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GENETIC ENGINEERING AND BIOTECHNOLOGY MONITOR

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CONTENTS

UNIDO's *Genetic Engineering and Biotechnology Monitor* 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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TO OUR READERS

After two years of effort, including additional months of accelerated reforms and fundamental changes to nearly all aspects of the Organization, the new vision for UNIDO has taken shape. Most of the original aims outlined in the General Conference held at Yaoundé (Cameroon) two years ago have been addressed, transforming UNIDO into an agency of which Member States can be proud, an agency that serves the global community, and particularly developing countries, in unique and important ways, and that is more effective and efficient today in spite of the limited and often uncertain resources put at its disposal. The process of reform has not always been easy, requiring hard work and dedication of staff in the light of the financial uncertainties they had to face during the transition period.

The reform process of UNIDO was initiated at an early stage when no particular financial constraints for the Organization were anticipated. It was prompted by the perceived need to respond to changing patterns of demand for the services of the Organization and was thus from the outset driven primarily by substantive and efficiency considerations. At the same time, the basic postulates of the reform – the need to define a sharper substantive focus, to adjust the organizational structure accordingly, and to enhance process efficiency – have laid the foundation for a more effective and leaner UNIDO that will be better able to respond to different scenarios of development and resource availability. In particular, the reform process has enabled UNIDO to respond already in 1995 to the shortfalls in income from assessed contributions expected for 1996-97.

Following the announcement by the the United States of America in April 1995 of its possible withdrawal from UNIDO, drastic plans were developed to cope with such consequences. This decision by the major contributor was confirmed during the General Conference held in Vienna at the beginning of December 1995. The most immediate and painful consequence of UNIDO's financial restrictions has been a sizeable reduction in its staff, with obvious effects on the Organization's programmes. Nonetheless, UNIDO has undertaken an in-depth assessment of present patterns of demand for its services in the various developing regions, and based on this analytical work, has identified the contributions that industrialization can make to developing countries – and in its turn its own support function – within the context of the overall development objectives: (a) to provide a conceptual basis for the grouping of present and future services in various areas of demand; (b) to establish a framework for assessing the impact of UNIDO activities; and (c) to strengthen the link with relevant development programmes of other UN system and bilateral agencies, as well as with the endeavours of the recipient countries themselves.

UNIDO has been the first among the UN agencies to promote biotechnology and take active steps to strengthen the capability of developing countries in genetic technologies through the establishment of the International Centre for Genetic Engineering and Biotechnology (ICGEB). Recently, we have been concentrating our work on aspects that influence the commercialization of biotechnology derived products. This work has culminated in the operation of the Biosafety Information Network and Advisory Service (BINAS), as well as in the establishment of close cooperation with the OECD aimed at addressing issues related to the international harmonization of regulatory oversight in biotechnology. During 1996, we plan to continue expanding BINAS and develop biotechnology risk assessment software. Other activities in biotechnology will include biodiversity prospecting, bioremediation technology for sustainable industrial development, technology transfer of mushroom biotechnology, and numerous training courses.

Virginia Campbell
Scientific Editor

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A. SPECIAL ARTICLE

THE FIELD TESTING AND COMMERCIALIZATION OF GENETICALLY MODIFIED PLANTS: A REVIEW OF WORLDWIDE DATA (1986 TO 1993/94)

by

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Summary

World-wide data of field releases (testing) and commercialization of genetically modified plants—with particular reference to developing countries—have been compiled and analysed. Results show that China and the USA are the only two countries where large-scale releases have been authorized for the purpose of commercialization. In China, genetically modified virus resistant tobacco has been used in industrial tobacco manufacturing for national consumption since 1992 and the cultivated area now stands at nearly 1 million ha or almost 5 per cent of tobacco plantations. In May 1994, the USA granted approval for commercial production of genetically modified tomato (the so-called FlavrSavr™) and sales began during the same month within the USA. Herbicide tolerant cotton and soybean were deregulated in February 1994 and a preliminary determination by USDA for virus resistant squash (WMV2 and ZYMV) was favourable in July 1994.

Field trials world-wide have been increasing steadily since the first such trials began in 1986 in the USA and France and over 1,450 have been conducted world-wide to date (nearly 400 in 1993 alone). The majority are taking place in the USA, Canada and Europe (particularly France, Belgium, the United Kingdom and the Netherlands).

Field trial activities in developing countries amount to 8 per cent of world-wide trials and are highest in Latin America and the Caribbean (5 per cent) with few field releases in Africa (less than 1 per cent) and Asia (2 per cent almost exclusively in China), and are following a somewhat different pattern from that of OECD countries. The first trial took place in 1987 with an increasing number of trials to 1993. It appears that fewer trials are currently under way in developing countries, with the exception of China, although many are planned for later this year for counter season planting in the Southern cone. The remaining slight reduction in field tests in Latin America in the first part of 1994 is more a result of the establishment of formal biosafety regulatory mechanisms that require a review of applications (hence a temporary delay) rather than a shift in overall policy towards biotechnology.

1. *Introduction*

The issue of biosafety arose shortly following the "discovery" of the possibility of genetically modifying organisms and the development of such techniques in 1971. The first regulations were prepared by the National Institutes of Health of the USA in 1976 to apply to laboratory procedures (51 Federal Regulation No. 16958). Far more complex has been the treatment of materials to be released into the environment, first for testing and now for commercial use. In this area, the USA, as an early entrant into biotechnology research, was an innovator in developing regulations, at least for plants. The Animal and Plant Health Inspection Service (APHIS) of the United States Department of Agriculture (USDA) established several of the key aspects of regulations in this area, namely the need for case-by-case and step-by-step evaluation.

This approach to legislation has been adopted by other countries, including the Philippines, but the bulk of the countries of the world are at this time lacking in biosafety regulations with the exception of many countries of the Organization for Economic Co-operation and Development (OECD). The list of countries lacking regulations includes virtually all developing countries with the exceptions of India, Mexico and the Philippines (synopsis in Maloney, 1994), with Argentina and Cuba having regulations in place but which are not incorporated into laws, and with Costa Rica, Bolivia, Brazil, Chile, China, Colombia, Indonesia, Malaysia, Nigeria, Thailand and Zimbabwe either having *ad hoc* committees or being in the process of adopting regulations (see also Krattiger and Lesser, 1994). The absence of regulations has led to concerns that private firms will test potentially hazardous genetically modified organisms (GMOs) at will in those countries lacking regulations (see UNEP, 1993). Even when care is applied, the larger number of relatives of food and fibre crops which exist in centres of origin make possible outcrossing of greater concern than for most developed country applications.

This indicates that it is imperative for countries to adopt appropriate regulations in the very near future. Failure to do so leaves them vulnerable to improper precautions and delayed access to innovations from those firms and agencies which prohibit introductions when there is no national body to rule on their safety. Thus the issue is not whether there ought to be regulations but how best to implement them.

The purpose of this paper is to review world-wide field releases of genetically modified plants, with particular

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* Krattiger, A.F. 1994. The Field Testing and Commercialization of Genetically Modified Plants: A Review of Worldwide Data (1986 to 1993/94). In *Biosafety for Sustainable Agriculture: Sharing Biotechnology Regulatory Experiences of the Western Hemisphere*. ISAAA: Ithaca & SEI: Stockholm. pp. 247-266. Reprinted with permission from the copyright holder. Available from: International Academy of the Environment, 1231 Conches, Geneva, Switzerland. Fax +41 22 789 2538. US$28 including postage. Forty per cent discount for orders from developing countries.

reference to developing countries, and to clarify a certain number of issues. Whereas data for Canada, Europe and the USA is readily available and has been reviewed extensively (Chasseray and Duesing, 1992; Ahl Goy and Duesing, 1993, 1994; Ahl Goy *et al.*, 1994; OECD, 1993), detailed and comprehensive data of Africa, Asia and Latin America and the Caribbean (LAC) is difficult to obtain or corroborate. An attempt was therefore made to compile world-wide release and commercialization data with particular reference to developing countries. It should be noted that the most detailed, comparable and comprehensive database is maintained by the Green Industry Biotechnology Platform (GIBiP), an association of major European plant biotechnology companies. The articles cited above present comprehensive analysis from this database.

The next section provides explanatory notes on the data and section 3 reviews commercialization activities. Section 4 briefly reviews field trial activities world-wide and analyses differences between developing and industrialized countries, and difference among major geographic regions. Section 5 lists detailed trial data of developing countries.

2. *Methodology and definitions*

2.1 Data gathering

In countries with biosafety regulatory mechanisms established, official field trial data is readily available from the respective governmental agencies. In addition, the European Union (EU) keeps records of field releases in its member states and OECD countries are required to disclose data on their releases.

The availability of data in developing countries, however, is uneven. Certain countries with biosafety committees (e.g. Chile, Argentina, Thailand) make their data readily available, including information on the current status of applications and rejected applications. Other countries with formal biosafety or biotechnology committees (e.g. Costa Rica) treat applications in strict confidence, even those that have been rejected. In either case, the committees—understandably—only provide official information related to field trials that have officially been approved. Data on trials before such committees were constituted are only available through informal contacts and rarely from official sources. The information presented in this paper has been obtained through official channels, where applicable, and through personal contacts for most developing countries. Essential data was also obtained from the GIBiP database maintained at Ciba-Geigy in Switzerland.

2.2 The meaning(s) of "One" field trial

A field trial with genetically modified plants has different definitions in different countries. It can be one crop at one site in one year, and it can be a category of a crop at a number of sites across a country. In the USA, a "Release Permit" is applicable to one precisely defined crop with a known modification and may be tested at more than one site in more than one state. Each proposed trial site must be listed in applications to APHIS and the permit obtained from APHIS indicates the sites where field trials may proceed (an exception to this are "deregulated articles" discussed below).

A field trial refers in this paper to release permits issued (US-terminology) and to submissions (Canadian terminology). In Canada, the distinction between "submissions" and "trials" is as follows: a given submission corresponds to a year, an applicant, a species, and a genotype. Each submission may be tested at various sites in one or more provinces and each site constitutes one trial.

In developing countries, the number of sites is often small (less than 10 for a given field trial) and the data presented here refers to one trial of a specific crop at one or more sites per country, where applicable.

Perennial crops (e.g. trees, strawberries, sugarcane) may be tested over a period of years. In such cases, the data presented here reflects the year when the trial was established and is not listed again in the years where the same planting of a trial simply continued.

2.3 Classification of modified characteristics

The various characters of modified plants were grouped into several categories, namely agronomic traits (A), bacterial resistance (BR), fungal resistance (FR), herbicide tolerance (HT), industrial production (IP), insect resistance (IR), marker gene(s) (M), nematode resistance (NR), quality characteristics(Q), and virus resistance(VR).

Agronomic traits include characteristics such as male or female sterility, and virus resistance generally refers to the insertion of a viral coat protein. No distinction has been made between coat protein-mediated resistance, or satellite or 54kb replicase technology. Industrial production to date essentially means specific enzyme production (e.g. in soybean). Quality characteristics include slow ripening (tomato), increased protein production (e.g. high amino-acid composition in potato), decreased protein production (e.g. low gluten content for brewing rice), low allergen production (e.g. low gliadin in rice), and pigment production in flowers. Modified fatty acid composition (e.g. the bay thioesterase gene in rapeseed producing laurate) was classified as a quality trait despite the fact that it is a component in detergent and other manufactured items.

2.4 Status of data

The status of field releases and commercialization aspects is as of July 1994, unless otherwise indicated.

3. *Commercialization of genetically modified plants*

3.1 Tobacco in China

Virus resistant tobacco has been field tested in China since 1991 and many trials included double constructs (Cauliflower Mosaic Virus [CMV] and Tobacco Mosaic Virus [TMV]). A single construct coat protein tobacco (CMV) was sown on approximately 35 ha in 1992 for seed increase and a double construct (TMV and CMV) tobacco is now under seed increase.

A CMV resistant tobacco has been used in industrial tobacco manufacturing for national consumption since 1992. The cultivated area now stands at nearly 1 million ha corresponding to an estimated 5 per cent of total tobacco plantations in China. The area is expected to grow to 30 per cent by 1995 and 70 per cent by the end of the decade. By early 1995, tobacco with resistance to two viruses (CMV and TMV) is also expected to be commercialized as seed increase is under way.

Virus resistant genetically modified tobacco yields an average of 5-7 per cent more leaves for processing and saves 2-3 insecticide applications out of approximately 7 applications (note that aphids transmit the major viruses that infect tobacco, hence the saving is on insecticides).

3.2 Tomato in the USA

In the USA, approval for commercial sale and human consumption of genetically modified tomato (the so-called FlavrSavr™) was granted by the Food and Drug Administration (FDA) of the Government of the USA in May 1994. The sale of these tomato began the same month within the USA, particularly California and the mid-west and consumer acceptance has essentially been positive.

A new system under the regulations of the USA allows for applicants to request that APHIS considers whether a given transgenic plant could be deregulated (so-called "Petitions"). Approved petitions by APHIS stipulate that there is no longer any need for APHIS review or approval for introductions of the plant into agriculture and the environment. A permit is not a license to commercialize a crop since food safety, pesticide or other regulatory questions may still have to be addressed by other regulatory agencies. Three crops containing a specific gene have been deregulated by APHIS, namely the FlavrSavr™ tomato developed by Calgene, the BXN™ bromoxynil (herbicide) tolerant cotton also developed by Calgene, and glyphosate (herbicide) tolerant soybean developed by Monsanto. In addition, a favourable preliminary ruling in July 1994 by APHIS for virus resistant squash (coat proteins of watermelon mosaic virus 2 [WMV2] and zucchini yellow mosaic virus [ZYMV]) squash developed by Asgrow) means that this crop will be commercialized if FDA approval is obtained.

4. *Field testing of genetically modified plants*

4.1 Overview of field trial history and current status

The first field trials were conducted in 1986 with herbicide tolerant tobacco in France and in the USA (herbicide tolerance was then used as a marker and this is still often the case today). Belgium was the third country to authorize such releases in 1987. By the end of 1993, all countries of the OECD, with the exception of Austria, Luxembourg and Turkey, have authorized field trials although the USA, Canada, France, Belgium, the United Kingdom and the Netherlands accounted for 82 per cent of the trials world-wide (table 1).

To date, just over 60 plant species have been transformed and nearly half have been field tested but the great majority of tests are done with six species, namely cotton, maize, potato, soybean, tobacco, and tomato. These crops can routinely be transformed but other crops are following steadily, such as various cucurbit species, rice and sugarbeet. Yet in Canada, one single crop, rapeseed, accounts for 65 per cent of all releases. Of the characters most widely tested, on a world-wide basis, virus resistance accounts for 37 per cent in the USA over the last year, herbicide tolerance for 30 per cent, and quality for 15 per cent.

Of all trials in OECD countries over the last year, herbicide tolerance represents the highest proportion of trials (36 per cent), followed by insect resistance (32 per cent), and quality and virus resistance (14 per cent each). Maize occupies the first place in the number of trials (30 per cent), followed by cotton, soybean and tomato (approximately 15 per cent each).

Figure 1 shows the number of field trials world-wide and it should be noted that the figures are based on permits rather than locations (see also above). In Canada, for example, from 1988 to August 1994, the total number of trials was over 1,700, whereas the total number of submissions or permits was around 350. In the USA during the same period, the number of release permits was 450. Early field trials were conducted at one site only (and this continues to be the case for many trials), but the average today in the USA (excluding notifications) is 1.5 states per permit. There are nevertheless exceptions, as in 1993 when a permit was issued in 1993 for cotton to be tested at 89 sites across eleven states of the USA. Permits in the Netherlands average 5-10 locations but one potato trial comprised 38 locations, and another one 49 locations.

Hungary is the only country in Eastern Europe that recorded field trials with transgenic crops (1993: PVY resistant tobacco and a tobacco with a marker; 1994: same as 1993, plus a potato line with a marker). No field trials are known to have occurred in Russia or in the newly independent States of the former Soviet Union.

The data for the developing countries of Africa, Asia, and Latin America and the Caribbean are also evaluated separately in figure 2. Overall, the highest activity has been recorded in Latin America, but it should be noted that China probably has more individual sites tested and may thus have by far the highest activity overall. The low level of activity in Africa is related to few countries having regulatory procedures in place. Another reason is that biotechnology research activities in much of Africa is low and hence little national demand has been generated to field test genetically modified plants, but with routine engineering of cassava and rice becoming increasingly possible this could change soon. Finally, seed companies are not well established in the region.

Virus resistance, insect resistance and herbicide tolerance—in decreasing order—represent nearly 90 per cent of the characters tested in developing countries (figure 3), and tobacco, maize, cotton and tomato—also in decreasing order—are the most often tested crops in developing countries. Maize, soybean and tomato are the crops most often tested in Latin America, whereas tobacco dominates Asia (i.e. China).

4.2 "Notifications" in the USA

APHIS recently issued a notification system (57 FR 53036; 31 March 1993) that warrants special attention. Under its scheme, applicants for subsequent, multiple trials need not seek prior approval but rather only inform the agency. The agency acknowledges such notifications if they meet the specific eligibility criteria: certain limitations on the type of genetic modification, on how introductions may be conducted, and crop species (cotton, maize, potato, soybean, tobacco and tomato). It is noteworthy that before notification was allowed, over 80 per cent of the field test permits were for these six crops.

Table 2 shows summary data for the six crops. Out of the 586 notifications acknowledged, cotton represents almost half with many trials for insect resistance and herbicide tolerance. Notifications for soybean and tomato represent around 15 per cent each with many trials in soybean for herbicide tolerance and most trials in tomato for quality characteristics. Figure 4 shows the percentage of each character tested under the notification system. Note that each modification was counted as a separate trial so that the data does not differentiate between single and multiple modifications. "Other" traits include bacterial resistance, industrial products and nematode resistance.

Noteworthy is that by far the largest proportion, 93 per cent, of notifications came from the private sector. Three companies alone represent 55 per cent of total notifications (Monsanto with 30 per cent, Du Pont with 14 per cent and Pioneer Hi-Bred Inc. with 11 per cent).

Table 1: Number of field trials worldwide
(modified and extended after Ahl Goy and Duesing, 1994)

Industrialized countries

Country/Region	1986	1987	1988	1989	1990	1991	1992	1993	1994*	Total
North America[1]										
Canada			10	28	40	39	40	89	113	359
USA[2]	3	9	12	21	32	66	107	135	60	445
Subtotal	3	9	22	49	72	105	147	224	173	804
Europe[3]										
Belgium		1	4	9	14	14	12	19	8	81
Denmark[4]					2	1	3	4	1	11
Finland			1	1	2		3	1	2	10
France[4]	2	5	9	14	26	31	22	29	30	168
Germany[4]					1	1	1	3		6
Italy[4]				1	1		1	7	4	14
Netherlands			1	1	1	13	16	20	32	84
Norway							1		na**	1
Portugal[4]								2	2	4
Spain			2	4	5			3	2	16
Sweden				1	1	2	2	3	8	17
Switzerland						1	1			2
UK		1	1	4	11	13	13	13	22	78
Subtotal	2	7	18	35	64	76	75	104	111	492
Asia										
Australia						1	6	7	12	26
Israel						1	1	1	1	4
Japan						2		3	3	8
New Zealand			4	4	3	1	1	2		15
Subtotal			4	4	3	5	8	13	16	53
Total	5	16	44	88	139	186	230	341	300	1349

Developing countries

Country/Region	1986	1987	1988	1989	1990	1991	1992	1993	1994*	Total
Africa					1	2	1	5	1	10
Asia				2	2	2	5	10	11	32
LAC		1	1	1		10	22	27	10	72
Other[5]								2	2	4
Total		1	1	3	3	14	28	44	24	118

Grand Total	5	17	45	91	142	200	258	385	324	1467

* Partial data for 1994. Unless otherwise stated to July 1994.
** na: not available.

[1] Excluding Mexico
[2] Data to June 1994. Excluding Notifications.
[3] Western Europe (EU, EFTA).
[4] Data to 15 March 1994.
[5] Hungary.

Figure 1. Number of field trials worldwide

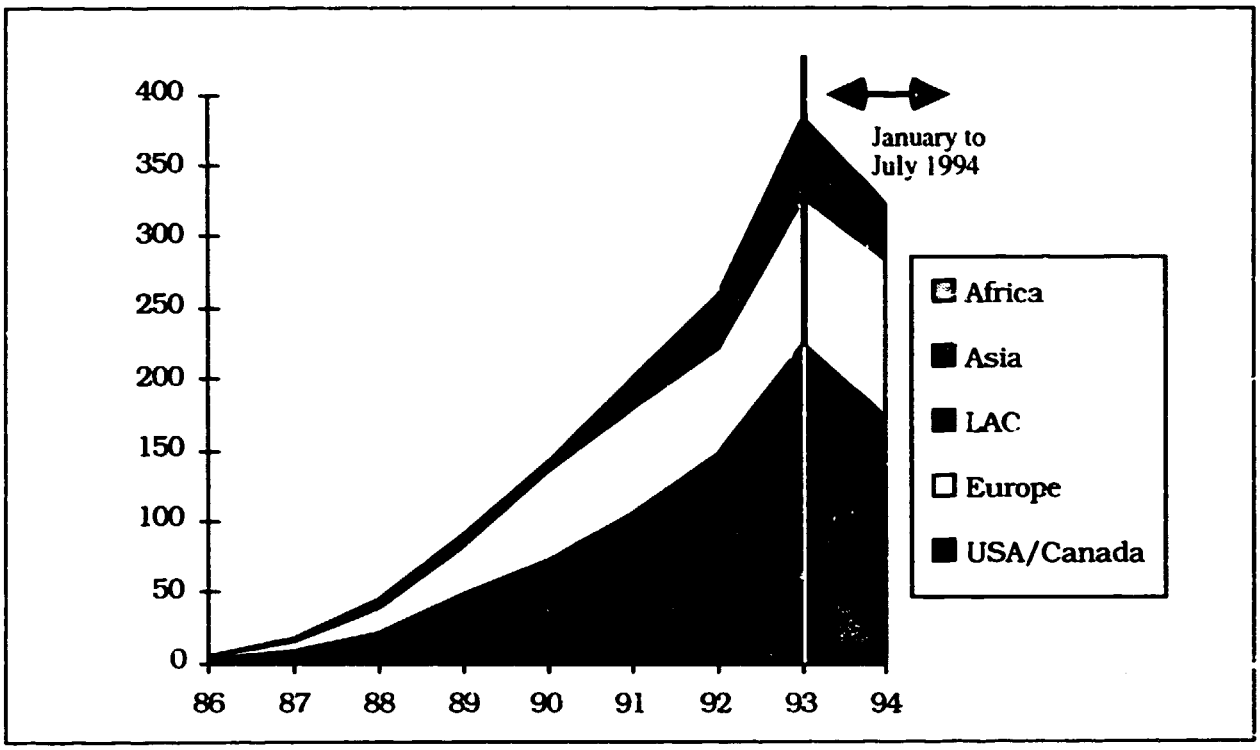
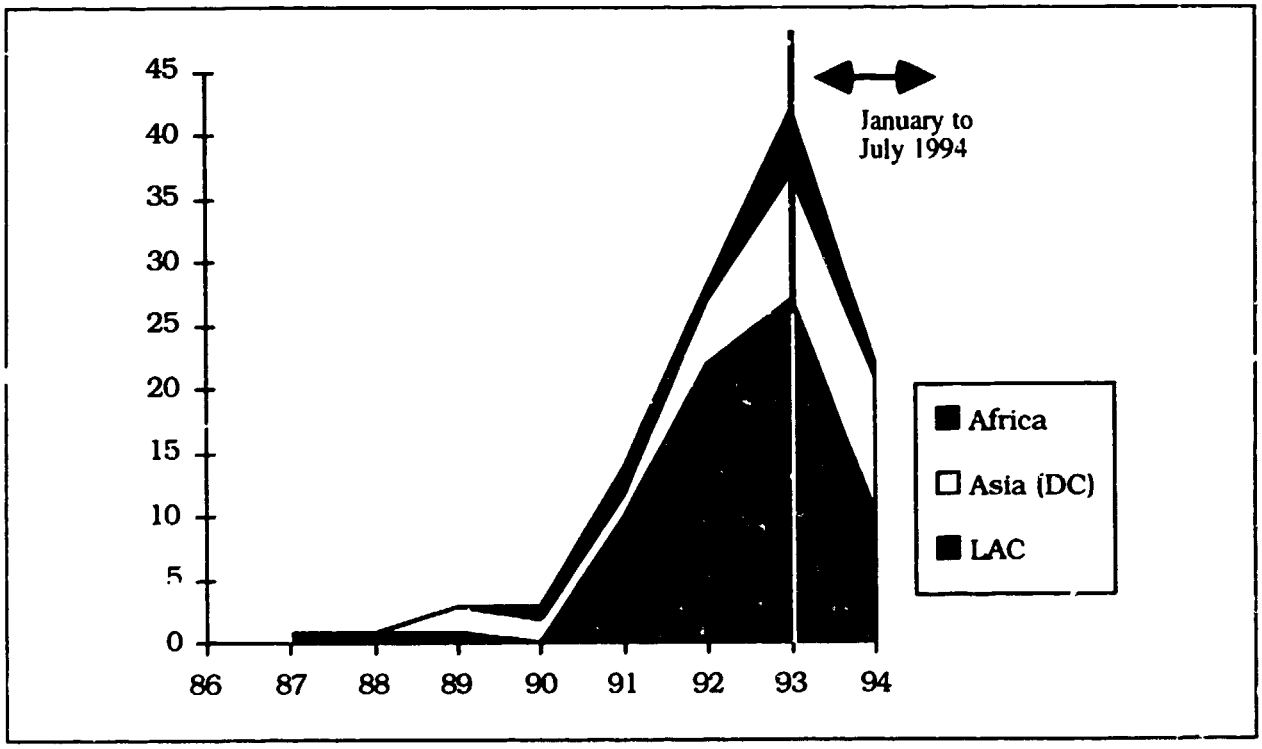
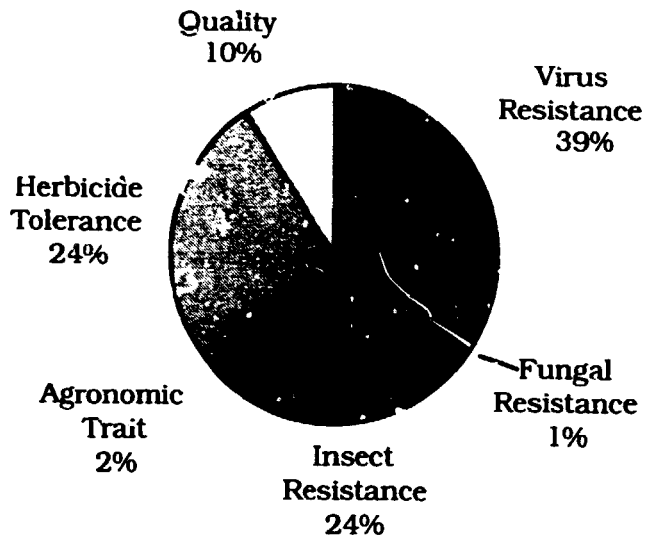


Figure 2. Number of field trials in Africa, Asia[1] and LAC



1 Developing countries only, including China.

Figure 3. Type of field trial in Africa, Asia1 and LAC



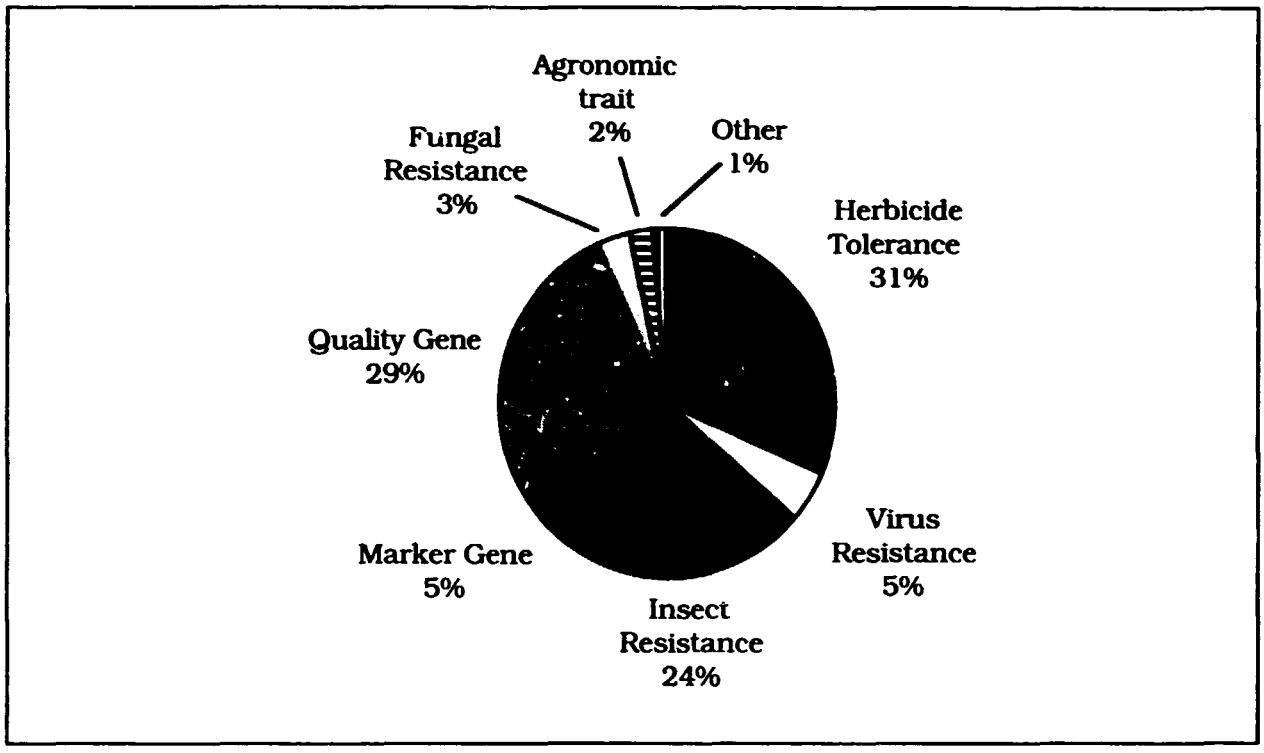
1 Developing countries only, including China. As multiple trait field trials were counted as one or more if the traits differed, the total exceeds 100 per cent in the original calculation. In this Figure, the numbers were scaled proportionately to 100 per cent.

Table 2. Notifications by crop (April 1993-August 1994)

Character	Cotton	Maize	Potato	Soybean	Tobacco	Tomato	Total
Total for Crop							
Number of Permits	271	46	55	99	23	92	586
Percent of Total	46%	8%	9%	17%	4%	16%	100%
Per cent of Major Trait[1]	(%)	(%)	(%)	(%)	(%)	(%)	
Herbicide Tolerance	37	63		76			
Insect Resistance	44	30	35				
Quality Gene	25		33	25		82	
Virus Resistance			24		48		

[1] Trait in relation to total number of notifications per crop. The figures correspond to the number of notifications containing one or more gene(s) of the given trait in relation to the total number of notifications and the total therefore may exceed 100%.

Figure 4. Notifications by Trait[1] (April 1993-August 1994)



[1] Multiple trait field trials were counted as more than one so the total exceeds 100 per cent in the original calculation. In this Figure, the numbers were scaled proportionately to 100 per cent.

5. *Detailed lists of field trials in developing countries*

5.1 Latin America and the Caribbean

Table 3 gives a list of countries, crops and traits of field trials in the region. Argentina, Chile and Mexico are countries where the highest number of trials have taken place, and overall there is a steady increase of trials to 1993.

Argentina had not established field trials in 1994 but there are many pending applications for seed, increase of herbicide tolerant maize, and one application to increase the seed of slow ripening transgenic tomato.

In Belize and the Dominican Republic few trials took place around 1990, and these were undertaken by private corporations maintaining winter nurseries in these countries. The trials were conducted under practices stipulated by APHIS and have been completed. None have been registered since 1992 in either of these countries. With the establishment of regulatory mechanisms in other countries of the region that lend themselves for winter nurseries (e.g. Argentina, Chile, Costa Rica, Mexico), companies now prefer to avoid countries where no formal review process is established, hence the various applications for seed production currently under review in these countries.

Chile also established a National Committee for the Protection of Agriculture (Resolution of 9 October 1993) under the Ministry of Agriculture and is currently considering several applications. Again, none have been authorized since the Committee's establishment late last year. As table 3 shows, Chile, also having recently established a Commission, follows the same pattern as Argentina with many field trials having taken place prior to the establishment of the formal process. Both countries are considering applications for the production of seeds of transgenic tomato.

In Colombia, the Centro Internacional para la Agricultura Tropica (CIAT; International Center for Tropical Agriculture) also applied to the regulatory authorities to field test cassava (marker gene), rice with a marker gene and another rice variety with resistance against a virus (Oja blanca), and a flower (*Stylosanthes guinensis*) with a marker gene and other crops expected to be sown/planted later this year.

Costa Rica formally established a Biosafety Advisory Committee in 1992 (Macaya, 1994) which has reviewed a series of applications that are nevertheless treated as confidential. The Committee rejected two applications in 1993 and is currently receiving several applications. It has not authorized any field trials since the Committee was constituted, although genetically modified plants did get tested in the field in Costa Rica prior to the Committee's establishment (table 3).

In Cuba, field testing has exclusively been done by the Centro de Ingeneria Genetica y Biotecnologia (CIGB). The center was the first to transform sugarcane (Australia followed later) and this is considered a most important achievement by Cuba. The potato trials with PVX, PVY and PLRV are planned to continue in 1995 and novel products are also expected to go to the field next year. Boniato (*Ipomoea batatas*) has been engineered for resistance to "tetuan" (*Cilas formicarius* var. *elegantulus*) and for the improvement of protein content of the tubercles. Also expected for field release in 1995 in Cuba are potato and tobacco lines with hydrolytic enzymes (e.g. glucanases, AP-20) to confer resistance to fungal infections.

Table 3. Field trials in Latin America and the Caribbean[1]

Country/Crop	1987	1988	1989	1991	1992	1993	1994*	Total
Argentina								
Cotton				HT+IR	IR HT+IR	IR		4
Maize				IR M	HT IR	A+HT HT+IR Q		7
Rapeseed					HT	A+HT HT Q		4
Soybean				HT	HT	HT		3
Sugarbeet					HT			1
Wheat						A+Q+M	1	
Subtotal				4	7	9		20
Belize								
Cotton					IR			1
Maize					IR	HT		2
Soybean					HT			1
Subtotal					3	1		4
Bolivia								
Cotton				HT IR				2
Potato				M	Q			2
Subtotal				3	1			4
Chile								
Maize					HT Q	IR 2 HT M	2 HT	8
Sugarbeet						VR+HT		1
Tomato					Q	Q	Q	3
Rapeseed	HT							1
Subtotal	1				3	6	3	13
Costa Rica								
Cotton					IR	IR		2
Maize					IR			
Soybean				HT	HT			2
Subtotal				1	3	1		5
Cuba								
Cabbage						IR		1
Potato						VR	3 VR	4
Rapeseed						M		1
Sugarcane						IR	IR	2
Tobacco					IR			1
Subtotal					1	4	4	9
Dominican Republic								
Soybean				HT				1
Subtotal				1				1

Country/Crop	1987	1988	1989	1991	1992	1993	1994*	Total
Guatemala								
Squash			VR					1
Subtotal			1					1
Mexico								
Maize						FR		1
Potato					VR			1
Squash						4 VR		4
Tobacco							FR	1
Tomato		IR		Q	IR 2 Q	IR	IR Q	8
Subtotal		1		1	4	6	3	15
Grand Total	1	1	1	10	22	27	10	72

* Data to August 1994.

1 A: Agronomic Traits; BR: Bacterial Resistance; FR: Fungal Resistance; HT: Herbicide Tolerance; IP: Industrial Production; IR: Insect Resistance; M: Marker gene(s); NR: Nematode Resistance; Q: Quality characteristics; VR: Virus Resistance.

Table 4. Field trials in Asia (Developing Countries)[1]

Country/Crop	1989	1990	1991	1992	1993	1994*	Total
China							
Pepper (Sweet)					VR	VR	2
Potato					VR	VR	2
Tobacco[2]	VR VR+VR	VR VR+VR	VR VR+VR	2 VR VR+VR VR+VR	2 VR VR+VR VR+VR VR+IR	3 VR VR+VR VR+VR VR+IR	21
Tomato				IR	IR VR+IR	IR VR+IR	5
Subtotal	2	2	2	5	9	10	30
Thailand							
Tomato					Q	Q	2
Subtotal					1	1	2
Grand Total	2	2	2	5	10	11	32

* Data to August 1994.

1 A: Agronomic Traits; BR: Bacterial Resistance; FR: Fungal Resistance; HT: Herbicide Tolerance; IP: Industrial Production; IR: Insect Resistance; M: Marker gene(s); NR: Nematode Resistance; Q: Quality characteristics; VR: Virus Resistance

2 A double construct in tobacco for virus resistance (TMV and CMV) in 1994 occupies around 35 ha for seed multiplication.

Table 5. Field trials in Asia (Industrialized Countries)[1]

Country/Crop	1988	1989	1990	1991	1992	1993	1994*	Total
Australia								
Apple							M	1
Carnation					2 HT+Q		HT+Q	3
Chrysanthemum						Q		1
Clover							2 HT+Q	2
Cotton					IR	2 IR	4 IR HT	8
Potato				VR	A	A VR	A VR	6
Rapeseed					A			1
Sugarcane						M		1
Tea Rose							Q	1
Tomato					Q	Q		2
Subtotal				1	6	7	12	26
Israel								
Tomato[2]				VR	VR	VR	VR	4
Subtotal				1	1	1	1	4
Japan								
Petunia						VR		1
Potato							VR	1
Rice						2 VR	Q	3
Tobacco				VR			VR	2
Tomato				VR				1
Subtotal				2		3	3	8
New Zealand								
Asparagus	M							1
Broccoli			HT					1
Kiwi				HT				1
Maize						IR		1
Potato	HT 2 M	2 HT 2 M	HT VR		VR	VR		11
Subtotal	4	4	3	1	1	2		15
Grand Total	4	4	3	5	8	13	16	53

* Data to August 1994.

1 A: Agronomic Traits; BR: Bacterial Resistance; FR: Fungal Resistance; HT: Herbicide Tolerance; IP: Industrial Production; IR: Insect Resistance; M: Marker gene(s); NR: Nematode Resistance; Q: Quality characteristics; VR: Virus Resistance.

2 1991: Field trial; 1992-1994 in net houses.

Table 6. Field trials in Africa[1]

Crop	1990	1991	1992	1993	1994*	Total
Egypt						
Potato		M				1
Subtotal		1				1
South Africa						
Rapeseed				HT		1
Cotton	HT	HT	IR	2 IR		5
Forage (Lucerne)				HT		1
Maize				HT		1
Strawberry					HT	1
Subtotal	1	1	1	5	1	9
Grand Total	1	2	1	5	1	10

* Data to August 1994.
1 HT: Herbicide Tolerance; IR: Insect Resistance; M: Marker.

Guatemala has been listed as a country where a squash trial took place in 1989. It appears, however, that the company performing this trial used its long-time winter nursery to multiply squash seed in a controlled greenhouse (net house). This trial has been listed in table 3 although some people argue that this should not be considered a field trial.

In Peru, the Centro Internacional de la Papa (CIP; International Potato Center) has been the subject of many rumours regarding possible field releases in the Andean region, particularly Peru and Bolivia, and in Africa. CIP did conduct a trial in a controlled greenhouse (net house) in Bolivia in 1991 but not in other countries. Currently, applications for field trials are being considered by the Peruvian, Egyptian and Tunisian regulatory authorities and these releases may take place, if permission is granted, in 1995. The inserted genes are for non-conventional virus resistance (coat protein of PRV, PRX and PRSV), insect resistance and bacterial resistance, although not all of the above genes are present in one single genotype.

CIAT in Colombia and the Centro Internacional de Mejoramiento de Maiz y Trigo (CIMMYT; International Wheat and Maize Improvement Center) in Mexico follow similar patterns to CIP. Both centres—as well as certain other institutes of the Consultative Group on International Agricultural Research (CGIAR)—are currently working with transgenic material in the laboratory and confined glasshouse, but it is the CGIAR's policy to only test in countries where formal authorization has been obtained. CIMMYT, for example, was seeking a permit—and obtained it—for importing transgenic maize calli for laboratory research (Carreón Zúñiga, 1994).

5.2 Asia and Australasia

In the developing countries of Asia, only China and Thailand have tested genetically modified plants (table 4). In China, the total number of sites varies but is generally very high. The virus resistant tobacco, tomato and potato trials of 1993 and 1994, for example, were tested in 15, 4 and 2 provinces respectively, at a few dozen locations each. Thailand is currently reviewing several applications, among them two separate applications for tomato seed increase with delayed ripening characteristics. Thailand expects to test a papaya ringspot virus (PRSV) resistant papaya shortly.

Of the industrialized countries of Asia and Australasia, Australia and New Zealand registered the bulk of trials with virus resistance and herbicide tolerance accounting for 25 per cent and 23 per cent of the characters tested (table 5).

5.3 Africa

Little activity has taken place in Africa so far and the only confirmed trials have been undertaken in South Africa and Egypt (table 6). As stated above, CIP filed field trial applications in Tunisia and Egypt. It is expected, however, that applications for cassava will soon be filed in several countries.

It is noteworthy that much of the information obtained during this study about field trials in Africa appear to be erroneous. First, when the source of the data was questioned on the institution that supposedly carried out the trial(s), this information was either "non-disclosable" or the data did not stand up to scrutiny. Second, some information even referred to field trials with crops where genetic transformation has not been successful at the time when the field trial(s) were claimed to have taken place (e.g. certain species of *Phaseolus*).

6. Conclusions and outlook

Biotechnology to date has established an excellent safety record and biosafety regulations have served an

important function in this regard by requiring from applicants substantial information on organisms for which environmental trials are sought. This process identifies the most likely problematic aspects of tests prior to environmental exposure. For regulators, the initial, small-scale tests are easily accommodated. At that stage the emphasis is on safety, which can be achieved through a combination of separation, physical barrier to transference, or sterility.

Many systems, such as the APHIS guidelines of the USA or the Philippine regulations specify four or five levels of isolation based on potential environmental threats. For APHIS, confinement "verifies that the pathogenic potential contained in the construction of the organism or performance of the field test has been removed, or will be contained" (McCammon and Medley 1990). The resultant difficulty is the absence of safety information generated from isolation trials, which can be used to structure subsequent, less restrictive ones. That limitation is compounded as products approach the commercialization stage when the multiple trials noted above are required. Isolation for multiple trials is neither feasible nor appropriate.

Initial trial protocols are sufficiently controlled to prevent most large-scale problems and this process seems well established and incorporated in legislation in a range of countries. Where the system is not as well refined is in characterizing the steps from initial, contained trials through to full commercial release. Yet this is the most critical issue for release as that level implies full exposure to the environment. Further conceptualization of this final stage is required to assure protection while not placing unnecessary delays on the adoption of appropriate biotechnology applications that may reduce the need for toxic chemical pesticides and increase production without the need for increased inputs.

Acknowledgements

I would like to extend my gratitude to a host of colleagues around the world—too numerous to mention—for supplying me with data in a short time and for openly sharing with me relevant information. Particular thanks go Peter Kearns, Patricia Ahl Goy, Chen Zhang-Liang, John H. Payne and Maria Antonia Fernandez for helpful discussions and for providing essential information.

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B. NEWS AND EVENTS

UNIDO news

UNIDO on the World Wide Web

Looking for UNIDO information? You could save time and resources by checking the UNIDO World Wide Web server (http://www.unido.org) first (figure 1, The UNIDO homepage). This attractive, user-friendly information service allows users with an Internet connection and a "World Wide Web Browser" such as Netscape (TM) or Mosaic (TM)—to access UNIDO's growing collection of public information, services and information products with unprecedented convenience.

Efficient and convenient information dissemination

The World Wide Web revolution

In 1992, when the European Laboratory for Particle Physics (CERN) introduced the World Wide Web, the number of computers connected to the Internet (hosts) reached one million. The need to memorize a myriad of computer commands, codes and "internet addresses" had been alleviated somewhat by earlier developments such as Archie (Peter Deutsch, Alan Emtage, and Bill Heelan at McGill University, 1990) and Gopher (Paul Lindner and Mark P. McCahill from the University of Minnesota, 1991). With the advent of the World Wide Web, navigating the ever-growing international network of computerized public information resources was as simple as selecting highlighted text called "hypertext links". Information resources that were once the domain of a relatively small group of specialists, students and the technically ambitious were now within the reach of a growing, interdisciplinary "global information culture". By 1995, the number of Internet hosts had exceeded 6 million.

Hypertext and the URL

A key ingredient to the success of the World Wide Web is its use of the Hypertext Markup Language (HTML), which allows the location of a very specific item of information, anywhere on the Internet, to be pinpointed and presented to the user as a line of text. The location is specified with a "uniform resource locator (URL)", which looks something like: http://www.unido.org/start/new/navigator.htmls (or the What's New Page of the UNIDO WWW server). Using HTML, this URL can be linked to the words "What's New?" so that the user may jump to this "page" of information by simply selecting the phrase, "What's New?". On most computers, this is done with a "pointing device" (a "mouse", for example).

Efficient information dissemination

Using the WWW saves time and resources. Information can be published while it is still current, quickly and efficiently. For example, during the UNIDO General Conference in December 1995, press releases and a journal of each day's proceedings were published nightly and distributed to Member States, the international press and the general public. A marked increase in usage of the UNIDO WWW server was noted during this period and could be directly attributed to this activity

The potential benefits to the environment are immediately obvious. Since the UNIDO WWW server was opened to the public on 6 October 1995, over 222 million bytes of information have been transmitted. Given that the average size (including the UNIDO logo) of a document on the UNIDO WWW server is about 4.5 kilobytes per page, over 49,000 pages of information have been distributed by UNIDO without paper. Of course, many WWW documents are printed on paper after they have been received, but when one considers the number of copies of a published document that must be printed to reach 49,000 readers, these figures become even more compelling!

A structured, user-friendly approach

Every effort has been made to keep the UNIDO WWW server as clean and consistent as possible. An automated document management system, designed and executed especially for UNIDO, makes it possible to efficiently manage a steady flow of new submissions—since September 1995, with only two staff members working on the server full-time, over 200 documents have been published.

One big full-text database

From the very first menu, the user is presented with a hypertext "search button" which allows every document on the server to be located by words from its text (figure 2, The UNIDO WWW server's search facility).

Navigational aids

In the early stages of the UNIDO WWW server's design, a "corporate image" for UNIDO WWW documents was developed, which included such amenities as a "clickable table of contents", links to previous document menus and other related points of interest, and the electronic mail address for the responsible officer. Every document that enters the UNIDO WWW server receives this corporate image via a set of automated procedures. In the future, changing the corporate image for all documents on the server will be automated as well (figure 3, a sample document on the UNIDO WWW server).

The structure of the server is clearly defined by a set of hierarchical arranged menus. Users who want to jump directly to a specific menu may simply select the text "outline" to jump to a "clickable outline" of all menus on the server (figure 4, The "clickable" outline).

Getting the right message to the right person

Clickable e-mail addresses

Every document on the server has a set of electronic mail contact addresses at its end. With most WWW browsing software—including Netscape (TM), Mosaic (TM), Lynx and others—the user may direct a message to the appropriate officer simply by selecting the hypertext link containing the e-mail address.

Online forms

Many points of interest on the UNIDO WWW server (for example, the India Intechmart -http://www.unido.org/services/ip/ipopportunities/ipmeetings/ipmeetings14.htmls) use "HTML forms" to assist the user in structuring

their reply to the relevant officer. If the user finds it impossible or inconvenient to fill out the form "online", an alternate version may be printed out and sent by mail or fax (figure 5, an online registration form).

Plans for the future

Downloadable information products

1996 will see the arrival of several downloadable "product samples" on the UNIDO server. Two such anticipated products are UNIDO's statistical databases and feasibility studies software (COMFAR).

Databases

Research and development is currently under way to make many of UNIDO's databases accessible to the WWW public. Especially important is the work under way to make Micro CDS/ISIS databases searchable via HTML forms. This groundbreaking work is being undertaken by UNIDO, in co-operation with other entities, including UNESCO (the maker of ISIS) and the Institute for Computer Information Engineering (Warsaw, Poland).

Addressing the whole Internet

Even given the benefits offered by the WWW, care must be taken to accommodate those who, by choice or necessity, still use older methods to retrieve documents via the Internet (E-mail, Gopher). To this end, all documents on the UNIDO WWW server are stored twice—once in the UNIDO "corporate image" framework, and once in the simplest possible HTML form, so that conversion to simpler formats (preformatted ASCII) can be automated and delivery via electronic mail and Gopher will be possible at a future stage in this fledgling (but extremely promising) information service's continuing development.

Selected references

Hobbes' Internet Timeline v2.2
http://info.isoc.org/guest/zakon/Internet/History/HIT.html

Summary of the Results, Second TIC/MIDS Internet Demographic Survey
http://www1.mids.org/ids2/ids2.504

For further information, please contact Robert Bullington at UNIDO on rbullington@unido.org

Figure 1

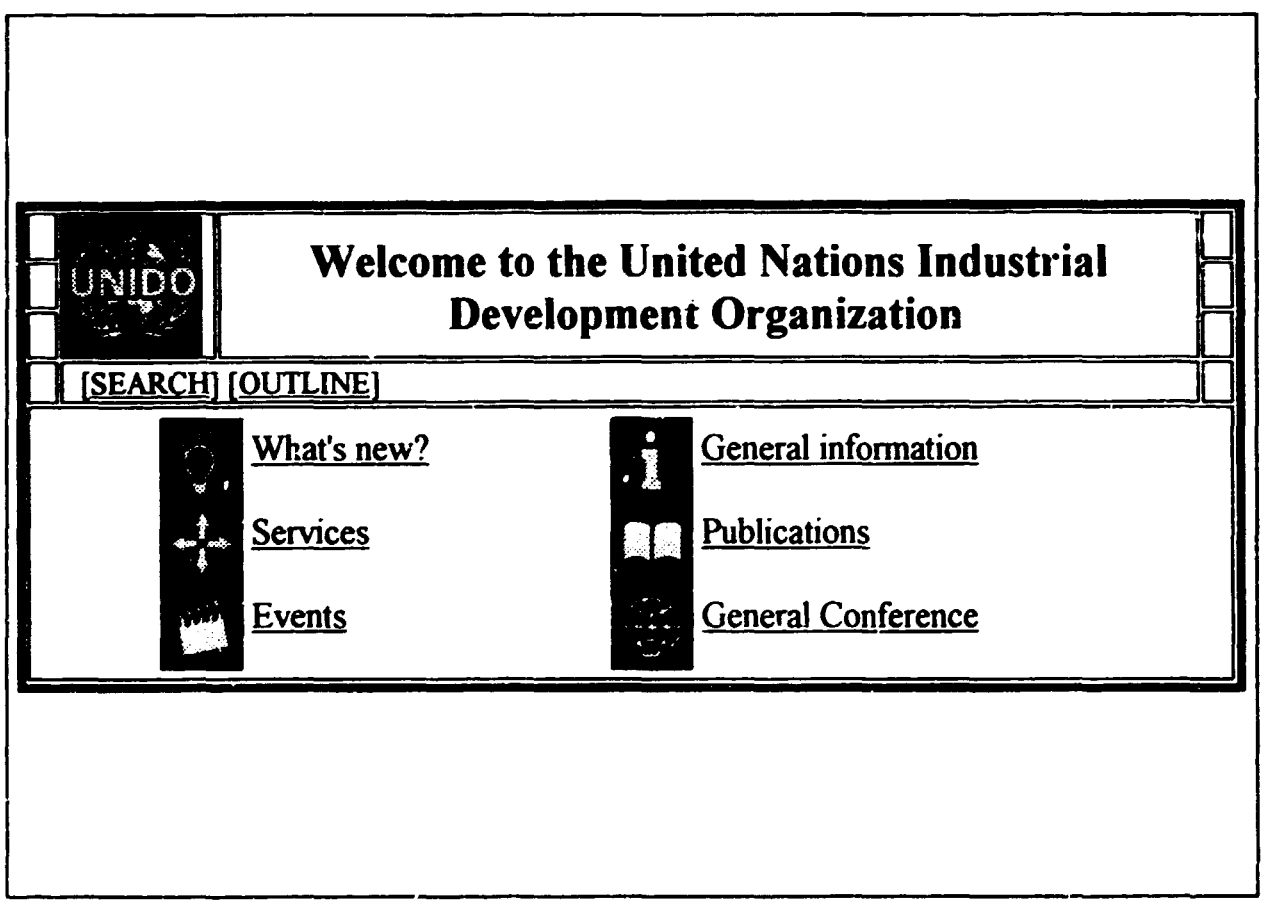

Figure 2

WAIS Gateway

This is a searchable index of information.
Note: *This service can only be used from a forms-capable browser.*

Enter keyword(s):

Here is the result of your search using the keyword(s) "**investment**":

1: Contacts
Score: **1000**, Size: **596 bytes**, Type: **Server parsed HTML file**
2: Registration Form - Comesa Forum
Score: **575**, Size: **1 kbytes**, Type: **Server parsed HTML file**
3: COMFAR 2.1, Computer Model for Feasibility Analysis
Score: **393**, Size: **1 kbytes**, Type: **Server parsed HTML file**
4: Preparation of pre-investment studies
Score: **303**, Size: **1 kbytes**, Type: **Server parsed HTML file**
5: Sri Lanka Investment Meeting
Score: **242**, Size: **7 kbytes**, Type: **Server parsed HTML file**
6: Investment Bonanza in Sri Lanka
Score: **212**, Size: **2 kbytes**, Type: **Server parsed HTML file**

Figure 3

[SEARCH] [END] [CONTENTS] [FIRST] [IP-MEETINGS] [FORTHCOMING]

INDIA INTECHMART 1996

New Delhi, 17-20 February 1996

Contents

Figure 4

UNIDO WWW Server - Clickable Outline

- What's new?
- Services
  - Industrial policies and private sector development
  - Operational support for sectoral development
  - Investment Promotion
    - Investment Bulletins
    - Investment Opportunities
      - Investment Promotion Meetings
      - Investment Climate
      - Investment Projects
    - Pre-Investment Services
      - Feasibility studies software and methodology
    - Investment Promotion Service Offices
    - Investment Promotion Agencies
    - World Investment Network Service
  - Technology for competitiveness
  - Environment and Energy
    - Environmental Awareness Bulletin
    - Cleaner Production
  - Human resource development
  - Women in industrial development
  - Enterprise restructuring and privatization
  - Small- and medium-scale industry and rural industrial development
    - Small and Medium Enterprise Resource Locators
  - Quality, standardization and metrology
  - Industrial information

Figure 5

INDIA INTECHMART

Oganized in co-operation with the Ministry of Industry of India
New Delhi, 17-20 February 1996

REGISTRATION FORM

Name:

Position:

Organization:

Full contact address:

Fax: E-mail:

Tel: Telex:

UN and other organization's news

Global IPM facility announced

A new Global Integrated Pest Management Facility has been formed as a joint effort of the UN Food and Agriculture Organization (FAO), the UN Development Programme (UNDP), the UN Environment Programme (UNEP) and the World Bank. The facility will fund projects that support low chemical, participatory approaches to pest management and "help reduce excessive and costly pesticide use, which poses a threat to both human health and the environment".

The Integrated Pest Management (IPM) Facility's activities will begin with a set of pilot projects in selected areas where a pest outbreak has occurred, where pesticides are used excessively and are not proving effective, and where IPM based on ecological pest management is likely to produce immediate, substantial and quantifiable benefits. The first Facility projects will focus on vegetable production in Kenya, cotton in Zimbabwe, and control of striga (a parasitic plant pest of sorghum, millet and other crops) in West Africa. Other projects under proposal include rice in Madagascar, vegetables in West Africa, Trinidad and Viet Nam, and cotton in China.

The three UN agencies and the World Bank have been working to establish the Facility for more than a year in consultation with IPM practitioners and NGOs. Creation of the Global IPM Facility was strongly endorsed by meetings of an inter-agency task force on IPM as well as the FAO/UNEP IPM Experts Panel. The Facility is seen as a means of implementing parts of the 1992 United Nations Conference on Environment and Development's Agenda 21 calling for programmes that put IPM within reach of farmers through networks of farmers, researchers and extension services.

The IPM Facility will be staffed by a small group of professionals with extensive international experience, technical skills, project implementation expertise and recognition by international research, development and donor communities. It will be hosted by the FAO, while drawing on existing networks of individuals, agencies and NGOs.

Key activities of the IPM Facility will include:

- Identifying specific scientific, technical, social and political constraints affecting IPM implementation, and proposing means of removing these constraints;
- Facilitating collaboration among national policy makers, development agencies and NGOs on planning and implementing IPM activities;
- Stimulating development of improved IPM concepts and practices through research that increases participation of farmers, extensionists and on-farm researchers;
- Identifying and assisting in preparation of high priority pilot and large-scale projects for investment by national, bilateral and multilateral sources;
- Documenting and evaluating IPM pilot projects and other experiences to provide best practices, policy and management options; and
- Advising national programmes on design, implementation and evaluation of IPM programmes.

(Source: *Global Pesticide Campaigner*, Vol. 5, No. 2, June 1995)

Chemical trade guide

The United Nations Environment Programme has issued a code of ethics to enhance safety in international chemical trade. This voluntary guide to standards of conduct sets out the chemical industry's commitment to improved health, safety and environmental protection; reduced risks; testing and assessment; periodic monitoring and follow-up. *Code of ethics on the international trade in chemicals* is available from UNEP Environmental Law and Institutions Programme Activity Centre, P.O. Box 30552, Nairobi, Kenya.

Electronic conferences on genetic resources

The UN Food and Agriculture Organization (FAO), through the International Conference and Programme for Plant Genetic Resources (ICPPGR), is organizing the Fourth International Conference on Plant Genetic Resources, to be held in Leipzig (Germany) on 17-23 June 1996. A Global Plan of Action for the conservation and sustainable use of plant genetic resources is currently being prepared, and will be presented for consideration and adoption at this Conference. The Global Plan will, among other things, propose policies and strategies for conservation, and for the strengthening of national capacities. Furthermore, it should ensure an optimal use of the available funds in accordance with Agenda 21, and provide a framework through which farmers' rights can be realized.

To promote the broadest participation in the preparation process for the FAO Report on the State of the World's Plant Genetic Resources, which will form the basis of the draft Global Plan, an electronic Bulletin Board Network (BBN) has been established to allow interested organizations and individuals to contribute to this process. BBN will provide a number of discussion groups on different topics (such as collections, genetic diversity, training and education, crop improvement and plant breeding), as well as access to documents, reports and databases. Contacts: for ICPPGR activities: ICPPGR@fao.org; for BBN: samy.gaiji@fao.org (Source: *Biotechnology and Development Monitor*, No. 23, June 1995)

United Nations chlorine phase-out sought

A coalition of 71 environmental groups and citizens is petitioning the United Nations to implement a world-wide phase-out of persistent organochlorine chemicals such as DDT, polychlorinated biphenyls, heptachlor, and chlordane.

Greenpeace released a report alleging serious damage to human reproductive systems from organochlorines, saying that infertility birth defects, and several cancers are linked to exposure to the chemicals.

Led by the Department of the Planet Earth, the groups petitioning the UN are targeting the third and final meeting in Washington in November 1995 of government-appointed experts on marine environment protection, impanelled as part of the Agenda 21 agreements from the UN's 1992 Earth Summit in Rio. The groups cite numerous studies of organochlorines that find them ubiquitous and that link them to deaths of coral reefs and marine mammals and to health effects in animals and humans.

The petitioners are seeking a phase-out similar to the Montreal Protocol on chlorofluorocarbons. They want the UN to affirm the antichlorine recommendations of the International Joint Commission; draft a phase-out and sunset plan targeting semi-volatile, bioaccumulative, and persistent organochlorine pesticides, chemicals, and by-products; negotiate with producing and consuming countries; convene an international convention to negotiate

a phase-out protocol; and levy a tax on organochlorine chemical production. (Source: *Chemical Week*, 7 June 1995)

Social issues

Nuffield Council on Bioethics: who owns human tissue?

A working group of seven UK medical and legal experts has published a report focusing on the ethical issues surrounding the question: who owns samples of human tissue once they have been removed from a patient's body? The Nuffield Council on Bioethics, in its report *Human Tissue: Ethical and Legal Issues*, comes to two linked conclusions: (1) a patient has no claim to such tissue; but that (2) hospitals, tissue banks and other organizations removing and storing such tissues should not be allowed to deal in such tissues for profit. Details from: Nuffield Council on Bioethics, 28 Bedford Square, London WC1B 3EG. (Source: *Biotechnology Bulletin*, May 1995)

European Patent Office on ethical aspects of biotechnological patents

Regulators, not patent offices, must take prime responsibility for the ethics of biotechnology, according to the European Patent Office (EPO) in Munich. The EPO's landmark ruling, reported in the 18 April 1995 issue of *FT Business Law Europe*, comes in the wake of a number of major controversies in which patent applications have been opposed--some successfully—on the basis that they violate the morality provisions of European patent law. Harvard's Oncomouse was granted a patent, the EPO having weighed up animal suffering and the risks to the environment against the potential benefits of the "invention" to mankind.

By contrast, it rejected an application where the genetic manipulation of an animal was for research into hair growth in the bald.

The latest decision could cut down on the large number of biotechnology patent applications that are opposed on morality grounds—a process that causes significant delays in Munich. The decision should pave the way for greater certainty for applicants across the biotechnology industry.

The latest EPO ruling came in the context of a case concerning Plant Genetics Systems' claim for a patent on a genetic engineering procedure for producing herbicide-resistant plants.

The decision on whether to grant a patent usually has to be made well before any thorough testing and evaluation of the invention's risks and safety has been carried out. In most cases, the EPO suggests, it would be better to defer the morality assessment to the growing number of regulatory authorities and other bodies that are responsible for ensuring that patents are used lawfully. Details from: FT Business Law Europe, 40 Anson Road, London N7 0AB or Tel.: 0171 700 7387, Fax: 0171 700 3734. (Source: *Biotechnology Bulletin*, May 1995)

Biosafety issues

European Federation of Biotechnology (EFB)—initiative on safety in biotechnology

The Institute for Applied Microbiology at the University of Agriculture and Forestry in Vienna (Austria) is actively involved in the activities of the Working Party for Biosafety of the European Federation of Biotechnology, at the organizational level. Some of the activities of the Institute which are of particular interest are:

- Establishment of institutional and participation in national biosafety committees.
- University biosafety education at the Institute for Applied Microbiology at the University of Agriculture and Forestry: "Pathogenic Species and Biosafety", a one-week course.
- The Working Party for Biosafety of the European Federation of Biotechnology (Web link available soon).

The terms of reference of the Working Party are to provide recommendations on the safety aspects of biotechnology with respect to the environment, the public, personnel and products. This shall be accomplished by the following:

1. To identify and monitor hazards associated with various applications in biotechnology.
2. To assess and quantify risks.
3. To provide an international platform for issues related to safety in biotechnology.
4. To produce statements and recommendations (based on science and technology).
5. To identify areas of insufficient knowledge or inadequate technology with respect to safety in biotechnology and to propose research and development in such areas.
6. To assist in the implementation of the recommendations and guidelines on safety in biotechnology.

The Working Party will meet regularly, in principle twice yearly. The regular meetings are attended by the Working Party members and the official observers. In 1993 16 countries and three organizations (WHO, EEC, OECD) were represented by 30 members. Sometimes guests are invited to give presentations on particular topics. Several committees have been set up following the identification of problems and subsequent definition of tasks.

In its efforts to further the understanding of safety aspects in biotechnological operations and to improve international harmonization, the Working Party has started a series of reports entitled "Safe Biotechnology" (Parts 1-5). Further publications are to be issued in:

- The EFB Newsletter
- Specialized scientific journals
- Scientific review journals (to address non-specialist scientists)
- Popular journals (to address interested population at large)

Where applicable, this will be done in cooperation with the Task Group on Public Perception.

The Working Party organizes workshops and symposia on its own initiative or in collaboration with national organizations, e.g. in the Biotechnology Symposium Paris (1988), ADEBIO-Grenoble (1989), Comett-Paris (1989), ECB5-Lingby (1990) and ECB6-Florence (1993).

The objective of the Working Party is to help maintain the excellent safety record of biotechnological operations through its activities and by creating an information network through its national members and members from international organizations.

For further information contact: Dr. Otto Doblhoff-Dier, Institute for Applied Microbiology, University of Agriculture, Nussdorfer Lände 11, A-1190 Vienna, Austria. Tel.: +43-1-3692924-464, Fax: +43-1-3692924-400. Source: *BINASNews*, Vol. 1, Iss. 3, 1995)

Process towards biosafety harmonization launched in Southern and Eastern Africa

The Southern and Eastern Africa (SEA) countries (Botswana, Ethiopia, Kenya, Malawi, Mauritius, Mozambique, Namibia, South Africa, Swaziland, Tanzania, Uganda, Zambia and Zimbabwe) have decided to take a regional approach in addressing the issue of safety in biotechnology. The SEA countries are at various stages of trying to integrate biotechnology into their agricultural, medical and industrial research programmes. This belated entry into biotechnology has both benefits and disadvantages in its own right.

The disadvantages include the fact that most "easy" projects in biotechnology have now been "picked over" and a number of the resulting products and processes have been patented. Those who entered biotechnology early have already commercialized some of their activities.

One of the advantages of late entry is that the global experiences with genetic engineering have shown that some of the earlier fears of potential disasters that could arise from genetically-modified organisms (GMOs) have proved to be unfounded. Those entering biotechnology can now look at safety in the conduct of biotechnology from a better-informed perspective. Biotechnology experimentation can now be carried out with due attention to biosafety considerations that are more real than imagined.

With the assistance of grants from the Special Programme for Biotechnology of the Ministry of Foreign Affairs of The Netherlands, a Regional Focal Point on Safety in Biotechnology (RFP/SB) has been established in the Biotechnology Research Institute of the Scientific and Industrial Research and Development Centre (SIRDC). The RFP/SB is also funded by the Biotechnology Advisory Commission (BAC) of the Stockholm Environment Institute.

The RFP/SB is manned by a Programme Officer who coordinates a regional network on biosafety issues. Each country has designated a representative who will operate a national focal point to coordinate biosafety issues within the country. The country representatives meet at the Regional Focal Point at set intervals to initiate and discuss approaches to managing biosafety issues regionally, and to propose a set of biosafety guidelines whose adoption they can promote in their own country. It is up to each country to finally adapt a chosen set of guidelines to its own use.

The importance of harmonizing biosafety guidelines on a regional basis lies in the fact that the SEA countries have considerably similar flora and fauna. There is considerable similarity in biodiversity and in a number of agro-ecological phenomena. This raises the probability that a violation of the agro-ecological system or the introduction of a GMO that is harmful to humans and the environment in one country, is quite likely to have its effect spill over into neighbouring countries. The planned harmonization of biosafety guidelines will thus have a mutually protective effect.

The planned sharing of experiences stands to benefit members of the network. For example, it is very likely that those countries who lag behind in drafting their biosafety guidelines will be assisted by those which are ahead of them. The network also plans to tap on the expertise of advanced countries in using established biosafety databases and in evaluating potential, planned releases of GMOs into contained facilities or into the field. It is further expected that this network will have the synergistic effect of stimulating the transfer of biotechnology expertise to the SEA countries. Further details from Chris J. Chetsanga and Joy Chigogora, Regional Focal Point on Safety in Biotechnology Institute, Scientific and Industrial Research and Development Centre, Harare, Zimbabwe. (Source: *BINASNews*, Vol. 1, Iss 3, 1993)

The objectives and strategy of BATS

A Priority Programme on Biotechnology was initiated by the Swiss National Science Foundation in 1992. The Programme interfaces basic research with product development, links activities carried out by various universities and institutes, and brings together scientific research, the Government and partners from industry. The setting of relevant research priorities should promote an appropriate diffusion of technology in Switzerland. One of the key objectives has been the initiation of biosafety research in the country. As a core project, the Agency for Biosafety Research and Assessment of Technology Impacts, BATS, started its activities in Basel at the beginning of 1993.

A survey of institutions and individuals expressing a need for information on biotechnology impacts suggested that there was a broad spectrum of topics that had to be addressed. It also revealed that the subjects of the survey had a wide range of knowledge on biotechnology.

In summary, a distinct need for evaluated knowledge on technology impacts was apparent. The availability of evaluated knowledge on technology impacts seems to be a prerequisite for the timely risk/benefit assessment of an evolving technology and for the implementation of adequate regulation.

There are two main sources of knowledge related to technology-impact issues, scientific data and what might be called "practical knowledge". They can be made available, on the one hand, by technology-impact research and technology assessment, and on the other hand, by electronic data processing. Thus, information management becomes a key activity because the knowledge required to meet the information needs is scattered and the amount of scientific and practical knowledge is huge and not easily accessible.

BATS has formulated its strategy on the basis of the information needs outlined above. The implementation of this strategy rests on two main elements:

- Technology assessment (TA) and
- An Information and Documentation (I&D) Service.

Technology assessment is considered to be a concept for a comprehensive approach to estimating the impacts of biotechnology. In this respect, the contributions of BATS are the following:

- Research on TA methodology;
- Research on biological and technical impacts (e.g., safety and ecological impacts);
- Coordination of research on economic, social, ethical and other impacts;
- Coordination of TA studies;
- Teaching related to TA (methodology, case studies).

In addition, BATS processes and transfers relevant knowledge concerning biosafety and technology impacts, while the focus of its activities is the acquisition and distribution of data on biotechnology benefits and impacts. The realization of these objectives is sought through:

(a) An Information and Documentation Service covering:

- International and biosafety research projects and relevant scientific literature;
- Regulations, guidelines and publicly accessible information on regulatory procedures;
- Reports on international meetings; and
- Technology impact assessment studies.

(b) Disseminating scientific information on biosafety and technology impacts by:
- Structuring, reviewing and summarizing scientific knowledge on particular topics;
- Teaching; and
- Organizing workshops and meetings.

A corresponding database functions as the centre of the I&D Service, where the processed knowledge is stored. The maintenance of the database involves networking possible suppliers, and an interactive relationship with users is being sought in order to gauge service efficiency and keep pace with evolving needs.

Further details available from Agency for Biosafety Research and Technology Assessment of the Swiss Priority Programme Biotechnology (BATS), Clarastrasse 13, CH-4058 Basel, Switzerland. (Source: *BIOASNews*, Vol. 1, Iss. 3, 1995)

General

Nanotechnology and biotechnology

In the development of nanotechnology, the interface between biology and technology will be hugely important. The acquisition of the tools of nanotechnology will be part of the next phase of evolution of biotechnology; without them many aspects of biological functions will remain unexplored.

It is becoming increasingly obvious that systems that combine biological and chemical molecules on the one hand, and physical devices and electrodes on the other, have a huge potential in many applications. However, the fragility of the biological systems that are readily manipulatable (cells, tissues) has meant that biotechnology's efforts to interface with physical systems have, thus far, been crude. Researchers can entrap cells in polymeric matrices or juxtapose slices of tissue and sensor surfaces. Using micromanipulative techniques, biotechnologists can even move individual cells and organelles around. At the molecular level, however, they have had to be content with manipulating populations of molecules.

Nanotechnology is changing that. Physicists and chemists have developed tools that operate at dimensions similar to those of biological macromolecular structures. Much of the progress in the biological application of nanotechnology will depend on using them.

Physical methods for observing and manipulating single molecules lie at the heart of all nanotechnology. Scanning tunnelling microscopy (STM) and atomic force microscopy (AFM) were both first applied to observe nanostructures of polymers in chemistry and to resolve structures around the angstrom level. In the last few years, there have also been many papers dealing with the observation of biological molecules and macromolecules (DNA, proteins) and, in the case of AFM, even of live cells.

Nanotechnology demands the organization of atoms and molecules in two- or three-dimensional space. Once an organizing framework has been established, molecules or atoms may subsequently be allowed to self-assemble around or within it. As the microelectronics industry has demonstrated, physical techniques can be used to provide the framework for this organization through the fabrication and machining of silicon materials. Arranging atoms through the use of nanomanipulative technologies is, in essence, just an extension of the manipulation. This approach to the production of a framework is closely linked to the ability to observe both the manipulations and the resulting structures, and there is clearly a reciprocity between the two.

Organizing frameworks could, however, also be self-assembling structures. This is familiar territory to biologists; phospholipid bilayer membranes are, perhaps, the best example, but some proteins and nucleic acids, too, can be thought of as self-assembling entities. And if vaccines can be thought of as machines for stimulating the immune system, then biologists have already developed self-assembling protein/nucleic acid nanodevices that are at least somewhat artificial.

Progress in nanotechnology has meant that there is now almost no clear border between (bio)chemistry and physics. Biotechnologists have depended, to a great extent, both in research and in the development of products, on their ability to constrain macromolecules. One only has to think of affinity chromatography, ELISA, and solid-phase synthesis or sequencing to understand how useful it is to be able to restrict the position of just one macromolecule in space. Now, through nanotechnology, biotechnologists can start to control two (or possibly more) interacting entities. Nanotechnology can also provide considerable insights into catalysis. In 1993, a group at the University of Liverpool used STM to study the oxidation of carbon monoxide at the surface of an oxygen-covered rhodium surface (the process is related to the catalytic removal of carbon monoxide from exhaust fumes).

Nanotechnology can provide biotechnology with a direct way of following a biocatalytic reaction by studying a very limited number of molecules. It should be possible, not only to describe the activity globally and numerically, but also to obtain information about the mechanistic aspects of the catalysis.

At some point in the near future, as a result of nanotechnological approaches, biochemistry will have to reconcile its descriptions of the behaviour of single molecules with the descriptions we already have (affinity, for example) for interactions of populations. There will be a period of transition before these ways of thinking about the biological world come together, just as there was in reconciling quantum and classical physics. (Extracted from *Bio/Technology*, Vol. 13, May 1995)

Biopiracy costs South $5.4 billion annually

According to a study released by the United Nations Development Programme (UNDP), developing countries would be owed as much as US$5.4 billion if they were compensated only 2 per cent in royalties for global seed industry sales of $15 billion and 20 per cent for pharmaceutical products derived from indigenous plants and knowledge. The 1994 report, *Conserving Indigenous Knowledge: Integrating Two Systems of Innovation**, by the Rural Advancement Foundation International (RAFI) for UNDP, contends that an estimated 80 per cent of the world's population depends on indigenous knowledge to

**Conserving Indigenous Knowledge: Integrating Two Systems of Innovation*, UNDP, 1994; Diversity, Vol. 10, No. 4, 1994. Contact: RAFI, Box 655, Pittsboro, NC 27312; Tel.: (919) 542-1396; Fax: (919) 542-2460; email rafiusa@igc.apc.org. To obtain a copy of the report: UNDP, Bureau for Policy and Programme Support, One United Nations Plaza, New York, NY 10017, Tel.: (212) 906-5312.

meet their food and medicinal needs. However, recipients of these benefits do not provide adequate compensation, involvement in decision-making or even recognition of this indigenous knowledge. The report includes a list of over 100 cases where the North has benefited from the South's resources, such as the case of Ethiopian barley derived from local farmers' varieties, which is worth US$150 million in the USA alone each year.

Industry's use of raw materials and indigenous knowledge is made worse by the growing use of patents which give protection to multinational corporations and Northern researchers for materials or knowledge that originated in the South. In the report, RAFI charges further that industrialized countries patent material derived from farmers' varieties, and as companies move into seed markets in developing countries, indigenous farmers "are finding themselves paying for the end product of their own genius". The report maintains that indigenous knowledge has not been simple accumulation, but rather the result of a "dynamic cooperative innovation system which continues to work ... and offer hope for planetary survivial. To destroy or ignore this system would ... deprive the world of one of its main sources of innovation and diversity".

The report outlines specific steps to strengthen active participation of indigenous people and their communities in formulation of policy, laws and programmes related to such issues as resource management. Recommendations include: considering further study of inventors' certificates and material transfer agreements; evaluating the possibility of a trust fund from remuneration of indigenous knowledge; establishing model agreements for Governments, corporations and indigenous communities; and convening a meeting with indigenous organizations and information experts to discuss needs and means for safeguarding development and exchange of indigenous knowledge. (Source: *Global Pesticide Campaigner*, Vol. 5, No. 2, June 1995.

AIDS prevalence in Europe: forecasts to 2010

There is no cure yet for AIDS. Treatments such as Wellcome's AZT and Roche's Videx slow down the replication of the virus, thus prolonging the life of the patient. As a result, whereas ten years ago the life expectancy of a patient diagnosed as carrying the AIDS virus was less than four months, now the average life expectancy is closer to two years. Two predictions from Datamonitor attempt to account for the variability which may occur in the prevalence of AIDS over the course of the next 15 years. The first, or "data-driven" forecast, uses retrospective trends in the disease together with a hypothesis that the spread of the disease will continue unchecked over the course of the next few years. The forecast is shown in table 1.

Table 1: Prevalence of AIDS in Europe, 1995-2010 (data-driven forecast)

	1995	2000	2005	2010
Absolute numbers	38,123	87,264	155,985	244,288

Source: *Datamonitor*

The second set of predictions assumes that the increases observed in annual incidence rates will slow as behaviour and social attitudes prevent the disease from spreading through the general population with the speed that it has moved through the high-risk groups. The "S-curve" forecast is shown in table 2:

Table 2: Prevalence of AIDS in Europe, 1995-2010 (S-curve forecast)

	1995	2000	2005	2010
Absolute numbers	29,684	36,107	39,153	40,830

Source: *Datamonitor*

Since available drugs act to keep AIDS patients alive, rather than curing the virus, the prevalence of the disease has increased. A higher prevalence rate has the potential to increase incidence since a greater number of people with the virus means a greater risk of the virus being transmitted to the non-infected population.

AIDS prevalence has increased much more rapidly than incidence in recent years, thanks to the rapid advances made in treatment of the disease. Thus the data-driven forecasts (table 1) predict a 600 per cent increase in AIDS prevalence by 2010, whereas the S-curve forecasts just a 38 per cent increase over the next 15 years. Details of Datamonitor Global Epidemiology reports, priced at $1,995.00 each, from Datamonitor, 106 Baker Street, London W1M 1LA or on 0171 625 8548; Fax: 0171-625-5080. (Source: *Biotechnology Bulletin*, June 1995)

Systemic antifungal market to grow by over 100 per cent

A CONNECT Pharma survey projects that the total systemic antifungal market will grow by over 100 per cent during the period 1993-1998. A report, *Antifungal Therapy: Advances and Commercial Opportunities*, shows that systemic infections are the fastest growing segment of the antifungal drug market, largely due to the rapidly increasing numbers of immunocompromised patients in areas such as AIDS. By the year 2000, as many as 120 million people may be infected with HIV. Of those who develop AIDS, it is estimated that 60-80 per cent will contract a fungal infection, and 10-20 per cent of these will die as a result.

Products from Pfizer and Johnson & Johnson account for 61 per cent of the total antifungal market. Diflucan from Pfizer dominates, with 18.5 per cent of the total market, and is predicted to have a sales potential of $1 billion. However, the report also notes that with all antifungals there is an increasing problem of resistance. Roughly 10 per cent of *C. albicans* strains are resistant to 5-fluorocytosine world-wide, with resistance levels of 23 per cent in the USA. As a result, companies are developing new derivatives and groups of drugs to meet the market for agents with low toxicity and broad activity (including Johnson & Johnson's Sporanox). An unresolved question: are there ways in which biotherapeutic products might help boost the immune system against fungal invasion? Details of the report, priced at £850.00, from:

CONNECT Pharma Ltd., Oxford Science Park, Oxford OX4 4GA or on 01865 784 177; Fax: 01865 784 178. (Source: *Biotechnology Bulletin*, June 1995)

The Jakarta Recommendation 1995: concerning conservation and sustainable use of tropical bioresources

The Second International Forum on Conservation and Sustainable Use of Tropical Bioresources was held in Jakarta, Indonesia, on 17-19 January 1995. The Forum was jointly sponsored and organized by the Agency for the Assessment and Application of Technology (BPP Teknologi), New Energy and Industrial Technology Development Organization (NEDO) and Japan Bioindustry Association (JBA).

As part of the continuing programme of the First International Forum on Conservation and Sustainable Use of Tropical Bioresources which was held in Chiang Mai, Thailand, in January 1994, the purpose of the above-mentioned Forum was to promote cooperation in solving the problems relating to the conservation and sustainable use of tropical bioresources.

At the conclusion of the Forum the 112 participating scientists and high rank officials from Indonesia, Japan, Thailand and Malaysia unanimously adopted the Jakarta Recommendation 1995. It calls for action to cooperate in the promotion of science and technology and the establishment of an information network for the conservation and utilization of tropical bioresources in order to promote social responsibility in sustainable development.

Recommendations

The Second International Forum on Conservation and Sustainable Use of Tropical Bioresources held in Jakarta, 17-19 January 1995, makes recommendations to all government agencies, academic institutions and industries concerned as follows:

General

1. To pursue the objectives of UN Convention on Biological Diversity 1992, which includes the conservation of biological diversity, the sustainable use of its components and the fair and equitable sharing of the benefit arising out of the utilization of genetic resources, by appropriate access to genetic resources, appropriate transfer of relevant technologies, taking into account all rights over those resources and to technologies, by appropriate funding.
2. To establish cooperation through competent organizations at bilateral and/or regional levels to enhance technology transfer and flow of information.
3. To establish and maintain relevant training programmes related to the conservation and sustainable use of biological diversity.
4. To promote research in the use of scientific and technological advances for the conservation and sustainable use of biological resources.

Technical issues

1. R&D for investigation, classification and phylogenetic analysis.
2. Systematic organization of national culture collection and cell gene bank.
3. Acquisition and transfer of new biotechnology (such as DNA analysis, recombinant DNA, cell fusion, and cell culture).
4. R&D for conservation, utilization and management of tropical bioresources (elucidation of phenomena, development of technology, etc.), utilization of traditional knowledge.

Framework of implementation

1. Establishment of a regional information network on biological diversity.
2. Establishment and management of bilateral co-ordination meetings on R&D projects.
3. Establishment of an information centre for tropical bioresources to facilitate programmes at the national level.

Infrastructure

To promote conservation and utilization of tropical bioresources by implementing the following points:

1. Training of personnel.
2. Access to resources and sharing of benefits.
3. Technology transfer and protection of intellectual property rights.
4. Social responsibility in sustainable development.
5. Programmes for public awareness.

(Source: *Japan Bioindustry Letters*, Vol. 12, No. 2, June 1995)

Biodiversity promises great prospecting

Some of the best prospects for filling our 21st century medicine cabinets reside in the plants, soil micro-organisms and marine organisms that lie beneath our collective noses. This was the predominant theme of a two-day conference entitled Biodiversity and Human Health held recently in Washington DC. However, concerned that these resources may be destroyed before they are tapped, conference participants drafted a strongly-worded petition against such destruction. It calls on federal officials and the US Congress to renew the Endangered Species Act, and it warns that faltering on this issue will have important "health consequences" that will "not only diminish our lives but also threaten our health and that of our children".

The biotechnology industry's efforts to develop new therapeutic products--whether through screening and chemically-enhancing metabolites from micro-organisms or through using genomics to comb through databases containing DNA sequence information about plants or other species—benefit by having access to as wide a range of such resources as possible, point out conference participants, as well as other experts. But those benefits may never be realized if currently endangered species--or others jeopardized because their habitats are under seige--vanish.

Although the scope of the biodiversity issue is undeniably global, conference participants framed their message primarily in scientific terms and aimed their political message at a somewhat narrow domestic target. Thus, the petitioners did not address the larger question of the US Government's failure thus far to sign the Convention on Biological Diversity. This treaty --which the United Nations Environment Programme began developing in 1988 - has been signed by more than 160 countries and went into effect at the end of 1993.

Many US industry representatives and environmental groups were urging Congress to ratify the treaty in mid-1994. But a last-minute outcry against several provisions including biosafety issues and intellectual property issues and a subsequent shift in the national political landscape to the right and away from environmental causes

has left the treaty in legislative limbo ever since. Industry groups, such as the Biotechnology Industry Organization (BIO, Washington, DC), have also backed away from endorsing any further move by the US Congress to ratify the treaty. Even so, State Department and other federal officials continue to track treaty-related developments. Indeed, even though the US has yet to sign it, the treaty carries enormous weight, if only because so many other countries have signed it.

Meanwhile, questions of economics further complicate the politics of biodiversity, with a major challenge being how to fairly compensate countries from which US researchers and companies derive medicinal plants or other valuable materials. The National Institutes of Health (NIH, Bethesda, MD) is developing a prototype agreement for collecting material "to assure countries and local officials that they will obtain benefits and financial rewards for their contributions". Although terms will vary and promises are difficult to detail, the draft spells out a "commitment to the source country" in return for commitments from that country to maintain the source material in a sustainable fashion.

The Healing Forst Conservancy (HFC, Washington, DC) is developing principles for companies in the private sector to consider when compensating countries for the medicinal use of their biodiversity. Thus, all countries that sign up and allow their source materials to be examined will be compensated, even if useful products come only from other explorations in other countries. (Extracted from *BioTechnology*, Vol. 13, June 1995)

Chugai to spearhead Pacific Rim Research Net

Chugai Pharmaceutical plans to construct a "Pacific Rim Research Network" to promote the development of new drugs using biotechnology. Chugai will start full operations at the Chugai Research Institute for Molecular Medicine, Inc. in Tsukuba and create Chugai Biopharmaceuticals Inc. in San Diego, California in July. The company will also initiate joint research programmes with Amrad of Australia in the field of molecular medicine.

The Pacific Rim Research Network is a specific step taken in accordance with the company's new mid-term business plan. This network will connect Chugai's research facilities in Tsukuba and Gotenba with nine affiliated research facilities in the US, Australia and South Korea to accelerate the development of innovative new drugs. The company intends to launch a tuberculosis diagnostic agent in the USA by the end of this year. The new tuberculosis diagnostic agent, which utilizes new technology to amplify ribosome RNA of mycobacterium tuberculosis, makes it possible to diagnose the disease in only about five hours, compared to four to eight weeks with conventional diagnostic agents. It was launched last year in Japan as DNA Probe Chugai-MTD and has monthly sales of about 50 million yen. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 5 June 1995)

Blockbusters hold R&D purse strings

As research and development becomes increasingly costly, many pharmaceutical companies have decided to get out of R&D completely. Others continue to pursue the elusive blockbuster drug, meanwhile concentrating their efforts in one particular therapeutic area.

As the pressure mounts to show better returns on research and development expenditure, the pharmaceutical industry's key players are making moves to consolidate their strength further in certain therapeutic areas.

Drug manufacturers are extending their drug portfolios within their chosen therapeutic areas whilst attempting to turn up trumps with the next blockbuster drug. If a pharmaceutical company holds a large share of a therapeutic area, it follows that it will be taken more seriously as an expert in that field, both by physicians and patients.

Building up clout within certain medical categories is increasingly seen as a route to enhanced profitability. But the mostly elusive blockbuster drug is still the best way to boost return on R&D investment. If a company has $2 billion sales of one drug, it will have a higher profit margin than if the sales are spread out over lots of drugs.

Many of these blockbusters will come from the research-only companies. In 1993, companies spent $23 billion on R&D. To get a 10 per cent year return on those R&D costs, they would have had to generate incremental sales of $225 billion.

Many firms have opted to get out of R&D altogether.

The effect of a blockbuster on a company's operating margins is dramatic. Johnson & Johnson went from zero to $206 million sales in eleven months with the launch of the schizophrenia drug *Risperdal*. Its gastric motility drug *Populsid* is also doing extremely well along with Astra's *Losec*. Sales of antipeptic ulcer agent *Losec* shot up from zero to $2.3 billion in a five-year period.

Once a pharmaceutical company's drug has reached blockbuster status, it follows that that company is viewed as being strong in a therapeutic area.

Therapeutic areas most likely to yield blockbuster drugs are those with high potential patient populations and with high requirement for new drugs. These include obesity, dementia, arthritis, atherosclerosis, cancers and the AIDS vaccine. For those companies fortunate to come up with a blockbuster drug, patent expiry is always around the corner and its effect is felt quickly and deeply. The average life cycle of a blockbuster drug is between seven and ten years, although it can be longer.

Devising sustained release formulations is one way of extending a drug's shelf-life. Pfizer did this with three-times a day *Procardia*. Just ahead of patent expiry it launched once-a-day Procardia XL. Others have gone down the consumer healthcare route, launching their products over the counter.

Many companies are showing interest in biotechnology companies. An organization can be good at discovery but not necessarily at development. Among those adopting this strategy are SmithKline Beecham and Roche, which recently bought control of Genentech. It is also important that companies make sure they have the structure to sell blockbuster drugs. (Extracted from *European Chemical News*, 12-18 June 1995)

Beijing hosts Second South-North Conference

The Second South-North Conference, held in Beijing on 6-10 November 1994, demonstrated that developing countries are participating meaningfully in the Human Genome Project. Both in overall session structure and the high level of scientific content, the conference exemplified the goals of its sponsors—United Nations Educational, Scientific and Cultural Organization (UNESCO), Peking University and the Chinese National Commission for UNESCO.

In this and previous conferences, UNESCO has established three major ways in which developing countries and populations can participate in the genome project:

- Give special attention to genetic traits, including inherited diseases or susceptibilities in native populations. Isolated populations are especially important in genetic analyses.
- Organize scientific work using the best available technologies for mapping and sequencing at least some representative sites. Special attention would be given to organisms or traits of particular value or interest to societies.
- Take part in moral and ethical discussions on beneficial uses of genetic technology and safeguards of individual privacy.

The First South-North Conference, held in Brazil in 1992, emphasized planning and initial work at a number of sites. This Second Conference concentrated on an update of scientific work and demonstrated substantive Chinese contributions, including a number of presentations on the genetic diversity of some 50 ethnic groups. Many delegates emphasized the sense of responsibility shared by the Chinese Government and investigators regarding human genome studies in a country with more than 20 per cent of the total world population.

Chinese researchers presented significant scientific achievements in the following areas:

- Rice genome studies, from long-range mapping to blight resistance;
- Human genome research, including long-range mapping of portions of the X chromosome; and
- Technology development, with contributions to YAC cloning and bio-engineering.

Disease-gene presentations were comparable to studies from the USA, Canada and Europe. Delegates from Brazil, Kenya and Shanghai made impressive presentations, respectively, on molecular biology techniques for genome research, studies of the intracellular protozoan parasite *Theileria parva*, and YAC cloning and mapping of the Duchenne muscular dystrophy gene region.

These South-North conferences have established that genome analysis is thriving globally, with some high-quality laboratory groups functioning in developing countries. (Source: *Human Genome News*, March-April 1995)

BMP Japan 95

This year the Society for Industrial Microbiology held its Fourth International Conference on Biotechnology of Microbial Products: Novel Pharmacological and Agrobiological Activities outside the United States for the first time, at the Oiso Prince Hotel from 23-26 April 1995, with Professor Teruhiko Beppu chairing the event which attracted 247 registered participants. The overwhelming presence of members from corporations accounting for 67 per cent of all participants underscored the great corporate interest in the Conference. Overseas participants amounted to 27 per cent (with Asian participation at 7 per cent). Among the non-American delegates, there was again a high 65 percentage of corporate participants. It is within the nature of the Conference that it centred on probing research into microbial metabolites as the core area of interest. And, indeed, it gave a real sense of the prevailing international trends in this area of research.

The programme was divided into the following six sessions, and in each of these sessions lectures on five themes were delivered.

1. Novel sources and their metabolites (17)
2. Agrobiologics (5)
3. Recombinant technology and secondary metabolism (8)
4. Novel targets (14)
5. Enzyme inhibitors (23)
6. Receptor agonists and antagonists (2)

The figures in parentheses () refer to the number of poster presentations given in each session. It is of interest to note that the greater the number of these presentations the greater also the research interest shown in the subject area. Session 6 had a rather poor showing with only two contributions made. Rather than pointing to a lack of interest it may be more appropriate to see this as an indication that it is still an area that belongs to the "future".

The keyword to sum up session 1 may be the notion of "diversity". Novo gave a poster presentation titled "High quality microbial extracts" introducing a screening system based on the concept of an enhanced sample processing capability technically known as "high-throughput screening". It was the only lecture which had people crowding in front of the poster board. To get a proper appreciation of what microbial diversity really means, there are analytical procedures consisting of image analysis of morphological characteristics and PCR analysis of separated colonies. For a full understanding of the diversity of secondary metabolites, methods have been developed involving the automation of culture extraction and computer analysis of the high-speed HPLC patterns. This demonstrates to what extent state-of-the-art technology is being used to establish microbial and metabolic diversity, including the storage and organization of all further information obtained in the process in databases.

In session 4, the presentations mostly centred on cancer, a theme accounting for about half of all poster presentations. The lectures indicated that the thrust of research into carcinostatic agents was aimed at the search for chemical substances with a high selectivity on cancer cells by targeting the signal conducting systems. It may be of interest to note that three lectures took up the low-molecular chemicals acting on the hematopoietic and immune systems.

Session 5 attracted the largest number of poster presentations. Topics concentrating on cholesterol metabolism were in the forefront, indicating how great the interest is in hyperlipemia and arteriosclerosis. The target enzymes given in the five lecture statements were Leukocyte elastase, Nitric oxide synthase, Tyrosine phosphatase, Glucosidase and Proteinase. The research group from Lederle announced their strategy for finding a chemotherapeutic agent for Altzheimer's disease. Their approach was to search for an inhibitor substance that suppresses beta-secretase, the enzyme which breaks down the amyloid precursor peptide. The first target is the specific splitting activity on the biotinylated peptide substrate with the choice of Cathepsin G as the proteinase locally present in the brain to become the beta-secretase candidate. The next step involved the use of a screening system for robotized assaying to search for the Cathepsin G inhibitor from a chemical library of microbial cultures, plant extracts and chemical substances. These efforts have so far led only to the locating of the plant constituent Genistein. The general impression was that the results are still to come.

In session 6, the members present from Panlabs gave a poster presentation on the active substance erythropoietin (EPO) derived from Actinoplanes. The murine EPO receptor gene has been introduced into an IL-3 dependent cell strain of FDC-P1 for expression and the EPO was the low-molecular fat-soluble substance detected by using the above cell strain as the indicator cell. The active substance is still in the process of being purified. Not yet clarified

have been issues such as the bond formed with the receptor and the competitiveness with EPO. There is a heightened interest in low-molecular agonists for the high-molecular ling membrane receptor, with hopes that the chemical substance concerned will be identified in all its aspects as soon as possible. (Source: *Japan Bioindustry Letters*, Vol. 12, No. 2, June 1995)

SELA/EU Biotechnology Project: Cooperation for Development

(Contributed by Alberto Díaz* and Antonio Leone**)

Introduction

Biotechnology is more than an industry, it is a group of techniques developed from decades of basic research and which are now being applied in various industrial sectors: human and animal health, agriculture, environment, etc. The New Biotechnology, born in the 1960s and characterized by the use of recombinant DNA techniques, cellular fusion and bioprocesses, draws the attention of scientists, technologists, industrialists, financiers, government officials, journalists and the general public.

In less than two decades, biotechnology has revolutionized the scientific approach to living matter. As a result of the developments achieved, products that may dramatically improve human and animal health, the quantity and quality of foods, and the environment appear on a continuous basis. The forecasts made in this respect were not adequate: overly optimistic forecasts were inaccurate in evaluating technological-industrial development needs and market requirements, while more conservative predictions did not account for the speed of the evolutionary process in the area of biological knowledge and potential transformations into products and services. Applications in the area of human health have developed most as a result of the scope of the basic research carried out in this field over the years and the successful therapeutic and diagnostic results in the various social sectors. Food and agriculture applications, on the other hand, have required more time to become known and accepted.

Rapid growth in this new bioindustry, which arose mainly in the United States of America, had very particular technological innovation characteristics and was based on a new type of dialogue between universities and enterprises. In Europe and Japan, the process followed its own particular paths within the novelties arising from biotechnology. The European Union was characterized by its preference for achieving joint developments, with the acceptance of the social sectors, while including developing countries in the projects and controlling potential dangerous effects arising from control over genetic information.

During its initial stage, biotechnology focused mainly on research and development results, and the obtaining of new products. Now, one must also include the marketing aspects, manufacturing processes, registry, legal and security rules, sales and distribution. Hence strategic alliances, mergers and acquisitions, licenses, international agreements and other forms of association emerge in order to reach markets as quickly and successfully as possible. Complementation increases among the important firms for the manufacture, financing and sales, but in general, the new ideas and products stem from smaller organizations with ties to the university sector.

Beyond the success of certain markets with enormous profits and investments, a new bioindustry is emerging. It focuses more on know-how, human resources and control over information.

The USA participated in bringing about these activities and continues to direct and control them. It is however the private enterprises that carry out the development, production and commercialization aspects.

SELA's Biotechnology Programme

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 cooperation 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 out a study on state-of-the-art biotechnology enterprises in that continent.

EC/SELA BRIDGE Project on Biotechnology

The 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 six-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 the 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 companies.

Although a large part of the efforts are 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 bio-insecticides, biomaterials, biological treatment for environmental pollution, etc.

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* Coordinator of the EC/SELA Biotechnology Bridge Project.

** Head of Projects of the Latin American Economic System (SELA).

In Europe, where three is a better structure and greater recognition in this area, small- and medium-sized enterprises, national institutes and governmental organizations carry out a wide variety of activities. In this regard, Latin America needs to disseminate related information more actively and continuously in order to achieve new and more effective forms of interaction.

The activities provided for in the EC SELA BRIDGE Project on Biotechnology for the six-month period in question are as follows:

(a) 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;
(b) Facilitate interaction among biotechnology organizations of both continents;
(c) Disseminate the Project's activities in magazines, congresses and seminars, granting special attention to achieving greater public acceptance in the progress made in this field;
(d) Cooperative interaction with other existing programmes in Latin America, such as the Bolivar Programme, Redbio, UNESCO UNIDO Regional Programme and others;
(e) Valuation of the R&D projects carried out jointly by Latin American and European researchers, in order to facilitate their transfer to interested industries; and
(f) Status of regulations, rules, controls, patents and bioethics in the region.

Proposal for a SELA/EU cooperation programme in biotechnology

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 relations between the two organizations.

From the EU's standpoint, this initiative represents the continuation of the actions initiated by the General Office for Foreign Affairs (DGI) and the General Office for Science and Technology (DGXII) in April 1987 at the SOBELA Meeting in Brussels.

From the standpoint of the SELA Permanent Secretariat, the programme forms part of the activities directed towards promoting technological innovation and business development in the region.

The general objective sought by the Programme will be that of strengthening inter-regional cooperation and promoting productive and technological enterprises among European and Latin American countries in the sphere of biotechnology. In this respect, efforts will be made to substantially increase mutual knowledge between Latin America and Europe in the area of biotechnology, as well as to overcome the lack of contact mechanisms, establishing a space for meetings between eventual European and Latin American partners with an aim to establish joint ventures that will increase the productivity of the Latin American productive apparatus and the transfer of results of the region's basic research to the productive sectors.

The development and dissemination of this strategic technology will be favoured by the programme through the three substantial subprogrammes (bio-industry, research and development project valuation, and technology transfer).

C. COUNTRY NEWS

Australia

Biosafety protocol update

Relevant Commonwealth departments and agencies have formed an interdepartmental committee to develop Australia's position on whether there should be a protocol on biosafety of genetically modified organisms, and in the event of international consensus for a protocol, to resolve what sorts of protocol could be acceptable.

In early March, two linked meetings were held in Bangkok to discuss regional and international cooperation on biosafety. Experts from 67 countries attended. The second of these meetings discussed a draft set of guidelines prepared by the UK and the Netherlands. The review Guidelines are expected to be discussed during the summer. (Extracted from *Australasian Biotechnology*, Vol. 5, No. 2, April 1995)

Survey on public perceptions of gene technology

The Federal Minister responsible for gene technology legislation, Senator Chris Schacht, has revealed that Australians believe the long-term benefits of genetic engineering were likely to outweigh the risks.

Senator Schacht was outlining further findings from the International Social Science Survey on public perceptions of gene technology.

"The findings complement those released in February, which showed community support for the use of genetic engineering to help achieve desired goals, such as improved health, better foods and developing pest resistant crops." The survey found those knowledgable about the technology were a little more optimistic about its long-term benefits.

To gain a broad picture of community feeling, the survey inquired about community concerns about the technology. Results were expressed in the form of a worry scale, from zero (no worry) to 100 (huge worry, terrible and very likely to happen).

"There is about the same level of concern about the use of chemical pesticides (65 points) as there is that gene technology could give rise to new diseases (67 points). There is slightly more concern about the use of chemical pesticides than about possible long-term risks in eating genetically engineered food (59 points). The same is true about fears that genetically engineered plants might spread into the environment and become weeds (58 points)."

"The survey will help focus Government information activities about gene technology to those areas of maximum community interest."

Further information: Alan Laird, DIST, Tel.: (06) 276 1182; Jonathan Kelley, ISSS, ANU, Tel.: (06) 297 2937. (Extracted from *Australasian Biotechnology*, Vol. 5, No. 3, June 1995)

China

Progress in plant genetic engineering research

In order to obtain new crops with features of high-yield, disease-resistant, insect-resistant, and high quality, China launched its plant genetic engineering research in the 1980s. Although China's plant genetic engineering research still lags behind the developed countries, it has achieved significant results in the following areas:

1. Virus-resistant crops

Researchers have succeeded in obtaining transgenic tobacco plants by introducing the coat protein (CP) of the tobacco mosaic virus (TMV) and cucumber mosaic virus (CMV) into tobacco plants. Large-scale field testings were already conducted in Henan and Heilongjiang provinces in 1992 and 1993 respectively. The transgenic tobacco plants containing CMV satellite DNA genes and TMV coat proteins were also put into intermediate testings. At the same time, researchers also cloned the coat proteins of rice Donggelu virus (RTV), rice dwarf virus (RDV), and barley yellow dwarf virus (BYDV) and have already introduced the BYDV into wheat plants using pollen tubes introducing method.

2. Insect-resistant crops

Researchers have modified and synthesized the insecticidal crystal protein gene (BT) Cry 1A and cloned the whole genome to tobacco, cotton, cabbage and poplar plants. Field testings for the insect-resistant transgenic tobacco plants have been conducted in many provinces. Researchers have also cloned the trypsin-prohibiting genes of cowpeas and arrowheads and have transferred them into tobacco and cotton plants. In order to solve the BT-resistance problem of insects, researchers also cloned the scorpion neural toxin onto the NPV expression vector. Preliminary results indicate that the expression products do show insecticidal activity.

3. Bacterium- and fungus-resistant crops

In order to obtain an anti-bacterial wilt gene to protect against diseases of potatoes, tomatoes and eggplants, Chinese scientists artificially synthesized and cloned several anti-bacterial genes--Cecropin B, Shiva 1, and Shiva A genes---according to the amino acid sequence of anti-bacterial genes derived from cocoons of silk worms, and transfer ed them to seven kinds of domestic potato plants. So far more than 500 transgenic potato plant strains have been obtained. Field testings indicate that some of these transgenic potato plants do enhance the potatoes' anti-wilt capability. In addition, researchers also isolated and cloned the paddy rice chitin enzyme gene and barley leaf-specific sulphur-violet gene, which have fungi-resistant activities. Research on sulphur-violet gene's biological function in transgenic tobacco plants is under way. Researchers have also isolated and purified the anti-bacteria protein from Bacillus spp A30, B034 and paddy rice, and have studied a part of the protein's characteristics.

4. Improvement in food quality

To raise the essential amino acid content of potatoes, Chinese researchers have artificially designed and synthesized a high essential amino acid content potato gene (HEAAE). Researchers first cloned the corn 10 KDa Zein gene and transferred it to potato genome. To facilitate the above gene's specific expression in potato tubers, the sweet potato Sporamin A promoter was used. Test results indicated that the amino acid content of the transgenic potato

tubers was much higher than in normal tubers. Two promoters for two potato genes Class I and GBSS were also isolated. In order to culture a high-sulphur amino acid content alfalfa strain, researchers cloned HNP1 and HNP2 genes and transferred them to the fibrous root of the leguminous plant forage grass. Results indicate that the sulphur amino acid content increases 7.7 per cent in the transgenic forage grass. Research on transfer of HNP1 and HNP2 genes to alfalfa is under way.

5. Genome mapping and gene locating research

In 1973, China was the first country to find the photosensitive genic male sterile (PGMS) rice strain. In the 1980s, Chinese scientists again found the thermal-sensitive genic male sterile (TGMS) rice strain. Researchers have located the two genes (pms 1 and pms 2) that control the PGMS on the No. 7 chromosome and the No. 3 chromosome of rice respectively; the gene that controls TGMS (tms) was also located on the No. 5 chromosome of rice. In addition, researchers also located the blast-resistant gene and the short-stalk feature gene of rice that will eventually be used as probes or markers for conventional breedings. (Source: *High Technology Letters*, Vol. 5, No. 2, February 1995)

European Union

New EC Biotechnology Programme

The European Union recently announced the beginning of the new Biotechnology Programme under the 4th Framework Programme of the European Commission. The Programme contains eight research areas which are:

- Cell factories
- Genome analysis
- Plant and animal biotechnology
- Cell communication in neurosciences
- Immunology and transdisease vaccinology
- Structural biology
- Pre-normative research, biodiversity and social acceptance
- Infrastructures.

A budget of 552 million ECU will be available for the period 1994-1998. The advanced notice of the first call for proposals for the Biotechnology Programme was published on 15 December 1994. The closing date was 24 March 1995. It is important to note that this call will focus on specific tasks and not the entire work programme. An information package is available upon request to inform you about the areas on which the first call for proposals will focus, and about the application procedure.

One of the new elements in the Programme is the "preparatory award" for SMEs. SMEs can receive a contribution of 75 per cent with a maximum of 45,000 ECU for the preparation of a full-scale RTD project proposal in one of the later calls for proposals. This preparatory stage can be for any of the eight research areas in the programme.

More information about these preparatory awards can be found in the specific information package for SMEs, which is also available upon request. More information and requests for information packages: European Commission, DG XII Biotechnology, Rue de la Loi 200, B-1049 Bruxelles, Fax: +32 2 295 5365. (Source: *Australasian Biotechnology*, Vol. 5, No. 2, April 1995)

Labels on hold

After a year of deadlock, European Union leaders have again failed to agree on labels for genetically-modified foods. The matter now passes to EU mediators.

The States are split over whether all "novel" foods should carry labels. The draft text under discussion at the EU Internal Market Council suggested foods should only be labelled if they differed in a "significant way" from existing products.

Austria, Denmark, Germany, Greece and Sweden want labels for all novel foods. The UK, Belgium, Finland, France, Ireland, Italy and the European Commission argue that this approach could disadvantage some products. It would be sufficient, they say, to alert consumers if constituents could cause allergic reactions, or conflict with dietary or religious restrictions.

The Commission's biotechnology advisory group warns against systematic labelling. It considers that labels should only be needed when "modern biotechnology causes a substantial change in composition, nutritional value or the use for which the food is intended". If not, then the nature of the biotechnological process is unimportant. (Source: *Chemistry & Industry*, 19 June 1995)

Finland

Growing world player in the biotech sector

Finland is developing as a significant player in the emerging European biotechnology sector. Indeed, Ernst & Young recently revealed that Finland had the sixth largest biotechnology sector in western Europe—only the UK, Germany, France, the Netherlands and Sweden have more companies. But it is not just the quantity that Finland can boast, it also has the quality—world players in specific niches.

One of the most prominent is Genencor International Europe, a growing force in the global industrial enzymes market.

Formed in 1990 by combining the biotechnology efforts of Eastman Kodak, Cultor and Genencor, the company has seen an impressive 20 per cent per year growth rate—in 1994 total revenues topped $140 million worldwide.

Although precise details of profitability are not reported, Juha Koivurinta, president of Genencor International Europe, discloses that the company has been more or less cash neutral in the past two years.

Genencor is an enzymes-focused company. It either makes enzymes that are used in other industries or uses them itself to make sophisticated, high margin speciality chemicals.

Two-thirds of all enzymes sales go into three sectors: detergents, textiles and starch alcohol. Genencor operates in these three markets on its own and operates in other markets through collaborations with others, such as Ciba. The two companies are working on applications in wood pulp pre-bleaching where enzymes can eliminate water pollution problems associated with conventional, chlorine-based bleach processes. Future targets include the enzymatic modification of lignin in chemical or mechanical pulps.

A potentially big money-spinner is the company's microbial technology for making indigo dye using glucose as the primary raw material. The conventional process for indigo dye uses hazardous starting materials such an aniline and chloroacetic acid. Genencor scientists, using a technique called pathway engineering, which involves enhan-

cing a number of steps in the synthesis of the chemical, have shown that it is possible to make indigo dye in a more benign way.

In recent times, the focus has been on improving the economics of the system. Denim companies are unlikely to pay an excessive premium for the blue dye.

Biotechnology in Finland is considered a green technology and has not attracted the same opposition from consumer and environmental activists that it has in other countries. The Finnish Government is also fairly supportive. The VTT Biotechnology and Food Research Institute, a State-owned contract research house, is a major player in collaborative private/public sector projects.

The Finnish Technology Development Centre (Tekes), a governmental agency belonging to the Ministry of Trade and industry and established to stimulate technical development in Finland, has been very active in promoting biotechnology.

Finland is bringing its new gene technology law into force on 1 June. The law, designed to implement the EU biotechnology directives 219 and 220, differs from the EU requirements in that it is expected to include additional clauses on ethical considerations related to genetic modification of organisms. The clauses were introduced when the Finnish Parliament amended the bill. How the ethical element will work in practice is not clear. Despite this lack of clarity, Finland's biotechnology sector has welcomed the law. (Extracted from *ECN Finland Supplement*, May 1995)

Germany

Guidelines for gene therapy

The German General Medical Council has drafted a guideline on the potential application of gene therapy. The Council sees four types of gene transfer: diagnostic processes, substitution therapy, additional therapy and suppression therapy. For all these activities, the Council sees no specific ethics problems, but it insists on the fact that germline gene therapy is inadmissible because of scientific, medical and ethical reasons. The Medical Council also recommends setting up a Commission for Somatic Gene Therapy that will have the function to advise local ethics committees in their individual decisions on applications of gene therapies.

Germany's national research society, Deutsche Forschungsgemeinschaft (DFG), has called for no further legislation restricting gene therapy because it would be "unethical" in view of the number of sick people who need help. The society pointed out that gene therapy is already regulated by national pharmaceutical laws, the Genetic Engineering Framework Act, the Federal Epidemics Act and the local ethics commission. (Source: *European Biotechnology Newsletter*, 4 April 1995 and *European Chemical News*, 5-11 June 1995)

German genetically-engineered products near market

For the purpose of launching research in the field of bioprocess engineering, a "Bioprocess Engineering Research Association" was formed seven years ago. Its members include the Universities of Stuttgart, Hohenheim and Tuebingen, along with the Fraunhofer Institute of Interface and Bioprocess Engineering in Stuttgart. The task of this Association is not only to develop new biotechnological methods and processes, but also to adapt them for practical uses. A technology transfer to small and medium-size enterprises is considered especially important. The project is financially supported by both the Federal Ministry of Research in Bonn and the Baden-Wuerttemberg Ministry of Education and Research. The conversion of the results of basic research into marketable applications are a significant achievement. One example is the biological reclamation of lands once holding military facilities. Soils heavily contaminated with explosives and polycyclic aromatic compounds could be purified by micro-organisms particularly suitable for this purpose.

The emphasis in the coming years will be on biocatalysis. Biocatalysts are naturally occurring substances such as enzymes aiding the manufacture of organic compounds for the drug or food industry. The advantage of using these proteins over working with conventional syntheses is, above all, that they produce "enantiomer-free" chemicals. Complex organic compounds usually occur in pairs of two types (enantiomers) differing from one another like an image and a mirror image. As a rule, only one of them is an effective drug and the other is superfluous or even toxic. Selective synthesis of the "right" component by means of biomolecules is thus of considerable interest from the economic standpoint.

Intense research is therefore being done in this field. In collaboration with industry, the Institute of Industrial Genetics at the University of Stuttgart has developed a process which produces t-Pa (tissue-type plasminogen activator) used as medication during heart attacks and thromboses from the *E. coli* bacterium. Normal *E. coli* bacteria are able to produce only fragments of the desired t-Pa drug. That is because a few crucial sequences in the building scheme, namely of transfer-ribonucleic acid, are missing and the bacteria cannot "read" the entire genetic information. Only after targeted artificial insertion of the missing sequences will the micro-organisms be able to complete synthesizing the protein. (Extracted from *VDI Nachrichten*, 31 March 1995)

Ireland

BioResearch Ireland establishes cytokine assay laboratory

BioResearch Ireland's National Pharmaceutical Biotechnology Centre (NPBC), based in Trinity College Dublin has set up a cytokine assay laboratory. The laboratory has established and validated a comprehensive range of ELISA-based and bioassay-based systems for human and veterinary cytokines and offers testing services to industrial and academic clients. This service represents a convenient and cost-effective solution for R&D groups lacking in-house cytokine analysis facilities.

Cytokines are soluble hormones which are produced by cells in response to various extracellular stimuli (e.g. infection, tissue injury, immunomodulating drugs, vaccines, fertility drugs, etc.) and in turn they induce various immune and inflammatory reactions. The course of the immune/inflammatory response, which may be beneficial to the host (e.g. immunity to specific infectious agents, non-specific boosting of the immune system, suppression of immunity to grafts) or detrimental to the host (e.g. autoimmune diseases, rheumatoid arthritis, psoriasis, multiple sclerosis, graft rejection, etc.) is dictated by the profile of cytokines induced. Consequently knowledge of the cytokine profile produced in response to a therapeutic agent pro-

vides, at the molecular level, a clear picture as to how this agent is eliciting its effect. With this information scientists can better understand the disease mechanism and can also elucidate how a therapeutic agent is interfering with the disease process.

Cytokines can be used in drug development and drug registration in:

- Assessment of lead drugs/biologicals;
- Screening for novel immune regulators;
- Elucidation of disease mechanisms and design intervention strategies;
- Elucidating the action of drug mechanisms;
- Provision of mechanistic data for regulatory authorities.

The cytokine assay laboratory is operated in parallel with the NPBC's research programme in the field of inflammation. The expertise of these researchers is available to assist clients using the laboratory in optimizing their tes. strategies and interpreting results, etc. (Source: *Press Release*, 28 June 1995)

Japan

Public acceptance and regulation of biotechnology in Japan

The Japanese, it is often assumed, would be more open to biotechnology and new bio-products than are Europeans or Americans. But, it turns out, there is less consensus on the use and regulation of biotechnology than is generally thought. Legal protection of plant varieties is being debated and Japanese consumers have expressed their concerns about genetic engineering research. According to the *Biotechnology and Development Monitor*, (No. 22, March 1995), the research to date suggests that Japanese consumers may be reluctant to buy products of genetically modified organisms.

The results of a survey carried out in 1993 by Darryl Macer, Yuko Kato and colleagues at the University of Tsukuba suggest that, while the vast majority express appreciation for research on biotechnology and genetic engineering, there are also significant levels of concern about possible adverse impacts. Despite bio-promotion and bio-education activities by the Japan Bioindustry Association (JBA) and by the Science and Technology Agency (STA), which preceded the survey, the evidence suggests that the public's concerns have not been completely allayed.

The conclusions drawn by the researchers included the following:

- On average, the concerns about the *consumption* of modified foods and medicines were somewhat greater than towards genetic engineering *research*;
- Between 14 and 24 per cent (depending on the product) of respondents said they had no concerns at all;
- The vast majority, however, expressed some degree of concern, especially regarding safety, quality, unknown health effects, long-term risks, unnaturalness and lack of information.

(Source: *Biotechnology Bulletin*, May 1995)

PAB preparing gene therapy vector guidelines

The Pharmaceutical Affairs Bureau (PAB) of the Ministry of Health and Welfare announced in March 1995 that work will start shortly on guidelines for evaluation of the quality and safety of drugs and vectors used in gene therapy.

The progress of the work is still not clear because the guidelines will be prepared by the Subcommittee on Drugs for Gene Therapy which the Executive Committee of the Central Pharmaceutical Affairs Council has recently decided to establish, but the Research and Development Division of the PAB will probably insist that matters concerning confirmation of quality and evaluation of safety in the manufacture of vectors used in gene therapy form the core of these guidelines.

Drugs for gene therapy are being actively developed, mainly by Japanese pharmaceutical companies in the wake of Hokkaido University receiving approval for clinical studies on gene therapy of ADA deficiency, the first approval of this type in Japan. (Source: *McGraw Hill's Biotechnology Newswatch*, 17 April 1995)

120 gene therapy studies under way in Japan

A survey conducted by a Koseisho study group revealed that at least 120 studies on gene therapy are being conducted in Japan and that clinical applications are under consideration in 15 of them.

These findings were presented by Shigetaka Asano, Professor of the Institute of Medical Science of the University of Tokyo and the study group leader, during a symposium organized by the group held in May in Tokyo.

The survey was conducted at the end of the last year by sending a questionnaire to 153 members of the Japanese Society of Gene Therapy.

Solid cancers, such as those of the kidney and pancreas, account for 30 per cent of the total number of studies. These are followed by genetic diseases such as adenosine deaminase deficiency (which are caused by abnormalities in single genes), leukaemia, and malignant lymphoma.

Clinical applications are considered in 15 studies, five this year and 10 next year. Since all clinical studies must be approved by institutional review boards and the government, however, a significant delay is expected.

Researchers will depend on companies for the confirmation of safety of vectors, a major challenge in gene therapy, in only about 50 per cent of the studies, because of a lag in studies in this area. (Source: *McGraw Hill's Biotechnology Newswatch*, 19 June 1995)

Japanese invest in US biotechnology

Japanese companies are continuing their robust investment in the US in advanced materials such as biotechnology products, engineering plastics, advanced ceramics, fibre composites and metals, and environmental technologies. Over the period 1990-1995, a report by Eldib identifies 200 collaborative transactions between US and Japanese firms, with typical investment levels of $10-25 million and projected sales of $10-15 million.

Biotechnology holds the prime interest for the Japanese in the US, accounting for around a third of total deals, with engineering plastics taking a further quarter.

The portion of US patents granted to Japanese companies has doubled since 1980, while that granted to France, Germany and the UK has fallen moderately, adds the Eldib report. (Source: *European Chemical News*, 19-25 June 1995)

Malaysia

Malaysia launches its first biodiagnostic company

In an important development in the Malaysian biotechnology scene, the country's first biodiagnostics company, Malaysian Biodiagnostics Research Pte. Ltd. (MBDr), was incorporated and launched recently.

The mission of MBDr is to improve the quality of health care in the Asia-Pacific region by spearheading the development of an innovative and responsive Malaysian biomedical industry. To this end, MBDr aims to commercialize Malaysian R&D results, manufacture and distribute a range of international biodiagnostic products, and provide world-class medical diagnostic services. MBDr is an associate company of MTDC (Malaysian Technology Development Corporation), a company set up by the Government to promote the commercialization of research in the country's universities and research organizations.

The company's first product is TYPHIDOT, a rapid, simple and specific test for the diagnosis of typhoid fever developed as an outcome of research performed at the Universiti Sains Malaysia over the past six years. The test is based on a simple format of antibody detection using *S. typhi*-specific antigens immobilized on filter paper strips. It is based on simple colour development and requires no sophisticated instrumentation. The sensitivity (95-100 per cent) and excellent negative predictability (96 per cent) of the test was established and validated through controlled clinical trials with actual patients. The test seems ideally suited to use in small district hospitals in endemic areas of the world.

Further information: Dr. Ong Kok Hai (Chairman) or Mr. Ambok Chening Meri (Director/CEO), Malaysian Biodiagnostics Research, 4, Jalan Jaya Lima, Taman Jaya, Bandar Tun Razak, Cheras, 56000 Kuala Lumpur, Malaysia; Tel.: 60 3 932 1353, Fax: 60 3 932 1354. (Source: *Australasian Biotechnology*, Vol. 5, No. 3, June 1995)

Malaysian National Biotechnology Directorate established

The establishment of the National Biotechnology Directorate (NBD) marks another important milestone in biotechnology promotion and development in Malaysia. Professor Abdul Latif Ibrahim, formerly from the Universiti Pertanian Malaysia (UPM, the Agriculture University of Malaysia) has been appointed as NBD's first Director. The NBD will initially be a unit under the Ministry of Science, Technology & Environment, and will have as its Advisory Board, the National Working Group of Biotechnology, a body under the National Council for Scientific Research and Development.

The formation of the NBD is seen as particularly significant as it marks the recognition by the Government that biotechnology needs a full-time national "champion" with scientific credentials and possessing executive powers and financial support to pursue a meaningful programme. The NBD is expected to come up with a comprehensive and wide-ranging programme to promote the development of biotechnology in Malaysia. The NBD is also expected to provide advice to the IRPA (Intensification of Research in Priority Areas) programme with regards to biotechnology-related research grant applications. It is hoped that the success of the NBD may spur the formation of other directorates in the other "thrust" areas of advanced manufacturing, advanced materials, energy, and microelectronics and information technology. (Source: *Australasian Biotechnology*, Vol. 5, No. 3, June 1995)

Recent achievements in Malaysian biotechnology

With an extensive and long-standing base of experience in tissue culture and in the newer techniques of genetic engineering, the Rubber Research Institute of Malaysia (RRIM) has recently succeeded in carrying out the genetic transformation of the rubber tree, *Hevea brasiliensis*. Using particle gun technology for gene transfer, RRIM researchers have succeeded in genetically transforming rubber callus, regenerating the transformed plant and showing that the reporter gene is expressed in the latex and latex vessels. In much the same way as therapeutic pharmaceuticals are being produced in the milk of transgenic animals (e.g. cows, goats), the RRIM finding has great potential in relation to the rubber tree being used as a genetically-engineered "factory" to produce useful products/pharmaceuticals (e.g. insulin, interferon). The product desired would them appear in the latex of the genetically transformed plant and can be easily separated and purified. This approach has several important advantages in comparison to the use of transgenic animals or bacteria for the production of recombinant proteins: relative ease of caring for rubber trees compared to care of animals or bacterial fermentation processes, ease of harvesting the latex, lack of hazardous materials (latex is free of bacteria and viruses), and an economically significant by-product (timber) at the end of the production life of the tree. (Source: *Australasian Biotechnology*, Vol. 5, No. 3, June 1995)

The Netherlands

Industry and social organizations reach agreement on modern biotechnology

A number of leading businesses in the Dutch foods industry and groceries trade, together with consumer and environmental organizations, have made concrete agreements on labelling and consumer information in respect of products made with the aid of modern biotechnology. As a result, it is hoped that a more responsible and credible approach can be adopted to the introduction of such products on the Dutch market.

As a general principle, packaged foods and ingredients which are themselves genetically modified organisms or which contain such organisms will already carry a designation on their labels identifying the use of modern biotechnology.

Procedures have been developed for the provision of timely information and for holding talks about such foods with consumer organizations.

Supplementary product information will also be made available by manufacturers, for instance via consumer telephone information lines and folders.

The Informal Consultation Group on Modern Biotechnology has presented a report on the consultation process to the Consumer Products Advisory Committee. The document is based in part on extensive consumer research that was conducted by SWOKA, the Institute for Consumer Research, at the request of the Consultation Group.

Details from: H de Vriend of Stichting Consument en Biotechnologie on 070 3885508. (Source: *Biotechnology Bulletin*, June 1995)

Singapore

Institute of Molecular Agrobiology (IMA)

The new Institute will focus on agrobiology R&D, specifically in the application of genetic engineering for improved plant and animal protection. It will identify and undertake research with commercial potential, collaborate with multinational corporations (MNCs) and license out inventions and technologies to industry. The Institute will be hosted by the National University of Singapore.

The objectives of the Institute are:

- To undertake innovative research in agrobiology at the genetic and molecular levels;
- To provide the focus to attract high calibre researchers to undertake world-class agrobiological research;
- To provide training at the postgraduate level in the area of agrobiology;
- To provide the international standing to support MNCs to set up agro-biotechnology R&D and manufacturing activities in Singapore; and
- To facilitate the development of niche technologies and commercialization opportunities in Asia.

The core research programmes to be undertaken at IMA are:

Plant molecular biology in the areas of plant developmental biology; viral, bacterial and fungal pathogens of plants; and defence mechanisms of plants;

Fish molecular biology in the areas of fish developmental biology and mechanisms of pathogenesis in fish; and

Animal molecular pathology and transgenesis in the following areas: mechanisms of pathogenesis in animals; animal cytokines; insect viruses and poxviruses; and genome analysis.

Support programmes to provide specialized technologies include:

Yeast molecular biology—yeast is an ideal tool for cloning and expression of eukaryotic genes for production of novel gene products;

Monoclonal antibody production—this is essential for studies of protein functions and development of diagnostics and vaccines;

Electron microscopy—research and development of techniques are needed for the study of cellular, tissue and organismal structures and localization and analysis of molecules within the cell and physiological studies at the cellular level. Since this is capital intensive, the Institute will tap, at the initial phase, the resources available in the universities.

The start-up date is planned for September 1995 with an interim laboratory located at the Fleming Science Park, Singapore. The eventual core size of personnel will be up to about 200 researchers, technical and administrative staff.

Further information from: Acting Director, The Institute of Molecular Agrobiology, National University of Singapore, Faculty of Science, c/o Dean's Office, #08-32, Blk. S16, 8th Storey, Lower Kent Ridge Road, Singapore 0511; Tel.: (65) 772 6890/772 3333, Fax: (65) 774 2857/777 4279. (Source: *Australasian Biotechnology*, Vol. 5, No. 2, April 1995)

Spain

Spain authorizes testing of genetically modified organisms

The National Biosecurity Commission has authorized field trials of 20 genetically modified organisms derived mainly from plants, which were endowed with new characteristics in the laboratory.

Among the transgenetic products authorized to be tested in selected areas in different parts of Spain were a variety of a tomato modified to ripen more slowly and a variety of genetically engineered tobacco which has been made more resistant to herbicides. This Commission, set up under the Law on Restricted Utilization, Voluntary Release, and Modification of Genetically Engineered Organisms, approved the tests because they are among the requirements necessary to avoid possible risks to human health and the environment which could result from this research.

The National Biosecurity Commission, whose status is still provisional, has received 11 requests to test new genetic varieties in restricted areas, eight of which have been approved. As long as it is not known how they behave in a natural environment, testing of these new organisms must satisfy certain security requirements, such as a minimum distance from similar species to avoid cross-pollination or physical barriers to inhibit animals. In addition, the researchers must release information about the organisms taken as a sample, the genes which are introduced, the environment into which they are introduced, and the security measures taken in case of an accident.

Among requests waiting to be approved are two microorganisms (*pseudomonas* bacteria) whose genetic code was altered to promote their capacity to absorb certain contaminants for use in soil decontamination.

The 1994 law on transgenic organisms incorporates the European Community directives into Spanish legislation and includes penalties of up to 50 million pesetas for the most serious infringements.

It also takes into account the possibility of this research leading to emergency situations or health risks in which case regulations on civil protection and health would become applicable. (Extracted from *EFE*, 2 May 1995)

United Kingdom

BBSRC/EPSRC joint programme in bioinformatics

The UK Biotechnology and Biological Sciences Research Council (BBSRC) and the Engineering and Physical Sciences Research Council (EPSCR) are establishing a new joint programme of support for bioinformatics. The lead secretariat for the programme will be BBSRC's Bioinformatics Group, which is working closely with other relevant areas of the Council, including the Chemicals and Pharmaceuticals Directorate.

It is intended that the group will have oversight of the SEQNET service at the Daresbury Laboratory and the bioinformatics activities of AGRENET at Harpenden, liaise with other research councils and funding organizations and develop a policy for the support of bioinformatics.

Details from: Debbie Harding, BBSRC, Polaris House, North Star Avenue, Swindon SN2 1UH or on 01793 413 341. (Source: *Biotechnology Bulletin*, June 1995)

Research to focus on biotech/catalysis

Biotechnology and catalysis are the key areas for chemical industry research over the next 10 years, according to the UK Chemical Industries Association (CIA).

The CIA has produced a report—*Chemical Industry Research Priorities*—designed to be complementary to the report of the chemicals panel of the UK Government's Technology Foresight Programme.

Biotechnology and catalysis were deemed joint top priorities overall, followed by materials and process technology. Separations, analytical chemistry and modelling were in joint fourth place.

The CIA report calls for "a major change in the way in which government research funding policy is determined and implemented: the concept of partnership between government, industry and the academic community must be vigorously pursued". (Source: *European Chemical News*, 1-7 May 1995)

Government promotes biotechnology

Many sections of UK industry are missing out on vital opportunities because they are ignorant of the potential benefits biotechnology holds for them, according to the Department of Trade and Industry.

To remedy this, the DTI has launched "Biotechnology Means Business", particularly aimed at raising awareness of biotechnology among sectors not currently using this technology, with the overall aim of making UK industry more competitive.

The Government has pledged £10 million ($15.8 million) to the project backed by a technical support service, seminars and technical literature.

The pharmaceutical industry is one section which has successfully exploited biotechnology but the chemicals industry falls into the "high opportunity available, low current awareness" category.

Ernst & Young (Cambridge: Tel.: ++1223 461200) has brought out a report "European Biotech 95: Gathering Momentum", that confirms the DTI's view that biotechnology has a promising future.

The study suggests that, unlike the situation in the US, European biotechnology companies are confident of growth and show few signs of downsizing or consolidation. (Extracted from *Manufacturing Chemist*, May 1995)

BBSRC and WFU on bio-communication

Members of the Women's Farming Union (WFU) are working with the Biotechnology and Biological Sciences Research Council (BBSRC) to introduce the UK public to new technologies in agricultural and food production.

The aim is to stimulate public awareness of, and interest in, new opportunities, which range from the development of crops naturally resistant to pest attack, through to plants designed to produce safe and cheap vaccines for animals, including humans. The main focus of the initiative will be an exhibition taken to seven agricultural shows during summer 1995. Details from BBSRC, Polaris House, North Star Avenue, Swindon SN2 1UH or on Tel.: 01793 413 200, Fax: 01793 413 201. (Source: *Biotechnology Bulletin*, June 1995)

United States of America

Bioindustry "haves" and "have nots"

By the beginning of 1995, the US biotechnology industry was made up of 1,050 firms. Each of these companies has been verified as having been started to utilize the new biotechnologies as the basis of their R&D or manufacturing efforts, and excludes suppliers, service providers and "deceased" firms. In addition, there are an additional 170 companies, often larger corporations, that are not necessarily based on biotechnology but have a significant biotechnology programme. All of these firms and corporations are described in the Institute of Biotechnology Information's new reference book by Dr. Mark Dibner, *Biotechnology Guide USA: Companies, Data and Analysis*.

Of 29 different categories used to classify the primary areas of R&D and/or manufacturing focus of the more than 1,200 listed biotechnology firms and corporations, therapeutics make up the largest segment of the industry, followed by clinical diagnostics and plant agriculture.

In spite of the overall growth of the biotechnology industry, analysis of some key indicators of its health reveals some frailty. While the average size of a US biotechnology firm is 91 employees, the median number is only 29. This discrepancy between average and median values is also seen with R&D budgets and expected revenues. While the average R&D budget and expected revenues for a firm are $9.7 million and $15.6 million respectively, the median values are only $2.5 million and $2.6 million. These differences are thought to be due to the wide, and apparently increasing, gap between the "haves" and "have nots" in the industry. Companies such as Amgen, Chiron and Genentech skew the average values, while the median more accurately reflects the "typical" biotechnology firm which is smaller in size, has limited financial resources for R&D and has few to no products in the market. In fact, of an estimated $16.44 billion of total expected revenue for the 1,050 biotechnology firms in 1994, nearly 40 per cent was contributed by just 10 companies.

The US Food and Drug Administration (FDA) has been approving about two to five biotechnology drugs (or new indications for using existing drugs) each year, and does not look likely to quicken its pace dramatically. Thus, by the year 2000, it is expected that only about 50 biotechnology derived drugs will be on the market and perhaps 20 biotechnology firms will develop and market these products, the remainder being developed and/or sold by larger drug companies, with some royalties going to biotechnology firms in many instances.

Details of the 710-page report, priced at $249 (plus applicable taxes and shipping), is available from The Institute of Biotechnology Information, P.O. Box 14569, Research Triangle Park, NC 27709-4569, USA or on +1 (919) 544-5111, Fax: +1 (919) 544-5401. (Source: *Biotechnology Bulletin*, June 1995)

Outsourcing seen as key survival strategy for cash-strapped biotechs

Outsourcing is becoming a preferred survival strategy for cash-strapped emerging companies trying to eke several years of product development out of two years' worth of cash, said industry observers at the annual Biotechnology Industry Organization (BIO) meeting in San Francisco in May 1995.

According to the biotechnology and life sciences segment of KPMG's new "how-to guide" for operations, *Blueprint for Growth: Building the Biotechnology Business*, the professional services firm said that they found that start-ups are outsourcing nearly all aspects of early research and pre-clinical work to academic medical institutions,

teaching hospitals and contract research organizations until the products reach later stage trials.

They are also exploring creative partnering and hiring executives from outside the biotechnology industry, often recruiting old professionals from the giant pharmaceutical houses, according to the study. Venture capitalists are looking to invest in firms that demonstrate an ability to manage cash efficiently and change direction quickly. Outsourcing, cheaper and more flexible than hiring staff, may be the answer. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 5 June 1995)

National Agricultural Library, Beltsville, USA

This large agricultural library has developed an extensive biotechnology information service. They have an excellent on-line information capability via World Wide Web: http://WWW.inform.umd.edu/E'tRes/Topic/AgrEnv/Biotech.

They can also be contacted on the Internet as follows:
biotech@nalusda.gov
gopher.nalusda.gov
telnet.inform.umd.edu
gopher.inform.umd.edu.

(Extracted from *Australasian Biotechnology*, Vol. 5, No. 2, April 1995)

IMAGE characterizes cDNA clones

The Integrated Molecular Analysis of Gene Expression (IMAGE) Consortium is an international group of laboratories collaborating to characterize clones from shared arrayed cDNA libraries, integrate all data, and make clones and data publicly available. Information and resources generated by the consortium are expected to facilitate gene mapping and sequencing as well as gene-expression studies.

Organized in 1993, the consortium is now working with over 100,000 arrayed clones from 18 different libraries. LLNL is arraying these libraries for replication and distribution world-wide. Each clone in the shared libraries is given a simple, unique identifier (IMAGE CloneID) that enables integration of sequence, map, and expression data generated around the world by laboratories of various sizes, expertise and interests.

IMAGE collaborators deposit their data into public databases. Over 70,000 sequences, at least 28,000 of which are non-overlapping, are already in dbEST (http://www.ncbi.nlm.nih.gov/dbEST/index.html). Most work has focused on the normalized infant brain cDNA library from Soares. The Soares library array consists of more than 40,000 clones; more than 20,000 single-pass sequences have been generated, and over 4,000 cDNAs have been mapped to chromosomes. Data from 106,394 clones have been loaded into the Genome Data Base (GDB), with more expected over the next few months. All clones in the IMAGE Consortium arrays have preassigned GDB accession numbers, so the mapping data submitted to GDB is highly amenable to crossing-database coordination and integration.

Towards the master array

Lennon, Polymeropolous, Soares, and several other mapping and sequencing teams participated in a 1991 DOE initiative to enrich the developing physical maps with gene loci and open broad access to resulting data and resources. DOE continues to support Soares' production of cDNA libraries for other tissues, with derivative normalization and subtraction from previously characterized clones. With NCHGR support, Soares is further developing technology for generating full-length cDNA libraries. As incremental improvements are made, they will be incorporated into the continuing production of the tissue-specific libraries.

Under IMAGE auspices, the normalized Soares brain libraries are the centrepiece of the cDNA sequencing effort supported by Merck & Co. at Washington University. In February, Merck announced the availability of 15,000 expressed human gene sequences; 200,000 to 300,000 are expected within the next 18 months. Rates of over 5,000 sequences per week are being achieved, providing a "tremendous boost toward identifying at least one cDNA clone per human g ", Lennon said.

Later this yea he IMAGE Consortium expects to make available a "master array"—a non-redundant set of cDNA clones representing the genes identified—from each human gene transcript.

Participation welcome

The IMAGE Consortium is currently arraying other high-quality cDNA libraries and invites the participation of any laboratory willing to abide by consortium guidelines. Participants agree to place all sequence, map and expression data arising from the use of IMAGE clones into free public databases. This data must be associated with the clone's unique identifiers. IMAGE clones are currently distributed freely and will soon be available from commercial distributors for a nominal fee.

For more information on IMAGE, send a message to info@image.llnl.gov or access the WWW site (http://www-bio.llnl.gov/bbrp/genome/genome.html). (Source: *Human Genome News*, March/April 1995)

Culture clubs need "sustained funding"

Microbial culture collections in the US are facing challenges that threaten their survival even though they are recognized as vital to basic research and to several industries.

These stores of micro-organisms, mammalian and plant cells, and other elements face restricted funding, a shortage of trained personnel and rapid changes in technology which make maintenance more expensive.

Despite the value of these living archives, microbiologists are finding it difficult to muster support for preserving them. They complain that few appreciate the role of such collections and their plight has little immediate appeal to elected officials or the public.

The National Academy of Sciences held a meeting in Washington, DC to review the situation.

Other national Governments are committing substantial sums to build, purchase, and maintain similar collections. Japan, for example, has been purchasing culture libraries from US companies and universities, in a move that is both envied and feared by US scientists in the industrial sector. Within the US, even the usual resources that might be tapped for support are on shaky ground these days.

Although a few biotechnology companies have interceded to rescue special microbial collections from retiring university professors, much of the industry lacks the cash for such gallantry. Meanwhile, the federal agencies, microbiology's historical supporters, are preoccupied with a Congress that is intent on reducing the federal deficit and slashing overall programme budgets.

Alternative approaches for funding include charging higher user fees or levying universal fees on relevant federal research programmes. But neither approach will have much impact if federal research budgets continue to shrink. Moreover, when the American Type Culture Collec-

tion (ATCC) recently raised some of its prices to offset a drop in federal revenues, orders from researchers dropped off.

The ATCC, a non-profit corporation that maintains nearly 150,000 cultures at its headquarters near Washington, is one of the two largest collections in the US. The other is supported by the US Department of Agriculture (USDA) in Peoria, Illinois. Besides these major holdings, there are dozens of smaller sets elsewhere in USDA and in other federal agencies, universities and corporations.

The small and medium-sized compilations at universities, developed typically over decades and often with considerable federal support, are the most at risk. But even the venerable ATCC and the USDA collections are facing budget uncertainties. Indeed, with some powerful members of Congress seeking to eliminate the entire USDA, anxieties over culture collections tend to be overshadowed by a more sweeping question of whether whole programmes will be dismantled.

Moreover, data management is becoming an increasingly costly effort for ATCC. This year, for the first time, ATCC began selling its information-loaded catalogue to recover costs. And, although comparable information is made available for free over the Internet, ATCC is thinking of selling its overall database.

If everyone moves quickly before the Internet begins charging, however, it may help to address another problem concerning the medium-sized and smaller collections. Because no one knows precisely what holdings are out there, their value, and the dangers they may face, the experts recommend developing a full inventory of the collections. One proposal is that researchers compile information on an internationally accessible electronic bulletin board as a first step. Once more is known about these archives, it will become more feasible to determine their value and how to maintain them.

These culture collections face a big philosophical problem: scientists find such work unglamourous compared with basic research. The worry is that the research community will not really appreciate what is there until after some of the now-corroding stores have disappeared. (Source: *Chemistry & Industry*, 1 May 1995)

D. RESEARCH

Research on human genes

DNA discovery seen as major step towards common kidney disease cure

The long hunt for the DNA behind a condition known as polycystic kidney disease (PKD) has finally revealed the genomic sequence and cDNA for most cases.

Scientists said that identifying the gene will spark intense research in this disease, perhaps leading to diagnostics and an effective treatment or cure. PKD is viewed as a good candidate for gene therapy.

Following the lead of cystic fibrosis researchers, the PKD research community is devoting an initial $40,000 one-year grant to the establishment of a PKD gene mutation registry, which will be similar to the CF consortium's effort, with one major difference; the information will be exchanged electronically on the Internet's World Wide Web, rather than in a printed newsletter, as was the CF genetic information. In addition, the National Institutes of Health will be funding more research into the disease.

Although there are three major teams working on the genetics, there are thought to be about 30 or 40 groups currently exploring various aspects of PKD and that number is multiplying.

In April, the scientific team from Johns Hopkins Medical Institutions, Los Alamos National Laboratory and IG Laboratories—calling itself the American PKD1 Consortium—published in *Human Molecular Genetics* the complete genomic sequence of the gene—called PKD1—that causes this disease.

That was followed, just a few weeks later, by a paper in *Cell* of the full genomic structure along with the cDNA of the same gene by a team, known as the International PKD1 Consortium, from Harvard Medical School's Brigham and Women's Hospital, the European Molecular Biology Laboratory in Heidelberg, Germany, the Imperial Cancer Research Fund, London, and Millennium Pharmaceuticals, Inc. This work was led by Stephen Reeders of Brigham & Women's, who was part of the original group that pinpointed the chromosomal region of the PKD gene in 1985.

It has taken nearly a decade to advance from the general location of the gene on chromosome 16 to the actual gene because of PKD1's "reiterated structure". Then the European Polycystic Kidney Disease Consortium (EPKD), found a family that had two conditions, PKD and tuberous sclerosis. In members of this family, the scientists identified a translocation of chromosomes 16 and 22, and reasoned that the PKD gene would most likely be found near the chromosomal breakpoints. EPKD published a partial genomic sequence and cDNA in June 1994.

PKD is one of the most common inherited diseases. About one half of the people who inherit the disease end up with renal failure. PKD also results in other complications, such as hypertension, kidney infection and kidney stones, liver cysts, chronic abdominal pain and several cardiovascular problems, such as brain aneurysms. There is no cure for the disease. Dialysis and surgery are the only options, although scientists are testing certain experimental drugs, such as taxol. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 15 May 1995)

Parkinson's foetal cell transplant success encouraging to biotech firm

The recently reported success in transplanting foetal brain cells into a Parkinson's disease patient has been noted with keen interest.

In a landmark study published in the *New England Journal of Medicine*, doctors transplanted human foetal cells—obtained from the tissue remains of seven abortions—into the brain of a Parkinson's disease patient, and those cells grew and produced dopamine. The patient's Parkinson's symptoms were clearly reduced.

The doctors took foetal cells from seven donors and implanted them into the man's brain. The procedure was done in two operations a month apart in February and March 1993.

The patient began to show improvement one month following receipt of the transplanted tissue and continued to make progress after that. Doctors put the patient on immunosuppressive drugs for six months to prevent rejection. There were no incidents of rejection and the drug treatment was slowly decreased and then stopped after six months.

The patient improved so well, that 18 months after the transplant he decided to have surgery to correct a long-standing ankle injury. Two weeks after surgery, while he was recuperating from the operation, he died suddenly from a massive pulmonary embolism associated with the ankle surgery. The autopsy findings, however, proved that the transplantation had worked. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 15 May 1995)

Tokai University identifies and isolates gene that causes spinal muscular atrophy

Professor Shigehiro Ikeda et al. of Tokai University, Department of Medicine, have successfully isolated and identified the causal gene of spinal muscular atrophy (SMA). This result was collected by the Ikeda genome dynamics project which was carried out until September, 1994 by the innovative science/technology promotion organization (ERATO) of the new technology agency that is a branch of the Science and Technology Agency. The confirmation of the isolation/identification of the ESMA gene came to light in the final month of the project. Contact with a magazine revealed that a French research team had also submitted a thesis on isolation/identification of the SMA causal gene The details remain unclear, but it seems that both teams found the SMA causal gene at about the same time.

SMA is the most serious neuromuscular disease after muscular dystrophy and myotonic dystrophy. It is an illness caused by the inheritance of a recessive gene and the clarification of the causal gene had long been awaited. The SMA causal gene found by Mr. Ikeda et al. is a gene (SMA gene) which is believed to be associated with the remaining life of a cell and with the central-nervous mechanism of planned cell death (apotothis). This gene has been found to be partially deficient in patients with spinal muscular atrophy type I. The discovery of this SMA gene seems to be a foothold for clarification of nerve cell differentiation, remaining cell life and apotothis. Mr. Ikeda et al. were able to isolate and identify the SMA causal gene

through the establishment of a strategic position in Canada where systematic analysis of genetically impaired lineage as well as a system of research cooperation had been arranged. Cooperative research with the Canadian genealogical disease network (CGDN) was arranged. In Canada, where there is a high frequency of genetic disease, the Canadian genealogical disease network (CGDN) has been promoted as a national project with the aims of clarifying hereditary disorders and genetic therapy. Ten sites have been prepared in Canada. The Ikeda genome dynamics project established a functional analysis group at Ottawa University, Department of Medicine in February 1992, and has been conducting research in cooperation with the CGDN. There are many projects in ERATO, and the Ikeda genome dynamics project is the first one which has established a research base outside of Japan (Source: *Nikkei Biotechnology*, 19 December 1994)

University of Tsukuba develops technology to verify condition of inserted genes

The joint team of Professor Kazumasa Taira of the Applied Biochemistry Department, University of Tsukuba, and Hamamatsu Photonics Co., Ltd. (Hamamatsu Photonics), developed a technology to confirm whether extraneous genes introduced into a cell are still connected or decomposed. The confirmation is made with a light-reacting fluorescent dye attached to both ends of the nucleic acid to be inserted into a cell. This dye enables a researcher to confirm the behaviour of inserted genes, so that the new technology is expected to be useful in developing new genetic drugs.

Inserted genes can be easily decomposed by an enzyme in a cell. Previously, no confirmation method was available to check if these extraneous genes were successfully inserted. There was no way to find out the detailed mechanisms for the onset of new function after the gene insertion.

The joint team targeted only ribonucleic acid (RNA) of the nucleic acids to be inserted, and attached two kinds of fluorescent dyes that react to specific light to the two terminals of the RNA, respectively.

The dye attached to one end would react to light with a wavelength of 0.5 micron and emit light with a wavelength of 0.53 micron; the dye attached to the other end would emit light with a wavelength of 0.6 micron.

If an RNA with the dyes is decomposed and the two dyes are separated, the emitted fluorescent light will be altered. Thus, it is possible to find the condition of the RNA. If it is confirmed that the inserted RNA is functioning properly inside a cell, it will be possible to design RNA's with a high insertion efficiency.

The technique to control the function of a host gene by inserting a segment of an extraneous gene into a cell is called the antisense technology. This technology can be used to treat difficult diseases such as cancer and AIDS by suppressing the function of the genes that cause the diseases. The newly developed technology appears to be useful for developing new antisense technological techniques and new biotechnological medicines. (Source: *Nikkei Sangyo Shimbun*, 31 March 1995)

Trojan tricks

The main problem in designing effective anticancer drugs is how to smuggle them past cell wall defences to where they are needed. US chemists have now designed a "Trojan" drug that can trick its way into the cancer cell and do battle.

Raymond Bergeron's team at the University of Florida has designed a replica of a polyamine that cancer cells need to survive: it stabilizes the cells' DNA by helping DNA repair itself. The tumour cell allows the polyamine look-alike to enter and then stops producing its own polyamines. This throws the cell's DNA into turmoil and the cell dies.

Bergeron's approach is new. Previous attempts have tried to block the enzymes that regulate the polyamines. They failed because the enzymes renew themselves frequently, making it impossible to deliver enough drug to keep holding back the refreshed stocks.

The team's polyamine analogue is called diethylnorspermine. Laboratory tests with rodents have shown that the drug readily enters tumour cells, raises polyamine concentrations and blocks production of the natural compound. Details of the work will be published in the *Journal of Medicinal Chemistry*.

SunPharm, a small pharmaceutical company in Florida, has already licensed Bergeron's drug and Warner-Lambert is co-sponsoring clinical trials studying cancers of the lung, the pancreas and the skin. (Source: *Chemistry & Industry*, 19 June 1995)

RIKEN discovers gene to induce differentiation of nerve cells

The Institute of Physical and Chemical Research announced it had discovered the "gene which induces differentiation of nerve cells", which is useful in clarification of the development and differentiation of cranial nerve cells. Cranial nerve cells have a considerable relation to brain functions, including memory, thought and vision. It is believed that the discovery of the gene that induces differentiation would be useful not only in the research on brain function, but also in the treatment of geriatric senility and nerve diseases, which will become problems in an ageing society. Nerve cell growth is arrested through action on specific sugar chains, and nerve cells undergo "metamorphosis" into long and narrow cells. This is the stretching phenomenon of nerve processes known as the "phenomenon of induction of nerve cell differentiation." The nerve processes formed in this manner make up the nerve network of the brain that transmit information.

What the research group of the Institute of Physical and Chemical Research discovered is the enzyme gene that induces differentiation of nerve cells. They confirmed the course from the arrest of growth to the stretching of nerve processes through experiments in which this gene is inducted into nerve cells. Furthermore, nerve cells whose differentiation is induced by this gene were also shown to produce the enzyme acetylcholinesterase which breaks down acetylcholine, the substance that transmits nerve information. Accordingly, it is believed to participate in the transmission of nerve information as well.

The cells of organisms differentiate to form cells of various tissues. Nerve cells similarly undergo metamorphosis into long and narrow cells that make up the nerve network of the brain. Sugar chains are the substances that work to bring about this metamorphosis. Sugar chains are reputed to have the function of inducing cellular transformation and of identifying harmful viruses. This research group also conducted research into sugar chains on the genetic level. Gangliosides of sugar chains have been

discovered to arrest the growth of neuroblastoma tumour cells, to promote cell differentiation and to extend nerve processes. The current results were born from research on the genetic level into the action of gangliosides.

In that research, the research group discovered the current genes by using the "selection method" of artificially creating enzymes that induce differentiation of nerve cells by selecting groups of genes that synthesize gangliosides and inserting them individually into nerve cells. (Source: *Nikkan Kogyo Shimbun*, 2 December 1994)

Progesterone takes on dual role

A recent discovery could lead to new treatments for nerve injuries and diseases like multiple sclerosis. A French team has found that the female sex hormone progesterone has another role in the body: it helps to protect and repair nerve fibres.

It is well known that glial cells in the central nervous system produce progesterone. This steroid is thought to modulate the transmission of nerve signals.

Now new research has shown that progesterone is also made by Schwann cells in the peripheral nervous system, where it appears to encourage the repair of damaged nerves. It does this by stimulating the growth of myelin, a fat-like substance that forms a protective sheath around nerve fibres.

The researchers, from the University of Bordeaux, INSERM in Bicêtre, and CNRS-College de France in Paris, studied progesterone and its precursor pregnenolone in the sciatic nerve of mice. On freezing, the nerve fibres degenerated quickly.

The team found that in the frozen zone, nerve fibres regenerated quickly. The Schwann cells started to restore the damaged fibres within one week by coating them with myelin (*Science*, 1995, **268**, 1500).

Both steroids increased the number of layers in the myelin sheath. When the synthesis or action of progesterone was inhibited, the result was sheaths with few layers. The scientists found no difference between the steroid-induced sheaths and normal sheaths.

The scientists propose two explanations. They suggest that the progesterone produced by Schwann cells might act on adjacent nerve cells indirectly, by activating a signalling mechanism that starts myelin synthesis.

More likely, they say, progesterone might directly enhance the formation of new myelin sheaths. Schwann cells contain receptors for progesterone. These receptors appear to control myelin-building. Progesterone might encourage Schwann cells to synthesize myelin's specific lipids and proteins.

The team is investigating whether progesterone also stimulates myelination in the brain and spinal cord. Initial results are encouraging, reports team member Etienne Baulieu. High concentrations of these steroids are also present in the human sciatic nerve. (Source: *Chemistry & Industry*, 19 June 1995)

Repairing brain damage with genetics

A new technique developed by researchers in the US promises new therapies for diseases such as Alzheimer's. Implanting genetically-engineered cells into a damaged portion of the brain could prompt its recovery.

The researchers are the first to use genetically-engineered cells to explore the role of the neurotransmitter acetylcholine (ACh) in the brain. Learning and memory are thought to depend on nerve cells that respond to ACh. For example, in Alzheimer's disease, the nerve cells that supply the higher brain regions (neocortex) with ACh degenerate. But until now, scientists have been unable to prove a direct link between a lack of ACh and mental processes.

Now a team from the University of California, San Diego, and the Veteran Affairs Medical Center, claims it has shown that ACh is necessary for learning and memory. They also report that they can restore learning and memory abilities to brain-damaged rats.

The group studied rats with damage in the area of the brain that provides ACh to the neocortex. Some of the rats received brain transplants of skin cells that had been genetically modified to express the enzyme choline acetyltransferase (dChAT). This enzyme converts choline, present throughout the body, into ACh. The other rats were treated with cells that could neither express the vital enzyme nor synthesize ACh.

All rats performed a range of behavioural tests. For example, to test spatial learning and memory, the rats had to learn to find a hidden platform in a water maze. The dChAT rats performed well compared with a control group of healthy rats, and they found the platform significantly faster than the other test groups. Apart from this, the rats' behaviour was unaffected (*Nature*, 1995, **375**, 484).

The researchers measured the amount of ACh in the brains of each group. They found that the dChAT rats contained four to six times more ACh than the other test groups and the control rats.

The results are important because they show that the brain can recover even though the cell implants secreted ACh locally. The particular brain damage under study disrupts long-distance neural connections. This suggests that the brain's function can be significantly improved without having to repair individual connections between cells.

This work supports the use of the drug *Tacrine*—the only approved medication for Alzheimer's in the US—which increases ACh levels by inhibiting its breakdown. (Source: *Chemistry & Industry*, 19 June 1995)

RB gene said to play major role in development of every human cancer

The RB gene—so-called because of its link to retinoblastoma—plays a key role in just about every human cancer.

Robert Weinberg of the Whitehead Institute for Biomedical Research in Cambridge, Mass., said the protein produced by RB appears to be the "sole guardian" of a vital decision point in the cell cycle called the restriction point. He said there was accumulating evidence that deregulation of the restriction point transition is a hallmark of all human tumours.

The restriction point lies late in the G1 stage of the cell cycle, and appears to be the place where the cell "decides" whether to progress through the cycle or not.

"The RB protein sits as a guardian at this gate in the late G1 stage of the cell cycle". "Its function is disrupted in almost all types of human tumours", Weinberg explained.

The disruption can take three main forms, he said. The most obvious form is a functional knockout of the gene itself—perhaps caused by point mutation—so that it cannot produce the needed protein. That is the case in such diseases as osteosarcoma and small-cell lung cancer.

In cervical cancer, the E7 oncoprotein of the human papilloma virus "sequesters" the RB protein, meaning it is not available to regulate the cell cycle.

Finally, there are diseases, such as breast or thyroid cancer, in which the RB protein is bound by the cyclin D1 and thus rendered inactive. That can happen either because of an overexpression of cyclin D1 or an under-expression of its kinase CDK4, Weinberg said.

Interestingly, CDK4 is inhibited by proteins known as p15 and p16 and in between 30 and 40 per cent of all cancers, he said, p15 and p16 are knocked out, leading to hyperactivity of the cyclin D1.

The three D cyclins (D1, D2 and D3) form a highly combinatorial and redundant system whose effects—either alone or in combination—are not yet entirely known. Not all cells have all three types; T-cells, for example, express D2 and D3 but not D1.

Another cyclin—E—has also been found to play a key role; in fact, in RB-negative cells that have been treated with E-cyclin antibodies, growth is also arrested. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 19 June 1995)

John Hopkins team find strongest cancer/smoking link

A Johns Hopkins research team has produced the strongest evidence yet linking cancer-enabling genetic damage to smoking.

Dr. David Sidransky, leader of a group searching for genes that play leading roles in the development of cancers, has found what he says is "a direct micro link between cigarette smoking and its effects and the p53 gene". Mutated forms of the gene are crucial in the development of cancer.

Sidransky calls it "molecular proof" that smoking increases the rate of mutation in the gene, which is known to play a central role in cancer development. The study also showed that adding alcohol to cigarette smoke increased the risk of genetic damage even more.

In a study of 129 patients, p53 mutations were found in 58 per cent of those who smoked and used alcohol, in 33 per cent of those who only smoked and in 17 per cent of the patients who neither smoked or drank. Sidransky's group performed molecular analysis to determine the pattern of mutations in the gene in tumours of patients with squamous-cell carcinoma of the head and neck.

Sequence analysis of the regions of the p53 were performed in the tumour samples of the 129 subjects and then statistically analysed to spotlight any patient with characteristics associated with mutations of the gene. The researcher said he believed his team's findings should put an end to any doubts about the smoking-cancer link, especially when added to the "large and growing body of epidemiological evidence that has demonstrated that cigarette smoking causes cancer."

According to the American Cancer Society, cigarette smoking is responsible for about 90 per cent of all lung cancer deaths. Smoking also has been associated with cancers of the oesophagus, pancreas, cervix, kidney and bladder. Sidransky is working on developing diagnostics to identify changes in genes critical to tumour development at early stages of disease. He said he feels that early detection and surgery is the most hopeful path in combating cancers. (Source: *McGraw Hill's Biotechnology Newswatch*, 17 April 1995)

Sluggish detox enzyme raises risk of breast cancer in women who smoke

Women with a sluggish version of an enzyme that detoxifies carcinogens in cigarettes face a far greater risk of getting breast cancer, according to researchers in the emerging field of molecular epidemiology.

This branch of science, a hybrid of classic epidemiology and high-tech genetics, is striving to make sense of such mysteries as why only one in ten smokers gets lung cancer.

Although scientists concede that this kind of research is at a very early stage, they hope that finding the genes controlling cellular sensitivity may one day help doctors pinpoint those patients most at risk so that they may give specific recommendations on how to improve the odds of avoiding the disease, said National Cancer Institute's (NCI) Neil Caporaso.

Unlike the rare genetic mutations that cause cancer, such as BRCA1, the so-called susceptibility factors need to collide with a specific environmental agent to trigger the process of carcinogenesis, he said.

In the breast cancer study, scientists found that women smokers who carried the slow version of a gene, known as NAT (for N-acetyltransferase)were eight times more likely to get breast cancer than non-smokers with either version of the enzyme. Smokers who were fast-acetylators did not have an increased breast cancer risk.

In comparing the genetic makeup of 159 post-menopausal Caucasian women who had breast cancer to 203 healthy ones, a joint scientific team from the National Cancer Institute and SUNY/Buffalo found two versions, or polymorphisms, of the NAT gene. Women with the fast acting gene, the fast-acetylators, had a much lower risk of breast cancer than the slow-acetylators.

The presence of this gene may help to explain the rise in breast cancer among certain populations. Earlier epidemiological studies had failed to conclusively show a link between breast cancer and cigarette smoking.

Although the researchers said that the smoking study is one of the strongest to date showing a connection between a specific susceptibility gene and cancer, other projects are seeking the genes that cause a variety of other types of tumours, such as brain and ovarian cancer. (Extracted from: *McGraw Hill's Biotechnology Newswatch*, 17 April 1995)

Research on animal genes

Gene to control salmon farming escapees

As fish farming became more common in recent years so have concerns that escaped salmon could overrun local populations of wild salmon. In Norway an estimated one million farmed salmon escaped to the wild in both 1988 and 1989.

Although the aquaculture industry has now enhanced the safety and reliability of sea-cages, public concern remains, particularly over genetically engineered (transgenic) salmon like those showing extraordinary growth portrayed last September in *Nature* (371, 209). Scientists are working on an international project to develop reversibly sterile fish that could avoid this problem altogether.

The EU-funded biosafety project, involving researchers from Ireland, Norway, France, the UK and Belgium, aims to produce a sterile transgenic salmon by introducing a gene inhibiting gonadotropine-releasing hormone (GNRH),

essential to sperm formation. A DNA molecule is being designed that will be transcribed into an antisense complementary strand, to inactivate the normal gene.

The main idea is to have a biosafety measure (sterility) in the event of escapees, but if ever the intention is to breed from the fish this has to be reversible, in this case by giving purified GNRH (by injection or feeding) when reproduction is needed. However, salmon GNRH is only expressed at very low levels in tissues, so the Irish contribution to the research is to develop a genetic switch that will control the GNRH gene in all salmon tissue.

The Norwegians have already cloned the GNRH gene and the French are studying how to inject the synthetic gene into salmon eggs. Belgian researchers are trying the same method in two other farmed species (tilapia and zebra-fish).

Opinions are still divided between enthusiasm and caution about the uses and release of genetically modified organisms (GMOs), but a reversibly sterile transgenic salmon would be an interesting use of genetic engineering technology applied to controlling escapees. (Source: *Technology Ireland*, May 1995)

Transgenic mouse develops prostate cancer

A mouse has been genetically engineered to develop a disease similar to human prostate cancer, according to a research team led by scientists at Baylor College of Medicine in Houston.

Such mice may prove useful in exploring the nature of prostate cancer, a disease that will kill an estimated 35,000 men this year in the USA alone. They will also provide an animal model for experiments on various treatment strategies, such as gene therapy, said the scientists. Currently no good animal models exist, partly because prostate cancer is a disease that appears to be unique to humans.

The transgenic mice were created through the insertion of a genetic construct that includes prostate-specific rat probasin promotor which drives expression of simian virus 40, which interacts with retinoblastoma and p53 tumour suppressors and protein phosphatase. Large, multinodular prostate tumours were found in one of the founder mice at about 10 weeks old. The Baylor team, along with collaborators from Flinders University of South Australia, University of California, San Francisco and University of Manitoba published their findings in the *Proceedings of the National Academy of Sciences*. (Source: *McGraw Hill's Biotechnology Newswatch*, 17 April 1995)

Recombinant hGH equals natural hormone

A research group at Japan's National Institute of Sericultural and Entomological Science has confirmed that recombinant human growth hormone (hGH), produced by genetically engineered silkworms, is equal to natural hGH in terms of the arrangement of 13 amino acids at the N end, molecular weight and biological activity.

The scientists succeeded two years ago in mass-producing recombinant hGH by incorporating the hGH gene (cDNA) into a virus vector and inoculating the resultant vector into a silkworm at the 5th larval stage.

When the new method is employed, about 400 micrograms (Mu g) of crude hGH are obtained from 1 millilitre of silkworm body fluid and approximately 160 Mu g of pure hGH are then extracted using only reverse-phase liquid chromatography. This process is so simple that it is expected to help markedly reduce production costs compared with conventional methods.

Mainly used for the cure of dwarfism, hGH's potential application is ageing prevention. It is possible to mass-produce the substance using bioengineered colon bacilli but this method requires such complicated steps including protein modification that it boosts production costs. (Source: *McGraw Hill's Biotechnology Newswatch*, 17 April 1995)

Ageing mice lose their faculties

A transgenic mouse that suffers similar symptoms to Alzheimer's disease patients promises to be a new valuable model for studying the illness and potential treatments. This mouse displays human-like features: its memory and ability to learn deteriorate as it gets older.

The mouse is genetically modified to express a human protein, β-amyloid. A portion of this protein accumulates in characteristic deposits (plaques) in the brains of Alzheimer's sufferers. Very few animals develop these plaques with age; rodents rarely display them at all. The lack of a suitable animal model has hampered studies of the role of β-amyloid in Alzheimer's and possible therapies.

The team from Marion Merrell Dow in Strasbourg and Scios Nova in California studied transgenic and normal mice aged 5-6 months and 9-12 months. The older transgenic mice had severe problems in several behavioural tests, while the young transgenics performed far better than their respective control groups. Apart from this, the team reported no other behavioural abnormalities or marked changes in activity.

Memory and learning difficulties get worse with age, the team conclude. Previous studies have shown that deposits of β-amyloid advance as this type of transgenic mouse gets older. Further work is now needed to see if there is a direct relationship between increased β-amyloid deposits and failing mental abilities. (Source: *Chemistry & Industry*, 19 June 1995)

Bio-engineering boosts silk worm output

Japanese research groups at Katakura Industries Co. and Kyoto University of Industrial Art and Textiles have developed bioengineered silk worms that produce one and a half to two times more proteins—firefly luciferase for example—than natural ones: the firefly luciferase is used as a marker for genetic recombination. When a silk worm is infected with the natural virus, cysteine protease is produced in its body, decomposing proteins also produced therein by means of genetic engineering.

Katakura Industries is considering employing the new-type vector (modified virus) for use in commercial production of high value-added products. (Source: *McGraw Hill's Biotechnology Newswatch*, 5 June 1995)

Ixion reports diabetes reversal in mice

Ammon Peck, an immunologist at the University of Florida in Gainesville, has propagated pancreatic tissue in culture and transplanted it, reversing insulin dependency in diabetic mice. The test results offer hope of a breakthrough technology in the treatment of Type I, Insulin Dependent Diabetes.

Peck said he was "surprised to discover the growth of new pancreatic tissue and to find that Islet-like structures grew within the new pancreatic tissue. It appears that we have isolated and grown in culture a population of stem

cells that can give rise to the development of both pancreatic tissue and Islets of Langerhans-like structures."

Ixion Biotechnology has a strategic alliance with the University of Florida and has the global rights to Peck's science not only for the diabetes work, but also for previously announced technology targeting oxalate and kidney stone diagnostics and therapies, a company official explained. (Source: *McGraw Hill's Biotechnology Newswatch*, 19 June 1995)

Forgetful fruit flies may help reveal genes controlling human memory

Researchers said they have discovered a gene that controls memory function in fruit flies—a finding that could have long-range potential in the treatment of human memory loss disorders.

Now that the gene in the fly has been identified, the hunt is on to see if a similar protein exists in higher animals, including man, said Dr. Mel Feany, a research fellow in the Department of Brain and Cognitive Sciences at Massachusetts Institute of Technology (MIT).

Feany and MIT's William Quinn, associate professor of biology, reported their findings in the journal *Science*. They report finding that a gene formerly identified by Quinn has the ability to produce a neuropeptide which controls the memory function of a common fruit fly. By altering the neuropeptide, which has a relatively small length of 600 base pairs, the scientists were able to create mutant fruit flies that could learn, but quickly lose that memory. (Source: *McGraw Hill's Biotechnology Newswatch*, 5 June 1995)

Research on plant genes

Gene analysis method to identify male sterility developed

Scientists at the Hokkaido National Agricultural Experiment Station have developed a simple method of identifying male sterile plant strains through genetic analysis, which can be used in the production of F1 (first generation hydrid) seedlings spread extensively as seeds for vegetables and flowers. The existence of mutation that causes sterility is detected by using the PCR (polymerase chain reaction) method. Previously, it took two to four years to assess one subject, but the efficiency has been raised to the point where 30 to 50 subjects can be assessed per day. The current stage confirms sterility in onions, but it seems that this technique will be applicable to sunflowers, beets and other crops. It is expected to become a powerful technique in the development of F1 seedlings.

F1 seedlings have the features of "abundant yield" and "disease resistance". Since the male and female strains must be restricted to produce uniform seeds, male sterile strains are used in the female. However, it took many years to determine whether or not the male sterile strain had developed using pairing tests, which prevented the cultivation of superior females.

The researchers notice that the gene which causes male sterility in onions is found in the intracellular organelle termed the mitochondria rather than in the cell nucleus. As a result, the decision was made to examine genes in the mitochondria. The results revealed that male sterility develops if mutation occurs in genes named cob. This indicates that chloroplast genes are squeezed in near cob genes of the sterile strain.

Thus, genes isolated from onion cells were replicated and amplified by the PCR method, and the discrimination of normal genes from male sterility genes was attempted. The results confirmed that the sterile strain could be confirmed at a glance of the electrophoretic pattern following use of the method of analysing the amplified genes termed electrophoresis. (Source: *Nikkei Sangyo Shimbun*, 22 December 1994)

The genetically engineered rubber tree

Researchers at the Rubber Research Institute of Malaysia's (RRIM) Biotechnology, Biochemistry, Molecular and Cell Biology Division have reported an important breakthrough in the successful genetic transformation of the rubber plant, *Hevea brasiliensis*. Using particle gun technology and an *Agrobacterium*-derived vector construct, the RRIM has succeeded in the transformation of *Hevea* callus tissue. Both transgenic callus and embryoid tissue expressing the inserted gene for kanamycin resistance and the reporter genes GUS (b-glucoronidase) and CAT (chloramphenicol acetyl transferase) were obtained. The entire transgenic rubber plant was then regenerated through tissue culture methodology. The expression of the GUS gene was detected in the leaves of the transgenic plant and, most importantly, also in the latex obtained from the plant. Further studies in fact, showed enhanced expression in the latex within the latex vessels of the transformed plant. It is believed that this work represents the first successful genetic transformation of *Hevea brasiliensis*.

The RRIM is excited about the potential of the transgenic rubber tree for production of pharmaceuticals and other useful products. The rubber tree is perceived to have many advantages over microbes and transgenic animals. In terms of care and maintenance, plants are much more cost-efficient compared to animals or microbial fermentation processes, requiring little more than sunlight and water. Glycosylation of proteins also occurs in the plant system and the expressed latex is free of bacteria, viruses and other potential pathogens. The expressed latex (200-300 ml per tapping from a mature tree) can be harvested non-destructively on alternate days throughout the year. The aqueous serum can be separated easily from the rubber by centrifugation.

The transgenic rubber tree is also amenable to clonal propagation (e.g. by bud grafting) and an unlimited number of clones can be generated from a single transformed plant. Finally, after an economic life span of thirty years, the rubber tree also yields a valuable tropical timber which is in great demand for export and furniture manufacturing. A possible disadvantage of this novel approach, however, is related to the fact that harvesting of the latex could be carried out only 3-4 years after planting. The work at the RRIM was done in collaboration with researchers at the University of Hertfordshire, United Kingdom and also at King's College, University of London. For further information, contact: Dr. H.Y. Yeang, Biotechnology, Biochemistry, Molecular & Cell Biology Division, Rubber Research Institute of Malaysia, P.O. Box 10150, 50908 Kuala Lumpur, Malaysia. Fax: 60 3 656 5251. (Source: *Australasian Biotechnology*, Vol. 5, No. 2, April 1995)

Desert shrub yields allergy-free latex

An unkempt, shrubby desert bush could be the source of a new form of latex rubber which will not trigger

allergic reactions, according to researchers at the US Department of Agriculture (USDA). With a little genetic engineering, it could help transform the US deserts into lucrative farmland without altering their natural ecosystem.

The plant is the unassuming desert guayule native to deserts in northern Mexico and the southwestern US. Guayule is one of many plants that produces tiny particles rich in *cis*-1,4-polyisoprene, a polymer found in natural rubber.

Currently, all natural rubber comes from the Brazilian rubber tree *Hevea brasiliensis*. However *Hevea* latex contains at least 50 proteins that can trigger allergic reactions in humans, ranging from a mild rash to fatal anaphylactic shock.

The team has discovered that guayule latex not only contains fewer proteins than *Hevea*, but that they are present at much lower concentrations. Clinical trials have shown that these proteins do not trigger allergic reactions.

It is more difficult to produce latex from guayule than from *Hevea*, where the liquid latex drips out of the rubber tree. Guayules need felling, grinding and processing.

Another drawback is that the guayule only produces rubber during the three-month desert winter, so the researchers have now started using genetic techniques to design a variety which can ignore the weather and make rubber all year round. (Extracted from *Chemistry & Industry*, 1 May 1995)

New genetically engineered wheat strain

Xu Zhaofei, a researcher at China's Institute of Wheat Research of Shanxi Academy of Agricultural Sciences, has made a breakthrough in breeding a new strain of wheat, the Winter Wheat monomer line 12057. The strain has been tested in Shanxi and was proven to be drought-resistant, with strong adaptability and high productivity.

The new monomer strain 12057 was obtained by introducing the main Shanxi wheat strain 12057 into a receptor, Abo monomer. Having conducted back crosses of several generations of the newly developed strain on outdoor fields, in greenhouses and places with various environmental conditions, Xu found that there were no significant changes in spike type, grain colour, spike tassels, and leaf shape; and no heterochromosome was found.

By inserting foreign genes into the monomer strain 12057, a variety of new strains, such as generations with different strain characteristics, a string with translocated genes, a strain with foreign origin, and a strain with amphidiploid, could be easily bred. Xu also obtained the seeds and plants with high-quality genes of monomer strain 12057 using the monomer analysis method to select the most favourable genes. (Source: *High Technology Letters*, Vol. 5, No. 1, January 1995)

Popular cereals

Dr. Graham Moore of the John Innes Centre in Norwich has not only shed light on the genetic make-up of wheat, but his discoveries may change science's understanding of all living things.

He started from a Japanese map of the genome of rice, one of the smallest in the cereal world, and a corresponding map for wheat. Many strands of DNA found in rice seemed similar, though not identical, to DNA strands in wheat.

It took the addition of a third set of facts on the organization of genes in maize to show that there are DNA homologies between rice and maize too.

Dr. Moore realized that by clustering rice's genes into 19 different blocks he could rearrange them to make up the wheat genome. Likewise for maize, millet, sorghum, and the rest of the cereal kingdom: ancestral DNA, repeated, chopped and stirred into different patterns by 60 million years of evolution.

For geneticists, Dr. Moore's work is a boon. Not only does it mean that information gleaned from the simpler rice genome can be extrapolated to other cereals, but it provides important clues as to how ancestral genes evolve. Dr. Moore suspects that similar DNA comparisons in other plants—and in animals—will yield further evidence. The human genome, after all, has lots of repeating sequences and homologies with the rest of the animal kingdom. Researchers on the human-genome project may find that there is much to learn about their ancestry from the genes of the humble mouse. (Source: *The Economist*, 6 May 1995)

Breakthrough in transgenic cotton research

The Cotton Research Institute of the Shanxi Academy of Agricultural Sciences (China) has obtained 26 transgenic anti-bollworm (anti-Heliothis) cotton plants. The plants were all proven to be positive by the State Biotechnology Centre. Markable results from the anti-bollworm tests of the plants leaves were achieved.

The Institute has developed a complete, effective transgenic system using the regenerated plants grown from cells and protoplasts. The Institute first transformed the anti-weed killer gene into cotton plants. So far, many third generation anti-weed killer cotton plants with stable characteristics have been obtained. The Institute then conducted transgenic anti-bollworm cotton plant research by transforming four kinds of bollworm-killer genes into more than 10 species of cotton plants. About 100 anti-bollworm plants selected from the above cultures will be put to further testing. (Source: *High Technology Letters*, Vol. 4, No. 12, December 1994)

Potato plant antibody genetic engineering research

The Biotechnology Research Centre of the Chinese Academy of Agricultural Sciences has selected a mouse hybridoma cell line, D73, for the production of monoclonal antibody against the three strains of Potato virus Y—pVy, PVY and Pvy. To test the effectiveness of the antibody, researchers inoculated the left half of the detached leaves of "A6" (*Solanum demissum* x *S. tuberosum*) with PVy, PVY and Pvy strains, and incubated the right half of leaves with diluted different concentrations of the purified monoclonal antibody (original 1 mg/ml) from D73 prior to the inoculations of PVy, PVY and Pvy. Test results indicated that the monoclonal antibody can obviously reduce the necrotic lesions of the leaves. Identification of heavy and light chain class and subclass of the monoclonal antibodies was also carried out by direct enzyme linked immunosorbent assay (ELISA) with goat antimouse kappa, lambda, r1, r2a, r2b, r3 and u-chain-specific antibodies conjugated to alkaline phosphatase separately. Results showed that the antibody consists of kappa, light chains, and r1 heavy chains. (Source: *High Technology Letters*, Vol. 5, No. 2, February 1995)

Breakthroughs in plant resistance genetic engineering research

Chinese scientists have successfully introduced the toxin protein genes (Bt gene) and the trypsin inhibitor gene (Cpt gene) of *Bacillus thuringiensis* into more than 500 crop plants, including Jinmen No. 7 (Jiangxi cotton), Jihe 321 (Hubei cotton), Youmen No. 3 (oil cotton), and Zhongmen No. 12 (China cotton); among them, more than 100 transgenic plants were identified. Insect-resistance testings at room temperature indicate that some of these transgenic plants show marked pesticidal capability with a bollworm mortality rate of 60-91.6 per cent. Hoping to find an effective way to control the large-area cotton bollworm problem in China by using resistance genetic engineering in a short period of time, large-scale field testing on transgenic plants is under way.

Chinese researchers started their plant genetic engineering and research in 1986. By 1991, Chinese researchers had already obtained four virus-resistant, insect-resistant, and salt-resistant tobacco plants and one weed killer-resistant soy bean transgenic plant. By 1994, the researchers made more breakthroughs in the following areas:

1. Tobacco research

1. The Institute of Microbiology of the Chinese Academy of Sciences (CAS) was the first to construct the chimaric gene of the early-stage resistant gene, such as the coat protein (CP) of anti-cucumber mosaic virus (CMV) and the late-stage resistant satellite RNA gene. The chimeric gene was then inserted into the agrobacteria. The chimeric gene-containing agrobacteria were then used to transform the tobacco plant G-140 in order to obtain a transgenic plant that was able to stably express the CP gene and satellite RNA gene.

2. The Genetics Institute of CAS cloned a wide-spectrum insect-resistant gene—the cowpea trypsin inhibitor gene, which was then modified and reconstructed onto a plant expression vector and inserted into the tobacco plants. Test results indicate that the transgenic tobacco plant is highly effective in insect resistance.

2. Soybean research

The Huazhong (Centrai China) Agriculture University constructed a genome library by isolating the favourable genes of the fast-growing root nodule bacteria from soil from the Jianghan Plain. The fast-growing genes were then inserted into the slow-growing root nodule bacteria from the soil of Heilongjiang area and obtained an engineered transgenic bacteria strain HN32. In recent years, because of the use of strain HN32, soybean production and economic profit increased 17,700 tons and 2.8 million yuan respectively in Heilongjiang, Guangxi, Sichuan and Inner Mongolia.

3. Potato research

The Genetics Institute of CAS found a new way of using a nuclease gene for controlling viroids. Researchers designed a nuclease capable of excising the viroids that were undergoing reproduction in nucleus. The nuclease gene was then inserted into potato plants in order to acquire transgenic plants. In 1993, the first nuclease gene transgenic potato plant was obtained. The achievement is believed to be significant in preventing degeneration of potato plants. Results obtained from field testings were said to be successful.

4. Technology to produce adversity-resistant seeds

1. The Jiangsu Academy of Agricultural Sciences bred a wilt-resistant cotton strain and a yellow- and wilt-resistant new strain. Both were tested on a field of 50,000 mu along the lower reaches of Changjiang River and increased production in that area by 50 per cent.

2. The Institute of Crop Breeding of the Chinese Academy of Agricultural Sciences bred a rice strain with drought-resistant and early maturing features. The new strain has been tested on several hundred mu of farmland.

3. The Guangxi Academy of Agricultural Sciences bred a new sweet rice strain, No. D1 which was tested to be drought-resistant, barren-resistant, early ageing-resistant, and high-yield. The new strain has already been widely used in China.

4. The Institute of Wheat Research of Henan Academy of Agricultural Sciences inserted the barley gene into wheat to breed a powdery mildew-resistant wheat plant.

The above results indicate that China's interest in genetic engineering research is very strong. (Source: *Science and Technology Daily*, 16 March 1995)

Putting plants to work

Better understanding of plant genetics has produced some successes. Recently, four separate groups around the world announced that they had each cloned a gene that caused *Arabidopsis*, tobacco, tomatoes or flax to produce a protein which enabled the plant to resist bacteria, fungi or viruses. Because the proteins involved have major components in common, the next step will be to design a single gene that codes for a protein that uses this common element to protect a wide range of plants against all these pathogens, but despite these advances, the suspicion is growing among geneticists that for most plant characteristics magic bullets do not exist.

Paul Christou, who recently moved from Agracetus, a Wisconsin biotechnology firm, to the John Innes Centre near Norwich, argues that inserting single genes may not do enough to increase the value of plants. Most of the more important traits, such as yield, are controlled by several genes operating together. Even some of the companies that have spent heavily on single gene transfer, such as Switzerland's Ciba, now agree.

Dr. Christou believes it would be better to transfer a set of genes encoding instructions for producing lots of enzymes, which catalyse important chemical processes in living things. Scientists already know a lot about the chemistry of enzymes. Given the genes to generate the ones that together catalyse the right reactions, plants might be convinced to produce their own protective pesticides, or pharmaceuticals or plastics, mimicking in miniature the processes that go on industrial chemistry reactors.

The idea of plants as factories-in-miniature is not new, but multi-gene methods are producing the first encouraging evidence that designing them for particular purposes is feasible. Chris Somerville, of the Carnegie Institution of Washington, DC, has inserted three bacterial enzymes into *Arabidopsis* to make substantial quantities of a biodegradable plastic belonging to a class of chemicals known as polyhydroxyalkanoates (PHAS). Britain's Zeneca and America's Monsanto are now trying to reproduce his results in commercial crops like soyabean and rape.

The practical difficulties of inserting blocks of genes into plants are not much greater than for single genes. The

real challenge is finding which sets of genes to put into a plant in the first place.

Dr. Christou thinks there are exciting opportunities beyond the ideas already offered by nature. Instead of replicating what exists, as happened with bacterial PHA genes, plants might be made to create novel synthetic pathways leading to altogether new products. As factories, plants offer three things: an abundance of feedstocks in the form of sugars or amino acids; a cocktail of enzymes that manipulate chemicals in ways that organic chemists cannot; and a neatly compartmentalized set of reaction vessels.

Different bits of plants are designed to do different things. Little cavities called vacuoles contain enzymes to break down food or make alkaloids such as nicotine. Chloroplasts contain the ingredients that convert sunlight into sugars. By mixing up the genes from different parts of a plant, chemicals normally kept separate could come together in new combinations, with unpredictable and perhaps useful results.

To test this possibility, Dr. Christou's team is taking genes that code for enzymes that make various alkaloids and inserting them into different compartments of tobacco plants. (Extracted from *The Economist*, 6 May 1995)

Rice gene that responds to stress

The research group led by H. Hirojika, head of the National Institute of Agrobiological Resources (NIAR) Transformation Laboratory, discovered that there is a gene in the chromosomes of rice plants that increases in response to stress. Normally the gene is quiet, but when the rice plant is subject to disease, injury, or other such stress, the gene makes a copy of itself and sends the copy to another site on the chromosome. This is the first time that copies of the same gene were found in rice. Being able to effectively utilize that gene will help in developing better breeds and in improving the efficiency of genetic analyses.

The gene is called a "retrotransposon". Though it is related to "transposon" genes, which move to other sites on a chromosome, a retrotransposon gene increases by making copies of itself at other sites without moving from its original location. No retrotransposon gene has ever been discovered in humans or other higher-order animals; tobacco was the only other plant in which one was found.

When NIAR investigated the chromosomes of actual rice plants, such as Koshihikari rice, from two to four of the retrotransposon were found. Then, when the researchers broke up tissue and cultured it, as many as 100 copies of the gene appeared in the same chromosome, and the researchers knew that the retrotransposon gene was increasing.

For quite some time the occurrence of unexpected variations in cultured rice cells has been known as "culturing variation". Although the cause was unclear, one explanation is that a retrotranspon takes over the functions of the gene it invades and thereby changes the characteristics of the rice.

The research group also confirmed that the retrotransposon becomes activated and then multiplies even in cases where the rice plant is gnawed by insects and becomes infected.

Genetic variation due to the retrotransposon occurs when stress is applied, and the rice plant seems to try to evolve into a plant that is better suited to the environment. If that phenomenon can be actively utilized, we can expect significantly faster breed improvements. (Source: *Nihon Keizai Shimbun*, 13 March 1995)

Research on bacterial genes

Researchers discover new bacteria

Drs. Richie Powell, James McInerney and John Patching of the Microbiology Department in University College Galway (Ireland) have recently discovered novel Archaebacterial rDNA sequences in sediments from the North Atlantic Abyss at a depth of 4,879 metres, or 3 miles.

The molecular methods used were based on ribosomal RNA gene (rDNA) sequence retrieval and analysis. These new techniques allow retrieval of sequence information from both culturable and non-culturable microbes, overcoming the identification and analysis problems associated with non-culturable organisms.

The UCG team subsequently found a further 30 of these organisms in the surface waters of Galway Bay. Simultaneously a US research group found similar bacteria in surface waters off the coasts of the USA and Antarctica. RNA analysis suggests that these Archaebacteria, as yet uncultured, represent approximately 5 per cent of bacterial activity in surface waters. This figure rises to ~4 per cent in Antarctic waters. The surprising quantity and distribution of these unusual marine Archaebacteria suggests that they may play an important role in oceanic nutrient cycles.

DNA sequence analysis shows that the marine Archaebacteria form a distinct group quite unrelated to any bacterial or Archaebacterial species previously known. Their nearest known neighbours appear to be the thermophilic Archaebacteria. However, DNA sequences of both these thermophilic microbes, and of those Archaebacteria found near hydro-thermal vents, are distinct from the marine Archaebacteria.

From an evolutionary viewpoint, these marine Archaebacteria form a new deep branch on the "Tree of Life". This discovery helps to increase our understanding of microbial community structure and diversity. Reports of their isolation by culture should soon follow. (Source: *Lebensmittel- & Biotechnologie*, 1995/2)

How bugs bask

Solar energy's advocates like to remind people that, bar the odd blast of steam or belch of lava from within, all the world's energy comes to it originally as sunlight, much of it captured through photosynthesis. They have a problem, though, when they try to proceed from this fact to the proposition that photovoltaic solar cells, which capture that energy directly, should supplant fuels made from the fossilised remains of plants that did so long ago. The problem is that plants are much better at it. The best solar cells manage to capture about 25 per cent of the energy in sunlight; photosynthesisers can secure 95 per cent. Plants and photosynthetic bacteria employ an extremely effective molecular-antenna system that absorbs individual photons and then quickly passes on the little burst of energy they carry to the "reaction centre". That is where photosynthesis proper splitting water molecules apart begins. A research team from the University of Glasgow and the Daresbury Laboratory in Cheshire has published details of the atomic structure of the "light-harvesting complex" in a strain of purple bacteria.

The team used three-dimensionsal X-ray crystallography which revealed two concentric cylinders, a couple of millionths of a millimetre across, of spiralling protein molecules enclosing a ring of overlapping chlorophyll the molecules of which initially absorb light. The ring structure means that when a photon excites one of the chlorophyll molecules, the energy transfers quickly around the ring to a point near a reaction centre, or to another light-harvesting complex which helps it on its way.

Now that one biochemical structure that efficiently captures solar energy is available as a guide, synthetic chemists can work on trying to make something like it themselves. It might become an ingredient in an efficient future solar cell. (Source: *The Economist*, 8 April 1995)

US announces breakthrough in splitting N_2

Scientists at the Massachusetts Institute of Technology claim a breakthrough in developing a way to cleave nitrogen molecules at room temperature and pressure—something that until now has only been achieved by nitrogen-fixing bacteria.

Their success, reported in a recent issue of *Science*, is seen as a first step in the long-held dream to synthesise organic compounds direct from atmospheric nitrogen, rather than having to resort to the high temperature, high pressure iron-catalysed Haber process.

Christopher Cummins and Catalina Laplaza used a three-coordinate complex centred around the transition metal molybdenum to break the triple bond between the two atoms in the nitrogen molecule. Two of these molecules could gravitate to each end of a nitrogen molecule and pull it apart, resulting in a molybdenum-nitrogen triple bond.

The MIT scientists' route has a parallel with the bacterial cleavage: although the mechanism by which bacteria fix nitrogen is not well understood, it involves the nitrogenase enzyme containing both molybdenum and iron. (Source: *European Chemical News*, 12-18 June 1995)

Code cracked of two organisms

For the first time, scientists have cracked the entire DNA code of two "stand-alone" organisms. Previously, only viruses had been sequenced fully, but these cannot survive without a host. Craig Venter of the Institute of Genomic Research and Hamilton Smith of Johns Hopkins University sequenced the genomes of the bacteria *Haemophilus influenzae* and *Mycoplasma genitalium*. (Source: *Chemistry & Industry*, 5 June 1995)

Bacteria vaccine gets to grips with cancer

A genetically engineered "live" vaccine can shrink tumours in mice without chemotherapy, US scientists claim, and it may also protect against cancer. The researchers believe this result to be "unprecedented".

The vaccine exploits a bacterium called *Listeria monocytogenes* which is found in unpasteurised milk. Unlike most other bacteria, *L. monocytogenes* can survive inside a living cell. This rare ability means it stimulates a strong immune response from its host.

Researchers from the University of Pennsylvania Cancer Center and John Hopkins University School of Medicine produced a strain of *L. monocytogenes* designed to secrete a tumour-specific antigen, in this case an influenza virus protein, which provokes an immune response against the cells associated with it. They also created kidney and colon cancer cells which make the same antigen. Both the bacteria vaccine and the tumour cells were given to the mice.

On their own, tumours do not generate much reaction from the immune system, but with the bacteria vaccine the researchers found a potent immune response. This is because the bacteria act as an extra stimulant, the team explains.

The vaccine provokes a team of fighter immune cells. Not only does this response protect the mouse from developing cancer, it is powerful enough to destroy even established tumours expressing the same antigen. It is a collaboration between the body's different defence cells that makes the response so potent, the team thinks.

This type of vaccine could prove useful against cancers associated with viruses like cervical cancer (human papilloma virus), cancer of the pharynx (Epstein-Barr virus) and liver cancer (hepatitis). About 10-20 per cent of cancers fall into this class.

Safety concerns are always a problem with live vaccines, but the team says the *L. monocytogenes* is "relatively benign". It does not produce bacterial toxins and is susceptible to a wide range of antibiotics including penicillin.

The study showed that of the 20 vaccinated mice, only four developed tumours whereas all the control animals succumbed. But the size of cancers in the vaccinated mice were much smaller than those which grew in the control group. (Source: *Chemistry & Industry*, 15 May 1995)

New species of E.Coli bacteria developed

The joint research team of the new technology agency headed by Mitsuru Yoshida, director of the Molecular Biology Research Laboratory, Daiichi Pharmaceutical Co., has succeeded in making a new species of *Escherichia coli* to bring about evolution at a rate approximately 10,000 times faster than in normal mutation. This is an experiment based on the new theory of "unbalanced evolution", which holds that one gene of a pair readily mutates at the time of cell division. A new species was created in a scant four days. There have been no examples of the creation of a new species by artificial acceleration of the biological evolutionary process.

The theory of unbalanced evolution is a hypothesis which states that mutation (replication error) occurs easily on one of two strands of DNA (deoxyribonucleic acid) which are unravelled at the time of cell division. In comparison to the conventional established theory, which holds that the probability of mutation occurring on either of two strands is equal, this new theory overturns it and attracts attention because of the expectation that it could unravel the mystery of evolution of organisms.

In the experiment, they introduced artificially synthesized cyclic DNA (plasmid) which had been altered into *Escherichia coli*. By changing the position of the mark that indicates the point where the reading of gene information they used the trick of reading genetic information only from the DNA chain on the side more likely to mutate according to the theory of unbalanced evolution. In addition, they removed the ability to correct the mutation in DNA. The probability of mutation occurring in the DNA altered in this manner was increased by approximately 10,000 times in comparison to the normal theoretical probability.

The gene that creates the enzyme which decomposes the antibiotic ampicillin was inserted into cyclic DNA to

observe the occurrence of mutation. *Escherichia coli* acquires resistance to ampicillin if this gene is present.

However, the *Escherichia coli* into which this altered DNA had been inserted loses its resistance within four days after the start of incubation. Instead, it acquires resistance to the antibiotic cefotaxime. The gene that creates the enzyme which breaks down ampicillin is surmised to change into a gene for the enzyme that decomposes cefotaxime as a result of the accumulation of mutations. The researchers believe that a new species was created in a short time, since *Escherichia coli* that decompose only cefotaxime without decomposing ampicillin have not been found. The part of the original gene which mutated is unknown, but a detailed examination of mutated genetic information is underway at present.

This pure cefotaxime-decomposing enzyme is a new substance which was first obtained from this *Escherichia coli*. In addition, the scientists found that it is possible to make useful new substances by using evolution.

The results of the current experiment have two items of significance. The first is that the theory of unbalanced evolution was empirically confirmed using an *Escherichia coli* model. The second is that it showed the prospect of being able to develop useful micro-organisms by accelerating evolution.

The theory of unbalanced evolution holds that replication errors occur in one of two strands of DNA because the replication mechanism is more complex in one than in the other. Because of this imbalance, it is possible to leave various genes to descendants. It conveniently accounts for the evolution of organisms into various forms as a function of environmental changes.

This has great practical possibilities as well. If technology can be established to the point that new species can be generated through 10,000-fold acceleration of evolution by this method, an entirely new path would be opened in the search for substances which are useful in medicine. (Source: *Nihon Keizai Shimbun*, 9 January 1995)

Bacteria degrades herbicide

Ohio State researchers have discovered a bacteria that rapidly, safely and completely degrades the man-made herbicide atrazine into its natural compounds.

Dr. Mark Radosevich, assistant professor of plant and soil sciences at the University of Delaware, who discovered the bacteria while working at Ohio State University, said: "This bacteria—known as M91-3—mineralizes atrazine, taking it down to its basic structures of carbon dioxide, ammonium chloride, carbon and nitrogen. The bacteria degrades atrazine to utilize the compound's nitrogen."

Radesovich looked at organisms in atrazine-contaminated soil and tried to isolate M91-3. The bacteria is also being studied in Switzerland, Sweden, at Ohio State, at the University of Minnesota and at the University of Dayton. Scientists are trying to determine an exact genus and species classification for M91-3, and they are also trying to decipher its DNA structure to find out what genes specifically attack atrazine-like compounds.

In addition to atrazine, Radosevich said that the bacteria seems to work well in degrading compounds in TNT and other triazene herbicides, such as cyanazine.

The bacteria has other qualities that make it useful. It grows quickly in culture; it attacks and degrades atrazine rapidly; it does not affect other natural microbes. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 1 May 1995)

Research on viral genes

Vaccine for SIV

Researchers in the UK have devised a vaccine for the **simian immunodeficiency virus**, which causes an AIDS-like disease in monkeys and apes. The vaccine contains live viruses which have been weakened by removing some of their RNA (*The Lancet*, 1995, 345, 1318 & 1342). (Source: *Chemistry & Industry*, 5 June 1995)

With gene deletion, Onyx turns cold bug into tumour-eating virus

A genetic deletion appears to be able to transform the mild mannered cold bug into a new breed of super-microbe—the tumour-eating adenovirus.

Data on the genetically altered adenovirus are so promising that Onyx Pharmaceuticals is increasing its research.

In nude mouse experiments, implanted human tumours that had grown to about the size of a pea disappeared within days after being infected with the mutant adenovirus.

"After a single injection of the virus, the tumour starts to go through necrosis, and after a few weeks it is basically gone", said Dr. Frank McCormick, Onyx's founder and vice president for research.

As the virus spreads from the injection site, cancerous tissues die and the "tumour collapses," he said.

Four months later, there was no sign of regrowth in the mice that the company followed the longest. About 50 mice have been treated so far.

Research began in earnest about one year ago, and now the company is eager to prove the principle in humans. The company has filed broad patents on the concept. McCormick said that his group is already exploring mutant adenoviruses against other cancer genes, including the retinoblastoma protein and the ras oncogene.

An adenovirus, with a gene deletion that allows it to grow only in malignant tissues, could be the answer to the gene therapist's dream of developing a replicating vector powerful enough to carry a cancer-fighting transgene to all corners of the tumour and stop at the edge.

Head and neck cancer patients will be the first to receive the mutant adenovirus therapy because scientists will need an accessible tumour mass that can easily be biopsied. They will be looking, in particular, to see how well the virus spreads through the tumour, and whether it stops when it hits normal tissue.

Should the technique work, mutant adenoviruses have the potential to treat any tumour in which the action of p53 has gone awry, including liver cancers—both primary and metastatic—and cervical cancers where p53's action is being held in check by proteins from another virus—papillomavirus, he said.

At least 50 per cent of human tumours involve a mutant, disabled p53, but there are a lot of tumour cells in which a normal, or wild-type, p53 is present yet the protein is not working for reasons that are unclear to scientists.

In normal cells, the adenovirus produces a protein, called 55k, that binds p53 and inactivates it. This action allows the virus to replicate as it pleases, eventually killing the cell.

McCormick reasoned that a mutant adenovirus, one missing the protein that disarms p53, might have the ability to kill cells where the p53 gatekeeper is asleep, while leaving normal cells with functioning p53 unscathed.

Onyx tested this mutant, crippled by the deletion of the genetic region that produces the 55k protein, against p53 positive and negative cells. They found that it only replicates efficiently in p53-negative cells, killing them, while it barely replicates in normal cells. In the animal studies, the virus has been shown to spread through the tumour, and there has been no spread into normal cells in the mice.

McCormick points out, however, that in these experiments, human tumour cells were grown in the mice, and adenoviruses do not infect mouse tissues. McCormick said that the research has moved to a rat model, using a kind of rat that can be infected by human adenoviruses. So far, there has been no apparent spread of the mutant virus to normal tissues. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 19 June 1995)

Research instrumentation

Nanopores get turned on

American scientists have designed an artificial membrane that can switch from filtering only anions to only cations, and back again. Applications range from models for biological membranes, to cheaper and simpler chemical separations.

Charles Martin and his colleagues at Colorado State University describe how metal cylindrical tubes run the whole thickness of their membrane. As well as altering its ion selectivity, they can vary the width of its pores. The smallest was 1.6 nm or 16 Å (the diameter of a large molecule is about 10 Å).

Martin used the pores in a polycarbonate filtration membrane to act as templates for his "nanotubules". These membranes contain cylindrical nanopores with radii around 25 nm that run through its complete width. Coating the walls of each pore with gold produced gold nanotubules.

By depositing gold films on each side of the membrane, the team established electrical contact between the pores and the surface. A simple change in the potential applied to the membrane reverses its ion selectivity. A negative potential makes the membrane favour cations, a positive makes it anion selective.

The tubes reject ions of the same charge and transport ions of the opposite sign, says Martin. Excess charge density on the inner walls of the tubules dictates whether anions or cations get transported. This is because at negative potentials, excess electrons gather on the walls inside the tubes while positive charges accumulate loosely within them, he explains. As a result, anions are excluded and cations get carried away. "The gold-nanotubule membranes can function as electronically switchable ion exchange membranes", the team reports (*Science* 1995, **268**, 700).

There are no examples of membranes working on this simple principle, according to Martin. The pores are the key, he adds. "The most elegant thing about this work is that the pores approach the size of molecules which opens up the possibility of filtering out an individual molecule from a mixture by size and charge."

Martin believes the membrane would be useful in industrial electrolytic processes. He is currently experimenting with the desalination of water. (Source: *Chemistry & Industry*, 15 May 1995)

Researchers use computer to generate artificial enzyme

NEC and Ezaki Glico Co. announced their initial success in the intentional modification of enzymes based on design guidelines obtained through computer simulation. This represents the realization of the modification control of the catalytic mechanism of enzymes, which has been the most difficult research task in protein engineering. It is the first empirical proof of artificial enzyme design techniques. Specifically, the natural enzyme neopullulanase, which breaks down starches, etc., was modified based on design guidelines obtained through structural analysis on the atomic level of enzymes and clarification of the catalytic mechanism using computers to efficiently produce an oligosaccharide having the function of effectively preventing caries.

They conducted computer analysis of the reaction mechanisms involved in the generation and decomposition of sugars by neopullulanase, suppressed hydrolytic reactions which block functional oligosaccharide generation by replacing specific hydrophilic amino acids in the periphery of the active section possessing that function with hydrophobic amino acids, and confirmed that the generation efficiency of oligosaccharides could be raised by 30 per cent over the efficiency of natural enzymes.

They analysed the reaction mechanism using modelling techniques which predict the steric structure of proteins and dynamic molecular calculations in dynamic structural analysis of enzymes and of intricate molecular complexes that react with them. They created artificial enzymes based on modified design guidelines obtained through analysing the reaction mechanism while displaying it through high-accuracy image display techniques.

The properties of the enzyme reactions can be altered and the production efficiency of products resulting from enzyme reactions can be raised by replacing part of the amino acids of enzymes. This technology is applicable in the food industry as well as in the fields of chemistry and medicine since it can be applied to a broad range of common enzymes and proteins in addition to saccharolytic enzymes.

For now, design guidelines are qualitative, but in the future, they will develop guidelines capable of quantitative prediction by adding the molecular orbital method that is capable of pursuing the reaction process on a microscopic level through computer analysis. They are going to establish a very reliable design technique. (Source: *Nikkan Kogyo Shimbun*, 12 January 1995)

DNA sequencing technology advances Human Genome project

Amersham International, the health science group, has announced a new technology that enables the development of novel DNA polymerases for use in DNA sequencing.

This new technology will find greatest application in automated DNA sequencing systems such as those used extensively within the world-wide collaboration to sequence the Human Genome.

"The technology could significantly accelerate the Human Genome project, bringing forward the medical benefits it holds out", says Dr. John Maynard, R&D

Director Amersham International, continuing "We anticipate that the prospects of clinical DNA diagnostics will also be improved by the introduction of these new polymerases."

The technology has been developed by Dr. Stanley Tabor and Dr. Charles C. Richardson at Harvard, the scientists who had previously modified bacteriophage T7 DNA polymerase to develop the world leading DNA sequencing enzyme Sequenase™.

Using knowledge of DNA polymerase 3-D structure, Tabor and Richardson have used genetic manipulation to understand the molecular basis of one of the key properties of Sequenase. Based on this knowledge, the Harvard scientists have used recombinant DNA technology to confer properties of Sequenase on other polymerases, including thermostable polymerases, to create a series of new polymerases with enhanced properties for use in DNA sequence analysis. Consequently, such advantageous properties as uniform band intensity and the ability to read long lengths of DNA can now be realized in other sequencing protocols, such as cycle sequencing.

"Under our agreements with Harvard we intend to make the fruits of the new technology broadly available to the research community as quickly as possible. Harvard and Amersham are committed to the joint advancement and commercialization of technologies in the field of DNA sequencing" says Maynard.

The licensing agreement is a continuation of the close relationship between Harvard Medical School and USB in developing and commercializing improved polymerases and methods for DNA sequencing. The new technology is covered by patent applications and joins the family of interrelated sequencing patents co-authored by Drs. Tabor and Richardson. Further details from Liz Miller Amersham International plc, Amersham Place, Little Chalfont, Buckinghamshire HP7 9NA, UK. Tel.: 0494 542917, Fax: 0494 542266.

Simulation software for enzyme molecular engineering developed

Fujitsu and the Protein Engineering Research Institute have jointly developed simulation software that will be useful in the molecular design of enzyme proteins. Fujitsu will begin selling the software, which runs on supercomputers. The software calculates the interactions between the atoms of enzyme proteins in an aqueous solution and can graphically depict, for example, how the overall form of an enzyme will be when part of the enzyme is altered. The software allows researchers to predict changes in enzyme activity and will be useful in the design of heat-resistant enzymes and drugs.

The software uses a supercomputer to calculate the electrostatic force (Coulomb force) acting between all the atoms of an enzyme protein that is surrounded by about 4,500 water molecules.

Fujitsu will sell the software, the basic program of which was developed by M. Sato of the Protein Engineering Research Institute, under the product name "COSMOBIO." The software will cost ¥2,000,000 and will be sold to biotechnology research organizations in universities and private firms. Fujitsu expects annual sales of 20 to 30 copies of the software.

Until now, interactions between distant atoms could not be calculated on a supercomputer, but by treating the separated atoms as a group, that calculation can be made with little error. By calculating the forces between the atoms, the changes in an enzyme's shape when one of its amino acids is replaced with another amino acid can be expressed three-dimensionally with computer graphics.

Because the simulation software can be used to predict the temperature at which an enzyme loses its activity (the transformation temperature), it will be useful in the design of enzymes that are resistant to heat. The software can also calculate the interaction between an enzyme and a substance that is affected by the enzyme's catalytic action, which may enable researchers to determine which amino groups to change in an enzyme that catalyzes other similar substances. The software will be a powerful tool in the design of highly effective pharmaceuticals that have few side effects.

Until now, the only way to find out how the transformation temperature and other such properties of an enzyme change when some of its amino groups are replaced was to genetically engineer the enzyme using a micro-organism such as *E. coli*.

Those kinds of experiments took one to two months to complete. With the new simulation software, however, the results become clear in about 100 hours. (Source: *Nikkei Sangyo Shimbun*, 17 March 1995)

Generai

The upstream sequence of cholera toxin B subunit gene: effect on CTB expression

In a work by Cao Cheng, Shi Chenguhua, et al. of the Institute of Biotechnology, Academy of Military Medical Sciences, Beijing, the effect of the cholera toxin *A* structure gene on the expression of the distal *ctxB* gene was studied by the deletion and frameshift mutation method. The results showed that the expression level of plasmid pUC19CTB, which was constructed by cloning the *Xbal* - *Eco*RI restriction fragment into pUC19 and *ctxA* gene was out-frame with the *lacZ'* gene, is about 30 μg/ml; if a frame shift mutation was introduced at the *Xbal* site of pUC19CTB, the cholera toxin *A* gene was inframe with *lacZ'* and could be translated, the expression level of *ctxB* decreased to 12 μg/ml; when a further deletion from *Xbal* to *Cla*I of cholera toxin *A* gene (about 550bp) was made and *ctxA* was outframe with *LacZ'*, *ctxB* expression was decreased twofold compared to pUC19CTB; if the *ctxA* was inframe with *LacZ'* so that *ctxA* gene could be translated, the expression level of CTB is much lower than the plasmid outframe with *lacZ'*. These observations could not be explained by the current knowledge about genetic regulation of the cholera toxin operon. The promoter found located in the cholera toxin *A* subunit gene, which is responsible for the expression of cholera toxin B subunit, may answer the question why 550bp non-coding sequence could enhance the expression of cholera toxin B subunit. (Source: *Genetica Sinica*, Vol. 21, No. 6, December 1994)

Antisense technology

AEA Technology has been awarded a two-year contract by Pfizer to develop antisense technology as a method of rapidly identifying the role of newly developed genes. The project will involve both the generation of antisense molecules and the techniques necessary for their application. A team of ten scientists from AEA's Technology's biotechnology services division will work with Pfizer research teams in Sandwich, UK and Groton, Connecticut.

The project forms part of Pfizer's wider biotechnology research initiative Pfizergen. (Source: *European Chemical News*, 17-23 April 1995)

Gene success at HGS

The US biotechnology company Human Genome Sciences claims to have obtained genetic information that represents between 80 and 90 per cent of all human genes, although the exact number is unknown.

HGS has decoded more than 500,000 partial human gene sequences, or expressed sequence tags. These can be used to identify whole genes. The company estimates that its collection represents 70,000-90,000 unique whole human genes.

"This achievement represents a major milestone on our path toward describing a virtually complete set of human genes", says William Haseltine, HGS chairman.

Scientists who wish to use the database must sign an access agreement. If they use proprietary data to develop a patentable discovery, HGS has an option to license the patent. (Source: *Chemistry & Industry*, 15 May 1995)

Easy-fit genes

Researchers at Hoechst's Japanese subsidiary in Tokyo claim to have solved one of the biggest drawbacks of genetic research. When scientists want to genetically manipulate a cell, whether it is to make transgenic animals or make protein-producing bacteria, they have to insert a stretch of DNA into the cell's genetic material. The Hoechst team has found a way of ensuring that the foreign DNA implant is absorbed and "written in" to the cell's DNA "without fail".

The technique depends on a molecule. Although "barely toxic" to living cells, it acts as a shuttle for adding DNA as it binds strongly to the double-stranded spirals. The compound can be added to a sample of the foreign DNA, the team explains, where it will bind to each section. The complex can then be injected into the cell's nucleus in the usual way. The shuttle compound attaches itself to the host's DNA greatly increasing the chance that the new material will be absorbed. (Source: *Chemistry & Industry*, 19 June 1995)

Biomaterials on tissue engineering

Biomaterials play a pivotal role in the field of tissue engineering. Biomimetic synthetic polymers have been created to elicit specific cellular functions and to direct cell-cell interactions both in implants that are initially cell-free, which may serve as matrices to conduct tissue regeneration, and in implants to support cell transplantation. Biomimetic approaches have been based on polymers endowed with bioadhesive receptor-binding peptides and mono- and oligosaccharides. These materials have been patterned in two- and three-dimensions to generate model multicellular tissue architectures, and this approach may be useful in future efforts to generate complex organizations of multiple cell types. Natural polymers have also played an important role in these efforts, and recombinant polymers that combine the beneficial aspects of natural polymers with many of the desirable features of synthetic polymers have been designed and produced. Biomaterials have been employed to conduct and accelerate otherwise naturally occurring phenomena, such as tissue regeneration in wound healing in the otherwise healthy subject; to induce cellular responses that might not be normally present, such as healing in a diseased subject or the generation of a new vascular bed to receive a subsequent cell transplant; and to block natural phenomena, such as the immune rejection of cell transplants from other species or the transmission of growth factor signals that stimulate scar formation. This review introduces the biomaterials and describes their application in the engineering of new tissues and the manipulation of tissue responses. (Source: *Bio/Technology*, Vol. 13, June 1995)

Sequence space

One approach to understanding sequence evolution is to plot the relationship of a protein's sequence to relative fitness for a specific task over the course of multiple cycles of evolution. The task can be as simple as its affinity for a receptor or as complex as its ability to turn on a specific downstream biological process. A multidimensional plot of different sequences fitness for a task is called a "fitness landscape". This is often pictured as a mountain range, with each peak representing a specific sequence that has the highest fitness for a task. Related sequences populate the mountain peak and descend into the surrounding valleys depending on their fitness. From there, less related sequences aggregate to climb another peak with another relative affinity for the task. If one is measuring affinity, for example, the stepwise affinity improvement of a sequence as you move up the mountain is called "hill-climbing." From this model, it is evident that entirely different sequences have the ability to have the same affinity for a specific task. For example, in nature, different antibodies that are capable of binding the same antigen demonstrate a diversity of sequences in the highly variable region that produces similar shape recognition.

Diversity in other proteins is more complex than antibody binding: In antibodies there is a structural framework on which are draped variable sequences, whereas in a protein there is no uniform structure and so diversity is often achieved through the use of sequences to allow the movement of structural elements. An examination of the sequence space of a small protein such as b-lactamase gives one an idea of the number of potential shapes different sequence combinations may allow. At the level of individual amino acid mutation, since the protein contains 285 amino acids and any one of the 20 naturally occurring amino acids can replace each amino acid, this protein has the possibility of 285 x 20 or 5700 different single amino acid mutations. If one could manufacture the entire universe of all the combinations of these single amino acid mutations, it would constitute 20^{285} or 10^{370} different sequences. Of course this is not possible, because it would have a mass of 10^{300} times the mass of the universe.

These numbers suggest that in a protein like β-lactamase all but a fraction of 10^{-300} of sequence space could be generated by recombination. Natural populations, such as antibodies, are thought to contain approximately 10^8 different sequences to accomplish the task of antigen recognition. At present, *in vitro* evolution techniques allow the creation of as many as 10^{10-15} molecules. (Source: *Biotechnology*, Vol. 13, June 1995)

Heart valves "may be grown"

Another science fiction dream may become a reality. Growing replacement body parts out of a patient's own tissues might now be possible, eliminating the problems of

rejection, according to Chris Breuer of the Children's Hospital in Boston, Massachusetts.

Breuer is part of a large research team, whose members are from centres spread across the USA, which is currently working on replacement heart valves. The team uses a technique called tissue engineering. This involves mincing a tiny sample of tissue from the patient's femoral artery, then growing the sample on culture plates for around two weeks, until there are about 20 million cells. These are then sorted into myofibroblasts, which form the smooth muscle of the artery, and endothelial cells, which line the blood vessels and prevent clotting. All heart valves are made of these two types of cells.

The team seeds the myofibroblast cells onto a "scaffold", a sheet of woven polyglactin fibres overlaid with a polyglycolic acid "grid" (both materials are biodegradable). The cells spread through the scaffold, and after two weeks have permeated it entirely. The team then drops the endothelial cells on top, and these quickly grow into a single layer.

The various parts of the heart valve can then be cut from the scaffold and transplanted into the patient, says Breuer. Once inside the body, the scaffold dissolves and is replaced by a collagen matrix secreted from the cells. It is this matrix that actually gives the valves their mechanical properties. After about six weeks, the polymer scaffold has disappeared completely.

The technique was only thought up nine months ago, says Breuer, and so far has only been tested on lambs. The valves worked perfectly within a week of the implant, he reports, and after six weeks looked exactly like natural valves.

The team is testing whether the implant's collagen matrix has the same structure and properties as a natural one. After that, they will see how long an animal with a tissue-engineered valve can survive. Only then will the technique be tested on humans.

According to Breuer, if the technique works, implanted tissue-engineered valves would be indistinguishable from the body's own tissues. There should be no rejection because the tissues come from the donor, and if the implant is put into a child, it should grow at the same rate as the rest of the body. (Extracted from *Chemistry & Industry*, 1 May 1995)

Natural antibiotics to fight infections in topical form

Protegrins—naturally-occurring antibiotics made by the body to attack foreign viruses and bacteria—are being developed in a cream or ointment form to be used to prevent infection from sexually transmitted diseases—including HIV, herpes, gonorrhoea, syphilis and chlamydia.

Robert I. Lehrer, professor of medicine at the University of California at Los Angeles, one of the discoverers of the substances and also discovered and named defensins, said the protegrin is a smaller molecule than the defensin, but has a similar role: to seek out and destroy any foreign virus or bacteria that appears in the body.

He noted that following the discovery of penicillin, most anti-microbials have come from products found in the soil. Protegrins, he notes, occur naturally in the body and are likely to have fewer side effects.

Lehrer says his studies and suppositions lead him to believe that defensins and protegrins – the latter discovered only in 1993 – have been around for millenia. He said that is stands to reason that for any creature to develop it would necessarily have to have substances that act as natural antibiotics to kill off invading bacteria.

The protegrins Lehrer located came from pig tissue. He reported in 1993 that the protegrin peptides were active against several bacteria in vitro, including *Escherichia coli*, *Listeria monocytogenes* and *Candida albicans*. He also reported that synthesis of the protegrin could be achieved relatively easily.

The protegrins he studied are composed of 16 to 18 amino acid residues, and contain two intramolecular cystine disulphide bonds. To date, Lehrer has discovered five protegrins and he has been able to synthesize each of them in the laboratory.

He said that producing protegrins and placing them in a type of medicated balm, ointment or cream could give women an enhanced ability to protect themselves against bacteria and virus such as those that cause AIDS and other diseases.

Lehrer said the protegrin synthesis process received a federal patent in May, and the University of California has licensed that technology to the biotechnology firm Intra-Biotics Pharmaceuticals, Inc. of Palo Alto. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 19 June 1995)

Positional cloning approach expedites gene hunts

For most scientists, searching for a disease gene means years of labouring over the mapping, cloning, and sequencing processes and considerably less time actually studying the gene and its function.

But this should soon change. A new approach called "positional candidate" is rapidly coming of age and should streamline the process of identifying disease genes within the next few years.

Based on the growing body of genome resources, the positional candidate strategy lets researchers combine information about a gene's chromosomal location with increasingly detailed genetic and physical maps, allowing for easier identification of a potential causative gene. According to the latest data, positional candidate studies already have led to the identification of over 50 disease genes.

One of the most intriguing uses of the positional candidate strategy is the recent identification of the gene causing achondroplasia (ACH), a common form of dwarfism.

The ACH gene story began in 1991 during the search for the gene responsible for Huntington's disease. That year, a group at the University of California, Irvine, reported that it had isolated an interesting cDNA that mapped to the middle of the chromosome 4 subregion possibly containing the Huntington's gene. Later studies failed to show that the gene, called FGFR3, played any role in Huntington's. Having already deposited the nucleotide sequence for FGFR3 in GenBank®, the group continued to search along the tip of chromosome 4.

The Irvine scientists did not realize it at the time, but this work with the FGFR3 gene would give them a head start later in the hunt for the gene involved in ACH.

In 1994, three laboratories reported that linkage studies had localized the ACH gene to a 2.5-Mb stretch on the tip of chromosome 4, the region where the FGFR3 gene resides. This time, investigators had no need to construct clones of the DNA region or design complex disequilibrium studies. With the sequenced FGFR3 gene as their

candidate, they acquired patient DNA samples and developed PCR primers to test for possible mutations.

Within a matter of weeks, the Irvine scientists got their answer: 15 of 16 people with ACH had the same point mutation in the FGFR3 gene.

The positional candidate approach relies on a three-step process that saves time and effort: (1) localizing a disease gene to a chromosomal subregion, generally by using traditional linkage analysis; (2) searching databases for an attractive candidate gene within that subregion; and (3) testing the candidate gene for disease-causing mutations.

With the tremendous progress in mapping human and mouse genomes and improving gene-discovery techniques, the positional candidate strategy already has amassed an impressive list of gene discoveries.

Since 1990, scientists have used this approach to find genes implicated in such conditions as Marfan syndrome, inherited nonpolyposis colon cancer, retinitis pigmentosa, long QT syndrome, Jackson-Weiss syndrome, Crouzon syndrome, Alzheimer's disease, and several others.

As impressive as this list is, recent international mapping initiatives promise to put many more human genes on the map during the next few years and make positional candidate investigations even more successful.

In February of this year, Washington University and the pharmaceutical company Merck, Sharpe and Dohme announced the first publicly available instalment of 15,000 ESTs. Launched last summer, this ambitious effort is expected to process about 200,000 cDNAs over the next 18 months. Lawrence Livermore National Laboratory is arraying clones from a cDNA library generated at Columbia University.

Meanwhile, an international EST consortium is being coordinated at the Sanger Centre. It includes the Stanford University Genome Center, Wellcome Trust Centre for Human Genetics, Généthon, Washington University, University of Cambridge, and Whitehead Institute-Massachusetts Institute of Technology. These groups joined forces to begin mapping 70,000 ESTs to 0.5-Mb intervals or better. To help speed this important initiative along, the Institute of Genomic Research donated primers for 15,000 ESTs.

Still, several challenges remain before positional candidate strategies become firmly entrenched. One concern is the need for a more comprehensive database of mapped genes. Although well over 4000 genes have been mapped, tens of thousands more must be identified to fill in blanks in the human genome.

At the same time, standard positional cloning efforts usually result in candidate intervals of 0.5 to 5 Mb, but mapping cDNAs to traditional somatic cell hybrids or by using FISH usually will not achieve this degree of resolution. Large-insert clone libraries or radiation hybrids may be needed to provide the necessary resolution.

Despite these challenges, both of which are now being addressed successfully, most experts are encouraged by the short-term success of positional candidate studies. (Source: *Human Genome News*, March-April 1995)

E. APPLICATIONS

Pharmaceutical & medical applications

Mucosal immunity

Researchers in Australia have developed a type of vaccine they hope will fight off *Pseudomonas* infections, from which up to 90 per cent of cystic-fibrosis patients die, by enlisting the less-known arm of the immune system. The technique could also lead to better vaccines for influenza, and may prove to be a powerful weapon against HIV, the AIDS virus.

Robert Clancy of the University of Newcastle in New South Wales and Allan Cripps of Canberra University have developed a *Pseudomonas* vaccine which works by activating the lymphatic system.

The vaccine made by the Australian scientists consists of dead *Pseudomonas* cells in a coating which can survive stomach acids but which dissolves in the milder environment of the intestine. At the end of the small intestine the cells come across pea-sized regions called Peyer's patches, mini-organs that serve as the front door to the lymphatic immune system. There, they stimulate the production in the lymphatic fluid of the immune system's T-cells and B-cells. The B-cells then produce antibodies. These T-cells and antibodies are different from those normally found in the blood; they are able to pass through the walls of blood vessels. So although they start in the abdomen, they can find their way to the clogged airways of the lungs.

Once there, the antibodies attack the bacteria, and the T-cells summon reinforcements in the form of general purpose bacteria-eating cells. In early tests on volunteers, the new vaccine worked well, so much so that Cortecs International, a British biotechnology company that specializes in oral vaccines, has put it into clinical trials. (Extracted from *The Economist*, 8 April 1995)

Source of possible Alzheimer drug

Marine worms may be the source of a new class of drugs to treat Alzheimer's disease, according to William Kem of the University of Florida. Kem has made a derivative of a compound called anabaseine, which the worms use to paralyse their prey. This compound binds to nicotine receptors in the brain's memory centre and seems to slow the degeneration of the learning and memory mechanisms associated with the disease. (Source: *Chemistry & Industry*, 1 May 1995)

Enzyme takes the sting out of taxol

Researchers at Genentech believe they have found a way of sidestepping taxol's serious side effects. Although it is an effective treatment for breast cancer, taxol attacks healthy tissue almost as readily as it does tumours.

The team has modified the compound to make a "prodrug", a harmless molecule which undergoes a reaction inside the body to release the active drug. Dubbed PROTAX, the prodrug is made up of the taxol molecule attached by a short linking group to a compound called cephem sulphoxide. The taxol is released when cephem sulphoxide reacts with the enzyme β-lactamase, which is not normally found in the body.

So that PROTAX will only release taxol to cancerous cells, the researchers have devised a way of amassing β-lactamase on these cells. They have developed an antibody which binds to a specific protein on the surface of breast cancer cells. By attaching the β-lactamase to this antibody, the team has made a neat little package which homes in on the hot-spots.

In theory, the patient would take a dose of the antibodies which would congregate on the cancer cells. A follow-up dose of PROTAX would then circulate around the body until it happened upon the β-lactamase joined to the antibodies on the cancer cells. The reaction between the enzyme and cephem sulphoxide would then take place, releasing taxol to attack the tumour.

The new antibody is generated in mice, explains team member Brent Blackburn, and then "humanized" in the laboratories so that the human immune system will not attack it.

So far, the treatment has only been tested on cultured human breast cancer cells, stresses Blackburn. Even so, the results are encouraging. When the cells have been treated with the enzyme-bound antibody, the prodrug is nearly as effective as taxol itself. However, PROTAX on its own seems to be only a tenth as toxic to cancer cells as taxol, which indicates that it probably will not harm healthy cells.

Taxol has several problems, explains Blackburn. It is almost insoluble, which makes it very difficult to get into the bloodstream; moreover, it can only be delivered in a toxic solvent. Plus, once in the body, it attacks bone marrow, nerve fibres and mucus membranes as well as cancer cells. Other groups have made prodrugs which are more soluble than taxol, but these are not targeted and still cause side-effects, he claims. (Source: *Chemistry & Industry*, 15 May 1995)

Food crops may hold key to "edible" vaccines

Food crops such as potatoes could hold the key to the low-cost production of "edible" high-tech vaccines such as the hepatitis B vaccine, according to scientists at Texas A&M University in Houston and the Roswell Park Cancer Institute in Buffalo.

A team led by molecular biologist Charles Arntzen reports that extracts from the leaves of genetically modified tobacco plants have been shown to cause immune responses equivalent to that provided by the conventional hepatitis B vaccine.

The scientists also report that they have produced the same immunogenic proteins in the tubers of potato plants treated with the same genetic material as that used to treat the tobacco plants.

The scientists transplanted a gene into tobacco and potatoes that is used by the hepatitis B virus to build a protein envelope. Once inside the plant, the gene causes the plant to manufacture the same protein. The plant-produced protein causes the immune system to produce antibodies against the disease in the same way as a conventional vaccine.

Arntzen suggests that genetically modifying food crops so they contain immunity-producing proteins could provide a major new tool for public health programmes, especially in developing countries.

Researchers at *Biosource Technologies* and the *Naval Medical Research Institute*, both located in the USA, recently produced an experimental malaria vaccine by infecting tobacco plants with a genetically engineered strain

of the tobacco mosaic virus. Studies at the Institute had shown that segments of protein on the surface of the parasite stimulate a strong immune response in humans against malaria. Synthetic genes were developed that manufacture these segments of the protein, which in turn were inserted in the nucleic acid of the tobacco mosaic virus by Biosource Technologies.

The tobacco plants infected with the altered virus produce large quantities of the surface protein, which is extracted by simply grinding up the leaves. The advantages of producing a vaccine this way instead of using the conventional method are that it is easier to store, and that it might be even safer, since the tobacco mosaic virus cannot infect humans. Moreover, it is cheaper since one plant may be able to produce more vaccine than a 300-litre fermenter. Biosource Technologies is also looking at possibilities of using edible plants to make vaccines against cholera.

Researchers at other institutes are currently working on plants producing potential vaccines against hepatitis B and foot-and-mouth disease. So far, these vaccines are, just as the malaria vaccine, all in experimental and/or testing stages. (Source: *New Scientist*, 21 January 1995 and *European Chemical News*, 17-23 April 1995)

Serial antigen tests may improve odds for women with ovarian cancer

Boston researchers have developed a new method for determining short-term ovarian cancer risk that they believe represents a major step towards an early detection test for the disease, which is often fatal because it is caught too late.

The technique, which relies on making several measurements over time of an antigen produced by ovarian tumours, will be tested in a forthcoming British trial involving 120,000 women. It has already been tested retrospectively using stored blood samples from women in Sweden.

The researchers from Harvard Medical School and Massachusetts General Hospital say the test appears to be the best candidate yet for screening of ovarian cancer, which will cause an estimated 14,400 deaths this year. Such a test would be greatly welcomed because ovarian tumours are highly treatable when diagnosed early.

At present, however, only about 25 per cent of ovarian cancers are detected in the early stages when 80 per cent can be cured. Those diagnosed in later stages are so treatment-resistant that the five-year survival rate is only 15 to 20 per cent. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 15 May 1995)

Cytokines under the spotlight

With no vaccine or cure in sight for AIDS, attention is switching to the role of cytokines, the proteins that act as messengers between cells of the immune system, might play in AIDS. Earlier in 1995 a team at the US National Institute of Allergy and Infectious Diseases (NIAID) reported that in some AIDS patients, intermittent administration of a specific cytokine—interleukin-2 (IL-2)—dramatically boosted the number of CD4, or T helper cells, the key immune system cells that are lost as the disease progresses.

With a growing suspicion that a shift in cytokine patterns might explain why HIV-infected individuals finally succumb to the disease, there is a growing range of research under way on cytokines, as indicated in the table below. It has been proposed that the ability to fight off HIV depends on the balance between two sub-sets of T helper cells, designated Th1 and Th2. Th1 cells secrete the cytokines IL-2 and gamma interferon, while Th2 cells secrete IL-4, IL-10 and other cytokines that activate antibody production.

Some selected cytokins

Cytokine	Major sources	Major effects
IL-1	Monocytes, macrophages, other immune cells	Induces wide range of inflammatory and immune responses
IL-2	TH1 cells	Stimulates T cell proliferation and differentiation; stimulates B cell proliferation
IL-4	T cells, macrophages, B cells	Induces differentiation of Th2 cells and of B cells
IL-10	T cells, macrophages	Inhibits monocyte/macrophage function; suppresses inflammatory cytokins; enhances B cell proliferation
IL-12	Macrophages, B cells	Stimulates differentiation of Th1 cells
TNF-alpha	Numerous cell types	Wide range of inflammatory and other immune responses

Source: *Science*, Vol. 268, p. 205, 14 April 1995

(Source: *Biotechnology Bulletin*, May 1995)

Construction of an engineered bivalent vaccine strain consisting of Vibrio cholerae CT-B and LPS-O antigens

Yu Xiuqin and Ma Qingjun of the Institute of Biotechnology, Academy of Military Medical Sciences, Beijing report that the engineered *E. coli* strain 1046 containing *V. cholerae* LPS-O and CT-B bivalent antigen genes has been successfully obtained by using DNA recombinant technique. *E. coli* 1046 (pMG305) could not only express CT-B antigen, but also secrete CT-B into medium as shown by GM1-ELISA. Meanwhile, whole cell O antigen-ELISA, bacterial agglutination test and hemagglutination inhibition assay demonstrated that LPS-O antigen could be expressed on the cell surface by *E. coli* 1046 (pMG305) and shown LPS bands specific for *V. cholerae* by SDS-PAGE assay. Mouse intraperitoneal immunization and challenge trial indicated that the *E. coli* 1046 (pMG305) provided good protection against virulent *V. cholerae*. The engineered strain reported here is expected to be a live oral vaccine candidate for *V. cholerae*. (Source: *Chinese Journal of Biotechnology*, Vol. 10, No. 4, November 1994)

Gene gun now takes aim at tumours

Until now, the gene gun has been used most often to introduce new traits, such as insect resistance, into plants, but now scientists are preparing for Phase I trials of a gene therapy in which the gun will be used to propel microscopic gold beads coated with DNA for various cytokines, into cutaneous metastases of breast cancer and melanoma, according to William B. Ershler, M.D., of the University of Wisconsin School of Medicine (UW). UW conducted the study in conjunction with Agracetus, the gene gun manufacturer.

In three consecutive experiments, tumour weight was reduced in between 30 per cent and 70 per cent of treated animals who had received sub-cutaneous injections of B 16 melanoma, renal cell carcinoma and fibrosarcoma.

Tumours were shot with DNA-coated gold pellets, carrying genes for IL-2, IL-4, IL-6, tumour necrosis factor alpha, gamma interferon and granulocyte macrophage colony stimulating factor. The researchers reported that co-transfection with two sets of cytokine genes, coding for IL-2 and IFN-gamma, eliminated tumours in 25 per cent of treated animals. These animals remained tumour-free for 60 days.

Results of these first in vivo experiments were published in the *Proceedings of the National Academy of Sciences*, 28 March, 1995.

The gun used in the current experiment is the fifth generation of that prototype, and is based on a helium pulse rather than the earlier models that used an electrical charge to propel the gold pellets. Gold is used because it is inert and non-cytotoxic.

The researchers said that there are indications that the helium pulse gun has more power and will be more effective than earlier models. Also, with the helium pulse gun, they are able to transfer DNA up to 50 layers deep into sub-cutaneous tumours. If all goes well, the trials should start in about 18 months.

Even though the gun may improve DNA delivery into cells, scientists cautioned that gene therapy in cancer is now only a very promising concept. It will take years of human tests to determine if the technique is at all effective in fighting cancer, no matter how genes reach the tumour cells. (Source: *McGraw Hill's Biotechnology Newswatch*, 17 April 1995)

Drugs combine to fight HIV

Preliminary results of two studies have shown that a combination of Wellcome's AZT and a new drug, 3TC, markedly reduced the level of HIV in the blood of infected patients.

The investigational drug 3TC, or lamivudine, is being developed by Glaxo, under licence from BioChem Pharma of Canada.

These American results confirm European data released in November 1994. The two studies, on a total of 618 patients, assessed the impact of the drug combination on laboratory markers of HIV disease.

The drugs were shown to have a prolonged and pronounced effect in both suppressing the replication of HIV and increasing the body's immune response.

They were also shown to significantly increase the number of DC4 cells in patients. Further trials involving both adults and children will start later this year. (Source: *Manufacturing Chemist*, March 1995)

Vaccines for sexually transmitted diseases advancing slowly

A vaccine to protect against gonorrhoea could soon be ready for human tests, according to Frederick Sparling, a microbiologist and physician at the University of North Carolina, School of Medicine, Chapel Hill. Sparling and his co-workers reported that there are a number of possible protein vaccine candidates against *Neisseria gonorrhoeae*, the causative organism of gonorrhoea.

Nevertheless, Sparling said that progress in the area is "frustratingly slow".

Sparling's group found that FrpB, a 70-kDa iron-repressed protein, is "immunogenic in naturally occurring infections". It is also well conserved in major isolates. Sparling foresees that FrpB could become a component in a multi-antigenic vaccine containing other proteins such as Por, a membrane protein, and Tbp2 (transferrin-binding protein 2).

Although many sexually transmitted diseases (STD) such as chancroid, syphilis and chlamydia, are treatable with antibiotics, resistant strains are cropping up. Not only are chlamydia and gonorrhoea economically important as causes of chronic infection, infertility and ectopic pregnancy, all of these STDs are implicated in an increase in sexual transmission of HIV, say the scientists. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 1 May 1995)

New gene venture

Ciba has signed a five-year deal with US-based Myriad Genetics to collaborate on the application of molecular genetics to discover genes that could lead to new therapeutic targets for the prevention, treatment and diagnosis of cardiovascular diseases.

Myriad's gene discovery strategy uses two complementary sets of technologies: the genetic analysis of large families performed by collaborators at the University of Utah and Myriad scientists, and Myriad's advanced proprietary gene mapping, gene isolation and DNA sequencing technologies.

In recent months, the company has made several discoveries, including the BRCA1 breast and ovarian cancer gene, the tumour suppressor function of MTS1 gene in many types of cancer, and the localization of BRCA2, a hereditary breast cancer gene, to a small region of chromosome 13. (Source: *European Chemical News*, 8-14 May 1995)

New MS treatment

Biogen has filed with the US FDA for US market approval for its recombinant interferon beta product (IFN-β-1a) for treatment of multiple sclerosis. Earlier the company filed a similar application in Europe with the newly operational European Medicines Evaluation Agency. It hopes to market the drug worldwide under the name *Avonex*. This is the first time the biotechnology company has filed in the USA for a drug it has developed itself. It will sell direct in the USA and several major European markets, but will seek commercial partners in other key areas. (Source: *European Chemical News*, 12-18 June 1995)

Novell drug discovery project

Warner-Lambert and BASF are entering into a "bench-to-market" collaboration.

The venture is thought to be unique in the pharmaceutical industry. The two companies will jointly research, develop and market a new class of drugs that inhibit the interleukin-1β converting enzyme (ICE).

ICE is the enzyme in human cells that generates the active form of interleukin 1β (IL-1β). IL-1β is a cytokine that is a key mediator in the early stages of inflammation and is also implicated in neurodegeneration and other disease states.

Drugs that inhibit ICE would be expected to block IL-1β production and could be used to treat various major diseases. Possible targets include rheumatoid arthritis, septic shock and Alzheimer's disease.

A multi-disciplinary team has been assembled for the collaboration, which takes advantage of the particular strengths of the two companies. (Extracted from *Manufacturing Chemist*, April 1995)

Turning tumours into vaccines

A new genetic therapy technique might combat a currently incurable form of cancer by turning tumour cells into a personalized vaccine, according to US researchers. The team has obtained promising results in mice, and hopes to start human trials by the end of the year.

Patrick Walsh and his colleagues from the University of Colorado's Health Sciences Centre wanted to force the mice's immune systems to attack skin cancers (melanomas) which had spread to other parts of the body. Although melanomas are curable if caught quickly, they are almost always lethal once they spread.

The team inserted a gene into melanoma cells which made them produce macrophage colony-stimulating factor (M-CSF). This encourages immune cells to produce several tumour-killing substances.

The researchers found that healthy mice developed lung tumours when injected with these cells. However, the cancers started to shrink within three weeks, and the mice survived. Injections of unaltered melanoma cells led to tumours which killed the mice within eight weeks. But, genetic therapies which work in animals are not always effective in humans. (Source: *Chemistry & Industry*, 19 June 1995)

Eight gene therapies clear RAC

The Recombinant-DNA Advisory Committee (RAC) of the National Institutes of Health (NIH) approved eight gene-therapy protocols at its June meeting — six clinical trials for cancer, one for AIDS and one for an inherited form of immune deficiency. The RAC also heard progress reports on the 106 protocols previously approved by NIH.

The approved protocols include:

- A trial for purine nucleoside phosphorylase (PNP) deficiency, replacing the missing PNP gene in T lymphocytes from two PNP-deficient patients.
- Two phase I clinical trials proposed to treat prostate and ovarian cancers. Both involve reinfusion of patients' lethally irradiated tumour cells that have been genetically engineered to express IL-2.
- An immunotheraphy protocol. The experiment will test an autologous tumour vaccine combined with direct injection of liposomal-DNA encoding HLA-B7 antigen.
- In another immunotherapy protocol ovarian-cancer patients' T lymphocytes will be transduced *ex vivo* with a gene encoding a chimeric receptor that binds to an antigen over-expressed on ovarian cancer cells, enabling the T-cells to recognize and destroy the cancer cells. The receptor is derived from a monoclonal antibody targeted to ovarian cancer cells. Two groups consisting of 21 patients each were approved.
- The RAC unanimously voted to reapprove an immunotherapy protocol incorporating the gene for carcinoembryonic antigen (CEA) directly into muscle tissue of patients with metastatic colorectal cancer.
- The RAC also unanimously approved a cancer study in which the Thymidine Kinase (TK) "suicide" gene is inserted into donor T-cells to prevent graft vs. host disease from developing when the transduced cells are infused into multiple myeloma patients after allogeneic bone marrow transplant.
- An AIDS protocol involves the *ex vivo* transduction of CDL+ T cells from asymptomatic HIV-infected patients with genes that are derived from F105, a broadly neutralizing human monoclonal antibody that binds to the HIV-1 envelope glycoprotein, gp120. In this case, the genes express an intracellular antibody ("intrabody") called sFv105, which is anchored inside the T-cell to the lumen of the endoplasmic reticulum and binds to nascent folded gp120 produced inside the cell, preventing it from moving to the cell surface. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 19 June 1995)

FDA clears Gen Trak for new DNA tests

Gen Trak has received approval from the US Food and Drug Administration to start marketing the CQuentials DR DNA Typing Kit, according to an official at the suburban Philadelphia biomedical firm.

The product allows researchers and clinicians to quickly and cost effectively analyse the DNA code of tissue to match donors with recipients for bone marrow and kidney transplants. This is the first product cleared for such use in the United States, and is based on a proprietary technology developed by Gen Trak, the official added.

Gen Trak is also working with the Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine to develop a DNA test based on the same technology for Beta Thalassaema, a genetic disease afflicting Mediterranean people. (Source: *McGraw Hill's Biotechnology Newswatch*, 19 June 1995)

Joint venture to market chinese-developed anti-malaria drug

The Institute of Microbiology and Epidemiology of the Chinese Academy of Military Medical Sciences (CAMMS), the Kunming Pharmaceutical Manufacturing Plant, and the Zhongxin Technological Corporation recently signed an agreement with Ciba-Geigy Pharmaceutical Company of Switzerland to develop, market and internationalize the new anti-malaria compound drug Benwuchun. Benwuchun, a

research product of the Institute of Microbiology and Epidemiology of CAMMS, is a compound of benwenchun and qinghaosu (arteannuin) derivative—haojiami (artemether). Benwenchun is effective in treating the pernicious malaria, the tertiana malaria, and the drug-resistant malaria. Results obtained from testings in Linken hospital in Hainan and in Sanya municipal hospital showed that averaged time of defervescence was 19.7 hours; the protozoan descending rate was 96.3 per cent; the blood protozoan negative transformation time was 32.5 hours; and the 28-day recovery rate was 96.1 per cent. Benwenchun can thoroughly kill the protozos without causing any side effect. The development of the compound Benwenchun and its serial products will meet the urgent needs for malaria drugs in developing countries.

Chinese researchers are planning to further conduct the clinical testings on Benwenchun and its serial drugs in Africa, East Asia and Europe after successful testings in Hainan in 1993 and 1994. (Source: *China Medical Tribune*, Vol. 15, No. 4, 26 January 1995)

New PCR kit

A new kit being issued by the National Institute of Science and Technology is expected to allow laboratories to use faster and cheaper Polymerase Chain Reaction (PCR) technology that can take hours or days instead of the current Restricted Fragment Length Polymorphism (RFLP) method, which can take six weeks. RFLP is still the most widely used form of DNA profiling.

The kit, specifically designed for use in forensic and medical laboratories, consists of 20 components, including eight vials of well-characterized human DNA, four vials of PCR-amplified DNA and two genetic ladders for measuring DNA fragments from 100 to 1,500 base pairs in length. Two human cell lines are also provided from which DNA can be extracted. There is also DNA from the same cell lines as well as PCR-amplified DNA from the cell lines and other samples.

The components are being provided by Roch Molecular Systems, of Alameda California, and Life Technologies, Inc., of Gaithersburg, Md.

The new standard is expected to have a wide effect on PCR use. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 19 June 1995)

Agricultural applications

Virus biocide field test

American Cyanamid Company has received permission from the US Environmental Protection Agency to conduct controlled, small-scale field tests of a new genetically altered bioinsecticide derived from a naturally occurring, insect-specific baculovirus.

The baculovirus has been proven to have "no significant risk to humans or other mammals, and has also been shown to have no unreasonable adverse effects in the environment", according to the company.

Autographa californica multiple nuclear polyhedrosis virus will be tested as part of Cyanamid's ongoing effort to discover, develop and market new, environmentally friendly products for use in commercial crop protection.

The new biocide will target only specific insect pests, including cabbage loopers, tobacco budworms and other crop-destroying caterpillars. (Source: *Chemical Manufacturing Reporter*, 12 June 1995)

Door opens for new antibiotics

Researchers in Germany have successfully completed a key step that could open the door to the commercial production of a new group of antibiotics. The compounds—angucyclines—are active against a wide range of microbes, especially gram-positive bacteria and *Candida albicans*.

Professor Karsten Krohn and his colleagues at the Universität Gesamthochschule in Paderborn have developed two new routes for making a number of the quinoide antibiotics.

Angucyclines are made naturally by species of *Streptomyces*. They were first synthesized in 1965, since when more than 200 have been made. But only one type—pradimicins—have reached the clinical trial stage. None are yet commercially available, and the aromatic compounds in the group have stayed stubbornly out of reach.

Now Krohn's group has managed to imitate the four-fused-ring angular structure that gives the group its name. But they cannot yet make the compounds in large amounts. (Source: *Microbiology Europe*, Vol. 3, No. 3, May/June 1995)

Rice that may inhibit herpes using genetic engineering

Rice that is not only nutritious but also protects against viral infections could be the outcome of studies carried out by a group from the University of Tokyo.

Among the many proteins in rice is a substance called cystatin, which tests have shown can inhibit the proliferation of viruses, including those that cause herpes and polio.

The researchers used the standard microinjection method to introduce an extra gene for cystatin into rice cells, and then cultured these genetically engineered cells to regenerate seedlings, which were then grown into full plants. The rice harvested from these plants proved to carry much more cystatin than normal rice kernels.

A liquid extract obtained from the rice showed 10 times greater capacity to inhibit proliferation of the polio virus in monkey kidney cell cultures, the researchers found.

It remains to be seen whether the higher cystatin levels will have any benefit when animals eat the rice. But assuming that the effect remains, the rice might eventually be developed into a kind of "functional food" consumed for its anti-viral benefits as well as its nutritional value. Since normal rice contains cystatin, chances are good that the high-cystatin rice will be safe. (Source: *The Nikkei Weekly*, 17 April 1995)

Scientists promote development of biological agrichemicals

Because of the health problems associated with pesticides, scientists are now developing a few of biological agrichemicals which are "natural", in the sense that they harness the powers of certain organisms that naturally kill crop-damaging pests.

One of the more promising natural killers is a bacteria called *Bacillus subtilis*. This bacteria is not harmful to humans, but it wreaks havoc among the bacteria that blight such important cash crops as melons and tomatoes.

Although it has been known that *Bacillus subtilis* secretes a lethal type of antibiotic, researchers at the Tokyo Institute of Technology report that this bacteria is far more deliberate in its destruction.

It turns out that not only does the bacteria release an antibiotic, but it also secretes a surface-active agent that blasts holes in the cell walls of the opposition so the antibiotic can get in easier and do its damage. And if that is not enough, the bacteria also has a way of robbing the opposition of iron ions, which is an important nutrient.

The university group says it has isolated the three genes responsible for this triple punch, as well as the genes that regulate their synthesis.

With genes in hand, it now plans to use genetic engineering techniques to produce super *Bacillus subtilis*, spelling doom for crop pests.

Fighting the pests is easy enough: just mix the killer bacteria into the soil. Moreover, since *B. subtilis* propagates with gusto on the dregs left over from tofu production, mixing the bacteria and the lees together in the soil is a nifty and natural way to provide both fertilizer and pesticide. (Source: *The Nikkei Weekly*, 20 March 1995)

Soyfoods and disease

Soyfoods have been consumed for centuries in Asian countries and soy protein has been used extensively by the food industry in Western countries for several decades. However, during the past five years there has been considerable interest among researchers in the potential anti-cancer effects of soy. In fact, soya beans are unique in that they contain the anti-carcinogen, genistein.

Soya beans are considerably higher in protein content than most other legumes, a fact which has no doubt contributed to their widespread use in the animal feed industry. About 37 per cent of the calories in soya beans are derived from protein, but it is the amino acid pattern of soy protein that is most notable. The limiting amino acids in soya beans, as for all legumes, are the sulphur-containing amino acids, methionine and cysteine. In the case of soy, however, the level of these two amino acids is high enough for soy protein to meet human protein needs by itself when fed at the recommended level of protein intake.

The traditional method of evaluating protein quality, the protein efficiency ratio (PER), undervalues legume proteins because it is based on the growth of laboratory animals, most commonly rats. Rats have a sulphur amino acid requirement which is about 50 per cent higher than humans, which means that the PER undervalues legume proteins such as soy. In recognition of the PER's inadequacy, the World Health Organization and the US Food and Drug Administration have adopted a new method for evaluating protein quality called the protein digestibility corrected amino acid score. This method compares the protein's amino acid pattern and the subject's amino acid requirements, and includes a correction factor for digestibility, to give a value for protein quality. When human amino acid requirements are used, soy protein receives a rating of one, the highest value possible.

That soya beans are such a good source of high quality protein is noteworthy, particularly because they are low in saturated fat and cholesterol-free. Incorporating soy protein into the diets of developing countries may help to address protein needs of populations with marginal protein intakes. However, in developed counties, where protein intakes typically greatly exceed biological need, it is the role of soya beans in the prevention and treatment of chronic diseases that is much more likely to attract both industry and consumers to soya bean-based foods.

One area in which soyfoods could prove to be beneficial is osteoporosis. They may aid in bone development and maintenance because soy protein does not increase urinary calcium excretion to the extent that animal proteins do, despite being equal in quality.

Soya beans are also rich in genistein and daidzein, two components which belong to a class of diphenolic compounds known as isoflavones. These soya bean isoflavones may directly inhibit bone resorption (break down). This is based on direct experimental data in animals, albeit preliminary, but it is also of interest to note the structural similarity between the isoflavones and oestrogen, which is known to promote bone health. In fact, the isoflavones are weak oestrogens. Additionally, they are very similar in structure to the drug ipriflavone, which has been used successfully in Asia and Europe to treat osteoporosis. Daidzein is, in fact, a metabolite of ipriflavone and to be maximally effective, ipriflavone needs to be metabolized. Soya beans are also rich in calcium and, despite containing both phytate and oxalate, two food components that inhibit calcium absorption, the calcium in soy is very well absorbed, to about the same extent as is the calcium from dairy milk.

It is clearly the role that genistein has in cancer prevention, and perhaps even treatment, which has attracted the interest of the research community.

Genistein is a weak oestrogen. Depending on the experimental system, genistein has anywhere from 1×10^{-3} to 1×10^{-5} the oestrogen activity of oestrogen. Weak oestrogens can function as anti-oestrogens by competing with the more potent endogenous oestrogens for binding to the oestrogen receptors within the body. Recent work in humans indicates there is enough oestrogen activity in soy to compensate for the lack of oestrogen production by the ovaries in perimenopausal and in postmenopausal women.

That soya beans contain a component with anti-oestrogenic activity is consistent with the lower breast cancer mortality rate in Asian countries where soyfoods are consumed. Of course, there are many dietary and non-dietary differences between Asian and Western countries which could contribute to this lower mortality rate. However, in a direct comparison, a recent case-control study conducted in Singapore found that premenopausal women who consumed the most amount of soy (55g day) had about a 50 per cent reduced risk of breast cancer compared with women in Singapore who infrequently consumed soyfoods.

Interestingly, *in vitro*, genistein inhibits the growth of breast cancer cells both with and without oestrogen receptors, suggesting genistein possesses other properties potentially useful against cancer. The hypothesised mechanism for the growth inhibitory effects of genistein against not only oestrogen negative breast cancer cells, but also a wide variety of cell lines, such as colon and lung cancer cells, which are not dependent on oestrogen for growth, is perhaps the most exciting aspect of the soy-cancer story.

There may even be a role for soy and genistein in cancer treatment, since *in vitro* data indicate genistein inhibits angiogenesis (blood vessel growth). Tumours stimulate the growth of new blood vessels to receive oxygen and nutrients, and to get rid of waste products; without new blood vessels tumours cannot grow beyond 1-2 mm and are clinically insignificant. There is also some preliminary work suggesting soy inhibits angiogenesis in humans. Additionally, *in vitro*, genistein is effective in inhibiting the growth of cancer cells with the multidrug resistant gene. This gene codes for a protein which kicks conventional chemotherapeutic drugs out of the cell's nucleus, making them ineffective. Also *in vitro*, genistein

enhances the effectiveness of cancer drugs against cells with the multidrug resistant gene, and works synergistically with other drugs to inhibit cancer cell growth.

Although the relationship between soy and cancer is still speculative, a growing amount of data suggests just one serving of soy per day may reduce risk for a wide range of cancers. At the very least soyfoods provide high quality protein, are low in saturated fat, cholesterol free, and high in calcium as well as other vitamins and minerals. (Extracted from article by Dr. M. Messina from *Chemistry & Industry*, 5 June 1995)

Bananas and biotech consumers

Fungi, viruses, and other pathogens wreak havoc on the world's bananas and plantains. The banana is a major tropical cash crop, bested only by coffee in the marketplace. And plantains are a food staple in many parts of Central and South America and Africa. While the banana market, valued at more than $5 billion has been the object of intense manipulation for decades, the giant herb itself has proved strongly resistant to genetic alteration for disease resistance or indeed any other trait. It was only two years ago in fact that the Fundacion Hondureña de Investigacion Agricola and Houston-based Agristar announced the development of a pesticide-free, fungus-resistant banana called Goldfinger, designed, via tissue culture methods, to repel black Sigatoka, a banana-destroying fungus. The development of disease-resistant bananas by conventional breeding has been hampered by long generation times, triploidy, and the sterility of most cultivars.

At present, the only effective method of controlling diseases that attack commercial bananas is massive amounts of aerial spraying. The ability to make disease-resistant bananas and plantains would confer at least two benefits: one to consumers, who do not want massive amounts of fungicide on their bananas, and one to the companies that would no longer need to spray in large quantities, solving their agronomic problem. Another potential benefit for consumers is that it might become possible to augment the standard Cavendish banana with which we are all familiar with the hundreds of other types of bananas that grow in Central and South America. Up to now, many companies have stayed away from banana development because manipulation by tissue culture micropropagation is prohibitively expensive and labour intensive (although, according to Wilson Kidde of International Agritech Resources, that too could change soon with the development of new liquid medium cultures).

Recent research by Charles Arntzen and colleagues at Texas A&M University and the International Atomic Energy Laboratories at Seibersdorf, in Vienna, describes a relatively simple procedure that will be immediately applicable in micropropagation laboratories currently active in banana-producing countries.

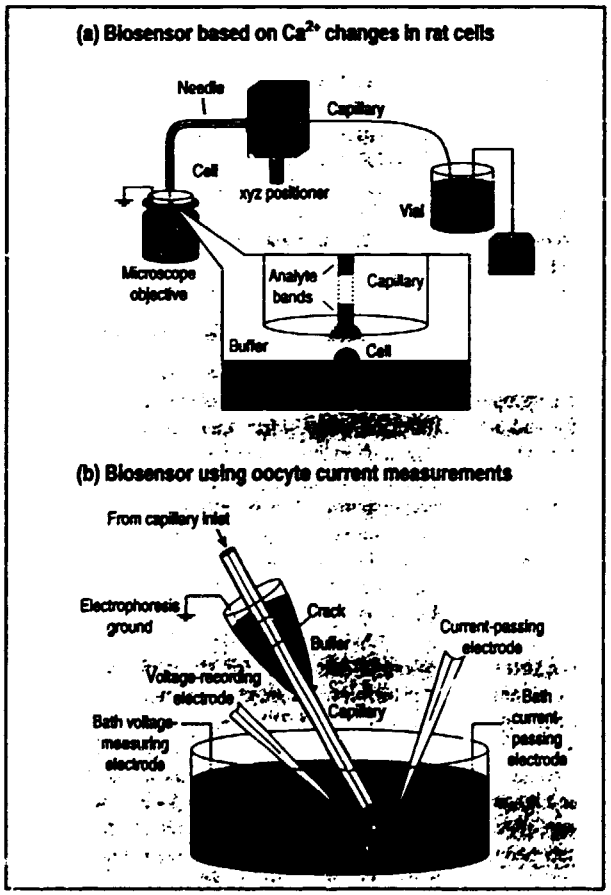
In addition, some of the work undertaken by the International Laboratory for Tropical Agriculture Biotechnology (ILTAB), which is a research and training laboratory dedicated to the control of tropical crop plant viruses and is currently involved in projects on rice, cassava, tomato, sugarcane, and yam, is to transfer this technology to scientists from developing countries in Central and South America. (Extracted from *Biotechnology*, Vol. 13, May 1995)

Chemical applications

Analytical chemistry

There have been several exciting developments in the area of biosensors recently. This field of analytical chemistry detects its targets using a biological recognition molecule which changes its electrical or spectroscopic property after interaction with the target analyte. A biosensor system based on the response of living cells have been used to detect the components of a complex mixture separated by capillary electrophoresis (J.B. Shear et al., *Science*, 1995, **267**, 74-77). The system uses ligand-receptor binding and signal transduction pathways to amplify the presence of an analyte (such as acetylcholine and adenosine triphosphate) biochemically after separation. Both optical and electrochemical techniques have been used to monitor the analyte interactions: (a) fluorescence determination of intracellular calcium concentrations from rat PC-12 cells and (b) measurement of transmembrane current in a *Xenopus laevis* oocyte microinjected with messenger RNA that encodes a specific receptor (see figure 1). The authors suggest that the system has the potential to identify biologically active ligands present in a complex mixture with exceptional sensitivity and selectivity.

Figure 1



The single cell biosensor systems (a) the device based on monitoring Ca^{2+} changes in one or more rat PC-12 cells using a Ca^{2+} sensitive dye. (b) the system based on membrane current measures on a Xenopus laevis oocyte expressing a cloned membrane receptor

A mercury biosensor based on the luminescence intensity changes of the firefly luciferase gene has been reported (M. Virta, J. Lampinen and M. Karp, *Anal. Chem.*, 1995, **67**, 667-9). It was constructed by gene fusion between a regulatory region of the *mer* operon and firefly luciferase. The luciferase gene was under the control of the mercury inducible *mer* promoter from transposon *Tn*21, with *Escherichia coli* as the host organism. The lowest detectable concentration of mercury was 0.1 fM and no interference was observed for cadmium, zinc, cobalt, copper and manganese ions.

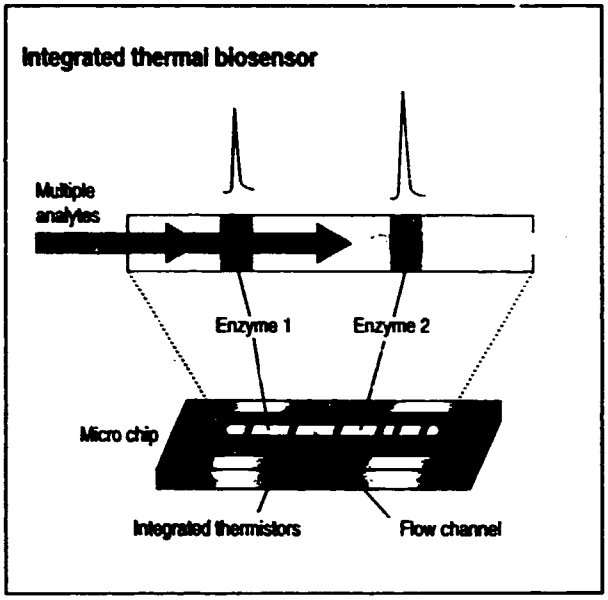
A DNA-based biosensor for the platinum anticancer drug cisplatin has been reported (H. Su, P. Williams and M. Thompson, *ibid*, 1995, **67**, 1010-13). The researchers made the sensor by attaching nucleic acid to the electrodes of a thickness-shear-mode acoustic wave device. They believe that the decreases in the series resonant frequency for interactions of DNA with both cis- and transplatin indicate two distinct kinetic processes and have interpreted them in terms of nucleic acid binding to the hydrolysis products of the two drugs. The sensor's reported detection limit for the drugs is about 10^{-7}M.

In similar work, P.C. Pandey and H.H. Weetall have described a DNA-based biosensor for detecting organic compounds (*ibid*, 1995, **67**, 787-92). The compounds were determined by a flow injection analysis system coupled with an evanescent wave biosensor using fluorescence to detect any compounds which intercalate within the DNA. Ethidium bromide, a highly fluorescent intercalator, was used as the reference compound for the detection. The biosensor was developed using immobilized double stranded DNA (dsDNA) over the surface of an optical fibre. At the biosensor's steady-state, there is a decrease in the response to the injection of another DNA intercalator that competes for the intercalation sites on the dsDNA, displacing the ethidium bromide. This reversible displacement was used as the basis for detecting a number of aromatic compounds.

A novel method for producing carbon paste electrodes for the development of biosensors has been published recently (C. Petit and J-M Kauffmann, *Anal. Proc. inclu. Anal. Comm.*, 1995, **32**, 11-12). The authors immobilized tyrosine in a solid paraffin and graphite matrix which proved to be useful for developing and applying robust polishable electrodes in flowing streams. The electrode response, at half peak value, was 23s and responded to dopamine linearly in the concentration range of 0.1 μmol/dm^3 - 1 mmol/dm^3. The detection limit for these electrodes is 50 nmol/dm^3.

An integrated thermal biosensor for the simultaneous determination of multiple analytes has been developed (B. Xie, et al. *Analyst*, 1995, **120**, 155-60). It consists of five thin-film thermistors located along a single microchannel, and the whole device is made on a quartz chip by micromachining (see figure 2). Two pairs of enzymes, urease-penicillinaseand urease-glucose oxidase showed that the device couid be used to detect two independent enzyme reactions at the same time. The researchers immobilized the enzymes on agarose beads which were then packed into distinct regions of the microchannel. Using this method, samples containing urea mixed with penicillin V or with glucose were analysed simultaneously. Linear ranges of up to 20 mmol/dm^3 urea, 40 mmol/dm^3 penicillin V and 8 mmol/dm^3 glucose were obtained using a sample volume of 20 μl.

Figure 2



Basic principle of the flow injection thermal microbiosensor. A pair of thermistors are placed upstream and downstream of each enzyme matrix, and an enzyme-free region separates two adjacent enzyme regions from each other

A second biosensing system using immobilized enzymes has also been described, this time for the simultaneous fluorimetric determination of glycerol and ethanol in wine (I.L. Mattos, J.M. Fernandex-Romero, M.D. Luque de Castro and M. Valcarcel, *ibid*, 1995, **120**, 179-82). The method uses a flow injection manifold and dehydrogenase enzyme immobilized on controlled pore glass. The team notes the simultaneous determination of glycerol (1-10 μg/ml) and ethanol (10-100 μg/ml) in different wines with recoveries between 97 and 105 per cent. The technique has a sampling frequency of 60 samples/h.

The final biosensor to be reviewed here immobilizes the siderophore pyoverdin in a sol-gel glass for the fluorimetric determination of iron(III) (J.M. Barrero, C. Camara, M.C. Perez-Conde, C. San Jose and L. Fernandez, *ibid*, 1995, **120**, 431-5). These researchers purified pyoverdin, a naturally occurring siderophore (iron chelator), from the bacterium *Pseudomonas fluorescens* and entrapped it in the sol-gel glass. They found that the pyoverdin's stability in the sol-gel was better than their previously reported technique of immobilization onto controlled pore glass. The detection limit for Fe(III) was 3 ng/ml. The selective biosensor was successfully used to determine iron in tap waters and human blood.

Two recent developments have been reported in the field of chemical sensors – where the molecular recognition molecule is chemical rather than biological. First, an electrode with an electropolymerised tetraaminophthocyanatocobalt(II) has been developed for detecting sulphide ions (Y-H Tse, P. Janda, H. Lam and A.B.P. Lever, *Anal. Chem.*, 1995, **67**, 981-985). The group electropolymerizedthe Co(II)phthalocyanine complex onto an electrode surface and showed that it is an excellent

sensor for the quantitative determination of sulphide and 2-mercaptoethanol over a wide pH range.

Finally, E. Wang, M.E. Meyerhoff and V.C. Yang have found an optical chemical sensor for the macromolecule heparin which works via selective coextraction into thin polymeric films (*ibid*, 1995, **67**, 522-7). Thin plasticised poly(vinyl chloride) films doped with a specific ion pairing quaternary ammonium compound, tridodecylmethylammonium chloride and a lipophilic pH indicator, 3-hydroxy-4-(4-nitrophenylazo)phenyl octadeconate, exhibit optical absorbance changes when they interact with heparin. The film absorbance changes as a function of heparin concentration in the range 1.2-18 μg/ml. The response time of the films depends on the diffusion rate of the heparin through the film and consequently on the molecular weight of the heparin species tested. (Reprinted from *Chemistry & Industry*, 3 April 1995)

Curbing carbon dioxide

Plants need a constant supply of carbon dioxide, and Professor Michael Melkonian from the Botanical Institute of the University of Cologne in Germany has proposed that factories could feed their stack emissions to algae in much the same way as water-borne waste is fed to micro-organisms in sewage plants. By "gassing" algae in reactors with fumes from a coal-fired power station, the professor found that the flood-light algae were happy to feast on the super-abundance of carbon dioxide. Emissions dropped from 15 per cent to only 1.5 per cent, and a bonus, the particular species used produced large quantities of carotenoids, the colouring used as additives in a variety of foods, including salmon. (Source: *Technology Ireland*, May 1995)

Enviro-immunology laboratory

Six Japanese firms, including Cosmo Research Institute and Iatron Laboratories, are planning to jointly establish an environmental immunology laboratory intended to develop technology for quickly and accurately assessing substances having an effect on the environment.

Most of the substances have such low molecular weight that they can hardly be subjected to immunochemical assessment.

The new project is aimed at pioneering hapten-applied low-molecular-weight antibodies—which smoothly react with environment-affecting substances—and applying them to the assessment of 66 kinds of substances contained in industrial waste and farm products.

When combined with protein for example, hapten acquires immunogenicity, meaning that it is capable of producing an immune response. The target technology is expected to help streamline operation of manufacturing plants and environmental analysis, markedly curtail analysis costs in R&D activities and expand business opportunities for the analysis-service industry. (Source: *McGraw Hill's Biotechnology Newswatch*, 17 April 1995)

Removing oil spills through microbial degradation

The Indian National Environmental Engineering Research Institute (NEERI), Nagpur, India, has developed a technology for the removal of oil spills using microbial degradation.

Oil spills are a health and safety hazard and cause lasting ecological damage. Using a physico-chemical approach in tackling them has its own limitations. Bioremediation of oil spills is an emerging innovation using a consortia approach of micro-organisms such as bacteria and fungi. Research shows that virtually all kinds of hydrocarbons are susceptible to microbial degradation.

NEERI studies say it is better to have a collection of micro-organisms with different hydrocarbon degrading capabilities, instead of using a single micro-organism for degradation of oil.

Aliphatic and aromatic compounds are the two main types of compounds that need to be degraded. An effective oil degrading consortium would need an efficient aliphatic utiliser, an aromatic utiliser and a biosurfactant producer, in addition to another organism to use downstream metabolites formed during degradation. The consortia should also have organisms with oil emulsifying capability.

Adopting a two step process, NEERI uses alkali treated sawdust to remove 95 per cent crude oil, followed by the custom-designed bacterial consorta attack.

The consortium of organisms was grown in appropriate media and inoculated with one per cent crude oil. The consortium could degrade 65 per cent of Gulf crude/Bombay High crude in 48 hours. This was shown in gas chromatography data and supported by gravimetric analysis.

Another environmentally important technology developed by NEERI on the biotechnology front is microbial desulphurisation of coal, oil, fuel gas at the precombustion stage.

Indian fossil fuels contain various forms of sulphur. Direct combustion of these fuels results in atmospheric sulphur dioxide pollution and acid rain. Cleaning these gases at the emission point using physico-chemical sources is costly and energy intensive. Also, it generates acidic waster waters that need further investment of cost and energy to cleanse. In contrast, microbial desulphurization is inexpensive, energy efficient and effective. (Source: *Tech Monitor*, January-February 1995)

Industrial microbiology

New, highly effective lipases for industrial applications

The production of lipases by prokaryots has great commercial potential. A project funded under the European Union's BRIDGE programme is looking particularly at *Pseudomonas lipases*, which belong to a distinct family of lipases and have excellent properties for application in areas ranging from foods to detergents. By obtaining structural information and studying the mechanism of the action of lipases, the potential to generate tailor made lipases for specific industrial applications is viable.

The complete structure of *Pseudomonas glumae* lipase has been established in the last year by X-ray analysts. This work has been published and the structural co-ordinates have been deposited in the Brookhaven Protein Databank.

Synthetic effort: Six triglyceride analogues have been synthesized and purified. Now the activity of *P. glumae* lipase and other lipases are being screened. The effects obtained for different lipases are being compared with their respective structural information, providing detailed information on the positional specificity of these lipases. In addition to these studies, enzyme substrate interactions will be investigated and the further synthetic substrates required are being synthesized.

For further information please contact: Dr. Constant Gitzinger, Commission of the European Communities (DG XIII), Jean Monnet Building, C5/025, L-2920 Luxembourg. Tel: (+352) 4301 33887 / 33519; Fax: (+352) 4301 34129.

Biohazards

Indifferent postal workers pose hazard

Environmental watchdog Greenpeace conducted two experiments to see how international postal services handle genetically modified organisms (GMOs).

"Clearly packets containing GMOs can be mailed freely around the world with little chance of being controlled, inspected or even, it would seem, noticed", Greenpeace discovered.

The group sent packages bearing labels such as "Warning: Biological Materials" and "Health Risk Due to Genetically Modified Material: Biohazard" from its offices in Washington D.C. to a number of international locales. The packages contained vials of water and harmless brewer's yeast.

While some of these arrived intact, others were damaged, reaching their destinations with evidence of leakage that "soaked the envelope" or prompted "growth on the envelope", and some failed to arrive at all.

At the time of mailing, no questions were asked about the packages, despite their provocative labels.

The Greenpeace studies were conducted as a follow-up to a 1991 Dutch study, in which several similarly marked packages were damaged in transit.

Greenpeace, which opposes release of any GMOs, is calling for an international protocol to monitor and control GMO transport and development. Until a protocol is in place, Greenpeace wants to see an international moratorium on GMOs. (Source: *McGraw Hill's Biotechnology Newswatch*, 15 May 1995)

F. PATENTS AND INTELLECTUAL PROPERTY RIGHTS

Zeneca receives patent for paper-making technology

Zeneca Plant Science has been granted a patent for its new technology which modifies the lignin in trees used for paper pulp.

The patent covers the modification of wood by switching off production of the cinnamyl alcohol dehydrogenase (CAD) enzyme.

Experiments in which CAD had been switched off yielded looser bonds between lignin and cellulose. By loosening the ties between the two plant fibres, the new technology makes lignin easier to remove from cellulose during the pulp-making process. Zeneca's hope is that paper-makers using the plants will be able to make more paper quickly and use less chlorine bleach, thereby improving water quality around paper mills.

Zeneca recently signed separate agreements with Nippon Paper Industries Co. Ltd. and Shell Research Ltd. to evaluate the lignin modifying technology (CMR, 17 April 1995, p. 17). Under the agreement, Zeneca will provide a gene that suppresses the CAD enzyme in plants, as well as the technology for using the gene suppressor. Shell and Nippon have developed the capability to insert the gene into lines of high-performing trees. The two firms also manage plantation forestry programmes through which the new technology may be commercialized by the late 1990s. Aside from the agreements with Nippon and Shell, Zeneca is also in advanced stages of negotiations with other paper and pulp companies. (Source: *Chemical Manufacturing Reporter*, 12 June 1995)

European Union rejects patents on life

On 1 March 1995 the European Parliament voted to reject the proposed European Union (EU) directive on "The Legal Protection of Biotechnological Inventions". After seven years of debate, the controversial bill was defeated by a large majority of 240 to 188 votes, with 23 abstentions.

The directive, first submitted in October 1988, was controversial due to its social, ethical, scientific and economic implications for various sectors of society. NGO opponents devoted years of work to raising public awareness, coalition building, campaigning and lobbying to defeat the proposal.

The fact that such a large majority rejected the directive surprised observers and activists alike. Genetic Resources Action International (GRAIN) analysts attribute the size of the majority to two factors: (1) Despite rallying cries to vote in favour of the directive in socialist and conservative parties, there was controversy about what the directive would actually permit. Many were concerned about whether the legislation would promote patenting of human genes and germ-line therapy. (2) Highly visible efforts of NGOs, including a vivid Greenpeace action outside Parliament the day before the vote and a flood of protest letters from NGOs and indigenous peoples exerted a great deal of pressure on Members of the European Parliament.

Other important events in Europe supported the position taken by the European Parliament. On 21 February 1995, the European Patent Office announced a landmark decision in favour of Greenpeace International regarding a patent on genetically engineered, herbicide-resistant rapeseed. The original patent, granted in 1990 to Plant Genetic Systems (Belgium) and Biogen (USA), has now been limited in scope by deletion of six claims. The Patent Office's Technical Board of Appeal has ruled that the patent may cover genetically-engineered plant "cells" but cannot extend to a whole plant, its seeds and any future generations of plants.

Two days later, 85 members of the Italian Parliament signed a resolution instructing their Government to "promote urgent initiatives towards the EU and other international organizations in order that the principle of patenting life forms—self-reproducing animals and plants—be refused". Further, the instruction reads that the Italian Government, through the EU and other international bodies, should "put into effect limited forms of protection of intellectual property rights that prevent any privatization of genes, and that are compatible with human rights". If formalized, this will align the Italian Government with Austria, Denmark, Luxembourg and Spain, each of which expressed formal reservations about the EU directive. (Source: *GRAIN press release*, 6 March 1995. Contact: GRAIN, Girona 25, pral. E-08010 Barcelona, Spain; Tel.: (34-3)301 13 81; Fax (34-3)301 16 27; e-mail grain@gn.apc.org.)

Are scientists playing god?

The leaders of more than 80 religious faiths want to ban the patenting of genetically-engineered animal and human genes, cells and organs. The religious coalition opposes US Government policy and the philosophy of the biotechnology industry.

The participants of the Joint Appeal Against Human and Animal Patenting argue that the "genetic blueprints of life" are the province of God and cannot be owned as patented inventions by any person or institution.

The Appeal accuses the Government of laying the legal and philosophical foundation for scientists and companies to assume the role of God. "Inventions are made to be upgraded, streamlined and perfected—raising the prospect of potential abuse and misuse of human and animal genetic material".

The biotechnology industry is criticised for wanting exclusive rights on discoveries. Patents are unnecessary, it says; many products are not protected by patents. The Appeal also thinks the industry is too greedy. Much corporate research funding comes from US taxpayers as government subsidies for basic research, it points out. But patent monopolies will charge patients exorbitant fees for life-saving drugs. So far the US Patent and Trademark Office has patented nine genetically-engineered animals and hundreds of human genes and cell lines. (Source: *Chemistry & Industry*, 5 June 1995)

Broad coalition adds voice to religious protest on gene patents

A broad coalition of scientists, consumers, environmentalists and indigenous groups added their voices to a growing debate by calling for an end to the patenting of human, animal and plant genetic materials.

The statement was the result of a meeting to formulate a strategy to combat the patenting of living things.

Members of the Council for Responsible Genetics argued that such patents are not necessary to the conduct of research and may actually impede medical progress through the privatization of publicly-funded research and the limiting of free scientific exchange.

Some scientists said many researchers have replaced the traditional collegial exchange in laboratories with a concern for protecting potential monetary gains. They argued that scientists have held off publication in order to get in their patent applications and rushed into work based on its profit potential rather than the public good.

Patenting creates an environment in which commercial interests dominate research policy, said Jonathan King, a professor of molecular biology at Massachusetts Institute of Technology and a consultant to the biotechnology industry on protein folding in pharmaceutical production.

King argued that the biotechnology industry would flourish in the absence of patents, driven by the sharing of basic science and competition to shape findings into useful products. Important discoveries such as insulin were based on a broad foundation of publicly-funded research, he said.

Philip L. Bereano, professor of public policy at the University of Washington and an organizer of the June conference, said the meeting focused on strategies to create a public dialogue on patenting. Possibilities included building networks among smaller non-profit groups, a petition campaign, a national public conference and potential legislation. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 19 June 1995)

Judge delays sales of Novo growth hormone

A US federal judge has issued a temporary restraining order preventing Novo Nordisk from introducing its human growth hormone Norditropin commercially on to the US market.

The order arises as part of patent litigation between Novo and Genentech. Both companies are waiting to see if the judge issues a preliminary injunction in the case. Novo said it hoped the district court would deny the request for the injunction.

Novo recently gained FDA approval to market Norditropin in the US. Since its first introduction in 1988 it has been used on 30,000 children world-wide. It has been prevented from selling in the US until recently because of the orphan drug status of the treatment and Genentech's and Eli Lilly's protected position under US orphan drug rules. (Source: *European Chemical News*, 19-25 June 1995)

Patenting statement issued by HUGO

The Human Genome Organisation (HUGO) has released a 15-page statement about the patenting of DNA sequences. The statement summary reads in part, "HUGO is worried that the patenting of partial and uncharacterized cDNA sequences will reward those who make routine discoveries but penalize those who determine biological function or application. Such an outcome would impede the development of diagnostics and therapeutics, which is clearly not in the public interest. HUGO is also dedicated to the early release of genome information, thus accelerating widespread investigation of functional aspects of genes. This statement explains our concerns.

The statement was prepared by HUGO President C. Thomas Caskey (Merck Research Laboratories), Rebecca Eisenberg (University of Michigan Law School), Eric Lander (Whitehead Institute), and Joseph Straus (Max Planck Institute) and approved by the HUGO Council. It appears in HUGO Europe *Genome Digest* (2(2), 6-9 April 1995)) and is available in hard copy by e-mail request from the HUGO Americas office. HUGO AMERICAS, 7986-D Old Georgetown Road, Bethesda, MD 20814, Tel.: 301/654-1477, Fax: 652-3368, e-mail: hugo@gdb.org (Source: *Human Genome News*, March-April 1995)

Reforms planned to attract more applicants

As the European Patent Organisation nears its 20th birthday, Stuart Nathan looks at its attempts to make patenting easier for European firms.

The organisation that grants patents, the European Patent Organisation (EPO), is reforming its rules to make its system more attractive to European inventors.

The EP Convention was first drafted in 1973 and adopted in 1977, creating the European patent system and the EPO. It allows inventors to protect their inventions in every European country by making one application to a central body. Most European patents are valid in eight States: Germany, the Netherlands, France, Britain, Italy, Spain, Sweden and Switzerland.

However, countries outside Europe now make as much use of the system as their European competitors, especially in the innovative industries which file the most high-tech patents.

It is the European firms working in high-tech fields like biotechnology which are the targets for the EPO's reforms to the Convention. These companies tend to be smaller than their US and Japanese competitors, it says. Although this makes them more flexible, they are at a disadvantage for patenting because they are invariably less well-resourced. Patents applications can cost DM45,500 (£19,800) on average.

An EPO survey confirms that these vital smaller companies are shunning the patent system. It calculates that about 57,000 companies in Europe have filed patents. This is out of 170,000 "potential applicants"—companies involved in production industries and with R&D departments.

Two-thirds of the 34,000 companies with over 100 employees have filed patents, but three-quarters of the smaller companies have not. Moreover, most non-applicants know little or nothing about the system.

Member States of the EPO have devised a set of strategies to reverse the trend. One priority is to streamline the EPO itself, cutting down on duplication in the national offices and the central organization in Munich. Any savings can be passed on by reducing application fees.

The largest single part of the cost of patenting is translation. Applications are made in one language, French, German or English. But when the patent is granted, the applicant must pay for it to be translated into the languages of every country in which it will apply. This can cost almost DM5,000 (£2,200) per language.

The EPO has several ideas for reducing this cost. It suggests requiring translations only in the event of litigation. Alternatively, applicants could translate only the abstract and claims sections of the patent so they could be collected and sold separately to researchers in their area. The claims section lists the aspects of the invention that the applicant's "claim" as their property.

The EPO is also considering making patent infringement litigation quicker and cheaper. It is studying a Dutch system called *kort geding*. This allows companies to present short summaries of their cases to a judge in a relatively informal hearing. They receive a provisional judgement within a fortnight or even, in urgent cases, the same day.

explains Jan Brinkhof, professor of industrial property law at Utrecht University.

The companies can still insist on a formal hearing if they disagree with the judge's decision, but 95 per cent of judgements are accepted. Companies prefer this route because speed is always a major factor when a patent is infringed as sales are lost, says Brinkhof. (Source: *Chemistry & Industry*, 5 June 1995)

Major changes in US Patent Law

As part of implementation of the General Agreement on Tariffs and Trade (GATT) and establishment of the World Trade Organisation, major changes to US patent legislation have been passed. The most important of these are a change in the term of a US patent from the current position of 17 years from the date of grant of the patent to 20 years from the date of filing of the application in the United States. This is to come into effect from 8 June 1995. As a result, the term of a continuation, Continuation-in-Part, or divisional patent will run for 20 years from the date of filing of the *parent* US patent. In addition, an inventor who is a resident of any member country of the World Trade Organisation will be able to rely on a date of invention after 1 January 1996 for all applications filed after 1 January 1996. At present, any resident of the USA, Canada and Mexico can rely on a date of inventorship to overcome a prior art reference or to establish priority in interference proceedings. Offering of a patented product for sale will become an infringing act, as of 1 January 1996.

The most important of these changes are the introduction of the 20-year patent term, and the ability to rely on a date of invention. The former means that applicants should consider their portfolios carefully, and if the new provisions result in a possible reduction of patent term consider filing of new continuation, Continuation-in-Part or divisional applications before the 8 June 1995 deadline. This will particularly affect applicants in the chemical, pharmaceutical and biotechnology fields, and applicants whose cases are likely to be involved in prolonged prosecution. (Source: *Australasian Biotechnology*, Vol. 5, No. 2, April 1995)

New US Patent and Trademark Office guidelines for examination of utility

In recent times the biotechnology examining group of the US Patent and Trademark Office has been requiring actual clinical trial data to support utility of an invention in the biotechnology field, and in most cases has refused to accept data from animal models, let alone *in vitro* results. Following extensive lobbying by the US patent profession, the Biotechnology Industry Organisation and other groups, special public hearings were held by the Patent and Trademark Office in San Diego in October 1994. Submissions were also lodged by a number of overseas bodies, including the British Chartered Institute of Patent Agents. New guidelines for examination have now been released, as a result of which only allegations of utility which are *truly* "incredible" will result in refusal of an application. This is expected to make the task of applicants very much easier. (Source: *Australasian Biotechnology*, Vol. 5, No. 2, April 1995)

Genome conference supports the patent system

An international conference of scientists involved in genome projects, industry groups and the patent profession held in January by the French Academy of Sciences has concluded that the patent system in its present form operates well, and requires no adaptation to deal with the problems of commercializing the genome project. Provided that the normal criteria of patentability, namely novelty, non-obviousness and utility are properly applied, researchers and companies are adequately protected, and excessively broad patents will not be granted. A more detailed report of this meeting appeared in *Nature*, (1995) 373-376. (Source: *Australasian Biotechnology*, Vol. 5, No. 2, April 1995)

G. BIOINFORMATICS

Biotechnology, environment and control

The above report is now available from Financial Times Energy Publishing. The report provides a comprehensive overview of the role of biotechnology in environmental protection, waste treatment, materials and fuel production, and agricultural and food production. It also discusses the associated environmental risks and ethical concerns, and outlines the regulatory response from national Governments.

Whilst the main focus of investment in biotechnology has traditionally been in the pharmaceutical and healthcare sector, environmental protection, resources and agriculture are expanding areas. This report examines the growing potential for biotechnology in these sectors and will prove essential reading for senior managers in environmental protection groups; waste management companies; the chemical industry; agriculture; the food industry; regulatory bodies and government departments.

Biotechnology, Environment and Control

- Reviews the types of biotechnological processes in use and under development, covering fermentation, selective breeding, mutations and genetic engineering techniques;
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- Examines the role of biotechnological applications in food and agriculture, with coverage of crop protection, crop enhancement, fertilizers and food;
- Outlines the potential environmental and ethical problems posed by the use of biotechnology and examines existing legislation which varies from country to country, depending on the demands of industry and pressures from interest groups.

Biotechnology, Environment and Control is available from FT Energy Publishing, Customer Services, P.O. Box 6, Camborne, TR14 9EQ, United Kingdom. Price: £300/ US$ 450.

US Institute for Biotechnology Information: Pharmaceutical Industry Guide

The Institute for Biotechnology Information has published an inexpensive compendium of over 400 US pharmaceutical companies, therapeutics-based biotechnology firms and contract research organizations (CROs). Entitled *Pharmaceutical Industry Guide: Drug Companies, Biotechnology Firms and CROs*, the publication details the locations, activities and key management contacts of 135 pharmaceuticalcompanies,210 biotechnologyfirmsspecializing in drug or vaccine development and 57 CROs. Copies of the publication can be purchased direct from the Institute for $19.95, plus (US only) $4.00 shipping and handling.

Details from: Institute of Biotechnology Information, P.O. Box 14569, Research Triangle Park, NC 27709-4569, USA. To place an order, call +(919) 544-5111 or Fax: +1 (919) 544-5401.

IT Publications

Many readers may not know of the excellent selection of publications available from IT Publications, the publishing arm of Intermediate Technology. Below you will find a very small selection of the titles that are available, followed by a list of booksellers and stockists around the world where books may be ordered. IT Publications is based at 103-105 Southampton Row, London WC1B 4HH, UK, from whom a catalogue of all their published books may be ordered.

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Intermediate Technology Development Group (ITDG) is one of the leading charities involved in the long-term relief of poverty in developing countries. Its aim is to locate and use technologies appropriate to the social, cultural, economic and environmental needs of communities throughout the world.

How to Run a Small Development Project, by a "Geneva Group".

Will help the managers of development projects to design and manage their projects well, in particular by emphasizing the importance of forward planning. Covers both starting up and running projects, and working with Northern partner organizations. 44 pp. 1986. (ITP). ISBN 0 946688 47 8. £5.95/US$ 11.50, paperback.

Sustainable Industrial Development, introduced by Marilyn Carr.

Successful, established AT projects: forestry in Swaziland, Kenyan stoves, micro-hydro in Nepal, boats and cement plants in India, industries in Ghana and small grain production in Botswana and Zimbabwe. Can the benefits be sustained beyond the project? 208 pp. 1988. (ITP). ISBN 0 946688 89 3. £10.95, paperback. Not available in the USA.

Appropriate Technology for Rural Development: The ITDG experience (Occ. Paper No. 2), by Derek Miles.

Originally prepared for an Expert Meeting organized by UNESCO in 1980, this paper outlines Intermediate Technology's basic approach to development work; and assess the lessons learned from 15 years' experience in development activities. 32 pp. 1982. (ITP). £5.95/ US$ 11.50, paperback.

The Economies of Small—Appropriate technology in a changing world, by Raphael Kaplinsky.

Describes the origins and development of the appropriate technology movement, and analyses both its changing concerns at the different stages of development, and also its abiding emphasis on scale and human values. 244 pp. 1990. (ITP). ISBN 1 85339 071 0. £25.00

US$ 47.50, hardback. ISBN 1 85339 072 2, £9.95/US$ 18.95, paperback.

The Management of Technological Change: An annotated bibliography, by Donnacadh Hurley with an introduction by Matthew S. Gamser.

This extensively annotated collection of titles aims to guide Governments and other decision makers in developing nations in the choices they make in technologies, and also in the development of mechanisms by which these selections can be implemented. 216 pp. 1987, (ITP/Commonwealth Secretariat). ISBN 0 946688 84 2, £9.95/US$ 18.95, paperback.

Mobilizing Appropriate Technology: Papers on planning aid programmes, edited by Matthew S. Gamser and others.

Discusses the role of AT in a national aid programme. If AT enters the project cycle at too late a stage it has little influence over the technological choice and the grassroots organizations that play a key role in development and change in rural areas. 112 pp. 1988, (ITP). ISBN 1 85339 045 3, £12.95/US$ 24.95, paperback.

The Other Policy: The influence of policies on technology choice and small enterprise development, edited by Ton de Wilde with Henk Thomas and Frances Stewart.

Foreign aid to developing countries often favours inappropriate technologies. This book reviews the policies promoting appropriate technology and identifies positive programmes of action that could be instituted at a national level. 512 pp. 1990, (ITP), ISBN 1 85339 063 1, £25.00/US$ 47.50, hardback. ISBN 1 85339 059 3, £14.95/US$ 28.95, paperback.

Science and Technology—Lessons for development policy, edited by Robert E. Evenson and Gustav Ranis.

The success of the newly industrialized countries of SE Asia is a prime example of the role that science and technology can play in development strategies. This book aims to identify those policies which have proved to be workable in most situations. 392 pp. 1990, (ITP), ISBN 1 85339 0623 1, £19.95, paperback. Not available in the USA.

Science, Technology and Development, by Atul Wad.

The author of this interdisciplinary book stresses that a full understanding of the introduction of new technology in all its aspects is the only way to achieve a workable compromise regarding science, technology and development. 316 pp. 1989, (ITP), ISBN 1 85339 075 5, £19.95, paperback. Not available in the USA.

The Technological Transformation of Rural India, by A. K. N. Reddy and A. S. Bhalla.

The economic development of developing countries is hindered, in no small measure, by their technological backwardness and their lack of indigenous technological capabilities to master the absorption of new technologies. Despite the efforts made in recent years to study the technological transformation of developing countries in the process of their industrialization and growth, very little, if any, evidence exists of the nature and extent of the technological transformation of *rural* areas, which are generally bypassed by the advances of science and technology.

This book presents a conceptual model of the process of commercialization of rural technologies in developing countries and then tests this model against some case studies taken from India's experience, concluding that India has placed far more emphasis on the survival of small-scale production units than on ensuring their efficiency and growth in a competitive environment. 192 pp. 1994, (ITP). ISBN 1 85339 199 9, £14.95, paperback. Not available in the USA.

Technology Choice: A critique of the appropriate technology movement, by Kelvin W. Willoughby.

A comprehensive review and critique of the theory of appropriate technology, which proposes a framework for integrating traditional economic development with its techniques—a sober look at the obstacles, and an appreciation of AT's value. 350 pp. 1990, (ITP), ISBN 1 85339 057 7, £14.95, paperback. Not available in the USA.

Technology Transfer: Nine case studies, by Sosthenes Buatsi.

Nine case studies in technology transfer which demonstrate the experience gained in different countries and different technologies. 82 pp. 1988, (ITP), ISBN 0 946688 29 X, £5.95/US$ 11.50, paperback.

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Belgium: ATOL vzw, Blijde Inkomstraat 9, B-3000, Leuven

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India: Selectbook Service Syndicate, E-10, Kailash Colony, New Delhi 110048.

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New Zealand: Small Resources International, Okari Road, RD2 Westport.

New Zealand: One World Books, P.O. Box 68-419, Auckland.

Philippines: APB Educational Materials, P.O. Box 1968, CPO Manila

Spain: Ecoserveis, Ceramica 38, 08035 Barcelona.

Sri Lanka: Lake House Bookshop, Sir Chittampalam A. Gardiner Mawatha, P.O. Box 244, Colombo 2.

Switzerland: SKAT, Vadianstrasse 42, CH-9000, St. Gallen.
USA: Women Ink, 777 UN Plaza, New York, NY 10017.
Zimbabwe: Grassroots Books, P.O. Box A267, Avondale, Harare.

Natural and Engineered Pest Management Agents, edited by Paul A. Hedin, US Department of Agriculture, Julius J. Menn, US Department of Agriculture and Robert M. Hollingworth, Michigan State University.

Natural and Engineered Pest Management Agents explores emerging technologies in crop protection based on new natural pest management agents and materials derived from natural models. It reviews the discovery and application of pesticides based on peptides, neuropeptides, natural products, and natural and engineered viral agents, and presents information on new approaches to designing pesticides through molecular and computer-aided design. The book also discusses registration of biopesticides and presents case studies.

Brief contents: Preface; Innovation in Discovery; The Career of Toshio Fujita; Natural Product Pesticides; Peptides and Neuropeptides; Natural and Engineered Viral Agents; Evolving Approaches to Pesticide Discovery; Biochemistry and Computer-Aided Design; Registration of Biopesticides; Author, Affiliation, and Subject Indexes. *ACS Symposium Series No. 551*. 752 pp. May 1994. ISBN 0 8412 2773 X. £89.00, hardcover.

Environmental Chemistry of Lakes and Reservoirs, edited by Lawrence A. Baker, Arizona State University.

This book presents a timely exploration of research topics in the environmental chemistry of lakes and reservoirs. It includes coverage of methodological advances in studies of lake geochemistry; cycling and distribution of major elements in aquatic systems; behaviour of trace metals, with an emphasis on processes that control their solubility and transport, and behaviour and fate of organic contaminants. *Environmental Chemistry of Lakes and Reservoirs* will be valuable reading for chemists, environmental engineers, biologists, and scientists involved in practical aspects of water pollution.

Contents: **Geochemical Analysis**; Long-Term Chemical Changes in Lakes: Quantitative inferences from biotic remains in the sediment record; Atmospheric Mercury Deposition to Lakes and Watersheds: A quantitative reconstruction from multiple sediment cores; Use of Oxygen-18 and Deuterium to Assess the Hydrology of Groundwater-Lake Systems; Ecosystem-Scale Experiments: The use of stable isotopes in fresh waters; Effects of Acidification on Chemical Composition and Chemical Cycles in a Seepage Lake: Inferences from a whole-lake experiment; Organic Phosphorus in the Hydrosphere: Characterization via ^{31}P Fourier transform nuclear magnetic resonance spectroscopy; **Cycling and Distribution of Major Elements**; Chemistry of Dissolved Organic Matter in Rivers, Lakes, and Reservoirs; Long-term Changes in Watershed Retention of Nitrogen: Its causes and aquatic consequences; Mass Fluxes and Recycling of Phosphorus in Lake Michigan: Role of major particles phases in regulating the annual cycle; Retention of Sulfur in Lake Sediments; Reaction of H_2S with Ferric Oxides: Some conceptual ideas on its significance for sediment-water interactions; Factors Affecting H_2O_2 in Surface Waters; **Geochemistry of Trace Metals**: Cycling of Mercury across the Sediment-Water Interface in Seepage Lakes; Contaminant Mobilization Resulting from Redox Pumping in a Metal-Contaminated River-Reservoir System; Cycles of Trace Elements in a Lake with a Seasonally Anoxic Hypolimnion; Manganese Dynamics in Lake Richard B. Russel; **Behaviour of Organic Pollutants**: Environmental Behaviour and Fate of Anionic Surfactants; Fate of Hydrophobic Organic Contaminants: Processes affecting uptake by phytoplankton; Differential Weathering of PCB Congeners in Lake Hartwell, South Carolina; Author, Affiliation and Subject Indexes. *Advances in Chemistry Series No. 237*. 627 pp. May 1994. ISBN 0 8412 2526 5. £120.00, hardcover.

Mass Spectrometry for the Characterization of Microorganisms, edited by Catherine Fenselau, University of Maryland, USA.

This new title presents various roles for mass spectrometry in the detection and characterization of microorganisms. It features GC-MS for clinical diagnosis of viral infection and summarizes the status of detection of biological agents and modifications in ribonucleic acids in microorganisms. Also described are electrospray, laser desorption, tandem mass spectrometry for protein processing and modification in viruses, and membrane liposaccharide structures in pathogenic bacteria. *ACS Symposium Series No. 541*. 238 pp. 1994. ISBN 0 8412 2737 3. £54.00, hardcover.

Biomarkers of Human Exposure to Pesticides, edited by Mahmoud A. Saleh, Jerry N. Blancato and Charles H. Nauman.

This title explores the role of biomarker data in evaluating the impact of human environmental and occupational exposure to pesticides. It focuses on two types of biomarkers: residue analysis of parent compounds or metabolites and end points representing interactions between xenobiotic and endogenous components. The book characterizes the molecular basis of various biomarker methods and examines structure-activity relationship and surveys biomarker measurement methods currently in use. It also examines methods for biomarker data analysis and applications of these methods to risk assessment.

Contents: Biomonitoring for Pesticide Exposure: **Molecular Characterization**: Modeling Cytochrome P-450 Mediated Acute Nitrile Toxicity Using Theoretical Linear Solvation Energy Relationships; Changes in Biochemical and Molecular Biological Parameters Induced by Exposure to Dioxin-Type Chemicals; Regulation of Muscarine Receptors as Biomarkers of Exposure to Insecticides; Correlations of Molecular Connectivity Indices with Toxicities of Organic Nitriles; Computer-Aided Molecular Modeling for Development of Biomarkers for Human Exposure to Pesticides; **Biomarker Measurement Methods**; A Biosensor for Monitoring Blood Cholinesterases as a Biomarker of Exposure to Organophosphorus Anticholinesterase Pesticides; Hair as a Target Tissue for Developing a Biological Marker for Precursors to 2,5-Hexanedione; Hemoglobin Adducts of Pesticides; Immunoassay for *p*-Nitrophenol in Urine; Isolation of Pesticide-Binding Protein from Rat Blood; Body Burden and Nonoccupational Exposure Assessment; Chronic Organophosphorus Exposure: Biomarkers in the detection of immune dysfunction and the development of lymphomas; **Data Analysis and Application to Risk Assessment**; Validation of a Pharmacokinetic Model to Predict Exposure of Ground Boom Mixer-Loader-

Applicators to Chlorophenoxyacetic Acid Herbicides: Comparison to conventional approaches; Dermal Absorption and Disposition of Formulations of Malathion in Sprague-Dawley Rats and Humans; Physiologically Based Pharmacokinetic Models: Examples of their use in exposure and risk assessment; Prediction of Anticholinesterase Activity and Urinary Metabolites of Isofenphos: Use of a percutaneous physiologically based pharmacokinetic-physiologically based pharmacodynamic model; Analytic Solution of a Linear Physiologically Based Pharmacokinetic Model Prototype Useful in Risk Assessment; Author, Affiliation, and Subject Indexes. *ACS Symposium Series No. 542*. 314 pp. May 1994. ISBN 0 8412 2738 1. £64.00, hardcover.

Beer and Wine Production: Analysis, characterization and technological advances, by B. H. Gump, California State University at Fresno, and D. J. Pruett, Qualpro.

This book describes how modern technology is used to produce and maintain the flavour quality of beer and enhance the quality of wine. It discusses the current understanding of the sensory aspects of natural phenolic and terpenoid compounds in grapes, and the sensory effects of certain competitive spoilage organisms present in fermenting grape juice. It also presents insights into how current analytical, filtration and enzymes technologies are used to analyse and process beers and wines. There are also chapters on home brewing and wine-making.

Contents: **Advances in Analysis and Characterization Techniques**: Technological Advances in the Analysis of Wines; Advances in Detection and Identification Methods Applicable to the Brewing Industry; **Sensory Characterization and Control: Sensory Science**: A brief review of principles; Flavan-3-ols and their Polymers: Analytical techniques and sensory considerations; Progress in Beer Oxidation Control; Monoterpenes and Monoterpene Glycosides in Wine Aromas; *Brettanomyces and Dekkera*: Implications in wine-making; **Technical Applications in Production**: Applications of Technology in Wine Production; Biotechnological Advances in Brewing; Use of Enzymes in Wine-Making and Grape Processing; Technological advances; Ultrafiltration: A new approach for quality improvement of pressed wine; Capture and Use of Volatile Flavour Constituents Emitted during Wine Fermentation; ***Advances in Home Brewing and Wine-Making***: Home Beer-Making; Chemistry in the kitchen; Home Wine-Making; Effect of societies, retail outlets, and competitions on wine quality. Author, Affiliation, and Subject Indexes. *ACS Symposium Series No. 536*. 280 pp. 1993. ISBN 0 8412 2714 4. £49.00, hardcover

Polymers for Microelectronics: resists and dielectrics, edited by L. F. Thompson, AT&T Bell Laboratories, C. G. Wilson, The University of Texas at Austin, and S. Tagawa, Osaka University.

Polymers for Microelectronics presents recent advances in chemically amplified resists for deep U.V, electron beam, and X-ray advanced lithographic technologies. It discusses top surface imaging and dry development resists and examines the fundamental chemistry of radiation-sensitive materials, including dielectric polymers for integrated circuits and interconnect systems. This book is valuable reading for polymer chemists, radiation chemists, and materials scientists. *ACS Symposium Series No. 537*. 544 pp. March 1994. ISBN 0 8412 2721 7. £95.00, hardcover.

Polymers of Biological and Biomedical Significance, edited by S. W. Shalaby, Clemson University, Y. Ikada, Kyoto University, R. Langer, Massachusetts Institute of Technology, and J. Williams, Becton-Dickinson.

This book provides comprehensive coverage of recent advances in polymers as materials of significance in biological and biomedical research. It addresses synthesis, surface activation, and characterization of biomaterials and examines the biological effects related to specific physical chemical factors, synthetic bioactive chain molecules, and polymers for controlled transport of active agents. Also provided is a preliminary section which contains reviews of rapidly-developing research areas and acts as concise introductory notes to the succeeding part of the book. *ACS Symposium Series No. 540*. 390 pp. 1994. ISBN 0 8412 2732 2. £75.00, hardcover.

Silk Polymers: materials science and biotechnology, edited by David Kaplan, Natick Research, Development, and Engineering Center, W. Wade Adams, Wright Research and Development Center, Barry Farmer, University of Virginia, Christopher Viney, University of Washington.

This book characterizes the mechanical and molecular structure of silks with an emphasis on development and application of high-performance and composite materials. It discusses the synthesis of native and synthetic silks and silk-like materials, with particular focus on genetic encoding and engineering. It also examines the structure-property relationship of silks and silk-like materials. *Silk Polymers: Materials science and biotechnology* will serve as an aid in the design of polymers targeted for specific functions.

Brief contents: Biology, Genetics, and Synthesis; Characterization, Properties, and Modeling; Processing and Applications; Author, Affiliation, and Subject Indexes. *ACS Symposium Series No. 544*. 253 pp. May 1994. ISBN 0 8412 2743 8. £78.00, hardcover.

Separations for Biotechnology 3, edited by D. L. Pyle, The University of Reading.

Focused, up to date and carefully refereed, *Separations for Biotechnology 3* covers recent developments, current research, and new and emerging technologies in the fundamental biological, chemical and engineering aspects related to the separation and purification of biological products such as therapeutic proteins, antibiotics and amino acids.

The book contains original contributions on the use of molecular biology and protein engineering to facilitate recovery, new techniques for affinity separations, mathematical modelling of individual processes and separation systems, and the validation of processes for safe use.

The scope of the coverage is wide, and encompasses both academic and industrial angles on the subjects covered. It provides a stimulating account of an intriguing area of science, with subject and author indexes enabling the reader to use the book for quick, easy research and reference.

Separations for Biotechnology 3 is a must for researchers working on fundamental and applied aspects of biorecovery, and for practising engineers and technologists involved in industrial production. *Special Publication No. 158*. xiv + 604 pp. 1994. ISBN 0 85186 724 3. £92.50, hardcover.

Diagnostic Biosensor Polymers, edited by Arthur M. Usmani, Firestone Building Products Company, and Naim Akmal, Teledyne Brown Engineering.

Diagnostic Biosensor Polymers reviews the latest advances in redox conductive polymers and membranes and describes new redox polymers useful in miniaturizing biosensors, as well as examining polymers for optical biosensors. The book investigates interesting membranes to enhance the performance of biosensors and features biocompatible polymers useful in implantable sensors. It also includes discussions on enzyme immobilization and methods to increase enzyme stability and describes the chemistry and technology of dry chemistries.

Brief contents: Biosensors; Biosensor Polymers and Membranes; Biocompatibility and Biomimetics; Immobilization and Stabilization Methods; Indexes. *ACS Symposium Series No. 556*. 368 pp. 1994. ISBN 0 8412 2908 2. £75.00, hardcover.

Bioregulators for Crop Protection and Pest Control, edited by Paul A. Hedin, Agricultural Research Service, US Department of Agriculture.

This book examines the current status and potential use of synthetic and natural bioregulators to increase crop productivity and improve crop protection. It discusses the naturally occurring products that are emerging as bioregulators for crop productivity and protection and describes mechanisms of interactions of natural bioregulators and their hosts. Also included is a tutorial chapter on the development of plant growth regulators. *ACS Symposium Series No. 557*. 220 pp. 1994. ISBN 0 8412 2918 X. £49.00, hardcover.

Porphyric Pesticides: Chemistry, toxicology, and pharmaceutical applications, edited by Stephen O. Duke, Agricultural Research Service, US Department of Agriculture, and Constantin A. Rebeiz, University of Illinois.

This book focuses on the use of porphyrins and porphyrinogenic compounds as herbicides, insecticides, and pharmaceuticals. It discusses the synthesis, chemical structure, structure-activity relationships, and mode of action of porphyrinogenic compounds used in insecticides and therapeutic agents. The book also describes the use of porphyrins and porphyrinogenic compounds as pharmaceuticals for the treatment of cancer and metabolic disorders. *ACS Symposium Series No. 559*. 312 pp. 1994. ISBN 0 8412 2923 6. £65.00, hardcover.

Genetically Modified Organisms: A guide to biosafety, prepared by the Secretariat of the United Nations Industrial Development Organization (UNIDO) in cooperation with the International Centre for Genetic Engineering and Biotechnology, Vienna, Austria, edited by George T. Tzotzos.

For a number of years the promise of biotechnology has been dimmed by concerns over the intrinsic safety of transgenic organisms. Although considerable knowledge of the properties of recombinant systems and a vast volume of data gathered from different applications of biotechnology are now available, these concerns are still evident. In the developing world, there are also fears that such countries might be used as testing grounds for recombinant products. Considerations of this nature have often overshadowed the benefits these countries might derive from the application of genetic engineering.

In response to these concerns, UNIDO, together with the United Nations Environment Programme and the World Health Organization, formed in 1985 the Informal Working Group on Biosafety. In 1991 the Food and Agriculture Organization of the United Nations also joined the Group.

The present volume was commissioned by the Group and is intended to help scientists and regulators to conceptualize the major issues underlying biological safety as well as to understand how these affect policies to regulate biotechnology.

Contents: Biological risk assessment: an editorial overview of some key policy and implementation issues (G. T. Tzotzos); Public perception of biotechnology (M. Leopold); Risk assessment and contained use of genetically modified microorganisms (GMMs) (J. Grinsted); Safety in the contained use and the environmental release of transgenic crop plants (P. J. Dale and J. Kinderlerer); Environmental release of genetically modified rhizobia and mycorrhizas (G. Hall); Microbial pesticides: safety considerations (M. Levin); Safety in the contained use and release of transgenic animals and recombinant proteins (D. Powell); Safety aspects of aquatic biotechnology (R. A. Zilinskas); Safety considerations in biotreatment operations (M. Levin); Glossary of terms. 224 pp. May 1995. ISBN 0 85198 972 1. £30.00 (US$ 55.00 Americas only), hardcover.

Collecting Plant Genetic Diversity: Technical guidelines, edited by L. Guarino, V. Ramanatha Rao, International Plant Genetic Resources Institute (IPGRI), and R. Reid, Department of Primary Industry, Australia.

The case for conserving biodiversity is well established on economic as well as scientific grounds. Biodiversity is essential for sustainable development, adaptation to a changing environment and the continued functioning of the biosphere—indeed, to human survival itself. Plant breeders are dependent upon the availability of a large pool of diverse genetic material represented by local races and wild relatives, since in themselves modern crop varieties provide too restricted a genepool for further breeding. Without the ability to draw from a diverse genetic reservoir, further improvement may not be possible. It is therefore essential that guidance is available on collecting plant germplasm.

In recent years it has become evident that there is no single publication that provides the prospective collector of plant germplasm with generic as well as specific, and theoretical as well as practical, information.

It was to fill this gap that IPGRI, together with FAO, IUCS and UNEP, cooperated to produce this book. The volume is a comprehensive reference work and is aimed at both new and experienced collectors as well as those with a general interest in plant genetics, breeding and biodiversity.

Contents: A brief history of plant germplasm collecting; Legal issues in plant germplasm collecting; An introduction to plant germplasm exploration and collecting: planning, methods and procedures, follow-up (J. M. Engels et al.); Assessing the threat of genetic erosion (L. Guarino); A basic sampling strategy: theory and practice (A.H.D. Brown and D.R. Marshall); Strategies for the collecting of wild species (R. von Bothmer and O. Seberg); Classifications of intraspecific variation in crop plants (P. Hanelt and K. Hammer); Information on previous plant germplasm collecting (M. C. Perry and E. Bettencourt); Published information on the natural and human environment (G.C. Auricht et al.); Published information on wild plant species (H.D.V. Prendergast); Aids to taxonomic identification (N. Maxted and R. Crust); Secondary sources

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Host Plant Resistance to Insects, by N. Panda, former Professor of Entomology, Orissa University of Agriculture and Technology, India, and G. S. Khush, Principal Plant Breeder, International Rice Research Institute, Philippines.

The overuse and misuse of insecticides some four decades ago created major environmental problems and was followed by the development of an "integrated pest management" approach to crop pests. This approach utilizes a combination of host plant resistance and cultural, biological and chemical control methods. Crop improvement programmes emphasize the breeding of crop varieties with multiple resistance to pests, and resistant varieties developed in recent years represent some of the greatest achievements of modern agriculture.

This book presents a broad overview of host plant resistance to insects. It shows how plants can defend themselves naturally and how insects have adapted to overcome these mechanisms through co-evolution. It also describes screening and breeding for insect resistance. It represents a major advanced textbook for entomologists, plant breeders and all concerned with crop protection.

Contents: Foreword by G. Rothschild; Introduction; Crop plant and insect diversity; Secondary plant metabolites for insect resistance; Insect-plant interactions; Host plant selection; Mechanisms of resistance; Factors affecting expression of resistance; Screening for insect resistance; Plant resistance and insect pest management; Genetics of resistance to insects; Breeding for resistance to insects. 448 pp. July 1995. ISBN 0 85198 963 2. £55.00 (US$ 99.00 Americas only), hardcover.

Biotechnology and Integrated Pest Management, edited by G. J. Persley, The World Bank, Washington DC, USA. Biotechnology in Agriculture Series.

This book presents a spectrum of views on the benefits and risks in the use of biotechnology in integrated pest management. It assesses the likelihood of new technologies being usefully incorporated into IPM programmes. It also discusses the types of new biotechnologies which would be most useful to facilitate the wider use of IPM strategies, which aim primarily at minimizing the use of chemical pesticides. Chapters are based on papers presented at a workshop held in Bellagio, Italy, and sponsored by the Rockefeller Foundation, UNDP and the World Bank.

Contents:

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- Slowing pest adaptation (R. Roush); Deploying pesticidal plants (F. Gould);

Part Eight: Other Components in IMP Systems:
- New diagnostics (M. Whalon); Virus/vector control (M. Irwin and L. Nault);

Part Nine: New Opportunities:
- Vector control (E. Evans); Human diseases (C. Curtis); Molecular genetics (V. Rodriguez);

Part Ten: Investment implications:
- Industry views (B. Miflin); International development agencies (G. Persley).

c. 450 pp. February 1996. ISBN 0 85198 930 6. approx. £55.00, hardcover.

Non-Food Uses of Agricultural Raw Materials: Economics, Biotechnology and Politics, by C. Spelman, Centre for European Agricultural Studies, Wye College, University of London, UK.

Interest has recently grown in the non-food uses of agricultural raw materials (ARMs), particularly in developed economies. Reasons for this include the fact that in Western Europe at least, land is now surplus to food production requirements and concern about the environmental consequences of exploiting finite fossil resources.

The end products sought for non-food uses are carbohydrates, fats and fibres derived from both conventional crops such as wheat, maize, oilseed rape, sugar beet and flax as well as less conventional crops or byproducts such as lupins, elephant grass, straw and agricultural waste. This book provides an integrated perspective on both the technology and economics of the processes involved. In many cases, ARMs have to compete with cheaper substrates such as oil. The author analyses two case studies in detail: bioethanol and a particular biodegradable plastic. Relevant political and legislative aspects, for example in the United States, Japan and the European Community, as well as in less-developed countries such as Brazil where ARMs are used for energy purposes, are also studied. The book is aimed at a wide range of readers in academic research (particularly agricultural economics), industry and policy-making.

Contents: Antecedents of non-food uses; Which raw materials will be used?; Technology; The cost equation: The economics of non-food competition between ARMs and NARMs; Policies affecting non-food uses; Conclusion. 160 pp. May 1994. ISBN 0 85198 769 9. £27.50 (US$ 49.50 Americas only), hardcover.

Turning Priorities into Feasible Programmes: Proceedings of a Regional Seminar on Planning, Priorities and Policies for Agricultural Biotechnology in Southeast Asia. This publication contains the proceedings of a regional seminar held in Singapore from 25-29 September 1994, organized by the Intermediary Biotechnology Service (IBS) and the Singapore Organising Committee. For IBS, this was the first in a series of regional policy seminars, aimed at strengthening the capacity of developing countries to manage policy-related issues in agricultural biotechnology.

Despite the diminishing budgets available for national and international agricultural research, a growing number of Governments, in particular in South-East Asia, view agricultural biotechnology as one of the priorities for national development. Many are investing, or planning to invest, in developing the necessary infrastructure and human resources. Establishing research programmes in agricultural biotechnology, however, raises difficult questions. Which priority problems can be addressed by biotechnology? Which technologies are relevant and accessible, and what will be their likely costs and impact? How can modern biotechnology be integrated with conventional agricultural research? How should decision makers deal with questions related to biosafety and intellectual property rights, which are issues that go beyond the agricultural sector as such? How can we ensure that investments in advanced research will result in products appropriate and beneficial for resource-poor farmers?

The regional policy seminars aim to stimulate a dialogue between policy makers, research managers, scientists, and representatives of other groups of society interested in these issues. One objective of the regional seminars is to initiate national follow-up activities in the participating countries, which further elaborate the findings and recommendations of the discussions. The proceedings of the seminars are expected to play an important role in this process.

For IBS and ISNAR, the regional seminars are an important step in developing, in collaboration with the national agricultural research systems, a programme in agricultural biotechnology, which is hoped to lead to adequate policies and stronger research management in this complex area.

Further details from: International Service for National Agricultural Research, P.O. Box 93375, 2509 AJ The Hague, The Netherlands. Tel.: (3170) 349-6100; Fax: (3170) 381-9677; Cable: ISNAR; Telex: 33746.

Agricultural biotechnology and the Public Good are the proceedings from the May 1994 annual meeting of the National Agricultural Biotechnology Council (NABC). The NABC is a cross-sectorial association of 21 US and Canada institutions. Although most of the papers tend to side with current biotechnology developments as an option for better health, environmental and economic standards, critical positions from NGOs and Southern scientists are included. The book delivers a lively debate on biotechnology.

Agricultural Biotechnology and the Public Good, NABC Report 6, 1994, 214 pp., ISBN 0 9630907 5 5. Order from: NABC/BTI, 159 Biotechnology Building, Cornell University, Ithaca, NY 14852-2703, USA. Copies are US$ 5.00 each.

The Cultural Dimension of Development: Indigenous knowledge systems is an impressive and welcome contribution from IT-Publications to the growing awareness on the importance of innovation and technology development by local communities. It includes 46 papers from a very wide variety of disciplines, from both academics and NGOs, South and North. There are 26 case studies and four bibliographic essays. It concludes that the knowledge of local people on their environment must be taken into account in the planning and implementation of development schemes. Recommended.

D. M. Warren, L. Jan Slikkerveer, David Brokensha (eds.), *The Cultural Dimension of Development: Indigenous knowledge systems*, IT Publications, 1995, London, 582 pp., ISBN 1 85339 2510. Order from: IT Publications, 103/105 Southampton Row, London WC1B 4HH, UK. Fax: +44 171 436 20 13. Copies are £16.95 or US$ 32.50.

Farmers' Rights and Plant Genetic Resources: Recognition and Reward: A dialogue are the proceedings of the fifth interdisciplinary dialogue organized by the M. S. Swaminathan Research Foundation (MSSRF), held in January 1994 in Madras, India. A wide selection of scientists, government officials and NGOs spent a week dealing with the recognition and reward for rural and tribal people for the conservation and enhancement of plant genetic resources: analysis of current IPRs and PBRs systems, current international scenario, traditional rights systems, and alternatives. Includes a model *sui generis* law on PBRs that incorporates an expanded concept of farmers' rights that recognizes communal rights. Although the seminar focused on the Indian reality, the discussion has implications for all countries in the process of enacting legislation to fulfil GATT IPR requirements.

M. S. Swaminathan (ed.), *Farmers' Rights and Plant Genetic Resources: Recognition and reward: A dialogue*, Macmillan India Ltd., 1995, 440 pp., ISBN 0 33392 291 5. Available from: MSSRF, 14, 2 Main Road, Kottur Gardens, Kotturpuram, Madras 600 085, India. Fax: +91-44 41 00 31. Priced at Rs.600.

The Indigenous Plant Use Newsletter is a varied and attractive eight-page publication from Africa which

includes short features on practical aspects of traditional biological resources use and associated knowledge.

For information please address: Jenny Mander, Institute of Natural Resources, P.O. Box 375, Pietermaritzburg, 3200 Republic of South Africa.

FAO Seed Review 1989-1990 is the latest published issue of this comprehensive compendium on agricultural crop seed production, processing, control, marketing, promotion and research. Compiled from questionnaires sent out by FAO, it includes generous data from nearly 90 countries, South and North.

FAO Seed Review 1989-1990, FAO, Rome, 1994, 543 pp., ISBN 92 5 103608 X. Available from: Publications Division, FAO, Viale delle Terme di Caracalla, 00100 Rome, Italy.

Local Knowledge, Global Science and Plant Genetic Resources: Towards a partnership are the proceedings of the International Workshop on User Participation in Plant Genetic Resources Research and Development (May 1992, Pangasinan, Philippines), organized by UPWARD, a network affiliated to the International Potato Center working with sweet potato and potato. It includes papers on ex-situ germplasm conservation aspects, local experiences in genetic resources management, and suggestions on formal/informal sector cooperation.

G. D. Prain and C. P. Bagalanon, *Local Knowledge, Global Science and Plant Genetic Resources: Towards a partnership*, UPWARD, Los Baños, 1994, 300 pp., ISBN 971 614 002 9. Available from: UPWARD, c/o IRRI, P.O. Box 933, Manila, Philippines. Fax: +63 2 817 84 70.

Bananas and Plantains is a major resource book on the subject from the INIBAP (the IPGRI affiliated International Network for the Improvement of Banana and Plantain). Bananas and plantains, considered by international agricultural research as one of the "minor crops", do have great importance both as staple starchy food for millions in the tropics, and a cash crop in many developing countries. Only 17 per cent of the total 76 million metric tons produced in 1993 were destined for export as a luxury commodity to rich countries; the rest were used for local consumption. The book covers all major aspects of banana production and use: cultivation, genetics, breeding, morphology, soils, fertilizing, pests and diseases, harvesting, processing, nutritional value, and world economic data. Includes a chapter on banana cultivation in East Africa highlands.

S. Gowen (ed.), *Bananas and Plantains*, Chapman & Hall, 1995, 612 pp., ISBN 0 412 36870 6. Order from: International Thompson Publishing Services, Cheriton House, North Way, Andover, Hampshire SP10 5BE, UK. Priced at £85.00.

Another book on bananas from INIBAP is ***The Improvement and Testing of Musa: A global partnership.*** They are the proceedings of the First Global Conference of the International *Musa* Testing Program (April 1994, Honduras), part of an international effort to produce disease-resistant cultivars, and make such cultivars available to NARS (national agricultural research programmes) for adaptive local research. Includes papers by scientists from Africa, Asia and Latin America.

D. R. Jones (ed.), *The Improvement and Testing of Musa: A global partnership*, INIBAP, 1994, 303 pp., ISBN 2 910810 02 X. Available from: INIBAP, Parc Scientifique Agropolis, 34397 Montpellier Cedex 5, France.

Seed Regulatory Frameworks and Resource-poor Farmers: A literature review is a concise but well articulated discussion on seed accessibility in developing countries, published by the Overseas Development Institute (ODI). Current conducts, problems and alternatives are examined. The author concludes that current breeding, certification and distribution schemes, and regulations often hinder resource-poor farmer access to seeds. New guidelines for more transparent and participatory regulatory frameworks are suggested.

Robert Tripp, *Seed Regulatory Frameworks and Resource-poor Farmers: A literature review*, Network Paper Series No. 51, ODI, January 1995, 53 pp. For information and orders: ODI, Regent's College, Inner Circle, Regent's Park, London NW1 4NS, UK. Fax: +44 171 487 75 90. Email: *odi@gn.apc.org*.

Small Enterprise Development — A quarterly international journal. Across the world there is a growing realization of the potential contribution of the small business sector to economic expansion and the achievement of improved living standards. *Small Enterprise Development* provides a forum for those involved in the design and administration of small enterprise development programmes in developing countries. It is genuinely international, and news and views are welcomed from any source.

Small Enterprise Development contains: detailed articles reporting original research, programme evaluations and significant new approaches; case studies of small enterprise development projects implemented by donor agencies; short practice notes from the various regions of the world describing programmes in operation and work of wider interest; reviews of books, pamphlets and other material; news of projects and grants from the international and local agencies. The journal tackles the major themes and pressing concerns of small enterprise development, such as technical assistance, finance for microenterprises, group cooperative enterprises and private sector involvement in enterprise development.

Subscription rates: institutional rate £60 US$ 100; individual rate £36/US$ 60. Available from: IT Publications Ltd., 103-105 Southampton Row, London WC1B 4HH, UK. Tel.: +44 171 436 9761; Fax: +44 171 436 2013.

Appropriate Technology. The quarterly magazine of practical change in the developing world. Reports from the field for anyone concerned with development in practice. Plus the latest in appropriate technology applications, news from intermediate technology, book reviews, foodlines, resources guide and a development diary.

Annual subscriptions: £19 US$ 37 institutions; £15 US$ 28 individuals. Available from: Intermediate Technology Publications, 103-105 Southampton Row, London WC1B 4HH, UK. Tel.: +44 171 436 9761; Fax: +44 171 436 2013.

New chemical reaction database: BioCatalysis

Synopsys Scientific Systems Ltd., a leading provider of computerized scientific information products and services, announces the development of a new chemical reaction database, BioCatalysis, which provides reliable, up-to-date information on the use of biomolecules as catalysts in organic synthesis.

Chemical companies and academic researchers are currently focusing a great deal of attention on the use of enzymes and microorganisms in synthesis, both as catalysts for novel processes and as versatile alternatives to traditional methods. Advantages offered by biocatalysts include excellent chemo-, regio- and enantioselectivity, coupled with important environmental benefits.

The BioCatalysis database offers access to the increasingly important subject of biomolecule-mediated organic synthesis and is supplied for use with popular reaction searching systems, including REACCS, ORAC and ISIS™/Host. For further information and licensing details contact Dr. Julian Hayward at Synopsys. Tel.: +44 113 245 3339; Fax: +44 113 243 8733.

Biocomputing

New Biotechnology Law Web Server (*http://biotechlaw.ari.net*).

The Biotech Law home page offers legal and scientific information of interest to researchers in biotechnology/pharmaceutical science. At this time, the site provides basic articles on methods of record keeping for inventors, an explanation of the US legal standard for inventorship and an overview of patent application preparation. The Biotech law home page also includes more advanced articles on intellectual property licensing, parallel importing of patented products, and the effects of electronic publication on US patent rights. In addition to a "heads up" guide to recently-issued US biotech patents, the home page provides links to additional sources of information on intellectual property protection, as well as links to selected scientific resources on Internet.

Canadian Biotech News

CBN now has a Web site. The address is: *http://www.igw.ca/bioweb*. For details email to: *pwinter@hookup.net*.

A new Education Mailing List—GENTALK

(GENTALK on *listserv@usa.net*).

There does not seem to be a specific area where teachers (and students) can address classroom problems in genetics and biotechnology. It is the intention of the GENTALK list to provide a forum for discussion of genetic problems, laboratory protocols, and current issues dealing with genetics and genetic engineering in general. Students are encouraged to participate by asking questions, and giving appropriate opinions.

Who uses GENTALK? Participants include mostly high school teachers and students. GENTALK focuses on technical and social issues of education and public policy. This includes laboratory protocols and bioethics. To subscribe to GENTALK, send the following command to *listserv@usa.net*—do not include a subject.

In the body of email:

SUBSCRIBE GENTALK yourfirstnameyourlastname.

For example: SUBSCRIBE GENTALK JohnDoe

Owner/Moderator: Doug Lundberg *lundberg@kadets.d20.co.edu*. Air Academy High School, United States Air Force Academy, CO 80840 USA.

WWW Site and BBS for Regulatory Information

For any of you interested in FDA regulation, there is a new WWW page devoted to Regulatory Affairs information. The URL is *http://www.cybernetics.net/users/RAinfo/reglink1.htm*.

The site features links to various FDA and other US government agency Internet sites as well as links to regulatory professional groups (including the just starting RAPS home page and a local North Carolina regulatory discussion group). There is also a free BBS (The Regulatory Forum) at (919) 848 9461. FDA guidelines and other information are available for downloading. Connect at up to 14400 using 8N1.

BIOSIS—An Electronic Public Debate

I just recently stumbled across a new biotechnology WWW site from the Science Museum in London that might be of interest to you. The BIOSIS prototype home page is billed as "An electronic public debate about biotechnology". The URL of the site is: *http://www.aladdin.co.uk/cfinney/biosis/welcome.html*.

From the page: "This is meant to be an interactive system. Don't just netsurf—participate. Read the information, contribute to the discussions, ask questions, fill in the questionnaire or register your vote in our poll of discussion issues."

It appears to be still under construction, but there are many valuable resources currently available. These would include current discussions on the topics of: The new human genetics– Genetic screening of individuals; Hi-tech food—Bovine somatropin (BST) in milk; Biotech in the environment (under development).

One of the most interesting aspects of this site is a well developed survey of the reader's perceptions of biotechnology. I would encourage you to take a look at this valuable resource.

What is ICPPGR Bulletin Board Network?

This BBN supports the major known communication tools (email, modem to TCP-IP) based on a strong link between a conventional Listserv, a Bulletin Board System (BBS) and a Web server. This BBN will provide discussion groups, access to news, documents, databases, maps and many other options. We are opening our system with discussion groups or conferences on the following topics (if you want more details about each conference, please contact us at this address: *icppgr@fao.org*):

"In-Situ Conservation Crop Improvement"—ICPPGR-In-Situ-L

"Ex-Situ Collections"—ICPPGR-Ex-Situ-L

"Genetic Diversity"—ICPPGR-Diversity-L

"Plant Breeding Improvement"—ICPPGR-Breeding-L

"Regeneration"—ICPPGR-Regen-L

"Training Education"—ICPPGR-Training-L.

Other conferences will be available (about forestry, policy, biotechnology, sustainable agriculture, genebanks and others). You can subscribe to one or more discussion groups and discuss with other experts, researchers, students about many issues. Feel free to subscribe—ICPPGR is promoting the broadest participation in this preparatory process. To be informed about all the new conferences, send email to *mailserv@mailserv.fao.org*—leave the subject blank and type in the body LIST.

There will also be a regular Newsletter (ICPPGR-News-L), where you will find information about ICPPGR activities (country reports, subregional meetings, Global Plan of Action, Report on the State of the World's Plant Genetic Resources), summaries of conferences, access to conference digests, the new options of our Bulletin Board Network (access to archives, to ICPPGR Web server). You are now invited to join this Bulletin Board Network.

How to participate: If you are an email user:

(1) Address your email to *mailserv a mailserv.fao.org*;
(2) Leave the subject line in your header blank;
(3) In the body of your mail, type the following command: SUBSCRIBE<name of the list>. Example: SUBSCRIBE ICPPGR-Diversity-L.

You can subscribe to more than one conference. You will receive a welcome message with the compiete description of the conference.

Address: International Conference and Programme for Plant Genetic Resources, Food and Agriculture Organization (FAO), viale delle Terme di Caracalla, 00100 Rome, Italy. Email: *ICPPGR a fao.org* (Tel.: +39 6 5225 5871; Fax: +39 6 5225 5533).

Boston University provides Gopher, Web servers

Gopher and WWW servers are available for the BioMolecular Engineering Research Center and Molecular Biology Computer Research Resource (BMERC) at Boston University (*http://bmerc-www.bu.edu*. Gopher: *bmerc-gopher.bu.edu*). These servers provide access to (1) the Protein Sequence Analysis System, an email server for analysing amino acid sequences; (2) ProLink, an integrated database of protein structure, sequence homology, and functional pattern data installed in a relational format under Sybase; and (3) specially designed software, data files, and support information. (Contact: Bill Schmidt, BMERC, Boston University, 36 Cummington St., Boston, MA 02215 (Tel.:617/353-7123, Fax:-7020, *gophradm a darwin.bu edu* or *wwwadmin a darwin.bu.edu*))

Jackson Laboratory announces Mouse Genome Database

The Jackson Laboratory in Bar Harbor, Maine, has announced that the Mouse Genome Database (MGD) superseded the Genomic Database of the Mouse (GBASE) on 31 January 1995. MGD will accommodate rapid data growth and changing information needs, taking advantage of software and network improvements. MGD includes all former GBASE data and is integrated with the Encyclopedia of the Mouse Genome, an application that generates a graphical display of mouse genetic linkage maps using MGD mouse locus and homology information. (Bioinformatics Home Page: *http://www.informatics.jax.org*, user support: *mgi-help a informatics.jax.org*(Tel.: 207/288-3371 ext. 1900, Fax: -2516))

Release No. 9 of the Whitehead Institute-Massachusetts Institute of Technology (MIT) mouse genetic maps is available through MGD and the mouse encyclopaedia. Data have been incorporated into locus information tables, PCR primer RFLP tables, and a new set of MIT data files for the encyclopaedia. Files may be downloaded from the encyclopaedia Home Page (*http://www.informatics.jax.org/encyclo.html*) or via ftp (*ftp.informatics.jax.org* from the directory *pub/informatics/encyclo/data/3.0/mit.jan.1995*).

CEPH Genotype Database downloads to PC and UNIX via ftp

The CEPH database of genotypes for all genetic markers tested in the reference families (*Genomics* 6, pp. 575-77 (1990) can be downloaded for PC and UNIX via ftp (*ftp ftp.cephb.fr* from the directory *pub/ceph genotype db*). V7.1 includes genotypes for some 6,000 genetic markers (over 2,500 of which are microsatellite markers), pairwise LOD scores between marker loci on the same chromosome, and database-management programs. The server also contains databases for published CEPH consortium maps.

CEPH Viewer browses, manipulates data

CEPH Viewer is a client-server database for browsing and manipulating CEPH physical mapping and linkage data (Nadkarni et al., *Genomics* 25, pp. 318-20 (1995)). Data imported into CEPH Viewer was downloaded by anonymous ftp from *ceph-genethon-map.genethon.fr* in the directory *pub/ceph-genethon-map*. (CEPH Viewer contact: Prakash Nadkarni, Yale School of Medicine, 333 Cedar St., New Haven, CT 06510 (Tel.: 203/785-7403; Fax: /737-2243.)

Biorep goes on the Internet

The Biorep database of biotechnology research projects in Europe was launched on the WWW service on 27 April 1995. Biorep is managed by the Library of the Royal Netherlands Academy of Arts and Sciences (KNAW) and is accessible at *http://www.knaw.nl*. In the Main KNAW Menu, under *Services and Sources*, are the Biotechnology Research Projects (Biorep). Updating of this database is in full swing and 1,300 projects from Denmark, the United Kingdom, Greece, Italy and Portugal have recently been added. BioResearch Ireland is updating the database for Ireland nd Irish researchers who have not already done so are asked to urgently return their information. The DIMDI network is host for Biorep.

For more information on Biorep contact the project manager: Mr. M. L. H. Lalieu, KNAW, P.O. Box 41950, NL-1009 DD Amsterdam. Tel.: +31 20 6685511, Fax: +31 20 6685079, email: *harrie.lalieu a library.knaw.nl*.

Irish National Centre for Bioinformatics (INCBI)

There are two main DNA/RNA databases in the world, GenBank in the USA and EMBL in Europe. Both contain the same sequences and exchange data with daily up-dates; the INCBI stores the EMBL version. The centre can also provide access to two protein databases (of amino acid sequences): SWISSPROT, the main one, and NBRF/PIR (where some sequences are deduced from DNAs). Other protein databases include PDB, which contains information on 3D structures, and PROSITE, which holds "motifs", short segments that are common to a number of related proteins.

To use the INCBI, subscribers should have a TELNET connection, and either XWindows or a Mac emulator for point-and-click use, or else use command lines. The main INCBI database interface is "ACNUC" (aka "QUERY"), a piece of software developed at Lyon specially to interrogate the EMBL DNA database. Users can scan the database by keyword, for example, or by gene, author, organism, journal, etc. They can also do homology searches, scan for reading frames, look for restriction sites, and perform other sequence analyses.

Already, some two dozen databases are available and linked on the World Wide Web, like "flybase" from the international *Drosophila* (fruitfly) genome sequencing programme. The hypertext connectivity of the WWW means that users will eventually be able to examine a gene sequence, then study the protein it codes for, look at its structure, compare that with the same protein from another organism, read the relevant journal abstracts, and all in a few minutes and without having to visit the library!

A good review of the current state of bioinformatics, including useful Internet and WWW addresses, is "Bioinformatics" by M. S. Boguski, *Current Opinion in Genetics and Development*, 1994 4, pp. 385-388.

The INCBI can be contacted at: Tel.: 01-702-1969; Fax: 679 8558; and (ideally) email: *incbi@acer.gen.tcd.ie*.

The new Bioline publications

Full text and graphics of scientific documents are published on the Internet by Bioline Publications. This international on-line service now provides a single document delivery service and immediate on-line viewing as an alternative option to email delivery.

These new developments of a collaborative initiative with the Base de Dados Tropical (Campinas, Brazil) and a growing number of publishers, editors and authors, offer great flexibility in ways of purchasing and viewing documents. Users may mix and match, choosing single documents from the whole breadth of coverage, or subscribe to selected journals on an annual basis. Users may request email delivery, as in the past, or may view documents straight away on the screen.

Bioline Publications is a scientist-run small company responding to the needs of biologists and technologists world-wide for easier, more immediate and cheaper access to biological information. In the biological sciences, it was the first organization to put together the necessary technology to do this. It is breaking new ground which may set the pattern for the future publication of biological research information.

Bioline Publications is a comprehensive bibliographic service offering:

- 24 peer-reviewed journals (electronic versions of printed journals);
- The first biotechnology online-only journal (BioSafety);
- Many technical documents, reports and newsletters;
- Books available as single chapters;
- Public domain software;
- A bulletin board (bioline-l) and news options;
- Links to other bibliographic sites on the Internet.

To look at Bioline Publications on the World Wide Web, use the URL: *http://www.bdt.org.br/bioline/index.html*.The whole system is also accessible by Gopher and email, for those without WWW access.

Further information, instructions, list of material and price list from Bioline Publications at Stainfield House, Stainfield, Bourne, Lincs. PE10 0RS. Email: *bio@biostrat.demon.co.uk*. Tel.: +44 1778 570618; Fax: +44 1778 570 175.

The 1995 list of material is as follows:

Journals

- Actinomycetes
- Agbiotech News and Reviews
- Avian Pathology
- Binary
- Biocontrol Science and Technology
- Biodiversity and Conservation
- Biometals
- Biopolicy International
- Biosafety
- Biotechnology and Development Monitor
- Biotechnology Letters
- Biotechnology Techniques
- British Poultry Science
- Ecotoxicology
- Environmental Values
- Food and Agricultural Immunology
- Memorias do Oswaldo Cruz
- Nanobiology
- Nutritional Medicine
- The Genetic Engineer and Biotechnologist
- Toxicology Modeling
- Toxicology and Ecotoxicology News
- Transgenic Research
- Tropical Biodiversity
- World Journal of Microbiology and Biotechnology.

Coming soon:

- Australasian Biotechnology.

Reports

Biotechnology:

EEC documents:

- EEC Council Directive 90/219/EEC on the contained use of genetically modified microorganisms
- EEC Council Directive 90/220/EEC on the deliberate release into the environment of genetically modified organisms
- EEC Explanatory Notes on above
- EEC Council Directive 90/679.EEC on safety at work
- EEC Amendment to above
- EEC Communication on Biotechnology Policy 1991
- EEC Biotechnology after the 1991 Report—a Stock-taking Note
- EEC Progress Report 1992: Pre-normative Research in Biosafety
- EEC Report 1993: "The Global Perspective 2010: the case for biotechnology"
- EEC 1993 Research Reports on Biosafety (BRIDGE projects)
- Council of Europe Report 1993 ADOC 6780—Developments in biotechnology and the consequences for agriculture
- Forum for Industrial Microbiologists (FIM) Opinion Paper on the Future of Microbiology and the Needs of Pharmaceutical Industries.

US documents:

- NIH Guidelines for Research involving Recombinant DNA Molecules with Appendices
- US Report on National Biotechnology Policy.

General regulatory documents:

- Grouping of Biological Agents, BG Chemie, Germany
- Information Centre for European Culture Collections 1993: Instructions for shipping non-infectious and infectious biological substances
- European Culture Collections' Organisation 1994 Issue of Instructions for Shipping Infectious, Non-infectious and genetically modified microorganisms
- UK Advisory Committee on Genetic Manipulation/ Health and Safety Executive Guidance Notes.

Biodiversity

- Convention Biological Diversity
- UNEP/Nairobi Conference Report
- UNEP/Norway Conference Proceedings
- UNEP Expert Panel Reports I-IV
- Green College Oxford Conference Report: IPR and indigenous rights and conservation
- UK Darwin Initiative (Biodiversity)

- WWF Position Paper on the Convention on Biological Diversity (October 1993)
- WRI Reports: The United States Needs a National Biodiversity Policy; Biodiversity Indicators for Policy Makers
- ATSAF Circular (Tropical and Subtropical Agricultural Research - partly in German)
- Microbial Diversity and the 1992 Biodiversity Convention (FIELD)
- WCMC Policy Document: The Biodiversity Information Clearing House Mechanism
- ABSP Workshop Report - Intellectual Property Rights, 1994
- ABSP Workshop Report - Biosafety/Intellectual Property Rights Project Evaluation

Culture collections (see also Newsletters, Books)
- European Culture Collections' Organisation Holdings and Services
- WFCC Guidelines for the Establishment and Operation of Collections of Cultures of Microorganisms

Conference reports
- 1st Slovene Congress on Microbiology, October 1993, Abstracts
- International Congress on Culture Collections Abstracts, Beijing, October 1992, Abstracts
- USAID Latin America/Caribbean Regions Biosafety Workshop
- Biotechnology '94 Conferences (Biochemical Engineering, Industrial Immunology, Applied Biocatalysis, Fermentation Physiology)

Newsletters

Public domain:
- AgBiotech, Canada
- Biodiversity Coalition Newsletter
- BioLink, USA
- Biorep Newsletter
- Bio Technology/Biodiversity Bulletin
- Centraalbureau voor Schimmelcultures, Netherlands
- European Biotechnology Information Service (EBIS)
- European Centre for Animal Cell Cultures (ECACC)
- European Tropical Forest Research Network (ETFRN)
- Federation for European Microbiological Societies (FEMS)
- The Genetical Society
- Information Centre for European Culture Collections (ICECC)
- International Council for Scientific Unions (ICSU) Science International
- International Organisation of Palaeobotany Newsletter
- Oleae Newsletter
- Polychaete Newsletter
- UK Federation for Culture Collections (UKFCC)
- World Federation for Culture Collections (WFCC)

Commercial:
- Environmental Health Briefing - Weekly Newsletter

Books
- WRI Biodiversity Prospecting
- "The Biodiversity of Microorganisms and the Role of Microbial Resource Centres" - a WFCC publication
- "Maintenance of Microorganisms and Cultured Cells", Academic Press, 2nd Edition, available by chapter.

WWW links to other bibliographic resources for biologists available on the Internet
- Microbial Germplasm Network (Oregon, USA)
- Genethon (France)
- ICGEB (Trieste, Italy)
- ERINYES (Australia)