technology transfer policy that allows non-profit organizations to retain title to inventions made while using federal funding. During the first 10 years after Bayh-Dole was introduced, the impact on technology transfer was dramatic: issued patents assigned to universities increased from 250 to 1,600 annually, the number of technology transfer offices rose from 30 to 200 and cumulative university licensing income is now counted in the hundreds of millions of dollars.

The process of getting university-owned technology into a commercial setting is an interdisciplinary process involving valuing the technology in a product context, patenting inventions and, ultimately, negotiating and drafting the contracts to grant companies rights to practice inventions. But how does the actual *transfer* begin? How do a university and a company make contact?

This marketing aspect of technology transfer may be both active and passive. Perhaps because licensing professionals differ in their marketing techniques and in their attitudes about marketing technology, the success of this process is variable. Once a company expresses interest in a technology, confidential information is usually exchanged and the negotiation process begins. Some groups use brokers who not only find corporate partners but act as a surrogate licensing office for some universities.

Somewhat more passive approaches include advertising inventions using, for example, Home Pages on the Internet.

One highly successful passive mode of marketing depends on disseminating scientific information at a peer level via publications. Scientists from both academia and corporations meet on common intellectual ground to exchange ideas at focused symposia.

When research synergies are recognized, a corporate scientist may become the technology champion, beginning a scientific relationship that can include sponsored-research funding. Technology is routinely developed with a corporate partner as joint owner/inventor, or the sponsor may be promised the first right to negotiate for a license as an obligation attached to funding the research.

Actively searching for technology is a more time-consuming, but also potentially a more rewarding effort, because a company can identify technologies before the competition enters the bidding. Some of the hottest technologies are discovered by big pharmaceutical and venture capital scouts looking to transform novel technologies into a new product.

Technology transfer is also vigorously pursued by a select group of universities that offer incubator space either on or off campus, where basic research is applied to product development. Virtual companies may operate for months at universities before obtaining significant private or venture funding to secure offsite laboratory space, and a very small minority of technology transfer offices, less than 10 per cent of the top 10 licensing offices, accept equity in startups as part of the licensing fee to facilitate transfer technology to cash-poor, early-stage companies.

Overall, if the technology is interesting enough, waiting for a new discovery is easy. The molecule of the year or a fat gene will have a host of suitors waiting in line to pay millions of dollars for an exclusive licence. Inventors of the highly innovative technology usually arrive at the technology transfer office accompanied by a corporate proposal to obtain a licence.

But what about the more mundane yet valuable technologies that are product candidates as a research reagent, diagnostic test or a drug serving niche markets? Finding these technologies a good home may require some imaginative matchmaking efforts. There is no single repository of information linking university technology with companies.

Successfully transferring technology requires a knowledge of biotechnology players on the part of the university and an understanding of university culture on the part of companies. One can reasonably argue that marketing is a critical aspect of the licensing process and is the real bridge between academic technology and product development.

University personnel with skills emphasizing intellectual property protection and contract negotiation may have portfolios of ageing, issued patents because they did not get the word out in time. In the health-care industry, where more than a decade is needed to bring a drug to market, a reasonably long market exclusivity has high value. The harmonization of patent laws and GATT provides a 20-year term of market exclusivity from the time of patent *filing*. However, when compared with the 17 years from patent *issue* in effect before GATT, this actually represents a shortening of market exclusivity.

Because companies are attracted to patent applications with licensing potential long before patent issue, the successful marketing of technologies is a critical element of both technology transfer and product development. (Source: *Genetic Engineering News*, December 1995)

C. COUNTRY NEWS

Australia

Australia develops diagnostics

At the Queensland University of Technology (QUT) a research programme is under way to develop diagnostic tests for Australia's hospitals and the international biotechnology market.

A university spokesman said rapid DNA testing for cancers was one of three important joint research projects now in progress at the QUT's Cooperative Research Centre for Diagnostic Technologies.

Initially, the researchers will be working with John Cohen of the Princess Alexandra Hospital in Brisbane to develop a DNA test to detect colon cancer.

The QUT is investigating the possibility of establishing an on-campus testing service for hospitals throughout Australia that will detect genetic diseases such as cancer and Alzheimer's disease. The researchers aimed to have the colon cancer test commercially viable within two years. (Source: *Biotechnology Business News*, 10 April 1996)

Survey reveals favourable response to genetic engineering

An Australian survey has revealed that people respond favourable to genetic engineering as a scientific tool, particularly in the areas of medicine, agriculture and the environment.

The survey, organized by the Australian Government's Department of Industry, Science and Technology, found public support for research into genetically engineered food, although clear labelling is wanted. But despite its support of genetic engineering to improve food, the public was less favourably disposed towards genetic engineering when it merely increased farmers' income, or provided cheaper or tastier food. (Source: *Biotechnology Business News*, 4 June 1996)

Canada

Research and development activities in Saskatoon

- Oilseeds—Saskatoon houses the world's largest initiative on *Brassica* oilseed (canola) breeding and research genetics. Research by both public organizations and companies spans various crops and technologies, although the greatest activity is focused on canola. Work under way includes haploid production, genetic transformation, disease tolerance, oil and meal improvement, herbicide tolerance, oil modification, and hybrid varieties. Flax biotechnology focuses on genetic transformation, with additional collaborative research aimed at modifying genes for fatty acid variation.
- Cereals—Current activity centres on wheat transformation, starch modification, haploid production methods for barley and wheat, and development of molecular methods for gene tagging.
- Legumes—Research centres on gene isolation and genetic transformation to improve alfalfa, peas, and lentils.
- Microbial Inoculants—Saskatoon is home to Canada's emerging inoculant industry. This initiative is centred on biofertilizers, biopesticides, and bioremediation. These capabilities are presently being strengthened with the establishment of a bioproduct centre.
- Livestock—To date, recognition has come principally through advances attributed to collaborative efforts of the infectious disease group of VIDO and the Western College of Veterinary Medicine. Simultaneous with continuing work on biotech vaccines, Saskatoon has become Canada's leading centre in animal molecular genetics. The Feed Resource Centre at the University of Saskatchewan is focused on the enhancement of animal nutrition and feed production, with emphasis on international markets.
- Horticulture—(Tissueculture/micropropagation)—An active group operates at the University of Saskatchewan's Departments of Biology and Horticulture. Activity is centred on ornamentals, vegetables, and forestry.
- Plant components—Methods have been established to separate useful components for food and non-food uses, and commercialization is occurring.
- Diagnostics—Food inspection diagnostic research and development is located at the University's Department of Applied Microbiology. (Source: *The AgBiotech Bulletin*, April 1996)

New transgenic canola varieties in use

Recent approvals of transgenic canola varieties have put Canada in the forefront of the development, evaluation, and move-to-market of transgenic field crops.

Several transgenics are already in use, including varieties resistant to AgrEvo's Liberty herbicide and Monsanto's Roundup. The variety Innovator, which is resistant to Liberty, was the first transgenic field crop grown commercially. Some 40,000 acres were grown in 1995.

Herbicide resistant canolas have been genetically altered to allow farmers to use herbicides that formerly damaged canola. One of the benefits of this system is that farmers now have more choices of herbicides to control weeds, including applications that have economic and environmental advantages.

Research in Saskatoon and in many other locations is currently under way to alter the qualities of canola, giving it many potential uses in industry, animal and human nutrition, and even medicine. Over 1,000 patents have been taken out for new industrial uses of canola. Here are a few examples of canola varieties being developed:

- Researchers at DuPont and the University of Delaware have succeeded in producing a transgenic canola with a higher lysine content, improving the value of the plant's protein. The transgenic canola nearly doubled the proportion of lysine over standard canola.
- Plant Genetic System's (PGS) new transgenic hybrid canola variety, which received full regulatory approval last year, offers Canadian farmers significant yield gains. PGS has shown a roughly 20 per cent yield increase compared to the checks used in variety registration trials. (Checks are varieties that researchers use as benchmarks to compare with their new varieties).
- Researchers at Zeneca Seeds are introducing antifungal genes into selected canola varieties to control the fungal diseases black leg and white mould.
- The first transgenic tests of canola plants that produce a type of plastic, poly-hydroxybutyrate (PHB), could occur as soon as 1996, according to Zeneca Seeds in Winnipeg. Zeneca has already obtained European

patents for a bioplastic made with PHB through a bacterial process. The plastic is marketed under the name Biopal. Producing the bioplastic in canola would be cheaper than the bacterial process, and the oil and meal would still be usable. Zeneca has already isolated and cloned the plastic-producing gene and two years ago they started to incorporate it into canola plants.

- Researchers at Calgene inserted a gene from the California Bay tree into canola to produce varieties with nearly 40 per cent laurate content. Laurate is commonly used to make detergents such as shampoos. Laurate canola was approved and grown commercially in the US last year. Calgene is researching another gene that will allow the commercial development of plant oils rich in myristate. Myristate can be used in applications similar to laurate.
- Calgene has also developed a transgenic rapeseed oil containing trierucin, which is used in a wide variety of industrial applications. This was achieved using a gene from the meadowform plant.
- Researchers have also created a biodiesel fuel from canola oil. Called supercetane, the fuel produces fewer air pollutants than normal diesel fuel. Though expensive to produce, this fuel might be ideal for use in environmentally sensitive areas.
- Calgary-based SemBioSys Genetics is conducting research aimed at producing interleukin, an immune-system booster and cancer fighter, from genetically-engineered canola. The company is also exploring the potential of hirudin, an anti-coagulant substance found in leach spit. Anti-coagulants are important in treating people who suffer health problems from blood clots (e.g. heart attacks). By transferring the gene for hirudin into canola, this agent could be produced at one-tenth the price at which it is currently available.
- Mycogen and Pioneer Hi-Bred International are collaborating on transforming canola and other crops with *Bt* genes. *Bt* genes cause plants to produce natural proteins that protect them against insect damage.

(Source: *Agritech, Issue 21*, May 1996)

China

Centre strikes biotech deal

In another sign of the growing links in science and technology between Hong Kong and mainland China, the Hong Kong Institute of Biotechnology Ltd. (HKIB) has signed a memorandum of understanding with the China Innovation Centre of Life Science, under China's State Science and Technology Commission, to cooperate in the development of health care and other biotechnology-related industries.

HKIB was set up as a venture company in 1989 on the campus of the Chinese University of Hong Kong with financial support from the Royal Hong Kong Jockey Club. With the return of Hong Kong to China next year, HKIB, like many other research organizations in Hong Kong, is looking to forge links in research and development with the mainland. (Source: *Nature*, Vol. 381, 9 May 1996)

Further agreements with major drug companies

In March, Roche Bioscience (Palo Alto, CA) announced an agreement with two Chinese research institutes concerning the discovery of drugs for pain and lower urinary tract infections. The agreement called for the use of molecular biology to identify receptor targets, and to investigate Chinese traditional medicines.

Roche will work with the Beijing Institute of Microbiology (Beijing) on the discovery and isolation of novel receptor targets, and with the Shanghai Institute of Organic Chemistry (Shanghai) on identifying new compounds based on Chinese medicinal products and the synthesis of organic compounds. The agreement stems from a long-standing "relationship" begun in the early 1990s with a group of Chinese researchers.

SmithKline Beecham (SB, King of Prussia, PA) announced its research collaboration with two other Chinese research institutes to elucidate the molecular mechanisms of disease, primarily in the areas of cardiovascular and bone disorders.

SB's agreement with the National Key Laboratory of Medical Genetics (Changsha) and the Shanghai Second Medical University/Rui Jin Hospital (Shanghai) goes beyond providing financial support for research. SB will establish a training programme for Chinese students and researchers from the Chinese institutes. (Extracted from *Nature Biotechnology*, Vol. 14, April 1996)

European Union

EP looks again at biotech ethics

In a major vote on EU pharmaceutical policy, the European Parliament has again stressed the ethical implications of biotechnology.

The vote was the outcome of two years of discussion in the EP's committees on suggestions from the European Commission for the framing of an industrial policy strategy for the pharmaceutical sector.

While acknowledging the potential of genetic engineering in the pharmaceutical sector, the resolution also pointed to "misgivings which have been expressed about the possible dangers of genetic experimentation."

European Parliament members called for the creation of an ethics committee within the London-based European Medicines Evaluation Agency—an idea which industry commissioner Martin Bangemann said he was prepared to consider.

The committee's members would be appointed by the EP and the Council of Ministers "on an equal basis...with the task of drawing up a Code of Ethics."

MEPs linked this demand with a reiteration of their frequently voiced argument that, "after safety, efficacy and quality, ethical factors should become the fourth condition for the patentability of medicinal products."

Pending agreement on the long-delayed Council of Europe Bioethics Convention, which the Commission has already said it would recommend for adoption by the EU, the EP wants the Commission to seek "voluntary commitment" on ethics based on the European Convention on Human Rights.

Although the resolution has no legislative force at this stage, the vote signalled to the Commission how Strasbourg is likely to react to future EU directives framed by Brussels under the framework of the strategy. (Source: *Biotechnology Business News*, 24 April 1996)

Comparative assessment set to play part in directive

Comparative assessment—a controversial principle strongly opposed by the chemical industry—looks set to be

included in the proposed European Commission directive on the marketing and use of biocides.

The principle means that where more than one chemical is available for use in a particular application, the chemical with the least environmental and health impacts should be chosen. As currently expressed, the proposal allows substances on the directive's "Annex 1" approved list to be removed if a more environmentally acceptable substitute is found.

At a first reading of the draft directive in April, the European Parliament voted for comparative assessment to remain, but introduced a clause giving manufacturers five years to phase out chemicals removed from the list.

It now seems likely that negotiations will be further extended, since the European Parliament also introduced over 60 other amendments to the directive, which are unlikely to be accepted by the Commission. These include deleting references to product data to be supplied "where relevant".

Once a final decision is made, the directive could be implemented by the end of 1998. (Source: *European Chemical News*, 20-26 May 1996)

European move on Alzheimer's

The European Parliament has approved a resolution calling on the European Commission to increase support within its Biomed programme for basic research into Alzheimer's disease. The resolution also calls for a special research programme for Alzheimer's, with its own budget, and suggests the concurrent setting up of a task force to coordinate efforts to combat the disease. (Source: *Nature*, Vol. 381, 9 May 1996)

Europe halts supermaize

Under pressure from the UK, Europe has for the first time blocked the approval of a genetically engineered crop plant. Officials in Brussels rejected an application from Swiss-based multinational Ciba-Geigy to sell Europe's farmers maize with an inbuilt protection against the European corn borer.

Corn borers that attack the maize are poisoned by a toxin that is normally made by the soil bacterium, *Bacillus thuringiensis*. Ciba-Geigy's scientists have spliced the gene that makes *Bt* toxin into the maize genome. They also gave the plant a gene that makes it resistant to glufosinate-ammonium, a herbicide sold by Ciba under the trade-name Basta. This means farmers can clear their crop of weeds without harming the maize plants. The plant has already been cleared for sale in the US and Canada.

Companies that want to market their products in Europe generally only need the approval of one country. The findings of that country's regulatory authorities are passed on to their counterparts in all other European countries, and then Governments vote to decide whether the application should go through unchallenged. So far, four genetically engineered plants have been approved in this way.

The UK objects to the maize because it also contains a gene that makes it resistant to the antibiotic ampicillin. This gene serves no useful purpose in the crop but is a useful marker that allows genetic engineers to screen out plants that have failed to take up the extra genes. Ampicillin is widely used to treat infections in both people and livestock, and the UK is worried that cattle fed on the corn might become resistant to treatment, or even that the gene will find its way into bacteria in people.

Sweden, Austria, and Denmark objected to the French approval on the grounds that France had not insisted that the maize should be labelled as genetically engineered. There is also concern that corn borers might develop resistance to the *Bt* toxin, and that the gene for herbicide resistance might spread into weeks.

The decision is likely to alarm biotechnology companies. They argue that Europe's strict laws handicap them while rivals in the US and Japan enjoy laxer rules. (Source: *New Scientist*, 4 May 1996)

SELA/EU bridge project on biotechnology

In compliance with the Latin American Council's guidelines, the Permanent Secretariat of the Latin American Economic System (SELA) has implemented a number of initiatives aimed at promoting technological development, innovation and competitiveness. Within the framework of these initiatives, the new technologies, and particularly biotechnology, have been granted preferential treatment.

In September 1990, the Commission of the European Communities and the Permanent Secretariat of SELA signed an agreement to implement a specific and broad effort forming part of a programme aimed at promoting co-operation between these two organizations in the field of biotechnology. In this manner, SELA and the EU clearly manifested their interest in creating an area for cooperation between Latin American and European laboratories and specialized enterprises.

The first project was carried out between 1991 and 1993, incorporating nine Latin American countries as a representative sample of what was going on in the region. The project results included: a database (DIBIO) on Latin American enterprises and institutions, the formulation of a proposal for a SELA/EU cooperation programme in the field of biotechnology (presented to the member States in September 1992 on the occasion of the XVII regular meeting of the Latin American Council) and the preparation of a thesaurus of the terminology used in biotechnology. Likewise, technological capacities were identified in participating countries. At the same time, the European counterpart of the project carried forth a study on state-of-the-art biotechnology enterprises in that continent.

Rapid evolution in the field of biotechnology calls for continuous work, otherwise the information quickly becomes obsolete. At the end of 1993, based on the progress achieved during the first stage of the programme, together with the expectations created in Latin America and information gathered during that time period, a 6-month Bridge Project was proposed to the EU. This project was aimed at following up the progress achieved to date and at providing an opportunity for the establishment of a long-term biotechnology programme with the European Commission.

This Link Project will place particular emphasis on the new realities facing biotechnology in the region, especially as regards micro-enterprises of high-level academic researchers as well as small and medium-sized enterprises (SMEs).

Although a large part of the effort is aimed at the biological sector (health, agriculture, etc.), other industrial groups will join in as a result of the horizontal activities relating to biotechnology. One of these activities is the regional chemical industry, which is rapidly focusing on fine chemistry, especially medicinal products, insecticides and bioinsecticides, biomaterials, biological treatments for environmental pollution, etc.

In this regard, Latin America needs to disseminate related information more actively and continuously in order to achieve new and additional forms of interaction.

The activities provided for in the SELA/EU Bridge Project on Biotechnology for the 6-month period in question are as follows:

- Updating and broadening the directory of enterprises and biotechnology centres in Latin America on the basis of their productive activity and for joint ventures with Europe;
- Facilitating interaction among biotechnology organizations of both continents;
- Disseminating the project's activities in magazines, congresses and seminars, granting special attention to achieving greater public acceptance in the progress made in this field;
- Organizing a cooperative interaction with other existing programmes in Latin America, such as the Bolivar Programme, Redbio, the UNESCO/UNIDO Regional Programme, etc.;
- Making an evaluation of the R&D projects carried out jointly by Latin American and European researchers, in order to facilitate their transfer to interested industries;
- Determining the status of regulations, rules, controls, patents and bioethics in the region.

An implicit task of the Bridge Project is to serve as the basis for the long-term programme between the two institutions. This endeavour fits into the framework of the EU's desire to increase cooperation with Latin America and the Caribbean in specific and fundamental issues for the economic development of the region, and the interest manifested by the Permanent Secretariat of SELA in strengthening dialogue and cooperation between the two organizations. (Source: *The Genetic Engineer and Biotechnologist*, Vol. 16, No. 1, 1996)

France

Moves to help biotech

France's Secretary of State for Research has indicated that a series of measures will be taken to help the biotechnology industry.

In particular, Anvar (Agence Nationale de la Valorisation de la Recherche), the national agency set up to exploit research, will ask small and medium-sized biotech businesses to bid for backing for their projects. In addition, the Cifre and Cortechs innovation funds are set to be increased by 15 per cent and 33 per cent respectively. (Source: *Biotechnology Business News*, 22 May 1996)

New genetic laws disappoint

The new French law governing the use of genetic and cellular treatments being finalized by parliament will disappoint the national biotechnology industry.

The industry had hoped that the legislation would concentrate all the necessary powers of approval for clinical trials and production in the Agence du Médicament—the government agency that clears pharmaceuticals for public consumption. But the legislators have split the powers between the agency, and the Ministry of Health.

Under the new law, the Agence du Médicament will be responsible for approving any genetic and cellular treatments that can be produced on an industrial scale. More individual therapies, however, including cellular *in vivo* therapies, will remain controlled by the Ministry of Health, which will seek approval from a representative committee of all the main health authorities.

By the end of last year, 12 genetic and cellular treatments were in clinical trials in France, out of 140 worldwide—of which 110 were in the US. (Source: *Biotechnology Business News*, 22 May 1996)

Germany

GMO amendments get go-ahead

Germany's federal cabinet has approved four amendments to the genetic framework act, simplifying procedures for approval of projects involving genetically modified plants or organisms.

The mandatory public hearing on the release of manipulated plants or organisms is to be eliminated in favour of a written approval procedure. For release of genetically modified plants, documentation is to be simplified and for projects in the lowest risk category under the framework act, laboratory journals will be accepted as proof of safety.

The amendments must still be approved by the parliamentary chamber of the federal states, the Bundesrat. The health ministry, which drafted the legislation, said it sees "no further scope" for simplifying legal procedures, although some easing of restrictions on production and research may be possible. (Source: *European Chemical News*, 26 February 1996 - 3 March 1996)

Researchers demand more freedom

The Deutsche Forschungsgemeinschaft (German Research Society) has recently published a memorandum which asks for more freedom in research, with particular emphasis on the medical and biotechnology sectors.

Science is seriously threatened by restrictive laws, tight administrative rules and legal controls, as well as incompetent administration, according to an interdisciplinary group of German experts. Taxation also does not favour scientific enterprise as is the case in other countries, and public opinion is at the very least, still sceptical, if not totally apprehensive towards innovative areas of medical and biotech research.

Especially hard hit are biotech, reproductive medicine, research on embryos and animal experimentation in general. In 1991 the embryo protection law was passed in the German Parliament and scientists who conduct research on fertilized human eggs are threatened with imprisonment.

The memorandum points out that research into preimplantation diagnostics, genetically inherited diseases and infertility has become impossible. Whereas microinjection of sperm (ICSI) to treat infertility is allowed, German scientists are not able to develop these techniques themselves, but have to license them from abroad. The memorandum criticises this legal ambiguity.

The memorandum claims that the Federal Science Ministry should be given more competence and power in the legislative process. Each new law should be scrutinized for possible negative effects on scientific progress. There should be no further laws which put restrictions on science. (Source: *Biotechnology Business News*, 10 April 1996)

Council on biosciences

The German Council for Research, Technology and Innovation, an expert panel directly linked to the chancellery, is setting out to draft recommendations on how further to promote biosciences on a national level.

By the end of this year, the Council will present its suggestions to the scientific community, industry and political representatives. It aims to produce "a coordinated strategy for Germany's development into a prime location for bioscientific research and application", the panel said after its inaugural meeting.

The Council states that the commercialization of biotechnology research needs to be improved. In the course of the year, the Council will draw up suggestions to improve the administrative and legal framework for biotech in Germany (including patenting and deregulation), and address ethical and cultural questions. (Source: *Biotechnology Business News*, 22 May 1996)

Germany clears biotech programme

Bavaria has recently approved a US$ 4.8-million biotechnology research programme to succeed its four-year *Forbiosich* (Research into Biotechnology Safety) programme, which ends in December 1996. The new programme will run for three years and will support a broader research base than its predecessor, which was restricted to retroviruses. Both programmes are supported by the Bavarian Research Foundation, established in 1993 with money from the state's extensive privatization programme. (Source: *Nature*, Vol. 380, 25 April 1996)

India

"Indian ginseng" brings royalties for tribe

An indigenous Indian tribe has been awarded the intellectual property rights to the active ingredient of a plant long known to it as helping to combat stress, in a move that the Government hopes will help end the "piracy" of tribal knowledge by both Indian and foreign drug companies.

The drug *jeevani*, which is based on this ingredient and is said also to provide an instant source of energy, has been developed from the plant *Trichopus zeylnicus* by the government-owned Tropical Botanical Garden and Research Institute (TBGRI) in Trivandrum, the capital of Kerala state.

After successful clinical trials, the Institute has transferred the manufacturing know-how to Arya Vaidhya Pharmacy (AVP), a large manufacturer of ayurvedic drugs—drugs based on traditional Indian herbal medicines—for $50,000.

The Kani tribe of the Agasthiyar hills in the southern state of Kerala will receive half of the know-how fee, and will also receive a share of a 2 per cent royalty on any future drug sales. This money will go towards 2,500 families of the Kani tribe who will cultivate and supply the plants to AVP at a price agreed with the TBGRI. (Source: *Nature*, Vol. 381, 16 May 1996)

Japan

HIV gene therapy group established

The Central Review Council for Gene Therapy Clinical Research of the Ministry of Health and Welfare has established a Working Group on HIV Gene Therapy Clinical Studies. At its first meeting, it reviewed the scientific and ethical suitability of "gene therapy of HIV carriers," the protocol of a clinical study on HIV-IT gene therapy submitted by Kumamoto University last November.

Because of the large amount of data submitted by Kumamoto University and also by Viagene Inc., the American company providing the vector, via the Green Cross Corporation, evaluation and examination of the data were divided up among the nine working group members, including the chairman, Shudo Yamazaki, director general, National Institute of Health, and each member was assigned a specific field. (Source: *McGraw Hill's Biotechnology Newswatch*, 4 March 1996)

Japan Tobacco will start HIV clinicals

Japan Tobacco Inc. (JT) is planning to start clinical testing of an anti-HIV drug which it has developed jointly with Agouron Pharmaceutical Inc.

The drug has already gone into Phase-I and -III clinical tests in Europe and the US, respectively.

Results of clinical tests so far conducted in the West show that the drug acts to reduce HIV in the blood of AIDS patients by as much 98 per cent. Other clinical tests also show that use of the drug in combination with Bristol-Myers Squibb's D4T results in an HIV-decrease rate of 99 per cent or more.

JT expects that manufacturing approval for the drug in Japan will be sought in 1998, aiming at an early-1999 sales start-up. The drug stops the function of the enzyme that is created when the AIDS virus starts propagating inside the body, helping to halt the action of the enzyme. (Source: *McGraw Hill's Biotechnology Newswatch*, 4 March 1996)

Rules on DNA vectors eased

The Science and Technology Agency (STA) has announced a revision of the rules on the approval of some recombinant DNA experiments, making it easier to use viral vectors and recombinant plants and animals developed overseas. Under the new guidelines, experiments using viral vectors will no longer need individual scrutiny by a committee within the STA; instead they will be able to gain approval from the safety committees of individual institutions.

Similarly, recombinant organisms produced overseas will no longer require individual assessment by the STA before they can be imported and used in experiments. Guidelines for field release of recombinant organisms have not been formulated as no applications for such experiments have yet been made, says the STA. (Source: *Nature*, Vol. 380, 18 April 1996).

Malaysia

Biodiagnostic company to expand product range

Malaysia's first biodiagnostic company, Malaysian BioDiagnostic Research (MBDr) has recently announced an expansion of its activities into developing a wider range of biodiagnostic kits, mainly for tropical infectious diseases. Following the successful launch of its first product, the TyphiDot diagnostic kit for typhoid fever, MBDr has been actively promoting this kit within Malaysia as well as in neighbouring countries (Indonesia, Philippines) which have high incidences of the disease.

Working closely with a research team based at Universiti Sains Malaysia in Kubang Kerian, Kelantan, MBDr is now developing more diagnostic kits for filariasis, tuberculosis, and bacterial diarrhoea. Filariasis is caused by the helminthic parasites *Brugia malayi* and *Wuchereria bancrofti* and can be treated effectively if diagnosed early. Failure to do so may result in elephantiasis. Accordingly, the USM/MBDr effort is focused on developing both antibody- and antigen-based assays for early detection.

Tuberculosis remains an important problem worldwide and promising research based on DNA probes for strain typing, rapid detection of *M. tuberculosis*, and differentiation of tuberculosis from tuberculosis-like diseases will hopefully result in improved diagnostic methods. (Source: *Australasian Biotechnology*, Vol. 6, No. 2, April 1996)

Taiwan

Three-tiered biotechnology programme

In 1982, Taiwan set forth a three-tier biotechnology programme, based on basic research (and training), technology transfer and industrial development. Since Taiwan's universities have been educational institutions, the development of a biotechnology infrastructure called for the creation of new research institutes.

Within the Academia Sinica (the Chinese Academy of Sciences), there are six institutes doing biological research: the traditional Chemistry, Biological Chemistry, Zoology and Botany, and the relatively new ones, Molecular Biology (IMB) and Basic Medical Sciences (IBMS).

The IMB's major research theme is the study of cellular responses to stress, while research at the IBMS is directed toward an understanding of the biology of the principal diseases in Taiwan (i.e., cardiovascular diseases, nasopharyngeal, cervical and hepatic cancers and hepatitis). A number of universities, such as National Taiwan University, National Chung Hsing University and Yang Ming Medical College, have improved their facilities and developed research projects in biotechnology mainly focused on diseases common to Taiwan, plant strain improvement and food processing. However, while there are active research projects at the universities and medical centres, the major thrust in biological research takes place in the institutes of the Academia Sinica.

The 15-year effort to build up Taiwan's infrastructure in biological research has been considered fairly successful. However, there is some concern that insufficient effort has been directed toward issues that directly affect Taiwanese society. It is with this in mind that the Institute of Biological Chemistry under Dr. Darrell Liu (formerly with the FDA) is looking into the possibility of doing research on the production of blood proteins to cut the high cost of importing blood-related products (e.g., serum and plasma).

A new institute of agricultural biotechnology is being planned that will focus on such problems as post-harvesting technology, ornamental plants, animal vaccines, aquaculture and waste treatment.

A major new initiative has been the establishment of a National Health Research Institute (NHRI). Like the NIR, the NHRI will become a major centre for intramural and extramural health research.

Now located within the IBMS in the Academia Sinica campus, the NHRI will eventually move into its own facilities at a site yet to be chosen. The extramural programme supports research into major disease categories, public health policy and medical and drug technology.

The second component of Taiwan's biotechnology programme is the creation of a non-profit, state-funded, technology transfer centre, the Development Centre for Biotechnology (DCB). DCB's mandate is to carry out development work and to transfer new products and technology to Taiwanese industry. DCB is faced with the challenge of providing a bridge between the research taking place in the Academia Sinica and the universities, and the manufacturing taking place in the private sector. Its development work has centred on diagnostic kits and animal vaccines, agricultural and specialty chemicals and traditional fermentation. It is widely acknowledged that technology transfer is a complex and difficult process even in highly industrialized countries. DCB's task is made difficult by a lack of applications-oriented research and even more so by the nature of Taiwan's industrial base. The greater part of Taiwan's industry consists of small and medium-sized companies with limited R&D capabilities. Furthermore, almost all of Taiwan's bioindustry is in traditional sectors such as brewing, amino acids and food, and the number of small biotech companies is negligible. (Extracted from *Genetic Engineering News*, 1 April 1996)

Thailand

The debate in Thailand

Thailand's current draft Plant Protection Act (modelled after UPOV Convention of 1978) has the country divided over who will benefit from such a law. Some people within the Ministry of Commerce and the transnational corporations (TNCs) expect the law to motivate TNCs to improve varieties and bring those new varieties into Thailand so the country can perform better on international markets. A second group, mainly made up of people from the Ministry of Agriculture and public breeding institutes, figures that breeders will probably benefit from such a law but are afraid of what impact it may have on farmers. At the same time, public breeders, farmers organizations and non-governmental organizations (NGOs) are finding common ground in opposing the law.

Some officials at the Department of Agriculture are coming around and recognizing this too. The evidence shows that 90 per cent of new varieties are improved by farmers. And evidence may point to more constructive solutions than pressure from developed countries or big industry. Within the framework of the *sui generis* window provided in TRIPs, a multisectoral Thai working group composed of people from the Thai Traditional Medicine Institute of the Ministry of Public Health, lawyers associations, universities, farmers groups and NGOs is developing a Farmers' Rights Law on genetic resources. The law takes as its starting point the fact that Thai farmers are active and important breeders with their own varietal development processes, their own ways of managing knowledge, their own criteria for selection which include productivity and their own needs for support as the essence of Thai agriculture. The Farmers Rights Law departs from Plant Breeders Rights (PBR) but tries to fulfil the country's obligations to TRIPs. Because it aims to be responsive to the majority of the country's crop improvers, rather than caving in to a few companies, it sits on other foundations: the objective is to ensure stability of the food system and sustainability of agricultural systems. The law would allow communities, individuals and government organizations to hold farmers' rights on genetic resources. Breeders and biotechnologists who exploit communities' genetic resources must give something in return.

The Farmers Rights Law is being elaborated, on the basis of wide consultation with rural communities, in tandem with a separate bill to protect Thai indigenous knowledge in the field of medicine. Therefore, the two will be proposed as WTO-valid counter-measures to the dubious Plant Variety Protection Act within the next few years. Extracted from: Witoon Lianchamroon, LOKDULYAPAV/TREE, "Intellectual Property Rights on

Genetic Resources: Case Study of Thailand", paper presented to the South-East Asian meeting of the Crucible Group, 7-9 May 1996, Cavite, Philippines. (Source: *SEEDLING*, June 1996)

United Kingdom

Politicians press case for Human Genetics Commission

A UK parliamentary committee has reiterated a suggestion first made in 1995 that the Government should set up a broad-ranging Human Genetics Commission to deal with the inter-relationship between many different aspects of genetic science. It says that it is confident that this suggestion—initially rebuffed by Whitehall—will now be accepted.

The proposal was made by the House of Commons select committee on science and technology, following a lengthy inquiry into the field. In its response to the committee's conclusions last year, the Government rejected the idea of a new body as unnecessary, in the light of existing specialist advisory committees. But in a highly unusual move, the committee organized a follow-up series of hearings to restate its case.

During these hearings, government ministers indicated that they were prepared to reconsider their earlier reaction and in a report on the hearings, the all-party committee says it now expects some form of body to be set up by the Government. The main aim of the body would be "to foster public confidence and understanding" of genetics. But it adds that "in practical terms the commission's function would be to advise the Government on the broad issues raised by genetic science." (Source: *Nature*, Vol. 381, 2 May 1996)

New GMO regulations become law

New regulations covering the contained use of Genetically Modified Organisms became law in the UK on 27 April 1996.

The Genetically Modified Organisms (Contained Use) Regulations 1996 were laid before Parliament on 3 April and take into account recent technological advances. They implement European Commission Directive 94/51/EC of 7 November 1994 on the contained use of genetically modified micro-organisms (GMMs).

They amend the 1992 Contained Use Regulations that implemented a European Council Directive by setting up a notification scheme for activities with GMOs, and laid down criteria for the classification of GMMs, according to the potential harm they represent to people or the environment.

The amending Regulations implement a European Commission Directive and correct some difficulties which have arisen in the practical application of the 1992 Regulations, whilst maintaining "high standards of human health and environmental safety", according to the UK Health and Safety Commission.

The principal changes are:

- A new and simplified system for classifying GMMs according to their potential harmfulness to people or the environment. The classification partly determines the procedure to be followed in notifying the activity to the Health and Safety Executive.
- Exclusion of people from the scope of the Regulations so that they are no longer regarded as GMOs under the regulations, i.e. when undergoing gene therapy; the old regulations covered people who had been treated by modern genetic techniques.
- Exemption of certain marketed products which have been cleared through relevant product legislation.

The 1992 Regulations remain unchanged concerning risk assessment, control measures to protect health and the environment and the disclosure of information to the public.

The UK Health and Safety Executive will publish a revised guide of the new Regulations at the end of May. For further details contact: HSE Information Centre in Sheffield, UK. Tel.: 44 114 2892345. Fax: 44 114 2892333. (Source: *Biotechnology Business News*, 8 May 1996)

UK gene therapy patients no longer classified as GMOs

Good news for gene therapy patients in the UK is that they are no longer classified as genetically modified organisms (GMOs). Until recently, the UK Government's official interpretation of the 1992 EC genetically modified organisms (contained use) regulations classified a gene-therapy patient as "a genetically modified organism which is not a genetically modified micro-organism and which is as safe in the containment facility as any recipient or parental organism." But on 27 April, a new set of UK regulations implementing another European directive (94/51/EC) came into force that exempts GMOs that are "human or a human embryo" from governmental bureaucracy. The UK had stood alone in Europe in regulating humans. Now, however, the Secretary of State for the Department of the Environment, appears to have reconsidered the GMO-status of gene therapy patients. Civil servants, and patients alike, must be heaving a collective sigh of relief. After all, it must have been an administrative nightmare filling in and processing 60-day notification and risk assessment forms for every time the patient went to the supermarket or emptied the rubbish bin. And with the holiday season coming up, export licenses are in short supply. (Source: *Nature Biotechnology*, Volume 14, June 1996)

UK may set up genetics advisory body

The UK Government has agreed to discuss setting up a transdepartmental advisory committee to monitor both the commercial applications and ethical implications of human genetics.

In doing so, the Government appears to have agreed with members of the House of Commons Select Committee on Science and Technology that the existence of such a body might help to reassure the public that the potential dangers of the applications of genetics were being adequately considered.

Two months previously, in its formal response to the report, the Government rejected its main recommendation. This was that a Human Genetics Commission be set up, with broad-ranging powers both to monitor and to regulate activities ranging from genetic screening to the way in which genetic information is used by insurance agencies. (Source: *Nature*, Vol. 380, 7 March 1996)

United States of America

A capital year

Biotechnology companies in the US almost doubled the amount of financing they received last year. And they formed almost three times as many partnerships with

pharmaceutical companies as they did in 1994. The financial community's interest in the sector appears to have revived.

Biotech companies received $6 billion from public and private offerings, venture funding and partnerships, according to US merchant bank Burrill & Craves.

The industry was involved in some consolidation over the year. For example, Chiron bought Viagene for $36 million and Rhône-Poulenc Rorer absorbed the rest of Applied Immune Sciences for $84 million.

At the same time, strategic partnerships were taking off. Hoechst Marion Roussel's collaboration with Cell Genesys in AIDS therapy was one of the largest single-product deals in the industry's history; it could be worth $160 million.

Pharmaceutical companies formed almost three times as many partnerships with biotech companies last year as in 1994, according to biotech consultants Feinstein Partners. There were 171 alliances valued at more than $4.7 billion compared with 66 raising $3.2 billion in 1994. Ciba's deal with Chiron brought in a hefty $2.1 billion alone. (Source: *Chemistry & Industry*, 15 January 1996)

AIDS study recommends more investigator-initiated research

An extensive study of the AIDS research programme at the National Institutes of Health makes a number of recommendations to the Office of AIDS Research (OAR) that could change the programme substantially. These include an infusion of new investigators by putting more emphasis on investigator-initiated hypothesis-driven research, increasing efforts to produce a vaccine against the human immunodeficiency virus, and augmenting research to understand the human immune system. The study recommends that NIH develop a comprehensive prevention science agenda to fight AIDS, which combines biomedical, behavioural, and social interventions. The 40-page report was developed by a panel of scientists, clinicians, representatives from drug companies, and members of the HIV community. (Source: *Chemical and Engineering News*, 25 March 1996)

US military tightens rules on DNA records

The US Department of Defense (DoD) has agreed to modify the rules governing the use of the DNA records it keeps on military personnel, in response to increasing public concern that the records could be misused.

The move comes as two US Marines are due to be court-martialled for refusing to contribute a DNA sample to what is believed to be the world's largest gene bank.

The DoD, which says it has built up its DNA records solely to aid the identification of troops killed in battle, now says that individuals can ask for their own record to be destroyed when they leave military service.

It also promises to destroy all such records itself after 50 years, rather than 75 years as it had previously promised, and has placed tight restrictions on the circumstances in which the information can be used for purposes other than identification of remains. But it still plans to continue the compulsory collection of DNA samples from soldiers and support personnel. (Source: *Nature*, Vol. 380, 18 April 1996)

Genetic data ban for US insurers

The US Senate had unanimously passed a health reform bill that explicitly bars insurers from using "genetic information" to deny coverage to applicants. The bill's House of Representatives counterpart, passed on 28 March, also includes such information among factors that insurers may not use to deny coverage, making it highly likely that both bodies will agree to this measure in any joint legislation. The main goal of the Senate bill is to prevent people from losing health insurance when they change or leave jobs. (Source: *Nature*, Vol. 381, 2 May 1996)

Ceiling principle "not needed" in DNA cases

DNA samples can be used for positive identification of crime suspects with greater certainty than has been assumed, according to a report released by the US National Academy of Sciences (NAS). As a result, the academy recommends that prosecutors should no longer use the so-called "ceiling principle" to estimate the probability of a suspect being mistakenly identified by DNA evidence.

The "ceiling principle" was recommended by an academy panel in 1992 as a means of estimating the chances of a mistaken identity in cases—quite common in the US legal system—where the suspect belongs to the same racial group as the perpetrator, but where information is scarce about the level of shared genetic information among members of that group.

The new report, prepared by a panel abandons the "ceiling principle". It argues that, with better genetic information now available about different racial groups, prosecutors should estimate the chances of mistaken identity by more direct and less conservative means.

The main reason for the change is "the great abundance" of data now available about different genetic populations. The panel's report states that the technology for DNA profiling, and the methods for estimating frequencies and related statistics, "have progressed to the point where the reliability and validity of properly collected and analysed DNA data should not be in doubt".

The academy agreed to take a new look at the role of DNA in legal proceedings at the request of the Federal Bureau of Investigation (FBI)—a move that prompted some scientists to complain that the academy's neutrality was being compromised. (Source: *Nature*, Vol. 381, 9 May 1996)

NIH proposes to disband RAC

A notice proposing to disband the Recombinant DNA Advisory Committee (RAC) of the US National Institutes of Health will soon be published in the Federal Register.

The RAC was established in 1975 in response to public fears about the fast progression of genetic technology. It comprises a panel of scientists, ethicists and other experts at NIH appointed to provide key guidance in the field of genetic engineering. Most notably, the RAC created the first formal review system for proposals to insert new genes into humans, and the first approval of a human gene therapy experiment.

The committee used to review every gene therapy proposal for humans in the US until last year when a trial programme was implemented that permitted many proposals to skip RAC review and go directly to the US Food and Drug Administration. An ad hoc group was established to study the programme and make recommendations for future gene therapy proposals. The research group led by Inder Verma of the Salk Institute, proposed disbanding the committee.

The announcement has received mixed reactions. Concern has also been expressed over leaving gene therapy strictly in FDA hands because the agency's focus is much narrower than the RAC. For example, the RAC could reject

a proposal on grounds of ethics, whereas the FDA can only reject proposals on the basis of safety and efficacy.

The NIH Office of Recombinant DNA Activities, which oversees the RAC, will continue to keep a registry of all gene therapy experiments in the US as well as keep a permanent staff of advisers on board. (Source: *Biotechnology Business News*, 4 June 1996)

USDA AgBiotech Office closes

The USDA Office of Agricultural Biotechnology has closed as of 19 February 1996. The office was set up in 1986 to coordinate USDA activities related to biotech. Its functions will now be distributed to other agencies, for which contacts are listed below. Contact:

- Biotechnology Information: Ray Dobert, Director, Biotechnology Information Centre, USDA National Agricultural Library. Tel.: 301/504-5340; Fax: 301/504-7098; e-mail: rdobert@nalusda.gov
- Biotechnology Regulations: John Payne, Acting Director, BBEP, USDA/APHIS. Tel.: 301/734-7602; Fax: 301/734-8669; e-mail; jpayne@aphis.usda.gov
- Technology Transfer and Patenting: Richard Parry, USDA/ARS. Tel.: 202/720-3973; Fax: 202/720-7549; e-mail: parryr@ars.usda.gov
- Media Press Information: Maria Bynum, USDA Office of Communications. Tel.: 202/720-5192; Fax: 202/690-3611; e-mail: mbynum@usda.gov (Source: *The AgBiotech Bulletin*, March 1996)

D. RESEARCH

Research on human genes

New altered tumour suppressor gene

Scientists from the Kimmel Cancer Center at Jefferson Medical College (Philadelphia, PA), working with a Japanese collaborator from Kyushu University, have discovered what seems to be an altered tumour suppressor gene implicated in a range of human cancers. The discovery could lead to the development of tests for individuals predisposed to certain cancers as well as drugs to head off the formation of stomach, colorectal and esophageal cancers, and perhaps a host of other cancers apparently caused by the aberrant gene.

The gene, called FHIT (for Fragile HIstadine Triad), is located in a fragile area on human chromosome 3 known as 3pl4.2, a site especially prone to breaks and gaps. For some 10 years this chromosomal region has been the target of an international effort to locate cancer-associated genes.

Scientists have long suspected an important gene would be found there. The first clue occurred in 1979, when a Harvard group found that this portion of chromosome 3 was translocated to chromosome 8 in several generations of a family with inherited renal carcinoma. At the time it was suggested that the translocation was knocking out the expression of an unknown tumour-suppressor gene, leading to cancer.

Last year, the Jefferson team, studying several tumour cell lines—nasopharyngeal, colon, esophageal and stomach—found large pieces of DNA missing in the same fragile area of chromosome 3. Shortly thereafter, the team, using recently developed amplification techniques, discovered the damaged FHIT gene.

It is possible the gene is altered by exposure to agents that affect DNA replication, such as nicotine, caffeine, alcohol, and other known carcinogens. A mutated FHIT gene could be inherited.

So far the investigators have linked FHIT damage to cancers of the airway and digestive tract by examining normal and malignant tissue obtained immediately after surgery in patients with such cancers. FHIT may also be involved with kidney, lung, ovarian, cervical and breast malignancies.

Masatake Ohta Ph.D., a visiting Japanese scientist at Jefferson and the first author of the new study, adds that understanding FHIT gene abnormalities may make a major contribution to the fight against esophageal cancer, a scourge in the Far East affecting millions of people.

Zinc deficiency, which is frequently associated with esophageal cancers in humans and rats, may cause proliferation of the epithelial cells lining the esophagus. The deficiency may mimic the loss of the FHIT protein, thus leading to cancer. (Source: *Genetic Engineering News*, 15 March 1996)

Anti-tumour activity with genetically altered immunotoxin

Researchers at the National Cancer Institute (Bethesda, MD) say that a genetically engineered immunotoxin (LMB-1) has shown anti-tumour activity for the first time in colon and breast cancer in a Phase I trial conducted at NCI. LMB-1 was engineered by Ira Pastan, M.D, and his team of researchers at NCI in 1991. The Phase I trial involved 38 patients with large solid tumours.

Patients were treated with doses of LMB-1 ranging from 10-100 micrograms per kilogram. One breast cancer patient had a complete remission, and one colon cancer patient had a greater than 75 per cent reduction in a large abdominal tumour mass and disappearance of cervical lymph node metastases, according to the scientists. Overall, anti-tumour activity was seen in five patients, stable disease in 18 patients and progression of disease in 15 patients. Although the positive responses only lasted from 3-9 months before the cancer began to progress again, Dr. Pastan called the results "incredibly significant...just proving the principle can work was an enormous accomplishment." (Source: *Genetic Engineering News*, 1 April 1996)

Gene with role in lupus

The National Institute of Health's National Institute of Arthritis and Musculoskeletal and Skin Diseases (Bethesda, MD) has identified a gene associated with increased risk of lupus kidney disease in African Americans. The gene controls production of Fc receptors, which can help white blood cells capture and destroy immune complexes. The researchers determined that inheriting a low capacity for destroying immune complexes can be a factor in lupus nephritis, since the complexes can build up in the kidneys and cause inflammation leading to tissue injury. (Source: *Genetic Engineering News*, 1 April 1996)

Low oxygen in tumours may trigger takeover by malignant cells

Lack of oxygen may be the trigger that allows transformed, precancerous cells to take over a tumour, changing it from benign to malignant. Thomas G. Graber and Amato J. Giaccia at Stanford University's School of Medicine, with colleagues there and at several other laboratories, find that oxygen-starved cells die in solid tumours in rats, but they do so selectively. Cells in which the p53 gene has been mutated survive much better in low-oxygen conditions than do cells with normal p53 genes. The function of the p53 gene seems to be to produce a protein when cells are under stress that causes the cells to stop growing or die. Thus, cells that lack a normal p53 gene lack this emergency brake. Because only the normal cells die, those with mutant p53 genes take over the tumour. Earlier research showed that radiation and certain drugs also can trigger the selective death of cells that contain functioning p53 genes, but neither of these experimental agents is likely to be the natural trigger for this process in tumours. Regions of low oxygen, however, are common in solid tumours, occurring whenever the growth of oxygen-supplying blood vessels cannot keep up with tumour growth. (Source: *C&EN*, 6 January 1996)

Growth factor gene linked to dwarfism

A study at the National Institutes of Health has linked a mutation in a growth factor gene to a type of dwarfism that is characterized by abnormal development of the limb and limb joints.

The identification of the gene and its critical role in skeletal development could lead to new approaches for repairing cartilage and bone defects and reconstructing joints.

Scientists in the Bone Research Branch at the National Institute of Dental Research identified the structure of the human gene that carries the blueprint for a growth factor called cartilage-derived morphogenetic protein-1, CDMP-1.

The researchers discovered that a mutated version of the gene is present in individuals with a form of dwarfism known as Hunter-Thompson type chondrodysplasia.

Identification of the human gene opens the door for using recombinant DNA technology to produce CDMP-1 commercially and evaluate its potential for skeletal repair and joint reconstruction.

Although the scientists still do not know exactly how the growth factor functions, recent work by study director Frank Luyten demonstrated that a recombinant form of CDMP-1 led to the formation of cartilage and bone when implanted under the skin of rats.

CDMP-1 is a growth regulator that is a member of the transforming growth factor-beta (TGF-beta) super family of proteins, which have many diverse functions in normal development. Despite the fact that Hunter-Thompson chondrodysplasia is quite rare and has been documented only in a few families from isolated communities, this study is the first example of a human disorder attributable to a mutation in one of these proteins. (Source: *Biotechnology Business News*, 12 March 1996)

Tunnel vision

The commonest form of tunnel vision is caused by a defect in a protein that acts like a haulage contractor, shunting around other proteins inside cells in the retina.

Researchers in Edinburgh, Munich and Naples have reported a defective gene that causes X-linked retinitis pigmentosa, which eventually blinds its mostly male sufferers.

Alan Wright of the Medical Research Council's Human Genetics Unit and his colleagues say that the gene is similar to another human gene called RCC1. This codes for one of a family of proteins called Ran, which move proteins around within cells.

Replacing the defective gene may be feasible, says Wright, particularly if the cells affected are the retinal pigment epithelial (RPE) cells at the back of the eye, which take nutrients from the blood and pass them to the retina's light-sensitive cells. These cells readily absorb any material in the eye, he notes. (Source: *New Scientist*, 11 May 1996)

New drug against cancer to be tested

A drug designed to stop cell proliferation in almost a third of all human cancers is to be tested in people this year. The drug sabotages tumour cells that make defective versions of Ras—a protein that tells cells to divide.

In many human cancers, abnormal Ras proteins get locked into their active form, and keep ordering the cells to make copies of themselves. The new drug is designed to break this cycle.

Said Sebti and Andrew Hamilton at the University of Pittsburgh in Pennsylvania have already tested their drug in mice implanted with human cancers that make defective Ras proteins. "The tumours stopped growing," says Sebti. The mice did not appear to suffer any toxic effects, suggesting that the drug—a synthetic peptide—will not cause the side effects common to most anticancer drugs. Human trials will begin by the end of the year, Sebti told a meeting of the British Biochemical Society in Liverpool early in 1996.

Some 90 per cent of people with pancreatic cancer make the defective protein, as do half of all those with cancer of the colon and 30 per cent of those with a common form of lung cancer

The drug does not destroy defective Ras proteins. Instead, it prevents them from entering the outer membrane of a cell from the cytoplasm inside. The defective proteins are harmless while floating around in the cytoplasm, but once they reach the membrane, they deliver messages to the nucleus, ordering the cell to divide.

The Ras proteins can only reach the cell membrane from the cytoplasm if they are labelled with a molecule that acts as a molecular "zipcode".

The new drug acts on lipid transferase, the enzyme that attaches the lipid code to the protein. The molecule occupies a part of the lipid transferase molecule that must dock with the Ras protein in order to pass on the code. Denied access to the docking site and the code, the defective protein stays in the cytoplasm.

The team designed the drug molecule so that it cannot be deactivated by enzymes. Also, the molecule has fat-loving characteristics that enable it to break through the cell membrane into the cytoplasm. (Source: *New Scientist*, 27 April 1996)

Mechanism of insulin resistance in obesity identified

The mechanism of obesity-induced resistance to insulin—which puts obese individuals at risk for developing heart disease and Type II diabetes—has been identified by a team of scientists at Harvard University. Knowing that the fat cells of obese individuals contain tumour necrosis factor-α (TNF-α) at levels that correlate with the extent of both obesity and insulin resistance, the researchers tackled the role of TNF-α in promoting insulin resistance. (TNF-α is a hormonelike compound that normally acts on immune system and inflammatory cells.) The researchers found that TNF-α induces resistance by phosphorylating a key substrate in the insulin pathway, insulin receptor substrate 1 (IRS-1), at serine residues. This altered form of IRS-1 inhibits the first step in the insulin pathway—autophosphorylation of the insulin receptor after insulin binds to it. Mutant cells lacking IRS-1 were not able to inhibit insulin phosphorylation. The team believes that in addition to being a substrate in the insulin pathway, IRS-1 also may act to inhibit the pathway. (Source: *C&EN*, 5 February 1996)

Magainin identifies two asthma genes

Magainin Pharmaceuticals Inc. has identified two genes believed to be critical in the pathogenesis of asthma, according to an official at Plymouth, MA headquarters. The genes, Asthma Associated Factor 1 (AAF1) and Asthma Associated Factor 2 (AAF2) are the subject of pending patent applications.

Roy Levitt, director of Magainin's Institute of Molecular Medicine, and his collaborators, determined that AAF1 and AAF2 appear critical in determining the allergic and inflammatory response characteristic of bronchial asthma, the official said. These genes regulate mediators of the allergic response, including serum IgE molecules. Variant forms of these genes occur widely and appear to be significant in susceptibility to asthma, the official added. (Source: *McGraw Hill's Biotechnology Newswatch*, 18 March 1996)

A third breast cancer gene?

Recent US research has confirmed that there may be three or more breast cancer genes.

In 1994, scientists at the National Institute of Environmental Health Sciences (NIEHS), the University of Utah and Myriad Genetics reported that mutations of the first identified breast cancer gene, *BRCA1*, seem to be responsible for approximately half of the 5-10 per cent of breast cancers that run in families.

The second breast cancer gene, *BRCA2*, was identified December 1995 and thought to be responsible for the rest of family incidents of breast cancer.

A research team made up of scientists from Duke University and NIEHS, studied 49 families, mostly from Canada, with extensive histories of breast cancer and determined that the second breast cancer gene may not be responsible for as many incidences of familial breast cancer as first believed.

Researchers studied 49 families whose incidents of familial breast cancer seemed unlikely to be attributable to the first breast cancer gene, *BRCA1*. Scientists expected to find a large number of mutations of *BRCA2*, but found only eight. The study results indicated that members of *BRCA2*- mutated families have an increased risk of male breast cancer.

Of the eight families with *BRCA2* mutations, half had members with pancreatic cancer at young ages. Scientists said this implies an association. Also of the eight mutated families, two had incidences of prostate cancer, compared to three out of 41 of the non-mutated families. (Source: *Biotechnology Business News*, 8 May 1996)

BRCA1 works outside cells and as growth inhibitor to stop cancer

BRCA1, the notorious inherited cancer gene identified in 1994, has been assumed to be a tumour suppressor gene which, if lost or mutated, leaves breast and ovarian cells dangerously prone to malignancy.

Now two research groups claim that they have confirmed that assumption, but in doing so have discovered something even more interesting.

BRCA1 appears to be a secreted protein that acts outside cells as well as a potent and very specific inhibitor of cell growth. In fact, the researchers suspect that the action of this protective gene and protein may be responsible for the well-known observation that pregnancy early in life significantly reduces later breast cancer risk, and, because the *BRCA1* protein appears to be active in some extracelluar signalling pathway, Dr. Jeffrey Holt, a cell biologist at Vanderbilt University, and his co-workers are excited about the possibility of designing drugs to alter that pathway and perhaps reduce cancer risk.

Women with a germline *BRCA1* mutation are at an enormously increased risk of breast cancer (about 85 per cent over a lifetime) and ovarian cancer (about 50 per cent). In sporadic breast cancers, the role of the mutated gene is less clear, but one allele of *BRCA1* is completely deleted in 50 per cent of sporadic breast tumours and 70 per cent of tumours of the ovary.

The researchers found that when several types of cancer cell lines were transfected with viral vectors containing *BRCA1*, the expression of wild-type *BRCA1* completely shut down breast and ovary cancer growth but not that of colon or lung cancer cells. (Mutated *BRCA1* had no effect on the cell lines.) Thus, it seems that the *BRCA1* protein not only inhibits tumour cell growth, but does it selectively.

In addition to transfecting cancer cell lines, the researchers injected viral constructs containing both wild-type and mutant *BRCA1* genes into mice that had been inoculated with tumours grown from human breast cancer cells. In one experiment, all five mice that had received the mutant genes were dead within 11 days. But the mice treated just once with normal *BRCA1* survived for an average of 24 days, with a range of 14 to 41 days.

On autopsy, two of the five animals that received normal *BRCA1* genes were entirely free of tumour. The other three mice had small tumours.

The authors caution that the experimental results need confirmation, and that the road to a new approach to breast cancer treatment will be long. And, they acknowledge, the data showing an extracelluar localization for the protein must be reconciled with a previous report that found the normal *BRCA1* protein residing in the nucleus, rather than being exported outside the cell. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 18 March 1996)

Research on animal genes

Mollusc shell macromolecules help determine crystal forms

Understanding how organisms control which polymorph (crystal form) of a mineral is precipitated at a given location is one of the major challenges in the field of biomineralization. For example many species selectively form either aragonite or calcite—two forms of calcium carbonate with similar crystalline structures—at adjacent locations. Lia Addadi and co-workers in the department of structural biology at Weizmann Institute of Science in Rehovot, Israel, have now shown that hydrophillic organic macromolecules extracted from aragonitic mollusc shell layers specifically induce formation of aragonite in the laboratory, whereas macromolecules extracted from calcitic layers induce the crystallization of calcite. The aspartate-rich macromolecules have yet to be characterized. The team also demonstrated that magnesium ions, which have been thought to influence the regulation of aragonite-calcite polymorphism, did not play a role in the selection of polymorph type in their experiments. (Source: *C&EN*, 8 January 1996)

Micro-satellites used to establish pedigree

Several purebred cattle associations are insisting on the use of DNA fingerprints to guarantee pedigree. DNA fingerprints can be obtained from tissue samples, including hair follicles.

The latest in DNA fingerprint technology uses micro-satellites, marker genes located along chromosomes. Some 1,000 satellites can be identified, and parentage verified by selecting a dozen. DNA testing also facilitates screening for disease. Test results can now be obtained in 24 hours. (Source: *The AgBiotech Bulletin*, April 1996)

New antibiotic protein extracted from Oryctes Rhinoceros beetle

Japan's National Institute of Sericultural and Entomological Science of the Ministry of Agriculture, Forestry and Fisheries and the Shikishima Central Research Laboratory have jointly succeeded in separating three new types of antibiotic proteins capable of efficiently killing

Escherichia coli, Staphylococcus aureus and *Streptococcus pyrogenes* from the larva of the Oryctes rhinoceros beetle. These antibiotic proteins have been named rhinocerosin, oryctin and tryphacin, respectively, and patents are pending for these proteins.

The probe for new antibiotic proteins was directed on the Oryctes rhinoceros beetle that exists only in Okinawa Prefecture in Japan. The beetle larvae proliferate in compost produced from cattle excrement, and subsist in environments easily infected by microbes such as pathological bacteria, viruses and moulds. The larvae capable of coexisting with these various types of microbes are conceived to have highly advanced biotic prevention mechanisms. The body fluid extracted from the larvae was investigated and discovered to display a pronounced antibacterial effect with respect to methicillin-resistant *Staphylococcus aureus* (MRSA) that is resistant to antibiotic substances, therefore attempts were made to separate and purify these proteins.

Rhinocerosin has the effect of killing *Staphylococcus aureus, Streptococcus pyrogenes* and *Escherichia coli* effectively. Among the three kinds of antibacterial proteins, tryphacin has a rather low bacteria proliferation suppression effect, but closely resembles the antibiotic agents available on the market due to its extremely low molecular weight.

Antibacterial proteins separated from larvae kill bacteria by opening holes in their cell membranes, so display a strong antibacterial effect even with respect to bacteria such as MRSA which have become resistant to antibiotic agents. To benefit from this characteristic, research is being advanced throughout the world, but up till now, there has been no announcement of any successful commercialization. Further information from: National Institute of Sericultural and Entomological Science Ministry of Agriculture, Forestry and Fisheries 1-2, Owashi, Tsukuba City, Ibaraki, Pref. Tel.: +81-298-38-6026; Fax: +81-298-38-6028 (Source: *JETRO*, February 1996)

Genzyme, Bristol-Myers fete birth of goat with gene for cancer antibody

She's not the first to carry a gene for a human antibody, and no one knows for sure whether her milk will actually contain much of the precious protein, but the staff at Genzyme Transgenics Corp. (GTC) had reason to ecstatically hand out cigars to celebrate the 20 March birth of Grace, the transgenic goat.

"She's the first animal that we produced out at our new facility in Charlton," said GTC Vice President of Transgenics Research Harry Meade. Prior to Grace, animals used in the GTC programme were produced at Tufts University.

"It shows that we're up and running—always a question with a new technology," said Meade. Her birth is also an important milestone in the company's collaboration with Bristol-Myers Squibb.

If Grace lives up to expectations, she could end up producing antibodies at 10 to 100 times the rate of the current standard technique—mammalian cell culture, he said.

Most reactors now yield about 100 mgs. of protein per litre, said Meade. In contrast, GTC currently has a lactating goat that produces about four to five mgs. of antibody per mil., the equivalent of about four grams per litre.

Grace has been genetically engineered using a microinjection technique that GTC licensed from DNX Corp., the Princeton, NJ firm that made headlines with its efforts to develop pigs that could become human blood and organ donors.

The inserted gene will allow her to produce the monoclonal antibody BR96, which homes in on cancer cells. Bristol-Myers Squibb (BMS) plans to deliver a chemotherapeutic called doxorubicin to malignant cells by attaching it to this tumour-seeking protein.

Based on experiments in which the antibody was produced in transgenic mice, scientists predict that Grace's milk will yield a version of BR96 with the ability to bind to human tumour cells. They will know for sure in about eight months when she is old enough to breed and lactate.

GTC, established in 1993, has so far created about 20 transgenic goats that make various therapeutic proteins, said Meade, a molecular biologist who grew up on a Pennsylvania dairy farm.

Farthest along is the goat-milk-derived form of antithrombin III, a plasma protein used to treat clotting disorders. It is slated to move into clinical trials later in 1996, and will be the first drug produced in the milk of a transgenic animal used to treat humans, according to Genzyme.

It took more than a year and about $6 million for the Charlton, MA, facility to reach this milestone, said Meade. Preparation included building the facility and importing goats, at the cost of $250,000, from New Zealand to ensure that they were free of scrapie.

GTC then had to find and train a staff to deal with the extraordinary conditions of working with transgenic goats, which includes a list of at least 130 standard operating procedures.

"There are more regulatory concerns than I initially thought there would be," Meade said. (Source: *McGraw Hill's Biotechnology Newswatch*, 15 April 1996)

Research on plant genes

Plant apoptosis

University of California (Davis) researchers have identified the process of apoptosis in plants. They believe that their finding may lead to new ways of genetically engineering disease-resistance in plants and help identify important genes involved in normal plant development.

The researchers observed abnormal changes in the DNA of the plant cell nucleus, leading up to apoptosis, during normal development and in response to toxins from a fungal disease.

Although apoptosis in recent years has been well-characterized in the animal kingdom, existence of such a process in plants has been an unresolved question among plant biologists. The scientists explored this area of research in an attempt to find out how genes normally involved with the developmental processes of plants might be involved in the plant's susceptibility to disease. As a research model, they were studying a fungal disease of tomato plants known as Alternaria-stem canker disease, which appears as a blackened area of dead cells at the site of infection. Previous research had shown that the Alternaria fungus produces a toxin that, alone or in the presence of the fungus, causes cell death.

The UC Davis researchers had observed that the Alternaria toxin produced the DNA abnormalities characteristic of apoptosis when tested on animal cells. Curious to see whether the Alternaria toxin would cause a similar reaction in plant cells, the researchers applied the toxin to

tissue from tomato leaflets and to tomato protoplasts. In both cases, the nuclear DNA fragmented, then formed apoptotic-like bodies that migrated to the edge of the cell. Finally, the treated cells disintegrated in only a few hours. The researchers then confirmed that the process was dependent on expression of plant genes and that the same events were observed in plant infection by the fungus. (Source: *Genetic Engineering News*, 1 May 1996)

Suicidal potatoes make sacrifice to save crop

Potatoes that have been genetically engineered to commit suicide if they are infected by disease could reduce the need to use pesticides on potato crops. If the potatoes are attacked by fungi the infected cells destroy themselves to avoid spreading the disease.

Barnase is an enzyme that destroys ribonucleic acids leading to a fatal halt in protein synthesis. Scientists from the Max-Planck Plant Breeding Institute in Cologne, took a gene that codes for barnase and attached it to one of the potatoes' controlling promoters. This promoter activates the gene associated with it when a pathogen attacks the plant. If a cell has been infected, the promoter turns on the barnase gene and kills it.

However, the researchers found that even a healthy, genetically modified plant makes small amounts of barnase, which could still be lethal. So they introduced an inhibitor into the plant, to counteract low amounts of barnase. Only when a pathogen attacks a cell will enough barnase be made to overcome the inhibitor and kill the cell. Both the barnase and inhibitor genes are derived form *Bacillus amyloliquefaciens*—a naturally occurring bacterium that occurs in soil.

The scientists now hope to get permission from the German authorities to start field trials, which will run for three years. Meanwhile, they are already starting to germinate seed potatoes of the new variety so that they will be ready. The scientists say that their genetic modification could drastically reduce pesticide use against serious diseases such as potato blight. (Source: *New Scientist*, 11 May 1996)

Suicide is also a plant's best friend

The cell suicide mechanism known as apoptosis, which protects vertebrates against cancer and infections, also keeps plants healthy. Scientists in California have found that apoptosis triggers "hypersensitive reactions" in disease-resistant plants, in which the first cells invaded by micro-organisms die and lock the invader in a cage of dead tissue.

A resistant cell that comes under attack by a fungus or bacterium emits a burst of hydrogen peroxide, which tells nearby cells to toughen their walls and begin producing antibiotic compounds. Chris Lamb and colleagues at the Salk Institute for Biological Studies in La Jolla have shown that this signal has a second effect: when resistant soya bean plants are attacked by the bacterium *Pseudomonas syringae*, the hydrogen peroxide from infected cells triggers a rush of calcium ions into these cells.

In mammals, an influx of calcium triggers apoptosis, and it seems to have the same effect in soya beans. Not only did the cells die, they also looked like apoptotic animal cells: their cytoplasm shrank, and the nuclei contracted into dense granules. Similar changes happened during the hypersensitive reaction of tobacco, the researchers found.

And when the research team used drugs to block the channels through which calcium enters cells, or grew the cells in calcium-free conditions, the bacterial infection did not cause cell death.

As in animals, the plant cells appear to cooperate in their demise. Drugs that inhibit cells from turning on enzymes known to be involved in apoptosis prevented cell death in soya bean cell cultures. The dying soya bean cells systematically chopped up their DNA into fragments of some 50,000 letters of the genetic code, just as happens in mammalian apoptosis.

All these similarities have led Lamb to think that apoptosis arose early in evolution, as a defence against disease. (Source: *New Scientist*, 4 May 1996)

Making insects hate rice

By taking a gene from the potato, Ray Wu's group at Cornell University (Ithaca, NY) has transferred resistance to a major insect pest of rice. Proteinase inhibitors block trypsin-like and chymotrypsin-like enzymes present in insect digestive systems. Using biolistic technology, the Cornell group introduced the potato proteinase inhibitor II gene (*pin2*) into suspension cells of various rice varieties. Challenging fifth generation transgenic plants, expressing *pin2*, with larvae of the pink stem borer, showed not only that the plants resisted disease but also that the larvae were unable to develop fully. (Source: *Nature Biotechnology*, Volume 14, April 1996)

Oilseed rape could cross-pollinate

One of the biggest worries about genetically engineered crops is that they will cross-pollinate with ordinary plants to make new generations of weeds. The biotechnology industry generally plays down these fears, but Danish researchers have now found evidence that cross-pollination could be a major problem in oilseed rape crops.

Denmark has a huge potential market for genetically engineered oilseed rape, says Thomas Mikkelsen, who led the research at the Risø National Laboratory in Roskilde. In Denmark, the crop plant (*Brassica napus*) is invariably infested with a weedy relative, *Brassica campestris*. Herbicides cannot distinguish between the crop and weed which are genetically very similar. But there are now genetically altered strains of oilseed rape that can resist specific herbicides. When sprayed with the herbicide, the genetic crop survives but the weeds wither, says Mikkelsen.

The team wanted to find out whether the altered crop could cross-pollinate with its weedy relative. They planted a mixture of altered *B.napus* and wild *B. campestris* in a greenhouse. Both crop and weed produced hybrid seeds, says Mikkelsen, and in many cases, the herbicide resistance was passed on.

Unexpectedly, the hybrids were not sterile, but produced hundreds of seeds. When planted, they grew into plants which could also cross-pollinate with both weed and crop varieties. The inserted gene survived the next generation and a large proportion (42 per cent) of the new hybrids were herbicide resistant. They also had the characteristic ability of weeds to lie dormant in the soil and sprout the following spring.

So far, the experiment has been confined to the controlled environment of a sealed greenhouse, but if the same process occurs in the field, farmers could almost be back to where they started, with a crop and a weed that are indistinguishable to herbicides. (Source: *Chemistry & Industry*, 18 March 1996)

Fungus for gene delivery

Researchers with the USDA Agricultural Research Service have patented a new process for delivering genes into plants. The process, which employs *Olipidium* zoospore fungus to ferry new genes into plants, has been used to transport marker genes into wheat. The fungus transfers DNA within an envelope comprised of material from the outer coat of the tobacco necrosis virus.

The researchers hope that the common soil fungus will provide an additional, low-cost transfer technology to compliment *Agrobacterium* and other methods. As the wide host range of the fungus includes broadleaf and grass species, it may provide a useful vector for legumes and many other crop plants.

Further information from: Lingyu Zhang and William Langenberg, USDA-ARS Wheat, Sorgum and Forage Research Laboratory, Lincoln, Nebraska, USA. Tel.: 402/472-3162. (Source: *The AgBiotech Bulletin*, April 1996)

Midge resistance in wheat studied

AgCanada's Winnipeg Research Centre has launched a Matching Investment Initiative project to develop midge resistance in wheat. The wheat midge is a major pest in western Canada.

Scientists will attempt to transfer midge resistance found in some winter wheat varieties to spring wheat. Field tests are registered for several sites around Winnipeg and Saskatoon.

Further information from: Dr. Jim Bole, Director, Winnipeg Research Centre, 195 Dafoe Road, Winnipeg, Manitoba R3T 2M9. Tel. 204/983-5533; Fax.: 204/983-4604. (Source: *The AgBiotech Bulletin*, March 1996)

Genes offer salt tolerance

Researchers at the University of California, San Diego say they have created mutant plant genes that block the uptake of salt in yeast cells. The technique offers a potential new approach for genetically engineering salt tolerant crop plants. Salts in agricultural soils are a major environmental and economic problem for farmers.

Researchers *Julian Schroeder, Francisco Rubio*, and *Walter Grassman* report finding a "transporter" gene that controls the blueprint of pathways for the uptake of the nutrient potassium. Under salty soil conditions, the potassium pathway encourages the uptake of sodium, which is toxic to plants and inhibits normal nutrient uptake.

Researchers then used chemicals to mutate transporter genes found in wheat roots, and transferred them into yeast cells. The cells were then exposed to sodium-rich environments. The surviving cells were found to carry a mutant version of the potassium transporter gene that produces salt tolerance.

The researchers will not be trying to insert these genes in plants, with the goal of achieving salt tolerant crops. (Source: *The AgBiotech Bulletin*, March 1996)

New selectable marker for wheat

Researchers at Monsanto have developed a new selectable marker, adding to the list of agents available for transformation of monocot species. The dual-gene system for herbicide tolerance combines two biochemical mechanisms for tolerance to glyphosate, and has been shown to be effective in wheat and corn, as well as several dicot species.

Genetic engineering of monocots has presented physiological and technical hurdles not seen with broadleaf species. One of the most limiting has been the lack of effective and alternative transformation selection systems. The new selectable markers for wheat developed at Monsanto lowers one of the barriers to developing a wider range of transgenic cereals and grasses. (Source: *The AgBiotech Bulletin*, March 1996)

Morphological changes in tobacco plant induced by antisense RNA expression of S-adenosyl-homocysteine hydrolase gene

Japan Tobacco Inc. has succeeded in inducing morphological changes into the tobacco plant by introducing an alien deoxyribonucleic acid (DNA) into the plant. The plant overall size has been made smaller, the single-petalled flower changed into a double one, and the plant is more resistant to plant viruses. The company judges that a fundamental technology has been established that can be applied to breeding plants other than tobacco, such as rice and horticultural plants.

S-adenosylhomocysteine hydrolase (SAHH) is known to control biological methylation reactions. DNA and protein methylation and demethylation are important in signal transduction in many organisms. Recently, it was also found to be a plant hormone (cytokinin) binding protein. Thus SAHH may be involved in the mechanism of cytokinin signal transduction.

To reduce the endogenous level of SAHH, transgenic tobacco plants expressing the antisense RNA of SAHH were produced. The transgenic plants displayed various phenotypic changes, including stunting, formation of lateral buds, delay of senescence and increased number of flower buds. The phenotype changes were also observed in the flowers, and the changes of anthers into petals as well as the appearance of male sterility were frequently observed. In addition, many of these transgenic plants displayed broad resistance to plant viruses.

The phenotypic changes varied depending on the transgenic lines, so any desirable phenotype can be selected. The technique can be applied to the creation of new varieties of plants, with flowering plants as good candidates.

Further details from: Japan Tobacco Industry Inc., Corporate Communications Dept. 2-2-1, Toranomon, Minato-ku, Tokyo 105, Tel: +81-3-3582-3111; Fax: +81-3-5572-1441. (Source: *JETRO*, February 1996)

Rice cDNA similar to maize NADP-dependent malic enzyme isolated

Nissan Chemical Industries, Ltd. has isolated a rice cDNA that is homologous to the gene for the maize NADP-dependent malic enzyme. The deduced amino acid sequence coded for by the cDNA indicates a high level of homology to the chloroplast type NADP-ME, including a transit peptide with pronounced hydrophobic properties at the amino terminus. The expression of this gene is regulated by external stress such as submergence.

The isolation of this rice cDNA paves the way for the flexible breeding of rice plants by applying genetic engineering and will enable rice plant breeding by the method of directly sowing unhulled rice seeds. The direct sowing method is ideal for large-scale paddy fields and is attracting attention as a method to bolster the international competitive strength of domestic rice farmers. The company plans further research with the aim of starting a seed business in the future.

Rice plant respiration on the cellular level includes a process for acquiring the necessary growth energy by con-

verting glucose into pyruvic acid, but further growth will be obstructed due to the lack of oxygen supply to the cells under water. The growth reaction will proceed efficiently as long as there is an adequate supply of malic enzyme, so inducing an appropriate volume of malic acid genes into the rice cells will enable rice plant germination and breeding even in paddy field water.

Further details from: Nissan Chemical Industries Ltd., Public Relations Dept., 3-7-1, Kandanishiki-cho, Chiyoda-ku, Tokyo 101, Tel.: +81-3-3296-8320; Fax: +81-3-3296-8210. (Source: *JETRO*, March 1996)

Transforming cassava

Suspension cultures, microballistics, and organogenesis are being explored as potential transformation systems for the important tropical and subtropical staple, cassava. Researchers at the University of Bath have identified a transient stage of callus development called friable embryogenic callus (FEC) that is an ideal source of totipotent cells for suspension cultures. The research team at the Scripps Research Institute then bombarded the cassava FEC suspension with microparticles carrying both the paromomycin resistance and *GUS* reporter genes. Regenerated transgenic cassava plantlets showed stable gene integration by using paromomycin selection. An alternative transformation approach has been used by a group at the Swiss Federal Institute of Technology, where they co-cultivated cotyledon explants of cassava with *Agrobacterium tumefaciens* regenerating transformed shoots. (Source: *Nature Biotechnology*, Vol. 14, June 1996)

Research on bacterial genes

Cellulose conversion

Knowing why certain bacteria are so effective in breaking down cellulose could eventually lead to efficient conversion of biomass into useful energy. For *Clostridium thermocellum*, a protein called CipA organizes several cellulase enzymes into a cohesive unit, which it leads to the cellulose material, says researcher David Wu at the University of Rochester, NY. The protein anchors itself to the cellulose, and the enzymes begin their work. Although considered more primitive than fungi, the bacterium's well-organized enzymes explain its superior efficiency in conversion. His team included researchers from MIT and Tzu Chi College of Medicine in Taiwan. (Source: *Industrial Week*, 4 December 1995)

Bacteria dish up toxic meal for mosquito larvae

Water-dwelling bacteria spiked with poisons could spell death for the larvae of mosquitoes that spread malaria and other tropical diseases. Researchers in Singapore have genetically engineered the bacteria so they make toxins that will only kill the mosquito larvae that eat them.

Alan Porter and his colleagues at the National University of Singapore hope that the bacteria will provide a cheaper, greener alternative to potentially dangerous chemical insecticides.

The researchers say that bacteria are already used to kill mosquito larvae in some temperate countries. But these treatments are too inefficient and expensive for more widespread use.

One such treatment is based on spores of the strain *Bacillus sphaericus*, which produces at least three toxins lethal to mosquito larvae. But the bacteria only grow if fed with expensive amino acids and proteins, and their killing power is blunted because many of the spores sink to the riverbed before they can be eaten by larvae swimming near the surface. Also, spores near the surface are degraded by ultraviolet light, and enzymes produced in the spores gradually destroy the toxins.

The team at the university's Institute of Molecular and Cell Biology transferred two toxin-producing genes from *B. sphaericus* into *Asticcacaulis excentricus*, an abundant aquatic strain of bacteria. They switched the genes using tiny loops of DNA called plasmids. Each gene makes a chunk of protein, and the two chunks fuse to form a potent toxin.

In laboratory tests, the researchers showed that the genetically engineered bacteria produced just as much toxin as the *B. spaericus*, and were just as lethal to mosquito larvae. And *A. excentricus* bacteria do not sink because they have whiplike tails called flagella that enable them to swim.

Its major advantage over *B. sphaericus* is that it floats much better. It also survives exposure to ultraviolet light, and produces no enzymes that degrade the toxin. *A. excentricus* should also be cheap to produce in bulk because it requires no expensive nutrients.

The research phase is nearly complete and development partners will soon be needed. (Source: *New Scientist*, 6 April 1996)

Lactoferricin displays antibacterial effect against Helicobacter Pylori

Morinaga Milk Industry Co. Ltd., with the cooperation of I. Imoto of the Mie University, School of Medicine, has discovered that a peptide derived from milk protein has an antibacterial effect against *Helicobacter pylori*, which is a cause of stomach and duodenal ulcers.

Lactoferricin is an antibacterial peptide obtained from lactoferricin, an iron-binding protein contained in breast milk and cow milk, hydrolyzed by the stomach digestive enzyme pepsin. The company's nutritional science laboratory conducted research using *Helicobacter pylori* supplied by Imoto who derived the bacteria from six ulcer patients.

The bacteria, and 100 μg of lactoferricin were added per millilitre of 196 peptone culture. The number of bacteria after 30 minutes was reduced to less than 10 per cent in four out of six cases, indicating the antibacterial effect in a culture bed of limited nutrition, although the effect differed with the specific type of bacteria.

Urease converts urea in the stomach into ammonia by which the stomach acidity is neutralized, so the bacteria proliferates without being attacked by the stomach acid. In the experiments, lactoferricin and *Helicobacter pylori* were reacted for 10 minutes in a 0.1 M phosphate buffer liquid containing urea, and the volume of ammonia generated was measured. The investigation showed that the enzyme activity is suppressed in addition to the number of bacteria being decreased.

Helicobacter pylori is recognized as a bacteria causing ulcers, and antibacterial agents are used widely in the United States and Europe. However, many healthy persons are also infected with ulcers, so no definite conclusion has been reached yet in Japan. Lactoferricin does not display a strong effect like medical drugs, so use as a food additive to prevent ulcer regeneration appears more promising than use as a medical drug.

Morinaga Milk Industry Co. Ltd., International Dept., 5-33-1, Shiba, Minato-ku, Tokyo 108, Tel.: 81-3-3798-

0216, Fax: +81-3-3798-0101. (Source: *JETRO*, November 1995)

Orstom institute finds lactic acid bacterium

France's ORSTOM research institute has isolated a new bacterium which can produce lactic acid via fermentation.

The institute has found the bacterium, *Bacillus thermoamylovorans*, in palm-tree wine, a traditional African drink made from palm-tree sap. The bacterium is said to be highly efficient, producing around 100g/l of lactic acid in less than 48 hours. A temperature range of 47-58°C is required, limiting contamination. Few vitamins and complex nitrogen compounds are required, unlike other bacterial strains which are currently used to produce lactic acid via fermentation.

Bacillus thermoamylovorans is also claimed to be a cheaper and more efficient means of producing lactic acid than chemical synthesis. In developing countries it could help to find uses for starch-based agro-industrial waste. (Source: *European Chemical News*, 11-17 March 1996)

Integrated expression in Salmonella

A German-Spanish collaborative team led by Carlos Guzmán has improved the two-plasmid system used in *Salmonella*-based delivery by incorporating the gene of interest, encoding a Shiga-like toxin subunit fused to *E. coli* hemolysin signal sequence (*hlyA*), on the same plasmid as the *hlyB* and *hlyD* transport genes. This construct design also allows the *hlyA*-Shiga-like toxin fusion and the *hlyB* and *hlyD* genes to be moved into a mini-transposon that is integrable into the *Salmonella* chromosome for stable expression. Such a system can be used to produce an attenuated *Salmonella* strain to deliver heterologous antigen proteins as vaccines. (Source: *Nature Biotechnology*, Volume 14, June 1996)

Pesticide eating microbes have a huge appetite

M. Ezzi & V. Sarangdhar, in a project sponsored by Burhani Foundation (India), have isolated three cultures capable of degrading an organochlorine pesticide, "Endosulfan". All the three cultures were identified as of the *Pseudomonas* species. Results show that a pesticide concentration of 1,000 ppm is cleared to almost non-detectable levels within approximately three days. In this context, it is interesting to note that in another study, concentration of lindane (another organochlorine pesticide) reduces to non-detectable levels after 45 days of incubation with *Cyanobacteria (Appl. Env. Micro.* 61 234-238 1995). The concentration of Lindane was just 0.5 ppm as against 1,000 ppm, used in this project.

Preliminary experiments show all the three isolates are able to degrade a concentration of Endosulfan as high as 10,000 ppm. Besides, trials with a few other organochlorine pesticides have shown positive results. One of the strains also seems to be viable in organophosphorus pesticides.

Hence, these cultures have a tremendous potential for commercial utilization. One of the most important applications of these isolates would be their use in the Effluent Treatment Plants (ETPs) of pesticide manufacturing industries. Use of microorganisms in the treatment of effluents would prove to be highly cost effective as against the present system of chemical treatment. For further details, write to M. Ezzi, c/o: Burhani Foundation (India) (BFI), Lawrence & Mayo House, 276, D.N. Road, Fort, Bombay-400001, India. Fax: 262 6924 (Source: *Newsletter*, 16 April 1996)

Research on viral genes

Crippled HIV could do you good

American scientists say that modified versions of HIV could ferry therapeutic genes into patients with genetic disorders. They have already created a weakened form of HIV that can deliver DNA into rats without causing disease.

Retroviruses, the group that includes HIV, are good vehicles for delivering genes into cells because they infiltrate chromosomes with their genetic material. The drawback is that most retroviruses cannot penetrate the nucleus which contains the chromosomes, so they must wait for its membrane to dissolve during cell division.

In 1992, scientists discovered that HIV and its close relatives, the lentiviruses, can slip through the nuclear membrane. Inder Verma and his colleagues at Salk and the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts, decided to make the most of this ability.

To create a safe vehicle for gene therapy, the researchers removed the genes that HIV needs to produce new virus particles. But the virus could still leap into chromosomes, because it had been made in the presence of a "helper" virus that gave a dose of the enzymes HIV needs to infiltrate a chromosome. The helper was altered so that it could not itself be packaged into infectious virus particles.

The researchers injected the vector, containing a marker gene called *lacZ*, into rats' brains. Using antibodies against the protein made by *lacZ*, they found that the introduced gene was still working a month after the treatment. With a conventional retroviral vector, no protein was detected, showing that the gene had not inserted into a chromosome.

Joseph Sodroski, an HIV researcher at the Dana-Farber Cancer Institute in Boston, says the work is impressive, but adds that the real challenge will be to convince the public that HIV can be a safe medical tool. Even though the researchers have removed HIV's deadly genes, there is a small chance the crippled virus could acquire replacements from the helper.

Verma agrees that HIV's reputation could overshadow the work, but sees a solution: the virus will be less risky if some genes on the helper virus come from lentiviruses that cannot reproduce in human cells. He aims to make a helper containing only 10 per cent HIV genes. (Source: *New Scientist*, 20 April 1996)

Milk protein derivative could help prevent HIV infection

The truism that milk is good for people's health could take on new meaning now that scientists find that bovine β-lactoglobulin (β-LG), milk's most abundant globular protein, could help prevent the sexual transmission of HIV, which causes AIDS. When modified by reaction with 3-hydroxyphtalic anhydride, β-LG blocks the HIV binding site of cells involved in sexual transmission of HIV, according to researchers at the Lindsley F. Kimball Research Institute of the New York Blood Center, New York City, led by A. Robert Neurath, head of the Institute's Laboratory of Biochemical Virology. At nanomolar concentrations, modified β-LG keeps HIV from

binding to its receptor, thus preventing infection. The findings could lead to a low-cost AIDS-preventive agent, because β-LG is available from whey, an inexpensive and widely available milk by-product. Neurath and co-workers Shibo Jiang and Asim K. Debnath believe the modified protein can be formulated in the same manner as over-the-counter spermicides for topical use as a barrier to HIV infection. (Source: *C&EN*, 12 February 1996)

HIB supressors identified

Two groups of scientists believe they have identified substances that seem to delay the onset of AIDS. Their discovery may help to develop new treatments and vaccines.

The substances are all proteins secreted by a group of white blood cells known as CD8+ cells. One of the research groups, based at the University of Maryland in Baltimore and led by Robert Gallo, the co-discoverer of HIV, has identified three proteins that seem to work together to block replication of the virus. The other, from the Paul Ehrlich Institute in Langen, Germany, has found that interleukin-16 (IL-16) has similar properties. Scientists already knew of all of these proteins, but they had not realised their ability to suppress HIV.

In the mid-1980s, scientists in San Francisco found that CD8+ cells, which are different from the immune cells attacked by HIV, secrete a "factor" that slows down the replication of the virus. This, they said, is why some HIV-positive people can fight off AIDS for longer than others. It could also be why African green monkeys never develop the ape equivalent of AIDS even if they are infected with the simian immunodeficiency virus. But until now, nobody has been able to isolate or identify the mysterious factor.

Gallo's team looked at the fluid produced by cultured CD8+ cells and isolated three proteins called RANTES, MIP-1a and MIP-1b. These are chemokines, substances that are involved in inflammation. In test tube experiments, they suppressed the replication of SIV and both mjaor strains of HIV.

The German group, led by Reinhard Kurth, looked at IL-16 isolated from both HIV-positive humans and African green monkeys. The two proteins only differ by seven of their 130 amino acids; and both suppress the replication of the most common HIV strain in the test tube, they say. HIV carriers with no symptoms have high IL-16 levels, they note.

Neither group knows how their proteins work. Gallo suggests the chemokines might attract killer cells to infection sites. Kurth notes IL-16 binds to receptors on the surface of CD4+ cells, which are attacked by HIV, and might stop the virus entering the cells.

Much more work is needed on the proteins' structures and mechanisms before they could be used as treatments or vaccines, but the mechanisms will give insights into how the virus works, which will help drug development. (Source: *Chemistry & Industry*, 18 December 1995)

Gene therapy prolongs T-cell survival in HIV-infected patients

Researchers at the University of Michigan Medical Center (Ann Arbor) have, for the first time in a clinical setting, demonstrated that antiviral gene therapy can prolong T-cell survival in HIV-infected patients, with no harmful side effects.

In the pilot study, three patients who tested positive for HIV were infused with genetic material that was manipulated to produce a defective HIV protein called Rev M10, which has been shown in the laboratory to block the action of Rev protein, which is essential to HIV replication. "These results were obtained in a small number of HIV-infected patients," Gary J. Nabel, M.D., Ph.D., professor of internal medicine and biological chemistry at the U-M Medical Center and investigator at the Howard Hughes Medical Institute noted, "and additional studies will be needed to help define clinical efficacy and the optimal methods of T-cell gene transfer. Such studies are now in progress."

Dr. Nabel added that two aspects of the study's clinical design were important. The gene transfer technique facilitated analysis of the survival of cells containing the antiviral gene compared to a negative control in the same patient, allowing informative conclusions to be drawn from a small trial. Also, techniques were developed to introduce antiviral genes into cells derived from HIV-infected patients, avoiding the need to obtain heterologous donor cells. (Source: *Genetic Engineering News*, 15 April 1996)

Compound increases survival and immune function in viral-infected laboratory mice

International Gene Group, Inc. (Cambridge, MA), a subsidiary of IGG International, Inc., reports that researchers from the Chandler Medical Center at the University of Kentucky have preclinical data suggesting that MMS1 increases survival and immune function in mice infected with murine immunodeficiency disease (MAIDS), an animal model for human AIDS.

MMS1 is a peptidoglycan molecule extracted from the cell wall of a fungal organism that is currently being developed by International Gene Group.

The researchers evaluated the efficacy of MMS1 in mice with induced infections of MAIDS. Three control groups were also studied. All of the control mice infected with the virus died within 16-24 weeks of receiving the virus; 100 per cent of the mice in the infected test group receiving MMS1 survived the 24 week period after receiving the virus.

In addition to the increased survival rate, MMS1 was associated with increased IgG levels in control animals and reduced hypergammaglobulinemia in infected mice. MMS1 also decreased lymphadenopathy and splenomegaly, conditions associated with MAIDS, and decreased the percentage of splenic cells infected with the virus. The compound was well tolerated by all the treated mice with no observed signs of hematopoietic toxicity measured by marrow progenitor cell content and peripheral blood indicies, according to the scientists.

The researchers also tested the MMS1 coupound on human T-cells in vitro. In these studies, MMS1 increased: the levels of IL-1 and IL-6, the proliferation of both T-cells and macrophages, MAP kinase protein activity after a 10-minute incubation and tryosinephosphate, a known marker of the immune system activation. (Source: *Genetic Engineering News*, 15 April 1996)

Research instrumentation

Potential solution to gene therapy delivery

Researchers at the University of California (San Diego) say they have developed a technique to increase the number of genes that can be transferred into target cells by at least 10-fold over current methods. To allow gene carriers such as viruses to insert therapeutic genes into human cells, the scientists push the gene carriers closer to

their targets in a slow-moving flow called "directed motion".

AASTROM Biosciences (Ann Arbor, MI) plans to develop the new technology, which they call the AASTROM™ Gene Loader, for commercial use in gene therapy.

To perform directed motion gene transfer, target human cells are placed on a porous platform, or cell bed. Then, the solution of virus gene carriers slowly flows through the cell bed. The flow brings many more gene carriers in contact with their targets, and the movement itself seems to enhance interaction between the target cells and the gene carriers.

By flowing the virus gene delivery packages close to the target cells, four key benefits are achieved: a high rate of successful transfer of the therapeutic genes to target cells (which may contribute to better clinical effectiveness of gene therapy); more predictable gene transfer results, which is important for commercial applications; use of much lower concentrations of virus, which simplifies virus production issues; and no need for polybrene, a polymer currently used to bind the virus to the target cell in the static transfer method. (Source: *Genetic Engineering News*, 1 May 1996)

Lasers image cellular activity

Cornell University (Ithaca, NY) scientists have developed microscope technology using pulsed lasers and fluorescent markers to detect and image cellular activity with sensitivity to detect and recognize tens of individual molecules. It can be used to map signal proteins, detect secretory granules and image plant chromosomes and mitochondria simultaneously.

A scanned laser in the 700-900 mm range (deep red to infrared) fires very short pulses (10^{-13} second) focused by the microscope so that two or three photons arrive at the same time (in 10^{-16} second) at a molecule and excite the fluorescence at the relevant molecule. The sample emits the fluorescence photons, producing a three-dimensional image that can be analysed on a computer. (Source: *Genetic Engineering News*, 1 April 1996)

Chip shots at screening

The next generation of chip-based biotechnology screening devices is headed for the green. In a two-year deal that expands their ongoing collaboration, Affymetrix (Santa Clara, CA) will supply Genetics Institute (GI, Cambridge, MA) with the GeneChip—a 1-cm^2 glass slide to which oligos are attached sandwiched, into a glass casing—for GI's drug discovery programme. Because the chip can monitor the expression of up to a 1,000 genes simultaneously, GI plans to use it as a high throughput screening device. As part of the deal, GI will maintain control over the commercial development of any discoveries that come from this collaboration, while Affymetrix will use any GI successes as bait to sell these "DNA probe arrays" to all comers.

One obvious target for chip-based detection is β-thalassemia. The brainchild of Andrei Mirzabekov's group (Argonne National Laboratory, IL), the chip is similar in size and structure to Affymetrix's: A 1-cm^2 gel-coated glass plate with up to 30,000 "DNA sensors" attached through a robotic mechanism. Following the application of the sample, the results are read out by a computer linked to a fluorescence microscope. (Source: *Nature Biotechnology*, Volume 14, April 1996)

AFMs detect diseases

A US molecular biologist has turned one of analytical chemistry's most powerful tools, the atomic force microscope (AFM), into a device that could detect many diseases before symptoms have developed.

AFMs work by moving a tiny, sharp tip, attached to a flexible arm, over the surface under study. The atoms on the surface repel the tip, which bends slightly. This bend is detected and amplified by a computer built into the microscope, forming a line-by-line image which shows the surface in molecular and even atomic detail.

Iowa State University researcher Eric Henderson has added a simple refinement to the AFM. If the microscope tip reacts very strongly to one particular molecule, he says, it will act as a very sensitive detector, able to spot a single molecule in a sample. This can be brought about by coating the tip with a substance that reacts with the molecules to be detected.

Henderson has created a variety of these coated tips. One type carries sections of DNA, another carries antibodies against specific viral or bacterial infections. These can be fitted onto an ordinary AFM, turning it into a device he has named the Atomic Force BioDetector.

The DNA tips carry strands that bind strongly to the genetic sequences associated with inherited conditions. Passed over a DNA sample from a possible carrier, it should detect the suspect DNA, allowing the condition to be diagnosed around ten times faster than current methods, says Henderson. Similarly, the antibody tips detect the molecules on the surfaces of viruses and bacteria that trigger the body's immune system. This should allow an instant diagnosis from blood or urine samples.

So far, Henderson has conducted experiments with pure samples of DNA and antigens, but not yet with serum and blood samples. However, he says that the results have been "promising". (Source: *Chemistry & Industry*, 15 April 1996)

Nerve "circuits" could replace animal tests

Researchers at John Hopkins University have designed a potential biosensor based on circuits made of nerve cells, or neurons. The device could replace animals for testing drugs and chemicals, and help improve medical devices and implants.

There are 10^{10}-10^{12} neurons in the brain. Their potential lies in their ability to connect with up to 10,000 other cells simultaneously, making them a powerful parallel processing computer.

Researchers have failed to exploit this ability until now because neurons do not grow easily, or survive long enough, outside the body. Richard Potember, Mieko Matsuzawa and colleagues at the National Institutes of Health have managed to overcome this obstacle by combining photolithography technology with peptides that are known to exhibit biological activity.

Potember covered a silicon substrate with diethylenetriamine (DETA). The amine molecules attach to silicon at one end and stand up like hairs on its surface. He encourages cultured nerve cells (from mice) to grow on the coating by splicing a synthetic peptide, derived from a protein called laminin, on to the end of each DETA group. Laminin directs the growth of neurons in the body.

Replacing DETA with a molecule called OTS ($CH_3(CH_2)_{17}SiCl_3$) makes it hard for the peptide to stick to the substrate. By patterning the substrate with DETA and OTS, Potember can control where the cells attach and

construct two dimensional networks of cells. Using photolithographic techniques, he can produce lines on the substrate, along which he can guide the growth of cells.

The result is similar to a microelectronic circuit. Potember found that the cells develop axons and dendrites on these peptide-modified surfaces. The resulting neurons remained "alive" for weeks.

The John Hopkins team, working with researchers from the US Food and Drug Administration, used similar substrates to study the electrical effects of implanted medical devices. They found that electric fields affect the cells differently depending on the direction of the applied field. A field applied parallel to the direction of neuron growth does "tremendous damage" to the cells. A perpendicular field has very little effect.

The John Hopkins team is also testing natural and manmade toxins, such as alcohol, directly on nerve cells and without using animals.

Potember is now concentrating on the next generation of "neural prosthetic devices". One day this chemistry might help to guide nerve growth in patients whose nerves have been cut or impaired, he says. (Source: *Chemistry & Industry*, 15 April 1996)

Looking at DNA

Chemists at the Georgia Institute of Technology (Atlanta) report a technique for imaging individual DNA molecules that they say could be used in developing new drugs. The researchers use a scanning force microscope (SFM) to map how nucleic acid ligands bind and alter DNA. They say the SFM image shows how compounds affect single DNA molecules and could have potential as an early screen for promising drug candidates. (Source: *Chemical Week*, 15 May 1996)

General

Genetic maps mark milestone in human genome project

Comprehensive genetic maps for mice and humans, published by two independent groups, "signify the completion of the genetic mapping phase of the Human Genome Project", according to Francis S. Collins, director of the National Center for Human Genome Research (NCHGR) at the National Institutes of Health. A genetic map specifies the genetic distance (probability of coinheritance) between genetic markers—short, highly ariable sequences spaced throughout the chromosomes. When one or more such markers are found to be inherited with a disease, a genetic map can be used to speed the search for genes associated with the disease. The mouse genetic map, consisting of 7,377 markers, was obtained by William F. Dietrich and Eric S. Lander of the Whitehead Institute for Biomedical Research, Cambridge, MA, and co-workers. The human genetic map, including 5,624 markers, was assembled by Colette Dib and Jean Weissenbach at Généthon, Evry, France, and co-workers. Now that this phase of the Human Genome Project is essentially finished, NCHGR is looking forward to a detailed physical map (a physical set of overlapping cloned DNA fragments) of the human genome, which it estimates will be achieved about a year from now, and complete sequencing of the human genome, which it believes will be attained before 2005. (Source: *C&EN*, 18 March 1996)

Complete DNA sequence of yeast deciphered

An international consortium of European, US, Canadian and Japanese researchers revealed the first-ever complete DNA sequence of yeast. The Martinsried Institute for Protein Sequence in Germany has put the full sequence on the WWW, at http://www.speedy.mips.biochem.mpg.mips.yeast.

Overall, 55 per cent of the sequencing was carried out with EC funds (19.8 million ECU or $24.7 million), supporting a network of close to 100 European laboratories. The UK's Wellcome Trust provided 17 per cent of the necessary funding.

In the US, 22 per cent of the yeast genome project analysis was carried out by laboratories at Stanford University (Stanford, CA) and Washington University (St. Louis, MO) as part of the Human Genome Research programme at NIH (Bethesda, MD).

The single celled yeast genome is distributed among 16 chromosomes and has over 12 million bases, representing over 6,000 potential genes. (Source: *Genetic Engineering News*, 1 May 1996)

Kinetics studies reveal assembly pathway for ribonucleoprotein

Using enzyme kinetics studies, researchers at the University of Colorado, Boulder, have determined the rate constants for all the steps in the assembly pathway of a simple ribozymeprotein complex. This ribonucleoprotein, which is made up of a single yeast protein and an RNA intron (a non-coding RNA sequence), excises itself from pre-messenger RNA, then splices the coding sequences together to produce messenger RNA. Researchers Kevin M. Weeks and Thomas R. Cech of the university's Howard Hughes Medical Institute showed that the RNA intron folds very slowly into its tertiary conformation—the catalytic active site—but rapidly reverts to its secondary structure unless it is bound to the protein. Moreover, their data indicate that the protein must wait for the RNA to fold before binding, and that the binding reaction proceeds at a very fast rate. In the last step of the pathway, the 5 ft. domain of the folded RNA rapidly associates with the RNA-protein complex to give the active splicing-machine assembly. The protein cofactor dissociates very slowly, unusual for a biochemical reaction. Cech speculates that dissociation of the protein component in vivo may be facilitated by various factors, because "everything is reversible in biochemistry". (Source: *C&EN*, 22 January 1996)

Fairer odds for DNA fingerprints

Everybody is supposed to be equal before the law. But is everyone equal when it comes to genetic fingerprinting? Some minorities have long suspected that the test may treat them unfairly. Now the National Research Council in the US wants to change the way the odds of guilt are calculated, in an effort to remove any lingering suspicion of bias.

When a criminal leaves a trace of genetic material at the scene of a crime, scientists attempt to match the DNA profile to the suspects. When they find a match they then calculate the likelihood of this profile occurring by chance in the general public. The odds are normally measured in millions to one.

However, among ethnic groups certain genetic traits occur more frequently than in the population at large.

Therefore, say the critics, the technique is more likely to finger suspects from ethnic groups.

In 1992 the NRC said that the forensic scientists should calculate the probability of a profile arising by chance in the general public—because not enough is known about the characteristics of subgroups. However, the NRC has now changed its opinion. It said that enough is now known about ethnic groups to make the comparison with the population of that group in crimes where eyewitnesses or video surveillance cameras have identified the criminal as belonging to a particular ethnic group.

If the suspect's race is unknown, scientists should prepare analyses based on a variety of ethnic groups, the committee says. Stephen Stigler, a statistician at the University of Chicago and a committee member, says these changes will make the evidence from genetic fingerprinting more reliable.

The committee also want prosecutors to save some of the evidence so that suspects can have it tested independently.

At present, all the sample from the scene of the crime is consumed in the DNA tests, and suspects do not therefore have the option of asking for a second opinion. (Source: *New Scientist*, 11 May 1996)

Model alternative to animal testing

Many prospective drugs that could harm patients can now be identified and discarded without wasting weeks on animal or cell-culture tests. By tinkering with images of molecules on their computer screens, researchers at the University of Surrey can tell within hours how potential drugs might be broken down in the liver or gut.

David Lewis of the university's school of biological sciences has created computer images of six key enzymes used by the human liver or gut to break down foreign substances. These enzymes, called cytochrome P450s, degrade 90 per cent of the foreign substances entering our bodies.

By manoeuvring three-dimensional images of molecules on his screen, Lewis can subject prospective drug molecules to close encounters with the six enzymes, linking pairs of molecules together. Then he can predict whether a molecule will be broken down by one of the enzymes, how fast it will be flushed from the body, and by what chemical mechanism.

A further advantage of the computer-based technique over animal or cell testing, says Lewis, is that he can screen hypothetical molecules, saving chemists the bother of synthesizing compounds that turn out to be duds.

To develop his screening system, Lewis had to make an educated guess at the 3-D structures of the six human cytochrome P450s. These have proved tricky to isolate and purify for structural analysis because in the body they are embedded in membranes and they are impossible to extract intact.

While 480 cytochrome P450s have been discovered in nature, the 3-D structures of only four are known. Frustratingly, researchers know the order of the amino acids that make up many of these P450s, but not how the strings of acids folds into structures that function as enzymes.

Lewis tackled the problem using a P450 with a known 3-D structure from the bacterium *Bacillus megaterium*. He found that there were close similarities between the order of the amino acids in the bacterial and human P450s. Through careful comparisons, he established the most likely structures of the six human enzymes that form the core of his system.

He tested his system with molecules such as caffeine, whose fate at the hands of the P450 enzymes is well known.

Glaxo-Wellcome, which funded the work, says the system also performed well when the company asked Lewis to predict the fate of molecules known only to the company. Bob Combes, the scientific director of the Fund for the Replacement of Animals in Medical Experiments, says the system will be useful for screening out toxic compounds before they are given to animals. (Source: *New Scientist*, 27 April 1996)

New type of RNA base pairing discovered

In findings with important implications for RNA folding, a group of researchers has discovered that a new type of RNA base pairing can occur between two uridine residues. The work was done by Markus C. Wahl, Sambhorao T. Rao, and Muttaiya Sundaralingam of the departments of chemistry and biochemistry at Ohio State University. The new type of base pair—in which two uridines are linked by a single conventional NH-O hydrogen bond and one novel CH-O hydrogen bond—shows that RNA can form internal attachments that are more complex and more flexible than was previously believed. According to Sundaralingam and co-workers, the uridine-uridine base pairs are "exceptionally flexible elements [that] may be expected to be exploited in the folding of large RNA molecules." (Source: *C&EN*, 1 June 1996)

Choice words spur genes into action

Altering DNA so that it encodes its information in a different genetic "dialect" can make it much more effective at producing protein. Molecular biologists in the US have used this technique to boost the production of proteins that are otherwise extremely difficult to make inside the cells of higher organisms.

Brian Seed and his team at the Massachusetts General Hospital in Boston were trying to produce large amounts of a protein called gp120, which HIV uses to latch onto the cells it infects. When the researchers inserted the relevant HIV gene into cultured cells it made only tiny amounts of the protein.

In desperation, Seed's team started looking at differences between the gene for gp120 and mammalian genes that produce proteins in generous amounts. A feature of the genetic code is that different DNA sequences can make exactly the same protein. This is because each of the amino acids from which proteins are built can be represented by several different codons—the three-letter genetic words that make up the genetic code. Alanine, for example, is encoded by GCC, GCT, GCA or GCG.

The researchers found that the gene for gp120 used different codons to those preferred by highly active mammalian genes. So they made a synthetic version of the HIV gene, replacing its codons with these alternatives. When this was spliced into a loop of bacterial DNA and inserted into cultured mammalian cells, the cells produced unprecedented quantities of gp120.

Seed's team also looked at a gene from the jelly fish *Aequorea victoria* which makes a protein that glows green. Cells that contain the protein also glow, so genetic engineers would like to use the gene as a marker, to reveal whether their attempts to introduce foreign DNA into cells have worked. But when the gene is inside the cells of mammals and plants it often produces too little protein to be useful. Seed and his colleagues have found that

substituting some of its codons can overcome the problem. Another group at the Massachusetts General Hospital has shown that similar re-engineering can also boost the protein's production inside plant cells.

Seed admits that his approach is not completely new. Genetic engineers working with bacteria use the same strategy to boost the production of hard-to-make proteins. But geneticists had wrongly assumed that genetic dialects are less important inside the cells of higher organisms. (Source: *New Scientist*, 6 April 1996)

Immune system suppression linked to widely used pesticides

Considerable evidence exists that exposure to widely used pesticides may suppress the immune system, making people significantly more vulnerable to infectious diseases and certain cancers. But the problem is being ignored, according to a report by the World Resources Institute (WRI) titled "Pesticides and the Immune System: The Public Health Risks".

The problem of immune suppression from pesticides may be particularly significant in developing countries, the report says, where infectious diseases cause nearly half of all deaths. A large fraction of the population of these countries is involved in agriculture, with a concomitant widespread and increasing exposure to pesticides. However, farmers and workers lack the knowledge and equipment to heed safety precautions even when using products that are banned or severely restricted in industrialized countries.

The evidence for immune suppression comes from three types of studies: laboratory tests, wildlife and human. Some pesticides from nearly every major chemical class have been found positive for immunotoxicity in laboratory tests, says researcher Sanjay S. Baliga, co-author of the report. Although no single study in humans proves that pesticides are causing increased disease, the weight of evidence from these studies gives cause for concern says WRI Vice President Robert Repetto, a former associate professor at the Harvard University School of Public Health and co-author of the report.

Hundreds of studies in human cell cultures and laboratory animals using accepted scientific methods show that many pesticides alter the immune system, the WRI report says. Such tests include those for macrophage, neutrophil, and natural killer cell activity; leucocyte count; lymphocyte count; and tests in which the animals are challenged with bacteria, fungi, or viruses after being given a dose of pesticide. If the animals exposed to pesticides are less able than the unexposed animals to defend themselves against micro-organisms, their immune systems are assumed to be compromised.

Wildlife studies also offer evidence that pesticides are immunotoxic. For example, seal pups captured off the relatively unpolluted north-west coast of Scotland were fed uncontaminated fish for one year. Then the seals were put in two tanks. Half the pups were fed Baltic Sea herring, which is polluted with pesticides and PCBs, while the other half were fed relatively uncontaminated herring from Iceland. The immune system responses of the pups fed Baltic herring were overall one-third as strong as those in the control group.

Epidemiological studies in central Moldova in the former Soviet Union have implicated pesticides in immune suppression, Repetto notes. In one study, teenagers in villages where pesticide application was greatest had two to five times as many respiratory tract infections as teenagers from areas of lower pesticide use.

In the US and several other countries, the overall cancer rate in farmers is lower than that of the general population. But studies show that farmers who use pesticides experience elevated risk for the same cancers that immune-deficient patients develop.

In their report, Repetto and Baliga say the "World Health Organization should take the lead in designing and organizing an extensive programme of research to address the risk of pesticide damage to the human immune system." They also recommend that thorough testing for immunotoxicity be required on all pesticides. (Source: *C&EN*, 18 March 1996)

Lactose operon repressor Elusive structure finally determined:

The crystal structure of the lactose operon repressor—a protein of enormous historic importance in understanding how genes are regulated and one that has challenged X-ray crystallographers for nearly 30 years—has been determined by a team of chemists, biochemists and molecular biologists at the University of Pennsylvania and Oregon Health Sciences University, Portland.

Mitchell Lewis, professor of biochemistry and biophysics in the school of medicine at the University of Pennsylvania, and Ponzy Lu, professor of chemistry at Penn, led the eight-member team that resolved the structure.

The protein regulates a cluster of genes used by the bacterium *Escherichia coli* to metabolize the sugar lactose. When there is no lactose around, the protein shuts down—represses—production of three enzymes the bacterium uses to metabolize lactose. But when lactose or certain other β-galactoside sugars are present, they bind to the protein, changing its shape and causing it to stop repressing synthesis of the enzymes.

The researchers have determined the structure of the protein under three different conditions: alone, bound to the two operator sequences on DNA that it targets, and complexed with a β-galactoside sugar that can cause its shape to change so that it no longer binds to DNA.

Because of its importance in understanding gene regulation, the protein has been the target of X-ray crystallographers in many laboratories for decades, with low-quality crystals reported as early as 1974. Crystal structures were also worked out for several critical regions of the molecule. In fact, Lu, Lewis, and colleagues crystallized the entire protein in 1990, but those crystals were not adequate for X-ray diffraction studies.

The new structure explains a number of things and suggests some new ways to think about the protein and its regulation of gene transcription. Among other aspects, the structure makes clear why the protein has been so hard to crystallize: each of its four N-terminal headpieces, which bind DNA, is connected to the main body of the protein by an α-helix that is disordered when the DNA is not present.

The protein is a V-shaped tetramer, actually a dimer of dimers that is held together only minimally at the V tip. This V shape is unlike any tetrameric protein seen before, says Lu. (Source: *C&EN*, 4 March 1996)

T-cell activation blocker

Researchers from the University of Pennsylvania (Philadelphia, PA) and the Centre National de la Recherche Scientific (Ville-juif, France) believe they have developed a novel peptide mimetic with pharmaceutical potential. Zhang et al. have synthesized cyclized peptides of the complementarity determining regions (CDR) of CD4. The

peptide analogues mimic the CDR sufficiently well to block the binding of CD4 to MHC II in a competition assay. This blocking is itself important, since the interaction initiates T-cell activation. But it is the mechanism that means the method may be extended to other systems. The cyclic peptide prevents CD4 from forming multiprotein complexes, a common mechanism of receptor interaction. Cyclic peptides that mimic other molecular interfaces may, therefore, prove useful as inhibitors of protein-receptor interactions. (Source: *Nature Biotechnology*, Vol. 14, April 1996)

How cancer spreads after a night on the tiles

Drinking to excess can leave you with something much worse than a bad hangover. Researchers in the US and Israel say that tumours are more likely to spread after a bout of heavy drinking. Their findings may help explain why heavy drinkers suffer more than twice the usual rate of breast, liver and digestive system cancers.

Gayle Page of Ohio State University in Columbus and her colleagues injected rats with tumour cells that try to migrate to the lungs, but which are usually destroyed by the immune system's natural killer cells. They found that forty times as many cancerous cells lodged in the lungs of rats given alcohol as in sober animals. But it was temporary: if the injection of tumour cells was delayed by 24 hours, they were no more likely to lodge in the lungs than normal.

The increased risk appeared when the rats' blood contained more than 0.2 per cent alcohol. The researchers note that many people with primary tumours are not aware of their presence, so the warning does not only apply to those being treated for cancer

Unlike other immune system cells, natural killers identify and demolish their target cells on sight, without needing prior experience of them. Killer T cells, by contrast, need to know their opponents. Although natural killer cells have been studied extensively, Page and her colleagues say that the effects of alcohol have previously been underestimated. This is probably because the process of extracting the cells from the blood washes away any alcohol, and gives the cells time to recover. (Source: *New Scientist*, 11 April 1996)

New method for selective production of hybridoma cells

Assoc. Prof. M. Tomita, Prof. S. Miyajima, Department of Chemistry for Materials, Mie University, and Prof. T. Y. Tsong, Department of Biochemistry, University of Minnesota, College of Biological Sciences, have developed a new method for selective production of hybridoma cells using pre-selection of B lymphocytes and the pulsed electric field (PEF) fusion method.

Biotinylated antigen was used for selecting B-lymphocytes which can produce antigen-specific monoclonal antibodies. Pre-selected B lymphocytes were then bridged by streptavidin, and combined with biotinylated myeloma cells. The final B cell-myeloma cell complex was theBcell-(antigen-biotin-streptavidin-biotin)-myelomacell. Finally, this B cell-myeloma cell complex was selectively fused by the PEF method. The fusion efficiency obtained by this method was about 10 times higher than that obtained by the non-specific polyethylene glycol (PEG) fusion method. Alternatively, avidin-antigen conjugate was used to select B lymphocytes. Bifunctional cross-linkers such as *N*-succinimidyl 3-(2-pyridyldithio) propionate (SPDP) and *m*-maleimidobenzoyl *N*-hydroxysuccinimide (MBS) were selected. Each reagent contains two hetero-functional groups which form covalent bonds with both Lys and Cys residues. Typical avidin-antigen conjugate is expressed as avidin-SPDP (or MBS)-antigen. The final composition of the selected B cell-myeloma cell was B cell-(antigen-SPDPorMBS-avidin-biotin)-myelomacell. The yield of this method was 20-30 times higher compared with the PEG method.

The research team suggests that the pre-selection of B lymphocytes and PEF fusion are critical for the selective production of hybridoma cells which produce specific monoclonal antibodies against the antigen. This method will contribute to the efficient production of monoclonal antibodies for medical purposes. Further details from: Mie University, Faculty of Engineering, 1515, Kami-hama-cho, Tsu City, Mie Pref.514; Tel.: +81-592-31-9429; Fax: +81-592-31-9471; E-mail: tomita@chem.mie-u.ac.jp (Source: *JETRO*, June 1996)

LLNL publishes chromosome 19 metric physical map

Researchers at the Human Genome Center of Lawrence Livermore National Laboratory have completed an integrated metric physical map of human chromosome 19 that spans over 95 per cent of the euchromatin (about 50 Mb).

The map is based on sets of overlapping cosmid clones (contigs); gaps between contigs were filled using various types of larger-insert clones. A "metric" scaffold was generated by using FISH in sperm pronuclei to estimate distances between selected cosmids. This FISH scaffold was integrated with other partial-order data generated by hybridization, STS screening, and restriction mapping using automated map assembly software.

The map, which is depicted in a special 4-page pull-out section, contains 51 "islands" of multiple clone types, with size, order, and relative distance known. Markers include more than 450 genes, polymorphic markers, STSs, and ESTs that are localized on average every 230 kb across the non-centromeric chromosome portion. Complete digest *Eco*R I cosmid restriction maps, also generated across 41 Mb, can be used to create subclone libraries for DNA sequencing. [More map data: *http://www-bio.llnl.gov/bbrp/genome/genome.html*] (Source: *Human Genome News*, January-March 1996)

Move over Mabs

Monoclonal antibodies (Mabs) may soon be displaced by a new class of peptide aptamers—called "pseudo-antibodies". The name comes from their similarity to antibodies: A "carrier protein" scaffolding supports a random peptide-constrained loop that serves the same function as a Mab's highly variable region.

Inventor Roger Brent (Massachusetts General Hospital, Boston, MA) says pseudoantibodies possess several unique features that may make them superior to antibodies. Brent says what really sets this technology apart is that it is designed to work intracellularly—something Mabs were never very good at.

So far, Brent and colleagues have used pseudo-antibodies to find peptides that interact with the cell-cycle enzyme, cyclin-dependent kinase 2 (Cdk2). Brent says that because of the small size of the pseudoantibodies' constrained loops, these studies should lead to fairly detailed structural information about Cdk2's epitopes. He suggests

that an obvious application of this type of information would be the development of peptide mimetic drugs. (Source: *Nature Biotechnology*, Volume 14, June 1996)

Bionic brain cells teach the language of nerves

Learning how to repair damage to the human central nervous system by deciphering the secret language of nerve cells is one of neurology's brightest hopes. And understanding neural communication could also lead to the development of computers that mimic the data processing capabilities of human nerve cells.

German researchers have now added another vital piece to the jigsaw by linking a number of isolated nerve cells together on the surface of electronic microchips for the first time.

Several groups have managed to grow bundles of nerve cells, or neurons, on silicon chips, but Peter Fromherz, professor of membrane and neurophysics at the Max Planck Institute for Biochemistry in Munich, says his is the only team to couple isolated neurons directly to semiconductor transistors.

Fromherz's first experiments were with neurons taken from leeches. Although they could transmit electrical signals to the microchip, the leech cells could not be persuaded to form synapses—the electrical connections that transmit signals between neurons. By swapping the leech cells for neurons taken from snails, Fromherz says he can now persuade the neurons to link up and build more complex brain-like structures.

The next step is to train the synapses to link up in a way that will allow the Max Planck team to investigate precisely how the nerve cells talk to each other. They plan to stimulate one snail cell at a time to see how the other cells respond. Neurons are thought to send signals when the electrical activity reaching them from other cells in the brain reaches a threshold level.

Voltage changes in the cell membranes have previously been detected using voltage-sensitive dyes, such as amphiphilic hemicyanine. This varies in fluorescence according to the strength of the electrical signal. But the sensitivity of the dye is relatively low, and it becomes toxic when it fluoresces, says Fromherz. By coupling neurons to transistors, Fromherz and his team hope they can watch how each cell behaves in an organized network of thousands.

The junction between the neuron and the transistor is achieved by positioning the cell so that its plasma membrane acts as the "gate" contact of the transistor. The connection is maintained by immersing the system in an electrolyte. The voltage in the cell is controlled by impaling it on a tiny charged needle.

The neurons are encouraged to grow along pathways coated with adhesive proteins that organize nerve cells into networks in the brain. The tracks are about 10 micrometres wide and are laid down on the silicon using photolithography masking techniques, similar to those used to create conventional microchips.

The chips have been miniaturized so that a single neuron covers around 16 closely packed transistors. German electronics giant Siemens has developed a microchip packed with up to 2000 transistors. This will allow Fromherz and his team to lay down a network of snail neurons of a similar complexity to a leech brain. The corrosion-resistant chip has been specially designed to work in the saline solutions used to promote cell growth.

Meanwhile, the Max Planck team has perfected a technique for measuring the distance between the cell membrane and the chip to which it is linked. According to Fromherz, this distance—which is typically 70 micrometres—is crucial for controllling the voltage in the cell. The researchers shine light on the surface, and that light is refracted differently depending on the distance between the chip and the neuron. So the wavelength of the reflected light varies, showing up as different colours. (Source: *New Scientist*, 1 June 1996)

Cancer's many points of departure

The widely held belief that most cancers originate from a single rogue cell may have to be rethought. By studying a patient with a rare chromosomal abnormality, scientists at the Imperial Cancer Research Fund (ICRF) in London have discovered that incipient tumours may actually develop from several cells.

This finding could open up new avenues of cancer treatment. The results suggest that precancerous cells can turn their neighbours into a similar cancer-inducing form. If biologists can discover the biochemical signals involved, it may be possible to design drugs to block them and make tumours less likely to form.

Marco Novelli and his colleagues studied a man with a rare condition called familial adenomatous polyposis (FAP) in which hundreds of precancerous growths, or adenomas, form in the colon—any one of which can develop into a tumour. FAP patients usually have their colons removed before the age of 30 to stop them getting cancer.

By a 100 million to 1 chance, the patient is also genetically "mosaic". Due to a mistake in cell division that occurred very early in embryonic development, some of his cells have the usual X and Y sex chromosomes, while others possess only an X—a condition known as an XO genotype.

The ICRF team examined the adenomas in a biopsy taken from the patient, and to their surprise found that 76 per cent of them contained both XY and XO cells. If these tumours had arisen from a single cell then each tumour should have been either all XY or all XO.

Novelli considered several possible explanations for the results, before settling on the theory that most tumours in FAP patients arise after a single precancerous cell converts one or more of its neighbours into a similar state.

The XO/XY adenomas could orginally have been XY growths in which some cells lost their Y chromosomes—mimicking what happened early in the patients's embryonic development. But chromosome loss of this sort has only ever been seen in tumours that are much more advanced than the precancerous growths studied by the ICRF team.

It was also feasible that the XY/XO mix in the adenomas could have resulted from random mergers between smaller precancerous growths. Given the high proportion of XY/XO adenomas, however, this is unlikely. Novelli thinks that tumours elsewhere in the body may well have similar "polyclonal" origins.

But the researchers do not yet know how a precancerous cell could turn its neighbours into a similar rogue form. (Source: *New Scientist*, 1 June 1996)

Regular amino acid alighnment discovered in heat-resistant proteins

The Takasaki Radiation Chemistry Research Establishment of the Japan Atomic Energy Research Institute has discovered that the helical structures of thermoresistant proteins display a unique arrangement of hydrophilic and hydrophobic amino acids aligned on the

outside and inside faces, respectively, of the helical structures of proteins. The alignment is a convenient model for thermoresistant proteins.

Proteins consist of a chain of amino acids, generally with a helical structure. The research team compared the amino acid alignments of three kinds of proteins with the same functions, which were derived from the mesophilic radioresistant bacterium *Deinococcus* and extremely thermophilic bacterium *Thermus*. In the helical structure of the protein from the thermophilic bacteria, it was discovered that hydrophobic amino acids were concentrated on one side, and hydrophilic amino acids on the other. In the mesophilic bacteria, the amino acids were aligned in an irregular configuration. The helical chains form proteins by folding in a complicated manner. If a shape is formed in which the hydrophilic amino acids are concentrated on the outside face and the hydrophobic amino acids on the inside face, then the structure will be highly stable and resistant to heat.

Proteins are used widely by the pharmaceutical, fermentation and food processing industries, but their major disadvantage is vulnerability to heat. In the future, artificial proteins may be manufactured and utilized, so the present discovery will certainly be applicable to design proteins with structures highly resistant to heat.

Further information from: Japan Atomic Energy Research Institute, Takasaki Establishment, 1233, Watanuki-cho, Takasaki City, Gunma Pref. 370-12, Tel.: +81-273-46-9233; Fax: +81-273-46-9687. (Source: *JETRO*, February 1996)

Technique for yeast transformation using drug-resistant gene

Takara Shuzo Co. Ltd. has developed a technique for yeast transformation using drug-resistant gene that is effective in improving the characteristics of industrial yeast. Patent rights in Japan and other countries have been applied for.

The new system eliminates the step of acquiring mutants indispensable for yeast transformation by conventional methods, enables easy transformation of experimental yeast, and improves the transformation efficiency of industrial yeast, from less than a few per cent to several dozen.

The conventional transformation system requires the acquisition of mutants, but most industrially used yeasts are polypoids from which mutants cannot easily be acquired, so yeast transformation efficiency had been quite low at less than a few per cent.

The new system uses a new antibiotic Aureobasidin A with an intense antibacterial activity with respect to yeast and a yeast vector containing Aureobasidin A-resistant mutation gene as the yeast selective marker. Wild yeast without the Aureobasidin A-resistant gene is killed in the presence of Aureobasidin A. Introducing objective genes into vectors containing AUR1-C and conducting yeast transformation will introduce the objective genes as well as AUR1-C into the yeast to enable efficient selection of character-transformed yeast in the presence of Aureobasidin A.

The new technology now enables the use of industrial yeast to produce sake, bread and miso and other products with much greater ease than before. The company started marketing the antibiotic Aureobasidin A—indispensable for the new technique—and a vector containing the antibiotic-tolerant gene AUR1-C in December 1995 for research use only. A license agreement from Takara is required for commercial use. Further details from: Takara Shuzo Co. Ltd., Higashiiru, Higashinotouin, Shijoutouri, Shimogyouku, Kyoto, 600-91; Tel.: +81-75-241-5122; Fax: +81-75-241-5156. (Source: *JETRO*, February 1996)

Saponins draw interest as boosters of immune system

Immunologists at the Butantan Institute (San Paulo, Brazil) recently reported that saponin from the South American *Quillaja saponaria* tree increased antibody synthesis in mice in response to BSA and rattlesnake venom antigens. The scientists also demonstrated that the mice were protected from the effects of the venom if they were immunized with saponin and venom.

In addition, saponin-immunized animals showed tumour necrosis activity almost three times higher than in controls. Interferon-gamma was produced only when BSA was injected along with saponin.

The Brazilian work is one of the latest examples of research into the benefits of saponins, a class of disease-fighting nutrients found in a wide variety of vegetables and legumes throughout the world.

So far, evidence shows that purified saponins play an important role in stimulating the immune system, warding off microbial and fungal infections, lowering cholesterol, fighting cancer and even acting as a spermicide and having potential as a sugar substitute—some saponins have 200 times the potency of sucrose.

In a report presented to the American Chemical Society last August, a team of researchers led by N.T. Nham, Ph.D., at the Science Production Union of Ginseng and Medicinal Plants (Ho Chi Minh City, Viet Nam) and K. Yamasaki, Ph.D., at the Institute of Pharmaceutical Science, Hiroshima University (Hiroshima, Japan), said that saponins derived from one plant (*Panax vietnamesis*) showed antifatigue action, increased the appetite and improved sleep, muscle force, memory, reduced articulation, bone pain, arteriosclerosis, mental, physical and sexual asthenia and effects in chronic granular angina and bronchial asthma. It sounds too good to be true, but researchers throughout the world are reporting a wide variety of benefits associated with purified saponins.

As a small sample of ongoing global research projects:

- Masayuki Yoshikawa at Kyoto Pharmaceutical University (Kyoto, Japan) found that an active ingredient in saponins curbs ethanol absorption, leading to the possible development of intoxication-fighting medications.
- The application of saponins in foods and cosmetics is being studied by Maruzen Pharmaceutical Co. Ltd. (Onomichi, Japan). So far, Osamu Tanaka and his team have determined that saponins have formed the basis of detergents in China and South-East Asia, and that saponins are promising as antidandruff and antidermatophytic agents in shampoos and cosmetics. As food additives, saponins inhibit yeast growth, thus prolonging shelf-life of cooked rice, pickled vegetables and fermented foods.
- At the University of Karachi (Pakistan), Khalid Aftab and colleagues are finding that saponins help regulate hypotension in guinea pigs.
- At the Royal Danish School of Pharmacy (Copenhagen), E. Lemmich and colleagues are using saponins as molluscicides for tropical diseases and are field-testing the compound in Zimbabwe. (Extracted from: *Genetic Engineering News*, 1 March 1996)

Angiogenesis research offers new approaches for disease treatment

Angiogenesis, the process whereby blood vessels grow normally in the development of embryos and during wound healing after surgery or injury, also has a dark side. Abnormal activity is associated with pernicious diseases, most notably solid malignant tumours, rheumatoid arthritis and certain diseases of the eye.

Scientists, however, believe the aberrant process may be the key to new treatment strategies for these afflictions. For example, the growth of solid tumours supplies a model of how normal body processes are mustered by pathological developments to nourish a sinister agenda. Here, the tumour provokes the release of growth factors that stimulate the sprouting of a local network of new blood vessels which ensure the delivery of nutrients and oxygen to the growing tumour. They can also open routes through which the primary tumour can dispatch cancer cells to other parts of the body, thus initiating metastasis.

Researchers now view this process as offering the intriguing possibility that blocking the simulators of angiogenesis just might starve the tumour to death. This is such an exciting concept that inhibition of angiogenesis as an anti-cancer strategy has been pushed to the forefront of the fight against cancer, as well as against other angiogenesis-related disease conditions. And a cluster of biotechnology companies have picked up the challenge and in some cases have advanced the strategy to clinical trials. (Extracted from: *Genetic Engineering News*, 1 May 1996)

E. APPLICATIONS

Pharmaceutical and medical applications

High-density lipoprotein receptor identified

A cell surface receptor that binds high-density lipoprotein (HDL) has been identified by researchers from Massachusetts Institute of Technology and the University of Texas Southwestern Medical Center in Dallas [*Science*, 271, 518 (1996)]. HDL is the cholesterol-carrying molecule in the bloodstream that plays a beneficial role in protecting against atherosclerosis. Earlier work suggests that it serves two, possibly related, functions: it transports and selectively releases cholesterol to tissues that use cholesterol to synthesize steroid hormones, and it picks up excess cholesterol from cells that are unable to degrade it and transports it to the liver for excretion. MIT's Susan Acton and Monty Krieger and their colleagues now find that HDL attaches to the previously identified SR-BI receptor, which also can bind certain modified lipoproteins. The receptor is located almost exclusively on cells of the liver (which excretes HDL) and the ovary and the adrenal gland (which synthesize steroid hormones), the researchers find—evidence that the receptor is biologically relevant to HDL-mediated cholesterol transport. Its identification opens the way for further investigation of how HDL delivers cholesterol to these cells and of HDL's protective role against circulatory system disease. (Source: *C&EN*, 29 January 1996)

Experts warn against Alzheimer's test

A panel of experts have warned that new tests which can identify a gene linked with Alzheimer's disease should not be used until more research has been carried out.

The panel, which included geneticists, epidemiologists, lawyers and industry representatives from North America and Europe, said that not enough was known about the Alzheimer's gene, APOE, and its role in the disease, according to a report in the UK medical journal, *The Lancet*.

They commented, however, that doctors may choose to use APOE genotyping "as an adjunct to other diagnostic tests for Alzheimer's disease."

Between 43 per cent and 77 per cent of Alzheimer's sufferers carry the defective APOE gene, but it appears in various forms in clinical experiments and wide-ranging studies of the population as a whole. This could result in the misdiagnosis of around 23-57 per cent of patients.

Concerns about the ethics of genetic testing and its possible abuse, for example by insurance companies and employers, prompted the setting up of the 33-member panel by the US National Institute on Ageing.

It is estimated that 17-20 million people world-wide suffer from Alzheimer's. Most patients are over 65 years of age, although it can strike people in their 40s and 50s. (Source: *Biotechnology Business News*, 24 April 1996)

Cell-Sci to report TB progress

Test results indicate that Cel-Sci's proprietary heteroconjugate technology is able to induce an important cellular immune response against a TB antigen. The results also showed that the antibodies produced by Cel-Sci's technology are able to recognize various TB strains compared with antibodies produced by conventional technology. Conventional antibodies are often not able to recognize antigens in the native TB. Cel-Sci's antibodies, on the other hand, were very effective in recognizing even multiple drug-resistant strains of TB.

Patented heteroconjugates are intended to selectively stimulate the human immune system in order to fight more effectively bacterial, viral and parasitic infections and cancer, when it cannot do so on its own.

Administered like vaccines, heteroconjugates may provide an exciting new class of products to treat and/or prevent these diseases.

TB is making a comeback in the USA and Europe due to the development of multiple drug-resistant strains, not responsive to conventional treatments. (Source: *Biotechnology Business News*, 8 May 1996)

Molecular tool for waterborne diseases

Researchers at Murdoch University's Institute for Molecular Genetics and Animal Diseases, in Western Australia, have developed a novel and sensitive DNA test to detect the waterborne parasite, *Cryptosporidium parvum*, which is a significant cause of diarrhoeal illness in developed and underdeveloped countries alike.

Waterborne outbreaks of cryptosporidiosis, for which there are no effective drugs available, have been recorded around the world—the worst in 1993 in Milwaukee, US, where an estimated 405,000 people contracted cryptosporidiosis from drinking contaminated water.

Several waterborne outbreaks have also been reported in Sydney. It particularly affects young children and the immunocompromised. Healthy adults, however, are also at risk.

As no effective drugs are available for the prevention of cryptosporidiosis, control of this parasite depends upon rapid and sensitive diagnosis in both clinical and environmental samples. Conventional techniques to detect the parasite are time consuming, insensitive and require the skills of highly trained operators.

It was these limitations that motivated the research team to apply molecular methods to the development of sensitive polymerase chain reaction primers for the detection and diagnosis of the parasite.

Commercial applications of the molecular diagnostic tool are promising and the Murdoch University team has already lodged a provisional patent on the invention. The university's report of the research notes that in the US, testing for the parasite in water systems serving more than 10,000 people was made mandatory this year. (Source: *Biotechnology Business News*, 8 May 1996)

Amgen begins first leptin trial

Amgen said it has begun the first human clinical trials of leptin, a recombinant form of the natural human protein produced by the obese (*ob*) gene and made in fat cells.

Preclinical data suggested that leptin helps regulate body fat deposition and, as a result, produces weight loss through effects on metabolism and appetite.

The initial trial is designed primarily to evaluate safety and tolerability of leptin across a variety of weight categories of people who have no other medical complications. The study is being conducted at multiple centres in North America and is likely to be completed by early 1997.

The start of the trial comes just one year after Amgen acquired the rights to develop and market products based on the *ob* gene and less than two years after the gene's discovery at the Rockefeller University in New York. (Source: *Biotechnology Business News*, 22 May 1996)

An end to gluttony

British researchers have found a compound that triggers a feeling of fullness and signals "stop eating". It could lead to new drugs that prevent over-eating.

The compound is a neuropeptide called GLP-1 which is found in all mammals. The researchers from Hammersmith Hospital, London, led by Stephen Bloom, have shown that rats injected with GLP-1 ate far less than a control group given salt water, even when the animals had been starved for a day.

The Hammersmith team report that GLP-1 appears to act on the hypothalamus in the brain. Injections into the brain of GLP-1 can even override the most powerful feeding stimulant known.

As a check, the researchers injected the rats with the neuropeptide and a known inhibitor of GLP-1. They found that the rats carried on feeding even after they had eaten their fill.

Although the Hammersmith scientists believe that GLP-1 could be the most potent inhibitor of feeding yet identified in the rat, it has not been tested on humans yet. Bloom believes that it will work in the same way, however. He says that it should not take pharmaceutical companies long to design an artificial version of GLP-1 which could be taken in a pill. He stresses that the drug would only prevent over-eating and would not repress a person's normal appetite. (Source: *Chemistry & Industry*, 15 January 1996)

Drugs from dogfish sharks and clawed frogs

Compounds derived from the dogfish shark and the African clawed frog show promise in combating sexually transmitted diseases, including AIDS and other widespread, stubborn or drug-resistant infections.

The substances, called magainins or squalamines, have already passed preliminary testing obstacles and are either being studied in patients or are nearing human use. One magainin, derived from the frog, is being used experimentally to treat diabetic leg ulcers in humans, and is in Phase III clinical trials.

Theshark-derivedcompounds—immunosteroidscalled squalamines—also show potency against sexually-transmitted diseases and certain cancers, including brain cancer.

One squalamine derivative is being used experimentally in brain cancer patients, and results of that trial are expected within a few months. Researchers, intrigued by anecdotal reports of low infection and cancer rates among sharks, began looking for protective agents in the sea creature. So far, Magainin Pharmaceuticals of Plymouth, PA., has identified 16 different agents from the shark that are under study. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 4 March 1996)

Baldder cancer detection

A team of researchers at the University of Pittsburgh Cancer Institute (UPCI) has discovered a new way to detect bladder cancer. The discovery is based on the detection of five nuclear matrix proteins (NMPs).

This group of NMPs is important in several ways. They are found only in bladder tissue, and not in other body tissues. Moreover, these appear to be the first NMPs specific to one type of cancer only, in this case bladder cancer, and which are not found in other types of cancer.

Detection of the bladder cancer NMPs should vastly improve the initial diagnosis of bladder cancer and in many cases allow physicians to treat disease at an earlier stage when it is easier to cure, according to the investigators. Traditional detection relies on cytology (detecting cancer cells shed in the urine). This method is problematic for two reasons. Early cancer may not produce many cells that are shed, and some cancer cells look very much like normal cells, thus eluding detection even by a careful pathologist. For these reasons, detection of early bladder cancer using cytology fails as much as half the time. (Extracted from *Genetic Engineering News*, 15 April 1996)

Whitehead Institute researchers devise drug development techniques

Researchers at the Whitehead Institute for Biomedical Research (Cambridge, MA) and the Howard Hughes Medical Institute have developed a method to identify a new class of amino acids that could serve as key leads for drug development. The new technique, called mirror-image phage display, represents an important advance in drug design research, according to the scientists.

The method exploits the differences between L-and D-amino acids. While L-forms are degraded by digestive enzymes and elicit a strong immune response, the D-form is neither biodegraded nor processed by the immune system. Peptides that are not degraded can become useful drugs (e.g., cyclosporin).

The Whitehead-HHMI technique begins with the chemical synthesis of D-forms of target proteins and using them to screen peptide libraries. The result of this screening provides researchers with the L-form of a peptide that binds to the D-form of the target protein. The researchers then make the mirror image D-form of the L-peptide, which would bind to the naturally occurring protein, which was the initial target.

The team used this approach to identify a peptide that interacts with the SH3 domain of the Src tyrosine kinase.

Currently, the researchers' ability to synthesize D-forms of proteins is limited to proteins that contain about 100 or less amino acids. However, as the ability to synthesize proteins improves, so will the utility of the mirror-image phage display method. The method can also be adapted to DNA and RNA libraries. (Source: *Genetic Engineering News*, 15 April 1996)

Biotech firms shift focus towards therapeutic HIV vaccine development

The bottom line in HIV vaccine development is that scientists still do not know what constitutes protective immunity against HIV infection.

The short-term prognosis for HIV vaccines is not encouraging. The belief that an HIV vaccine may be the only, or at least the most effective method for preventing the virus's devastation of the host immune system, drives the search for new, more powerful vaccines.

The focus is shifting towards therapeutic vaccines, which would buttress the immune system and prevent AIDS, but would not block the initial infection.

Unfortunately, many of the obstacles that have thwarted HIV vaccine development in the past continue to challenge researchers and clinicians. These obstacles are:

- The need to induce humoral (antibody), cellular (cytotoxic T lymphocyte-mediated), and mucosal

(preventing viral entry at mucosal surfaces) immunity.
- HIV resides in immunoprivileged sites and can remain latent for years.
- HIV causes immunosuppression, further hindering the body's ability to contain the virus and prevent opportunistic infections.
- How the virus destroys immune cells is not fully understood.
- No good animal model exists.
- HIV continuously mutates: different strains are prevalent in various parts of the world; field isolates often differ from the laboratory strains used to develop vaccines; and, after infection, HIV can mutate within the host, and an infected person can harbor multiple forms of the virus.
- The appropriate clinical end points for evaluating therapeutic vaccines are not clear.
- The risks involved in testing attenuated versions of this fatal virus in humans may hinder their development.

Whereas the need to try dramatically different approaches to HIV vaccine development has been voiced, a lot has been learned about the virus and the disease by pursuing a logical, stepwise course, even though traditional approaches to vaccine design have not yet proved successful.

Initial attempts to construct vaccines based on HIV envelope proteins have elicited a good humoral response in general, but an inadequate cellular immune response, and the question remains whether such vaccines can induce cross-strain immunity. In 1994, the National Institutes of Health (NIH) declined to pursue large-scale pivotal trials with the existing subunit vaccines.

One of the problems with recombinant peptide vaccines may be that current formulations express a monomer, whereas the envelope proteins typically exist as trimers and tetramers on the surface of the virus, and the three-dimensional configuration of the proteins may be critical to achieving an immune response.

To boost the immunogenicity of peptide subunit vaccines, several companies are experimenting with various combinations of proteins, including envelope and core proteins, and are incorporating adjuvants, aimed in particular at enhancing cell-mediated immunity.

However, there is cause for some optimism in the results of animal tests with an attenuated HIV vaccine. The deletion of specific genes weakens the virus, allowing it to infect cells, but not to cause illness.

The US National Institute of Allergy and Infectious Diseases recently released a position paper describing its vision of the optimal strategic approach to HIV vaccine development. The daunting challenge presented by the spread of HIV and AIDS demands a coordinated effort that combines the work being done in academia, industry, and government laboratories.

The statement calls for "more and better defined partnerships between NIAID and industry sponsors of vaccine development."

NIAID intends to "establish collaborative partnerships with private sector sponsors who have vaccine products in development", with the intent of facilitating progress towards product licensure. These collaborations would focus on individualized, concept-specific milestones, options, and decision-making criteria, which would guide product development through the stages of preclinical animal studies, and Phase I, II and III trials. Each partnership will devise, and continually re-evaluate, the specific criteria of efficacy and safety data required to proceed to the next level of development.

In addition, NIAID is developing an intermediate clinical trials concept that would allow for smaller-scale efficacy testing to more rapidly distinguish between vaccines that have promise and those not worth pursuing further. Initial intermediate trials could begin within 2 to 3 years, assuming successful development of pox virus vaccine vectors, which now lead the pack. (Extracted from *Genetic Engineering News*, 1 January 1996)

Controversial AIDS vaccine fails to delay disease

The results of a five-year US study announced recently show that an experimental AIDS vaccine based on the genetically engineered HIV envelope protein gp160 does not affect the course of disease in HIV-infected volunteers.

The study, conducted under the auspices of the Walter Reed Army Institute of Research in Washington DC and the National Institute of Allergy and Infectious Diseases, followed 608 volunteers for five years, until December 1995. Half were given the gp160 vaccine and half a placebo.

The study found that the vaccine, produced by Microgenesys Inc. of Meriden, Connecticut, led to an elevated immune response in those injected, but did not slow progression of the disease. "No clinical improvement" could be attributed to the vaccine, used as adjunct therapy for HIV infection, said a statement released by the Department of Defense. (Source: *Nature*, Vol. 380, 25 March 1996)

Antigen-free haemoglobin acts as blood substitute

Haemoglobin extracted from outdated blood supplied by blood banks is the basis for Hemolink, a red cell substitute entering Phase II clinical trials. Developed by Canadian-based Hemosol Inc., Etobicoke, Ontario, from blood approved for transfusion, Hemolink would be used to counteract oxygen shortage during acute blood loss, as might occur during surgery or after an accident. The product also would replenish lost fluid. Extracting haemoglobin is more complicated than it sounds, because "red cells contain about 90 different proteins", says Hemosol scientist Gord Adamson. The extraction process strips away blood-group antigens so Hemolink can be given to any patient regardless of blood type. The purification steps greatly reduce the already low risk of transmitting a blood-borne disease such as AIDS. To form Hemolink, free haemoglobin is cross-linked and polymerized with oxidized raffinose, which enables the product to circulate in the blood for a couple of days before being excreted. Hemosol plans to develop a freeze-dried formulation that could be shipped to remote areas and reconstituted for use in natural disasters or military casualties.

Gene spray

Patients with the hereditary lung disease cystic fibrosis have shown signs of improvement after receiving a form of gene therapy. Stephen Hyde of the University of Oxford and his colleagues treated patients with sprays containing healthy copies of the gene that is defective in people with CF. They packaged the gene in liposomes and sprayed them into patient's noses.

Hyde found evidence that the inserted gene was working in 6 of the 12 patients. None reported any side effects. Next, the team will experiment with increased doses. (Source: *New Scientist*, 11 May 1996)

Heart patients could benefit from blood-feeding hookworms

As repulsive as hookworms may be, they could be a source of better drugs to treat heart diseases associated with excessive blood clotting. Researchers at Corvas International, a pharmaceutical company based in San Diego, and Yale University School of Medicine have isolated a family of three small anticoagulant proteins from the blood-feeding hookworm *Ancylostoma caninum*. The proteins, comprising 75 to 84 amino acids, prevent clotting by inhibiting two key enzymes involved in the cascade of reactions leading to blood coagulation. Two of the proteins inhibit factor Xa, an enzyme midway in this cascade. The third protein inhibits the cascade-initiating complex formed by another enzyme and a nonenzymatic co-factor: factor VIIa and tissue factor. This latter inhibition presents a unique opportunity. It shows that the series of reactions leading to a blood clot can be stopped at the earliest stage. A drug that interferes at this level may be more effective at lower doses and safer to use than those acting at later stages because the number of molecules that must be stopped to prevent clotting increases exponentially with each stage in the cascade. (Source: *Chemical and Engineering News*, 11 March 1996)

Peptide analog reverses autoimmune paralysis

A team of researchers in the US, the UK, Germany, and Israel has used a myelin peptide analog to reverse paralysis in a mouse model of multiple sclerosis, opening the possibility of a new class of drugs to treat this and other autoimmune diseases.

Autoimmune diseases develop when healthy tissue is attacked by T cells—a type of white blood cell that normally destroys only cells infected with viruses, parasites, or cancer, for example. This turn of events triggers severe inflammation in the target tissue. In multiple sclerosis, T cells orchestrate the destruction of myelin, the proteolipid sheath that is the nerve cells' electrical insulator.

About 330,000 people in the US have multiple sclerosis, according to the National Multiple Sclerosis Society, New York City. This chronic, often disabling disease of the central nervous system most frequently strikes adults between 20 and 40 years old. The disease is more common among people of Western European heritage who live in temperate climates and affects twice as many women as men.

The researchers—led by neuroscientst Lawrence Steinman of both Stanford University and the Weizmann Institute of Science, Rehovot, Israel—knew that a major target of T cells in the brains of multiple sclerosis patients is a 14-amino-acid segment of a myelin protein known as myelin basic protein. The team sought to block the binding between T cells and that peptide segment to prevent myelin destruction.

The scientists created an animal model by inducing inflammation of brain myelin in mice by inoculating them with a T-cell clone specific for the myelin peptide. They prepared 13 analogs of the peptide, each time substituting alanine at a different site in the peptide fragment. They administered each analog separately to a batch of newly inoculated mice and to mice that had become paralyzed by the inflammation.

One of the analogs both reversed paralysis and abated inflammation of the myelin tissue.

In shutting off the immune response to the protein peptide, the analog also prevented the immune system from responding to other peptides in the myelin sheath.

Probing this phenomenon further, the researchers discovered that the analog binds T cells only weakly. They found it works by stimulating the immune system to produce interleukin-4, the hormonelike compound that activates the immune system cells that naturally fight inflammation.

Until now scientists have believed the only way to treat an autoimmune disease effectively is to suppress the entire immune system. The group's work shows it may be enough to block the initial mechanism that triggers an autoimmune response—which could be significant in designing drugs for autoimmune diseases. (Source: *Chemical and Engineering News*, 29 January 1996)

Protein offers target for antimalarial drugs

By probing the role of histidine-rich proteins unique to the malaria-causing parasite *Plasmodium falciparum*, a team of researchers at Washington University's Howard Hughes Medical Institute, St. Louis, has opened a route to new drugs to combat the disease. The histidine-rich proteins, which contain as many as 51 repeating sequences of histidine-histidine-alanine, circulate in the bloodstream of people stricken with malaria. Their presence in blood is the basis for a finger-prick diagnostic test for the disease.

The malaria parasite has become increasingly resistant to chloroquine, the main drug used to treat the disease. Resistance to other antimalarial drugs also is on the rise, especially in South-East Asia.

P. falciparum survives in red blood cells by ingesting their haemoglobin, which the parasite degrades in its digestive vacuole. This proteolytic process releases free haeme, a cytotoxic iron-porphyrin complex. Lacking the enzymes to degrade haeme, the parasite detoxifies the complex by polymerizing it into insoluble hemozoin, a crystalline compound in which the iron of one haeme is linked to the propionate carboxyl group of the next.

The researchers focused their efforts on the histidine-rich proteins. Using immunofluorescence techniques, they showed that these proteins are present within the digestive vacuoles as well as in the red-cell cytosol. They observed that sequences in the *P. falciparum* proteins are similar to the haeme-binding sequence of a human histidine-rich glycoprotein. To investigate whether the parasite proteins also bind haeme, they isolated native parasite protein and cloned and expressed it an *Escherichia coli*. Both the native and the recombinant proteins bound haeme and both promoted formation of hemozoin.

In contrast, human histidine-rich glycoprotein did not polymerize haeme. Neither did bovine serum albumin, lysozyme, or a variety of poly(amino acids) such as polylysine or polyasparagine. Polyhistidine trapped haeme as a red pellet and did not yield spectra consistent with hemozoin.

And in another piece of evidence pointing to the histidine-rich protein as the key to haeme polymerization, chloroquine inhibited the protein-mediated synthesis of hemozoin. (Extracted from *Chemical and Engineering News*, 29 January 1996)

From herbs to drugs

Herbal extracts of Chinese wormwood have been used for centuries to treat fever. The active compound, qinghaosu artemisinin, has shown great promise against malaria. Now US and Israeli chemist claim to have developed artemisinin analogues that could lead to new inexpensive drugs.

Gary Posner and his colleagues at the John Hopkins University, Baltimore, and the Weizmann Institute in

Rehovot, have been studying the way artemisinin kills the malaria parasite *Plasmodium falciparum*. They say they have stripped down the complex molecule to the bare essentials needed for activity.

Artemisinin contains three main rings, one with a bridging peroxide unit that forms a trioxane group. The researchers believe that iron from the digested haemoglobin of the parasite's victim (the mosquito) reduces this unit, releasing a highly reactive iron(IV)-oxo species. This compound rips apart the parasitic cells.

However, artemisinin is complex, making it expensive to synthesize on a large scale. The chemist wanted to find safe, simple and cheaper analogues by isolating just the drug's active unit.

As the team predicted, the silicon-containing analogue had strong antimalarial activity—in the test tube at least. The tin compound had little activity because it blocked formation of the iron species. This result backs up the researchers' theory of how artemisinin works.

Posner and his colleagues have two lead compounds, which Posner says would probably cost a few dollars per gram to manufacture on a large scale. The molecule's structural simplicity should allow them to fine-tune their properties. However, Posner points out that *in vivo* and toxicological tests are needed before clinical use can even be considered. (Source: *Chemistry & Industry*, 13 May 1996)

Whooping cough paves the way for malaria vaccine

A toxin produced by the whooping cough bacterium, *Bordetella pertussis*, could provide the key to developing more successful vaccines against malaria and HIV.

Getting vaccines inside cells, rather than floating free in the bloodstream, may be crucial to destroying the malaria parasite and HIV. Cells infected with malaria or HIV are destroyed by the immune system's killer T cells, but these can only be primed to recognize a pathogen's proteins if they appear on the surface of antigen-presenting immune cells. And for this to happen the proteins must first enter these cells.

Nicholas Carbonetti of the University of Maryland at Baltimore used to work with Rino Rappuoli, a vaccine researcher at the Sclavo Research Centre in Siena, Italy, who has developed a whooping cough vaccine based on the pertussis toxin. This protein enters human cells and destroys them. But the protein was made harmless by changing a couple of its amino acids. It was still able to enter human cells, however.

Carbonetti and his colleagues have now made genetically engineered *B. pertussis* that secretes harmless versions of the toxin, incorporating peptides from a virus that causes meningitis in mice, or a mouse malaria parasite. The researchers added these hybrid proteins to cultured mouse cells, which they then exposed to T cells that could recognize the viral or malarial peptides. The cultured cells were rapidly destroyed, showing that they had been penetrated by the hybrid proteins. The next test will be showing that the hybrid proteins stimulate T cell responses in animals. (Source: *New Scientist*, 1 June 1996)

Anti-Streptokinase IgG immunoassay developed

BioResearch Ireland, in collaboration with the Royal College of Surgeons' Medical School in Dublin, have developed a simple ELISA for the detection and/or quantification of anti-SK IgG in human serum. The assay has been thoroughly validated against a highly sensitive SK neutralization assay, indicating that it is largely detecting neutralizing activity. Anti-SK IgM antibodies, which may be present in the early days after treatment with SK, are not detected.

The BRI test will detect anti-Streptokinase IgG within two hours in the patient's serum. It will thereby allow selection of an appropriate therapeutic regime.

Approximately 20 per cent of patients presenting with acute myocardial infarction (AMI) have had a previous cardiac event and many have been treated with streptokinase. Streptokinase (SK) is a widely used thrombolytic agent, but also an immunogen and allergen. Anti-SK antibodies have been detected at significant levels in some patients for up to four years following SK *in vivo* administration. Although the clinical significance of the antibodies is not clear, there is evidence that anti-SK antibodies may neutralize SK activity *in vivo*, resulting in a reduction in its thrombolytic efficacy.

Apart from previous SK administration anti-SK antibodies may also arise from streptococcal infections. There is a need for a convenient test to determine whether patients have circulating anti-SK antibodies. Indeed, because of the relatively high incidence of anti-SK antibodies in the general population, all patients should be checked for anti-SK antibodies prior to SK administration. (Source: *Press Release*, 29 April 1996)

Better protease inhibitors

Advanced Tissue Sciences (ATS, La Jolla, CA) reports that results from its pivotal clinical trial for Dermagraft-TC in the treatment of severe burns have successfully reached its primary endpoint—adequate preparation of the wound bed for successful grafting. The results of the study showed that Dermagraft-TC—made from engineered human dermal tissue and a synthetic epidermal layer—was equal or superior to the cadaver skin that is normally used for this procedure. As a result of this study, ATS is preparing a premarket approval application (PMA), which it plans to submit to the FDA sometime in 1996.

Meanwhile, Organogenesis (Canton, MA) has announced that it has begun a clinical trial to test the efficacy of its manufactured human skin product, Graftskin. The trial is designed to treat venous ulcers in diabetics. Organogenesis says the FDA has already informed the company that its PMA will receive expedited review status when filed. (Source: *Nature Biotechnology*, Volume 14, April 1996)

Beyond protease inhibitors

Despite a growing collection of effective HIV reverse transcriptase (RT) and protease inhibitors, the search for agents that interfere with other components of this virus is accelerating.

One still unexploited target is HIV's Gag protein, which plays a prominent role in assembling new viral particles and is essential for infectivity. Stephen Goff of Columbia University (New York) and his colleagues learned that Gag associates with the host-cell protein, cyclophilin, which plays an important role in folding and reshaping cellular proteins. Moreover, cyclophilin is at least an indirect target of the immunosuppressant drug, cyclosporin, which is believed to disrupt the refolding of yet another protein in T cells.

Meanwhile, Goff points out, the interaction between Gag and cyclophilin is "unique to the Gag from HIV-1—a curious fact." Together these findings suggest another, potentially exploitable point of HIV vulnerability. Indeed,

chemically modified cyclosporin derivatives apparently disrupt cyclophilin-Gag interactions, according to Heinrich Gottlinger of the Dana Farber Cancer Institute (Boston, MA). Some derivatives show high anti-HIV activity *in vitro*, but are relatively free of immunosuppressive activity, he says.

The HIV integrase protein is another candidate target. This protein binds to RT-produced DNA copies of the HIV genome and helps to integrate them into host-cell DNA. Other research groups report progress towards identifying HIV integrase inhibitors. (Source: *Nature Biotechnology*, Vol. 14, April 1996)

Biotechnology beats brain tumours

Brain tumours remain difficult to treat and almost impossible to cure. Now, encouraging results from a genetically engineered vaccine offer new hope for these and some other cancers. Clinical trials could start this year.

Brain tumour cells, or glioma cells, secrete a growth factor called TGF-β. This suppresses the body's immune system and allows tumour cells to grow without being detected. In particular, it inhibits white blood cells called cytotoxic T and B cells, and deactivates natural killer cells.

A team from the University of California, Los Angeles and the Sidney Kimmel Cancer Center in San Diego has genetically modified glioma cells in rats with brain tumours to block the production of TGF-β. To do this, they used specially designed genetic material called antisense vectors. These are mirror images of TGF-β, which attach to precursors of the growth factor and instruct them to stop developing. The genetically modified cells operate like a vaccine on the tumour.

All 11 treated rats survived the 12-week study and showed no signs of harbouring residual cancer cells after the therapy. All five control rats died. Significantly, the rats appeared to remain immune even when they were subjected to the cancer again.

Prevented from producing TGF-β, the glioma cells provoke a more robust immune response. This allows the immune system to destroy the cancer completely. And once activated, immune cells are no longer affected by TGF-β secreted from unaltered tumour cells.

In this way, genetically engineered tumour cells appear to increase the effectiveness of cancer cell vaccines, the team says. Their findings suggest, they say, that inhibiting immunosuppressive factors, such as TGF-β, will aid future efforts to develop genetically engineered tumour cell therapies for treating brain and other tumours.

TGF-β is overproduced by many other forms of tumours including most colon, breast and prostate cancers. Furthermore, it is possible that this approach may work in tumour cells that secrete other immunosuppressive factors, such as interleukin or prostaglandin. (Source: *Chemistry & Industry*, 15 April 1996)

Snake skins model new enhancers

New biodegradable compounds could improve the effectiveness of drugs that are absorbed through the skin. They hold particular promise for treating conditions that would benefit from direct application, such as skin diseases and arthritis.

Transdermal drugs have to overcome the skin's resistance to large and polar molecules, and avoid causing too much irritation. Several chemical drug enhancers currently on the market increase drug absorption but cause a lot of irritation. Natural enhancers are more friendly but are less potent.

Howard Rytting and his colleagues at the University of Kansas have designed a new class of enhancers called alkyl *N,N*-dialkylamino alkanoates, based on the skin enhancer *Azone*. By adding ester groups to *Azone*-type molecules, they produced a range of compounds which are "quite mild" but just as effective as *Azone*.

Studies with rabbits have shown that these compounds are less toxic and cause less skin irritation. They have two further advantages: they enhance skin penetration with a number of classes of drugs, in some cases by a thousand times more than control experiments; and they can be degraded by enzymes.

Rytting's enhancers boosted the penetrating power of the arthritis drug indomethacin by a factor of 430 compared with a control group, and by 100 compared with *Azone*. Other successes were noted with the anti-inflammatory agent hydrocortisone, 5-flurouracil for treating cancer and clonidine for reducing blood pressure.

Rytting has pioneered the use of snake skins to serve as model membranes to measure the amount of drug penetration. Human skin deteriorates quickly and is hard to obtain. "The outer layer of shedded snake skin is similar to human skin in terms of thickness, lipid content, water permeation and drug absorption", he says. Because it lacks hair follicles, it is tough to penetrate; if a drug makes it through snake skin, then human skin should be no problem, he adds. (Source: *Chemistry & Industry*, 15 April 1996)

R&D jv seeks new antibiotics

A fundamental new approach to discovering drugs to treat resistant bacterial infections by applying gene-based technology will be developed in a five-year collaboration programme by Pfizer and Microcide Pharmaceuticals.

Results could provide major new classes of antibacterial drugs and a significant competitive advantage in the antibiotic market-place, according to Microcide.

The research project will utilize Microcide's essential genes and targeted genomics technologies which are expected to accelerate the identification of breakthrough antibacterial compounds. Pfizer will contribute its discovery and development experience in infectious diseases and build collections of novel bacterial targets and potential leads.

Bacterial resistance is the biggest challenge in antibacterial research. While improvements are being made by extensive chemical modifications in antibiotics, this strategy is becoming less productive, according to Pfizer. (Source: *European Chemical News*, 1-7 April 1996)

Fighting bacteria with lasers

Scientists at London's Eastman Dental Institute are studying the use of laser-activated chemical compounds to circumvent antibiotic resistance. Under laser light the compounds produce an excited state of molecular oxygen and toxic-free radicals, which kill bacteria by punching holes in cell membranes. Researcher Michael Wilson says the strategy works on both aerobic and anaerobic bacteria and should be appropriate for dental problems. He has not yet tested the method on people. (Source: *Industry Week*, 4 March 1996)

Genzyme's Seprafilm gets FDA marketing nod

The first biodegradable product to demonstrate clinical efficacy in reducing adhesion formation in general abdo-

minal surgery—Genzyme's (Cambridge, MA) Seprafilm—was recommended and approved for marketing in the United States on 25 March 1996. Seprafilm contains glycosaminoglycan, which degrades to N-acetylglucosamine, glucuronic acid, and a urea derivative, all of which are innocuous. The product has shown no evidence of toxicity.

Postoperative adhesions occur when tissues react to the trauma of surgery by attaching to other, normally separate, tissues. The adhesions can cause complications ranging from infertility to intestinal obstruction, and they may interfere with follow-up surgeries.

An abdominal surgery trail demonstrated that, of the patients whose surgical incisions were treated with Seprafilm, 51 per cent showed no signs of adhesion during a follow-up examination. Only 6 per cent of untreated controls remained free of adhesions. A similar study of postsurgical uterine adhesions showed a 37 per cent decrease in the number of adhesions in treated patients.

Genzyme is test-marketing Seprafilm in the Netherlands, the United Kingdom and Sweden. (Source: *Nature Biotechnology*, Vol. 14, May 1996)

Vaccine lead for meningitis

Researchers from the Laval University Hospital Centre in Quebec City have discovered a protein that could lead to the development of a new human vaccine to give protection against all types of meningococcal meningitis, a priority research area identified by the World Health Organization.

IAF BioVac, the Canadian vaccine subsidiary of BioChem Pharma, plans to start Phase I clinical trials in 1997. The team has cloned and identified the gene responsible for producing the protein, enabling access to large amounts of the protein for trials. (Source: *European Chemical News*, 10-16 June 1996)

Livestock applications

Human lactoferrin from transgenic cow's milk

The Dutch biotechnology company, Pharming, said it has produced the world's first samples of human lactoferrin from transgenic cow's milk. The human lactoferrin is of "excellent quality", according to the company, and initial research has shown that the biological activities of transgenically produced and natural human lactoferrin from breast milk are indistinguishable. The clinical nutrition section of Verenigde Bedrijven Nutricia of the Netherlands and Pharming will now jointly initiate pre-clinical testing of the protein, for the purpose of developing products to treat or prevent gastrointestinal infections in patients with low immunological response. (Source: *Biotechnology Business News*, 21 March 1996)

Goat's milk drug source

With a product developed by Bristol-Myers Squibb Company, a genetically altered goat has been born in expectation of producing an anti-cancer drug cheaper and in greater quantities. Genzyme Transgenics Corporation expects the goat's milk to produce a kilogramme of the antibody within a year.

"This achievement indicates that the transgenic antibody is properly folded and thus can fulfill its intended role as an antibody designed to deliver the drug doxorubicin to a variety of carcinomas", says Perry Fell, director at Bristol-Myers.

Genzyme had previously produced the same antibody from the milk of a genetically altered mouse, which resembles a goat in its lactation system. Although the mouse is notable for many properties, goats can produce far more milk. Last May, Genzyme developed transgenic goats that produce another monoclonal antibody at four grammes per litre of milk. (Source: *Chemical Marketing Reporter*, 15 April 1996)

New pig breeding technologies from Guelph

The University of Guelph has produced North America's first piglets from oocyte (unfertilized egg) transfer. The new breeding technology combines traditional embryo transfer, innovative oocyte transfer technology, and *in vitro* embryo fertilization to achieve new methods of herd improvement.

The oocyte transfer involves the removal of unfertilized eggs from the ovaries of donor sows or gilts and implanting them into the oviducts of inseminated recipients. Guelph is also working on new methods for *in vitro* fertilization and cryopreservation of swine embryos produced from slaughtered and carcass-evaluated gilts, as well as methods for storing and transferring embryos recovered from valuable donors.

Pregnancy rates greater than 85 per cent for embryos stored for more than a day in the laboratory are attributed to a new culture medium for embryos and simplified surgical transfer methods.

The research at Guelph is supported by Struthers Research Inc., the National Research Council, and Ontario's Agriculture Ministry. Improved storage methods are essential to efforts to export embryos internationally. (Source: *The AgBiotech Bulletin*, April 1996)

Canadian technology aids in the growth of Atlantic salmon

Researchers at Newfoundland's Memorial University and University of Toronto, have been experimenting with fish genes in salmon hatchery eggs to stimulate rapid growth since 1989. They have found that injection of the genes into eggs result in fish that grow at six times the normal rate. Ten out of every thousand will grow at this rate. The gene receptive fish will be ready to eat in two years instead of an average of three years.

It requires twelve consecutive generations of treatment for all salmon offspring to accept the genes and become fast-growing. Although Canadian fish farmers are reluctant to wait twelve years for a fast growing breed of salmon, New Zealand fish farmers have begun raising salmon bearing this altered gene. Meanwhile a Scottish hatchery has agreed to start injections with fifty thousand of their fish.

The gene is sold by A/F Protein Inc. which is based in Boston. Contact: Elliot Entis, A/F Protein Inc., 72 Bonad Road, West Newton, MA, USA 02165. Tel.: 617/576-8153; Fax: 617/542-8506. (Source: *The AgBiotech Bulletin*, March 1996)

Agricultural applications

Synthetic canola variety available

Researchers at Agriculture and Agri-Food Canada's Saskatoon Research Centre are pioneering a concept aimed at producing synthetic canola varieties.

Synthetics are a new type of variety intermediate to open-pollinated and hybrid forms. They are composed of a mixture of hybrid and parental plants and offer more stability over a wide range of environments than their pure stand counterparts.

The first AAFC variety, ACS-C6, a Polish canola, was recommended for registration at the end of February. It yields 2 per cent higher in oil and 1 per cent higher than the average for Tobin and Parkland. Currently in seed multiplication, the variety is expected to be commercially available by 1997. Further information from Dr. Kevin Falk, AAFC Research Centre, 107 Science Place, Saskatoon, Sask. S7N OX2. Tel.: 306/956-7614, e-mail: Falkk@em.agr.ca.(Source: *The AgBiotech Bulletin*, April 1996)

Plants store sulphur for health

UK researchers have reported the first evidence that a plant can store elemental sulphur which makes it resistant to microbial attack. This discovery comes centuries after man first used sulphur as a powerful fungicide. The data also provide a rare example of cells harbouring an antimicrobial substance, say the scientists.

Disease ravages 20-30 per cent of the world's cocoa crop every year. The team from the University of Bath and the University of Bristol's Long Ashton Research Station is part of a programme that aims to improve techniques for rapidly testing new strains of cocoa for resistance to the devasting soil-borne microbe, *Verticillium dahliae*. This pathogen invades the vascular system of cocoa plants.

The team studied *V. dahliae*-resistant strains of the cocoa plant called *Theobroma cacao*, which originates in Brazil where there are about 22,000 possible sources of resistance.

It appears that the plant defends itself with four antifungal compounds. The most abundant of these is a pentacyclic triterpene called arjunolic acid, followed by two phenolics, 3,4-dihydroxy-acetophenone and 4-dihydroxyacetophenone.

Finally, the researchers "unambiguously identified" elemental sulphur (S_8 broke down into S_2). At first, they thought that it must have come from a sulphur-containing organic compound, but further tests revealed that this was not the case.

The team did not find elemental sulphur in plant strains that were susceptible to the fungi. They think that sulphur accumulates in vessels and cells that have already reacted to the pathogen and, in some cases, may be dead. The sulphur persists for at least 60 days, which suggests that it never reaches living cells where it could be metabolized.

These results also suggest that these levels of sulphur are toxic to fungi because many fungi can also metabolize sulphur at low concentrations. Inorganic elements have not been implicated directly in disease resistance before.

The team is not sure where the sulphur comes from. Inorganic sulphate taken up by higher plants is usually converted to organic sulphur, such as amino acids. Bacteria can make sulphur as can a few fungi algae. (Source: *Chemistry & Industry*, 15 January 1996)

Mushroom for progress

Growing edible mushroom involves carefully formulated compost, and precise temperature and air control. Niels Mathieson of Naerum in Denmark has found a new additive that can make the process easier and boost the yield.

Mathieson's magic ingredient comes from the edible oil industry. Before animal, vegetable and fish oils can be refined for human consumption, they are bleached with an acid-activated dried clay called "bleaching earth". After this process, the clay contains 20-50 per cent fat, but it is not economic to recover this, so the spent clay is usually dumped. The quantities involved are large, says Mathieson—Hamburg produces 15,000t/a.

Mushrooms are grown in a compost of straw, chalk, gypsum and manure. Mathieson claims that a compost containing as little as 3 per cent spent bleaching earth will yield up to 9 per cent more mushrooms than a conventional medium. The fats in the clay encourage the mushroom's growth, he says. Also, the clay binds ammonia, which is produced by composting and is toxic to mushrooms. However, says Mathieson, when it is bound, the fungi can use it as a safe source of nitrogen. European patent application 0691072. (Source: *Chemistry & Industry*, 5 February 1996)

Go-ahead for genetically altered chicory

The European Commission has announced that the EU committee on the release of genetically modified organisms (GMOs) has given the go-ahead for marketing of a genetically altered form of chicory.

The decision will allow the Dutch authorities to issue a consent to the Bejo Zaden company to market—for breeding activities only—genetically modified male chicory with partial tolerance to the herbicide, glufosinate ammonium.

Consent would extend to chicory bred from this product by crossing with traditional varieties.

An evaluation by the committee created under the 1990 Directive on Deliberate Release into the Environment of GMOs indicated that "there is no reason to believe that there will be any adverse effects on human health or the environment from the uses notified", said the Commission.

Although the committee had also agreed that there were no safety reasons to justify mentioning on the label that the product had been obtained by genetic modification, a requirement should be imposed pointing out on each seed packet that the product is to be used for breeding activities and that it may be tolerant to glufosinate ammonium. (Source: *Biotechnology Business News*, 4 June 1996)

Biological control for locusts

Researchers in Africa have developed a workable method of biological control for locusts using a naturally occurring fungus. Locusts are sprayed with an oil-based formulation of fungus spores, known as "Green Muscle", and are killed by the infecting spores usually within one to two weeks. In the latest trials in Niger, Green Muscle reduced the locust population by 70 per cent after one month.

International concern about high levels of pesticides used to kill locusts during the last major outbreak from 1986 to 1988 led to the formation of Biological Control of Locusts and Grasshoppers, a project designed to explore opportunities for biological control of locusts in Africa's Sahel region. Locusts are a significant threat to millet, sorghum and vegetable production in this region.

The project was implemented in 1989 by the International Institute of Biological Control (UK), the International Institute of Tropical Agriculture (Nigeria) and AGRHYMET (Niger). Researchers quickly identified strains of the *Metarhizium flavoviride* fungus that were highly virulent to locusts; however, fungal spores could not survive and germinate in the arid Sahelian climate because they require highly humid conditions. Experiments using water-based sprays were unsuccessful due to high evaporation rates.

Researchers found that by applying spores of *M. flavoviride* fungus in an oil-based formulation, the

spores not only germinated, but stuck more easily to the locust cuticle. *M. flavoviride* kills locusts by breaking through the cuticle and producing spores within the insect, creating a cycle in which reproducing fungi gradually reduce locust populations.

According to Dr. Roy Bateman, a member of the research team, there are challenges before Green Muscle can be widely adopted in the region. For example, although researchers consider the fungus harmless to humans and the environment, some locust-affected countries may be apprehensive about releasing fungal pathogens into the environment. Dr. Bateman also stated that for use to become widespread, it will be necessary to provide rural communities with easy access to the fungus; this will require time and resources to build numerous local spore production facilities. In addition, because *M. flavoviride* may take up to two weeks to develop and spread, farmers may still turn to quick-killing toxic pesticides when their high-value crops are attacked by locusts. Contact: The Pesticides Trust, Eurolink Business Centre, 49 Effra Road, London, SW2 1BZ, England; Tel.: (441 71) 274-8895; Fax: (441 71) 274-9084; e-mail: pesttrust@gn.apc.org. (Source: *The Pesticides News*, March 1996 and *Global Pesticide Campaigner*, June 1996).

Transgenic flax provides platform for sustainable agriculture

CDC Triffid, a linseed flax variety genetically engineered to grow in contaminated, as well as in normal soil, received its final regulatory clearance in May. Developed by a team led by Alan McHughen at the University of Saskatchewan's Crop Development Centre (Canada), CDC Triffid was the world's first transgenic field crop grown commercially by farmers. The transgenic flax has commercial importance for linseed oil production but more importantly the flax has immunity to a common class of herbicides used by cereal farmers around the world. This enables farmers to grow CDC Triffid in soil that has a herbicide level that prevents crop rotation. McHughen says that while the herbicide is active in the soil, broadleaf crops like flax or canola cannot be grown and that this forces the farmer into environmentally and agronomically unsustainable practices, such as summer fallowing or continuously growing cereals with natural resistance to the herbicide. With the completion of these studies and the conclusion by Agriculture and Agri-Food Canada that CDC Triffid and its products were substantially equivalent to conventional flax varieties, the line can be grown commercially in Canada in the same manner as other conventional linseed varieties. (Source: *Nature Biotechnology*, Vol. 14, June 1996).

Just in time for summer: Transgenic cherry tomatoes

After almost four years of investigation, the USDA (United States Department of Agriculture, Washington, DC) has finally given Agritope (Beaverton, OR) the green light for growing its transgenic cherry tomato 35-1-N. This species has been enhanced for fruit ripening—allowing the tomatoes to be left on the vine longer and thereby reducing labour costs. What set off the USDA's red flags in this case was the fact that DNA from the plant pathogen *Agrobacterium tumefaciens* has been engineered into the fruit-ripening genetic machinery. The USDA's fears that the plant might pose environmental dangers—apparently through recombination of this DNA into other agrobacteria—has finally been overcome through a combination of data supplied by the company and public commentary at USDA-sponsored hearings. (Source: *Nature Biotechnology*, Volume 14, June 1996)

Bulk cloning of pulpwood species

Nippon Paper Industries, and Prof. M. Tanaka of the Faculty of Agriculture of Kagawa University, have jointly succeeded in bulk propagation of *Eucalyptus citriodora* and *Eucalyptus globulus*, which are high-yielding pulpwood species, using tissue culture of clones.

In the past, these species could not be propagated by cuttings, unlike other pulp species, so seeding was the only way for propagation, with high costs and slow growth. The culture rockwool system consists of rockwool containing a liquid medium enclosed in a fluorinated film. No saccharides are used, but high-concentration carbon dioxide is injected and propagation shoots are planted. The entire system is designed to fit in a plastic frame. By culturing this system under a carbon dioxide atmosphere, root generation and growth can be improved noticeably and substantial clones can be produced rapidly. The rockwool is made in Denmark by melting diabase to form fibres.

After planting of shoots and growth into clones, the rockwool is separated from individual clones for replanting directly into soil. Replanting is very easy because there is no need to wash away agar and saccharides before replanting in the soil. The pulp material yield from *Eucalyptus citriodora* is doubled compared to the *Eucalyptus citriodora* grown by seeding. Further details available from Nippon Paper Industries, International Department, 1-12-1, Yuraku-cho, Chiyoda-ku, Tokyo 100, Tel.: +81-3-3218-8090, Fax: +81-3-3213-6762. (Source: *JETRO*, March 1996)

Substance preventing crop insect damage extracted from cypress seed

Japan's Forest and Forest Products Research Institute of the Ministry of Agriculture, Forestry and Fisheries has succeeded in extracting a substance that prevents crop insect damage from the seed of the coniferous tree hinoki (Japanese cypress, *Chamaecyparis obtusa*). Two substances effective against moth larvae have been identified, and experiments in which these substances were mixed into imitated feed confirmed that these substances are effective in suppressing crop damage.

The substances in immature hinoki seeds (cones) were extracted with the organic solvent ethyl acetate. Various chemical components were separated by column chromatography and thin layer chromatography and identified by nuclear magnetic resonance spectroscopy. Analysis showed that compounds have the effect of suppressing crop damage by insects. Structural analysis revealed that the compound is a polyterpene family chamaecidine.

This compound was mixed into an artificial feed prepared from mitrocellulose, and experiments were conducted by supplying the feed to moth *spodoptera litura* larvae, which damage potato and other crops, to investigate the antifeedant activity. Chamaecydin was confirmed to be effective at a concentration of 1,000 ppm, which is intermediate in the effects of other known antifeedant activity substances. The future plan is to use chamaecydin as a lead substance and to develop a more powerful antifeedant activity substances by changing the chemical structure.

Agricultural chemicals synthesized artificially are associated with problems such as environmental pollution

and the evolution of insects with greater resistance. In this respect, the new substance is anticipated to enable the manufacture of next-generation version agricultural chemicals consisting of a natural compound, featuring great safety and without adverse influences on the natural environment. Further details from Forest and Forest Products Research Institute of the Ministry of Agriculture, Forestry and Fisheries, 1, Matsunosato, Kukizaki-cho, Inashikigun, Ibaraki Pref. 305, Tel.: +81-298-73-3211, Fax: +81-298-73-3795. (Source: *JETRO*, April 1996)

New range of insecticides

DowElanco has developed a fermentation process to produce a new range of insecticides, marketed under the name *Naturalyte*. The company expects US registration for its first insecticide, called *Spinosad*, in late 1996.

Spinosad is effective against all *Lepidoptera*, including tobacco budworm and cotton bollworm. Cotton is targeted as a the main market. The product is harmless to insects such as ladybirds.

The insecticide is derived from the naturally occurring soil microbe *Actinomycete* in a two-part fermentation process. In the first part, the bacterium replicates to a critical concentration; replication then stops and the bacteria turn to *Spinosad* production. Finally, the bacteria cells are killed and the *Spinosad* is harvested.

Dow will launch *Naturalyte* in the US in 1997, in the Pacific Rim in 1998 and in Latin America in 1998-1999. (Source: *European Chemical News*, 10-16 June 1996)

Scorpion-poison spiked insecticide

The US Environmental Protection Agency (EPA) is asking for public comments on American Cyanamid's plan to conduct field trials of a baculovirus that is genetically engineered to express a toxin protein from the North African scorpion. EPA will decide whether an experimental use permit is required.

The *Autographa californica* multiple nuclear polyhedrosis baculovirus is a naturally occurring insect-specific pathogen that targets two economically important pests that affect cotton and vegetables: the tobacco budworm (*Heliothis virescens*) and the cabbage looper (*Trichoplusia ni*). Unfortunately, the natural baculovirus acts too slowly to save crops from destruction, since four or five days pass before insects stop feeding and die.

To speed things up, American Cyanamid has deleted a part of the baculovirus's egt gene, which is responsible for an enzyme that, paradoxically, leads to increased feeding activity by infected insects. This deletion speeds insect killing by 15 to 30 per cent.

The company has also added a gene—called AaIT—from *Androctonus australis*, the North African scorpion, to enable the baculovirus to express a protein toxin that paralyzes the insects.

The doubly modified baculovirus, dubbed V8EGTDEL-AaIT, is expected to kill targeted insects up to 60 per cent faster than the natural baculovirus. According to American Cyanamid the AaIT toxin is completely insect-specific and has no effect on the nervous systems of other types of arthropods, such as spiders, and is completely safe for people and wildlife. (Source: *McGraw Hill's Biotechnology Newswatch*, 15 April 1996)

Seed dip breaks witchweed's spell

Dipping maize seeds in a tiny amount of herbicide could protect the crops of millions of African subsistence farmers from the ravages of witchweed. This purple-flowered parasite (*Striga hermonthica*) devastates 80,000 hectares of farmland annually in Kenya alone and destroys crops worth an estimated $10 million each year.

Experiments over the past two years in Kenya have shown that dipping the seeds triples the yield of maize.

George Odhiambo and Gordon Abayo of the Kenyan Agricultural Research Institute in Kisumu pioneered the new approach with Jonathan Gressel, a plant geneticist at the Weizmann Institute of Science in Rehovot, Israel. An important ingredient is the use of a herbicide-resistant strain of maize developed by Pioneer International, an American seed company.

Pioneer's strain withstands herbicides that block the action of an enzyme called acetolactate synthase. Without this enzyme, weeds cannot make vital amino acids, and die.

Over the past two years, Abayo and Odhiambo proved the effectiveness of their technique. On average, each plot of undipped seeds yielded just 180 grammes of maize, whereas seeds dipped in the herbicide imazapyr, yielded almost 620 grammes per plot. Five times more witchweed grew in the plots with untreated seeds.

Witchweed latches onto the roots of its host, scavenging vital water, minerals and sugars.

As the treated seeds grow, the herbicide diffuses into the growing tissue and surrounding soil, killing any witchweed before it can take hold. Eventually, after the maize has been harvested, the herbicide itself decays in the soil.

Even the poorest subsistence farmer could afford the approach because so little herbicide is required, says Gressel. Just 15 grammes, costing around $5, is enough to treat a hectare, and could bring a farmer an extra $100 per hectare in improved yields.

But because the Pioneer strain was developed for use in America, it yielded only half the maize afforded by native African varieties. "It was vulnerable to local fungi and viruses", he says. Working with Joel Ransom of the International Maize and Wheat Improvement Centre in Nairobi, Abayo and Odhiambo are now crossing the Pioneer strain with African varieties. They hope to develop a herbicide-resistant maize that is suited to local conditions. (Source: *New Scientist*, 11 May 1996)

Fighting postharvest rot

Taking aim at the estimated $35 million market-place for preventing post harvest spoilage of citrus, apples and other pome fruits, Ecogen (Langhorne, PA) has developed the first biofungicide to enter this market. Commercial-scale trials, conducted by Ecogen, show that the most successful use of its new product, Aspire, is through a combined approach that also uses conventional fungicides. The cost-effectiveness and enhanced efficacy of the Aspire approach in fighting blue, green and grey moulds has attracted a "favourable response" from fruit-packing houses. (Source: *Nature Biotechnology*, Vol. 14, June 1996)

Chemical applications

Microbial enzymes neutralize chemical warfare agents

Enzymes from marine micro-organisms could be used to combat chemical warfare agents during war or terrorist attacks, according to scientists at the US Army Edgewood Research, Development and Engineering Center (ERDEC), Aberdeen Proving Ground, Md. Research chemist

Joseph J. DeFrank and colleagues have isolated and characterized organophosphorus anhydrolases that can detoxify nerve agents rapidly enough to meet military needs—that is, to greater than 99.9 per cent detoxification in 10 minutes or less. The enzymes, produced by *Alteromonas* and other halphilic marine bacteria, can neutralize various nerve agents, including sarin, the agent used last year in a terrorist attack in a Tokyo subway. The ERDEC scientists believe the enzymes can be used to rapidly decontaminate facilities, equipment, and vehicles. The idea is to freeze-dry the enzymes so that they are easily stored and transported. They can be reconstituted simply by diluting with water and then sprayed on contaminated surfaces. As little as 1 g of enzyme theoretically can destroy as much as 10 lb of nerve agent. Farmers may also benefit from these enzymes: DeFrank thinks they could be used to clean up organophosphorus pesticide wastes. (Source: *Chemical and Engineering News*, 15 January 1996).

Food and food processing

New Zealand chemist probe pregastric enzymes

Pregastric enzymes taken from the tongue and epiglottal regions of baby goats have for centuries been a mainstay in the manufacture of strongly flavoured cheeses such as Parmesan and Romano. Chemistry professor Chairman J. O'Connor and colleagues at the University of Auckland in New Zealand are exploring the chemistry of pregastric enzymes from goats, calves and lambs. If the enzymes from lambs—which are plentiful in New Zealand—and calves could be used in cheese-making, they could provide an alternative to the goat enzymes. In addition, the enzymes from any of the animals might have other uses in the food industry, modifying waste fats, for example. Among O'Connor's findings: A pregastric lipase isolated from mature goats functions best at a surprisingly high 52°C—higher than normal goat body temperature. "This has major implications for the production of cheeses", O'Connor says. The enzymes isolated from calves, unfortunately, catalyze mostly additions, rather than the reactions that transform triglycerides into the more useful mono- and diglycerides. (Source: *Chemical and Engineering News*, 5 January 1996)

Extraction industry applications

Separation of sulphur from coal using micro-organisms

Japan's Central Research Institute of the Electric Power Industry (CRIEPI), Agency of Natural Resources and Energy, MITI, has identified the mechanism of adsorption of specific bacteria onto the sulphur substances in coal. The CRIEPI has been developing a desulphurizing system which separates iron sulphide from coal by bonding bacteria to the iron sulphide to provide affinity with water, but this system has the disadvantage of the slow growth of bacteria. If another micro-organism can produce the adsorption factor, bacteria with faster growth can be used in the adsorption of sulphur. The micro-organism used for coal desulphurization is an iron oxidizing bacteria. The sulphur content of coal includes organic sulphur which is bound to carbon and inorganic sulphur which is bonded with iron as iron sulphide. Only iron sulphide can be separated with the CRIEPI system.

With the CRIEPI system, coal is pulverized, mixed with the bacteria and suspended in water. Both the coal and the sulphur content as iron sulphide repel water, but the iron sulphide acquires affinity with water when iron-oxidizing bacteria are adsorbed. According to testing, the time taken till the coal and iron sulphide are separated is between 1 and 2 minutes. The bacteria are not adsorbed by the coal powder.

By blowing fine bubbles into the water, the coal powder which is water repellent comes up together with bubbles but the iron sulphide, which has affinity with water, sinks so these two substances can be separated.

The research group at the CRIEPI found that the substance necessary for making the iron-oxidizing bacteria adsorb on iron sulphide is a protein with a molecular weight of about 20,000. The disadvantage of the iron-oxidizing bacteria is slow growth but incorporating a gene producing the protein in a fast-growing micro-organism, such as *colibacillus*, allow use of easy-to-handle *colibacillus* for the adsorption process.

A coal desulphurization test using a trial-produced compact system confirmed that the iron sulphide content, which had been 2.5 per cent before the processing, was reduced to below 1 per cent and that the coal recovery rate was 70 per cent. Further details from The Central Research Institute of the Electric Power Industry, Public Communications Division, Ohtemachi Bldg. 7F, 1-6-1, Ohtemachi, Chiyoda-ku, Tokyo 100, Tel.: +81-3-3201-6601, Fax: +81-3-3287-2863. (Source: *JETRO*, March 1996)

Industrial microbiology

Showa breaks through biodegradable barrier

Showa Highpolymer of Tokyo has announced the development of a biodegradable thermosetting resin claimed as the first in the world.

The product, an amino protein resin, is still in the laboratory stage development but the company hopes to build a pilot plant in the near future. It is looking to housing for electrical equipment such as TV sets and office machinery as the "most hopeful" application.

The company says the resin offers similar or better mechanical properties to currently available thermosetting resins and good processability. Typical properties include flexural strength of around 8MPa for a 3mm thick sample and heat distortion temperature of around 130-140°C.

The new product is claimed to biodegrade better than natural wood. Test results showed more than 60 per cent weight loss after 31 weeks in standard soil. In water with activated sludge, weight loss was over 20 per cent after eight weeks and in moist soil, around 10 per cent after eight weeks.

Showa recommends compression moulding for the product but is considering developing a type suitable for injection moulding. Typical processing conditions are a moulding temperature of 140-160°C and pressure of 50-100Pa. Time depends on the moulding temperature, but typically for 1mm thickness processing time is one minute. The material can be easily coloured.

Showa completed a 3,000 ton/year plant for its first biodegradable polyester, *Bionolle*, at the end of 1993. The thermoplastic resin has mechanical properties similar to polyethylene. (Source: *European Chemical News*, 26 February to 3 March 1996)

Liposome—an industrial view

The microscopic spheres known as liposomes have found a wide range of applications in cosmetics and, more

recently, in medicine. First discovered by Alec Bangham at the Institute of Animal Physiology in Babraham, near Cambridge in the early 1960s, lipsomes can arrange themselves in a variety of forms, including lamellar crystals, liquid crystals and colloidal solutions.

Lipsomes are made up of molecules, known as amphiphiles, which have water soluble polar "heads" (the hydrophilic end) and water insoluble organic "tails" (the hydrophobic end). In aqueous solutions these molecules form organized structures as a result of hydrophilic and hydrophobic interactions. At lower concentrations, single chain amphiphilic molecules such as soaps, form micelles. These are small spherical structures where the molecules are arranged so that the polar heads on the surface of the sphere shield the non-polar tails in the interior from the polar water molecules. Natural polar lipids such as lecithins, however, contain two chains and these are too bulky to be packed into the small hydrophobic core of a micelle. Instead, they form lipid bilayers and, to reduce exposure at the edges, these bend and self-close into spherical structures called liposomes. In doing this, the liposomes also encapsulate part of the solvent in which they are suspended into their interior. It is this feature that makes them potentially useful in medicine as "drug carriers".

Liposomes vary in both size and the number of layers they contain, and they are usually described as small or large unilamellar (single layer) vesicles or, in the case of many concentric bilayers, large multilamellar vesicles. Their size can vary from 20 nm to 100 μm, while the thickness of the bilayer is around 4 nm. Usually, homogeneous unilamellar liposomes in the size range 80-200 nm are used for medical applications. This is because very large vesicles are not stable enough, while small liposomes cannot encapsulate enough of the drug to be of use.

Liposomes have several properties which make them useful in various applications. The most important of these attributes are the small, uniform and controllable size, and the special membrane and surface characteristics which can control the biological fate of the liposomes. As a result, liposomes can be used, for example, as solubilizers and dispersants for difficult-to-dissolve substances; sustained release and delivery systems for micro-encapsulated substances; and as carriers of hydrophobic molecules in cosmetics.

In addition to the normal physico-chemical properties, liposomes prepared from natural lipids often have special biological characteristics, including biocompatibility, biodegradability and (specific) interactions with biological membranes and various cells. In fact, liposomes usually interact with cells by endocytosis, allowing them to carry encapsulated material across the cell membrane into the cells—very rarely do they fuse with the membranes. All of these useful attributes help explain why liposomes are the most widely studied and used drug delivery system (Extracted from *Chemistry & Industry*, 18 March 1996)

Applications abound for novel chemistry

The novel use of enzymes promises new polymers and plastics with a wide range of applications, including superabsorbent nappies, self-cleaning contact lenses and environmentally friendly batteries.

Jonathan Dordick of the University of Iowa has made a selection of polymer gels by combining enzymes with traditional polymer chemistry. Usually, enzymes are used alone. Dordick employs commercially available enzymes called subtilisins—proteases found in laundry detergents—to modify a range of sugars. He then adds on an acrylate group and polymerizes the compound. The resulting gel consists of sugar molecules pointing off a polyacrylate backbone.

This gel would be impossible to make chemically without the enzyme, explains Dordick.

As sugars are complex molecules with many functional groups, they are difficult to deal with chemically. However, the enzyme can selectively modify one particular functional group, allowing great control over the final product. Dordick can produce a range of gels by varying the type, location and orientation of the sugars on the polyacrylate backbone, and the concentration of the monomer and crosslinking groups.

Some of these gels can absorb over 1,200 times their weight in water. They have weak bonds and are very viscous like shampoo. Other stronger gels have been prepared which can absorb nearly 100 times their weight. These gels are strong enough to be cut by a knife and maintain their structure. Significantly, Dordick's gels are almost completely biodegradable.

Possible applications for the polymers include drug delivery devices. The biologically inert gel could contain a therapeutic protein which would be able to diffuse into the body.

Trapping enzymes in polymers opens up all sorts of applications, such as self-cleaning materials. Examples might include plastic sleeves for drainpipes, which contain lipase that breaks down greases and fats; and coatings for ships' hulls, which contain protease that attacks the "glue" of barnacles.

Thanks to his work with enzymes, Dordick has also come up with a plastic that could be used in cheap, lightweight, environmentally friendly batteries. He uses two commercially available enzymes to make poly(hydroquinone) from hydroquinone. This reaction cannot be done under chemical conditions, only electrochemically, which is expensive. Using the enzyme approach, Dordick is able to overcome the need for electrochemistry and can produce a polymer that has a more regular structure than that produced electrochemically.(Source: *Chemistry & Industry*, 15 April 1996)

Plastic antibodies: molecularly-imprinted polymers

Analytical chemists have long searched for materials which can be used to bind specific individual chemical compounds in a cocktail of many others. Modern separation science, or chromatography, faces a major challenge in the separation of complex mixtures into their individual components. Many chromatographic techniques used to separate small molecules (molecular weight less than 1,000 daltons) involve partitioning the sample between two physical phases—gas, liquid or solid.

For instance, in liquid chromatography, the sample, which is dissolved in the liquid phase, interacts with a chemically-modified solid phase. The solid phases used for liquid chromatography have chemical characteristics which allow them to interact with chemicals in the sample. The interactions of the analyte, as well as other components in the sample, with these stationary phases are the most important factors involved in chromatography and determine whether the analyte can be separated from the sample's other components.

Most materials used as solid phase adsorbents in chromatography act in a relatively non-specific manner. That is, they rely on chemical properties that are common to a large number of chemicals, so they can be used to analyse a wide variety of compounds from several chemical

classes. Examples of this include octyldecylsilane-derivated silica, which is commonly used in high performance liquid chromatography (HPLC), and silica gel, which is commonly used in thin-layer liquid chromatography (TLC).

The general applicability of these materials for the separation and analysis of large numbers and classes of compounds is perhaps their most important attribute. However, this feature may be problematic, particularly if the analytical chemist wants to analyse for compounds that are very similar to one another and are not separated using these conventional solid phase adsorbents.

Molecular imprinting technology is a rapidly emerging field in which synthetic polymers are made in the presence of the analyte of interest or "print molecule". After polymerization, the print molecule is removed, leaving a rigid polymer which contains an "imprint" of the molecule. In contrast to the relatively non-specific nature of conventional solid phase adsborbents, these molecularly-imprinted polymers, or MIPs, are highly specific since they contain a pocket in which only the analyte of interest can fit. As a result of this specificity, MIPs have many useful applications in analytical chemistry.

Using existing polymer synthesis techniques, MIPs for a wide range of print molecules are likely to be made. However, with the development of new functional monomers, ones that can bind particularly unique functional groups on a desired print molecule, the application of MIP technology in the fields of industrial, pharmaceutical, agricultural and analytical chemistry should expand greatly. Although improving the specificity of MIPs is very important in many applications, cross-reactive MIPs, those able to bind several compounds, may also have useful applications in situations where the analyst wants to purify an entire chemical class of compounds from a mixture of contaminants. Here, the MIPs may be produced using a generic or surrogate print molecule representative of a particular chemical class, or a mixture of print molecules from a single or several classes of compounds. New procedures for MIP synthesis, such as new *in situ* methods and further improvements in MIP particle characteristics, will probably evolve to enhance both their ease of handling and general application.

The applications of MIPs in analytical and biochemistry is already in an expansion state. The development of "plastic" antibodies and enzymes allows receptors to be tailor-made economically and with predictable specificity. Some of the disadvantages of using biomolecules is their production cost and susceptibility to matrix effects which may be overcome using MIP technology. The durability of MIPs make them particularly applicable for use as sensor elements, either immobilized on an electrode surface or in a membrane configuration. In this mode, they may find wide application for *in situ* analysis, in biological, therapeutic or environmental monitoring. The analytical chemist of the future will indeed make use of MIP technology as part of his or her repertoire of analytical techniques. (Extracted from *Chemistry & Industry*, 18 March 1996)

Chitin and chitosan fibre process without organic solvent

Omikenshi Co. Ltd. has established a technique to process chitin and chitosan contained in crab and shrimp shells into a fibre without using organic solvent and has commercialized the functional fibre under the brand name of Crabyon.

The chitin molecular structure closely resembles that of wood pulp cellulose that is the raw material for rayon. The new process directly converts chitin and chitosan into the viscose state, then viscose fused uniformly with cellulose viscose, processed into a new type of fibre.

Chitin and chitosan have antibacterial and antimould effects, promote healing by activating damaged cells, and stop bleeding, so efforts are being made to apply the fibre to medical treatment. The fibre also has moisture retention characteristics. The new fibre effects are retained with stability. The component ratio can be adjusted with ease and the fibre can be spun together with other kinds of fibres. In addition, properties such as strength and elongation are retained properly, and excellent dyeability is also displayed.

The new fibre is applicable to the manufacture of fabrics for producing underwear, stockings and home wear, bedding such as sheets and blankets, interior ornaments, tools and non-woven cloth. For non-woven cloth, in particular, the plant growth promotion effect of chitin can be utilized effectively in agriculture. Further details from Omikenshi Co. Ltd., 3-5-13, Awaji-cho, Chuo-ku, Osaka 541. Tel.: +81-6-205-7106, Fax: +81-6-205-7301. (Source: *JETRO*, March 1996)

New enzymes

Genencor International (Rochester, NY) has introduced two enzyme products for use in textiles. The first product, an engineered component liquid cellulase, is used to finish cotton knits, polynosic rayon, linen, and light-weight lyocell and lyocell-blended fabrics. Genencor says the enzyme reduces fabric weakening and delivers the equivalent surface of competing products. The second product is a concentrated liquid fungal catalase enzyme that eliminates residual hydrogen peroxide (H_2O_2). (Source: *Chemical Week*, 29 May 1996)

Spider silk: a biomaterial for the future

For all their fragile appearance, spider webs are incredibly robust. Spider silk is made up of protein similar to finger nails and feathers, although the way in which the amino acids are arranged differs from these horn-like counterparts. Nevertheless, spider silk has many attractive properties, including strength and elasticity, which make it a potential component in high stress areas such as protective clothing. Biotechnologists have found that spider silk could also be used in artificial tendons and non-allergenic sutures. The only major obstacles to this wealth of application is mass production. Unlike silk worms, spiders are not easy to factory farm. Research has therefore focused on alternative approaches to generating the silk, and this has meant searching for a better understanding of the silk's structure and nature.

Researchers have now managed to engineer bacteria to make spider silk proteins in large enough quantities to make fibres tougher than *Kevlar*, the main component of bullet-proof vests. These fibres can be woven into bullet-proof clothing and used to make climbing ropes, artificial tendons, and other items requiring a combination of high strength and elasticity.

Spiders are among a group of organisms that have the ability to produce silk. These threads are used throughout the spiders' life for mobility, protecting the egg sac, and catching and swathing prey. Scientists have long tried to discover how spider silk gains its remarkable properties. The most studied spider has been the golden orb-weaving

spider, *Nephila clavipes*, which has been examined most extensively because of its large size. *N. clavipes* can synthesize as many as six different types of silks, each with unique mechanical, biochemical and functional properties. Each type of silk is make by a different gland in the spider's abdomen. Several different silks are used to build the web.

Dragline silk produced by the major ampullate gland has been studied the most because of its superior mechanical properties. Besides forming the dragline, this silk is used to construct the frame of the web. The material making up the web has to perform several difficult functions. It must be able to absorb the energy of a flying insect so that the prey neither breaks through nor bounces off the trap. The dragline must also support the weight of the rappelling spider. Dragline silk is, in fact, stronger than a steel cable of the same diameter. The combined high tensile strength ($4 \times 10^9 N/m^2$) and elasticity (35 per cent) of major ampullate silk translates into a toughness that is superior to all man-made or natural fibres. For example, dragline silk and *Kevlar* have similar tensile strengths, but the silk is about seven times more elastic. In addition to being the toughest silk, dragline is the only silk that has the ability to supercontract. When wetted, this fibre contracts to about 60 per cent of its relaxed dry length. The mechanical properties of the fibre return to their original values once the silk is dried and restretched, whereas many materials are considerably weaker after wetting.

These outstanding physical and mechanical properties, as well as the fact that the silk is non-allergenic, make it a very desirable high-performance engineering and medical material.

The large number of spiders needed to produce just a small amount of dragline silk has prevented the use of spiders for commercial silk harvesting. Instead, recombinant DNA technology has been used to enable bacteria to produce the silk proteins. Artificial silk, elastic and silk-like proteins have been synthesized for structural analyses.

The general approach has been to synthesize DNA oligonucleotides which encode silk peptides chemically and then ligate them to plasmid expression vectors. The plasmids are small, circular pieces of DNA that can be replicated in bacteria. Once introduced into bacterial cells, the genetic information from the plasmid is decoded to make recombinant silk protein. This protein is recovered by a simple purification and can be drawn into a fibre.

Most of the artificial silk polymers are based on the silkworm silk protein sequence. While these polypeptides were initially synthesized to study their β-sheet formation, the polymers are now being made into fibres and thin films. The fibres are currently being tested to determine how mechanical properties and fibre formation relate to protein structure. Silk thin films are being investigated for their ability to serve as enzyme and cell immobilization matrices.

We have used a slightly different approach to synthesize spider dragline silk protein, which involves the specific construction of multiple repeats. Synthetic genes encoding 8, 16 and 32 MaSp-2 repeats have been successfully expressed in the bacterium *Escherichia coli*. The synthetic gene encodes a fusion protein that links the repeats of MaSp-2 to a polyhistidine peptide, which can be purified in one step by affinity chromatography.

Recombinant techniques can be used to customize proteins with properties tailored to the end use. As the function and structure relationships of the silk and silk-like proteins become better characterized, it will become possible to produce fibres with strength, elasticity, or combinations of the two. Medical applications include banding material for arteries, artificial blood vessels, and sutures 1/10th the diameter of current silk sutures. Artificial silk fibres may also be used as high performance materials useful for reinforcing fibres in composite materials, ropes, and for catching aircraft landing on carriers. More applications will no doubt arise with the production of synthetic fibres with properties entirely different from the native silks.

The orb-weaving spider uses silk in nearly every aspect of life and has developed various types of silks for many purposes. Basic protein structure-function relationships are becoming clearer as scientists probe the unique combination of protein structural repeats that make spider dragline silk a truly outstanding material. As attempts to mimic spider silk are pursued through genetic engineering, this ancient material will become a fibre for the future. (Extracted from *Chemistry & Industry*, 18 December 1995).

Energy and environmental applications

Modified plants make mercury safer

Florida's wetlands could be among the first to benefit from a new genetically engineered plant that can convert toxic mercury into a less dangerous form. Its creators believe that similar plants could prevent agricultural residues containing heavy metals, such as mercury, from contaminating the Everglades.

A team at the University of Georgia in Athens is working with a gene called *merA*, which occurs naturally in bacteria found in mercury-polluted soil. The enzyme encoded by *merA* is called mercuric ion reductase. It converts mercury (II) ions (Hg^{2+}), which are extremely toxic and accumulate in living tissues, into the less hazardous metallic mercury. But scientists cannot use the bacteria to clean up contaminated soils because its effects are confined to a very small area and the metal remains in the soil.

So the Georgia team inserted *merA* into a plant which can grow on soil poisoned by Hg^{2+} compounds. The metallic mercury evaporates from the plants' cells, where it is diluted and dispersed by the air.

The task was far from simple. The team first transplanted *merA* into a plant seven years ago, but saw no effect, as the gene is not compatible with a plant's metabolism. They had to take the gene apart and partially rebuild it, adding several new sections that would allow the plant to make the enzyme. They then transplanted the new gene into the weed called *arabidopsis*, often used in plant genetics.

The experiment was a startling success, claims team leader Richard Meagher. The modified *arabidopsis* plants thrived on a growth medium containing 50-100 μM of $HgCl_2$—more than twice the concentration needed to kill normal plants. And modified seedlings needed only 10 minutes to start converting Hg^{2+} to Hg metal.

The technique could also be useful with other metal pollutants. Silver, gold, copper and cadmium also bind to mercuric ion reductase, and could theoretically be removed from soils by *merA*-containing plants, says Meagher. However, these metals would not be volatile and the plants would have to be harvested. (Source: *Chemistry & Industry*, 15 April 1996)

Aquatic weeds for wastewater treatment

Scientists of the Indian Institute of Chemical Technology (IICT), Hyderabad, India have designed a special lagoon system containing aquatic weeds that can remove

toxic heavy metals and organic wastes from water bodies to help in pollution control. Annoying aquatic weeds such as water hyacinth (*eihhornia crassipes*), *pistia strtiotes* and *lemna minor* can absorb toxic inorganic and organic pollutants.

Aquatic plants thus seem to be nature's own efficient and cost effective alternative to costly conventional treatment procedures. (Source: *NAM S & T Newsletter*)

Heavy metal accumulating plants

All over the world, mines and chemical factories have left barren waste-lands in which poisonous metals such as zinc, lead, nickel and manganese have soaked deep into the soil. No one can live here; almost nothing can grow.

While most plants can tolerate only tiny quantities of heavy metals, a few positively lap them up—absorbing and storing huge amounts of them. This gives them a free run at colonizing such otherwise hostile environments as metal-rich igneous rocks and, of course, toxic-waste tips.

Oxford University's Andrew Smith, with colleagues in Manchester and Sheffield has been probing the secret of these hyper-accumulators of heavy metals—plants, it has to be said, that are often a lot prettier than sprouts. The one they looked at was a species of *Alyssum*, a relation of the garden flower, that specializes in accumulating nickel. They showed that the plants protect themselves from the poisonous effects of nickel by swathing the nickel ions in histidine molecules, thus rendering them biologically inactive.

Histidine is an amino acid—one of the building blocks of proteins—so it is produced naturally by all plants. But *Alyssum* produces it in huge quantities. Dr. Smith wanted to see if histidine would have the same effect in plants that did not overproduce it, so he tried spraying the amino acid on to species that cannot normally tolerate nickel. He found that as they absorbed the histidine, they, too, were able to tolerate much higher levels of the metal without ill effect.

But the tolerance lasted only as long as the plants had a histidine supply—and spraying histidine is expensive. Which is where, with luck, the sprouts will come in. *Alyssum* and its relatives are slow-growing creatures. With little competition in their hostile environments, they do not need to put themselves out too much. Dr. Smith and his colleagues hope that if they can find the genes responsible for producing the extra histidine, they could insert them into faster-growing plants, preferably ones with extensive roots that can penetrate deep into the polluted soil. Plants, in other words, would then act as botanical vacuum cleaners, sucking poisonous metals from the soil. (Source: *The Economist*, 2 March 1996)

Technology for cleaning lakes and marshes

Hitachi Ltd. has developed a new technology for cleaning lakes and marshes by using a magnetic separation type water bloom removal system based on superconductivity. The magnetic separation system uses a closed-cycle refrigeration with built-in superconducting magnets that enables removal of water bloom more than 10 times faster than existing systems with the same amount of electric power.

The new system consists of a superconducting separation system, and a solar energy-driven fluidized bed filtration system. A newly fabricated flow type plankton monitoring system was developed at the same time. The superconducting separation system uses the magnetic filters in the fluid channel provided at the central part of the electromagnets which generate an intense magnetic field to create a magnetic gradient to collect and remove the pretreated water bloom effectively. The electromagnetic unit and a compact helium refrigerator are combined into a unit assembly.

Since the separation system is of the superconducting type, power consumption is minimal, and since the refrigerator type requires no liquefied helium or liquefied nitrogen, commercialization is highly probable. The magnetic field space of the superconducting magnets is large with a length of 320 mm and diameter of 48 mm, and the field intensity is 10,000 G. The treatment volumes 15 l/min, and roughly 95 per cent of water bloom and approximately 100 per cent of additives can be removed. The power consumption is 8 kW, and even if the diameter becomes 1.5 m and the treatment capacity is increased to 10 m^3/min, the power consumption can be suppressed to less than 15 kW.

The solar energy-driven fluidized bed system consists of a filtration tank filled with a material of up to 1-mm particle diameter and a solar panel for driving a pump, and the assembly is floated on the lake or marsh. The water is pumped upward from the filtration tank bottom and the filtration material flowed upward in a fluidized state, hence the name fluidized bed filtration system. The microbes proliferating on the filtration material surface capture and decompose the waste and phytoplankton coming into contact with the filtration material surface, and the water is cleaned.

Since the filtration material is fluidized and cleaning is achieved by utilizing the reactions of microbes, there is no fear of clogging like conventional types of filtration systems. The company plans to conduct evaluation tests with a demonstration system during the coming fiscal year with the aim of commercializing the system.

The flow type monitoring system takes pictures of the phytoplankton with particle sizes ranging from about a few micrometers to 2 mm in the lake or marsh water continuously (30 frames/s) with a TV camera from outside while passing the lake and marsh water through the central part of a 3-mm cell made of glass and passing clear water along the peripheral parts. The flow inside the cell is controlled rigidly by fluid dynamics, so there is hardly any turbulence. Further details from Hitachi Ltd., Public Relations Department, 4-6, Surugadai, Kanda, Chiyoda-ku, Tokyo, 101, Tel.: +81-3-3258-1111, Fax: +81-3-3258-5480. (Source: *JETRO*, January 1996)

F. PATENTS AND INTELLECTUAL PROPERTY RIGHTS

Lobbying continues over patents

The UK Bioindustry Association (BIA) is trying to form a European body to represent interests in biotechnology. Its main aim will be to lobby the European Parliament to treat the latest European biotechnology patents directive more kindly, and to make the subject more acceptable to the public.

Recent research has shown that Europe is falling behind the US and Japan in obtaining biotechnology patents.

The Senior Advisory Group on Biotechnology, a Brussels-based group of industry executives, has already met with 40 MEPs to discuss harmonizing patent protection. The industry is keen to prevent the newest version of the draft directive from being diluted and modified beyond recognition.

The original draft directive took over five years to reach the European Parliament in March 1995, where it was rejected. The new draft directive surfaced from the Commission earlier this year. According to patent attorneys, its success will depend on the priorities of the Member State holding the presidency at the time of the ministerial councils.

The latest document confirms the patentability of biological material, which includes any containing genetic information, but it states that the human body and its parts in their natural state are not patentable. Germ-line therapy, where modified genes are passed on by reproduction, is not patentable under the new draft. And transgenic animals are only eligible when there is a "clear benefit to society". (Source: *Chemistry & Industry*, 6 May 1996)

BIO opposes patent changes for therapeutics and diagnostics

The US Biotechnology Industry Organization (BIO), Arlington, VA, expressed deep concern over proposals for legislation to eliminate patent coverage for therapeutic and diagnostic methods.

At recent US Patent and Trademark Office (PTO) hearings, BIO said that changes to existing legislation were not necessary and that any adjustments to deal with patent protection for therapeutic and diagnostic methods could be done internally with the PTO or administratively.

The purpose of the hearings was to determine whether the problems identified by the proponents or pending legislation in both the House Representatives(HR1127) and the Senate (S1334) could be solved administratively rather than legislatively.

The HR1127 bill would preclude or ban patents drawn to therapeutic, medical and diagnostic methods or procedures. But the bill would permit patents when the procedure or method is performed by or as a necessary component of a machine, manufacture, or composition of matter that is otherwise patentable.

The S1334 bill would exempt certain persons from infringement liability, such as: a patient, physician, or other licensed health-care practitioner, or a health-care entity with which a physician or licensed health-care practitioner is professionally affiliated. The liability exemption would not cover those persons who use the methods or procedures that are performed by or as a necessary component of a machine, manufacture, or composition of matter that is otherwise patentable.

The main proponents of the legislation are a coalition of 17 medical societies and associations led by the American Society of Cataract and Refractive Surgery and the American Medical Association.

BIO recommended that the PTO form a new unit to examine only patent applications directed to medical procedures and techniques, and hire new patent examiners with proper technical backgrounds in the surgery or train existing examiners who have backgrounds in related areas. (Source: *Biotechnology Business News*, 22 May 1996)

WHO wants patent confusion cleared up

The World Health Organization wants changes in one of the new international trade agreements to clear up confusion over whether or not it protects the patent rights of biotechnology processes and products.

While intellectual property rights have long been protected by several specific conventions and most countries protect pharmaceutical patents, they have not always been enforced.

It was the increasing number of patent infringements and the growing trade in counterfeit goods, including drugs, that led to patent protection being included in the Uruguay Round agreements—so that countries can now retaliate through trade measures.

The Agreement on Trade-Related Aspects of Intellectual Property Rights lays down minimum standards and enforcement measures for protecting patents, copyright, trademarks and industrial design.

It includes compulsory patenting of pharmaceuticals for the first time. But a report from a WHO task force, set up to consider the effects of the new trade rules on the health sector, says that biotechnology has been "left in doubt".

The key issue, according to WHO, is the extent to which individual countries make use of "possible exclusions in this domain" to increase their local production of biotechnology products. China, it points out, makes considerable use of plant-based medicines.

The Agreement is subject to review and revision within the next four years and WHO will be pressing for changes to clarify the position on biotechnology. (Source: *Biotechnology Business News*, 10 April 1996)

Patent rights and international exhibitions

The Australian Patent Office has issued an official notice regarding the consequences for patentability of an invention being exhibited at an international exhibition before an application for a patent on that invention has been lodged. Unless the exhibition is an official or an officially-recognized international exhibition within the meaning of Article 11 of the Paris Convention, the disclosure of the invention at the exhibition will be a bar to the subsequent grant of a patent for that invention. Only a small number of exhibitions is officially recognized, and further information can be obtained from the Director,

Market Development, Department of Tourism, GPO Box 1545, Canberrra, ACT 2601.

Disclosure of the invention at an international exhibition which is recognized by the Australian Commissioner of Patents will not be a bar to patentability in Australia. However, such an exhibition in general will not be recognized as an international exhibition by most other countries, and the disclosure of the invention may invalidate a patent in countries, such as the United States, Japan and the countries of the European Patent Convention.

More detailed information can be obtained from the Notice which appeared in the Australian Official Journal of Patents on 7 March 1996, or by inquiry to the Commissioner of Patents, Australian Intellectual Property Office, P.O. Box 200, Woden, ACT, 2606. (Source: *Australasian Biotechnology*, Vol. 6, No. 2, April 1996)

European biotechnology directive

Following the rejection by the European Parliament of the previous draft of the European Council directive on biotechnology, a new draft has been prepared by the European Commission for consideration by the European Parliament and the Council of Ministers of the European Union. The text has been clarified in relation to a number of points, including the distinction between a discovery and an invention and the concept of "farmer's privilege", which gives farmers the right to propagate patented animals and/or plants on their own farms, and a specific exclusion of patentability of methods for germ-line therapy. The draft has been prepared following extensive consultation with European Parliamentarians and with industry representatives, and was to have been discussed at a public meeting between representatives of the Parliament, the European Commission and the Council on biotechnological issues. A major point of contention is the provision of the European Patent Convention which excludes animal and plant varieties as such from patentability, although there is no specific exclusion of plants and animals *per se*. In its present form the draft directive states that the exclusion of animal and plant varieties as such "does not prejudice the patentability of plants and animals". (Source: *Australasian Biotechnology*, Vol. 6, No. 2, April 1996)

NGO says patent laws for plants hurt biodiversity

The 65-year-old US Plant Patent Act (PPA) has not succeeded in carrying out its purported aims of encouraging plant breeding or contributing to genetic diversity, according to a recent report by the Rural Advancement Fund International (RAFI). RAFI undertook an examination of the Act at a time when developing countries are under pressure from northern Governments and the World Trade Organization (WTO) to adopt similar intellectual property systems for plants. WTO requires Member developing countries (countries whose Governments are signatories to the General Agreement on Tariffs and Trade) to adopt plant patent systems by the year 2000; least developed Member countries have until 2004.

The Plant Patent Act, enacted by the US Congress in 1930, is the world's oldest intellectual property system designed for patenting living things. It grants monopoly protection for 17 years to the "inventor" of new varieties of asexually propagated plants—primarily nuts, fruits and flowers. RAFI states that the US market for PPA patented crops is worth more than US$ 16.9 billion per year. Since southern countries contain the vast majority of biodiversity in fruits and flowers world-wide, adopting similar plant patenting systems could have profound implications.

According to the report, early proponents of the Plant Patent Act intended it to provide an impetus for plant breeders to develop new and useful plant varieties. The RAFI report states that, instead, breeders using PPA have tended to seek patents on increasingly minute variations within species; patents have been granted on hundreds or even thousands of varieties of a single species. Twelve species, including rose, chrysanthemum, peach, dianthus and African violet, account for more than 68 per cent of PPA patents.

In addition, many of the "new varieties" awarded patents have actually been traditional or naturally-occurring varieties that were simply taken from developing countries. RAFI states that 88 of the first 200 patents were issued for such "bio-pirated" plants.

According to RAFI, the main beneficiaries of the Plant Patent Act have been a small group of highly specialized breeders, whose numbers have declined since the Act's inception from a post-World War II average of 16 per million US residents to six per million in 1994. In recent years, multinational corporations have amassed a significant share of the breeding and seed industries.

RAFI notes that compared to many other plant patent systems PPA does have some advantages as a model for developing countries, such as an inexpensive application process that does not require specialized technologies. Because protection is granted on the basis of drawings and relatively simple descriptions, it would be feasible for farming communities and small breeding programmes to meet description criteria. In addition, it preserves farmers' rights to save and develop planting material for their own purposes. PPA-style legislation could also allow the South to cover major food and export crops, such as potatoes, tea, coffee, coconut, sweet potatoes, flowers and nut crops.

None the less, these advantages would not necessarily serve farmers in developing countries. RAFI points out that those with money and power will seek to amend any intellectual property system to strengthen their monopolies, even if the original legislation is written with the intent of defending farmers. In addition, rural farmers may lack time to apply for patents and may not have adequate legal and financial resources to defend their claims in international patent disputes.

Contact: RAFI, 71 Bank Street, Suite 504, Ottawa, ON, KIP 5N2, Canada. Tel.: (613)-567-6880; Fax: (613) 567-6884; e-mail: rafican@web.apc.org. (Source: *Global Pesticide Campaigner*, June 1996)

Patent information sources on the WWW

www.infor.und.edu:8080/EdRes/Topic/AgrEnv/Biotech/Biotech_Patents
Full text biotechnology patents and recent biotechnology patent titles

www.ladas.com/bulletins
Intellectual property bulletins from Ladas & Parry, patent attorneys

www.ladas.com/guides/biotech/biotechnology.USA.html
An overview of US patent practice in biotechnology inventions

biotechlaw.ari.net/
Legal and scientific information relevant to biotechnologists from Foley and Lardner, multidisciplinary attorneys, including a European IP law page

www.charm.net/~rafi/19941.html
An introductory discussion about patenting human genes from the Rural Advancement Foundation International (RAFI)

(Source: *Nature Biotechnology*, Volume 14 March 1996)

G. BIOINFORMATICS

Books

The Global Biodiversity Assessment

If climate change radically alters the patterns of agriculture throughout the world, as inevitably it will, where will the genetic material come from to produce the new crop varieties on which human survival will depend? Gene banks may provide a partial answer, but the greatest gene bank of all is nature, and this is being destroyed at an increasing rate.

This is the conclusion of the *Global Biodiversity Assessment*, the most comprehensive analysis of the science underpinning biological diversity ever undertaken. Funded by a $2 million grant from the Global Environment Facility, it is the work of over 1,500 scientists from all over the world coordinated by UNEP.

The Assessment finds that the Earth's biological resources are under serious threat. Biodiversity—the myriad of genes, species and ecosystems that collectively make up what we call Nature—may have taken 4 billion years to evolve, but it seems destined to be largely destroyed in just four human generations. Rates of species extinction are estimated to be 50 to 100 times the natural background rate: this could increase to 1,000 to 10,000 times with the forest loss projected for the next 25 years.

Unless direct action is taken now to protect biodiversity, we will lose forever the opportunity of reaping its full potential benefit.

Our knowledge is fragmentary. Only some 1.75 million, or 13 per cent, of the total number of species on Earth, estimated by the Assessment at between 13 and 14 million, have ever been scientifically described.

Unlike the climate change and ozone treaties, the Convention on Biological Diversity was not preceded by a comprehensive scientific assessment. Scientists persuaded politicians and lawyers that biological resources were being destroyed so fast that the future well-being of the human race could be imperilled. This urgency drove the negotiations of the treaty, but its implementation has floundered in political infighting over conflicting priorities for budget allocations, largely because of the lack of consensus on the science base. The purpose of the Assessment is to provide the scientific foundations needed to develop effective policies for conserving biodiversity and for benefiting from the use of its resources.

Sections of the report cover the magnitude and distribution of biological diversity; its maintenance and loss; inventory and monitoring; functional properties and dynamics at the ecosystem level; economic and non-consumptive values; human impacts; and conservation measures. A key chapter looks at biodiversity's role in providing the raw materials for biotechnology; many countries have a dominant interest in ensuring both continued access to genetic resources and equitable sharing of the benefits.

The Assessment concludes that the best way to save biodiversity is to value it, whether as a resource for direct use on a sustainable basis, or for its indirect functions, such as maintaining freshwater supplies or providing a sink for greenhouse gases.

Global Biodiversity Assessment is published for UNEP by Cambridge University Press, as a 1,140 page report (hardback $120/paperback $44.95) and a 56 page Sumary for Policy Matters ($14.95). Copies are available from Cambridge University Press or UNEP's distributors, SMI (Distribution Services) Limited, P.O. Box 119, Stevenage, Hertfordshire SG1 4TP, UK.

Balancing the Scales: Guidelines for Increasing Biodiversity's Chances Through Bioregional Management

By Kenton R. Miller, Director of WRI's Programme in Biological Resources and Institutions, World Resources Institute, February 1996/150 pages; large format paperback/ISBN: 0-915825-85-6/List price: $14.95

World-wide efforts to protect biodiversity have focused on setting aside discrete areas for conservation. But this strategy is under siege due to the demands of growing human populations in need of more land and resources. As a result, scientists, resource managers and community leaders are calling for shifting the scale of wildland management programmes from national parks and reserves to entire ecosystems. *Balancing the Scales* makes the case for protecting biodiversity wherever it is found: in farmlands, utilized forests, fishery grounds, and not just within the boundaries of protected areas. Drawing on case studies of Yellowstone, the Serengeti, Australia's Great Barrier Reef, Costa Rica's La Amistad Biosphere Reserve, and other sites, the author explains the challenges and opportunities of "bioregional" management. Resource managers, community leaders, and policy makers will find this report a practical, thorough guide to some of the most promising strategies for protecting biodiversity in an increasingly populated world.

Contents:

Introduction/Examples of Early Bioregional Management Experience/La Amistad Biosphere Reserve/Greater Yellowstone Ecosystem/The Wadden Sea/Greater Serengeti Ecosystem/Great Barrier Reef Marine Park/The Mediterranean Regional Sea/CAMPFIRE Program/North York Moors National Park/The Hill Resource Management Program/ Guidelines for Bioregional Management

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The Life Industry: diversity, people and profits

By Mirgo Baumann, Janet Bell, Florianne Koechlin and Michel Pimbert

The conservation of biological diversity in the context of rapid technological change and the commercialization of biological resources raises many fundametal scientific, economic, socio-political and ethical questions.

Most of the world's biological diversity is located in countries of the South. The North and its private industry is increasingly using these countries as reservoirs of biological and genetic resources to develop new products such as crop varieties, drugs, biopesticides, oils and cosmetics. The diversity of the living world—biodiversity—has

become the raw material of the new biotechnologies and the object of patent claims.

The Convention on Biological Diversity aims to conserve the variety of genes, species and ecosystems which sustain life on Earth. This internationally legally binding instrument also seeks to facilitate the just and equitable sharing of benefits arising from the use of biological resources.

However, the negotiations around the Convention have highlighted major differences in interest and priorities among stakeholders. For example, Southern countries demand ready acccess to the new biotechnologies in compensation for the use of biological resources that orginate within their terrorities. The Northern countries, for their part, insist on the recognition of intellectual property rights for their technologies and payment for genetic products derived from materials they have obtained from the South. Indigenous peoples and other rural communities are also demanding that their knowledge of the uses of plants and animals, as well as their innovations and intellectual contributions to the maintenance and development of biodiversity, be acknowledged and rewarded. Meanwhile, the pharmaceutical industry is interested in the hereditary characteristics of indigenous peoples: patent claims on cell-lines of indigenous communities from developing countries are pending.

What are the likely impacts of these trends on the self-determination of peoples (and ultimately on human rights); biodiversity conservation; the relationship between science and society; the growth of the biotechnology industry; and development models in the North and South? Can the conflicting perspectives of different social actors be reconciled? And, if so, under what conditions and with what implications for conservation and development?

This book presents and also reflects the collective learning and debate from NGOs, some arguments from leading experts on the issues as well.

Available from *Intermediate Technology Publications*, Southampton Row, London WC1B 4HH, UK. ISBN 1 85339 341 X. Price: £11.95

BIA launches Euro patent booklet

In the continuing battle by industry to gain an acceptable European directive on the patenting of biotechnological inventions, the UK BioIndustry Association (BIA) has launched a new publication designed to make European parliamentarians more aware of the issues involved.

The BIA says the booklet, *Innovation from Nature: The Protection of Inventions in Biology*, has been designed to encourage open and informed debate by all interested parties.

The booklet addresses a range of issues, including the ethical concerns surrounding the patenting of human genes and the genetic engineering of animals.

The publication of *Innovation from Nature: The Protection of Inventions in Biology* was sponsored by the law firm, Simmons & Simmons.

Complimentary copies of the booklet are available from: *the Bioindustry Association*, 14-15 Belgrave Square, London SW1X 8PS, UK. Tel.: 44 171 245 9911; Fax: 44 171 235 4759.

WHO Guidelines on Ethical Issues

Guidelines on Ethical Issues in Medical Genetics and the Provison of Genetics Services was published in 1995 by the Hereditary Diseases Programme of the World Health Organization (WHO). Written by Dorothy Wertz (Shriver Center), John Fletcher (University of Virginia), Kåre Berg (University of Oslo), and Victor Boulyjenkov (WHO, Geneva), the book suggests basic guidelines for providing medical services related to genetics. The authors consider ethical issues associated with modern medical genetics and seek to demonstrate how these issues could be addressed. Includes international bibliography on ethics and legislation. Free of charge. 117 pages, paper. [Contact: V. Boulyjenkov. Fax: +44-22/791-0746]

Aquaculture markets

Emerging Aquaculture Markets III—A Worldwide Study on Feeds and Veterinary Products is a 1,200 page report on markets in feeds, feed additives, drugs, vaccines, diagnostics and growth hormones.

Coverage includes markets, trends and projected annual production volume and values for selected species in 75 countries and regions. Cost of the publication is US$ 5,495. *US Aquaculture—A State-by—State Market Study*, a 90 page supplement to the larger report, is available for US$ 195.

Contact: Technology Management Group (TMG), 25 Science Park, New Haven, CT 06511-1968 USA. Tel.: 203-495-1960; Fax: 203-498-7842; e-mail: tmgmail@yalevm, ycc.yale.edu

Plant Genetic Engineering

Educating Citizens and Preparing Future Scientists

Dr. Wagdy A. Sawahel

Public education in biotechnology and genetic engineering as well as preparing future scientists will be well served by an early introduction of biotechnology courses and research into schools. An educated public is essential for the development of good managers, politicians, lawyers, journalists and academicians, as all of these role players in biotechnology industry are drawn from the public.

This book partly fills the existing gap in the literatures by providing a well-planned framework for increasing genetic literacy, well-defined objectives, strategies and teaching approaches for the development of plant genetic engineering education systems for the general public, school, under and post-graduate students. In addition, it includes an outline of the ethos behind the programmes, the topic studied, the research element, the assessment and the potential achievement of such programmes. Furthermore, it contains plant genetic engineering and biotechnology universities guide.

This book, therefore, should be valuable to students who are aiming for undergraduate (B.Sc.) or postgraduate degrees (M.Sc. & Ph.D.) in plant biotechnology and teachers, lecturers, researchers, scientists and educationalists who are involved in the field of genetic engineering and biotechnology from the educational research and curriculum development point of view.

Published by Mittal Publications, A-110, Mohan Garden, New Delhi - 110059 (India). Price Rs 125, $10, £5.

Indigenous African food crops and useful plants, their preparations for food and home gardens in Ghana

Is the report on a field survey done under the auspices of the Institute for Natural Resources in Africa of the United Nations University. Very thorough work on rural, urban and peri-urban home gardens, extremely rich in food garden maps, tables with traditional food nutrient contents, mean production and price averages by ecological zones, species diversity indices, etc. Concludes that a lot more

work is needed to assess the full importance of home gardens in both local nutrition and biological diversity, and calls for policies that promote the expansion of these biodiversity-rich livelihood production systems.

JGK Owusu and others, *Indigenous African food crops and useful plants, their preparations for food and home gardens in Ghana,* UNU/INRA Natural Resources Survey Series No. B1, 1994, 111 pp. For information please address: Prof. Bede N. Okigbo, Director, UNU/IRA, Private Mail Bag, K.I.A., Accra, GHANA. Fax: (233-21) 50 07 92. E-mail: okigbo@ncs.gh.com

The Seed Keepers

The erosion of genetic diversity and the extinction of seed varieties is a major threat to people's food security and survival. Just a few decades ago Indian farmers were growing over 30,000 different varieties of rice, but since the Green Revolution most of those local varieties are extinct or threatened with extinction. The book describes the *Navdanya* concept of conservation, a national *in situ* genetic resources conservation initiative inspired by Dr. Richharia, the eminent rice scientist who started his work in the 1930s. Also discussed are the impact of biotechnology in agriculture and the need for an alternative to IPRs for local genetic resources.

Vandana Shiva and others, *The Seed Keepers*, Navdanya, 1995, 156 pp. Copies available from: The Research Foundation for Science, Technology and Natural Resource Policy, A 60 Hauz Khas, New Delhi 110 016, India

Agrobiodiversity and Farmers' Rights: The Final Milestone

Is the report from a technical consultation on implementation held at the M.S. Swaminathan Research Foundation, Madras, 15-18 January 1996. Although not a consensus document, includes recommendations for national legislation on both plant variety protection and farmers' rights in gene-rich third world countries. Guaranteed access rights to genetic resources, technologies and the market are recommended. Of worry is the fact that "farmers" are narrowly defined as "a person engaged in the cultivation of crops" (what about pastoralists, fisherfolk or forest people?). Proposes an interesting mechanism to redistribute income to tribal and rural families at the community level, through which those communities would at least have some control participation.

Agrobiodiversity and Farmers' Rights: The Final Milestone, M. S. Swaminathan Research Foundation, Madras, 15-18 January 1996, 24 pp. Request copies from: MSSRF, 3rd Cross Street, Taramani Institutional Area, Madras 600 113, India. Fax: (91-44) 235 13 19. E-mail: mssrf@sm8.sprintrpg.sprint.com

Agroecology: The Science of Sustainable Agriculture

Is a new and revised edition of Miguel Altieri's pioneering book that helped alternative agriculture gain scientific recognition. The first part introduces the theoretical basis of agricultural ecology, the second deals with the design of alternative production systems, the third covers alternative production systems (i.e. polycropping, cover crops, agroforestry), the fourth has chapters on ecological management of insects pests, pathogens and weeds, and the last chapter describes the transition towards a sustainable agriculture. This edition has been enriched with the results of new research, and the author thanks traditional farmers from all over the world who have shown him "centuries-tested methods of ecological agriculture".

Miguel A. Altieri, *Agroecology: The Science of Sustainable Agriculture (second edition),* Westview Press/Intermediate Technology Publications, London 1995, 433 pp, ISBN 1-85339-298-2. Order copies from: IT Publications, 103/105 Southampton Row, London WC1 4HH, UK. Fax: 44-171-436 20 13. Priced at £16.95.

Improving Food Security: A guide for rural development managers

By Michael Hubbard, 1995, 151 pp, ISBN 1-85339-311-8, priced at US$ 19.50 or £9.95

Is a guide for rural development managers, whether in Government or voluntary organizations, who are struggling to improve nutrition and reduce poverty through local level interventions. The focus is on local food security, and it links nutrition improvement with higher incomes and local food markets development. Special emphasis on the importance the improvement of women's income and education has for household food security. Suggests area-specific measures intended to prevent famine and other disasters. *Do It Herself: Women and Technical Innovation* (Helen Appleton (ed.), 1995, 310 pp, ISBN 1-85339-287-1, priced at US$ 28.50 or £14.95) investigates the contributions of women to technical innovation at the grassroots level, using 22 case studies from 16 countries in Africa, Asia and Latin America. The book explains technical skills and knowledge of women contributing to food security. Some examples are: cropping indigenous vegetables in Kenya, cassava production in Uganda, vegetable gardens in Venezuela. Shows how women constantly adapt and innovate, or contribute to the adaptations and innovation of others.

Both books above are available from IT Publications, 103/105 Southampton Row, London WC1 4HH, UK. Fax: 44-171 436 20 13

Biopiracy or Green Petroleum: Expectations & Best Practice in Bioprospecting

Is sort of a manual for Governments and other policy makers on the legal aspects concerning "the search for economically valuable genetic and biochemical resources from nature". Although the author never pretends to convey a critical perspective on bioprospecting—and does not—it is full of information on access to genetic resources (prior informed consent, benefit sharing, transfer of technology, IPRs), economic valuation of genetic resources and proposed bioprospecting agreement terms.

Kerry ten Kate, *Biopiracy or Green Petroleum: Expectations & Best Practice in Bioprospecting*, Overseas Development Administration, London, 1995, 621 pp. Request copies from: Environment Policy Department, ODA, 94 Victoria St., London SW1E 5JL UK.

International Yearbook of Industrial Statistics 1996

A unique and comprehensive source of industrial information, the annual International Yearbook of Industrial Statistics is the only international publication providing economists, planners, policy makers and business people with world-wide statistics on current performance and trends in the manufacturing sector. Covering more than 120 countries and areas and giving up-to-date statistical indicators, the data facilitates detailed international comparisons relating to the manufacturing sector. They enable analysis of growth patterns, structural change and industrial

performance in individual industries. The Yearbook succeeds UNIDO's Handbook of Industrial Statistics and also replaces the United Nations' Industrial Statistics Yearbook, volume I (General Industrial Statistics). Its information is compiled from the UNIDO General Industrial Statistics Database, i.e. data obtained directly or through the Organization for Economic Co-operation and Development (OECD), from national statistical sources and from UNIDO estimates. These data have been adjusted to the requirements of international comparability and to standards promulgated by the United Nations, as necessary. Part I refers to the manufacturing sector as a whole and its branches. Statistical indicators are presented in terms of a common currency, percentage distributions, cross-country averages, ratios and real growth rates that facilitate international comparison among selected country groups and/or countries. Data for manufacturing branches are arranged according ISIC rev. 2 at the three-digit-code (major-group) level. Part II comprises a series of country/area-specific tables. These show detailed data on selected basic statistics at the 3- and 4-digit code levels of ISIC for 1985 and the latest three years (up to 1993) for which data were reported by national statistical sources as well as selected indicators that were derived from the basic statistics. The basic statistics presented are: number of establishments, employment, wages and salaries, output, value added, gross fixed capital formation and production indexes. All value data are presented in current national currencies.

ISBN: 1-85898-471-8
Price: £99.95.

Published in English only, by Edward Elgar, 8 Lansdowne Place, Cheltenham, Glos. GL50 2HU, UK. E-mail: info@e-elgar.co.uk.

Molecular Biology and Biotechnology

(2nd revised edition)
by H.D. Kumar

This book is a selection of kernels of molecular biology and modern biotechnology organized in a logical sequence of topics, starting with a historical and biochemical background, progressing through the structure and function of the genetic material, the gene concept, aspects of bacterial genetics, and some techniques of gene cloning that have spurred advances in many biomedical and agricultural disciplines, culminating in diverse aspects of the biotechnology of plants, microorganisms and animals. The kernels have been harvested from a wide selection of current literature in the rapidly advancing frontiers of modern life sciences. Bare essentials of immunology: plant and animal cell, environmental, pharmaceutical, agricultural and health-related aspects of biotechnology, are covered in a concise and assimilable form. Coverage of catalytic RNA, RNA editing and abzymes, will convey to the readers that the time of the rather neglected RNA has come and that they may soon look forward to the advent of a new and exciting RNA world!

The book includes a glossary of useful terms and a short list of recent books and reviews for supplementary reading. Professor Kumar has been engaged in the teaching of genetics and biotechnology for a number of years, and says that he wrote this book to cater to the needs of undergraduate students. Professor Kumar's objective was to introduce the beginner students of science, agriculture, medicine and environment to some essentials of cell biology, elementary and pre-requisite biochemistry, molecular genetics, modern gene concepts, cell and tissue culture of plants and animals, genetic engineering, immunology, microbial fermentations and energy. Although a large number of books on biotechnology have been published recently, most are either multi-authored edited volumes or deal with one or two areas exhaustively rather than covering a broad spectrum of topics in a general, introductory manner. Furthermore, these books are prohibitively expensive and beyond the reach of students in the developing countries. This book is one that can be afforded by most students in India, at least.

ISBN: 0-7069-9756-5
Price: Rupees 95.-

Published by Vikas Publishing House Pvt. Ltd., 576 Masjid Road, Jangpura, New Delhi 110 014, India.

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The OECD has published several documents on crop biotechnology and sustainable agriculture. They all have as an underlying assumption that biotechnology could help sustainability in third world agriculture by offering alternatives to synthetic fertilizers and pest control, which would in turn lead to reduction of agriculture related environmental damage. Questionable premise, in our opinion, since most biotechnological research is usually focused on universal one-shot solutions rather than to the locality-specific, integrated approaches, which are proving to be the basis for true sustainability. Some problems identified in the reports are: accessibility of new technologies to small farmers (Colombia), increased patent applications as a limitation to access of technology and biological resources (India), weak national research programmes and human resources development (Mexico).

Ghayur Alam, *Crop Biotechnology and Sustainable Agriculture: Lessons from India*, Technical Papers No. 103, Paris, December 1994, 88 pp.

Luis R. Sanint, *Crop Biotechnolgy and Sustainable Agriculture: Lessons from Colombia*, Technical Papers No. 104, Paris, January 1995, 82 pp.

José Luis Solleiro Rebolledo, *Crop Biotechnology and Sustainable Agriculture: Lessons from Mexico*, Technical papers No. 105, Paris, January 1995, 74 pp.

Limited copies available from: OECD Development Centre, 94 rue Chardon Lagache, 75016 France.

World Wide Web Sites

Some sites of special scientific interest

http://inet.uni-c.dk/~iaotb/bse.htm
An excellent site linking various official, scientific and other sources relating to BSE, CJD, etc., including the UK Ministry of Agriculture and Food (MAFF) and the *British Medical Journal*.

ftp://ftp.hsfp.c-strasbourg.fr/pub/HFSP
The International Human Frontier Science Programme (HFSP) which funds transnational research into the "complex mechanisms of living organisms, including man".

Researchers from eligible countries (including Ireland) can apply for funding; deadline is 1 September 1996; forms and information are now available for the 1997 grants for short-term fellowships and workshops.

http://www.jpl.nasa.gov/galileo/index.htm
The latest on the Galileo probe, including up to the minute information on where it is now; radio signals from the probe take about 46 minutes to reach Earth.

http://www.sas.upenn.edu/~smfriedm/einstein.html
A site devoted to the great man, with endless quotes, links to the institutions bearing his name, and much more.

http://www.terraquest.com/
Terraquest's "virtual expeditions" to Antarctica and now Ecuador, with information on wildlife, ecology, geology, etc.

http://go2.guardian.co.uk
The *Guardian's* online "OnLine" supplement, covering science, technology and computing. Just one of the many popular scientific publications on the Web: others include *New Scientist* **(http://www.newscientist.com).**

http://www.esf.org
The European Science Foundation's homepage, with details about its conferences, colloquia, etc.

Shopping for Biotechnology Products on the Web: A User's Guide

Mark Goodstein

Below is a list of sites that should be useful for anyone working in a biotechnology company.

Biotechnology product and services sites

Company	Web Address	Online Catalogue?	Search Engine?	Online Ordering?
Beckman Instrument's (Fullerton, CA)	http://www.beckman.com	yes	yes	no
Boehringer Mannheim (Indianapolis, IN)	http://biochem.boehringer.com	yes	yes	no
Digital Instruments (Santa Barbara,CA)	http://www.di.com	yes	no	no
Glyko (Novato, CA)	http://www.glyko.com/glyko/	yes	no	no
Hitachi Software Engineering (San Bruno, CA)	http://www.hitsoft.com	yes	no	no
Life Technologies (Gaithersburg, MD)	http://www.lifetech.com	yes	yes	no
Millipore (Bedford, MA)	http://www.millipore.com	yes	yes	no
Nature America (New York)	http://guide.nature.com	yes	yes	no
New England Biolabs (Beverly, MA)	http://www.neb.com	yes	yes	yes
Novagen (Madison, WI)	http://www.novagen.com	yes	yes	no
Promega (Madison, WI)	http://www.promega.com	yes	yes	no
R&D Systems (Minneapolis, MN)	http://www.rndsystems.com	yes	yes	yes
Sigma (St. Louis, MO)	http://www.sigma.sial.com	yes	yes	yes

URLs for Web

Bioinformatics and Computational Biology

BioSCAN for rapid search and analysis of biological sequences: http://genome.cs.unc.edu/project.html

Sequence alignment and modeling system: http://www.cse.ucsc.edu/research/compbio/sam.html

Heterogeneous Database Management Systems: http://gizmo.lbl.gov/HDBMS/HDBMS.html

NIH Molecular Modeling (3-D structure and physiochemical properties): http://molbio.info.nih.gov/modeling/

Biotechnology and Molecular Biology

Bio-wURLd collection of links: http://www.ebi.ac.uk/htbin/bwurld.pl/

BME*net* biomedical engineering: http://bme.www.ecn.purdue.edu/bme or gopher://fairway.ecn.purdue.edu/

Biotechnology Section, WWW Virtual Library: http://www.webpress.net/interweb/cato/biotech/

Biotechnology Information Center, USDA National Agricultural Library: http://www.inform.umd.edu:8080/EdRes/Topic/AgrEnv/Biotech/

Molecular biologists' Internet introduction, links: http://www.ifrn.bbsrc.ac.uk/gm/lab/docs/iftmb.html

Journal of Molecular biology: http://www.hbuk.co.uk/jmb/

Nature magazine: http://www.nature.com/

Science magazine: http://www.aaas.org/science/

Ethics and Education

Biotechnology law, pharmaceutical and biotechnology clientele: http://biotechlaw.ari.net/

Ethics and Genetics, A Global Conversation: http://www.med.upenn.edu/~bioethic/genetics.html

Eubios Ethics Institute: http://www.biol.tsukuba.ac.jp/~macer/index.html

Genetics educational sourcebook: http://www.netspace.org/MendelWeb/

Genscope software project for biology teachers: http://copernicus.bbn.com/genscope/home.html

Rural Advancement Foundation International (RAFI): http://www.charm.net/~rafi/rafihome.html

International

Biotechnology research projects in Europe: http://www.library.knaw.nl/cgi-bin/biorep_search.pl/

Chromosome editors (HUGO): http://gdbwww.gdb.org/gdb5.6/docs/editors.html

European Molecular Biology Laboratory: http://www.embl-heidelberg.de/

European Molecular Biology Network Newsletter (embnet.news): http://www.be.embnet.org/embnet.news/

Japanese Human Genome Project: http://www.genome.ad.jp/

Model Organisms

***Arabidopsis* cDNA Sequencing Analysis Project:** htttp://lenti.med.umn.edu/

DogGenomeProject: http://mendel.berkeley.edu/dog.html

Non-Redundant *Bacillus subtilis* (NRSub) database: http://acnuc.univ-lyon1.fr/nrsub/nrsub.html or http://ddbjs4h.genes.nig.ac.jp/

Rat strain information, lab code names: http://www.anex.med.tokushima-u.ac.jp/index.html

Nucleotide Sequences

IMGT nucleotide sequence information for immune system genes: http://www.ebi.ac.uk/contrib.imgt

Molecular Probe Data Base of synthetic oligonucleotides: http://www.ist.unige.it/interlab/mpdb.html

Proteins

Cambridge Crystallographic Data Center: http://csdvx2.ccdc.cam.ac.uk/

Coiled-coil region prediction in amino acid sequences: http://theory.lcs.mit.edu/~bab/paircoil.html

Department of Crystallography, Birkbeck College, London: http://www.cryst.bbk.ac.uk/

Kabat protein sequence database: http://immuno.bme.nwu.edu/

NAOMI 3-D protein-structure program: http://www.ocms.ox.ac.uk/~smb/Software/N_details/naomi.html

Protein Data Bank: http://www.pdb.bnl.gov/

Protein Science magazine: http://www.prosci.uci.edu/

Secondary structure assignment database (DSSP), program: http://www.sander.embl-heidelberg.de/dssp/

Protein structural classification: http://www.prosci.uci.edu/scop/

Protein scientists' WWW resources: http://www.prosci.uci.edu/ProSciDocs/WWWResources.html

TECHNOLOGY AND INVESTMENT OPPORTUNITIES

TECHNOLOGY REQUESTS

MANUFACTURING MEDICINAL, AROMATIC AND OTHER BIO EXTRACTS USING SUPER CRITICAL FLUID EXTRACTION TECHNOLOGY

The proposed project involves processing of 1,200 metric tons per annum of herbs, botanicals and spices for extracts with application in the pharmaceutical, cosmetic, dietary supplements, food and nutrition industries. The purpose of the project is to increase production capacities by expansion of the plant to develop new products and markets in the fields of flavours, colourants, etc.
Est. investment cost: US$ 6 million
Collaboration sought: Joint venture

*(For futher information, please contact:
Mr. J. Raghunath Rao, Chairman, Novo Agritech Ltd., 4-63/1 2nd Floor, HUDA Colony, Chandanagar, Hyderabad 500 050, India. Tel: 91-40-284344; Fax: 91-40-247887.)*

PRODUCTION OF MOZZARELLA CHEESE

The company is seeking assistance in establishing a modern plant to produce 5 metric tons of mozarella chesse per day at Chitoor. The plant will handle about 75,000 litres of milk per day. The site of the plant has been selected because of an abundant supply of local milk. At present the demand for the cheese is steadily increasing, but the supply is unable to meet this demand.
Est. investment cost: US$ 8.2 million
Collaboration sought: Joint venture; technology transfer; buy back arrangement

*(For further information, please contact:
Dr. V. Nagaraja Naidu, Director, Heritage Foods (India) Ltd., 6-3-541/C Punjagutta, Hyderabad 500 082, India. Tel: 91-40-391221; Fax: 91-40-3320854; e-mail: ICMAIL.03HFICL@SUPVSR)*

MANUFACTURE OF TROPICAL FRUIT PULP AND CONCENTRATE

The company proposes to set up a state-of-the-art fruit processing plant with an installed capacity of 19,500 tons per annum for processing the pulp and concentrate of various tropical fruits. The project is planned for the Chittoor district of Andhra Pradesh, situated in the fruit belt of the Deccan plateau.
Est. investment cost: US$ 11.3 million
Cooperation sought: Transfer of technology; Buy back arrangement

*(For further information, please contact:
Mr. D. Ravi Shankar, Chairman, Leafin Agro Ltd., 1-2-593/34/A, Surya Kirin Apts., Gagan Mahal Colony, Domalaguda, Hyderabad 500 029, India. Tel: 91-40-7639047; Fax: 91-40-7637396.)*

MANUFACTURE OF STARCH

The company is currently manufacturing Sorbitol. As a backward integration process, the company is in the process of establishing a production unit for making starch and intends to double the capacity of Sorbitol from 8,000 to 16,000 tons per annum by increasing the daily manufacturing capacity from 150 to 500 tons per day by the year 2000.
Est. investment cost: US$ 15 million
Collaboration sought: Joint venture; buy back arrangement

*(For further information, please contact:
Mr. T.V. Sundeep Kumar Reddy, Managing Director, Starhem Industries Ltd., 1-7-1, i floor, T.S.R. Complex, S.R.Road, Seconderabad 500 003 (A.P.), India. Tel: 91-40-813777; Fax: 91-40-813999.)*

EXPANSION OF PROCESSING FACILITIES FOR PICKLES

A totally export oriented unit with a sales turnover of US$ 1.37 million per annumproposes to expand the existing facilities.
Est. investment cost: 2.28 million
Collaboration sought: Joint venture

*(For further information, please contact:
Mr. Shankar Raja, Director, Great Western Industries Ltd., 280 Main Road, Nr. Hope Farm, White Field, Bangalore 560 066, India. Tel: 91-80-8453145; Fax: 91-80-8452882)*

PROCESSING OF HERBAL PRODUCTS

Herbal products are processed to produce tablets, capsules, liquids, semi-solids and powders for different ailments. The process involves cultivation of medicinal herbs, collection and grading of herbs and minerals, product development, pulverising/milling, shifting of powders, mixing, extraction/heat process, drying/evaporation, tabletting, capsulation and packing. Cost of project: US$0.33 million; Machinery: US$80,000.
Development status: Commercialized
Collaboration requested: Joint venture, licensing.

*(For further information, please contact:
Mr.Deepak Joshi, Madhur Pharma & Researcg Laboratories, 7 Bellary Road, Bangalore 560 032, India. Tel: 91-80-3333393; Fax:91-80-3333392.)*

TECHNOLOGY OFFERS

PROCESSING OF HERBAL PRODUCTS
Herbal products are processed to produce tablets, capsules, liquids, semi-solids and powders for different ailments. The process involves cultivation of medicinal herbs, collection and grading of herbs and minerals, product development, pulverising/milling, shifting of powders, mixing, extraction/heat process, drying/evaporation, tabletting, capsulation and packing. Cost of project: US$0.33 million; Machinery: US$80,000.
Development status: Commercialized
Collaboration requested: Joint venture, licensing.

(For further information, please contact:
Mr.Deepak Joshi, Madhur Pharma & Researcg Laboratories, 7 Bellary Road, Bangalore 560 032, India. Tel: 91-80-3333393; Fax:91-80-3333392.)

NATURAL FIBRE GEO/AGRO TEXTILES
Eco-friendly geo/agro textiles is manufactured using natural fibres of jute and coir. The product is used for soil erosion control, landscaping, greening, weed control, mulching, soil stabilization, coastal and canal line protection and engineering applications. Total project cost: US$1.5 million.
Development status: Launch phase
Collaboration requested: Joint venture, know-how, marketing expertise.

(For further information, please contact:
Mr. G.K. Prakash, Aspinwall Geotech Ltd., P.B. No.2, Calvetty, Cochin 682 001, India. Tel: 91-484-224331; Fax: 91-484-224469.)

RAW CASHEWNUT PROCESSING
Raw cashew nuts are processed to obtain internationally acceptable quality grades of cashew kernels. The raw cashew nuts are processed in different stages like cooking/roasting, cutting/shelling, peeling and grading. The processes are done in hygeinic conditions and the graded kernels are packed in vacuumised and carbon dioxide induced lead free tins. Cost of machinery: US$60,000.
Development status: Commercialized
Collaboration requested: Turnkey, technical expertise.

(For further information, please contact:
Mr. S. Sivaraju, Kalpana Agro Processors Pvt. Ltd., 11 floor, Annie Bhanu Buildings, 31/83 N, North street, Marthandam, K.K. Dist. 629 165 (TN). Tel: 91-4651-70884; Fax: 91-4651-71195.)

DEXTROSE/SORBITOL
Manufacturing of dextrose through starch hydrolysis and sorbitol by glucose catalytic hydrogenation. Cost of project: US$1.7 million; machinery US$1 million.
Development status: Launch phase
Collaboration requested: Turnkey

(For further information, please contact.
Mr. K. Nageswara Rao, Spring Flower Organics, 75 Astalakshmi Nagar, Alwarthirunagar (P.O.), Valasaravakkam, Madras 600 087, India. Tel: 91-44-4826684.)

ESSENTIAL OIL
Essential oils are mainly processed by steam distillation and then treated by vaccum fractionation process for improving purity of the oil to almost 95 per cent. Major essential oils are ocimum, mint oil, fennel oil, clove oil, cumin oil, capsicum oil, cardamon oil, pepper oil, palmarosa oil, de-mentholised oil and lemon grass oil. These oils are used mainly in pharmaceuticals, food and beverages and perfumery and cosmetic industries. Cost of project: US$315,000; machinery: US$200,000; Know-how: US$15,000.
Development status: Commercialized
Collaboration requested: Know-how; consultancy; technical expertise.

(For further information, please contact:
Mr. R. Bhattacharjee, Jagadhguru Engineers & Consultants Pvt. Ltd., Om Murga Illam, 39/7 Sarojini Street, T. Nagar, Chennai 600 017, India. Tel: 91-44-452537; Fax: 91-44-4825277.)

MICRO IRRIGATION, GREEN HOUSE TECHNOLOGY & OPEN FIELD CULTIVATION
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INDIA
INTECHMART

FOR THE SOUTHERN REGION

Bangalore, 19-22 March 1997

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