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

Genetic Engineering and Biotechnology Monitor

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A. POLICY, NEWS AND OTHER EVENTS

UNIDO News

International Centre for Genetic Engineering and Biotechnology

We reproduce hereunder an abstract of a paper which appeared in Biochimica et Biophysica Acta, Vol. 951 (1988), pp. 43-441, submitted by the ICGEB in honour of Dr Arthur Kornberg's 70th birthday. Copies of the full article may be obtained from Elsevier Science Publishers, B.V., Amsterdam, The Netherlands.

Presence of transcription signals in two putative DNA replication origins of human cells*

Attilio Falaschi,[1] Giuseppe Biamonti,[1,2] Fabio Cobianchi,[1] Eva Dubrovsky Toth,[1] Georgiana Faulkner,[1] Mauro Giacca,[1] Daniela Pedrochini,[1] Giovanni Perini,[1] Silvan Riva[1] and Carla Tribioli[1]

(Received 21 September 1988)

Key words: Replication origin; Nuclear factor III; Major late promoter; DNA replication; (HeLa cell)

We describe the purification and cloning of human DNA replicated at the onset of S phase in HeLa cells synchronized with aphidicolin. A survey of the overall structural properties of these sequences did not show any distinctive features except for an enrichment in Cot$_{1}$ DNA. The two longer fragments were completely sequenced and studied in more detail. Both were shown to contain transcriptional signals associated with promoters and or enhancers, such as the binding sites of Sp1, T antigen and nuclear factor III. In one instance, a binding site for a known cellular transcription factor (USF MLTF) was located inside the sequence by footprinting. Accordingly, by CAT assay and Northern blot, the same sequence was shown to contain an active promoter. The significance of these findings with respect to the role of transcription in initiation of DNA replication at the origin is discussed. None of the tested fragments exhibited autonomously replicating sequence (ARS) activity in transfected cells. The problems connected with the detection of ARS activity in human cells are critically examined.

* Dedicated to Arthur Kornberg on the occasion of his 70th birthday.

Abbreviations used: CAT, chloramphenicol acetyltransferase; ARS, autonomously replicating sequence; DMEM, Dulbecco's modification of Eagle's minimal essential medium; LTR, long terminal repeat; NF, nuclear factor; HTF, HpaII tiny fragments.

Correspondence: A. Falaschi, International Centre for Genetic Engineering and Biotechnology, Padriciano 99, 34012 Trieste, Italy.

[1] International Centre for Genetic Engineering and Biotechnology, Trieste.

[2] Istituto di Genetica Biochimica ed Evoluzionistica del CNR, Pavia (Italy).

United Nations and other organizations' news

United Nations vaccination aims

The United Nations hopes to vaccinate all third world children against six preventable diseases by 1990. This goal will require that 80 per cent of children under two years of age be vaccinated against polio, measles, tuberculosis, tetanus, whooping cough and diphtheria. According to statisticians, once 80 per cent of a population is vaccinated, the rate of disease transmission declines sharply. Experts believe that universal vaccination will lead to greater acceptance of family planning, as well as saving millions of lives and reducing the cost of health care. The vaccination programme, which will cost $500 million year after the 80 per cent target is reached, is being co-ordinated by UNICEF and WHO. Only 10 per cent of third world children were immunized against six preventable diseases in 1978, but the vaccination rate has increased to 50 per cent currently.

The vaccination programme will face major challenges in Africa, due to its hot, humid climate, poor roads and limited electrical capacity. New technology, such as insulated boxes that can maintain the temperature of vaccines below 45°F for 48 hours, is helping the vaccination effort. The Nigerian Government hopes to raise the average immunization level to 50 per cent by the end of 1988, against the current 25 per cent. The US provided a $3.5 million grant to UNICEF to purchase storage freezers for Nigeria. The central freezers supply a network of insulated cool boxes that can keep vaccines cold for one week. Smaller, portable containers can keep the vaccines cool for 48 hours. UNICEF is also issuing vaccination records that are printed on plastic paper, which is more durable in the humid African climate. Some 15 sub-Saharan nations have met UNICEF's goal over the past two years, including Gambia. (Extracted from New York Times, 26 April 1988)

OECD report attacks national policies

The Organization for Economic Co-operation and Development (OECD), in a report** just published, says that member States are not paying enough attention to the potential uses of biotechnology in the control of environmental pollution. The report suggests that widespread public hostility towards genetic engineering could "cause considerable delays in the diffusion of many harmless and beneficial products and processes".

Awareness of this hostility, rather than empirical research, has, says the report, encouraged environment ministries to maintain a defensive position against hypothetical risks of the release of genetically altered micro-organisms, instead of exploiting the many ways in which biotechnology might help them to monitor and clean up the environment. Positive examples already being exploited in the United States and in France include the use of biosensors as pollution monitoring devices and the development of improved waste treatment systems.

** Biotechnology and the changing role of government (OECD, Paris, 1988).

ICGEB Meetings, Courses, Workshops to be held in 1989

The following is the final list of courses and workshops organized by ICGEB during the course of 1989

Subject	Organizer(s)	Date, Venue
COLLOQUIUM MEETING: ICGEB PANEL OF SCIENTIFIC ADVISERS	A. Chakrabarty, K.K. Tewari	1-3 March ICGEB, New Delhi, India 100 participants
WORKSHOP: MOLECULAR GENETICS OF YEAST	G. Tocchini-Valentini J. Abelson B. Hall J. Szostak C. Guthrie L. Frontali C. Magni J. Kurjan J. Pulitzer	29-31 March ICTP, Miramare, Trieste, Italy 30 participants
RESEARCH COLLOQUIUM: EUROPEAN AFFILIATED CENTRES	I.C. Gunsalus	9-12 April ICGEB, Trieste, Italy 80 participants
PRACTICAL COURSE: GENETIC MANIPULATION OF STREPTOMYCES	D.A. Hopwood M.J. Bibb C.J. Bruton K.F. Chater Deng Zixin H.M. Kieser T. Kieser Zhou Qi Zhou Xiufen	9-24 April Huazhong Agricultural University, Wuhan, China 20 participants
PRACTICAL COURSE: COMPUTER APPLICATION IN MOLECULAR BIOLOGY	D. Brutlag J. Collins A. Bairoch	3-13 July ICGEB, Trieste, Italy 30 participants
PRACTICAL COURSE: MOLECULAR GENETICS OF CHLOROPLASTS	K.K. Tewari J. Bennett R. Wu H. Daniell A. Cnanm S. Chauhan A. Tyagi V. Kumar	2 July - 10 August ICGEB, New Delhi, India 20 participants
PRACTICAL COURSE: METHODS IN EUKARYOTIC GENE EXPRESSION	I. Boros J. Brady C.M. Nguyen Huu R. Brent	Mid September Biological Research Centre, Szeged, Hungary 20 participants
PRACTICAL COURSE: DIAGNOSIS OF PARASITIC DISEASES	H.A. Perez E.L. Benedetti A. Hernandez J.L. Ramirez	15 September - 6 October IVIC, Caracas, Venezuela 20 participants
WORKSHOP: GENETIC PATHOLOGIES AND THE HUMAN GENOME	L.L. Cavalli-Sforza	6-10 October ICGEB, Trieste, Italy
PRACTICAL COURSE: MOLECULAR VIROLOGY	E. Wagner T. Shenk J. Stevens I. Verma H. Pan P. Roy	1 November - 10 December ICGEB, New Delhi, India 20 participants

Information: Ms. D. Viti, International Centre for Genetic Engineering and Biotechnology, Padriciano 99, I-34012 Trieste, Italy.

Information on courses and meetings held at ICGEB in New Delhi may be had from The International Centre for Genetic Engineering and Biotechnology, National Institute of Immunology Campus (N.11), Shahid Jeet Singh Marg, New Delhi 110067, India.

Status of Signature/Ratification of Statutes of ICGEB
(as of January 1989)

Member State	Statutes	Protocol	Ratification or Acceptance
Afghanistan	13 Sep. 1983 1/ 28 March 1984 2/	15 Aug. 1984	9 July 1988
Algeria	13 Sep. 1983	4 Nov. 1985	11 Sep. 1987
Argentina	13 Sep. 1983	4 April 1984	
Bhutan	31 May 1984	31 May 1984	7 May 1985
Bolivia	13 Sep. 1983		
Brazil	5 May 1986	5 May 1986	
Bulgaria	13 Sep. 1983 1/	4 April 1984	23 June 1986 3/
Chile	13 Sep. 1983	4 April 1984	
China	13 Sep. 1983		
Colombia	21 Nov. 1986	14 Sep. 1987	
Congo	13 Sep. 1983		
Cuba	13 Sep. 1983	4 April 1984	30 June 1986
Ecuador	13 Sep. 1983		
Egypt	13 Sep. 1983	2 Jan. 1986	13 Jan. 1987
Greece	13 Sep. 1983	4 April 1984	
Hungary	13 Jan. 1987	14 Sep. 1987	13 Jan. 1987
India	13 Sep. 1983	4 April 1984	9 July 1985
Indonesia	13 Sep. 1983		
Iran	29 April 1988	29 April 1988	
Iraq	28 Feb. 1984	23 Oct. 1984	19 Feb. 1985
Italy	13 Sep. 1983	4 April 1984	

1/ Signature ad referendum
2/ Confirmation of signature ad referendum
3/ Ratified with a declaration

Member State	Statutes	Protocol	Ratification or Acceptance
Kuwait	13 Sep. 1983		21 Oct. 1986 3/
Mauritania	13 Sep. 1983		
Mauritius	19 Sep. 1984	19 Sep. 1984	5 Jan. 1989
Mexico	13 Sep. 1983 1/	25 Oct. 1984 1/	21 Jan. 1988 3/
	21 May 1984 2/		
Morocco	19 Oct. 1984	19 Oct. 1984	
Nigeria	13 Sep. 1983	2 May 1985	
Pakistan	4 Nov. 1983		
Panama	11 Dec. 1984	11 Dec. 1984	12 Aug. 1986
Peru	22 March 1984	4 April 1984	
Senegal	29 June 1984	29 June 1984	4 May 1985
Spain	13 Sep. 1983		
Sudan	13 Sep. 1983		
Thailand	13 Sep. 1983		
Trinidad and Tobago	13 Sep. 1983	8 Feb. 1985	
Tunisia	27 Oct. 1983		
Turkey	22 Sep. 1987	22 Sep. 1987	10 Jan. 1989
Venezuela	13 Sep. 1983	4 April 1984	15 Oct. 1985
Viet Nam	17 Sep. 1984	17 Sep. 1984	
Yugoslavia	13 Sep. 1983	4 April 1984	18 March 1987
Zaire	13 Sep. 1983		

1/ Signature ad referendum
2/ Confirmation of signature ad referendum
3/ Ratified with a declaration

[illegible] in the [illegible] [illegible] of [illegible], [illegible] the report [illegible] on the [illegible] criteria and [illegible] for risk assessment [illegible] new agency [illegible]. This [illegible] "[illegible] regulations" [illegible] prefer [illegible] for [illegible] rather than [illegible] up efficient [illegible] Also [illegible] is the lack [illegible] risk assessment, which [illegible] talented researchers.

[illegible] of universities, [illegible] instead of [illegible] with [illegible] industrial [illegible].

[illegible] private sector investment [illegible] remains [illegible] high risk, [illegible] research [illegible] report [illegible] scientific information and the development of databases, regulatory mechanisms to ensure intellectual property and the freedom to publish findings [illegible] university collaboration with industry, as well as better [illegible] public confidence.

Given that more patent applications for commercially useful biotechnology inventions arise from basic research than from industrial, applied research, the report stressed that the biotechnology boom should not tempt Governments to neglect the role of pure science. (Source: Nature, Vol. 33[illegible], 2 June 198[illegible])

[illegible] field release [illegible] safety

Over [illegible] representatives from [illegible] nations met in Paris during April to draw up biotechnology safety criteria and set another milestone when they established a working party under US auspices to [illegible] of small scale field tests.

The Group of National Experts on Safety in Biotechnology of the Organization for Economic Co-operation and Development (OECD) appointed the US delegation to head a new working party established to design Good Developmental Practices (GDP) criteria for small scale field tests of plants and micro-organisms. The panel will meet in September to consider a revised GDP draft that US delegates [illegible] complete by [illegible]. The full OECD group will take up the committee's finished product at its next meeting, scheduled for April 1989.

The GDP concept builds on the Good Industrial Large Scale Practice (GILSP) criteria that the OECD group adopted last year. As long as an enterprise follows the GILSP guidelines for using low risk and negligible risk "contained" organisms, it need not receive specific approval from regulatory agencies of nations, such as Japan and the United Kingdom, that have adopted them.

The same approach was followed in the draft of "GDP General Principles" submitted to the OECD group by Frank Young, commissioner of the US Food and Drug Administration, who led the US delegation. The draft GDP principles reflect the National Academy of Sciences' conclusion last year that "assessment of the risks of introducing r-DNA engineered organisms into the environment should be based on the nature of the organism and the environment into which it will be introduced, not on the method by which it was modified".

[illegible] the [illegible] of the US delegation [illegible] representatives from the US Environmental Protection Agency (EPA), who are currently writing a new EPA policy for regulating small scale field tests in the US that is reportedly more restrictive than that outlined last June in the Reagan administration's "coordinated framework" preferred a GDP that simply described safe field testing practices, rather than specific criteria for low and negligible risk organisms. (Source: McGraw-Hill's Biotechnology Newswatch, 2 May 1988)

UNDP/UNESCO/UNIDO Regional Programme of Biotechnology for Latin America and the Caribbean

The United Nations Development Programme, within [illegible] Regional Development Programme for the [illegible] has organized, with the collaboration of the specialized agencies UNESCO and UNIDO and in close consultation with the countries, this Regional Programme for the establishment of an appropriate framework for the development of concerted [illegible] and collaborative projects in this area.

The main goal is to strengthen biotechnology in the region so as to develop products, services and technologies to be able to tackle local problems of significant social and economical impact.

The most widely endorsed strategies underlining this proposal are the following:

(a) Scientific and technological integration among the countries of the region is a necessity and should be fostered. Thus, this Programme is open to the participation of all the countries of the region according to their capacities, national interest and commitment.

(b) Co-operation among the countries of the region should increase substantially.

(c) Research and development should be integrated with the productive sector.

(d) Available resources should be concentrated in a limited number of projects of high socio-economic impact to increase the possibility of success.

The Programme officially started its activities with the first meeting of its Regional Executive Council and the active participation of the following countries: Argentina, Colombia, Costa Rica, Cuba, Chile, Guatemala, Mexico, Peru, Uruguay and Venezuela. Several other countries, including Brazil, are considering joining the Programme in the near future.

The immediate goals of the Programme are the following:

(a) Elaborate and implement Regional Specific Research and Development Projects (at laboratory, pilot plant or industrial level) to solve regional problems of outstanding socio-economic importance through the application of biotechnologies.

(b) Develop mechanisms by which investments in research, development or production will be facilitated.

(c) Strengthen the scientific and technological infrastructure necessary for the execution of this Programme.

(d) Study the feasibility of an information network to facilitate the exchange of data related to biotechnology.

[illegible] relevant for the [illegible] results [illegible] multidisciplinary undertakings and studies in the ethical and practical aspects of the development and release of living organisms and technologies.

Strategy

The Programme is implemented by [illegible] been divided into two subprogrammes.

UNESCO is responsible for the activities of research and development at the laboratory level, and for the training of human resources in the basic sciences required by the Programme, within the framework of the subprogramme "Basic Level Research and Technologies and Products".

UNIDO will undertake activities such as the detection and evaluation of technologies suitable for scaling up in pilot plants and their development to the industrial level, and the training of personnel in specific aspects of industrial application of the technologies within the subprogramme "Development of Technologies and Industrial Applications of Biotechnologies".

This division calls for projects which [illegible] simultaneously or sequentially, require both basic research and industrial development. Both programmes are carried out in a coordinated and integrated way.

Other specialized agencies of the United Nations system are expected to collaborate in the execution of particular activities within their respective fields of competence.

Operation

Each participating country has established a National Committee for Biotechnology which coordinates the activities of the Programme in each country and proposes regional R&D activities to be carried out by the Programme. These committees include scientists, industrialists and government representatives.

The Regional Executive Council is the highest policy and decision-making body of the Programme and constitutes its maximum authority. It is made up of a single delegate of the Government of each participating country and by representatives of UNDP, UNESCO and UNIDO. The latter are non-voting members.

The Regional Executive Council meets annually and its venue rotates among the participating countries.

The Council decides upon the policies of the Programme, the annual work plan, the distribution of the budget and the evaluation of the specific projects. Furthermore, it nominates four representatives for the Tripartite Meeting and for the Task Committees.

Each executing agency appoints (in consultation with the participating governments) a Technical Co-ordinator who is responsible for the co-ordination and execution of the activities in the work plan.

The evaluation of the activities of the Programme is carried out, in accordance with the regulations and rules of procedure of UNDP, in Tripartite Review Meetings. These meetings are [illegible]

Activities

[illegible]

Objectives [illegible]

The main activity [illegible] specific projects [illegible] relating [illegible] quantity [illegible] with the [illegible] of the [illegible] Information. These projects have been evaluated, and those [illegible] and approved in the first meeting of the Executive Council.

The following projects [illegible] of previous

1. **Title: Trypanosomiasis and leishmaniasis in several endemic areas of America.**

Objectives: [illegible] their specificity and [illegible]

Participants:

[illegible] Instituto Nacional de Parasitología "Dr. Mario Fatala Chaben" (Argentina)

[illegible] Instituto de Investigaciones Bioquímicas "Fundación Campomar" (Argentina)

[illegible] Instituto de Inmunología y Biotecnología (Argentina)

BIOTOXA S.A. (Argentina)

[illegible] Médicas (Colombia)

[illegible] Universidad de Chile (Chile)

[illegible] Universidad de San Marcos (Peru)

[illegible] Instituto de Medicina Tropical

[illegible] Universidad Central de Venezuela (Venezuela)

Length: 36 months

Director: Dr. Andrés Nava (Argentina)

2. **Title: Development of diagnostic kits for plant viruses.**

Objectives: Development of [illegible] probes and monoclonal antibodies against beet, corn and citrus viruses.

Participants:

Universidad Nacional de La Plata (Argentina)

INGEBI (Argentina)

- Universidad del Valle (Colombia)

- Universidad Nacional de Colombia (Colombia)

- Universidad de Costa Rica (Costa Rica)

Universidad Nacional Agraria La Molina (Perú)

Ministerio de Ganadería, Agricultura y Pesca (Uruguay)

- Instituto de Investigaciones Biológicas "Clemente Estable" (Uruguay)

- Instituto Venezolano de Investigaciones Científicas (Venezuela)

Length: 36 months

Director: Dr. María Luisa Mayoral (Venezuela)

3. **Title: Enzymatic degradation of agro-industrial debris.**

Objective: Develop the technologies to produce cellulolitic enzymes and single cell proteins from lignocellulose residues.

Participants:

- Universidad Católica de Valparaíso (Chile)

- Universidad de Chile (Chile)

- Universidad Agraria La Molina (Perú)

Universidad San Antonia Abad del Cusco (Perú)

- Universidad de Oriente (Venezuela)

- Universidad Simón Bolívar (Venezuela)

Length: 52 months

Director: Dr. Victor Carrizales (Venezuela)

4. **Title: Industrial production of penicillin amidase and its use for the production of 6 APA.**

Objective: Scale up to pilot plant the production of catalyst and its evaluation in industrial conditions.

Participants:

Universidad Nacional de Colombia (Colombia)

Centro de Ingeniería Genética y Biotecnología (Cuba)

Unión de Empresas Médico Farmacéuticas (Cuba)

Centro de Investigación sobre Ingeniería Genética y Biotecnología (México)

GENIN S.A. (México)

Length: 42 months

Director: Dr. Ofelia Valdés (Cuba)

5. **Title: Development of new methods for labelling DNA probes and their use for the diagnosis of malaria, entorophaties and hepatitis.**

Participants:

- Centro de Ingeniería Genética y Biotecnología (Cuba)

- Universidad Católica de Chile (Chile)

- Universidad de Chile (Chile)

- Centro de Investigación sobre Ingeniería Genética y Biotecnología (México)

- Universidad Cayetano Heredia (Perú)

Length: 36 months

Director: Dr. Paul Lizardi (México)

6. **Title: Development of technology for the production of lactose.**

Objective: Obtain an enzyme able to degrade lactose from milk sera.

Participants:

- Universidad Nacional de Colombia (Colombia)

- Centro de Ingeniería Genética y Biotecnología (Cuba)

- Universidad Católica de Valparaíso (Chile)

- Centro de Investigación sobre Ingeniería Genética y Biotecnología (México)

- Universidad de Montevideo (Uruguay)

- Universidad Simón Bolívar (Venezuela)

Length: 36 months

Director: Dr. Lidia Casas (México)

(Source: MIRCEN News, July 1988)

Social issues

Towards a people oriented biotechnology

In March 1987, a Dag Hammarskjold Seminar with participants from 19 countries was arranged at Rogéve, France under the title: "The Socio-Economic Impact of New Biotechnologies on Basic Health and Agriculture in the Third World". It issued the declaration below:

"Biotechnology is a global issue. It cannot be assigned such attributes as positive, negative, or neutral. Like any other technology, it is inextricably linked to the society in which it is created and used, and will be as socially just or unjust as its milieu. Therefore, we conclude that in today's world this most powerful new technology is more likely to serve the interests of the rich

and powerful than the needs of the poor and powerless.

"We fully recognize the potential of biotechnology to improve the quality of life of humanity. But it is important to emphasize the risks and hazards associated with biotechnology, including serious and possibly irreversible health, safety, environmental and socio-economic consequences as well as the use of such technology in biological warfare.

"In agriculture, for instance, while biotechnology may promise to increase production and reduce costs, it is more likely to accentuate inequalities in the farm population, aggravate the problem of genetic erosion and uniformity, undermine life-support systems, increase the vulnerability and dependence of farmers and further concentrate the power of transnational agribusiness.

"In health, for instance, biotechnology promises more effective diagnostic tools and new ways of preventing and curing diseases. However, the pharmaceutical industry is more likely to focus on the most profitable commercial opportunities and divert attention from the basic health requirements.

"In view of the above, we make the following recommendations:

AT THE CITIZEN LEVEL, that:

- We accept a major role in the development of public discussion and policy related to biotechnology; we monitor industry activities in this field; we commit ourselves to taking action in this field with the relevant UN bodies including FAO, GATT, ILO, UNCTAD, UNEP, WHO and WIPO;* we agree to carry our concerns back to the networks with whom we are engaged, such as Health Action International (HAI), International Baby Food Action Network (IBFAN), Pesticide Action Network (PAN) and Seeds Action Network (SAN) in order to facilitate co-operation; we seek to promote appropriate technologies that are socially just and ecologically sustainable, including regenerative agriculture, alternative crop protection strategies, preventive medicine, recycling of resources and wastes, etc.

AT THE NATIONAL LEVEL, that:

- A dialogue be established to determine the real needs of society and the main requirements for a national biotechnology strategy based on these needs; the socio-economic and environmental implications of such a strategy be fully considered; the regulatory requirements for the safe testing and introduction of the technology be established and stringently enforced; the control over the technology be assigned to the public sector and the monopolization of the technology by private interests be resisted.

* Food and Agriculture Organization; General Agreement on Tariffs and Trade; International Labour Organisation; United Nations Conference on Trade and Development; United Nations Environment Programme; World Health Organization; World Intellectual Property Organization.

AT THE INTERNATIONAL LEVEL, that:

- A wider [illegible] the impact of [illegible] and begun as soon as possible, particularly the initiatives [illegible] UNIDO, UNEP, FAO/SIDA* and other international bodies; that all Governments take measures to [illegible] appropriate biotechnologies and further explore the opportunities for South-South co-operation in all aspects of the development and use of biotechnology, in particular with regard to the utilization of genetic raw materials; the evolution of research and development in biotechnology be closely monitored so that the interests and rights of the Third World are kept foremost in institutions working on these issues; changes in existing intellectual property rights discussed in WIPO which [illegible] the rights of the Third World be closely monitored, and that a major revision of the Paris Convention be encouraged in order to safeguard the interests of the Third World.

"In conclusion we wish to reaffirm that a national biotechnology policy must be geared to meet the real needs of the majority of the world's people and the creation of more equitable and self reliant societies while working in harmony with the environment." (Source: Development Forum, U.N., No. 4, July August 1988)

Biotechnology bane or boon for third world?

Recent progress in biotechnology is giving this business a more solid grab than the "green revolution" two decades ago. The new science will find countless ways to penetrate third world markets, replace import commodities, threaten Governments with starvation, or simply wage biological war against them.

Canadian economics professor Patrick Mooney, 1985 Alternative Nobel Peace Prize winner and author of Seeds of the Earth (1977) and The Law of the Seed (1983) issued this alert during the Twelfth Pan American Seminar on Seeds recently held at Montevideo, Uruguay.

According to Mooney, in the early 1980s, the U.S. Mobil and British Petroleum consulted the Massachusetts Institute of Technology (MIT) on the feasibility of investing in new technological areas. MIT provided genes of animals and vegetables. It was estimated that the seed market would swell beyond $50 trillion. Moreover, applied to agriculture, the new technology was likely to open new market lines valuable [illegible] an additional $100 billion in two decades. For instance, it is estimated that tissue culture techniques will raise sugar cane yields from 70-90 tons per hectare to 150 tons, and tomato yields per hectare from 20-40 tons to 400.

Furthermore, transnationals companies do not intend to create varieties that grow without fertilizers, irrigation and pesticides. Instead of searching for plague resistant varieties, they

* United Nations Industrial Development Organization International Centre for Genetic Engineering and Biotechnology; United Nations Centre for Science and Technology for Development Advance Technology Alert System.

develop pesticide resistant plants. TNC's are now running 79 programmes aimed at making different crops fit for enduring pesticides.

If Ciba Geigy succeeds in creating an Atrazine resistant variety, Atrazine sales will grow by more than $125 million. If Monsanto gives birth to a crop that endures Glyphosate, its market will swell by $150 million. When Hoechst develops plants for Basta, this agrochemical will sell an additional $200 million yearly. The market for pesticide-resistant varieties is reckoned at $3.1 billion per year by the mid 1990s, and at $6 billion by the end of the century.

Adapting a plant to a chemical is a lot cheaper than doing the opposite. Developing a new variety costs $2 million while formulating a new herbicide requires $40 million. It is no coincidence that out of 10 companies that control the world seed market, eight also engage in production of agrochemicals. Moreover, all 10 leading companies selling agrochemicals are, without exception, active in seed sales. Since the late 1960s, petrochemicals and pharmaceutical producers have been the largest purchasers of seed-related firms.

Embryo production is the latest strategic goal. Embryos are sold accompanied by small protective capsules containing fertilizers, fungicides and herbicides ready to mix with soil. This is currently used for celery, tomato, carrots and green pepper, and research is under way to include wheat, barley and sorghum. Farmers will have no choice; they will be forced to buy the whole kit.

In October 1986, Sudanese farmers were ready to introduce gum arabic to the market. As they prepared for harvest, a New York company announced the discovery of a new industrial process for the production of natural gum, of supposedly higher quality than farmed rubber. The third largest Sudanese export item lost its market overnight.

In November 1986, vanilla farmers from Madagascar were in search of prospective buyers. However, all 70,000 islanders growing this crop lost their main source of income when natural vanilla beans went into production in the laboratories of a Texas firm.

Right now it is scientifically and economically feasible for the industrialized world to find substitutes for commodities currently imported from third world countries, worth $14 billion.

According to Occidental Petroleum's chairman, food resources will mean during the 1990s what energy meant during the 1970s and 1980s. Chicago business consultants hold that farm products have a potential market 10 times larger than pharmaceuticals.

The largest world seed companies are ranked as follows by Enrique Estramil, phytology researcher at the Faculty of Agronomics in Uruguay: Royal Dutch Shell, Pioneer Hi Bred, Sandoz, Cargo, Dekalb Pfizer and Ciba Geigy. The latter also ranks second among the world's largest pesticide dealers; Shell comes in third, and Sandoz is nineteenth.

Since the end of the 1960s, Shell has purchased 11 seed companies, Pioneer 39, Sandoz 37, Cargo 39, Dekalb 34 and Ciba Geigy 26. The world's genetic resources, on which current and future global food security rests, are increasingly being monopolized by this type of firm.

Nicaragua and Ethiopia are two good examples of third world countries which have regulated transnational activities, preventing their control over this strategic resource.

Nicaragua allocates to genetic conservation over 50 per cent of its agricultural budget, thus spending more than Brazil in gathering genetic material samples. When the US decided on a food blockade of their country, Nicaraguans realized that food self-sufficiency was a goal to attain.

Traditionally a bean seeds importer, Nicaragua was able to export different varieties after two years' work. Nicaraguan scientists are now working on tissue cultures to develop new export crops while simultaneously gathering varieties of medicinal and fruit species which up to now had only grown in the wild in rainforests.

Nature taught Ethiopia a tough lesson on the benefits of the Green Revolution. One million people starved to death during the 1985 drought. Drought occurs frequently in Ethiopia but starvation to this extent is a newcomer. Hybrid maize did not survive in 1985 because it needed plentiful water. The new wheat strains failed completely. Those who had sown their own sorghum and millet seeds - low yield varieties but resistant to Ethiopian weather - were the only farmers who got some grain. Death reached as far as the Green Revolution had penetrated.

Samples of the native crops harvested during the drought were eagerly gathered and stored. Now, the world's poorest country has the largest gene bank in the third world. Twelve regeneration centres have been set up to supply farmers with their own native varieties. (Source: Development Forum, Vol. 16, No. 4, July August 1988)

Regulatory issues

Regulations for Latin America

Latin America is set to become the first region in the South to introduce safety regulations for handling genetically engineered organisms in the laboratory.

Guidelines on recombinant DNA technology, in areas such as health and agriculture, have been approved by a specialist American study group and were published in April. They are now being sent to regional Governments for incorporation into national legislation.

The guidelines focus on this type of technology because the study group felt that if regulations were introduced governing biotechnology in general, they would not be controlled by one law nor a single agency.

Experiments are graded by risk, each requiring specific regulations according to international laboratory classification. Group 1 organisms do not need any special safety procedures. They include widely used organisms and plants, such as those used to make cheese and beer. Fungi which may affect the environment are included in group 2. More dangerous organisms, including bacteria causing brucellosis in cattle, come under group 3. The last group is for viruses such as HIV.

The guidelines also set out general regulations for biotechnology work on new drugs, animal food additives, medical materials and foods.

The study group recommended that each country should set up a technical advisory committee on bio-safety to co-ordinate the regulation of recombinant DNA technology. These committees, it was suggested, would be supported by a regional permanent technical secretariat for biotechnology safety, responsible for compiling and disseminating information.

Work will start soon on controls for other bio-technologies. These will be for the large-scale use of recombinant DNA technology; the transportation and introduction of genetic materials into countries; and the release of modified organisms into the environment.

The need for regulations in Latin America was highlighted by a scandal in Argentina in 1988 over trials of a genetically engineered rabies vaccine by a US company. The Government later stopped experiments, saying it had not been informed of the recombinant vaccine's use, and is now contemplating further action. (Source: South, June 1988)

EEC regulations to cover organism experiments

Two draft directives which aim to establish EEC wide rules governing experiments with genetically modified organisms have been proposed by the Brussels Commission for eventual approval by the 12 member Governments.

With concern being expressed about the environmental impact of such experiments, EEC Commissioner, Stanley Clinton Davis, has said that only "a strong framework of legislation" for assessing the risks involved will assure the public that the authorities are fulfilling their responsibilities.

The first directive, dealing with laboratory use of these micro-organisms, says the legal framework should provide adequate protection and at the same time allow society to benefit from "this rapidly evolving technology". The directive differentiates between micro-organisms presenting a minimal hazard - such as those used in insulin or interferon manufacture (Group I) - to which relatively simple rules of good hygiene and safety practice are applied, and other micro-organisms - vaccines for example (Group II) - where containment, waste control and in some cases emergency response procedures are essential.

In all cases users would have to declare that they are carrying out operations involving genetically manipulated micro-organisms and submit a hazard assessment. Sixty-days' notice must be given to the authorities to allow inspection of the premises being used. A system of notification to the competent authorities must then be established to allow monitoring and control procedures to be carried out. Member Governments are obliged to inform the EEC Commission about the identity, proposed uses and potential risks of the micro-organisms involved in experiment, and to pass on details rapidly in the event of an accident.

The preamble to the second directive, which deals with the deliberate release into the environment, says it would be easy to imagine the public's response in case of harm to people. Therefore some form of protection is urgently needed. On the other hand, the Commission admits that the use of modified organisms would lead to improvements in health and the environment by the development of more precise agricultural inputs and more effective treatment of waste.

As international experience in this field is still limited, the EEC is not proposing any general guidelines, but a case by case notification and endorsement procedure which would be mandatory for industry and research institutions in line with OECD recommendations laid down in 1986. Firms or institutes would have to seek permission from the relevant national authorities, evaluating the foreseeable risks, giving details of the project and the geographical area involved. The authorities have 90 days in which to reply.

There is a special marketing procedure if tests lead to the development of a product. The Government of the member State concerned must notify, via the Brussels Commission, the authorities in the other EEC countries. They then have three months in which to raise objections with the Commission acting as arbitrator.

The draft EEC rules attempt to harmonise existing national procedures. In some countries like Italy, Spain and Portugal no guidelines or rules apply. In the UK the general requirements of the Health and Safety at Work Act and the Genetic Manipulation Regulations are applied to researchers and industries.

EEC environmental ministries may discuss the proposals in November, but it is unlikely that they will become law before the early 1990s.
(Source: Manufacturing Chemist, May 1988)

Biotechnology regulations are called too stringent

The biotechnology industry and some US federal regulatory officials are criticizing an Environmental Protection Agency proposal to require detailed risk analyses in the experimental use of micro-organisms.

The proposal to more strictly regulate the release of man-made and naturally occuring organisms comes at a time of increasing interest in using genetically engineered life forms to replace chemical pesticides, clean up toxic wastes and improve agricultural yields.

EPA says the new rules are intended to "ensure the protection of public health and safety, while minimizing the regulatory burden of R&D activities". Environmentalists have been pushing the agency to adopt tougher guidelines to regulate the growing biotechnology industry.

The proposed regulations would affect all government agencies that share jurisdiction with EPA for overseeing the biotechnology community, including the Agriculture Department, Food and Drug Administration, Commerce Department and National Institutes of Health.

Some regulatory officials and industry members say the rules are based on an incorrect perception that exaggerates the risks involved with small-scale uses of micro-organisms.

Consequently, they believe the guidelines would have a detrimental effect on research and development in the growing fields of environmental and agricultural biotechnology.

EPA says biotechnology is a controversial area, making it difficult to satisfy all interests involved. Two years ago, a federal inter-agency task force asked EPA to extend existing regulations

[illegible] the use of toxic chemicals in outdoor tests and commercial uses of living microorganisms, especially those produced by genetic engineering.

Under its proposals, companies and researchers would be required to obtain authorization for almost all experiments with living organisms. Exemptions from federal regulation for small scale field testing and some types of academic work currently available under the Toxic Substances Control Act would be virtually eliminated. (Source: Chemical Marketing Reporter, 25 July 1988)

New DNA guidelines for Latin America

The first guidelines for recombinant DNA genetic engineering work in Latin America have been adopted by a group of Pan American scientists, in an effort to encourage biotechnology work while providing adequate protection.

At a conference of the Interamerican Institute for Co-operation in Agriculture (IICA) held at San Jose, Costa Rica, the participants were spurred by a decision of Pan American agriculture ministers in Ottawa last year to encourage biotechnology as a means of revitalizing agriculture in the region. The adoption of the guidelines has also stemmed from fears of "dumping" of uncontrolled genetic engineering experimentation in joint ventures with scientists from more developed countries. Latin Americans are also concerned that agriculture development in the region may suffer if genetic engineering work is not tailored specifically.

The guidelines are based on similar rules already adopted in other countries. They allow regulatory committees to be set up, define the type of experiments requiring approval, classify hazards and put controls on experiments with plants, medicines and foods.

The guidelines will be distributed throughout Latin America with a grant from the Interamerican Development Bank. (Source: Nature, Vol. 331, 1. February 1988)

General

Bio weapons are forsworn by researchers

Over 500 working biomedical scientists have signed a pledge not to engage in research or teaching that would lead to the development of biological or chemical weapons. The list of signatories includes several Nobel laureates and scientists from leading research universities around the USA.

The "pledge against the military use of biological research" represents a growing concern within the biomedical community that the US Biological Defense Program is quietly moving towards a biological arms race, one that would directly threaten the nation's health and for which there would be no treatment.

The United States, the Soviet Union and 100 other countries are signatories to a treaty that bans the development, production and stockpiling of biological weapons, but since the Reagan Administration took office, the entire budget for the Biological Defense Program has increased over 400 per cent, and the treaty is being slowly eroded, the scientists contend. (Extracted from Chemical Marketing Reporter, 25 July 1988)

Biotransformation - the technique of the future

By the 1990s, economic and legislative pressure will have forced manufacturers into using biotransformation techniques - the use of biologic catalysts in chemical production - according to Dr. Peter Baker of the UK's Laboratory of the Government Chemist. The comments came at a one day meeting designed to promote technological transfer of biotransformation techniques from universities in the UK to industry.

"Fifty per cent of drug doses given today are next to useless because they contain non-active isomers which are ineffective and can even be harmful," he said. Many drugs and agrochemicals are racemic mixtures and often one isomer is harmful Dr. Baker explained. This had been the case with the drug thalidomide. Biological catalysts resulted in only a single enantiomer being produced.

Products manufactured using biologic catalysts would not only be safer but could also be given in smaller and more potent doses, and he called for a major research programme to investigate the effects of enzymes on a variety of industrial substrates.

Dr. Baker explained that biotransformation would have an important role to play in the manufacture of fine chemicals, the manufacture of bioanalytical devices and the development of detoxification processes. (Extracted from Manufacturing Chemist, February 1987)

Biotechnology products move nearer market

So far, nine biotechnology drugs and vaccines have been approved by the US Food and Drug Administration (FDA). Yet nine times as many biotechnology products, 81 in all, are in development in the US, including 67 products in clinical trials and 14 that, having completed such trials, are awaiting FDA's marketing approval, according to the Pharmaceutical Manufacturers Association (PMA), Washington, D.C.

PMA has no precise data on the dollar investment represented by those 81 products. However, it estimates that an average new drug costs about $125 million and requires 7-10 years to develop.

In all, 50 companies are involved in developing the 81 products. Companies are developing 24 of the products jointly, an indication that small biotechnology companies are turning to big drug producers for developing, testing and marketing expertise.

Forty of the 81 products are for cancer treatment, making cancer the most frequently targeted disease of biotechnology products. Moreover, companies are developing a variety of therapies against cancer, including colony stimulating factors, interferons, interleukins, monoclonal antibodies and tumour necrosis factors.

An abbreviated list of the 81 products follows. Missing are three categories: peptides, "other products" and vaccines. Peptides include such products as a trial peptide for congestive heart failure, while other products include factor VIII:C and epidermal growth factor. Vaccines are being tested against hepatitis B, malaria, Haemophilus influenzae, cancer and respiratory viruses.

Biotechnology products in development

Product name	Company	Indication	US development status
Anticoagulants/thrombolytic agents			
Prourokinase	Collaborative Research Sandoz	Heart attack	Phase II III*
Tissue plasminogen activator	Genetics Institute Wellcome Biotechnology	Acute myocardial infarction, deep vein thrombosis, acute stroke, pulmonary embolism	Phase II III, application for marketing submitted
Tissue plasminogen activator	Integrated Genetics	Heart attack, pulmonary embolism, stroke	Phase III
Tissue plasminogen activator	Biogen SmithKline Beckman	Acute myocardial infarction	Phase II
Colony stimulating factors			
Granulocyte colony stimulating factor	Amgen	Chemotherapy effects, AIDS, leukaemia, aplastic anaemia	Phase III
Granulocyte macrophage colony stimulating factor	Genetics Institute Sandoz	Chemotherapy effects, AIDS, leukaemia, aplastic anaemia	Phase II
Granulocyte macrophage colony stimulating factor	Hoechst Roussel Immunex	Chemotherapy effects, AIDS, leukaemia, aplastic anaemia, bone marrow transplants, Hodgkin's disease	Phase II III
Granulocyte macrophage colony stimulating factor	Schering Plough	Adjuvant to chemotherapy, adjunct to treatment of infectious diseases	Phase I*
Dismutases			
Superoxide dismutase	Bio-technology General Bristol-Myers	Reperfusion damage	Phase II
Superoxide dismutase	Chiron	Reperfusion damage	Phase II
Superoxide dismutase	Eastman Kodak Enzon	Reperfusion injury, kidney transplant, burns	Phase II
Erythropoietins			
Erythropoietin	Amgen	Anaemia	Application for marketing submitted
	Ortho	Chronic renal failure	In human clinicals
Erythropoietin	Integrated Genetics	Anaemia	Phase III
Human growth hormones			
Human growth hormone	Bio-technology General Du Pont	Human growth deficiency in children	Phase III
Human growth hormone	Genentech	Chronic renal failure Burns	Phase I, II Phase I
Interferons			
Interferon-alpha (topical)	Exovir	Recurrent genital herpes	Application for marketing submitted
		Oral herpes	Phase III
		Genital warts	Phase II
Interferon-alpha2a	Hoffmann-La Roche	AIDS related Kaposi's sarcoma, chronic myelogenous leukaemia, renal cell carcinoma	In late clinical trials
Interferon alpha	Interferon Sciences	Genital warts, genital herpes	Application for marketing submitted
Interferon alpha2b	Schering-Plough	Kaposi's sarcoma	Application for marketing submitted
		Malignant melanoma	Application for marketing submitted
		Multiple myeloma	Application for marketing submitted
		Bladder cancer	Application for marketing submitted
		Ovarian cancer	Phase III
		AIDS, Kaposi's sarcoma with azodothymidine	Phase I
Human leukocyte interferon alpha (injectable)	Viragen	Leukaemia, AIDS, renal cell carcinoma, bladder cell carcinoma	Application for marketing submitted

Product name	Company	Indication	US development status
Human leukocyte interferon alpha (topical ointment)	Viragen	Genital and oral herpes	Phase III
Interferon alpha	Wellcome Biotechnology	Hairy cell leukaemia, severe papillomavirus induced infections	Application for marketing submitted
Interferon beta	Cetus Triton Biosciences	Cancer, bacterial infection	Phase III
Interferon gamma	Amgen	Cancer, infectious disease	Phase II
Interferon gamma	Biogen	Rheumatoid arthritis, renal cell carcinoma	Phase II III
Interferon gamma	Genentech	Cancers (small cell lung, melanoma, colorectal)	Phase III
Interferon gamma	Interferon Sciences	[illegible]	Phase I
Interferon omega/tau	Amgen	Cancer, infectious disease	Phase II II.
Interleukins			
Interleukin 2	Cetus Johnson & Johnson	Cancer immunotherapy	Phase II
Interleukin 2	Hoffmann La Roche Chiron	Cancer immunotherapy	Phase I
Interleukin 2	Cetus	Cancer	Phase III
Interleukin 2	Immunex Corporation Research	Cancer immunotherapy	Phase I
Recombinant human interleukin 2	Hoffmann La Roche	Lung cancer, malignant melanoma, renal cell carcinoma, lymphoma	In clinical trials
	Immunex	Ovarian carcinoma	In early clinical trials
Recombinant human interleukin 2 + LAK cell therapy	Hoffmann La Roche	Lung cancer, malignant melanoma, renal cell carcinoma, lymphoma, colon cancer	In clinical trials
Recombinant human interleukin 2 Referon A combination	Hoffmann La Roche	Malignant melanoma, renal cell carcinoma, B cell lymphoma	In early clinical trials
Monoclonal Antibodies (MAb)			
MAb	Centocor	Septic shock	Phase II III
MAb	Centocor	Colorectal cancer, pancreatic cancer	Phase II
MAb	Centocor	Ovarian cancer	Phase I
Antiplatelet MAb	Centocor	Antiplatelet prevention of blood clots	Phase I
MAb	Cetus	Breast cancer	Phase I
MAb	Damon	Lung cancer	Phase I
MAb	Eli Lilly	Cancer	In clinical trials
MAb In	Bristol Myers Oncogen	Lung cancer	Phase I
MAb	Immunex Becton Dickinson	Prevention of graft host disease in bone marrow transplants	Phase I
MAb	Immunomedics Johnson & Johnson	Colorectal cancer	Phase I
MAb	Lederle	Cancer	In clinical trials
MAb	Ortho	Heart and liver transplant rejection	Application for marketing submitted
MAb	Genetics Institute NeoRx	Colorectal cancer	Phase I
MAb	NeoRx	Malignant melanoma	Phase I
MAb	NeoRx	Ovarian cancer	Phase I
MAb	Xoma	Melanoma	Phase III
MAb	Xoma	Colorectal cancer	Phase II
MAb	Xoma	Bone marrow rejection, transplant graft vs. host disease	Phase III
MAb	Pfizer Xoma	Septic shock	Phase III
Tumour necrosis factors			
Tumour necrosis factor	Biogen	Cancer	Phase I
Tumour necrosis factor	Cetus	Cancer	Phase II
Tumour necrosis factor	Genentech	Cancer	Phase II

* As classified by the Food and Drug Administration (FDA), Phase I tests include in vitro studies, animal studies and only very small human (clinical) studies to establish a drug's usefulness. Phase II tests involve larger clinical samplings and are usually controlled trials of a drug and a placebo, for example. Phase III tests involve the largest clinical samplings and include multiple groups; after completion of a Phase III clinical trial, a company may file a new drug application with FDA. Source: Pharmaceutical Manufacturers Association (Washington, D.C.). (Source: Chemical Week, 20 July 1988)

HUGO: Human genome organization founded

Loosely modelled on the European Molecular Biology Organization (EMBO), the Human Genome Organization (dubbed HUGO) has now been officially launched to promote collaboration in the world wide effort to map and sequence the human genome. HUGO, which will not have its own laboratory, will have three offices in North America, Europe and Asia. Victor McKusick of Johns Hopkins University is the acting president and John Tooze of EMBO acting secretary. (Source: Biotechnology Bulletin, Vol. 7, No. 5, July 1989)

OTA weighs in on gene-mapping project

The US Office of Technology Assessment (OTA) has suggested to a House Energy and Commerce subcommittee that co-ordination among federal agencies is a less problematic choice for guiding the multi-billion-dollar, human-gene-mapping project than assigning a "lead agency" such as the Department of Energy (DOE) or National Institutes of Health (NIH). OTA's 219 page report "Mapping Our Genes. The Genome Projects: How Big, How Fast?" estimates that the cost of gene-mapping projects will rise from $47 million in the first year to $226 million by the fifth year, then cost $...0 million year "until at least the year 2000". That parallels estimates of the National Research Council, which has recommended spending $200 million year for 15 years to decode all of the estimated 100,000 genes in human chromosomes. The Research Council had urged Congress to assign one of the agencies now supporting gene mapping work the lead role in co-ordinating federal efforts and suggested DOE, NIH or the National Science Foundation. However, OTA says that "it is not clear that this would improve efficiency, communication or co-ordination" and warns that it could actually "diminish rather than enhance accountability to Congress". A major push for a US gene mapping project is concern in Congress that non-US researchers would decipher the human genetic code first and reap the commercial benefits of finding the links between particular genes and diseases. (Source: Chemical Week, 4 May 1988)

Experiment on humans would use altered cells

Researchers at the US National Institutes of Health are seeking approval for the first time to conduct a medical experiment that would put genetically engineered cells into human beings.

"The proposed procedure, while not a therapy, would initially be used to help follow the progress of [an experimental] cancer therapy" developed by Steven A. Rosenberg and co-workers at the National Cancer Institute. Rosenberg and W. French Anderson of the National Heart, Lung and Blood Institute have proposed tagging a newly discovered type of cancer fighting cell with a marker gene and then injecting the altered cells into patients.

The insertion of the marker gene is not expected to have a therapeutic effect. But it could open the door to real gene therapy experiments aimed at curing diseases such as muscular dystrophy, cystic fibrosis and sickle cell anaemia.

The proposed experiment will have to be approved by at least four NIH bodies before seeking the final green light from NIH director James B. Wyngaarden. NCI says the process could take a year or longer.

The experiment is thought to [illegible] cells called tumour infiltrating lymphocytes, which can be isolated from cancerous tissue that has been excised from the body. When TILs are stimulated in vitro with interleukin-2 (IL-2), a natural immune system activator, and injected back into the body, they appear to exert a more potent antitumour effect in some patients with skin or kidney cancer. But without being able to track the stimulated TILs in the body, the NIH scientists cannot be sure the cells are arriving at the tumour. Hence their interest in using a marker gene. (Radioactive tracers are not practical in such an experiment.)

If the trial experiment is successful, the NIH team might then try to engineer TILs to produce their own IL-2. (Extracted with permission from Chemical and Engineering News, 20 June 1988. Copyright 1988, American Chemical Society)

Biotechnology boosts separations

The dollar value of separation systems used in commercial biotechnology will grow 16 per cent a year from $351 million a year now to $1.0 billion a year in 1997, according to a new study.

Without cost-effective separations, biotechnology might not be able to realize the potential it now seems to have, Business Communications Company, the Norwalk, Conn., market analysts note in a summary of the study.

The simpler and lower molecular weight separations entities of the past are being replaced by more complicated molecules of higher and higher molecular weight that are mostly protein or polypeptide in nature.

Centrifuges, currently a $110 million a year business, will increase 7 per cent a year through the year 1997, the study asserts. But, while centrifuges now represent 31 per cent of the systems for biotechnology, by 1997, they will represent only 14.7 per cent of total sales of separations systems into biotechnology. The most rapid growth will come from "affinity" technology, which will grow in sales from about $12 million to $122 million in 10 years.

The commercial success of biotechnology products derived from monoclonal antibodies (MABs) and recombinant DNA (rDNA) technology, such as insulin, human growth hormone, interferon, and certain vaccines can be directly attributed to the development of new separation technology that includes affinity sorption separations. Affinity technology represents only about 3 per cent of the total value for separations systems for biotechnology now, but in 1997 will be some 6 per cent of the total.

Liquid chromatography in biotechnology is usually high performance, high pressure liquid chromatography or HPLC. HPLC is definitely focusing on biological biotechnology separations. HPLC was once limited to use by analytical chemists, but the technology is expanding to larger scale systems because it is a powerful tool for handling and separating complex solutions.

Systems for liquid chromatography for biotechnology represent sales of $90 million in 1987, but this will increase at a rate of 19 per cent a year to reach $545 million in 1997. Liquid chromatography sales in biotechnology now

% of about 25 per cent of the market for separations systems for biotechnology, but this will increase to some 30 per cent of total sales of separations systems for biotechnology in 10 years reflecting the improvements being realized for larger scale, more efficient systems.

It can be argued that electrophoresis is a subset of chromatography, but sufficient differences are evident that it can be treated as a separate technology. Electrophoresis is most commonly applied to the analysis of biomolecules, but in some cases it is the only production method available.

Electrophoresis is by nature high resolution, especially for proteins and DNA separations. This is a current market of $35 million in biotechnology and is projected to increase to $3½ million in 10 years. This represents an average annual increase of 10 per cent a year over the near to mid term. (Source: Chemical Marketing Reporter, 4 July 1988)

Biotechnology gets high marks from opinion leaders

In the next decade, biotechnology will have a greater impact on society than will any other scientific development. So reports the Wirthlin Group (McLean, Va.) in a survey conducted for Monsanto of 100 people who take or influence policy, including congressmen and their staffs, executive branch officials and members of the media. When asked which technology would have the greatest economic impact during the next 10 years, 28 per cent of respondents named biotechnology; 24 per cent cited superconductivity as having the greatest impact; 11 per cent thought computer technology would. However, among nearly half of the respondents who said they were very interested in biotechnology, only 10 per cent believed that their understanding of it was very good. (Source: Chemical Week, 4 May 1988)

Good future ahead for biotechnology?

New problems and opportunities are rising for companies in the emerging biotechnology industry. After more than a decade of rapid evolution, the industry is now making the critical transition from an environment characterized by "embryonic R&D boutiques" to one heavily populated by "full fledged, well established businesses" led by seasoned executives.

Business strategies vital to the success of the more than 300 US companies participating in this industry transition were discussed among industry executives at a meeting sponsored by Consulting Resources, Lexington, Mass. More companies in this industry will be undergoing strategic, organizational and structural changes as they mature from the embryonic to the growth phase of industry development. Strategic issues critical to biotechnology companies at this stage of industry evolution are thought to be:

- Making the transition from being technology-driven to being market driven;
- Successfully shifting from "diffusion" to "differentiation";
- Moving down the learning curve to reduce costs;

Revenues up an average of 48% for 18 biotechnology firms

	FIRST QUARTER 1988					
	Revenues[a]	Earnings[b]	Change from 1987		Profit margin[c]	
	($ millions)		Revenues	Earnings	1988	1987
Amgen	14.573	0.488	37%	110%	3.3%	2.2%
Applied Bioscience	10.431	0.883	50	44	8.5	8.8
Applied Biosystems	37.323	5.135	74	149	13.8	9.6
Biogen	6.747	-0.935	60	def	def	def
Calgene	9.163	0.044	25	86	0.5	4.1
Centocor	15.721	1.993	31	29	12.7	12.9
Cetus	19.610	6.974	22	def	def	def
Collagen	1.512	-0.664	12	def	def	11.8
Cytogen	1.792	3.125	29	def	def	def
DNA Plant Technology	1.540	0.355	15	def	def	def
Genentech	74.424	15.211	93	235	20.4	11.8
Genetics Institute	2.630	-5.993	50	def	def	def
Immunex	5.155	0.596	44	def	11.6	def
Integrated Genetics	3.436	0.923	1	def	def	4.0
Liposome	1.518	0.550	69	def	def	def
Molecular Genetics	1.421	0.384	36	def	def	def
Ribi ImmunoChem	0.339	0.468	21	def	def	def
Synergen	1.749	1.180	22	def	def	3.6
TOTAL	**197.511**	**2.311**	**48%**	**def**	**1.2%**	**def**

a Includes sales, contracts research, royalty, and interest revenues. b Excludes extraordinary and nonrecurring items where possible. c After tax income as a percentage of sales. def = Deficit.

- Forming strategic alliances with business partners capable of offering complementary strengths;

- Shifting from industry advocacy to self advocacy.

(Source: Biotechnology Newswatch, May 1988)

Revenues still rising for US biotechnology companies

Research contracts continued to help US biotechnology firms increase their revenues in the first quarter of 1988. And in some cases, most notably Genentech, product sales helped swell revenues and profitability well above the year earlier results.

Combined revenue of the 14 companies sampled in the survey increased 49 per cent to a total of $198 million in the first quarter of 1988 compared with last year's first quarter. As a composite, the group registered a profit; combined earnings amounted to $2.3 million compared with a loss of $11,000 in the first quarter of 1987.

Many of the firms sampled are still actively in pursuit of the products and patents that they hope will ultimately make them profitable. Food and Drug Administration and Environmental Protection Agency approvals have allowed some to approach their goals.

In some cases, however, the most profitable companies have become victims of their own success.

A number of biotechnology companies have found it difficult to secure new research contracts and financing since the October stock market crash. These firms continued to show losses because they were either funding more of their own research or were financing clinical testing of proprietary new drugs. (Extracted with permission from Chemical and Engineering News, 6 June 1988. Copyright 1988, American Chemical Society)

Campaigners urge levy on exports of germplasm

Developing nations will be able to make money from their plant genetic resources, if a campaign on their behalf is successful. The Seeds Action Network, a coalition of non-governmental organizations, met in Copenhagen to discuss the campaign. It would impose a tax on improved commercial crops and plants developed from genetic material freely given by third world countries.

The idea is that the revenue, probably the United Nations Food and Agriculture Organization (FAO), would pay for improvements in plant breeding, seed conservation and production in developing countries.

Commercial seed companies from the developed world have had free access to genetic material from plants of the third world. They have been able to protect the new varieties through plant breeders' rights and to sell them on the world market. Yet the third world countries are unable to do the same. The irony is that the poor world pays heavily for such improved varieties, despite the fact that it is often the source of fresh material.

Controversy over the "fairness" of such a system has continued for more than two decades. Companies claim the right to recoup the money they spend for years on research to produce the improved varieties. Third world countries argue that their germplasm is not just another crop.

In 1983, the FAO created the International Board for Plant Genetic Resources (IBPGR). Within the space of a year, it set up the International Network for Genetic Research (INGER) and began plans to establish plant breeding and seed production centres in developing countries. At present, the IBPGR is a think-tank. The Seeds Action Network says that the IBPGR should be more effective if it got out of the clutches of the agricultural establishment and the companies that sell seeds, and that it should put into the field. The meeting at Copenhagen resolved to campaign at world level. (Chemical and Engineering News, 27 June 1988)

New directory of cell lines

A small group of researchers in the Netherlands, Belgium and America has set out to create a skeleton structure. According to its statement of purpose, the new ADR is to foster international multidisciplinary communication and to provide with existing publications and collections of scientific data. Its ultimate goal is to facilitate the sciences that underlie the biological sciences.

Towards this end, the new group's aims include:

- Arranging scientific conferences;

- Publishing;

- Suggesting research priorities conducive to the advancement of biotechnology and the general welfare;

- Providing forums on what to do when topics and meet with disagreement, rejection and policy makers;

- Promoting biotechnological activities without establishing biotechnology companies;

- Providing reliable information to the public education;

- Promoting legislation, both national and international, to operate with;

- Establishing professional standards to which affiliated members.

ADR membership is open to persons "who professionally participate in biotechnological research".

The society does not charge a membership fee this year. Instead, a temporary executive committee will handle the group's work, to continue until it is replaced by full officers elected by the membership at its first meeting.

For information on membership of the ADR, contact the Secretary for Biotechnology, Wim de Jonge, c/o McCormick, Biotechnology Group, 55 Broadway, 31st Floor, New York, NY 10006, USA. (Bio/Technology, Vol. 6, June 1988)

Antibody lines and hybridomas from Sigma

A new catalogue of cell lines and hybridomas was published in March 1988. The 438 page, 4th edition contains descriptions of over 2,800 cell lines and hybridomas derived from about 75 different species.

The cell line and hybridoma descriptions have been separated into two sections for the first time. The current medium for propagation of each line is given with the line's description. An expanded list of cell culture media formulations and a list of commercial suppliers are included. The general index contains the ATCC number, name of the line and page number for easier use.

Separate indexes by species, tissue of origin and monoclonal antibody can be used to locate a line. [illegible]

Four new hybridomas producing monoclonal antibodies are available from the American Type Culture Collection Cell Bank:

(1) ATCC [illegible] human-mouse hybrid cell line producing monoclonal antibody to human T cell leukaemia virus type I (HTLV I). US Patent No. 4,[illegible]

(2) ATCC HB9 [illegible] Mouse-Mouse hybridoma producing monoclonal antibody to gp70 protein of Feline Leukaemia Virus (FeLV). US Patent No. 4,[illegible]

(3) ATCC HB [illegible] Mouse-Mouse hybridoma producing monoclonal antibody to [illegible] human B cells and derived cell lines. US Patent No. 4,[illegible]

(4) ATCC TRL [illegible] Mouse-Mouse hybridoma producing monoclonal antibody to the B chain of the plant toxin, ricin.

[illegible] popular hybridomas from the American Type Culture Collection, after three years of unavailability, are again in stock:

ATCC HB [illegible] Mouse-Mouse hybridomas [illegible] producing monoclonal antibody against human HLA specificities.

For information contact: ATCC, [illegible] Parklawn Drive, Rockville MD 20852, USA. Telex: 908768.

New findings at AIDS meeting in Stockholm

Almost [illegible] cases of AIDS have now been reported to the World Health Organization [illegible] said [illegible] Mann, Director of WHO's Global Programme on AIDS [illegible] the next five years.

[illegible] are likely to be [illegible] Centers for Disease Control (CDC), although [illegible] these predictions are far [illegible] AIDS has been [illegible].

For Europe, Jean Baptiste Brunet, of the Claude Bernard Hospital in Paris, predicted a cumulative total of [illegible],400 AIDS cases by the end of [illegible] with a [illegible] increase in the proportion of [illegible] associated with intravenous drug use, particularly in southern Europe.

No predictions are possible for Africa for a variety of reasons, one of which is that the availability of adequate figures on the proportion of people already infected with the human immunodeficiency virus (HIV) is patchy. At least in Kinshasa, capital of Zaire, it is certain that between about [illegible] and [illegible] per cent of blood donors, pregnant women and factory or bank workers are infected. The brighter side of these figures is that they have remained constant for up to four years, said Kosenge N'Galy from Zaire's Department of Public Health.

Robert Gallo of the National Cancer Institute in Bethesda said that laboratory research was now in a period of steady incremental progress rather than the dramatic advances of the first few years.

Nevertheless, both Gallo and Luc Montagnier from the Pasteur Institute were able to provide delegates with a few new facts to whet their appetites. Montagnier referred to emerging evidence that [illegible] monkeys infected with HIV 2, the predominant HIV in west Africa, develop AIDS-like symptoms. If this is confirmed, AIDS research may at last have an animal model. He also predicted that serum antibodies to the product of the HIV *nef* gene would become an earlier indication of HIV infection than other antibodies.

Gallo drew attention to accumulating evidence that a new herpes virus he recently discovered in his laboratory is a co-factor in the progression from HIV infection to AIDS, and to laboratory data that suggest that Kaposi's sarcoma in AIDS patients is not the result of a second infectious agent. Instead it seems to be caused by a novel growth factor released by HIV infected cells. (Source: Nature [illegible] 333, 16 June 1988)

The global benefits of spending big

This year, more than 40 per cent of the World Health Organization's budget for the prevention and control of disease will go to AIDS. The programme was discussed at the 41st World Health Assembly in Geneva.

WHO plans to spend approximately $US [illegible] million this year on the prevention and control of diseases. Of that, $[illegible] million (40.4 per cent) is going on AIDS. Expenditure on other diseases will be as follows:

- $[illegible] million ([illegible] per cent) on acute respiratory infections (estimated annual deaths 10 million, 4 million of them in children).
- $[illegible] million ([illegible] per cent) on diarrhoeal diseases (4 million deaths).
- $[illegible] million ([illegible] per cent) on malaria (about 1 million deaths).
- $[illegible] million ([illegible] per cent) on tuberculosis (1 million deaths).
- $[illegible] million (4 per cent) on immunisation against the six diseases — diphtheria, neonatal tetanus, whooping cough, measles, tuberculosis ([illegible] million deaths each year) and poliomyelitis ([illegible] cases a year).
- $[illegible] million (1.4 per cent) on research on tropical diseases (1.5 to 2 million deaths a year).

WHO's relatively low budgetary allocations to the major infectious diseases do not reflect the

degree of concern about these diseases but rather the low relative cost of treating patients. Whereas the estimated cost of the lifetime care of an AIDS patient is between $20,000 and $100,000 in industrialized countries, and $100 and $1,500 in Africa, 30 cents' worth of oral rehydration salts can clear up most episodes of diarrhoea. Most cases of bacterial pneumonia, which causes around 80 per cent of acute respiratory infections in children in developing countries, respond to a few days' treatment with the drug cotrimoxazole, which again costs around 30 cents. And it costs just $10 to vaccinate a child against the six major infectious diseases that kill children.

Financial cost is not the only issue. In some parts of the world, AIDS exerts what Jonathan Mann, head of the WHO's Global Programme on AIDS, calls a "displacement effect" on already limited health resources. "In many African cities," he says, "you may have hospitals with, say, 500 beds and 600 patients to be treated. Clearly, any AIDS patients being admitted will displace space and resources, including pharmaceuticals and staff time, that might be used for curable diseases."

In urban areas of Central and East Africa where between 5 and 20 per cent of the adult population are thought to be infected with the human immunodeficiency virus, up to half of hospital beds are occupied by AIDS patients, the World Bank reports. Some hospitals in the developing world, according to World Bank News (14 January), are now refusing to admit people with AIDS because of a lack of medicines, space and staff.

To ease the current and anticipated burden of AIDS on already overextended health systems, officials of the Global Programme on AIDS are urging African public health authorities to organize community and home-based care of infected people.

Those who believe that AIDS is already attracting too much funding will find no comfort in forecasts of its future demands. By 1991, WHO's Programme on AIDS, which has a current budget of around $100 million, could require as much as $650 million, according to the United Nations Development Programme. This figure does not include the costs of diagnosing, treating and - if a vaccine should become available - preventing the disease by immunization. In the US alone the lifetime cost of treating the 15,000 people diagnosed with AIDS in 1986, estimated at $1.2 billion, could soar to $5.9 billion for the 74,000 new cases predicted by 1991. This would bring the cumulative cost of the 270,000 cases diagnosed between 1981 and 1991 to around $22 billion.

To officials of WHO, the amount of money and energy going into the fight against AIDS is justified for several reasons.

- AIDS poses a growing threat to the world's population. Between 5 and 10 million people are believed to be infected with HIV. If 10 to 30 per cent of them develop AIDS over the next five years, there will be between 1 and 3 million cases.

- AIDS could ruin current efforts to save children in developing countries. In some areas, particularly in African cities, up to 10 per cent of pregnant women are infected with HIV; perhaps half of these women will infect their offspring.

- The disease is selective. The 1987 World Health Statistics Annual notes that HIV selects "young and middle aged adults, including business and government cadres and members of other social, economic and political elites, leading to potential for economic and political destabilization in areas of the developing world most severely affected by HIV".

- Although there is no cure for AIDS, the disease is probably more easily prevented than the major killer diseases. It is possible to halt the spread of HIV "simply," through changes in human behaviour, coupled with screening of blood for transfusion and avoidance of pregnancy in women infected with HIV.

- The effort against AIDS has many spin-offs. A well-run blood transfusion service, for example, set up to screen for HIV, makes it easy to screen for hepatitis B, syphilis and other diseases.

- AIDS is bringing fresh impetus to the health sector.

If these arguments are valid, the effort being spent on AIDS is good value. In any case, there is no evidence that AIDS is diverting funds that would have gone to the control of other diseases. Ralph Henderson, director of WHO's Expanded Programme on Immunization, says: "The total cost of protecting all the children of the developing world from the six child killing or crippling diseases would amount annually to about $600 million."

What is special about AIDS, in Mann's view, is that it is an enemy bringing the world not only danger, but opportunity - for seeing health not just as a medical problem, but as a way of linking conflicting principles and interests. "This is the first really global problem the world has had to face," he says. "No other disease has created such a global awareness. Not even the threat of nuclear war brought the developing and developed world so closely together against a common enemy." (Source: New Scientist, 12 May 1988)

The World Data Centre at the Life Sciences Research Information Section, RIKEN, Saitama, Japan

The World Data Centre on Micro-organisms (WDC) was relocated from University of Queensland, Australia to RIKAGAKU KENKYUUSHO (RIKEN), Japan in 1986. The English name of RIKEN is the Institute of Physical and Chemical Research. RIKEN holds the Japan Collection of Micro organisms (JCM) and the WDC is housed in the same building as JCM. This is a report on the activities of the WDC after the relocation.

Information collection

The WDC has sent 400 survey forms to culture collections in preparation for the fourth edition of the World Directory and also some other culture collections. About 60 per cent of the culture collections returned the forms to the WDC by the end of March 1988. The WDC will update the data file in the computer based on the forms.

The number of collections in the third edition of the Directory holdings is shown in table 1.

Table 1. The number of culture collections by their holdings

Bacteria	244	Viruses	
Yeast	116	animal	35
Fungi	141	bacteria	4
Algae	43	insect	1
Lichens	1	plant	7
Protozoa	28	Others	11
Cell lines	21		

The distribution of culture collections in the world is shown in table 2.

Table 2. Number of culture collections by countries

Argentina	5	Jordan	1
Australia	49	Kenya	1
Austria	1	Malaysia	3
belgium	3	Mexico	8
Brazil	10	Netherlands	9
Bulgaria	3	New Zealand	6
Canada	23	Nigeria	2
Chile	1	Norway	2
China	6	Papua New Guinea	1
Colombia	1	Philippines	6
Czechoslovakia	10	Poland	6
Denmark	2	Romania	1
Finland	2	Senegal	2
France	11	Singapore	2
German Democratic Republic	1	South Africa	2
		Spain	2
Germany, Fed. Rep. of	14	Sri Lanka	1
		Sweden	2
Greece	1	Switzerland	1
Guatemala	1	Thailand	11
Hong Kong	1	Turkey	1
Hungary	6	USA	28
India	12	USSR	4
Indonesia	4	Uganda	1
Iran	1	United Kingdom	10
Ireland	2	Venezuela	1
Israel	2	Yugoslavia	1
Italy	8	Zimbabwe	2
Japan	12		

(Source: MIRCEN News, Jan., 1988)

UNESCO Regional Workshop on bioinformatics

The UNESCO Regional Workshop on "Bioinformatics - Data Base, System Analysis and Process Control in Biotechnology" was held from 10-14 November 1987, at Osaka University as an activity of the UNESCO Regional Network for Microbiology for South East Asia.

The abundant amount of information and data are continuously spouting out in the field of biology. They should be assembled, sorted and put in the forms available on your demand for efficient use. Several organizations offer this kind of service, e.g., the protein data bank of Brookhaven, the data bank of crystalline analysis of Cambridge. Analyses on the correlation between the structure and the function of natural macromolecular compounds and microbial products will provide assessment of their physiological activities. An advanced technology for a fully automated on line control system will be available in the near future by development of sensing techniques and accumulation of software for optimal control based on mathematical or sometimes linguistic models of microbial processes. Utilization of computers is indispensable for the construction of models and development of the software for adaptive control, and data processing for on-line control.

The workshop aimed at an exchange of information and experience for development of bioinformatics, and an interdisciplinary research area between biology and information science. The workshop was conducted to provide a forum to discuss effective utilization of the new techniques and future development including co-operative research of bioinformatics. (Source: MIRCEN News, July 1988)

Conservation of the microbial gene pool

Developments in biotechnology have highlighted the need for a comprehensive range of biological material for industrial and research applications. Gene banks are needed for strain selection, hybridization, genetic manipulation or direct production purposes and the culture collections of the world thus represent an essential microbial resource.

Some 400 centres maintaining micro organisms and cultured cells are listed in the World Directory for Culture Collections. The number of cultures held in these collections exceeds half a million. Maintained with the cultures is a wealth of scientific information on incalculable value to biotechnologists. This data is being made more accessible through networking systems. Associated with the resource centres is a wide range of expert knowledge available for the support of the international microbiological community. Specialist skills in taxonomy, identification, preservation and patenting are widely available and represent a highly specialized human resource.

Each collection has been built up by experts, usually over prolonged periods, and represents an enormous investment in terms of labour and resources. It has been calculated that the total investment in the establishment of a microbial resource centre containing 2,000 unique strains and having been established over a period of 25 years is in the order of $4 million. This figure includes a calculation of the value of present stocks and an assessment of past effort in terms of manpower, equipment and overheads, but does not include any value for the isolation and characterization of strains before deposit, since this is incalculable. The cultures in such collections are irreplaceable. Similar strains may be recovered from the environment, but because of the huge genetic diversity in nature and the stresses imposed by isolation and preservation methods, recovery of identical phenotypic characters can never be guaranteed. Because of this, existing collections of micro organisms are unique.

It is in the interests of all organizations concerned with pure and applied microbiology to work to protect existing resources for the future benefit of mankind.

Further information may be obtained from the Secretariat of the World Federation for Culture Collections: Biotechnology Centre, Cambridge University, 307 Huntingdon Road, Cambridge CB3 0JX, United Kingdom. (Source: MIRCEN News, July 1988)

GEPLACEA

GEPLACEA, the Group of Latin American and Caribbean Sugar Exporting Countries, is a regional organization made up of 22 Latin American and Caribbean cane sugar producing and exporting countries. It acts as a body for consultation, co-ordination and exchange of information for member countries on issues related to production and maketing of sugar and its derivaties. It was established in Cozumel, Mexico in November 1974 and is comprised of the following countries: Argentina, Barbados, Bolivia, Brazil, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Peru, Trinidad and Tobago, Uruguay, Venezuela.

GEPLACEA is the most important group of cane sugar producing countries in the world and represents approximately 45 per cent of the world total of cane sugar. It accounts for approximately 26 per cent of the world sugar output, representing about 45 per cent of the world sugar exports.

Objectives

To provide member countries with alternatives and the elements for adopting common positions.

Foster solidarity [illegible] when the countries face special situations.

Co-ordinate policies designed to achieve fair, remunerative price levels.

Take action to strengthen co-operation and exchange of know how among the bodies and agencies in charge of implementing foreign marketing policies in member countries.

Promote the exchange of scientific and technological knowledge in the spheres of agriculture, use of [illegible] by products and the sugar production process.

Further information can be obtained from: Secretariado Boletin GEPLACEA, Programa de Difusión, AV. Ejercito Nacional 373 - [illegible] piso, 11520 Mexico, D.F. Mexico. Tel.: 250-7566, Telex: 017 71642 GEPME. (Source: MIRCEN News, July 1988)

ICDA Seeds Campaign

The ICDA Seeds Campaign started eight years ago with the main campaigning focus on preventing national monopolistic control on plant genetic resources and pressing for the adoption of an international convention to regulate the exchange and conservation of genetic resources by the United Nations. Emphasis is also placed on the development educational aspect of the seeds issue in order to raise awareness and stimulate public participation in the Seeds Campaign.

ICDA considers the seeds campaign as a fundamental part of the struggle for sustainable agriculture in both developed and developing countries in so far as erosion of genetic diversity and increasing monopolistic control over genetic resources by a few multinational corporations threaten the very basis of sustainable agriculture.

The work of ICDA's seeds campaign includes or has included:

Publication of information [illegible] activities in ICDA News, the [illegible] newsletter of ICDA.

Publication of SEEDLING, the [illegible] newsletter of the Seeds Campaign. SEEDLING reports on new developments in the seeds issue, news from the different national [illegible] groups, lobby preparations and results, meetings, etc.

Publication of a study on the European seed industry, [illegible] and [illegible] involvement in the seeds sector in Europe and review of the current [illegible] research activities [illegible].

Preparation of a slide show [illegible] by national seed groups. This [illegible] different European languages.

Support for the work of national seed groups by providing information and research.

Organisation of regular Seeds Campaign meetings where organisations involved in Seeds Campaign come together, report on their work and discuss [illegible].

[illegible] ICDA Seeds Campaign, [illegible] Telephone (31) [illegible] (Source: MIRCEN News, July [illegible])

The WFCC's Endangered Collections Committee

A symposium [illegible] was held to identify the WFCC [illegible] Endangered [illegible] Committee and held in conjunction with the [illegible] Taxonomy and Rapid Identification [illegible] Prague, [illegible]. The meeting was chaired by [illegible] attended by [illegible].

The meeting [illegible] papers, followed by general discussion. The papers were as follows:

[illegible]:	[illegible]
[illegible]:	[illegible]
[illegible]:	[illegible] endangered collections.
K. Yamasato:	How a culture collection becomes endangered.
R.E. Kirsop:	Case histories of endangered service collections.
M.C. Srinivasan:	Reflections on endangered culture collections and their rescue, with special reference to developing countries.
Z. Wang:	Present status and the development of culture collections in China.
M. Goodfellow:	Problems of preserving private culture collections.

It was clear from the presentations and from the discussions that a similar analysis of the factors leading to collections becoming endangered was made by all the speakers, coming from widely different regions of the world.

The topic is of sufficient interest and international importance to warrant further discussion. Consequently, the papers presented will be published as Part I of a two-part publication, the second part to take place on the occasion of the 6th International Congress of Culture Collections in Maryland, USA, in October-November 1988.

Part I will be published shortly and, as well as the presented papers, will include a summary of the proceedings by Professor Jolwell, proposed guidelines for the rescue of endangered collections and the questionnaire drawn up by the Committee on Endangered Collections. (Source: MIRCEN News, July 1988).

Conservation of microbial genetic diversity

Microorganisms isolated from natural ecosystems serve as one of the best examples of genetic diversity found in nature. At MACS Research Institute, a data bank has been established which contains cultures used in biohydrometallurgy and data on related commercial processes such as microbial leaching or beneficiation for the use of mining organizations in developing nations. Bacterial strains belonging to Thiobacillus, Arthrobacter, Bacillus and related genera from natural niches such as acidic mine waters, waste areas, soils, sediments and deposits in the mining areas have been isolated and conserved with this goal in mind. The genetic diversity witnessed among these genera ranged from high metal tolerance, high acidic pH tolerance to fluctuations in temperature during growth. To keep the cultures growing in such environmental conditions, methods were devised to preserve the gene pool. A novel method of storing cultures in native sites from which they were isolated was found to be better than conventional methods of preservation. The storage with activity check was tested over a period of three years and it stood the test of time. Further details may be obtained from: A.D. Agate, Microbiology Department, MACS Research Institute, Pune 4, India. (Source: MIRCEN News, July 1988)

Third Cuban Seminar on Interferon and Second Cuban Seminar on Biotechnology

The organizing committees are pleased to announce the Third Cuban Seminar on Interferon and the Second Cuban Seminar on Biotechnology which will be simultaneously held in April 1989, at the International Conference Centre in Havana, Cuba.

The 1984 and 1986 Seminars were characterized by the wide participation of delegates from different countries (1984: 700 delegates from 34 countries and 1986, 912 delegates from 44 countries) and the active intervention of outstanding researchers in almost all the topics presented.

The organizing committees of these events continue making efforts to provide all the conditions for the exchange of ideas and experiences on these topics of great interest.

The main topics are:

- Production and clinical trials with interferon and other biomodulator molecules;
- Molecular biology and genetic engineering of interferon, other cytokines and biomodulator molecules. The biotechnology approach for their production;
- Production and purification of monoclonal antibodies. New development and applications;
- Molecular biology and biotechnological approaches for the development of new types of vaccines and diagnostic tools;
- Biotechnology applied to agriculture and industry. Production of biomass and bioenergy. Molecular biology and genetic engineering of plant cells;
- New developments of the recombinant DNA technology;
- Development of auxiliary techniques and reagents for molecular biology and genetic engineering;
- Molecular virology: viral vectors, transformations, HTLV and other retroviruses;
- Short term methods for viral diagnosis;
- Molecular biology, biotechnology and genetics of mammalian cells;
- Fermentation and biotechnology.

The scientific programme will include lectures and the presentation of papers and posters. The organizing committees will choose the papers for oral presentation.

Abstracts of all accepted lectures and papers will be included in the official bulletin of the seminars which will be distributed during the events.

Further information may be obtained from: Interferon y Biotecnologia '89, Apartado postal 6162, La Habana, Cuba. Tel.: 20 3102 and 20 0072, Telex: 512330 ING GEN CU and 511072 CUBACIB. (Source: MIRCEN News, July 1988)

B. COUNTRY NEWS

Austria

Genentech's Vienna venture

Executives from Genentech (South San Francisco, California) and Boehringer Ingelheim (Ingelheim, Federal Republic of Germany) were in Vienna at the end of May for the opening of their joint Research Institute of Molecular Pathology (IMP). Set up to generate product ideas for cancer therapy from a programme of basic research in cell and molecular biology, IMP is the latest of several links formed between the two companies in the past seven years.

The two companies are jointly forging ahead with the production and sale of tissue plasminogen activator (t PA). Boehringer has marketing rights to t PA everywhere except the United States and Japan. In Canada, the two companies have formed the joint marketing company Genentech Canada.

Boehringer now sells t PA made at its Karl Thomas (Biberach, Federal Republic of Germany) subsidiary, where an $85 million eukaryotic cell

facility has recently been completed. Production of t-PA there came on stream last year.

By its association with Genentech, five per cent of which it owns, Boehringer Ingelheim has been able to gain access to the best of recombinant DNA technology, and a share in some of the early profits therefrom. For its part, Genentech is able to learn a great deal concerning clinical trials, approval procedures and marketing from one of the 20 largest pharmaceutical companies in the world. (Extracted from Bio/Technology, Vol. 6, 5 July 1988)

Brazil

Strategic centres of excellence

Biotechnology in Brazil is developing around a few regional and local centres which have good infrastructure and strong university connections.

One of the biggest programmes is Biotechnologia Agricola (Cebtec), set up in 1986 by the state of Minas Gerais north of Rio de Janeiro. A number of important biotechnology companies and several universities are involved. Minas Gerais plans to invest nearly 1.1 billion cruzados ($US 82 million) over the next few years and to increase the number of researchers from 244 to 386.

The state market for biotechnology is expected to reach $US 440 million by 1990. The immediate aim is to harmonize biotechnology activities and provide scientific and commercial support.

Another big centre in the making is Biotechnologia Rio de Janeiro (Bio Rio) with an initial investment of $US 24 million, which could increase to $US 150 million over the next few years. By then it will occupy 200,000 square metres on the campus of the Federal University of Rio de Janeiro. Bio-Rio is trying to surmount traditional barriers between university research centres and the private sector.

Bio-Rio will also foster international co-operation in priority areas of biotechnology, seeking to set up joint ventures between Brazilian and foreign companies and promote training. Eight companies have already expressed their desire to join. The project will generate 2,000 new jobs and produce vaccines, medicines, fertilizers and new plant varieties, among other products. Professor Jorge Guimarães, Bio-Rio's co-ordinator, estimates that up to $US 800 million a year will be generated by the project by 1990.

In São Paulo state, biotechnology seems to be clustering around two centres. One, located in Sao Paulo city, links the university, the Institute of Technological Research (IPT) and Butanta, all with long traditions in biological research. IPT, for example, has a good reputation for research on fermentation and enzymatic processes, and the development of deterioration-resistant materials, including textiles, inks and leather.

São Paulo's other centre is developing around the towns of Campinas Piracicaba with their long agricultural traditions. The Campinas Agronomy Institute (IAC) and the Escuela Superior de Agricultura Luis de Queiroz (Esalq) in Piracicaba are Brazil's leading agricultural research centres. In Esalq, the Centro de Biotechnologia Agricola (Cebtec) has done extensive research on plant biotechnology and micro propagation. Esalq expertise in research on eucalyptus trees is recognized world wide. Genetically improved eucalyptus trees have achieved a production level of 120 cubic metres per hectare per year in small trials, against 30 cubic metres per hectare a year using traditional methods

The University of Campinas (Un.camp) has set up a multidisciplinary, biotechnology related research centre with an initial investment of $US 7 million. When fully operational it will have a staff of 50, involved mainly in molecular biology and the biochemistry of natural products. Agricultural and pharmaceutical products are priorities. Once the centre has established a solid scientific and technological base, it will seek private capital.

Other states supporting biotechnology include Paraná, Rio Grande do Sul, Bahia and Brasilia DF. The Agronomy Institute of Paraná (Iapar) has been researching cold resistant and disease-free plants with encouraging results.

Most Brazilian work is focused on traditional biotechnology, including industrial processes that manipulate whole micro-organisms and plants, enzymology, classic genetic improvements, plant selections and fermentations. A few institutes are moving into modern biotechnology, based on recent advances in molecular biology, genetics, biochemistry, immunology and cell tissue culture, all of which need a more solid scientific base.

The Brazilian Agricultural Research Organization (Embrapa) is the first Brazilian organization to use cell and tissue culture techniques. Embrapa's genetically improved seed potatoes are one of its successes.

At the National Centre for Temperate Fruits, in Rio Grande do Sul, techniques to produce virus free strawberry plants have increased yields from three to 12 tons per hectare. And at the Centro de Energia Nuclear na Agricultura (Cena) in Piracicaba, experiments with disease free bean plants have increased yields by 40 per cent. Enhanced nitrogen fixation resulting from soil inoculation has significantly increased productivity of black beans, from 500 to 1,200 kilograms per hectare.

Notable advances have also been made in biological pest control. Esalq is developing the fungus Metarhizium anisopliae as an effective killer of the cigarinha sugar cane pest, which can cause up to 40 per cent losses. Esalq has also developed varieties of cane resistant to the herbicides ametryn and diuron.

In pharmaceuticals, Biobras is the leading Brazilian firm, producing interferon in a joint venture with Argentina's Sidus. It exports insulin to 11 countries. Biofil has developed a cellulose film as an artificial skin cure for burns and skin ulcers.

Enzymology is an active research and development area, where significant advances have already been made. At the Institute of Biology (University of São Paulo), researchers have transferred from rats to yeast the gene responsible for the synthesis of alpha amylase, which converts starch to alcohol. This could have important industrial applications making possible the conversion of starch feedstocks such as cassava directly to alcohol.

Research on yeasts is also under way at the Centro Nacional de Pesquisa de Uva e Vinho (CNPUV) of Embrapa, where a new yeast has been developed. It is proving useful in the production of white table and sparkling wines.

In mining, techniques have been developed for the bacterial leaching of materials using Thiobacillus ferrooxidans and Thiobacillus thiooxidans. Two firms - Bioplan and Biomining have been formed to exploit commercial opportunities. (Source: South, June 1988)

New biotechnology centre in Santa Catarina

At the end of 1987, Minister of Science and Technology Luiz Henrique da Silveira and the chairman of the CNPq [National Council for Scientific and Technological Development], Crodowaldo Pavan, joined with the governor of the State of Santa Catarina, Pedro Ivo Campos, and the State Secretary of Science, Technology, Mines and Energy, Odilon Sebastião Saimoria, in signing the declaration establishing the Santa Catarina Centre for Biotechnological Development. The initial investment in the project will be on the order of $4 million, including $2 million from the CNPq, $1 million from the State of Santa Catarina, and $1 million from the business sector.

Establishment of the centre is part of the recently established Santa Catarina biotechnology programme and is one result of the talks initiated with the Government of the Federal Republic of Germany by the CNPq and the Government of Santa Catarina. Those talks were brought to a successful conclusion during last October's meeting by the Brazilian Federal Republic of Germany Joint Commission.

At first, the centre will work on four or five products such as the amino acid lysine. The centre will also produce vitamins B_2 and B_{12}. It will also develop a pharmaceutical based on the fermentation of free plant cells, a process which has been under exhaustive study in countries with advanced technology. Lastly, the centre will develop caffeine for use as a cardiatonic, a type of drug much used in Brazil and one whose import volume in 1985 amounted to a total of $2.3 million.

In addition to establishing the centre, the State of Santa Catarina's draft law exempts domestic firms participating in the project from payment of the ICM [Merchandise Distribution Tax]. The law also provides that in state purchases, preference must be given to products manufactured by the centre in question. This is a pioneering step that has not been seen for 30 years. This is the first time since 1947, when the State of São Paulo Foundation for the Protection of Research (FAPESP) was established, that a Brazilian state has legislated in the area of science and technology.

Augusto Ferreira Sirio, professor at the São Paulo State University, has been invited to be director of the Centre for Biotechnological Development. He will supervise a team who recently obtained their doctorates in Europe - chiefly in the Federal Republic of Germany and France - and who are returning to Brazil specifically to carry out the plan, thus putting into effect the CNPq's programme for inducing people with special training to settle in this country. (Source: Agency CNPq, March 1988)

Bioplanta's role in biotechnology

Imagine a eucalyptus forest resistant to pests and insects, in which the trunks have special characteristics for certain industrial processes, and the leaves and branches are specific for essence production. Or else a jacaranda which reaches adult age within a few years, owing to the insertion of the eucalyptus' rapid growth genes in its genetic code.

For the present, this is still science fiction, but the first steps in this direction are already being started at Bioplanta, a subsidiary firm of the Souza Cruz group established in Sao Paulo, which is engaged in pioneer work all over the world: namely, the genetic mapping of eight eucalyptus species.

Souza Cruz is one of the country's largest private companies to invest in biotechnology. This investment already amounts to $12 million, accumulated since 1983, when Bioplanta was founded, although the new company does not anticipate profits until 1995. According to its superintendent director, Peter Seelig, plant biotechnology will be an activity of global importance by the turn of the century, and Souza Cruz is preparing to have a considerable share of that market. So much so that the group has already invested $3 million per year in the development of basic research in the Bioplanta laboratories.

But the "fiction" is not so far from materializing. The eucalyptus genetic mapping research began recently, and is being done jointly with Acesita Energy, primarily to recover the density of the eucalyptus wood burned in its furnaces which, during the past 10 years, has been greatly reduced because of a neglectful policy of merely raising the production volume. If Acesita should now recover the original density of the eucalyptus trees, it would save nearly $21 million annually, at the current price. As a result of the project's first phase Bioplanta will deliver 145,000 improved eucalyptus cuttings (resistant to viruses and pests), produced through micropropagation, to Acesita by October.

During the next two years, the genetic mapping will enable Bioplanta to identify the "parents" of a given eucalyptus which has the improved characteristics of density and to reproduce it by crossbreeding. In six years, the goal is to perfect the genetic improvement and engage in mapping to produce vigorous hybrid plants: and in 15 years to achieve plant genetic engineering which will make possible the use of molecular markers to produce species with new characteristics.

The company is also engaged in studies to produce black pepper cuttings tolerant of the Fusarium fungus, with greater productivity. The significance of this research lies in the fact that Brazil is currently exporting $130 million worth of black pepper annually, and could expand its market position. Through vegetative propagation and in vitro tissue cultivation, it is also producing cuttings of citrus and temperate climate fruits and vegetable seeds that are more disease resistant and free of viruses. Moreover, Bioplanta is a world leader in research on the Mycorhiza fungus which, through mutual associations with plant roots, has afforded more growth and economy in fertilization, particularly of the phosphorous type. (Source: O Globo, 17 April 1988)

Research into fish breeding

Erica Pinto, assistant professor of genetics and animal improvement at Rio de Janeiro State Federal University (UFF) is carrying out research on genetic improvements in fish on a farm in the municipality of Mage, in Rio de Janeiro. She predicts that by December, she and her team shall start making chromosomic changes to produce fish with more flesh and fewer bones.

Dr. Paul explains that, to make the changes, she will inactivate a batch of chromosomes from the

sperm, with only the capacity to fertilize eggs from a female selected with characteristics that it is wished to reproduce preserved. The offspring will have only characteristics from the female. Through gynogenesis, perfect offspring are procured at the very first breeding, whereas using the traditional method, offspring with the desired characteristics are not procured until after the 14th generation. When the generations of perfect fish are ready, a parental stock will be made. Initially, they will work with tambaqui and snapper.

Dr. Paul found extranumerary chromosomes (smaller than normal chromosomes) for the first time in fish of the Prochilodontidae family, to which the curimbata, a Brazilian river fish, belongs, and succeeded in proving that they are capable of transmitting genetic information. Up until then, researchers had claimed that the extranumerary chromosomes were not responsible for characteristics of the animal body.

The researcher and her team divide their time between the laboratories in the Niteroi district of Vital Brazil, the farm in Mage, and the establishment of an Integrated Fish Breeding Centre in Iguaba, in the Lagos Region of the state of Rio de Janeiro, on land donated to UFF. They recently made the first collection of material from the sea to begin the research, which will be carried out in six different projects.

The results of the Iguaba studies will be turned over to the region's fishing community and will be directed towards an increase in production and rational exploitation of the sea's resources. (Extracted from Journal do Brasil, 31 May 1988)

Enemies within strike cassava hornworm

A Brazilian entomologist has found a virus that is a natural enemy of the cassava hornworm, a pest that damages as much as half the cassava crop in southern Brazil. This solution reduces reliance on insecticides, and so is particularly important for farmers with limited financial resources.

Lurking within infected hornworms is a virus called Baculovirus erinnyis. Aurea Tereza Schmitt, of Empresa de Pesquisa Agropecuaria de Santa Catarina, liquefied larvae of the cassava hornworm. Sprayed onto a cassava crop, the mixture killed 90 per cent of the cassava hornworms attacking the crop.

Schmitt later developed a method of freezing infected hornworm larvae. Tests showed that virus from a four-year frozen sample of infected hornworm larvae killed 67 per cent of the cassava pests. Farmers can now buy frozen B. erinnyis and its mode of application has been publicized in pamphlets, newspapers and television. (Source: New Scientist, 19 May 1988)

Canada

Fungus to reduce fertilizer amounts

A Penicillium fungus could reduce the amount of phosphate fertilizers used by farmers by up to 90 per cent, according to K. Kucey of Agriculture Canada. The fungus makes phosphate soluble, so it can be absorbed more easily by crops. The fungus can even transform natural phosphates in the soil into soluble forms. It will also allow farmers to use mineral phosphate instead of highly processed phosphate fertilizers. The mechanism whereby the fungus works is not fully understood, but it may be simply a result of by-products of fungal metabolism. The fungus could be commercially available to farmers in a few years. (Extracted from New Scientist, 9 June 1988)

Sunlight boosts crop yield

Research by crop physiologists at the Lethbridge Research Station in Canada and at other locations around the world, has shown that crop yield is related to the interception of solar radiation by leaves of growing plants. The biological constants are being studied that are needed to predict yield from this relationship. The effect on it of other environmental factors such as drought could change the relationship.

The formula for increasing yields is simple. Cover the ground surface with a crop as early in the spring as possible and keep it there as long as possible. If the crop could intercept 95 per cent of the sunlight from early May to mid September, the potential yield of small grains would be 13 tons per hectare based on a photosynthetic efficiency of 2.4 per cent measured at the Lethbridge Research Station. If efficiency is increased to about 7 per cent, yields of 37 tons per hectare could be achieved. For corn, the potential silage yield would be almost 110 tons of dry matter per hectare.

The reason why full crop potential is not reached is that about three square metres of leaf area per square metre of ground surface is needed to intercept 95 per cent of the sunlight. This leaf area takes time to develop and does not usually occur until July. One way to accomplish this more quickly would be to seed cereal grains in two directions or to use a narrow-row grain drill (16 cm rows) and increase the seeding rate to about 150 kg/ha. For corn, planting paired rows that are 20 cm apart on 75 cm centres and increasing plant populations from 60 to 100 thousand plants/ha will accomplish the same result.

With yields in this range, inherent harvesting and lodging problems occur. In addition, diseases such as common root rot will appear in susceptible crops. Agriculture Canada, in co-operation with Alberta Agriculture and innovative Alberta farmers, is actively working on new techniques to put these new cropping systems into practice. (Extracted and adapted from: Agricultural Canada, Weekly Letter No. 2724) (Source: Agricultural Information Development Bulletin, Vol. 10, No. 1, March 1988)

Chile

Chilean National Committee for Biotechnology

The Chilean National Committee for Biotechnology (NCB) was constituted in 1983 under the sponsorship of CONICYT. Since that time this Committee has been working in the study and preparation of scientific research and training activities in the area of biotechnology.

The NCB has also been active in the field of international technical co-operation, serving as the Chilean focal point for regional and international activities of the UNDP-UNESCO-UNIDO Regional Latin American Biotechnology Program, for the Organization of American States initiatives in biotechnology and for the participation of Chile in the ICGEB.

On 17 August 1987, by the official resolution No. 478, the President of CONICYT formally established this Committee and appointed the officers to serve in it.

Objectives of the NCB

- To promote the development of biotechnology in the country;

- To stimulate the development of sciences and technologies related to biotechnology;

- To co-ordinate the different institutes or laboratories existing in the country in a national network to improve joint efforts and to concentrate resources;

- To promote the elaboration of interdisciplinary and interinstitutional research projects in the main priority areas;

- To stimulate the training of young scientists in areas of special relevance for biotechnology;

- To channel the international and regional contacts in biotechnology;

- To prepare a National Programme of Biotechnology.

The National Committee has working groups on:

(a) Bacterial mineral leaching

(b) Biological nitrogen fixation

(c) Plant tissue culture

(d) Anaerobic degradation of biological residues

(e) Diagnostic reagents for human, animal and plant diseases

(f) Lignocellulosic agricultural and forestry residues

(g) Massive culture of microalgae

(h) Biotechnology of industrial enzymes

(i) Biotechnology of animal embryo manipulation.

Further information can be obtained from: The Executive Secretary, CONICYT, Casilla 297-V, Santiago, Chile. (Source: MIRCEN News, July 1988)

Cuba

Vaccine research

By the end of 1988 Cuba may have a vaccine against at least one strain of meningococcal meningitis B - an eagerly anticipated outcome of five years' work by a team of 20 Cuban doctors, microbiologists, immunologists and technicians.

Meningococcal meningitis, in its various forms, affects millions worldwide each year, killing around 10 per cent of victims, especially the young and elderly, with a preference for males. The bacteria attack the membrane around the brain and spinal cord, leaving many who survive with serious disabilities including blindness, deafness and brain damage.

Although effective vaccines are available against other forms of the disease - designated A, C, Y and W 135 - protection against the group B variety has been hard to achieve. Research is under way in many countries, but Cuba is leading the field.

Children over six months are most at risk. Over two thirds of those who die from the disease in Cuba are under five, and it is the fourth biggest cause of death for under 15s. The problem is made worse because in children it is often difficult to diagnose the disease in the early stages, when it is easier to control. They may not show the characteristic symptoms of meningitis - headache, fever, rash, nausea, a stiff neck and dislike of light - which in adults distinguish it from minor infections like influenza.

Most bacterial vaccines, including those against the other groups of meningococcal meningitis, are based on the polysaccharide capsule which covers the outer membrane of the bacteria. The capsule, which is harmless to humans, can usually stimulate B lymphocytes (or B cells) to produce antibodies to the bacteria itself. But in the case of group B meningitis, the capsule alone has little effect.

To overcome this, the Cuban team used proteins from the outer membrane of the group B bacteria (underneath the capsule). They combined them chemically with the polysaccharide capsule of group C bacteria, which can stimulate antibody production.

Use of the membrane protein activates an additional part of the immune system, called T lymphocytes. Once activated, T cells will "help" the B cells to make antibodies to the group B bacteria. This technique had earlier been used in Finland to develop a vaccine to haemophilus influenza B which had posed similar problems.

Experiments on human volunteers in Cuba in 1985 were encouraging. In 98 per cent of the cases the vaccine produced adequate antibody responses and in 65 per cent of cases the antibodies were able to control the infection. These tests were carried out on adults, "although we realized that the main problem was in young children," says Dr. Mario Valcárcel of the Cuban Health Ministry's Department of Epidemiology, one of the main initiators of the research.

The preliminary tests showed that the vaccine had no side-effects and large-scale clinical trials began in February 1987, with the vaccination of 140,000 boarding-school children aged 12-14 in the seven most affected provinces. This was followed in May by vaccination of all those aged six months to 24 years in the province of Ciudad de Avila, which has the highest incidence of the disease. Further trials are planned for the 6-12 months age groups.

The final results of these trials are expected by the end of 1988 or early in 1989 and stocks of vaccine are being built up in anticipation of a national vaccination programme.

It remains to be seen, however, whether the Cuban vaccine will protect against any strain other than the B4 from which the membrane proteins are taken. Dr. Dennis Jones of the public health laboratory in Manchester, UK, believes it may have a wider application. He says there is a significant overlap between the outer membrane proteins of different strains within the same group of bacteria.

The Cuban vaccine may therefore offer some protection against the B15 strain prevalent in the UK.

Work is under way in Norway as part of a joint Norwegian, Danish and US project to combine

polysaccharide C with proteins from B15 and B2 strains, but field trials are not expected before the end of the year.

The Wellcome Foundation in the UK is experimenting with a vaccine made from purified polysaccharide B which has been chemically treated to increase its antibody stimulating properties. This would provide comprehensive protection against all B strains, but field trials are a long way off. For the present, the Cuban vaccine offers the best hope for at least partial protection against this destructive disease. (Source: South, April 1988)

Denmark

Novo receives key biotechnology approvals

Novo Industri has received two key approvals involving genetically engineered products. The Danish health authorities have granted the firm marketing approval for its gene-spliced insulin while the Danish national food agency has given Novo the green light to produce its fat digesting detergent enzyme Lipolase.

Before Novo can start producing the enzyme, made by gene spliced mould fungus Aspergillus oryzae, it will need environmental approval from the West Sjaelland Council which is expected to be granted in August enabling Novo to be in a position to start production at Kalundborg by the end of October. Novo currently produces the enzyme in Japan at its Hokkaido facility. Approval is also being sought for Lipolase production in the US.

The fat digesting enzyme is already being marketed in some countries in powder detergents and Novo is developing a liquid form of the enzyme for liquid detergents.

Novo has also received its first marketing approval from Denmark for its gene-spliced human insulin. This is the first approval to be granted following the positive opinion obtained from the EEC's Committee for Proprietary Medicinal Products under the "high tech" registration procedure. Novo expects to receive marketing approvals from the other 11 EEC member States in the next few months.

The human insulin is produced using gene-spliced baker's yeast at Novo's Kalundborg facility. (Extracted from European Chemical News, 25 July 1988)

European Economic Community

Biological resources

On 11 April the Council adopted a common position on the proposal for a decision on the revision of the multi annual research action programme in the field of biotechnology (1985 1989). As proposed by the Commission, the estimates for the necessary funding will be increased from 55 to 75 million ECU in order to permit the extension to Spain and Portugal of the activities envisaged under the programme and the intensification of the current research effort in the sector of the programme that concerns the assessment of risks associated with information biotechnology. (Source: Bulletin of the European Communities, Vol. 21, No. 4, June 1988)

Europeans plan gene sequencer project for EUREKA

Several European firms are willing to join forces in the development of a gene sequencer. The idea is to develop a fully integrated system combining all the necessary steps, from the centrifuge to the gene sequencer itself, including the electrophoresis step, the production of probes, etc.

This highly ambitious project has been elaborated by British and French firms Amersham and Imperial Cancer Research Fund, Bertin and CEPH (Centre d'Etudes du Polymorphisme Humain). This is the second important commitment of Bertin to biotechnology. Federal Republic of Germany and Swiss industrialists have also expressed interest.

The scheduled budget for four years will be between ECU 50 and 60 million. The project will be presented at the next EUREKA conference in June. Applied Biosystems and Du Pont are the leaders, with Pharmacia-LKB, Hitachi and EG&G in good position. (Source: European Biotechnology Newsletter, 5 February 1988)

European efforts in protein engineering summarized

Protein engineering (PE) has not yet resulted, quite obviously, in a multitude of marketing breakthroughs and it cannot yet be claimed by biotechnology as a significant conquest. Still, much effort is being spent in Europe to make this dream a reality. Some proteins have gone through an important part of the PE loop, in particular in the health sector. Below are listed such proteins which have been significantly modified and for which PE is more than just a concept.

TPA (1, 2, 3, 5) is perhaps the best example of PE. Dr. Collen's team has a second generation TPA in which the finger and growth factor domains have been deleted. Half life is much prolonged, permitting bolus injection, as proved in rabbit jugular vein and dog coronary artery models. Besides, it had already been possible to combine TPA's and urikinase's properties in a single hybrid protein. By substituting amino-acids and carbohydrate groups, Kabigen has succeeded in multiplying half-life by 5-10. Celltech is also working on second generation TPA.

Probably because its 3D structure is known, INSULIN (5) has been extensively studied. Now it is designing, at will, insulins with different activit, kinetics. Nevertheless, although the 3D structure is unavailable most of the time, significant functional alteration of a native protein can be designed on other bases. Transgene and Yeda Groups have increased the activity of HIRUDIN (6, 7, 8) on thrombin, in vitro and in vivo, using predictions based on primary sequence studies. As in other cases, it is expected soon to obtain the 3D structure, thanks to NMR data and also because crystallization is at hand. Transgene has improved the stability of ANTI TRYPSIN (6, 9) towards oxidation, following a similar approach. Animal tests are under way. Moreover, it has been possible to shift the specificity, making anti trypsin an inhibitor of thrombin in place of elastase. Folding mutants (9) have been obtained, opening the way to a better understanding of conformational aspects.

ANTIBODIES (10, 11) are being engineered by several teams in Europe. Recent achievements include the insertion of the hypervariable region of rat antibodies, directed against T cells, in human antibodies. This results in hybrid antibodies with in vivo therapeutic potential. Rees and colleagues have impressed the scientific community with computerized models where mutation modelling is

linked to the effect of true mutations in site directed mutagenesis: antibodies with 10 times higher affinity have been obtained. Unilever and Behring intend to invest in this sector. Moreover, rewarding work is being carried out on small proteins like snail cardiotoxin where active sites have just been identified by site directed mutagenesis (12). Other small proteins currently engineered with success include phospholipase (13) and neurotoxins.

INTERFERON (14, 15, 16) is receiving attention by major firms, including ICI Pharmaceutical, Hoechst and Roussel-Uclaf, where analogues have been synthesized. ICI Pharmaceutical is also modifying Epidermal Growth Factor, with the help of the recently elucidated structure. Only recently involved, Roussel Uclaf is now deeply engaged in PE.

BLOOD FACTOR VIII has major implications in therapeutics. By deleting its central fragment, it has been possible to increase both its secretion rate by its host and its stability, while preserving intact its activity (6).

Besides the redesigning of proteins with physiological activity, numerous are the initiatives aiming at construction drugs from knowledge of target proteins. Excellent work is under way on BETA-LACTAMASES, so as to derive antibiotics capable of overcoming resistance to lactams (17). Although not truly engineering them, Glaxo is studying INTERLEUKIN 2 and INTERLEUKIN 1 BETA (.9), to understand receptor binding, thanks to models derived from computer algorithms. A region involved in binding has recently been identified, using site-directed and random mutagenesis. Hoffmann-La Roche (20) is investing effort in designing IL 2 agonists and antagonists and Hoechst in redesigning interleukin 2.

Elucidation of an enzyme from TRYPANOSOMA BRUCEI has opened the way to the design of specific drugs (21) and inhibitors to renin have been derived from its structure. Passive engineering also plays a key role in vaccine development. Important, although preliminary achievements are numerous such as in AIDS, RHINOVIRUS (22), POLIOVIRUS or FOOT AND MOUTH DISEASE (23). In the case of the DIPHTHERIA TOXIN (24), the knowledge of its toxin has been used to identify regions with potentialities as vaccine carrier and immunogenicity of hepatitis and poliovirus is being enhanced by fusion. PERTUSSIS TOXIN is being studied for vaccine development.

As testimony of the promises of engineered proteins, several new firms are launching sizeable efforts: Hoffmann-La Roche (20) is studying proteins of the immunological models. Firms like Merrel Institute, Organon Teknika (Steroid hormone receptors) are building their own capacities in PE. Glaxo Geneva (19) is investing major efforts in interleukins and interleukin receptors, to elucidate structure activity relationships.

1. Dr. D. Collen, Leuven R&D, Benedenstraat 60A, Groot Bijgaarden, Leuven 3000, Belgium. Tel.: 32 16 214230.

2. Mr. Roger Bishop, Marketing Manager, KabiGen, Strandbergsgatan 49, 11287 Stockholm, Sweden. Tel.: 46 8 138000.

3. Celltech, Dr. Tim Harris, 244 250 Bath Road, Slough SL1 4EN, UK. Tel.: 44 753 34655.

5. Novo, Novo Alle, 2880 Bagsvaerd, Denmark. Tel.: 45 298 233.

6. Dr. Michael Cortney, Transgene, 16 rue Henri-Regnault, 92411 Courbevoie Cedex, France. Tel.: 33-88222490.

7. Dr. R. Burk, Ciba-Geigy K 681.5.44, 4002 Basel, Switzerland. Tel.: 41-61-361833.

8. Prof. H. G. Gassen, Technische Hochschule Darmstadt, Fachbereich 9, Institut fuer Organische Chemie und Biochemie, Petersenstr. 22, 6100 Darmstadt, FRG. Tel.: 49-6151-2176.

9. Prof. R. H. Pain, University of Newcastle, Department of Biochemistry, Ridley Building, Newcastle upon Tyne, NE1 7RU, UK. Tel.: 44-632-328511.

10. Dr. Rees and colleagues, Molecular Biophysics Laboratory, University of Oxford, Oxford OX1 3QU, UK. Tel.: 44-865-56789.

11. Dr. H. J. Fritz, Max-Planck Institut fuer Biochemie, Am Klopferspitz 18a, 8033 Martinsried, FRG. Tel.: 49-89-85781.

12. Dr. Andre Menez, Service de Biochimie, Bat. 142, CEN Saclay, 91191 Gif-Sur-Yvette, France. Tel.: 33-1-69088303.

13. Dr. G. H. Haas, State University Utrecht, Padualaan 8, Transitorium III, 3584 Utrecht, Netherlands. Tel.: 31-30-533186.

14. Dr. Tebbing, General Manager Research I, ICI Pharmaceuticals Division, Mereside Alderley Park, Macclesfield SK10 4TG, UK. Tel.: 44-625-513743.

15. Dr. Gilles Moreau, Roussel-Uclaf, 111 route de Noisy, 93230 Romainville, France. Tel.: 33 1-48439310.

16. Dr. K. Dittmar, GBF, Mascheroder Weg 1, 3300 Braunschweig, FRG. Tel.: 49-531-61181D.

17. Dr. Ghuysen, Institut de Chimie, Bat. B6, Université du Sart-Tilman, 4000 Liège. Belgium. Tel.: 32-41-561396 or 95.

21. Dr. Hobden, Glaxo Institute of Molecular Biology, 46 rte des Acacias, 1227 Carouge, Switzerland. Tel.: 41 22 433200 UK. Tel.: 44-659-2211.

23. Dr. Rob Meloen, Centraal Diergeneeskunde Instituut, Netherlands. Tel.: 31-3200T3723.

24. Dr. Michel Kaczorek, Unité des Applications du Genie Genetique, Institut Pasteur, 28 rue du Docteur Roux, 75015, Paris, France. Tel.: 33-1-45688000. (Source: European Biotechnology News, 5 February 1988)

EC plans to sequence yeast genome

A two-year pilot project to sequence one yeast chromosome was passed in mid February in Brussels by the advisory committee of the EC's Biotechnology Action Programme. The project will provide 2 million ECU to between 20 and 40 laboratories. Formal approval from the EC is expected soon.

The project could be expanded in 1991 under the BRIDGE programme to sequence the entire yeast genome, in conjunction with Japan and the United States. Project leader Andre Goffeau said the EC might make as much as 10 20 million ECU available for the sequencing of yeast and other "industrial microbes" under the auspices of BRIDGE.

Fifty yeast laboratories from almost every EC country but especially from France, Federal Republic of Germany and Belgium have expressed an interest in the pilot project. Each laboratory would receive 10-15 kilobases (kb) per year to sequence using methods of their own choosing. In addition, each laboratory would check the results of one other laboratory.

The chromosome to be sequenced, chromosome 3, was chosen because of its small size as well as access to an organized library of overlapping clones thanks to Maynard Olson of Washington University in St. Louis and others in the United States. Chromosome 3 contains about 360 kb of DNA; the entire yeast genome contains about 15,000 kb. By contrast, the human genome consists of 3 million kb.

A centre to coordinate the sequence data is essential, says Goffeau. A likely candidate is the Martinsried Institute for Protein Sequence Data near Munich, Federal Republic of Germany.

Goffeau is optimistic that the yeast sequencing project will attract widespread industrial support, which may be essential for the project's well-being. A preliminary study revealed broad interest from breweries, pharmaceutical companies and biotechnology firms in five or six EC countries. (Source: Nature, Vol. 332, 7 Apr... 1988)

Animal drugs vetted

The European Parliament has called for a new procedure for assessing veterinary drugs produced by genetic engineering. The Parliament wants manufacturers to demonstrate that such drugs are not damaging ecologically or "socio-economically" by making European agriculture even more productive.

The resolution was aimed at bovine somatotropin, a protein hormone that increases milk yields in cows. It is uncertain whether individual European countries, including Britain which is now testing the drug, can approve its general use prior to a ruling by the EEC.

David Wilkins, the chief veterinary officer of Britain's Royal Society for the Prevention of Cruelty to Animals, told the European Parliament new fears for the welfare of cows treated with BST. He says farmers will be tempted to use the hormone illegally in lactating cows in order to boost growth in calves. This would harm animals more than the uses for which BST is approved. (Source: New Scientist, 14 July 1988)

Egypt

Desert variety of sesame

The Harvests Division of Cairo University's Department of Agriculture has succeeded in inventing a new type of seed for sesame cultivation. It is grown on desert land and does not need much water. A single feddan yields 7.5 ardebs (roughly 42 US bushels) on average, and provides a generous profit of 1,000 Egyptian pounds every 10 months for its owner. It was confirmed by Dr. 'Abdallah Fathi, professor of harvests at the Cairo University's Department of Agriculture and the originator of this experiment, that it had gone past the experimental stage and become a reality. The local population has begun to plant the sesame seed in the various provinces, and many of the local farm co-operatives have succeeded in growing it. Demand for the seed has greatly surpassed supply, especially since the seed is distributed free of charge, although everyone who has a sesame crop is expected to give back double the amount of seed they received in order to give to others, and so forth. However, it has become clear that many do not feel obligated to return double the amount or even the same amount. (Source: Al-Akhbar, 11 April 1988)

Federal Republic of Germany

Molecular biology threatened

After years of internal debate, the Federal Republic of Germany Government is considering legislation that may jeopardize both research and using recombinant DNA technology. The views being drafted seem certain to have far-reaching, if not devastating, effects. The nation's first broad environmental safeguard is preparing for a fight against genetic engineers of that promises to be as intense as the battle over nuclear energy.

Opinion has been crystallized by the report of the "Enquete Kommission" appointed in 1984 by the Bundestag (Parliament) to study the "Prospects and Risks of Genetic Engineering". In January 1987 the report urged more than 170 specific measures covering such areas as cloning of human beings, release of genetically manipulated micro-organisms and genome analysis by employers and law enforcement agencies. The Bundestag has begun hearings on some of these issues, which are meant to lead to a new "gene law" by early next year.

Meanwhile, another measure on waste materials produced by genetic engineering has provoked a sharp response from the few researchers who have heard about it. It consists of a set of regulations to fill a gap in the Federal Republic of Germany Water Management Act.

The first draft of the regulations would handle any plasmids or vectors containing foreign DNA as if they were pathogens and require that the bacteria be chemically or thermally treated "to destroy all materials capable of reproducing" outside the laboratory or production facility.

The measure was provoked by the pharmaceutical company Hoechst AG's plan to produce human insulin using genetically manipulated Escherichia coli bacteria. Although the Hoechst plant near Frankfurt was initially approved by local authorities, plans have now been stopped by a citizens' initiative.

Molecular biologist Ernst Ludwig Winnacker, director of the Munich Gene Centre, argues that the wastes should be treated according to their pathogenicity. Hoechst says that the insulin producing bacteria are indeed incapable of surviving in the outside world, but the principal author of the proposal, Jürgen Hahn of the Federal Health Office (Bundesgesundheitsamt), says that the law is meant to anticipate "not the pathogenic but rather the ecological consequences" of an accidental release. The operative principle is that, once released into the environment, new genes cannot be brought back.

The same arguments can be expected as the Bundestag nears passage of a gene law. (Extracted from Nature, Vol. 332, 21 April 1988)

Firms lift biotechnology R&D

Federal Republic of Germany's chemical and pharmaceutical industries spent about DM 800 million on biotechnology R&D in 1987, according to estimates

from the Federal Republic. A [illegible] consultant [illegible]. During the same period, the Federal Republic of Germany [illegible] has spent about DM 200 million to support biotechnology research and development.

Research into human and animal pharmaceuticals accounts for about 55 per cent of the total with specialty chemicals picking up about 25 per cent of the funds. Ranson estimates that about half the pharmaceutical funds and 15 per cent of biotechnology research in specialty chemicals is [illegible] amino acids and enzymes are not abroad.

Other areas of research to receive funds [illegible] trade analysis, equipment (9 per cent), plant [illegible] technology (6 per cent), equipment design (5 per cent), biopesticides (3.5 per cent) and food processing (2 per cent). Ranson's estimates do not include biotechnology as an environmental issue. (Source: Business Technical News, 25 July 1988)

India

[illegible] yielding fungal strain

The Indian Discovery of a fungus at one of the Indian Council of Medical Research (ICMR) Institutes has sent waves of excitement through the Indian medical and pharmaceutical community. While screening soil samples for microbial killing agents, scientists at the Vector Control Research Centre (VCRC) in Pondicherry have stumbled upon a strain of the fungus Tolypocladium cylindrosporum that yields large quantities of cyclosporin - an immunosuppressive drug widely used for managing patients undergoing organ transplants.

Cyclosporin is manufactured and marketed by Sandoz, which obtains it from the fungus T. inflatum. According to VCRC microbiologist Dr. K. Balaraman, a secondary metabolite in T. cylindrosporum produces an essentially similar product, as three week old fungal cultures. Animal studies are soon to begin to test the efficiency of the product which the VCRC is now able to produce in purified crystalline form.

The ICMR is now in the process of identifying an Indian company to undertake commercial production of cyclosporin. (Source: Nature, Vol. 332, 21 April 1988)

Madurai Kamaraj University develops high technology products

An autonomous set up, "Madurai Kamaraj University Biologicals" will make high technology products, developed in the university's School of Biology and ready for commercialization, available to both foreign and Indian firms.

High technology products developed include immuno diagnostic kits for detection of diseases like leprosy; production of monoclonal antibodies against particular diseases like malaria; unisex cultures (a technology for producing unisex cultures of fish - for instance, producing only male fish for eating purposes, since these can be fattened easily); and growth hormones for retarding sexual maturity and prolonging the somatic growth. (China has already developed this technology and two researchers from the Madurai Kamaraj University spent some time in China collaborating with Chinese scientists on this project.)

Other items are related to: (a) use of streptomyces for production of antibiotics (a large number of streptomyces are available in the soil); (b) single nucleotides (which are bases for DNA sequencing) for research purposes; (c) biocides for protection of plants against insect attacks; and (d) skin bank for the treatment of acute burns.

Dr. S. Krishnaswamy, Vice Chancellor of the University, said many foreign firms had shown interest in purchasing the technology. The unit, launched in April, could become a self supporting system generating enough financial resources in the course of time. (Source: The Hindu, 15 April 1988)

AIDS research centre to be set up in India

India has set up a centre in Madras dedicated to research in acquired immune deficiency syndrome (AIDS). It will eventually become a fully fledged institute under the Indian Council of Medical Research (ICMR).

Dr. Bhushan Pavri, the retiring director of the National Institute of Virology in Pune, has been made project director of the new centre. A nine member expert committee has been set up to formulate the centre's research projects. ICMR says the centre will co-ordinate surveillance and epidemiological work and carry out virological and immunological studies "in the entire spectrum of HIV infection". It will also be the only facility in the country for treatment of AIDS victims.

One research project to be taken up by the centre is on the role of the retrovirus-like intracisternal A particle (IAP) recently isolated by Pavri from a prostitute with atypical sero-response to HIV. According to Pavri, the IAP, seen for the first time in humans, could act as a precursor to HIV. Interestingly, studies at the ICMR Institute of Leprosy in Agra have shown antigenic cross-reactivity between HIV and mycobacteria that cause leprosy and tuberculosis.

Some ICMR scientists suggest that Mycobacterium avium intracellulare (MAI) infection, widely present in India, may be protecting Indians against AIDS in the same way that dengue virus infection protects against yellow fever. ICMR is planning further studies to look for common antigenic patterns and gene sequences between HIV and mycobacteria. Meanwhile, Dr. M.G. Deo, director of the Cancer Research Institute in Bombay, has suggested that the cross reactivity can be exploited to develop an AIDS vaccine containing a number of strains of MAI. (Source: Nature, Vol. 331, 1 February 1988)

Indonesia

Sheep feed grown on spare land

According to a recent report in the World Service of the British Broadcasting Corporation (BBC), a scientist at the Research Institute for Animal Production at Bogor (Java, Indonesia) has developed an effective system of cultivating forage crops for local sheep.

While locally sheep farmers have tended to provide a good standard of feed for their animals, this has involved many hours of labour in searching out, cutting and carrying back prime fodder from the farmer's vicinity.

With a proper system of feed production and management, however, high standards can be maintained using only a small portion of the farmer's land.

At the Research Institute, Dr. Chris Peacock cultivates three basic feed crops on a small plot next to the sheep houses. Leucaena has been planted around the outside in two rows, then inside that is a grass called Panicum maximum, developed in Australia, and found to be highly suitable for Java. Inside this is a crop of sweet potatoes, and the tops can be fed to the sheep when the potatoes are harvested.

The basic idea of this system is to show how forages can be planted on spare, small bits of land in a village, such as along fences, rice bunds, and underneath banana trees.

In one village where the Institute works, about four hectares out of 48 were found to be unused, but in this small area a balanced ration could be obtained for the sheep. Current work at the Institute is concerned with determining just how many sheep can be supported on small plots.

Preliminary results have shown, in any case, that a proper forage production system does not require too much land, and improves feed quality, while reducing time spent in this activity. (Source: Agricultural Information Development Bulletin, Vol. 10, No. 1, March 1988)

IPM raises crop yields

Integrated pest management in rice crops has prompted the Government to ban 57 insecticides based on organophosphates, chlorinated hydrocarbons and pyrethroids. A field trial of the IPM raised yields 20 per cent and saved the Government $35 million. The United Nations Food and Agriculture Organization hopes to expand the programme from rice to other crops. FAO entomologist P. Kenmore devised the IPM programme, which is intended to control the brown planthopper, a major devastator of rice crops. While farmers in a control group sprayed insecticides 4.5 times in a 10 week season, farmers in the programme sprayed buprofezin an average of less than once. Rice yields rose from 6.1 to 7.4 million tons/hectare. Kenmore says the programme is the first time pesticides have ever been banned for ecological reasons rather than to protect human health. Pesticides that had been in use were more devastating to predators of the plant hoppers than to the plant hoppers themselves. Carbamates that are less damaging to the predators may still be used. The FAO hopes to expand IPM to the Philippines, Malaysia, Thailand, Bangladesh, Sri Lanka and India. (Extracted from New Scientist, 16 June 1988)

Ireland

Beckman designates BioResearch Ireland as its first European biotechnology reference centre

The multinational scientific instrumentation company Beckman will establish Ireland's new contract research organization, BioResearch Ireland, as its first European Biotechnology Reference Centre. $1.5 million has been allocated for in seed funding for the continuation and expansion of the National Biotechnology Programme.

The agreement (between Beckman and BioResearch Ireland) means that BioResearch Ireland is now a partner in the R&D programme of the world's leading scientific instrumentation manufacturers. BioResearch Ireland, which is currently a division of EOLAS, the new Science and Technology Agency, will market, manage and develop the biotechnology research expertise in Ireland's universities and research institutions on a commercial basis. (Extracted from International Industrial Biotechnology, 8 February 1988)

Israel

Biotechnology in Israel

Israel's biotechnology sector, comprising several dozen companies, 15 of which have already brought products to market, is gaining international recognition for a broad spectrum of activities. Although sales from this sector are still small, topping $35 million in 1987, of which $20 million was derived from exports, Josef Dankowitz, deputy director of the Ministry of Industry and Trade's chemical division predicts that it will be a major source of revenue by the end of the century.

"Exports from biotechnology will leap to $100 million within the next four to five years," Dankowitz claimed. This is supported by the backing already received by Israeli biotechnology concerns from multinational firms such as Du Pont, Bristol Myers and American Cyanamid.

The key to success, as identified by many biotechnology company chiefs, is sustained research and development. Active operation with research institutes has played a crucial role in the development of the industry.

Yeda Research and Development and Yissum Research Development both function to commercialise technological developments within the Weizmann Institute and the Hebrew University of Jerusalem respectively. In addition to its marketing role Yissum is well placed to advise overseas partners of the tax concessions available.

Major biotechnology involvements of Yissum include International Diagnostic Systems (30 per cent holding) and Unipharm Partnership (25 per cent Yissum). Yeda played an important role in the establishment of Bio Master.

Biotechnology Generals, Israel has taken advantage of such local capabilities. A core activity of BTG is the development of proprietary vector and expression systems with both US and Israeli partners.

Funding for BTG's activities came mainly from its US parent. But the firm has also established a commercial tie up with Sweden's Pharmacia for pharmaceutical grade hyaluronic acid. BTG also obtained technologies for superoxide dismutase, hepatitis B vaccines and bovine growth hormone from the Weizmann Institute.

As Israeli biotechnology firms move products closer to the marketplace they are seeking joint venture activities with foreign companies. These arrangements may be research collaborations or marketing deals.

This shift into export oriented activities by biotechnology firms echoes the experience of the chemical industry. The base created by researchers, coupled with the dramatic advances being made in the other sectors of the chemical industry, should paint a picture of continued growth and an increasing share of international markets.

Israeli biotechnology companies seeking joint ventures

Company	Principal activities
AL Research & Development	Plant tissue culture and propagation
Abic Ltd.	Pharmaceuticals and anti-cancer chemotherapies

Bio Lir	Microencapsulation
BioHytech (Israel)	Diagnostics
Biokoor Industrial	Biocatalysts, biosensors and cell culture for chemicals production
Bio-Lab Laboratories	Nitrogen fixing bacteria and tissue culture
Biological Industries	Plant and biomedical biotechnology
Biotechnological Applications	Biopesticides
BioTechnology General (Israel)	Human therapeutics including SOD, hGH, and hyaluronic acid and animal growth hormones
Gelman Sciences Technology	Polyacrylamide gels for electrophoresis
Hy Labs	Bacteriological media
International Diagnostic Laboratories	Diagnostic products
Interpharm Laboratories	Human therapeutics including hGH, beta interferon and monoclonal antibodies
Israel Institute for Biological Research	Gene expression systems, vaccines, protein engineering
Koor Foods	Algal research
Life Science Research Israel	Contract research
Maker Chemicals (Bio Maker)	Immunochemicals, bioactive peptides and fermentation products
Orgenics	Human diagnostics and research products
Red Chemicals	Purified proteins and blood products
Rafa Laboratories	Pharmaceuticals, vaccines and diagnostics
Rahan Meristem	Plant propagation
Savyon Diagnostics	Diagnostics
Teva Pharmaceutical Industries	Pharmaceuticals, fine chemicals, diagnostic equipment and pregnancy kits
Yeda Research and Development	Commercializing biotechnology products at Weizmann Institute
Yissum Research and Development	Commercializing biotechnology products at the Hebrew University of Jerusalem
Zer Group	Medical diagnostics and fertility kits

(Extracted from European Chemical News, Southern Europe and Mediterranean Supplement, July 1988)

New antibiotic

A topical antibiotic that sticks to wherever it is applied has been discovered by researchers at Tel Aviv University. The antibiotic is produced by the bacterium Myxococcus xanthus, which grows on tree bark and in soil. The bacterium secretes an antibiotic when competing with other bacteria for food. The antibiotic kills at least 50 kinds of bacteria. It acts locally, and is not taken up by the bloodstream. It is far more effective than tetracycline. The compound (named TA for Tel Aviv) sticks to teeth, gums, plastic, metal, etc. (Extracted from New Scientist, 9 June 1988)

Fishing in the desert

Amid the sand and gravel flats of Israel's Arava Valley, farmers participating in a unique experiment are literally pulling fish out of the desert - a record-setting 12 tons of fish annually per 1,000 m^2 of pond area, according to a Tel Aviv University press release. Using a method devised by Tel Aviv University scientists, these farmers are breeding a specially developed hybrid tilapia - Israel's popular St. Peter's Fish - in high-salinity ponds fed by underground water sources.

Previously unexploited, such water sources proliferate throughout arid regions all over the world. They are high in mineral content and therefore rich in production of algae, which serve as a plentiful food source for certain eurythermic fish.

This new method of desert pisciculture was created by Professor Lev Fishelson of Tel Aviv University's Department of Zoology, and his students. Employing a new method for keeping the brackish waters clean, they found that fish density per square metre could be increased dramatically: in normal commercial ponds two or three tilapia can be raised per square metre, while the desert ponds yielded up to 30 fish per square metre without detriment to growth.

It was found that 80 per cent of the tilapia's metabolic demand could be met through the natural production of algae alone, which meant appreciable savings on feed. By efficiently utilizing the annual 365 days of sunshine, production was maintained all year round. Annual yields averaged over 40,000 kg per acre, 15 times higher than in normal commercial fish ponds.

In a related experiment, scientists bred ducks simultaneously in the fish ponds, feeding them mainly on grains and algae. The ducks, besides providing the farming community with an additional food source, produced waste which served as a natural means of fertilizing the ponds, thereby sustaining the food cycle.

Speaking of his development, Fishelson said, "The need for cheaper sources of animal protein for human consumption is assuming great importance worldwide. The development of integrated fish and duck farms, which can achieve the very high yields at a fraction of current commercial costs, holds out hope for such protein source countries." (Source: European Science News, February 1988)

Italy

Products market growth anticipated

Research spending by joint ventures is rising. Switzerland's Sandoz and Italian drug maker Italfarmaco (Milan) will open an $8 million research centre in Milan later this year. Merck & Co.'s Italian subsidiary Merck Sharp & Dohme Italia (Rome) is building a $55 million molecular biology institute at Pomezia, scheduled to start operations

in 1990, in a joint venture with Italian company Sigma Tau.

Both Government backed and private research initiatives are now under way in the area of biotechnology to help close the gap between Italy and other countries where biotechnology research has sprinted ahead. The Italian Government has launched two such programmes, each scheduled to run five years. In 1987, the Government launched a $320 million programme to fund biotechnology research in human and animal health, chemicals, energy, the environment and the agriculture and food processing industries. The research ministry awards contracts to companies that bid to carry out pre-selected research projects. Projects in enzymes, biodegradation of waste, polypeptides and monoclonal antibodies already are under way.

A second programme valued at $60 million, provides funds for university based fundamental research projects; the programme incorporates some industry collaboration. Notes Montedison's Simonit: "Italian public research spending figures are still not enough, but the rate of increase is the largest in Europe".

The same might be said of industry's efforts in biotechnology development. Having lagged behind developments in the Federal Republic of Germany, France and the UK, Italy's biomedicine market is now growing extremely fast, compared with others in Europe.

Consulting firm Teknibank (Milan) projects that the Italian market for biotechnology products will grow almost sevenfold within five years, rising from $113 million in 1987 to $740 million in 1992. Most of that will be accounted for by diagnostic products; sales of biotechnologically produced therapeutics will increase sharply after 1990. Sales of enzymes, also Teknibank, should reach about $60 million by 1992.

Among Italian manufacturers, Montedison and Enichem each have biotechnology research programmes on human health and plants, and both companies have plant biotechnology research under way in the US. Sclavo's Sorin Biomedica subsidiary is marketing diagnostics. Sorin, together with Sclavo's chemical subsidiary Diffivo, has now acquired Composizioni di Ricerca Chimiche, a company that has developed a biological insecticide.

Sclavo has the biggest biotechnology research team in Italy. In fact, with a complement of 240 people it is second in Europe only to the team at Institut Pasteur (Paris). Sclavo's research director Sergio Silvestri, expects Sclavo's alliance with Du Pont to increase the Italian company's efforts in biotechnology research, particularly in diagnostics and vaccines, beginning with a whooping cough vaccine. (Extracted from Chemical Week, 25 May 1988)

Enichem continues to boost biotechnology research

Enichem (Milan), the chemical arm of Italy's State owned energy group Ente Nazionale Idrocarburi, will bolster its biotechnology research programme with a five year research contract on plant biotechnology with La Sapienza University in Rome. La Sapienza's genetics and molecular biology department will carry out a programme to develop resistance in potatoes to insects and diseases. Early this year, the company signed another agreement for plant biotechnology research with the Max Planck Institute in Cologne, Federal Republic of Germany. Last year, Enichem opened its own research centre at Princeton, N.J. Enichem's plant biotechnology programme represents a substantial investment by a utility in search of high profits. Marketed out by its Sclavo health care joint venture, the utility has a new Port. (Source: Chemical Week, 25 May 1988)

An international team has [illegible]

An international team has isolated the tissue plasminogen activator (TPA). Montedison (Florence, Italy) has taken a 20 million DM license for mammalian cell culture technology and a TPA producing mouse cell line from Genentech Inc (Milton, Conn.). DM Bergamo will make Montedison's TPA raw material and will receive royalties on Montedison's TPA sales. (Source: Chemical Week, 4 May 1988)

Japan

Japanese research has [illegible] focus

A new world of undersea biotechnology is the focus of a research programme planned by Japan's Ministry of International Trade and Industry (MITI). The project will inventory the 1,500 varieties of marine plants and animals including kelp, isolating useful chemicals and finding ways to produce them through genetic engineering.

The researchers will need to develop new technologies for cultivating cells in conditions similar to those under the sea. One goal is to study micro organisms that could clean up marine pollution and find ways to improve and cultivate them on an industrial scale.

MITI, a highly influential government department with responsibility for creating new industries and protecting declining sectors such as steel, has targeted biotechnology as a vital industry for Japan's future. The Ministry launched its biotechnology programme in 1978.

At least 15 Japanese companies have said they are interested in joining the marine projects which will be based at two centres in Japan at a cost of $70 million. Foreign participants are welcome, MITI said, but none has yet come forward. (Source: New Scientist, 21 July 1988)

The Netherlands

Mogen tests [illegible] of potato

The plant biotechnology firm Mogen International has been given the green light from the Dutch authorities to begin field tests with a genetically engineered potato. Mogen first originally been awarded the necessary Nuisance Act licence in April, but faced opposition from the environmentalist organization Stichting Natuur en Milieu. That appeal has now been rejected by the State Council of the Netherlands.

Mogen has developed a potato plant that is resistant to the potato virus X. The firm has incorporated the genetic blueprint for the virus coat protein into the potato. Greenhouse tests show that the potato is tolerant to the virus but the firm now plans to test the potato under field conditions. (Source: European Chemical News, 27 June 1988)

New Zealand

Biotechnology in New Zealand

The Crawthron Institute in New Zealand has set up a company called "Nelson Biotechnology" to help firms to maximize their success in launching into the biotechnology growth industry. In order to sell itself, the company is distributing leaflets to all biotechnology-related firms giving them suggestions for new products and markets. Examples of such applications are given, such as drugs used against coronary heart disease which are produced from fish processing wastes; thickeners are produced from dairy wastes; and brewing yields health foods and drugs.

The team of microbiologists, biochemists and chemists working in well equipped laboratories is currently engaged on fuel from horticultural and paper industry waste, new foods from flour milling waste, breakdown of toxic wood wastes and enzymes for food processing and medicine. A good example of waste as a medium is the growth of the highly priced, and therefore highly prized Shiitake mushroom growing on waste.

Contact: Dr. Henry Kaspar or Dr. Don Grant, Crawthron Institute, 98 Hastings Street, P Bag Nelson, New Zealand. Telephone: 82-819. (Source: International Industrial Biotechnology, February, 1988)

Peru

Germplasm bank saves Andean tubers

Three years ago Peru's National Programme on Andean Crops was formed, enabling Peruvian scientists to begin to study the requirements and characteristics of the native crops.

With the help of USAID, the US International Board for Plant Genetic Resources and Lima's International Potato Centre, Roland Estrada set up in 1981 an in vitro germplasm store for the three main Andean tubers - oca, ulluco and mashua - at San Marcos University in Lima. Estrada, head of the university's laboratory of genetic resources and biotechnology, acted in time. More and more farmers were being encouraged to displace native crops with wheat and barley. Coupled with this was the threat from political unrest. The University of Ayacucho, for example, lost 70 per cent of its collection of oca and ulluco varieties when terrorists took over the area and prevented scientists from reaching their field collections.

Each in vitro accession (distinct clone) of the oca species of plant that forms tubers. He has also set up accessions of ulluco and 119 of mashua. Estrada, who worked on tissue culture of potatoes at the International Potato Centre, has used chemicals developed to retard the growth of stored plantlets of other tubers. Mannitol, at a concentration of 4 per cent in the growth medium, stops oxidation of mashua plantlets taking up nutrients as fast as they would under normal conditions. This osmotic stress technique, however, does not work for oca. Estrada retards the growth of the oca plantlets by adding the plant dormancy hormone, abscisic acid, to the growth medium. He is now carrying out tests to find out whether such measures induce genetic variability in the crops.

Nick Galwey at the University of Cambridge is experimenting to see whether quinoa is a suitable crop for Britain. At the Institute of Horticulture at Littlehampton, Alan Brunt has been "cleaning up" the Andean tubers, freeing them of the many viruses that reduce their productivity. Brunt found that tubers sent to him from Peru were riddled with viruses. He has so far discovered and characterized three viruses previously unknown to science.

The virus-free material can then be safely exported to countries and grown in fields without danger of introducing new and potentially lethal viruses to existing crops. So far, Brunt has sent samples of Andean tubers back to Peru and Bolivia to be assessed in the field. He has also exported tubers to Papua New Guinea and Nepal but it is still too early to know how they are progressing. (Source: New Scientist, 2 June 1988)

Sri Lanka

Disease-free cassava developed

Sri Lankan agricultural scientists are working on a project to perfect a new technique which they have developed for the preservation of cassava germplasm.

The new technique when perfected would help them to conserve cassava germplasm in vitro and also to eliminate several diseases such as cassava bacterial blight African mosaic, super elongation and frog skin. These diseases can completely destroy a crop.

A senior scientist at the Central Agricultural Research Institute (CARI) in Peradeniya was quoted as saying that the meristem culture method can be used for maintenance of germplasm as the meristems are free from micro organisms. According to the researcher, meristems are endowed with a high propagation rate with phenotypic stability. The conventional mode of vegetative propagation often exposes the crop to a wide range of pests and diseases. One of the prominent advantages of the meristem culture technique is that it enables disease-free germplasm to be exchanged with other international research institutions for further research and evaluation.

In the mean time, Sri Lankan scientists have succeeded in developing thousands of pineapple plantlets from pieces of apical meristems. Research is also being conducted at the CARI to produce in vitro cultures for international exchange of potato germplasm. (Source: Agricultural Information Development Bulletin, Vol. 10, No. 1, March 1988)

Sweden

Production plant opens for monoclonal antibodies market

In the research village Ideon Lund, Sweden, Monoclarb will finish the construction work of the latest and most up to date plant for production of mammalian cells in Europe. The plant will mainly produce monoclonal antibodies for both diagnostic and therapeutic use. Since its start up in 1983, Monoclarb has developed a number of products which have been internationally recognized within the field of, for example, bloodgroup typing.

Monoclarb is concentrating its strength on cost effective, high quality bulk production of monoclonal antibodies, which are then packed and marked by the partner. Monoclonal antibodies are forecast to replace a lot of traditional products used for diagnostics today, and have also opened up a complete new field within drug treatment. The

world market for monoclonal antibodies is estimated to reach a level of $200-300 million by 1990. (Source: Manufacturing Chemist, May 1988)

United Kingdom

AFRC's grants for university molecular biology research

Research grants totalling over 2 million pounds sterling have been announced by the Agricultural and Food Research Council (AFRC). Forty grants were approved, with the largest individual grants going to the Royal Veterinary College (121,000 pounds sterling) for research on an increasingly widespread bacterial disease of pigs, and to the university of Edinburgh (118,000 pounds sterling) to identify genes controlling the response to selection for body size.

Four awards to university departments are for new Linked Research Groups, all in molecular biology. The Groups involve university departments working closely with an AFRC institute.

Details from: The University Support Unit, Agricultural and Food Research Council, 160 Great Portland Street, London W1N 6DT or on 01 580 6655. (Source: Biotechnology Bulletin, Vol. 7, No. 5, June 1988)

SERC calls for increased biotechnology spending

Britain needs to spend a good deal more on biotechnology research if it wants to be in a position to exploit some of the most important industrial and commercial opportunities of the twenty first century, according to a new report published by the Biotechnology Directorate of the Science and Engineering Research Council (SERC). The potential is indicated by the fact that the biological component of the UK economy is already worth 50 billion pounds sterling a year.

The SERC report contrasts the 6 million pounds sterling UK protein engineering programme announced last year with the US Government's spending of 40 million pounds sterling a year and Japanese plans to spend 100 million pounds sterling over six years. It also rejects the idea that the biotechnology interests and activities of all the research councils should be merged to produce a new "super directorate". Details, including free copies of SERC Biotechnology Support 1970-2000, from: SERC Biotechnology Directorate, Polaris House, North Star Avenue, Swindon SN2 1ET or on 0793 44000. (Source: Biotechnology Bulletin, Vol. 7, No. 5, June 1988)

Biotransformations LINK up

Chemical syntheses by living cells or biotransformations are to be the focus of the sixth LINK research programme, which was approved last month by the Department of Trade and Industry. The DTI will give 1 million pounds sterling towards the estimated 4 million pounds sterling cost of the programme over its first three years, provided another 2 million pounds sterling is raised from industry. The Science and Engineering Council will put in the remaining 1 million pounds sterling.

The first project to be funded is a collaborative effort by three universities: Kent, Exeter and Warwick. Scientists there will study the stability of biocatalysts (whole cells) particularly in organic or low water solvents, investigate redox reactions, and try to broaden the range of biocatalysts available, especially those that will form carbon-carbon bonds.

The programme's co-ordinator Peter Baker of the DTI's Laboratory of the Government Chemist, said the programme will have a big impact on biotransformations research in Britain, but added that it hinges on industrial interest. (Source: Manufacturing Chemist, 2 May 1988)

Government moves to chart the spread of AIDS

The British Government has decided against anonymous testing for infection with the human immunodeficiency virus (HIV), which causes AIDS. Instead, almost 100,000 pregnant women attending antenatal clinics will be asked to volunteer to have their blood tested.

If too many women refuse to have the test, however, it may force the Government to introduce anonymous testing of blood samples without the consent of the people concerned. Tony Newton, the Minister for Health, announcing the publication of the report of a working party on surveillance of HIV infection and AIDS, said last week that the group recognized that such "anonymized testing" might be required in future. He wants more debate on the issue, and asked for views by the end of August.

The working party chose pregnant women partly, because they provide blood samples routinely, in antenatal clinics. The rate of refusal, the group believes, would also be low because the result of the test has implications for the health of the mother and baby. Smith said that in Sweden, Norway and Finland, where there is voluntary testing of stored blood samples from pregnant women, 1 per cent or fewer refuse the test.

In Britain, people who do not want to know the result of their test will be offered the option of having their blood tested anonymously. It would then be impossible to trace the result back to them.

Doctors in east London have carried out a study of the prevalence of HIV infection in pregnant women, without seeking their permission. Raymond Heath, professor of virology at St. Bartholomew's Hospital, will soon publish the results of a survey of 1,500 blood samples taken from about 1,500 pregnant women who attended Homerton Hospital in east London between late 1987 and early 1988.

A spokesman for St. Bartholomew's said that initial analysis of the results suggests that four women, or 0.3 per cent, were infected with HIV. The health authority's ethical committee had approved the study on the grounds that the authority needed to know the prevalence of the virus in the general population in order to plan its services. (Source: New Scientist, 2 June 1988)

Biotechnology company shows profit

Celltech (Slough, UK) is emerging as an antibody engineering world leader, opening a new 6 million pounds sterling research centre and commissioning the world's largest mammalian cell culture fermenter. Celltech earned profits of 661,000 pounds sterling on 11.4 million pounds sterling turnover in the year ended 30 September 1987 against an operating loss of 1.8 million pounds sterling turnover of 7.6 million pounds sterling the previous year. The profit was the first Celltech has shown in seven years.

Celltech employs the unusual method of air lift fermentation wherein a gas purge furnishes aeration and agitation without moving parts or mechanical

seals. The gentler agitation thus provided has proved essential in handling shear-sensitive mammalian cells. Business spread includes contract production, sponsored drug development and contract R&D. Successful partnerships include production of erythropoietin for Ortho Pharmaceuticals, a subsidiary of Johnson & Johnson, and a project with American Cyanamid to increase the human gene content of monoclonal antibodies (MABs). Celltech is focusing on septic shock and cardiovascular and auto immune diseases. (Extracted from Process Engineering, May 1988)

Long term agreement to produce cholesterol lowering drugs

British Bio-Technology (BBL) has entered into a long term agreement to develop cholesterol lowering drugs with McNeil Pharmaceutical, a subsidiary of Johnson & Johnson. The agreement, signed in April, involves the joint development of new chemicals arising from BBL's research into improved cholesterol reducers.

BBL says it has been working on novel "second generation" synthetic inhibitors of the liver enzyme, HMG-CoA-Reductase. The enzyme is essential in the production of cholesterol. Other companies, including Merck, Sharp and Dohme, are already developing inhibitors of the enzyme but BBL says that because its drug will be totally computer-modelled and synthetic, it will have a cleaner side-effects profile than the competition and be easier to patent.

Under the agreement BBL will conduct the research, including chemical synthesis and pharmacological testing, while McNeil will carry out pre-clinical toxicology and clinical testing. BBL may also be involved in clinical tests.

BBL believes that HMG-CoA-reductase inhibitors will become a major class of drug in the future. It predicts that sales will be worth around four billion by the end of the century.

The company will continue to concentrate on large market areas such as heart drugs and asthma agents in line with its aim to become a major drugs firm. However, the first pharmaceuticals it will introduce will be for the niche veterinary market.

Earlier BBL signed agreements for the marketing of its range of synthetic genes in Japan, southern Europe, South America and Israel. The new deals follow the US institutional agreement signed early this year with Beckman Instruments.

First set up in May last year, British Bio-Technology Developments Group contributed a loss of £530,000 to turnover in the year to end April 1988. The company hopes the new contracts will "substantially" increase this figure.

Although it is the only commercial supplier of synthetic genes worldwide, British Bio-Technology, says it is difficult to estimate what the size of its new markets will be. After the US the company targeted Japan, with its growing biotechnology industry, as a potentially big market for genes. It plans to extend distribution of its products globally, with agreements in key regions currently under negotiation. (Extracted from European Chemical News, 25 July 1988 and 20 June 1988)

Hopes to revive UK rose oil industry

English Floral Fragrances (UK) is developing aromatic rose oils using biotechnology. The start up firm hopes to revive the UK rose oil industry, which died out in the 1700s. It extracts rose oil from flowers grown on a ten-acre site in Yorkshire, using a new low-boiling organic solvent under high pressure. The process retains the more volatile elements of the oil which can be lost with other extraction processes. EFF is now testing six rose varieties to see which produces the sweetest smell when grown in Yorkshire. It hopes to plant one million roses in 500 acres to start commercial production in the early 1990s. It will enter a world market now worth 65 million pounds sterling/year. EFF hopes to exploit the niche market for all-natural fragrance products, and will push its native English identity. (Extracted from The Financial Times, 1 July 1988)

Amersham International to lead EUREKA Labimap project

Amersham International is UK project leader for a major new European molecular biology development project which was granted EUREKA status at the sixth ministerial conference in Copenhagen on 16 June. The aim of the project, entitled Labimap 2001, is to automate the time-consuming, labour intensive molecular biology techniques used in biotechnology research. The potential market for these techniques, which also have applications in clinical diagnosis and industrial microbial processes, is estimated to be worth 1 billion pounds sterling. Labimap 2001 is expected to take about four years to complete, with a total budget of around 40 million pounds sterling.

The project is concerned with developing and marketing a series of compatible, automated instruments and associated new biochemical reagents for the range of molecular biology operations - including DNA extraction, cloning, hybridization and sequencing. Currently this laboratory work is mostly manual, repetitive and tedious, and involves skilled technicians. In automating and simplifying the procedures, there is also scope for speeding up many of the steps involved.

The initial feasibility phase of the project is expected to last 18 months, during which Amersham will work with the Imperial Cancer Research Fund (ICRF) in the UK, the French project leader Bertin & Cie, a high technology services company, and the other French participant, Centre d'Etude du Polymorphisme Humain (CEPH), a leading research institute based near Paris. (Source: Biotechnology Bulletin, Vol. 2, No. 6, Jul, 1988)

Study to focus on monoclonal antibodies

Chem Systems International plans to evaluate and compare the main types of commercial processes in use for producing monoclonal antibodies. The study reflects the growing number of commercial technologies stemming from the need for improvements in the quality and quantity of monoclonal antibody based products. According to Colin Le Quesne at Chem Systems' London office, who will co-ordinate the project, global sales amount to some $300 million annually for the 100 or so products now on the market. By 1990, sales might reach $2 billion. Collaborating in the study will be staff at the biologics division of the Centre for Applied Micro biology and Research at Porton Down, England, part of the UK's Public Health Laboratory Service. (Reprinted with permission from Chemical Engineering News, 4 July 1988. Copyright (1988) American Chemical Society)

Cyanamid to build research centre

A new research centre is to be built at Gosport, Hampshire, by Cyanamid (UK), the research based pharmaceutical, medical and chemicals company.

Cyanamid's Lederle pharmaceutical business already has the company's largest research centre outside the US, including a sterile development unit which has played a key role in the development of anti-cancer products, and the new 9 million pounds sterling centre will continue this work.

There will be a particular focus on the development of monoclonal antibody conjugates arising out of an existing joint venture with Celltech. The centre expected to be completed by early 1990. (Source: Biotechnology Bulletin, Vol. 7, No. 5, June 1988)

Biotechnology information at the British Library

The British Library Biotechnology Information Service, initially launched with the help of funds from the European Commission, provides a comprehensive service to industry and research worldwide. The service can provide information on research and development as well as information on the business aspects of biotechnology.

For the scientific researcher, the library carries a comprehensive range of journals and books relating to biotechnology. The Biotechnology Information Service, based at Holborn, has access to an international stock of scientific, technical and commercial information which includes 32,000 current journals, 19,300 books and pamphlets, 1,400 abstracting journals, 3,000 directories, 100 databases and 27 million patent specifications. The Aldwych reading room, 9 Kean St., London WC2B 4AT, houses the literature on the life sciences and technologies, medicine and biotechnology. Some of the stock is on open access but the main stock, on closed access, can be brought to the reader in a few minutes. The open access collections include reference books, abstracting journals and biographies, dictionaries and new books. The Holborn reading room, at 25 Southampton Buildings, Chancery Lane, London WC2A 1AW, carries patents and literature on the inventive sciences, engineering, industrial technology and business.

The researcher or reader who is interested in biotechnology business will find the business information sources in the British Library are mainly located at the Holborn branch of the Science Reference and Information Service. Publications held in this area include trade directories, business books and market research reports, business journals, trade journals, and publications dealing with company information including commercially produced loose-leaf and card services, and directories.

An Online Search Centre is available at the Holborn branch of the Library. The Centre deals with inquiries in all areas of science and technology as well as handling searches for business and Japanese information which are referred to other specialist services. The Japanese Information Service has a staff who are familiar with the language and who can help solve the problems encountered by the non-Japanese speaker when confronted with that language.

A search may be conducted of a wide range of existing databases, but the Biotechnology Information Service is developing its own database containing information on commercial and non commercial organizations. There will be facilities to pick a particular company and list all its known products. This database already contains information on European companies engaged in biotechnology and its development is planned for 1988.

There is a small initial charge of 15 pounds sterling to set up a search plus the usual charges for computer connect time and reference printing. The staff, experienced in searching, will help keep the cost of a search to a minimum. Searches can be arranged by visiting the library or by telephone, telex, fax, electronic mail or letter.

The Biotechnology Information Service also offers one-day seminars which aim to explain the many services offered by the British Library to the biotechnology industry and research community. The seminars give an overview of biotechnology and, then, go on to outline the main sources of scientific and business information including official publications, information from the culture collections and databanks, and on line information. Sources of information on patents are discussed and there is an introduction to the classification of patents in biotechnology.

The seminar is not restricted to the material held by the British Library and the services which they can offer, but deals with the complete spectrum of information sources from reference libraries, through industrial research clubs to personal contacts at conferences and workshops. Reference books, journals and databases which are leading sources of biotechnology information are listed as are other libraries which carry relevant information.

Other seminars which are available through the Science Reference and Information Service of the British Library include topics such as "Patent Information" and "Business Information". The latter includes online demonstrations and practical work.

The Biotechnology Information Service has a specialist staff with experience in the biotechnology industry which enables them to understand and help the inquirer. The Service, in conjunction with BioCommerce Data Ltd., publishes a monthly newsletter "Biotech Knowledge Sources" (BKS). BKS aims to alert
the reader to new information sources in biotechnology.

Further information and help can be obtained from: The British Library Biotechnology Information Service, 25 Southampton Buildings, London WC2A 1AW. Telephone: 01 323 7293. (Source: International Industrial Biotechnology, 8:2, March-April 1988)

UK trial for AIDS vaccine

Europe's first major clinical trial of a potential vaccine against human immunodeficiency virus will take place this summer at St. Stephen's hospital in London, where 24 uninfected low-risk volunteers will be tested to see if the vaccine produces any side effects and is able to induce antibody production.

The vaccine is a synthetic 30-amino acid peptide called hgp-30, that matches the p17 protein located just under the outer envelope of the AIDS virus. The vaccine was developed by Alpha 1 Biomedicals, which in a joint venture with the Cel-Sci Corp., called Viral Technologies, has licensed marketing rights to Japan's Nippon Zeon.

According to the chairman of Viral Technologies, Maximillian de Clara, a diagnostic kit based on the protein is to be developed with another company. Given that a sudden drop in antibodies to p17 in infected individuals is accompanied by onset of "frank" AIDS, de Clara suggested that hgp 30 may in the future find a role in stabilizing the disease. (Source: Manufacturing Chemist, 2 May 1988)

United States of America

Americans plan gene therapy on people

A team of scientists have asked the guardians of safe practice in genetic engineering in the US for permission to put an artificial gene into humans. The experiment, the first on humans to be presented to the Government's reviewers, is a "dry run", says its authors.

The procedure will not cure disease, but it will test the methods for inserting foreign genes into humans. It will also help to ease the controversial technique into practice slowly.

W. French Anderson, the principal author of the experiment, and the National Institutes of Health, which must review it, are trying to anticipate objections.

A subcommittee of the DNA committee recently decided to forward the proposal to the full committee for consideration in October. In the mean time, Anderson must ensure that his technique works on mice.

The new attempt is modest, says Anderson, chief of haematology at the National Heart, Lung and Blood Institute, a part of the NIH. The gene has no therapeutic value. It will serve simply as a marker in special cells that researchers have found to be effective against advanced cases of cancer.

The gene confers resistance to neomycin, an antibiotic. To enable human cells to accept the gene, Anderson "stitches" it to part of a mouse retrovirus called N2. The virus is harmless but can still establish itself in human cells.

The retrovirus will plant the gene in tumour infiltrating lymphocytes (TILs), white blood cells found in tumours. Steven Rosenberg, the head of surgery at the National Cancer Institute, extracts these cells from tumours and grows them in vitro.

Since 1986, Rosenberg has used TIL cells to help several patients unsuccessfully treated before. Some showed rapid remissions of cancers that were considered incurable.

Therapy with TIL cells does not always work, however, and the cells are difficult to trace once they are back in a patient. Radioactive labels sometimes "rub off" onto other cells or disintegrate before their carrier cells die.

Anderson's engineered gene would solve that problem, just as "tracer" genes have been introduced into genetically engineered agricultural products.

If human cells accept the tracer genes, Anderson may attempt next to splice genes for interleukin-2 (or other cancer fighting chemicals) with TIL cells. (Extracted from New Scientist, 4 August 1988)

US Japan R&D pact sets up joint efforts in science, technology

After a year and half of conflict and some acrimony, the US and Japan finally completed the intricate renewal of their bilateral science and technology exchange agreement.

The agreement lists the fields in which the two countries will co-operate, and it contains provisions to enable more American scientists to do research in Japan, but it also contains some national security and intellectual property clauses that could prove troublesome if pressed by federal agencies hostile to Japan's technological might.

The fields of joint research worked out - all highly relevant in a high-technology world - are biotechnology and other life sciences, information science and technology, manufacturing technology, automation and process control, global geosciences and environment, database development, and advanced materials including superconductors. The list can be modified when oversight groups think other areas should be included. The whole point is to get more American researchers into Japan's government and industrial laboratories and to make Japan contribute more to US technical development than it has in the past.

The policy elements in the agreement are at least as fascinating as the technical elements, and probably even more crucial in the long run. That is because the policy elements reflect accelerating tensions over economic competitiveness.

The new agreement renews one instigated and signed by President Carter and Prime Minister Masayoshi Ohira in 1980. The earlier agreement was to remain in effect for five years and was administered on the US side by OSTP.

Symbolically, though, the original agreement ranked high as the only technical pact between the two countries signed by the heads of State. However, the previous agreement bears almost no resemblance to the new one, which because of key, controversial language on intellectual property rights and guidelines on national security protection, is being seen as representing, first, a watershed in US-Japan technical relations, and, second, a device by which OSTP can claim control of US international science and technology policy.

At the moment, the research items are merely parts of a wish list. The projects do not yet exist and must either generate their own funding on the US side or absorb existing projects under separate agreements between US and Japanese science agencies.

Problems could arise with the Japanese over the national security and intellectual property aspects of the agreement. These provisions arose strictly out of concerns about loss of American know how by negotiators representing the Commerce Department, the Defense Department, the Office of the US Trade Representative, and OSTP. The State Department and NSF did not think they were necessary.

The intellectual property section naturally contains customary legalistic wording. In one case, it attempts to ensure that researchers who think they have discovered something patentable can keep their "business confidential information" protected from disclosure by other members of the joint team. The information can be revealed to others only when all the participants in the research project agree to its release.

Another intellectual property facet gives ownership of intellectual property rights to researchers who have made the major contribution to the discovery, subject to the differing patent laws of each country. (The US stands virtually alone in the world in giving patent rights to the first to invent. All other countries except the Philippines operate on a first to file system.) (Abstracted with permission from Chemical Engineering News, 25 July 1988. Copyright (1988) American Chemical Society)

Several small-scale Japan-US pacts already in place

Fields of research	Agency involved
Agricultural research	Department of Agriculture
Fire research, wind and seismic effects, telecommunications	National Bureau of Standards
Marine activities, geophysical studies, Landsat ground station	National Oceanographic and Atmospheric Administration
Water, air, solid waste, toxic substances, epidemiology	Environmental Protection Agency
Co-operation on major health problems of Asian countries, exchanges and vision research, exchanges and cancer research, problems of the aging, co-operation on indexing for biomedical information systems, co-operation on laboratory animal models, recombinant DNA, vaccine development, cardio-vascular disease toxicology	National Institutes of Health
Alcoholism and mental health	Alcoholism, Drug Abuse and Mental Health Administration
Consumer protection and regulation	Food and Drug Administration
Health statistics	Department of Health and Human Services
Geological sciences	Geological Survey
Exchange of information, provision of technical assistance for research and restoration of endangered species	Fish and Wildlife Service
Definition and design studies of Space Station, emergency landing site for the Shuttle, flight of the Spacelab-J microgravity mission and Payload Specialist on the Shuttle	National Aeronautics and Space Administration
Research reactor performance calculations, loss of coolant flow in fast breeder reactors, severe accident research, containment analysis, assessments on partial loss of coolant, radioactive waste management, information exchange	Nuclear Regulatory Commission
High-speed rail, aviation, urban mass transportation management/systems	Department of Transportation
Radioactive waste management, fusion, high-energy physics, large superconducting magnets, long-term effects of radiation exposure, research and development in energy	Department of Energy
Earthquake engineering, biotechnology, materials sciences, computer software, opto-electronics, photoconversion, photosynthesis	National Science Foundation
Biotechnology and other life sciences, information science and technology, manufacturing science and technology, automation and process control, global geosciences and environment, database development, advanced materials including superconductivity	Office of Science and Technology Policy

US biotechnology grows above estimates

Biotechnology has been developing faster in the US than expected. But, according to a report from the US Office of Technology Assessment (OTA), most funds are being used for health care while progress is lagging in the use of biotechnology in agriculture and waste disposal. US Government and industry spending in R&D tops $4.3 billion per year.

The OTA study reveals that 12 federal agencies are spending about $2.7 billion per year with the national institutes of health taking the lion's share with $2.3 billion. Yet despite the promise of biotechnology in the agriculture sector the US Department of Agriculture is spending only $84 million per year, about 1.4 per cent of its research budget. Similarly, waste disposal is also underfunded.

"In both fields," the study reveals, "technical barriers exist because of incomplete knowledge of basic processes involving plants, micro-organisms and microbial ecology." Using biotechnology to dispose of wastes is still largely experimental and is driven by regulation.

The OTA recommends that the environmental protection agency should increase its spending on biotechnology R&D. "The Federal Government needs to take a lead in such research because of the financial risk required to achieve progress in the field," says the report. (Source: European Chemical News, 25 July 1988)

Biotechnology's role in new drugs

Biotechnology remained prominently in the news when the Pharmaceutical Manufacturers Association sponsored a meeting in New York City related to drug development in the field.

Working with the Food and Drug Administration, PMA has identified and characterized 81 biotechnology- based products that have reached clinical trials in the USA.

In a study with the Patent and Trademark Office, PMA analysed 206 patents issued in 1987 covering all applications of the newer biotechnology. Of these, 96 per cent concerned pharmaceuticals and health-care products, suggesting enormous potential for medical applications in coming years. Also, 60 per cent of new biotechnology patents went to US organizations, reflecting American leadership.

Of the 81 products, 40 are related to cancer treatment, making cancer the most frequently targeted disease in biotechnological development. Moreover, the colony stimulating factors, interferons, interleukins, monoclonal antibodies and tumour necrosis factors among these represent diverse approaches to treat the same disease.

William Szkrybalo, director of PMA's bio technology programmes, commented that 52 per cent of the 206 biotechnology patents were for recombinant DNA techniques, 41 per cent for monoclonal anti bodies, and 7 per cent for DNA diagnostic probes. Breaking them down by intended use, Szkrybalo noted that 68 patents advanced genetic engineering technology generally, 20 were for vaccines, 52 for diagnostics, 37 for therapeutic agents, 15 for products such as monoclonal antibodies that could be used for both diagnostics or therapy, and se en miscellaneous. (Abstracted with permission from Chemical Engineering News, 18 July 1988. Copyright (1988) American Chemical Society)

Postal ban proposed on exchange of dangerous microbes

Responding to pressure brought by the Foundation on Economic Trends, the US Postal Service is proposing to ban sending disease causing microbial agents and toxins through the mail. The ban would mean that some 100 microbes that are now exchanged between research institutions under special packaging requirements will have to be sent by other means.

The Assistant Postmaster General announced the new policy at a Congressional hearing on the dangers of sending biological materials through the mail.

Rules set down by the US Department of Health & Human Services (HHS) currently require that virus containing microbes be placed into three successively larger containers along with enough packing material to absorb the culture if the vial should break. The outermost container must carry a universal biohazard symbol and a hotline number at the US Centers for Disease Control (CDC). The most dangerous microbes must be sent by registered mail so that the sender receives confirmation that the package was arrived safely. The Department of Trans portation also has authority over the interstate shipping of hazardous cultures of over 50 ml.

The ban proposed by the postal service would cover the specific list compiled by HHS of some 100 microbes that are known to cause human disease. Some are responsible for dreaded diseases such as Ebola fever or plague, but others are routinely exchanged in many areas of scientific research. All species of mycoplasma and mycobacteria are on the list, as are hepatitis and herpes viruses, simian virus 40, and all serotypes of Escherichia coli which can cause intestinal disorders.

The CDC and the American Type Culture Collection (ATCC), the US repository for all isolated microbial strains and genetic material, are the two most frequent mailers of biologically hazardous materials.

The CDC report that no problems have been encountered with the current policy governing the shipment of disease-causing microbes. The CDC hotline averages only 50 calls per year reporting damaged packages with biohazard labels, and only three per year turn out to be actually leaking. No one has so far developed disease from a leaking package.

But what most concerns Congress is that no federal agency now monitors whether or not the packaging rules for disease causing microbes are being followed regularly. (Source: Nature, Vol. 333, 30 June 1988)

EPA backed field trials of potato biopesticide begin in US

Ecogen Inc. has begun large scale field trials of a genetically altered "bifunctional" bioinsecti cide on potatoes, under an experimental use permit recently granted by the US Environmental Protection Agency (EPA). In its first year of small-scale field tests, the product (trade named Foil), which incorporates a novel strain of the bacterium Bacilius thuringiensis, proved to be active against both beetle and caterpillar pests of potato plants.

The large scale field trials will evaluate Foil on 17 plots in Oregon, Washington, North Dakota, Pennsylvania, Delaware, Maine, Virginia and Massachusetts. In the trials, the product will be used against the Colorado potato beetle, the European corn borer and the cabbage looper. Ecogen estimates that the annual US market for potato insecticides directed against the Colorado potato beetle is worth $10 $15 million. (Source: Biotechnology Bulletin, Vol. 7, No. 6, July 1988)

USDA licenses five field tests

The US Department of Agriculture's Animal and Plant Health Inspection Service (APHIS) recently issued five permits to allow field testing of genetically engineered tomato and tobacco plants two each to Monsanto Agricultural Co. and Agrigenetics Advanced Science Co., Madison, Wis., and one to Sandoz Crop Production Corp., Des Plaines, Ill.

The Sandoz firm will field test genetically engineered tobacco plants designed to resist leaf eating caterpillars such as the tobacco budworm in Cleveland County, N.C. If successful, this could reduce the use of chemical pesticides.

Using genetic engineering techniques, a naturally occurring protein is introduced into the tobacco leaf. The protein, which is not toxic to humans, wild or domestic birds, fish or mammals or most other insects, will kill leaf eating, caterpillars and similar pests which eat the treated plant.

Monsanto and Agrigenetics will field test genetically engineered tomato plants in Columbia County, Wis., and Jersey County, Ill., similarly designed to resist leaf eating caterpillars such as the tobacco hornworm, the beet armyworm and the tomato fruitworm.

Monsanto will also field test in Jersey County genetically engineered tomato plants designed to tolerate the herbicide glyphosate, which degrades rapidly in the field and is less toxic to animals than many other herbicides commonly used.

Agrigenetics will conduct a field test of genetically engineered tobacco plants, also in Columbia County, designed to resist the alfalfa mosaic virus, an organism that stunts plants and reduces yields. In this procedure, a gene is introduced into a tobacco chromosome telling it to produce the coat protein, a harmless part of the alfalfa mosaic virus.

APHIS' environmental impact assessments concluded the trials are safe and will not have a significant impact on the environment. The assessments included reviewing the companies' genetic-engineering methodologies and determining if the new genes or their products have any harmful plant characteristics. (Source: Chemical Marketing Reporter, 4 July 1988)

ABC update

Founded in 1983 by nine member firms, the US Association of Biotechnology Companies (ABC) has grown 18-fold in membership in five years. Today, ABC represents 166 biotechnology companies, with members from 12 countries. The Association has recently expanded its membership to include a Council of State Biotechnology Centres, which is being organized by Mark Titner, director of the North Carolina Biotechnology Centre. Details from: Association of Biotechnology Companies, 1120 Vermont Avenue, NW, Suite 601, Washington, DC 20005, USA or tel. +1 (202) 842 2229. (Source: Biotechnology Bulletin, Vol. 7, No. 6, July 1988)

Release regulators refining their roles

The smooth operation of the Environmental Protection Agency (EPA) is essential for all groups seeking US approval of experiments to deliberately release genetically engineered micro-organisms. At its May meeting, EPA's Biotechnology Science Advisory Committee (BSAC) examined how efficient the agency's review process has become and considered how it might be refined further.

One past stumbling block in the review process - namely the need for co-operation between federal agencies - apparently is being overcome, according to BSAC member James Tiedje from Michigan State University (East Lansing, MI).

BSAC is now contemplating whether larger scale tests will require special review procedures. There are four critical "categories of difference" between small and large scale deliberate release tests, according to BSAC member Douglas Rouse from the University of Wisconsin (Madison): the persistence of microbes; their dissemination; the greater possibility of horizontal gene transfer; and the potentially increased scope of health, environmental, and financial consequences of a test.

Perhaps the most difficult issue before BSAC - one that is still far from being resolved - is how EPA should evaluate claims by companies that information they submit must be kept confidential. Currently, BSAC members are divided on this issue cognizant that some claims for confidentiality are essential but uncertain where the threshold ought to be set.

A proposal now before BSAC would attempt to make as much information public as possible, and would make this decision as early in a product's development as possible. (Extracted from Bio Technology, Vol. 6, July 1988)

OTA foresees quicker handling of biotechnology field tests

Although urging continued caution in approving environmental releases of genetically engineered organisms, the Congressional Office of Technology Assessment (OTA) supports "streamlined review" of field tests when experience shows they are likely to pose little risk to human health or the environment. "There are reasons to be cautious, but there is no cause for alarm," OTA noted in a 152 page report. Uncertainties still exist on gene spliced microbes' migration and effect on the ecology, the report says. But widespread problems "do not now seem likely," it says, and small scale field tests may be the only way to resolve the uncertainties. The report also concludes that since more experience is gained, streamlined review may be possible for several categories of organisms, such as "an organism substantially identical to one that has already been reviewed and approved for field testing; organisms not containing any genetic material from a potential pathogen; or organisms whose DNA contains nothing new but marker sequences in noncoding regions." (Source: Chemical Week, 11 May 1988)

New molecular modelling laboratory

The University of North Carolina, Chapel Hill, has established a teaching and research laboratory for molecular modeling. It is an unusual, if not unique, facility for a US campus. It brings together in one place a wide range of state of the art modeling software and hardware and provides a centre for an equally diverse graduate level course, for continuing education and for short courses.

The new laboratory is the brainchild of J. Phillip Bowen, assistant professor in the division of medicinal chemistry and natural products of UNC's school of pharmacy, and Tom J. Major, dean of the school of pharmacy. It is a campus wide, interdisciplinary effort among several UNC departments and centres. It also involves co-operation with the private sector and with several nearby institutions.

Located in the school of pharmacy, the new laboratory will also be used by the Biological Sciences Research Centre of the UNC school of medicine. Researchers at the centre study the development of the brain and nervous system. (Abstracted with permission from "Chem. & Engineering News, 6 May 1988. Copyright (1988) American Chemical Society)

MBI receives major grant from the W.K. Kellogg Foundation

The W.K. Kellogg Foundation of Battle Creek has awarded a three year, $10 million grant to the Michigan Biotechnology Institute (MBI) for expansion of the Institute's biotechnology research programmes to develop new, large scale processes that use renewable agricultural and natural resources to manufacture a diversity of industrial products.

The grant will help improve Michigan's economy and create jobs by providing opportunities for the development of new biotechnology based businesses through the commercialization of MSI technology. MBI is a non profit corporation founded in 1981 as a state and national resource to develop industrial applications of biotechnology using natural and renewable resources. The Institute works with universities and industry, developing technology to the economically proven, scale-up stage for transfer to industry for commercialization.

The new industry will manufacture corn products for cereals and other food uses as well as non-food products such as speciality and bulk chemicals used in the manufacture of products such as biodegradable road de icers, solvents, composite plastics, polyesters, nylon and food ingredients. (Extracted from News Release, Summer 1988)

New AIDS institute

Harvard University has announced plans for a university-wide institute to "expand and accelerate AIDS research".

Virologist Myron Essex, currently head of the Department of Cancer Biology at the Harvard School of Public Health, will head the new institute. He will be joined by senior Harvard investigators including William Haseltine, Martin Hirsch and Jerome Groopman.

Essex stressed that an important overall objective of the AIDS Institute is to involve more than just experts in virology and immunology. In addition to biological and clinical studies, research centres will be established in epidemiology, policy and education, and international co-operation. At least 70 Harvard faculty members are expected to participate in the institute.

One aspect of the new institute is the desire to help attract more funding from the government, foundations and industry for AIDS research. (Source: Nature, vol. 333, 19 May, 1988)

Development of cultural marine algae products

American Cyanamid (Wayne, NJ) will jointly develop products from cultured marine algae with Cyanotech (Kailua Kona, HI). The two year agreement utilizes Cyanotech's marine algae for nutritional compounds for use in pharmaceutical, veterinary and agricultural applications. Cyanamid ventures will use its expertise in small scale fermentation and Cyanamid Agri-Research, and retain the rights to products by bioactive substance screening. Cyanamid has world wide marketing rights to any jointly developed products. (Extracted from Chemical Week, 29 June 1988)

[illegible] Network for Agrotechnology Transfer

The United States Agency for International Development has funded the International Benchmark Sites Network for Agrotechnology Transfer (IBSNAT); the project is operated by the Department of Agronomy and Soil Science of the University of Hawaii in Honolulu.

The goal of the IBSNAT project is to provide agricultural development agencies with the means to overcome bottlenecks that currently prevent the timely integration of new or alternative crops, cultivars, products, and practices into existing farming systems that would render them more productive, stable, sustainable, and equitable for the resource poor farmers of the developing world.

The IBSNAT project will develop a methodology for the transfer of agro production technology that combines elements of transfer by analogy with systems analysis and simulations that result in desired outcomes.

By combining soil, crop, weather and farm management data bases with simulation models and an expert system, IBSNAT is developing a decision-support system that will allow government agencies to undertake long-term strategic planning and farmers to make day-to-day tactical decisions.

This systems-based approach emphasizes interdisciplinary team work; understanding gained from the physical, biological, social and economic disciplines is needed for efficient and effective agro-technology transfer.

The objectives of the IBSNAT project are to:

- Accelerate the flow of agro technology from its site of origin to new locations;
- Maximize the successes and minimize the risks associated with the transfer of agricultural technology; and
- Assess the long term effects of agricultural practices on the agro-ecosystem.

For more information, write to the University of Hawaii, 2500 Dole Street, Krauss Hall 22, Honolulu, Hawaii 96822. (Source: Agricultural Information Development Bulletin, Vol. 10, No. 1, March 1988)

Union of Soviet Socialist Republics

Device for cell fusion and electrical [illegible]

Soviet scientists have created a device which can "weld" the cells of tissues without disturbing their vital activity. This was reported at the Electrochemistry Institute of the USSR Academy of Sciences. The device, the size of a small television set, produces electric impulses by which the cells are processed. Specialists have used the cells of plants and animals in experiments. It turned out that the most convenient and promising subject of research were bacteria. The device can unite two bacteria with totally different properties, one without disturbing the vitally important processes taking place in them. Within a short period of time such a double cell divides, but the newly formed daughter cells are, as a rule, unlike their "parents" in their properties. Specialists used this circumstance to obtain completely new bacterial cells with properties set in advance. The hope to use them for medical purposes, for producing, for example, proteins, amino acids and other compounds which are used in medicine, agriculture and the chemical industry, and for cleansing sewage. The device can not only "weld" cells but also pierce small orifices in their membranes, through which, according to the wishes of the experimenter, the most diverse substances can be introduced, in particular, stimulators. (Source: TASS, on January 1988)

Cellular engineering at Ukrainian botanical institute

Cellular engineering, which involves the transplantation of the genes of one cell into another, is being conducted in the department of

cytophysiology and cellular engineering of the UkSSR Academy of Science Institute of Botany in Kiev. Yuriy Yuryevich Gleba, the first person in the Soviet Union to produce cellular hybrids capable of producing offspring, is directing the work. Gleba's work has included far-ranging experimentation, such as the crossing of tobacco cells with human cells. Researchers have thus far produced a potato-tomato hybrid, as well as hybrids such as jimsonweed-henbane, goutweed-carrot, and even soybean-blue tobacco. Few, if any, however, have been brought to the stage of a fully fledged fruit-bearing plant, a flowering plant, or even a rooted plant. The cellular engineers hope to cross rye with tundra moss. One of the most promising areas of cellular engineering is the hybridization of domesticated species of plants and wild species. A recent success recorded at the institute was the joining of wheat protoplasts. (Extracted from Sotsialisticheskaya Industriya, 6 March 1988)

Roche forms Soviet test kit joint venture

Hoffman-La Roche has signed a deal with NPO Biotechnologica, the Soviet Ministry for Medical and Microbiological Industries' firm, to establish a joint venture to produce medical diagnostic test kits in the Soviet Union. The new venture, Diaplus, will be capitalized at SFr 10 million and Roubles 500,000 with Roche holding 40 per cent.

Diaplus will start operations in early 1989 by marketing kits produced in Switzerland. It will later build kits and eventually manufacture all components at a plant in Moscow by early 1994. The kits will be produced for the Soviet and other selected markets. This deal represents Roche's first joint venture agreement with the Soviets. (Source: European Chemical News, 25 July 1988)

C. RESEARCH

Research on human genes

Retinoblastoma gene linked to new malignancies

Retinoblastoma gene loss may contribute to the development of breast cancer and small-cell lung cancer in addition to the relatively rare retinoblastomas.

A few years ago, researchers learned that retinoblastomas, highly malignant tumours that arise in the retina of the eye, are caused by the loss or inactivation of a particular gene, known as the retinoblastoma (RB) gene. More recent research suggests that RB gene inactivation may also contribute to the development of two additional types of cancer, namely breast cancer and small-cell lung cancer, that occur much more frequently than the uncommon retinoblastomas.

The new results may eventually have implications for treating breast cancer and small cell lung cancer, and also for predicting who will get the malignancies. Moreover, the RB gene studies are providing a better understanding not just of carcinogenesis, but of normal cell growth as well.

In particular, they lend further credence to the view that growth inhibitory forces may be just as important to the life of the cell as growth stimulatory forces. The assumption is that the protein encoded by the RB gene normally suppresses cell division. Its loss then causes retinal cells to grow out of control and become cancerous.

One reason why cancer researchers find the RB gene so interesting is that its inactivation may be an early, perhaps even an initiating, event in carcinogenesis. This appears to be the case for retinoblastoma at least.

About half of retinoblastoma patients have an inheritable form of the tumour in which they acquired one bad or deleted copy of the RB gene from their mother's egg or father's sperm. This almost guarantees that retinoblastoma will develop. Some 90 per cent of these individuals get the eye cancer at an early age, usually before they are 3 years old. Another mutation to knock out the second copy of the gene in retinal cells is also required, but this is apparently a frequent event.

Researchers began looking at the RB gene in breast cancer cells partly because of observations about the inheritance patterns of the malignancy. Over the past several years, improved therapies have greatly increased the survival rate of the retinoblastoma patients, and clinicians began to find that children who had been successfully treated for the inheritable form of the disease developed other types of cancer, especially sarcomas such as osteosarcoma (a bone cancer), at higher than expected rates.

Moreover, clinicians are seeing more cases of breast cancer in the survivors of inheritable retinoblastoma, although it is too early to tell whether this represents a true increase in the incidence of the disease in the group. The mothers of children with osteosarcoma do have an increased risk of developing breast cancer, however.

These observations suggested that the same RB gene defect that confers susceptibility to retinoblastoma might increase susceptibilities to the other cancers as well. This was soon confirmed for osteosarcoma. In retinoblastoma cells, both copies of the RB gene are either deleted or so badly rearranged that they cannot be functional. The same thing was happening to the gene in osteosarcoma cells.

Two groups have now shown that comparable RB gene abnormalities occur in breast cancer cells. Eva Lee, Wen Hwa Lee and their colleagues at the University of California School of Medicine in San Diego describe results showing that two of nine lines of breast cancer cells have the abnormalities and also fail to make detectable RB protein. In addition, Yuen Kai Fung of the University of Southern California School of Medicine and his colleagues have found RB gene deletions or other abnormalities in 5 of 16 lines of breast cancer cells.

Moreover, the researchers are finding the RB gene defects in at least a small per centage of primary breast cancers.

Small cell lung cancer, unlike retinoblastoma or breast cancer, does not appear to have a hereditary component, but is associated with heavy cigarette smoking. Nevertheless, William Harbour, a bone Minna, Frederic Kaye and their colleagues at the National Cancer Institute - Navy Medical Oncology Branch have found RB gene abnormalities, comparable to those in retinoblastoma, in about 70 per cent of the small cell lines that they examined. The researchers also found the defects in one of eight primary small cell lung cancers and in cells derived from a related lung tumour, known as pulmonary carcinoid.

They may not have detected all the mutations that inactivate the RB gene in small cell and pulmonary carcinoid lines, however. Measurements

the messenger RNA transcribed from the gene indicated that its expression is greatly reduced or shut off completely in about 80 per cent of the cell lines. Harbour and his colleagues speculate that the RB gene, which is very large - about 200 kilobases - may be especially susceptible to mutation by the chemical carcinogens in tobacco smoke.

The loss of a functional RB gene is apparently sufficient to put retinal cells on the path to cancerous transformation, although additional genetic mishaps may be required for progression to full malignancy. If RB gene inactivation is also the first step toward producing breast and small cell lung cancer, then it might be possible to treat the malignancies by replacing the lost gene and restoring normal growth control. Attainment of that goal is far in the future, however. A more readily achievable clinical application of the work on the RB gene might be the identification of women who are at high risk of getting breast cancer.

Studies of retinoblastoma are relevant to uninherited cancers, too. Two fifths of the victims of retinoblastoma have inherited a predisposition to it in the form of a faulty retinoblastoma (RB) gene.

The tumours attack when a victim cannot produce the protein described by the RB gene. So the RB gene actually prevents the cancer - a prime example of a tumour suppressor gene.

Every cell contains two copies of each gene, one from each parent. One suppressor gene can produce enough protein to suppress tumourous growth; so for retinoblastoma to strike, both copies of the RB gene must be damaged. Dr. Alfred Knudsen, of the Fox Chase Cancer Centre in Philadelphia, proposes that those inheriting the predisposition start out with one bad RB gene in each cell. If any cell then loses its spare copy of the gene, the cancer can start. When there is no predisposition, the probability that a single healthy cell will lose both its copies of the RB gene is low; so non-inherited retinoblastoma is rare.

The RB gene is the only suppressor gene to have been copied and studied in a laboratory. Dr. Robert Weinberg of the Massachusetts Institute of Technology, whose laboratory made the first RB genes, has found a chemical link between the suppressor gene and an oncogene. He used oncogenes found in a cancer causing virus, called adenovirus, which contain a recipe for a protein called E1A. This protein can bind itself to the protein described by the RB gene; that stops the RB gene from working. His results open up the possibility that some oncogenes do their damage by interfering with the function of tumour suppressor genes.

Will any of this enlightenment on the causes of cancer lead to a cure? Possibly, but not for some time. Dr. Weinberg suggests that suppressor genes could be restored to tumour cells to halt their growth. But putting genes into a cell will be difficult for decades to come. And if some cells are missed, they will go on producing more malignant cells. Dr. Knudsen speculates about a far off day when tumour cells can be attacked by a tailor made virus, designed to infect them with healthy tumour suppressor genes. The emphasis would be on reforming tumours, not destroying them.

The bad news is that some genes can cause cancer. The good news is that other genes can stop it. In the 1970s some genes were found which were responsible for the unruly growth of cells in tumours. Like all genes, they contained recipes for making proteins. These particular proteins were messages that told cells to grow. More recently scientists have discovered genes that tell cells not to grow. Damage to these genes can cause cancer, too; but when they are working properly, they guard against it.

The genes that make cancers grow - oncogenes - are not born evil. They are good genes gone bad. They start out as useful genes, making proteins that encourage cells to grow and divide when they are young, or when they need to. But when they are damaged they become hyperactive, making the cells grow aimlessly and relentlessly.

Researchers in the US, however, have recently reported the first indication of a direct link between oncogenes and tumour suppressor genes. DNA viruses that bear oncogenes may bind to and inactivate the product of the retinoblastoma gene. Two proteins from an adenovirus and SV40 virus bind to the retinoblastoma protein, and presumably interfere with its normal function.

Peter Whyte, working with Ed Harlow and colleagues at Cold Spring Harbor Laboratory, in New York State, identified a particular region of a protein (called E1A) from an adenovirus that seems to drive cells to divide. Without this region, the E1A protein cannot bind to the retinoblastoma product. Elizabeth Moran, also at Cold Spring Harbor, showed that a mutated E1A protein without this region regains its ability to turn a cell cancerous once you transplant a similar region from a protein of the SV40 virus, known as the large T antigen.

Understanding the growth and division of a cell may eventually lead to effective therapies for cancer.

Bernard Mechler at the University of Mainz in the Federal Republic of Germany has already shown that the technique works in fruit flies. He and his colleagues have isolated a tumour suppressor gene, the absence of which disrupts development in Drosophila and produces lethal brain tumours. When it is introduced back into mutants lacking the gene, the flies develop normally.

Weinberg, among others, is now attempting to see if this approach will work in the laboratory, causing tumour cells to revert to normal. Eric Stanbridge, of the University of California at Irvine, has already shown that cancerous retino blastoma cells can be rescued by adding the chromosome bearing the missing gene, but such cells are unstable and often lose the additional chromosome. Weinberg hopes to add just the retinoblastoma gene. (Extracted from Science, Vol. 241, 15 July 1988, The Economist, 30 July 1988 and New Scientist, 28 July 1988)

Progress in predicting breast cancer relapses

The understanding gleaned over the past several years of the gene changes that underlie cancer development is beginning to lead to new strategies for predicting the prognosis of breast cancer patients. Researchers have identified specific gene abnormalities that appear to be correlated with an increased risk of the cancer reoccurring after the primary tumour is removed surgically. If further clinical investigations bear out the promising pre liminary results, the outcome could be more accurate tests for determining breast cancer prognoses.

The need for such tests is great, and there is currently no sure way of telling who will experience a recurrence of the cancer and should thus receive preventive treatment with chemotherapeutic drugs.

In the past, the decision to give a woman chemotherapy was usually based on a finding that the cancer had already spread to her underarm lymph nodes at the time the original tumour was removed. Women with negative nodes did not generally receive chemotherapy. But lymph node status is an imperfect indicator of breast cancer prognosis. Although about 70 per cent of the women whose nodes show no signs of cancer metastatis will remain free of the disease for at least 5 years without further treatment, the other 30 per cent will have a recurrence.

In fact, in May of this year the US National Cancer Institute (NCI) recommended that women with negative nodes be given drug or hormonal therapy after all. The decision was based on as yet unpublished studies showing that such treatments could lower the breast cancer recurrence rate in the women.

Nevertheless, the drugs used for cancer chemotherapy have unpleasant or dangerous side effects. The best approach would be to devise more accurate ways of identifying women who will experience metastasis so that the others could be spared the chemotherapy.

Robert Callahan of NCI described his group's identification of two separate genetic abnormalities in breast cancer cells that may be associated with a poor prognosis. The work was done in collaboration with Rosette Lidereau of the Centre Rene Huguenin in St. Cloud, France, and Iqbal Ali, also of NCI.

One of the abnormalities the researchers identified is an amplification of the int 2 oncogene. The protein encoded by the int-2 gene presumably acts positively to foster the development of malignant tumours, possibly stimulating cell division and the blood vessel formation needed for the growth of solid tumours.

A growing body of evidence suggests that loss of tumour-suppressing genes can also contribute to tumour growth and malignancy. The second genetic alteration that the Callahan group has linked to poor breast cancer prognosis, a deletion of a region of chromosome 11, may involve the loss of such a suppressor gene. In any event, a study of some 150 breast cancer patients at the Centre Rene Huguenin has shown that cancer recurred more frequently in women whose tumour cells had one or the other of the two abnormalities than in women whose tumour cells did not have either.

Patricia Steeg and her colleagues at NCI have recently identified a gene, which they call NM23 that appears to suppress the metastatic potential of cancer cells. A pilot study of 25 breast cancer patients suggests that lack of expression of this candidate suppressor gene may be associated with a poor prognosis. Expression of the gene was low in the primary tumours of all of the 16 women with four or more positive nodes. It was high in the tumours of six of the nine women with three or fewer positive nodes, but low in the other three.

The function of the NM23 gene is unknown. Determination of its nucleotide sequence did not reveal any similarities to other genes. Steeg is currently mapping the chromosomal location of the gene. It would be interesting if it turned out to be located in the deleted region on chromosome 11 that was identified by the Callahan group.

George Martin at the National Institute of Dental Research has also isolated receptors on metastatic cells that bind to laminin a glycoprotein in the basement membrane that is supposed to keep cells in one place.

Researchers at the National Institute of Health at Georgetown University, in Washington DC, have made antibodies that attach to the laminin receptors on tumour cells and to an enzyme known as type IV collagenase. Antibodies to laminin could prevent adhesion by tumour cells or carry toxic chemicals directly to the cancerous cells. Martin has been able to synthesize peptides that may block adhesion.

Researchers at Bethesda are testing these strategies in animals to stop, or at least slow, metastasis. Tests on humans are at least two years away, but the research bears hope for identifying the disease earlier.

Dr. Lance Liotta of the National Cancer Institute in Bethesda, Maryland, has shown that some genes known as ras oncogenes trigger the production of several enzymes and other proteins that let tumour cells invade other parts of the body. For example, ras oncogenes contain the coded recipe for enzymes that can break down tissue. Metastatic cells get into the blood because these enzymes eat into the layers of tissue and outer membranes of blood capillaries that stand in their way. Tumour cells then move from the bloodstream to invade a new organ and form a secondary cancer.

Scientists at the State University of New York at Stony Brook have found a molecule on the surface of tumour cells known as plasminogen activator that may play a role in destroying tissue. Man-made antibodies that interfere with plasminogen activator can block metastasis in chicken embryos.

Metastatic cells restructure their own skeletons so that they can move around more easily. Dr. Liotta has shown that in the cells that cause breast cancer in women, ras oncogenes stimulate the production of a protein called autocrine motility factor (AMF). This lets the cell form protrusions known as pseudopods (false feet) which help it move. One American pharmaceutical company, Merck, has developed a drug that blocks the action of AMF.

One recent discovery about metastatic cells which has particularly excited researchers is how they loosen themselves from the main body of tumour cells. A number of proteins, such as fibronectin, may be involved in triggering changes in the adhesive properties of tumour cells. Fibronectin is found all over the body, particularly between tissues and blood capillaries. Its normal function is to help control the organization of muscle and other tissues in growing embryos. Suspiciously, Rous sarcoma virus, which causes tumours, stimulates the production of fibronectin receptors on the surfaces of infected chicken cells.

Dr. Martin Humphries at the US National Institute of Health and some colleagues have made a peptide a short chain of protein dubbed GRGDS that can inhibit the activity of fibronectin. Mice injected with melanoma cells died within six weeks. Luckier mice injected with melanoma cells and GRGDS were still alive after 15 months. However, the peptide was unable to overcome injections of large numbers of tumour cells. Dr. Humphries and his team are now trying to synthesize more powerful chemical substitutes for GRGDS that could serve as a drug. (Extracted from Science, Vol. 241, 29 July 1988, New Scientist, 28 July 1988 and The Economist, 14 May 1988)

CIF may transform cancer cells

A naturally occurring compound may transform cancer cells back into normal cells, according to dermatologist G. Lipkin of New York University (New York, NY). Contact inhibitory factor (CIF) apparently helps the cancer cells respond to normal growth regulators. Normal cells stop growing when they contact other cells, but cancer cells do not. Normal cells require some blood serum in the growth medium, but cancer cells do not. Normal cells cannot grow in suspension, but cancer cells can. CIF protected hamsters from injected cancer cells that killed unprotected hamsters. A next step will be to identify the structure of CIF. (Extracted from Science News, 28 May 1988)

Drugs to inhibit cancer cell reproduction

DNA topoisomerases might be inhibited by a class of drugs that would halt cancer cell reproduction, according to W.E. Ross of the University of Florida (Gainesville). The DNA topoisomerases are needed to alter the structure of DNA to allow synthesis of new RNA and DNA. The inhibitors bind to the DNA and then entrap the topoisomerases. An existing drug called camptothecin works by inhibiting topoisomerase I. A modified form of the drug has been effective against leukaemia and some solid tumours in mice with manageable toxicity. (Extracted from Science News, 4 June 1988)

Survival of high cancer cells

Researchers have provided new clues to why some cancer cells are up to 100 times more resistant than others to a spectrum of anti-cancer drugs. Figuring out the exact biochemistry behind drug tolerance could lead to new strategies for overcoming originally early cancer cells.

Scientists at the Joint Centre for Radiation Therapy at Harvard Medical School in Boston have illustrated in vitro a set of tactics used by these tumour cells: a metabolic pathway known as the glutathione redox cycle, which diminishes a drug's ability to kill the cell. They say two drug resistant, malignant cell lines became three to four times more sensitive to a common cancer drug, adriamycin, after being treated with an inhibitor called buthionine sulfoximine that blocks the glutathione redox cycle. Although other scientists have suggested the redox cycle is involved in drug resistance, this has not been demonstrated previously.

In similar tests the same cell lines became five to 10 times more sensitive to adriamycin when exposed to verapamil, a compound that binds to and closes off the protein pump.

Then the researchers tested the cells' resistance when both the protein pump and the redox cycle were blocked. When they combined the two it completely restored the sensitivity to the drugs. They also saw this reaction in cell cancer cell lines that were genetically drug resistant but had never been exposed to chemotherapy.

Clinical trials of buthionine sulfoximine in combination with chemotherapy will probably begin later this year. (Source: Science News, Vol. 134, 6 August 1988)

Antibody produced as leukaemia treatment

A superantibody to fight cancer cells has been developed by researchers at the UK's Medical Research Council and the University of Cambridge. The superantibody is created by attaching part of a rat antibody to a human antibody, to create a hybrid. The technique has already been licensed to Celltech, Wellcome, Scotgen, Unilever and Behring (FRG). The rat antibodies are collected from rats that have been injected with human white blood cells. The DNA for the hypervariable region of the rat antibody is then connected to the DNA that codes for human IgG antibody. The DNA is then used to produce the hybrid antibody, which will destroy all white blood cells with the given antigen. This may be an effective treatment for leukaemia. The hybrid antibodies are especially useful because they can be used repeatedly, without themselves being attacked by the immune system. (Extracted from New Scientist, 31 March 1988)

Anti-sense DNA as cancer cell block

Some cancer researchers are focusing on genes that cause cancer cells to replicate and grow rapidly. Synthetic substances such as anti-sense DNA appear to be very promising in preventing uncontrolled growth, although clinical use is still far off. Anti sense DNA could also be used to block genes that make cancer cells resistant to chemotherapeutic drugs and to block viral genes. Several researchers are investigating to determine whether anti sense DNA can stop the AIDS virus from duplicating. Anti sense DNA indirectly blocks the activity of genes by interfering with the function of the messenger RNA, which directs the formation of cellular protein. Anti-sense DNA matches a portion of the messenger RNA and attaches itself to RNA to prevent the cancer cell from producing a growth promoting protein, which causes cancer cells to divide too quickly. Johns Hopkins University researchers have developed a technique for chemically modifying anti sense DNA fragments so that they are not degraded after they enter the cell.

Scientists at the National Cancer Institute and the University of S. Florida have stopped myc, a cancer causing gene, from becoming overactive in [illegible] stimulated. When anti sense DNA is added to cancer cells grown in laboratory dishes, it blocks the myc gene. (Extracted from New York Times, 19 April 1988)

Compound helps cut to drug resistance

A synthetic amino acid that reduces cellular levels of glutathione increases the effectiveness of certain anti cancer drugs, according to researchers at the National Cancer Institute in Bethesda, Md. About half of the cancer patients treated with alkylating agents and cisplatin become resistant to those drugs and other unrelated drugs and radiation as well. Human ovarian cancer cells that have become drug resistant have increased levels of glutathione. By treating such cells with both the anti cancer agent melphalan and buthionine sulfoximine, a compound that inhibits production of glutathione, Robert F. Ozols and his colleagues increased the killing effect of the melphalan. Buthionine sulfoximine has a similar effect in animals, and NCI is considering the compound for clinical trials in drug resistant patients with advanced ovarian cancer. (Reprinted with permission from Chemical Engineering News, 6 June 1988. Copyright (1988) American Chemical Society)

Oncogene product can control other genes

Researchers have confirmed for the first time that a protein produced by an oncogene can bind to human DNA and directly control the activity of other cellular genes.

Molecular biologist Michael Karin of the University of California, San Diego, and his co-workers made the discovery while studying the human metallothionein IIA gene, which is believed to be involved in the regulation of zinc metabolism. Thus, this gene may be essential for normal cell growth. Karin's laboratory defined a region of DNA that controls the gene's activity, then searched for proteins that bind to this DNA region. He was able to identify several proteins that initiate gene transcription.

One of these transcription initiators, called AP1, is coded by a gene that was found by Karin to have an amino acid sequence very similar to that of the cellular counterpart of a known viral oncogene called jun.

This is the first example of a well documented transcription factor that has been shown to act as an oncogene, Karin says.

Scientists have long suspected that both growth and cancer involve the activation of genes or a change in the activity of genes. Oncogenes have been found to be associated with the abnormal or excess production of growth factors and the cell membrane receptors that respond to these factors. Oncogenes also have been linked to the production of the signal chemicals that deliver the growth message to the cell nucleus.

AP1 also stimulates the gene that codes for the enzyme collagenase. This enzyme digests connective tissue and is important in the process of wound healing. But collagenase also may help tumours to invade healthy tissues. (Abstracted with permission from Chemical Engineering News, 13 June 1988. Copyright 1988, American Chemical Society.)

Chemical link between ethanol and cancer

Evidence that ethanol and its metabolite acetaldehyde in combination react with nucleic acid molecules has been reported by researchers at the University of California, Berkeley. Molecular biology professor Heinz L. Fraenkel-Conrat and faculty scientist Bea Singer showed that [illegible] reasonably stable product [illegible] temperature and neutral pH in the reaction $R\text{-}NH_2 + CH_3CHO + CH_3CH_2OH$ [illegible], where R represents the purine or pyrimidine ring of a number of nucleosides. The [illegible] the nucleoside derivatives form rapidly in aqueous solutions containing only 200 mM each acetaldehyde and ethanol, conditions that [illegible] those present in people consuming [illegible]. Human epidemiological studies and studies [illegible] have suggested a link between [illegible] consumption and certain types of cancer [illegible] [illegible] [illegible] stable product [illegible] Fraenkel-Conrat [illegible] suggest that the findings might provide [illegible] link between alcohol consumption and [illegible] that could lead to cancer, and they [illegible] experiments in tissue [illegible] (Abstracted with permission from Chemical [illegible]

[illegible]

Researchers have reported new and surprising observations about a family of proteins that control gene activity in human and other cells. Their report provides a glimpse of one of the most fundamental "on off" switches in the biological machine, and suggests that mechanisms of gene regulation are even more mysterious and subtle than previously assumed.

Robert Tjian of the Howard Hughes Medical Institute at the University of California, Berkeley, and his colleagues worked with a family of DNA binding proteins that specifically bind to a DNA region featuring the base sequence [illegible] CCAAT. Scientists find the CCAAT motif, often called the CCAAT box, in various places along DNA strands in viruses, yeasts, mammals and other organisms, where it has been associated with DNA transcription and replication. The researchers cloned for the first time several individual members of this mixed family of DNA-binding proteins, and found to their surprise that even a single variety of protein could initiate both transcription and replication.

In related studies, the researchers appear to have settled a longstanding question by showing that in the family they examined, a single gene [illegible] for a spectrum of CCAAT box binding proteins. Molecules of messenger RNA - key "middlemen" in the process of protein synthesis - apparently can be cut into pieces, "shuffled" and then spliced together in more than one way before being used as templates for the protein product or products. This method of creating a variety of proteins, or "family members" from a single gene has never before been [illegible] with genes affecting transcription. It provides a mechanism for a single DNA site to respond to different, related proteins.

The research provides a new generation of questions about gene regulation. What is the significance of the different forms of regulatory proteins? If a single protein can perform [illegible] two distinct functions, what factors determine the [illegible] it will actually [illegible] And perhaps most intriguing: what regulates the splicing of messenger RNA, and thus regulates the ultimate diversity of these regulatory proteins? (Source: Science News, Vol. 134, 23 July 1988.)

Arthritis [illegible]

The [illegible] painful, swollen joints of rheumatoid arthritis [illegible]. Medical scientists at the [illegible] Research Centre [illegible] have discovered what happens [illegible] in the bodies of people with rheumatoid arthritis.

[illegible]

[illegible]

The starting point for the chain of events [illegible] they proposed is a group of molecules that normally appear on certain cells of the immune system. These molecules are called the human leucocyte class II antigens, or HLA class II. These proteins normally appear on the surface of cells, such as macrophages, that present antigens (usually proteins) to the white blood cells, called T cells. The HLA class II

...ecules assist in presenting the antigen, rather as a hand would hold up an item. The T cells then initiate an attack on that item, by activating other kinds of cells and releasing a variety of messenger molecules known as cytokines.

The researchers first tried to prove their hypothesis by studying the thyroid. In the initial attack on Hashimoto's thyroiditis, Feldmann and his colleagues found HLA class II molecules on the epithelial cells of the thyroid. These cells do not normally carry HLA proteins. Because HLA class II proteins were present, however, the cells became capable of presenting fragments of protein as antigen.

Antigen presenting cells cannot distinguish between self proteins and foreign proteins. They will present any protein on present fragments of their surface in association with HLA class II molecules. Normally, this does not create a problem because antigen presenting cells are usually present in relatively small numbers and only when a T cell's antigen triggers an immune response. In Hashimoto's thyroiditis, Feldmann's group found that the thyroid cells and the B cells were present in "enormous numbers". Even if the B cells' antigen specificity is unknown, studies suggest that they are specific to the tissue affected in an autoimmune disease. The main Feldmann and his colleagues found was that T cells targeted at other T cells in the body's own tissues -- so called "autoreactive" T cells. They also discovered that the cytokines needed to maintain the HLA class II molecules on the surface of the cells were present in tissue samples from diseased thyroids.

Most of the epithelial cells drawn from the patient by those people with an immune disease lose the HLA class II molecules from their surface when certain cytokines are present. There are many different cytokines the cells which need to be involved in maintaining HLA class II molecules are interferon gamma and tumour necrosis factor. The hypothesis is that abnormally high levels of cytokines cause the tissue damage found in the disease.

Having proved the sequence of events in thyroiditis over the past few years, the researchers turned their attention to rheumatoid arthritis, joining forces with Tony Main at the Kennedy Institute of Rheumatology in West London. The group confirmed a finding made by Dan Blaschke in Boston and George Janossy in Britain in 1982 that inflamed joints have an unusually large numbers of cells with HLA class II molecules on their surface. In these people, the cells may form a layer two cells thick.

Feldmann and his colleagues needed to know whether the HLA class II molecules were manufactured by cells in the joint, or whether they came in from elsewhere -- from the blood, for example. Earlier this year, they found that large quantities of messenger RNA (mRNA) containing the information necessary to make HLA class II molecules were present in samples of diseased joint tissue.

Furthermore, the researchers found that the cells synthesized the mRNA molecules only if they kept them in culture. This suggests, Feldmann says, that the cycle of interactions outlined for the thyroid is also true for rheumatoid arthritis.

The autoreactive T cells that become activated in the joint release molecules that maintain production of HLA class II molecules, as well as factors that activate other cells of the immune system, such as microphages and antibody producing cells. The current belief is that cytokines such as interferon gamma, interleukin 1 and tumour necrosis factor -- which T cells and antigen presenting cells produce -- cause pain and swelling and destroy cartilage and bone.

If factors can somehow interrupt the chain of events leading to disease, they might be able to design an effective therapy. Researchers have shown that in animal models of thyroiditis and rheumatoid diseases, antibodies that bind to HLA class II molecules block any interaction with T cells and thereby cure the experimental disease. Antibodies to T cells can have the same effect.

Using the antibody developed at Charing Cross, the latest results from Feldmann's group show that it is possible to prevent subsequent synthesis of HLA class II molecules by adding antibodies that will bind to them. Neutralizing the action of molecules such as interferon gamma might also work.

Feldmann and Main are now planning clinical trials. Known cell antibodies to HLA class II antigens and cytokines from people with rheumatoid arthritis. Doctors will inject the antibodies into the affected joints to study their short term effects. Maini says that the treatment may be better than currently available therapies.

There are few clues as to why some people develop autoimmune diseases such as rheumatoid arthritis and others do not. People who carry a particular variety of HLA molecule (for example, one called HLA DR4) are at more risk of rheumatoid arthritis than those without this molecule. Studies of identical twins also show that the genetic influence, although important, is not the only factor. Viral disease is one possible explanation. Some viruses that affect sheep and cattle cause chronic arthritis that resembles rheumatoid arthritis, for example. (Source: New Scientist, 4 August 1988)

Purification technique for stem cells in the marrow

American researchers have announced that they are close to isolating and purifying the immature cells in the body's bone marrow that control production of all kinds of blood cells, including those in the immune system. The advance may lead to greater success in bone marrow transplants and the treatment of people who have been exposed to radiation.

Scientists have been trying for 30 years to find a reliable way of purifying the immature cells known as stem cells. In the past, it has been difficult to distinguish stem cells from other cells in the bone marrow, which includes many types of blood cell. Only about one in 2,000 cells in the marrow is a stem cell.

Irving Weissman, an immunologist at Stanford University in California, claimed recently that his group was close to purifying human stem cells. Fred Hiemenz, an expert on bone marrow transplants from the City of Hope Hospital in Los Angeles, has joined the team at Stanford to speed up the development of the technique for use in humans.

Instead of trying to separate the cells by their size or density, Weissman's group concentrates on the character... proteins that appear on the surface of the c... The researchers identified nine proteins tha... alone or in various

combinations, allowed them to distinguish the stem cells from others. The scientists then raised antibodies that recognized and bound to just one of these "marker" proteins.

They tagged mature blood cells and their immediate precursors with antibodies carrying plastic beads. The researchers used magnets to remove these cells. Most of the cells left behind were stem cells. The researchers had to sort these into different types of cell. They did this by fluorescent activated cell sorting. By the end of the procedure, the sample consisted almost entirely of stem cells: it was between 97 and 98 per cent pure.

The Stanford group reported that it could save the lives of mice that had received a normally lethal dose of radiation. The animals reconstituted their red and white blood cells within a few days and their immune systems functioned normally. The success rate was 50 per cent and the researchers needed only 30 stem cells for each mouse. Normally, it takes an injection of 200,000 to 300,000 bone marrow cells to reconstruct the blood and immune system of a mouse. The work promises to open up a wide range of medical uses. Stem cells control production of the body's short lived blood cells and immune cells, including red blood cells, platelets, macrophages and lymphocytes. But no one understands how stem cells change into blood cells with specific functions, although they know that the thymus gland has a role.

The safety and availability of bone marrow transplants will increase once it is possible to purify and grow human stem cells in the laboratory.

Bone marrow normally donated by a close relative contains immune cells called T lymphocytes that can attack the recipient's body. Purified stem cells from the patient's own marrow should make it possible to avoid this complication. The need to find a donor with a matching tissue type will also be eliminated. However, without the T lymphocytes there is a danger that the host cells will reject the purified cells.

Other applications include the treatment of leukaemia, AIDS and inherited blood disorders such as sickle cell anaemia and thalassaemia. (Reprinted New Scientist, 14 July 1988)

Antibody catalyses C-O bond formation

Chemists at the University of California, Berkeley, have generated antibodies that can speed a carbon-oxygen bond forming reaction. The Claisen rearrangement of chorismate to prephenate runs 1,000 times faster in the presence of a specially tailored monoclonal antibody than without the antibody, according to Professor Paul A. Bartlett and Associate Professor Peter G. Schultz and their colleagues. This rate enhancement is about one third of the acceleration achieved by the naturally occurring enzyme that catalyzes the same transformation. The researchers generated the catalytic antibodies by using an antigen that is a stable analogue of the conformation that chorismate is thought to adopt in the transition state of the reaction. "The antibody may be acting by a mechanism that does not involve nucleophilic or electrophilic attack," Schultz says. "Instead it may be looking in the conformation of the transition state." Donald Hilvert and researchers at the Research Institute of Scripps Clinic, La Jolla, in work as yet unpublished, have independently generated an antibody that carries out the same reaction. (Reprinted with permission from Chemical Engineering News, 18 July 1988. Copyright (1988) American Chemical Society)

Molecular Biology Briefs

Scientists at Emory University in Atlanta have tested a specific method to diagnose DNA for a fatal form of leukaemia. The test uses synthetic segments of DNA that are complementary to the suspicious DNA in these tiny genetic defects. The test could be used to screen for inherited diseases.

Douglas C. Wallace and his colleagues discovered that people suffering from Leber's hereditary optic neuropathy (LHON) have a defect in the mitochondrial DNA that codes for a protein involved in the first step of ATP production. This defect results in the amino acid histidine being substituted for the arginine during the protein's synthesis.

LHON results in optic nerve death and often begins between the ages of 20 and 30. Since mitochondria are present in only the mother, if she carried the defect, either one of her children will inherit it. Yet only a minority of the people who inherit the defect develop blindness.

Another interesting aspect of these patients is that there is a bias toward males (about four males to every female). It is not yet known why this difference exists in the sexes. Researchers speculate that it may be a genetic factor that is possibly sex linked.

Wallace and his colleagues found the genetic defect in only 11 of 38 LHON patients; they failed to detect it in any of 49 controls. The researchers conclude that if the test does detect only genetically positive cases, it is likely that the 27 people who tested negative have the problem with a defect in another DNA.

[illegible] suggest [illegible] attempts [illegible] wall [illegible] mitochondrial [illegible] other. [illegible] different [illegible] difficult [illegible] deficiency [illegible] Nature [illegible]

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...ards at them by hydrolysing the chains in a statistically random fashion at the thioester positions. (Reprinted with permission from Chemical Engineering News, 13 June 1988. Copyright (1988) American Chemical Society)

Muscular dystrophy protein localised

Researchers from several groups have served in ... the cellular location of the protein called dystrophin, whose absence causes Duchenne muscular dystrophy. Lack of the protein causes progressive weakness and wasting of muscles in victims of the disease, which primarily affects boys. When Louis M. Kunkel, associate investigator at Howard Hughes Medical Institute at Children's Hospital in Boston, and colleagues first identified dystrophin late last year, they suggested that it was located ... normal individuals at triadic structures - ... junctions in muscle tissue where two membranes meet. Kunkel's research team has now shown by ... electron microscopy that dystrophin is instead found ... the muscle cell membrane on the side facing the cell interior. Eiichi Arahata of Japan's National Institute of Neuroscience in Tokyo also located dystrophin on the surface membrane of skeletal and ... heart muscle cells by using immunological techniques.

Researchers in Paris found dystrophin in the ... kidneys, testis and brain.

The protein is very rare in these tissues ... at 1 per cent of that in skeletal muscles where ... exists for only 1.0% per cent of the protein ... found at such low concentrations, ... it may be critical in tissues such as the ... Its absence in children with DMD may explain ... they are mentally retarded.

... Kunkel of the INSERM molecular genetics ... Paris, and his colleagues, ... have developed the hypothesis that ... type of the rare protein in brain ... The level of the copies of the ... messenger RNA transcript from the gene to ... protein. The messenger RNA is the ... between a gene and its protein product, ... provides a way to tell that the gene is active.

The ... research has found the messenger RNA ... dystrophin in different human tissues, but ... lymphoblastoid cells, at ... in muscles. In ... dystrophin probably has no physiological ... other, researchers include.

... Kunkel, at Harvard University ... Boston, found that the ... membrane, ... with the location ... greatly reduced levels of it.

... researchers located dystrophin in ... neuromuscular junctions within muscle cells ... in contraction. But the method of ... may have resulted in contamination ... researchers.

... and other colleagues speculate ... dystrophin "strengthens the ... parts of the internal ... surface membrane".

... cells, without dystrophin, the ... muscle cells could tear during ... This would lead to the degeneration of ... (Source: Chemical and Engineering News, 6 June 1988, page 21, and New Scientist, 7 July 1988 and 7 July 1988)

Secretin derivatives, IGF-II expressed

Wakunaga Pharmaceutical Co., Osaka, which was the first Japanese company to express porcine secretin in E. coli., has now synthesized derivatives of active human secretin, a duodenal hormone that stimulates the pancreas. The company chemically synthesized the secretin gene, adding additional coding for glycine and basic amino acids at its C terminus. To this, it coupled the DNA sequence for the N-terminus of human growth hormone. The hybrid DNA was inserted in E. coli to obtain derivatives having a different cleavage site for endopeptidase. One derivative exhibited 30 per cent higher activity than the native porcine hormone.

Wakunaga has also produced insulin-like growth hormone II (IGF-II) in E. coli. IGF II consists of 67 amino acids, and stimulates growth of skeletal tissue. The company prepared the total DNA sequence by chemical synthesis, to which a part of the human growth hormone gene was linked at its N-terminus. The expressed product was in the active form. The company plans to supply recombinant human secretin and IGF II as test samples for the research market, and ultimately develop them as pharmaceuticals and diagnostic agents. (Source: McGraw Hill's Biotechnology Newswatch, 2 May 1988)

Improved monoclonals

Researchers are anxiously awaiting ... results of therapy using chimeric monoclonal antibodies (which contain rodent antigen-binding sites but are otherwise of human origin). Nevertheless, UK commercial attention is already turning toward even more extensively "humanized" antibodies that contain a bare minimum of rodent sequence. Celltech (Slough, Berkshire, UK) is actively pursuing this approach, while Wellcome Biotechnology (Beckenham, Kent, UK) has a particular interest in the recent humanization of a rat monoclonal that is already into clinical trials.

The latest step in reshaping rodent monoclonals to minimize their recognition as foreign by the human immune system has been pioneered at the Medical Research Council's (MRC) Laboratory of Molecular Biology (Cambridge, UK). Instead of containing a complete rodent antigen binding site in the form of the variable domains of the light and heavy chains of the antibody molecule, the reshaped monoclonals contain only the three short "hypervariable" sequences of rodent available domains. These regions are engineered into a human variable domain framework, which then constitutes about 80 per cent of the whole variable domain.

In reality, the technology is not so much the humanization of rodent antibodies as the site directed mutagenesis of human antibodies; oligonucleotides are used to provide the recombinant immunoglobins with the hypervariable region (or complementarity determining region) sequences of rodent antibodies.

Celltech's interest in adopting this technology currently focuses on a mouse monoclonal being developed for cancer imaging and therapy in collaboration with American Cyanamid (Wayne, NJ). At least 0.5 mg of the antibody must be given for imaging and about 5 mg for therapy. Unfortunately, a single imaging dose is sufficient to invoke a HAMA (human against mouse antibody) response. Consequently, Celltech plans to push a chimera containing only the antigen binding site of the mouse antibody into clinical trials later this year; the human testing of a more humanized version is anticipated by the end of 1989.

Other antibodies that Celltech intends to humanize include one against tumour necrosis factor (that the company hopes will find a place in the therapy of septic shock) as well as various hybrid effector molecules.

Other companies that intend to license Mab's antibody humanization technology include Unilever (Sharnbrook, Bedfordshire, UK), Behringwerke (Marburg, FRG), Scotgen (Aberdeen, Scotland) and Wellcome. Unilever and Behringwerke will apply the technique to cancer, while Scotgen wants to treat human cytomegalovirus infection. (Extracted from Bio Technology, Vol. 6, May 1988)

Mab via human cells produced

Takeda Chemical Industries (Japan) has successfully produced a monoclonal antibody via human cells only. The product will pave the way to the development of a monoclonal antibody vaccine. Three types of monoclonal antibodies have been made via human-human hybridomas, which consist of fusions of human cancer marrow cells and human B lymphocytes. Takeda is currently using chimpanzees to produce the antibody on an experimental basis. (Extracted from Japan Economic Journal, 16 April 1988.

Experimental adrenal grafts for Huntington's chorea

Physicians reported what appears to be the first surgical grafting of adrenal tissue into the brain of a patient with Huntington's disease. The experimental procedure, using the patient's own adrenal tissue, was performed in early March at the Vanderbilt University Medical Center in Nashville, Tennessee. It is similar to an experimental therapy used on patients with Parkinson's disease, another neurological disorder. The Parkinson's surgeries, which have now been reported at several medical centres, have so far met with uncertain results.

The rationale behind the therapy comes from evidence that the neurological problems associated with Huntington's may be due in part to brain damage caused by a brain chemical, quinolinic acid. Experiments with rats suggest that transplants of tissue from the adrenal medulla to the caudate nucleus in the brain may be able to block such damage.

The operation builds on experiments at Vanderbilt in which researchers injected kainic acid - an algal extract normally used to kill intestinal worms - into rat brains to simulate the effects of Huntington's disease. Without transplants, the injected rats died. With transplants, 85 per cent survived.

However, many researchers doubt that transplants such as these have sufficient scientific rationale yet. Many scientists believe that more animal studies should take place before doctors make attempts to treat humans.

Concern in the US about the safety and efficacy of the transplants has led to the National Institutes of Health (NIH) banning transplants of foetal tissue because of legal, medical and ethical questions. The US Department of Health and Human Services has told the NIH to appoint an outside advisory committee to examine the implications of using foetal tissue.

At a recent symposium at the Massachusetts Institute of Technology (MIT), Anders Bjorklund of the University of Lund cast light on how implants work. To study the mechanism, Bjorklund's group injected suspensions of cells from the brains of foetal mice into rats' brains damaged by injection of quinolinic acid - a toxin with effects similar to those produced by kainic acid. They found that grafted rats functioned better than those without grafts. Tissue samples treated with a stain that identified mouse cells indicated that in the first few days the implant grew out into the host brain and vice versa. Bjorklund also cited evidence that the grafted cells communicate with the rest of the brain.

Meanwhile Canadian and American researchers have identified a new marker for the disease. The marker will significantly improve diagnosis for the disorder and advance the search for the dominant gene, according to Michael Hayden of the University of British Columbia, Canada.

The new marker, called D4S95, is a fragment of DNA located at the end of the short arm of chromosome 4. John Wasmuth, a molecular geneticist at the University of California at Irvine, first isolated the marker nearly nine months ago. Since then, researchers at the University of British Columbia have been working to confirm its location in relation to previously described markers for the gene for Huntington's disease.

Nothing is known about the cause of the disease, and there is no cure or effective treatment. Gene markers are useful because they can sometimes be used to diagnose the presence of the disease gene before symptoms appear. Armed with this knowledge, an individual may choose not to have children or to abort affected foetuses.

The D4S95 marker is better than previous markers because it is physically closer to the disease gene on the chromosome. This means that there is less risk that the marker will be separated accidentally separated from the disease gene during the normal "recombination" of DNA along a chromosome and give misleading results.

D4S95 is also a good marker because it is "polymorphic" - it comes in 20 different forms in the general population. This enables researchers to track the passage of the disease gene on a particular chromosome through a family. If everyone in a family has the same variety of marker, you cannot tell the chromosomes apart.

Although researchers are now very close to the disease gene, the hunt has to find it is still on.

Between 500 and 1,000 new cases of Huntington's are diagnosed in the United States each year. This hereditary disease, which typically does not become apparent until middle age, results in severe neurological degeneration and death. Vanderbilt says it plans to perform experimental adrenal transplants on a total of 24 Huntington's patients. (Source: Science News, Vol. 133, 23 April 1988, and New Scientist, 21 April 1988)

Parkinson's linked to scavenger mechanism

Experiments carried out by Turkish researchers indicate that the degeneration of brain cells caused by Parkinson's disease occurs because a mechanism that mops up the reactive compounds of oxygen in the body fails.

In making this discovery the researchers have found a way of testing whether the treatment for the disease - a drug called L-dopa - actually speeds up the degeneration of brain cells.

No one knows what caused Parkinson's disease, but there are a number of theories. By finding out how the brain cells are destroyed, researchers can begin to select between the different hypotheses and work towards better treatment of the disease.

Neuroscientists already have evidence that reactive compounds of oxygen destroy cells in the substantia nigra. These compounds form free radicals that kill cells by disrupting the lipid molecules in the cell membrane.

Normally, a variety of antioxidant scavenging systems protect the cells by mopping up the reactive oxygen compounds. Some researchers believe that in patients with Parkinson's disease, the substantia nigra deteriorates when the antioxidant scavenging system stops working.

There have been several reports of defective antioxidant mechanisms in the brain. Autopsies have shown that patients with the disease have reduced levels of antioxidative chemicals - catalase, peroxidase, glutathione (GSH) and glutathione peroxidase - in their substantia nigra.

[illegible] and colleagues from [illegible] University and Istanbul University, both in Turkey, have measured levels of antioxidant compounds in red blood cells and found that loss of these compounds is not restricted to the brain. They compared red cells from patients with the disease with red cells from healthy individuals of the same age and found that those with Parkinson's disease had lower levels of [illegible] and GSH peroxidase.

This suggests that the scavenger mechanisms in the substantia nigra might break down as a result of a genetic or generalized deficiency in antioxidant compounds. Researchers are not sure why the substantia nigra is singled out for attack if the deficiency is widespread.

[illegible] and Geoffrey Hauser from the Department of Pharmacology in the University of British Columbia, Canada, have suggested that it might be the dopamine in substantia nigra cells which makes them vulnerable. [illegible] pigmentation of the substantia nigra, which gives it its name, [illegible] between childhood and early adult [illegible] pigment [illegible] formed by oxidation of dopamine [illegible] being mopped up by the scavenging system.

At present, treatment of Parkinson's disease [illegible] trials [illegible] United States and Canada, but [illegible] need to assess the benefits of antioxidant treatment. (Source: New Scientist, 26 May 1988).

[illegible] revolutionize bioengineering

A team of molecular biologists in Australia has developed a new technique that the researchers believe can switch off genes in higher organisms, or prevent virus infections. The researchers from the Commonwealth Scientific and Industrial Research Organization (CSIRO), announced the discovery at the ANZAAS congress.

The technique involves a molecule of ribonucleic acid (RNA) that has certain properties. The molecule can be designed to slice other RNA molecules, causing them to lose their function. The "gene shears" can therefore disrupt the flow of genetic information encoded in DNA that is used to make protein via an intermediate, messenger RNA.

The head of the CSIRO's Division of Plant Industry, Jim Peacock, believes that the gene shears could open a new dimension in molecular biology. He said that the CSIRO has successfully tested the method *in vitro*. The results indicate that the technique can effectively prevent the production of protein from messenger RNA molecules of plants, animals and bacteria. The gene shears also seem to block the RNA messages of viruses.

Genetic engineers have searched for a way to switch off genes for more than a decade. Until now, the only technique to show any real promise was the use of molecules of "anti messenger RNA". These are made from the unread strand of the double stranded DNA molecule. These anti-messengers bind to molecules of messenger RNA and stop them functioning.

This technique has proved unwieldy and unreliable, however. The new approach using gene shears promises to be simpler and more versatile because it involves a natural property of RNA, Peacock said.

The CSIRO is not giving full details of the discovery until the scientists involved have published the research formally. The technique, however, is believed to involve a discovery that was made recently about self cleaving molecules of RNA.

Peacock told ANZAAS that it should be possible to adapt the gene shears to inactivate virtually any gene, or to destroy the genetic blueprint of a virus before it could begin replicating in the cells of its host. The molecule consists of a short sequence of RNA that researchers can design in such a way that it will cut the RNAs of genes or viruses very precisely.

The CSIRO has patented the technique. The technology could be a major export earner through licensing agreements with commercial developers [illegible] (Extracted from New Scientist, [illegible] May 1988)

Research on animal genes

[illegible] genes [illegible]

[illegible] two genes that [illegible] airway hyperreactivity in mice. The [illegible] Roy [illegible] and Wayne Mitzner of Johns Hopkins University in Baltimore reported the first [illegible] the discovery of the second [illegible] and its preliminary mapping [illegible] chromosome.

[illegible] and Mitzner exposed inbred mice with airway hyperreactivity to serotonin and acetylcholine, two neurotransmitters known to trigger decreased pulmonary functioning in animals and humans with airway hyperreactivity. They found a separate gene controlled the animals' responses to each chemical - thus the gene designations A[illegible] and Ser. Some mice had one gene and some had both, but

either gene adversely affected the animal's pulmonary activity. Levitt cautions there is no evidence yet that these genes exist in humans.

Family and twin studies indicate a genetic factor in airway hyperreactivity and asthma. A number of humans with airway hyperreactivity, however, exhibit no symptoms and their condition requires lung-function measurements to detect. (Source: Science News, Vol. 134, 6 August 1988)

Enzymes are key to universal malaria vaccine

Swiss immunologists are close to mass-producing a vaccine that could for the first time protect against all types of malaria parasite.

Ulrich Certa, of the pharmaceuticals company Hoffmann La Roche, and colleagues at the Cantonal Hospital in Geneva have sequenced a gene that could make the synthetic proteins needed to mass produce the vaccine. The Swiss researchers are now testing the vaccine on monkeys and expect to announce their results next month.

Until recently, researchers looking for a vaccine had concentrated on using proteins on the parasite's coat to stimulate the body's immune system. This type of vaccine is unlikely to protect against all strains of the parasite because each strain has different surface proteins. Antibodies produced to attack one strain of parasite would not recognize another strain. Some parasites can also escape attack by changing the proteins on their outer coat.

Certa is investigating the possibility of using a different type of protein: one of the parasite's own enzymes. Enzymes are integral to the parasite's metabolism, so it could not easily evolve a sufficiently different replacement enzyme.

Certa has been working on a protein called p41, which is an aldolase enzyme that catalyses the breakdown of glucose to provide the parasite with energy. As the parasite matures and reproduces inside red blood cells, the cell's glucose consumption increases at about 20 times its normal level. The p41 protein makes the body produce antibodies to the parasite's aldolase and stops the parasite from growing. The antibodies do not affect human aldolase because its structure is very different from that of the parasite's.

In earlier experiments, Certa immunized monkeys using purified p41 taken from the parasites at the blood stage of the disease. The vaccine protected the monkeys from attack by strains of malaria parasites from as far apart as Africa, the US, China and Honduras.

Recently, Certa confirmed that the antibodies raised against the protein attack all the strains because the protein's amino acid sequence is virtually the same in each strain.

Certa has now sequenced the p41 gene and is ready to make synthetic p41 molecules by inserting copies of the gene into the bacterium Escherichia coli. This is the first step towards mass producing the vaccine. (Source: New Scientist, 9 June 1988)

Blood forming stem cells purified

One of the major obstacles to understanding how different types of blood cells are formed has been not knowing what cells produced them. Now researchers have found a way to isolate the bone marrow stem cells in mice that give rise to all blood cell types. Irving Weissman and Shelley Heimfield of Stanford University School of Medicine in California and Gerald Spangrude, presently of the Royal Melbourne Hospital in Victoria, Australia, report that as few as 30 of these stem cells can restore blood cell production in a mouse subjected to a lethal dose of radiation.

The new findings represent a culmination of ideas and efforts by many investigators to identify which cells in the bone marrow ultimately form the eight or nine different lineages of cells in circulating blood. The information should lead to better treatments for blood disorders as well as advancing basic research on blood-forming tissues.

For example, if a similar cell can be identified in humans, researchers may be able to transplant stem cells instead of whole bone marrow into people who receive large doses of radiation. Also, it may be possible to maintain the stem cells, in vitro, transfer genes into the cells, and then reinject the altered cells into a person who has a specific genetic or acquired blood cell defect such as sickle cell anaemia, thalassaemia, severe combined immune deficiency, or leukaemia.

The new information should answer some basic questions about the development and differentiation of haematopoietic cells. For instance, a burning debate has been whether bone marrow stem cells are already programmed to become a certain kind of cell - a B lymphocyte for example - or whether the biological environment dictates the cell's final differentiated state.

Weissman's data support the latter hypothesis. The stem cells are obviously capable of producing all lineages of blood cells when injected intravenously, a procedure that exposes them to many different biological environments in the body. But if they are injected directly into the thymus gland, they differentiate only into T lymphocytes. This result implies that something about the microenvironment of the thymus gland directs their differentiation into T cells. (Source: Science, Vol. 24., 1 July 1988)

Fish get growth hormone gene transferred to carp

Scientists in Maryland and Alabama are using a string of DNA to fish for advances in genetic engineering. So far the catch has been good: a gene with hormone gene transferred from rainbow trout into carp has produced bigger, faster growing fish.

The scientists injected the gene with a hormone gene into thousands of carp eggs, out of which grew 4 - 5 inch. Preliminary results show that 40 of the fish have incorporated the gene into their DNA, and most of those are making trout growth hormone and growing significantly faster than normal carp. This is one of the first successful attempts at genetic alteration of fish in the United States, says Thomas Chen of the University of Maryland's Center of Marine Biotechnology in Baltimore, who is conducting the research along with scientists from Johns Hopkins University in Baltimore and Auburn (Ala.) University.

Although most of the fish carrying the trout gene are growing faster, a few are growing more slowly than normal, and the researchers would like to know why. The difference may relate to where a carp incorporates the gene into its DNA.

The research could prove a boon to the aquaculture industry, because altered fish may keep

eating and growing during the winter months, when most normal fish do little of either. If this turns out to be the case, genetic alteration might allow fish farmers to shorten the time it takes to produce full grown fish. However, the genetically altered fish might not survive well in the wild, outside of aquaculture ponds. (Source: Science News, Vol. 133, 11 June 1988)

Hamster hair loss gene located

Shiseido Co. Ltd., Tokyo, has cloned the depilation gene from the giant sebaceous gland of a male hamster. In vivo, expression of this protein was induced by testicular hormones. The company plans to further study this hair loss gene to clarify mode of action, the first step in developing a hair-tonic to counter its effects. (Source: McGraw Hill's Biotechnology Newswatch, 2 May 1988)

Genetic selfishness in an all male club

Frogs and snails and puppy-dogs' tails may make little boys, but in the wasp Nasonia vitripennis, a selfish chromosome apparently can dictate which offspring will be male. Scientists report that an extra chromosome carried by males of the species selfishly destroys the other paternal chromosomes - thus enhancing its own transmission but resulting in all males.

A tiny, parasitic wasp that lays its eggs in the pupae of flies, N. vitripennis normally produces only females from fertilized eggs and only males from unfertilized eggs. If an extra chromosome called psr (paternal sex ratio) is present in the sperm, however, all five of the normal chromosomes contributed by sperm disappear after fertilization. With its "fertilized" status cancelled, the egg then becomes a male capable of making more psr containing sperm.

Uri Nur and other researchers at the University of Rochester in New York report that "because the psr chromosome enhances its transmission by eliminating the rest of the genome, it can be considered the most 'selfish' genetic element yet described".

Because it is an extra chromosome not found in normal wasps, psr is classified as a supernumerary chromosome, or "B" chromosome. Scientists have found B chromosomes in more than 800 species of plants and animals thus far. In the mealy bug, for example, the B chromosome switches a role on those chromosomes that remain active whether offspring become male or female. But psr takes this trickery to the extreme by simply eliminating the possibility that offspring will be female.

Although it is still unclear exactly how psr functions, Nur says he and his colleagues suspect "it is like an infection in that it tends to spread [through a population of wasps]". If this is the case, he says, mutations of unknown environmental factors may periodically stop psr transmission, before the all male results extinguish the species. The scientists have found the chromosome among wasps collected in Utah, but not in those from New York. The highest observed percentage of males carrying psr in any specific population was 26 per cent, Nur says. (Source: Science News, Vol. 133, 30 April 1988)

Fingerprinting undermines the case for killing whales

There is now less reason to kill whales as part of scientific research. Workers at the University of Cambridge have developed a way to monitor the size of whale populations and the age and genetic status of individual animals using the technique of genetic fingerprinting.

At the end of last year, the International Whaling Commission (IWC) agreed reluctantly to issue Japan with a permit to harvest 825 Minke whales and 50 sperm whales for research.

Rus Hoelzel and William Amos of the Department of Genetics at Cambridge have shown that DNA fingerprinting, developed by Alec Jeffreys of Leicester University for use in humans, is equally applicable to whales. In humans, the technique confirms identity through analysis of samples of body tissue or fluids.

Hoelzel and Amos obtain DNA samples from whales with a small dart that abstracts skin. They fire the dart from a crossbow or a rifle into the hide of a whale swimming underwater. The dart has at its tip a hollow metal cylinder which abstracts a pellet of skin weighing somewhere around 0.5 milligrams.

The researchers say that the operation is painless to the animal. Amos says that the sample yields far more information than is available traditionally through radio-tracking, tagging or counting.

They report that the test can identify individuals, patterns of paternity and, in some cases, maternity, with greater certainty. From these data, the researchers believe that they can gain a better understanding of the geographical dispersal and reproductive biology of whales.

Also, by examining mitochondrial DNA, they can assess the amount of genetic variation within individual populations of whales. The genetic diversity within populations affects markedly its prospects for survival.

Amos says that the case for killing whales to collect physiological data is now without foundation. He says that this information is already available from studies carried out during heavy whaling in the 1960s and 1970s. (Source: New Scientist, 2 June 1988)

A setdown to clouding in caterpillars

Viruses may soon supplant bacteria in many cloning systems used to make expensive drugs. Work that began as an investigation of new ways to control pests now promises developing countries an opportunity to challenge the industrialized world's dominance of the market in genetically engineered products.

Viruses which infect caterpillars, known as baculoviruses, have evolved very efficient means for surviving between caterpillar hosts. By the time a virus kills its unfortunate victim half of the caterpillar's body weight may be made up of virus particles. Each particle is composed of viral DNA, the genetic blueprint for making more virus, surrounded by a coat that is mostly composed of only one protein and protects the DNA inside against dessication and ultraviolet radiation. It continues to do so for up to 10 years if necessary before the virus particle infects a new host and starts the cycle again.

The speed and efficiency with which a baculovirus takes over control of the caterpillar's cells and orders them to make the protective protein appears to be unrivalled. In the last year or two biotechnologists have realized the potential of such

viruses for producing high value protein products, human body control substances such as interferon or insulin, which are increasingly being developed for use as drugs, and vaccines and viral or other antigens for use in diagnostics.

High value proteins are being made today by inserting the genes for them into the genome of a cell culture, which may be bacterial, mammalian or yeast. The cell culture then obeys the instructions of the inserted genes and makes the wanted protein. As the culture divides and multiplies, its capacity to manufacture the protein grows steadily.

Supplanting cell culture

Several high value products are now made commercially in this way and many experts believe that the next generation of medical drugs will be composed mainly of human body control substances, lymphokines made in the same way; that is, as biotechnologists say, they will be cloned. But new research on baculoviruses to clone proteins, carried out largely at the UK Natural Environment Research Council's Institute of Virology in Oxford and supported by a number of private companies, is forging ahead so fast that it begins to look as though baculoviruses may soon supplant cell culture systems for manufacturing many, perhaps most, cloned products.

Led by their Director, Dr. David Bishop, scientists at the Institute have been working for several years on viruses that infect insects. They have made a special study of viruses that mammals catch from insects, including those spread by mosquitoes, gnats and ticks. The Institute has developed a vaccine to protect against louping ill, a disease of sheep very common in eastern Europe, and it has helped to develop viruses which are now used as commercial pesticides. Its work on baculoviruses began because of their potential as caterpillar pest control agents.

It was the work for pest control that led to the idea of using baculoviruses to clone protein products. Why not replace the gene for making the protein which protects virus particles with a gene for making some valuable human protein or viral antigen for use in a vaccine? It would mean that caterpillars could be infected with the altered baculovirus and used as living bioreactors to manufacture proteins and vaccines.

The potential of baculoviruses used in this way can be gauged by the fact that one caterpillar may come to contain one billion virus particles before it dies. Normally these particles would be spread through the soil as the caterpillar's body decayed, or through birds eating the dead caterpillars. Particles can survive for up to 10 years before they are again eaten by a caterpillar, whereupon the alkalinity of its mid-gut breaks down the coat and the virus again becomes infective.

500 species

Dr. Bishop and his colleagues have shown that if the gene for the polyhedrin protein coat protein is replaced by a human gene or a gene for some other wanted product, that product can be extracted from dead caterpillars with relative ease. There are about 500 separate species of baculoviruses, each specific to one particular species of caterpillar, and most of them are potentially useful as means of cloning proteins.

One single caterpillar costing a fraction of a penny to feed can produce up to three milligrams of a high value pharmaceutical protein. This makes cloning in caterpillars appear much cheaper than cloning in bacteria, with the added advantage that the proteins are made in forms which more closely resemble those made in human cells than the proteins made by cultures of bacteria.

Dr. Bishop's team is already working with firms using baculoviruses to make valuable products. Among the first will be diagnostic test kits for hepatitis B and for human immunodeficiency virus (HIV, commonly known as AIDS). Baculoviruses will be used to make single antigens, surface coat proteins recognized by the human immune system, for hepatitis and immune viruses. Diagnostic kits for both conditions, made in this way, are expected to be marketed this year. The team has already cloned more than 12 proteins in baculoviruses with excellent results.

The second step will be to use baculoviruses to clone vaccines, hormones and lymphokines. A cheap hepatitis B vaccine is one likely product; other vaccines, too, can almost certainly be made more cheaply in this way than by any cell culture system.

Further in the future lies a still more exciting possibility, the ability to make new and complex compounds in insect cells by using viruses as vectors to carry the several genes needed into the cells.

Dr. Bishop's team has been studying the promoter, the piece of DNA attached to the protective protein gene which drives it to work so fast. By selectively removing more and more of the promoter he has found it possible to control precisely the rate at which the gene makes its product. By using sophisticated genetic engineering to tack on different amounts of promoter to each of several different genes inserted into a single baculus virus, it is possible to make the virus transduce a cell to make different products simultaneously at different rates. In this way insect cells could be transduced to manufacture complex chemicals that require several different enzymes for their synthesis, none of which occur naturally in living cells, and each of which has to be present in the right quantity for the product to be synthesized. The gene for each enzyme will be introduced into an insect virus, with just the right amount of promoter attached to each gene to get the virus to make the correct amount of the enzyme.

Dr. Bishop's next eventually to make insect cells manufacture antibiotics such as modified cephalosporins, which cannot be made by fungi, moulds or other micro-organisms. It may also be possible to make vaccines that will work without boosters, viruses simultaneously behaving like antigens and characteristics of the virus disease organisms. His team also hopes to introduce into baculoviruses for another purpose, to make the viruses more effective and more widely specific as insecticides. Some baculoviruses are already used as insecticides, but their extreme specificity, although environmentally ideal, restricts their usefulness.

If the work of introducing genes into baculoviruses could be done in central laboratories and the work of growing the caterpillars farmed out to the countryside, Dr. Bishop says, the new technique could enable the developing world to take making insects out of the industrial world's formula of high virus production from genetic engineering. The Far East, with its cheap labour farming experience, may stand to gain most of all. (This article first appeared in Spectrum, No. 214, 1988)

Genetic engineering to the aid of sericulture

Since the last decade emphasis has been given by the molecular biologist to study the biosynthesis of silk proteins and very recently to detect the genes responsible for the production of proteins and their regulation of expression. The fibroin silk protein of the silkworm has been isolated and comparisons made between the indigenous multivoltine and exotic bivoltine races. In both the races the major amino acids found are glycine, alanine and serine. It has been found that the fibroin protein is hardly synthesized during the moulting stages and the massive synthesis occurs during the last day of the last (fifth) instar. Dr. M. Rashidul Haque of the Laboratory of Genetic Engineering, University of West Chatt., Bangladesh, thinks it considerable scientific interest if the fibroin gene be artificially involved in a silk-like DNA by restriction enzymes and then cloned into bacteria for proper multiplication. In addition to the production of silk protein in micro organism, the rDNA technology will help to detect the genes for 'naturality' of silk thread and to transplant those in mulberry silkworms to produce artificial silk, turning their discontinuous silk filament into continuous thread. (Extracted from Int. Silk, Dec. XXI.No. 5, 5 September 1988)

Research on plant genes

Whole tissue plants regenerated

Researchers at the Department of Energy's Brookhaven National Laboratory, Upton, N.Y., in collaboration with a team at the Max Planck Institute for Plant Breeding Research in Cologne, Federal Republic of Germany, have developed a method for introducing foreign DNA into tobacco cells by electroporation. The team regenerated whole tobacco plants from cells that had taken up the gene for resistance to the antibiotic kanamycin. Until recently, plant genes could be introduced into plant cells only by using the bacterium Agrobacterium tumefaciens, which causes crown gall disease in dicotyledonous plants. (Source: Science, 11 June 1988)

Field plant regenerated from plant cells

Researchers at Monsanto have successfully regenerated fertile corn plants from "hybrid" corn cells, a major advance with many potential applications. Due to the prior inability to regenerate fertile plants from hybrid cells, the only way that hybrid vigor could be exploited was through the crossing of two inbred lines. Now, the ability to regenerate hybrid plants from cells will allow the selection of desirable traits at the cellular level. The new method of regeneration has been used to produce corn plants from a single hybrid cell line. (Extracted from Bio/Technology, Vol. 6, May 1988)

Natural resistance to foreign DNA

A compound that appears to cleave DNA molecules by a novel mechanism has been isolated from an Australian plant. Chemistry professor Sidney M. Hecht and his colleagues from the University of Virginia in Charlottesville found a variety of plants that contain three DNA-cleaving molecules from the shrub Bikkia tillocratis. The compounds are resorcinols bearing long unbranched alkyl groups at position five. The researchers note several unusual aspects of the compounds' behaviour. The 5-alkylresorcinols require no copper ion to cleave DNA, even though they do not contain useful metal ion ligands; the molecules bind to DNA despite the lack of functionalities normally thought to be needed for DNA association; and their DNA cleaving ability increases upon storage or when solutions of the compounds are exposed to air, and is directly proportional to the length of the alkyl substituent. The researchers suggest the resorcinols are initially oxidized at position four of the benzene nucleus. The resulting 1,4,5 trihydroxy benzene derivatives could then chelate copper ion, forming a complex that can degrade DNA in the presence of oxygen (Reprinted with permission from Chemical Engineering News, 6 June 1988. Copyright (1988) American Chemical Society)

Biochemists insert foreign gene into maize

Plant biochemists have successfully inserted a foreign gene into maize plants and shown that the gene is active. This is the first time that biochemists have made a cereal express a foreign gene. It could enable biochemists to make strains of maize and other major cereal food crops, such as rice and wheat, that are resistant to certain pests, herbicides and diseases.

Biochemists have already made resistant forms of tobacco and tomato by infecting them with extra genes. They do this by using Agrobacterium tumefaciens to take up the foreign gene and then infect the plant. Although A. tumefaciens readily infects dicotyledonous plants, it does not infect most monocots, to which most cereals belong.

About two years ago, Michael Fromm and colleagues at Stanford University, Palo Alto, California, developed a method, called electroporation, of enabling plant cells that have been stripped of their cell walls - "protoplasts" - to take up DNA directly. Unfortunately Fromm was not able to grow these infected protoplasts into maize plants.

Now scientists at the Garden State Protection Corporation in Palo Alto, Earthem in New Jersey and Biogrowth in California have succeeded where Fromm failed.

Carl Rhodes and her colleagues at Earthem have made cell line which protoplasts can grow into whole plants. Like Fromm, they applied an electric field to the protoplasts that allowed them to take up a gene that would make them resistant to the antibiotic kanamycin. Resistance to kanamycin is a common property, but the researchers used the antibiotic resistance as a marker, providing an easy way of determining whether the protoplasts had taken up the foreign gene.

Rhodes' team grew its modified maize protoplasts over a layer of special "feeder cells". These were from a maize called Black Mexican Sweet, whose cells divide rapidly. Rhodes believes that feeder cells may have been crucial to the success of the experiment, by providing the protoplasts with factors or nutrients that stimulate them to divide.

The feeder cells encouraged the protoplasts to divide and establish callus tissue - a mass of undifferentiated plant cells which can be grown to whole maize plants. By including kanamycin in the growth medium the researchers weeded out those that did not carry the resistance gene; the DNA of the plants that survived the kanamycin treatment did indeed carry the gene.

The resulting plants were, however, sterile. Rhodes does not see this as a great problem. As cell lines age they mutate. Rhodes suggested that the sterility may be due to mutation in the cell line they used to make the protoplasts. (Source: New Scientist, 21 April 1988)

Sugar beet grows resistant to herbicide

Plant scientists in Belgium have grown genetically engineered sugar beet that survives the action of a weedkiller. It is the first time that researchers have managed to grow sugar beet plants from single cells carrying a foreign gene for herbicide resistance. The researchers aim to produce a variety of sugar beet that survives when sprayed with a herbicide that kills weeds.

The scientists, from Plant Genetic Systems, have inserted into cultured cells of sugar beet a gene taken from the bacterium, Streptomyces. The gene orchestrates the production of an enzyme, phosphinothricin acetyltransferase, that deactivates the herbicide, phosphinothricin.

The company used standard techniques for inserting the foreign bacterial gene into sugar beet cells. The Streptomyces gene is first spliced into a plasmid, or genetic vector, of another bacterium, Agrobacterium tumefaciens. When A. tumefaciens is co-cultured with cells of the sugar beet plant, the plasmid moves from the bacterial cells to the plant cells, carrying the Streptomyces gene with it.

It will take at least seven years to develop the herbicide resistant sugar beet into a product. Sugar beet is a biennial plant and so development time for new strains is longer than for annual crops. (Source: New Scientist, 2 June 1988)

The gene that sets people sneezing

A research team from Melbourne University in Australia claims to have isolated the gene in rye grass that is responsible for causing hay fever in humans. The gene produces a protein that is carried in the air with pollen. The protein interacts with human cells to cause allergy and hay fever. The discovery of the gene should lead to better diagnosis and treatment for sufferers of hay fever and asthma.

It opens the way for the production of synthetic peptides made from the gene that scientists can use in diagnostic tests and in therapy aimed at making sufferers less sensitive to pollen. In the long term, such peptides could form the basis of a vaccine against hay fever and asthma.

Last year, the team cloned the rye grass gene. So far, the researchers have unravelled half the sequence of the gene and it is hoped to determine the full sequence later this year. A provisional patent has been filed and the group has begun to negotiate with pharmaceuticals companies to commercialize the research.

Several other research teams working on allergies have also tried to isolate this and other allergy genes. A team at the University of Western Australia in Perth last year isolated a gene from the house dust mite that could also cause allergies. (Source: New Scientist, 19 May 1988)

Wild bean gene may foil weevils

A gene found in a wild bean plant from Mexico may soon be added to the list of new biological approaches to pest control. By breeding the gene into cultivated bean plants, United States researchers have been able to introduce a natural resistance to the bean weevil, a major threat to stored beans.

Unless stored beans are fumigated with a chemical pesticide, weevils often eat as much as 15 per cent of them before they leave the pod. Since dry beans provide half or more of the protein for much of the world's population, an inexpensive way to prevent such losses is of major social and economic significance.

The gene raises hopes to produce a bean called arcelin that is highly toxic to the weevils. (Source: International Herald Tribune, 21 April 1988)

Chinese garden a hoax

A French researcher has discovered the secrets of the therapeutic properties of an extract of the leaves of the ginkgo tree, used by Chinese healers to treat allergies for more than 5,000 years. Pierre Braquet, director of research at the Henri Beaufour Institute in Paris, has isolated a chemical called ginkgolide B from ginkgo leaves and shown how the plant's benefits alleviate allergic inflammation.

Once a path gen has interfered as the body's normal response is to attack the infected area with specialised cells of the immune system known as eosinophils. These cells are armed with deadly peroxidases which destroy pathogens. People with allergies produce eosinophils even when they might be infected with fairly harmless foreign material, such as house dust mite. If there are pathogens in the area, the peroxidases do exist, the eosinophils destroy body cells and produce symptoms of allergic reactions.

Scientists do not fully understand how eosinophils arrive at a specific site. One possibility is that a substance in the body called platelet activating factor (PAF) triggers the production of eosinophils. Braquet has shown that ginkgolide B inhibits the activity of PAF, thereby preventing allergic reactions. (Source: New Scientist, 2 April 1988)

New N fixing enzyme

Researchers at the North Carolina State University in the US have discovered the role of a third bacterial enzyme, nitrogenase reductase, in converting atmospheric nitrogen to nutrients. The enzyme is found in Azotobacter vinelandii and is known as the only significant metal-containing

Until two years ago, only two nitrogenase enzymes containing molybdenum were fully identified. In 1986 the AFRC Nitrogen Fixation Laboratory in Sussex, UK, revealed the existence of the molybdenum-based enzyme. All three enzymes are similar, each with a distinct gene unit and a smaller iron-sulphur protein. The two newest, however, may use a process a third

Plant biotechnology firms are attempting to transfer the ability to fix nitrogen of certain bacterial species to plants. Transferring the genes responsible is not going to be an easy task as not all have been identified even for the first nitrogenase.

This effort is unlikely to bring forth manipulated plants until the next century but will cut the need for artificial N fertilizers and will reduce the associated environmental concerns. (Source: European Chemical News, 27 June 1988)

The enzyme that could make plants grow faster

Molecular biologists at the University of California at Los Angeles (UCLA) have determined the

...t the structure ...t the world's most abundant protein, known as RuBisCO.

The finding may lead to ways to improve the way RuBisCO triggers photosynthesis in plants. By using techniques of genetic engineering to modify the structure of the protein, scientists might be able to create plants that grow faster.

According to the research at UCLA, the RuBisCO molecule consists of 3,492 atoms. It is one millionth of a centimetre high and just over one billionth of a centimetre wide. The position of the atoms has been determined to within a billionth of a centimetre.

...id Eisenberg from UCLA has spent 15 years trying to unravel the three dimensional structure of RuBisCO. He says the protein exhibits a ... shuttle ... the natural ... it binds both ribulose bisphosphate carboxylase oxygenase.

The enzyme initiates photosynthesis by transforming carbon dioxide from the air into sugars ... which energy is stored by plants. "RuBisCO is an enzyme that synthesizes," Eisenberg said.

The researchers interested in new ways to produce a more nutritious, disease-resistant crop will also be able to use the findings. They may be able to alter structures of only a fraction of 1 per cent of all proteins. (Source: New Scientist, 7 July, 1988)

How ... of enzymes help ... to defend themselves

A biotech ... just in ... but a way to turn the natural stimulant which triggers the immune system of plants. Plants defend themselves by producing ... which, phytoalexins, a group of substances which are produced when stimulated by a ... by fungi or bacteria. Chris Bowler, of the Imperial Cancer Research Fund, has found a way to produce the ... in potatoes, which means that farmers may ... be able to ... their crops against fungus diseases. Here helps the ... enzyme, which ... to ... a ... which ... fungicides.

... is ... by the ... technique of ... enzyme into the reverse ... direction in which it would ... a reaction ... to ... The enzymes that naturally break down ... to form simple sugars ... to be ... agents ... To produce the ... the ... and the ... were ... with just ... of ... and ... Because the ... are insoluble in such solvents they ... out. This upsets the thermodynamics of the reaction so that it starts to run backwards, synthesizing the ... from the sugars which are ... its breakdown products.

... is now experimenting to find the optimum for reverse ... He believes the same techniques will be used to make other oligosaccharides.

Oligosaccharides on the surface of mammalian cells are important in immune recognition and in forming structures to bind into hormones, for example. Some oligosaccharides are already synthesized chemically for medical research, but they are expensive. (Source: New Scientist, 23 June 1988)

Helping nature protect plants

Anthony C. Waiss and Carl A. Klinger at the Agriculture Department's western Regional Research Center in Albany, California, have found that varieties of Physalis (a genus including the tomatillo and cape gooseberry) and of petunia contain chemicals that can dramatically stunt Heliothis zea ... also known, depending on the host, as tomato fruitworms, corn earworms or bollworms. The researchers extracted the active chemicals and added them to the fruitworms' diet for six days. Some of these chemicals were so potent that insects ... on them grew to just 3 to 10 per cent of the weight of insects fed a pesticide free diet. Their current approach ... protoplast fusion ... merges the ... contents of a cell from each selected genus, and then regenerates the hybrid. While they have not developed a satisfactory hybrid yet, Waiss predicts it is just a matter of time. Ultimately, once the genes responsible for producing the stunting chemicals have been identified and mapped, Waiss says they can be spliced into the desired crop plant through recombinant DNA techniques. And a benefit in this approach to chemical insect control, he notes, is that the active agents should be present only in the leaves, not in the edible fruit. (Source: Science News, Vol. 134, 9 July 1988)

Research on yeast and fungus genes

Waste degrading fungus improved

The tools of biotechnology are being used to improve the properties of a fungus that is being studied for its ability to degrade hazardous waste. The white rot fungus Phanerochaete chrysosporium ... or white rot fungus produces a peroxidase enzyme that degrades the wood polymer lignin and also attacks such environmental pollutants as chlorinated biphenyls, aromatic hydrocarbons, and chlorinated dibenzodioxins. Microbiology professor C.A. Reilly and graduate student Thomas Buntain at Michigan State University have now developed a technique for making the gene that codes for the peroxidase in an ... of the fungus. The shuttle vector system may lead to ... do for making plentiful quantities of the enzyme large enough for industrial use. (Reprinted with permission from Chemical Engineering News, 11 June 1988. Copyright (1988) American Chemical Society)

Fungus breaks the mould of phosphate fertilizers

Soil researchers in Canada have ... a naturally occurring species of ... fungus which makes phosphate ... that it ... be absorbed more easily by ... gas.

Several micro-organisms are known to make phosphates dissolve, but ... one at the rate of the penicillium isolated by Kej Kucey at the Agriculture Canada Research Station in Alberta. The fungus can also maintain high rates of dissolution in soil, where many of the better known organisms die off.

The fungus, which was originally isolated from soil, can stop phosphate fertilizers degenerating into insoluble forms once they have been applied. It can also transform natural phosphates in the soil into soluble forms, which makes good use of native phosphate.

It may also mean that farmers can use less soluble forms of phosphate to start with, such as rock phosphate. At the moment these must first be dissolved in acid, then dried. Developing countries

can neither afford the expensive equipment necessary to do this, nor afford to import large quantities of prepared phosphate fertilizer. But many countries, such as Malawi, have massive natural rock phosphate deposits which they could exploit by using the fungus.

Kucey says he does not understand the precise mechanism by which the fungus acts on the phosphate, but thinks its metabolism produces organic acids as a by-product. These acids attach themselves to the metal ions on the insoluble phosphates, leaving the phosphates free to dissolve into water in the soil, ready for the plant to absorb.

The idea is being considered for practical exploitation by Philom Bios, a Canadian company that is field testing the organism across Canada and has applied for patents on the technology.

Initial tests have been successful. Further tests are planned for the US and Europe. If they are successful, the fungus could take its place as an agricultural product in a few years. (Source: New Scientist, 9 June 1988)

Research on bacterial genes

Disease evolution of plague

In the 14th century, the black plague stormed through Europe, killing at least one quarter of its inhabitants. Then, as mysteriously as it had come, it disappeared. Now molecular biologists have found a clue that may help explain why diseases like the plague rise and fall — and rise again.

The researchers base their conclusions on studies of two strains of bacteria, Yersinia pestis, which causes plague, and Yersinia pseudotuberculosis, which confers resistance to plague but causes only mild symptoms. Hans Wolf-Watz of the University of Umea, Sweden, with Roland Rosqvist and Mikael Skurnik of the Swedish Defense Research Establishment, first examined two genes believed to help Y. pseudotuberculosis invade cells. The genes code for invasin and YopI, proteins found at the surface of Y. pseudotuberculosis. Y. pestis contains altered forms of the genes that do not produce proteins. The scientists mutated the Y. pseudotuberculosis genes for invasin, for YopI or for both proteins and administered bacteria containing the altered genes to mice. They then measured the bacteria's virulence by counting the number of mice that died.

The results show that a mutation in one or the other of the two genes barely changes the bacteria's virulence, but mutations in both genes make the bacteria remarkably more deadly. Apparently, the presence of invasin and YopI results in a mild, controlled infection but their absence allows bacteria to ravage cells and cause disease, the researchers say.

Next, the scientists closely examined the YopI genes of Y. pestis and Y. pseudotuberculosis. They found only one small genetic difference between the two strains. This difference and one in the invasin gene account for Y. pestis' virulence, they conclude.

Finally, in a sort of reverse of the first experiment, they transplanted the YopI gene from Y. pseudotuberculosis into Y. pestis. Confirming expectations, Y. pestis became notably less virulent.

The researchers propose that plague epidemics may have come and gone when nearly harmless strains like Y. pseudotuberculosis, with a flick of two genes, became Y. pestis and then, with another switch, mutated back to a non virulent form. But an evolutionary hypothesis cannot be based on genetics alone. Other variables, such as the size of the host population, can determine the course of a disease. In a large population, many mutant forms of bacteria can exist, but when the host population is small, only the less virulent strains survive. (Source: Science News, Vol. 134, 13 August 1988)

New methods aid microbial identification

Developing improved methods for identifying bacterial infections remains one of the important goals for microbiology. Although biotechnology has played a major and well publicized role in this regard through monoclonal antibody and DNA probe based diagnostics, a variety of alternative approaches are also being followed.

Elliot Juni of the University of Michigan (Ann Arbor) distinguishes some of the bacterial characteristics that can be recognized today: chromosomally determined phenotypic traits, cellular composition, DNA or ribosomal RNA sequences, and the ability to genetically recombine. In his presentation here during May's 88th Annual Meeting of the American Society for Microbiology, Juni emphasized the utility of transformation studies. He has found that by using various defined cells and samples of Branhamella catarrhalis, he can determine relatedness between pairs of strains via the quantitative level of growth of recombinant colonies when mixed with a bacterial sample. Crude DNA will effectively transform a closely related strain, will inefficiently transform a less closely related strain, and will fail to transform a non related strain. The technique can also be used to identify members of a "geno-species" (where organisms have evolved considerably but are still relatively closely related) or to show the relationship between genera within families.

Going from the internal workings of the bacterial cell outward to the cell membrane or wall, Myron Sasser from the University of Delaware (Newark) described a technique he is developing based on fatty acid profiles determined by gas chromatography.

Sasser reported that the method could distinguish various strains of Listeria from each other, as well as from species of Brochothrix, Erysipelothrix, Kurthia and Lactobacillus. The key is the ratios of the various fatty acids, rather than their absolute levels, while ratios between different fatty acids are sometimes needed to distinguish different pairs of micro-organisms.

Sasser's database now includes the profiles of more than 300 aerobic and 150 anaerobic species and subspecies and has the ability to identify some 300 fatty acids and related compounds. The software which runs on Hewlett Packard (Palo Alto, CA) equipment is currently being marketed by a start up company called Microbial ID (Newark, DE).

In yet another innovative identification approach, scientists at Mesa Diagnostics (Albuquerque, NM) are bouncing polarized light off specially prepared cultures to obtain their light scattering "signatures". Mesa is commercializing the technique known as multi parameter light scattering (MLS) via a series of semi automated and fully automated instruments.

The novel approach may even work for monitoring the status of cell cultures and for making sure that

recombinant cell lines are still producing as expected. (Source: Bio/Technology, Vol. n, July 1986)

Major plant scourge at last identified

For more than a century, farmers have been fighting Pierce's disease of grapes, phoney peach disease and several "scorches" diseases that leave trees looking parched without discovering the small viruses thought to cause at least some of these blights. Now a researcher has identified and named the common culprit: Xylella fastidiosa, the first pathogenic bacterium affecting plants to be discovered in almost 50 years.

The bacterium is so small it passed through filters made to trap such pathogens, leading to suspicions it was a virus, explains John L. Wells, a plant pathologist at the USDA's Eastern Regional Research Center in Philadelphia. While the organism physically resembles that causing legionnaire's disease in humans, Wells says that genetically it bears no resemblance to any known bacteria. He called it Xylella to denote where it resides in the xylem, the woody conduit through which nutrients pass up a plant's stem or trunk.

Transmitted by insects, principally leaf hoppers, Xylella has very catholic tastes. It stunts ragweed and Johnson grass, yellows periwinkle and causes scorches in almonds, plum sycamore, oak, maple, mulberry even American elms. Cherry trees have carried the highest concentrations of the pest, although they show no symptoms. In most cases, Xylella appears to blight by disrupting a plant's hormone balance, Wells says. In fact, hormone treatment has put some affected trees, including peaches, in remission. In most cases, however, diseased plants must simply be pulled out. But help is on the way. Grafting roots of resistant plants to susceptible trees appears to offer one solution; another is to treat plants with antibiotics. (Source: Science News, Vol. 133, 23 April 1988)

Bacteria at heart of new "biosphere"

A drilling experiment in Sweden may provide evidence to support a controversial theory that oil and gas are not formed from biological material. If Thomas Gold, who proposed the theory, is right, enormous fuel reserves may exist deep in the Earth.

Gold proposes that a type of heat loving bacteria found to be associated with volcanic vents on the floor of the Pacific Ocean might be part of a new "biosphere" deep in the Earth. Such bacteria gain their energy from hydrogen rather than from sunlight, he says.

The conventional theory for the production of hydrocarbons is that biological material compressed at high temperatures and pressures formed oil and gas. Part of the supporting evidence for this theory is that oil and gas contain compounds with biological origins.

Gold, a fellow of the Royal Society, believes that heavy hydrocarbons were trapped deep within the Earth as it was formed. At high pressures these hydrocarbons formed petroleum compounds.

In 1986, he won, with the Swedish State Power Board, the right over the past two years to drill a deep hole to test his theory. The drilling team recovered samples of a magnetic iron mineral (magnetite) and oil from a depth of about six kilometres. The material proved to be very similar chemically to oil and shale much nearer to the surface. Gold's theory is that the deep reserves of hydrocarbons have seeped to the surface over geological time scales, thus accounting for the chemical similarity observed.

The magnetite was also contaminated with biological material, although, says Gold, "no organic sediment is known at that depth". Gold's theory is that the bacteria come from his proposed biosphere of bacteria as the oil seeps upwards. He has sent his samples to laboratories that specialise in analysing bacteria.

Gold's theory will be examined more closely during the coming months, because the Swedish Power Board, the Swedish Government and industry are together putting forward $4 million to drill to a depth of 7.5 kilometres in the same place. (Source: New Scientist, 23 June 1988)

Corynebacterium electio injected

Mitsubishi Petrochemical Co., Tokyo has been injecting DNA into intact Corynebacterium cells via electroporation, a method of increasing membrane permeability by an electrical pulse. Until now, only the protoplast method has been used to insert heterologous DNA into this bacterial genera, but takes a couple of weeks for the protoplasts to regenerate. The "Gene pulser" manufactured by Bio Rad Laboratories, Inc., Richmond, Calif., was used for the studies. (Source: McGraw-Hill's Biotechnology Newswatch, 2 May 1988)

Making bugs that self destruct

Researchers are working on developing genetically engineered bacteria that destroy themselves when their work is done. The technology is based on the discovery of bacterial "suicide genes", genes that help regulate the life cycles of bacteria. When the genes are switched on, for instance, the bacteria die.

Work in suicide genes is not widespread. TMC Inc. (Newark, NJ) is active, targeting waste management and vaccines.

TMC has teamed up with Soren Molin of the Technical University of Denmark (Lyngby) which is developing a suicide gene, known as the hok gene, from the bacterium Escherichia coli. The gene - which is lethal in a wide range of bacteria - codes for a small protein that disrupts the electrical potential across a bacterial cell membrane, destroying the membrane and, thus, the bacterium.

Molin has developed two systems - built in E. coli - that activate the hok gene. The keys to both systems are small segments of DNA called promoters, which act as switches, turning the genes they regulate on or off. In the first system, the promoter attached to the hok gene, known as the trp promoter, is controlled by the amino acid tryptophan: when tryptophan is present in the surrounding media, the trp promoter is in the off position, and the hok gene does not make its protein. When tryptophan is absent, the trp promoter switches on, activating the hok gene. That causes production of the gene's killing protein, destroying the bacteria.

Molin's second system has the hok gene controlled by a promoter called fimA. That is a reversible promoter, i.e., it exists in two orientations and randomly flip flops from one to another. One orientation turns the hok gene on; the other turns it off. Molin engineers bacteria so that initially the fimA promoter is oriented in the off position. However, a certain probability exist

that the fimA promoter will flip flop to the on position, activating the hok gene to produce its killing protein. Hence, a constant fraction of the bacteria will die off. In fact, survival rates for bacteria engineered with this system are 10^{-10} to 10^{-12}, making the bacteria "quite safe" for environmental release.

TMC's aim in waste management is to engineer bacteria that degrade such toxic wastes as polychlorinated biphenyls (PCB). One approach would be to develop a suicide gene with a promoter controlled by PCB. The presence of PCB would turn the promoter off, preventing the suicide gene from making its lethal protein. However, after the engineered bacteria destroyed all the PCB, the absence of PCB would turn the promoter on. The suicide gene would then make its protein, killing the bacteria and avoiding any potential danger from the bacteria remaining in the environment.

In vaccine development, TMC believes that suicide-gene technology could make vaccines better, safer and easier to administer. The idea is to engineer bacteria to make an antigen from a particular pathogen, say, a virus. The engineered bacteria would also contain a suicide gene controlled by a reversible promoter. The vaccine would be given orally, stimulating the body's secretory immune system, which produces antibodies in mucous membranes, including the mouth and gut. It is therefore a first line of defence against pathogens.

Potentially, such a vaccine would have a lot of advantages. The viral antigen is presented by a live organism, which boosts the body's immune response. The organism presenting the antigen dies off, preventing possible side-effects from over exposure to the antigen. And administering a vaccine orally is the safest and easiest way. (Source: Chemical Week, 11 May 1988)

DNA types monopoly on genetic code

The genetic code, built into the structure of DNA, is not alone. A second genetic code is written into the structure of the enzymes that couple molecules of transfer RNA with amino acids. Since the 1960s, molecular biologists have understood how DNA's genetic code links genes with proteins. The code is an alphabet of just four chemical bases. Each sequence of three bases, a "codon", codes for a particular amino acid.

But to turn this code into reality - a particular protein - a cell needs enzymes. These biocatalysts "transcribe" DNA into a nucleic acid intermediary, messenger RNA (mRNA). Messenger RNA then leaves the nucleus of the cell and engages with the ribosomes, small structures in the cytoplasm where protein synthesis takes place.

Here another kind of nucleic acid, transfer RNA (tRNA), comes into action. Molecules of tRNA selectively pick up amino acids, and carry them to the ribosomes. Three bases on a tRNA molecule called the anticodon pair up with the codon on the mRNA. The system ensures that the amino acids are linked up in the right sequence, following the instructions originally encoded in the sequence of the DNA bases.

The interaction that joins tRNA and mRNA is well understood; it is simply a matter of bonding between complementary bases, which also holds DNA's two strands together. What is still largely mysterious is the "second" genetic code - how one tRNA manages to pick up the right amino acid. This is a "bilingual" interaction, between a nucleic acid and an amino acid. The mediators in this key coupling are specific enzymes, known as aminoacyl transfer RNA synthetases. The enzymes recognise both partners in the encounter, and pick up an amino acid first. No one yet knows exactly how the enzymes then recognise the right tRNA, but the enzymes apparently do not look at the anticodon. Research by Ya-Ming Hou and Paul Schimmel at the Massachusetts Institute of Technology suggests that the enzymes focus instead on a part of the molecule distant from the anti codon.

Hou and Schimmel studied mutants of a tRNA molecule, from the bacterium Escherichia coli, that is normally specific for the amino acid alanine. The researchers showed that by changing a single base pair (G U) in one region of tRNA, they could change the amino acid specificity of the molecule. That is the tRNA would no longer pick up alanine. Furthermore, the researchers found that the introduction of just this single base pair into other tRNA molecules, normally specific for cysteine and phenylalanine, turned them into alanine recognizers.

As yet, researchers can only speculate as to how the code works. It might depend on stereochemical interactions between the paradoxons and the amino acids. The part of the enzyme that picks up the amino acid is physically near to the paradoxon. A direct interaction between the two might underlie the recognition process. It is apparently a more deterministic, "nondegenerate" code than the classical one, where an anticodon can often recognize more than one codon. There are 20 aminoacyl transfer RNA synthetase enzymes - each recognizes all the tRNAs that are specific for a given amino acid (there can be as many as six due to the "degeneracy" of the classical code).

Dr Hou speculates that the second genetic code may be older than the classical code, in evolutionary terms. It could help to explain why the classical code is a sort of "frozen accident" - it might have arisen: it might have been "superimposed on a more fundamental, deterministic code", says Dr Hou. What links the two codes, he points out, is the transfer RNA: paradoxons and anticodons are physically united in the same tRNA molecules. (Source: New Scientist, 19 May 1988)

Cracking the DNA code

Biologists have been able to efficiently separate strands of circular DNA, the tightly coiled chains that are found in all of the cell's genes as well as in the mitochondria of human organisms. Two scientists at the University of Texas Health Science Center at San Antonio scientists have developed a new separation method, a refinement of a technique called pulsed field gel (PFG) electrophoresis, which sorts particles by causing them to move in an electrical field within a gel. The new technique plays off of DNA's normal rapid zig zag during electrophoresis, and "steers" the molecules into a circular pattern that unwinds the DNA strands. (Source: News Release, 15 July 1988)

Research into trypanosome genes

Trypanosomes may store genetic information somewhere other than in DNA, according to researchers at the University of Amsterdam. A mutation of the codon for amino acid 170 of cytochrome oxidase apparently does not prevent the trypanosomes from still making the correct protein. Although messenger RNA for the enzyme exists, DNA probes have not yet

found a corresponding section of corrected DNA. Thus, the researchers speculate that the mRNA may be created in some way other than templating off the cell's DNA. In addition, a long mRNA for apocytochrome B has a sequence of 34 additional uridines not coded for in the mitochondrial DNA. The trypanosomes may have lost information from DNA but still retain it in some unknown way. (Extracted from New Scientist, 2 June 1988)

Research on viral genes

Links between leukaemia virus and neurological disorder using gene amplification technology found

The human T-cell lymphoma leukaemia virus type I (HTLV-I) has been detected in patients with chronic progressive myelopathy (CPM), a neurological disorder that causes paralysis and occurs in several parts of the world. Using the company's proprietary gene amplification technology, Cetus Corp. scientists working with researchers at the State University of New York detected HTLV-I DNA in the blood and spine fluid of certain CPM patients who were HTLV-I antibody positive. Details from: Cetus Corp., 1400 Fifty-Third Street, Emeryville, CA 94608, USA or in UK (415)420-3300. (Source: Biotechnology Briefing, Vol. 1 No. 6, July 1988)

Mode of action of new antivirals elucidated

A family of compounds that inhibit the growth of cold and certain other viruses do their work by binding to a pocket in the viruses' protein shell, X-ray crystallographic studies show. However, virus mutations that block the entrance to the pocket can thwart the antiviral action of the drugs.

Nine compounds that are part of a series of antivirals synthesized at Sterling Winthrop Research Institute in Rensselaer, NY, have been studied by Thomas J. Smith, a post-doctoral scientist in Professor Michael G. Rossmann's group at Purdue University's department of biological sciences, and his colleagues. One of the compounds is in early clinical trials of its effectiveness against cold viruses and related viruses that cause more serious illnesses in humans.

The researchers' crystallographic studies show that the compounds - which consist of rings attached to each end of an aliphatic chain - bind at the crest of a barrel-like structure in one of the proteins that is part of the outer shell of a large family of animal viruses known as picornaviruses. Certain strains of these viruses cause colds, polio, hepatitis A, and encephalomyocarditis.

The researchers believe the presence of the antiviral drug molecules within the protein stabilizes the spherical protein coat so that it cannot break open and release the viral RNA contained inside. The virus is not killed, but cannot replicate within the cells of the animal or human it has invaded. (Abstracted with permission from Chemical Engineering News, 13 June 1988. Copyright (1988) American Chemical Society)

Pathologists find barley destroyer

Plant pathologists have identified the carrier of a viral disease that destroyed barley crops in Montana in 1985 and 1986 and threatens to do the same this year. Nancy Robertson and Thomas Carroll, of Montana State University, discovered that the brown wheat mite, Petrobia latens, hitherto regarded as a harmless inhabitant of barley fields, carries virus like particles from infected barley plants to healthy ones.

Electron microscopy of infected barley revealed these particles which were about 54 nanometres by 130 nm to 4,000 nm. According to Robertson, they are unusually long for plant viruses and resemble insect viruses. The disease causes curling and yellowing (chlorosis) of the barley leaves. Robertson and Carroll are now trying to find out which symptoms are caused by the virus and which by the mite.

The epidemic is, at present, confined to northern Montana and bordering regions of Canada. (Source: New Scientist, 23 June 1988)

Altered fowlpox virus may be used against rabies

Genetically engineered fowlpox virus can protect animals from rabies, according to E. Paoletti of the New York State Department of Health. The virus was modified by inserting a gene from the rabies virus that codes for a glycoprotein. The modified fowlpox virus elicited antibody formation in inoculated animals. The inoculated animals did not develop any symptoms when they were subsequently infected with the rabies virus. Fowlpox virus will not replicate in animals other than birds. Further testing is necessary to confirm the findings. Initial use of a rabies vaccine would be in veterinary medicine, but it would also be useful for humans. (Extracted from New Scientist, 14 April 1988)

Researchers find elusive hepatitis virus

The Chiron Corporation announced that it has discovered the virus that causes non A, non-B hepatitis, which infects 300,000 people each year through blood transfusions in the US alone.

Several viruses can cause hepatitis. Hepatitis A is rare in developed countries. Hepatitis B, which was identified in 1968, infects some 200 million people worldwide. Screening and immunization has almost eliminated it from blood supplies, at least in the developed countries. Only 5 per cent of cases of hepatitis in the US are from hepatitis B.

The elusive non A non-B virus causes the remainder of blood-borne cases. While half of these infections lead to acute, or temporary disease, the rest develop into chronic hepatitis. One fifth of these chronic infections, or 30,000 in the US yearly, develop into cirrhosis of the liver. Last year, Michael Houghton and colleagues at Chiron isolated the genome of what they believed to be the non-A non-B virus.

Only the techniques of recombinant DNA allowed the team to deduce the immunological mechanisms of a virus no one had seen. Houghton first cloned the virus's entire genome into bacteria. His colleague, Qui Lim Choo, and others on the team then spent two years screening millions of separate copies of the clones searching for one that produced the right viral protein. The protein had to bind to an antibody that Houghton assumed must exist in blood infected with non A non B hepatitis.

Last year, the team believed they had found the protein, one from the virus's outer coat and thus likely to trigger the body to produce antibodies against it. In its first test, an assay containing the protein bound to antibodies in blood from chimps and non A non B hepatitis but not to blood from chimps with other types of the disease. A similar

blind test on 50 people with non A non B hepatitis identified half the infected blood.

All but 1 per cent of 255 healthy volunteers registered negative, which fits with figures on the number of undetected cases that slip by existing blood tests. These are indirect tests for antibodies to core protein in hepatitis B and for liver damage that is common to people with hepatitis.

The company's assay for infected blood, which it will submit to the Government soon for approval, consists of this viral protein placed in small wells on a plate. If an infected blood sample is poured on to the plate, antibodies that the infected individual has raised against the virus will bind to the viral protein. Another antibody labelled with a marker will bind to the first antibody and thus label the blood as infected. (Source: New Scientist, 26 May 1988)

Virus finds sanctuary in the bone marrow

The bone marrow, where all new blood cells form, probably harbours quantities of cells infected with the human immunodeficiency virus. Recent research by Thomas Folks and colleagues at the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Maryland, suggests that some precursor cells in the bone marrow may form a reservoir for HIV.

Folks and his colleagues at the NIAID had already found the virus macrophages, and their precursors, monocytes. Macrophages are large mobile cells that can swallow and destroy bacteria and sometimes viruses.

The scientists wondered how early the virus strikes during the cell's evolution from precursor to maturity. To find out, Folks extracted bone marrow from a cadaver - the person had not been infected with HIV - and extracted a subset of immature cells from the bone marrow.

He used a novel technique, developed by Steven Kessler at the Naval Medical Research Institute in Bethesda, which involves attaching minute magnetized beads to a monoclonal antibody that in turn attaches only to cells of this particular subset. A magnet placed next to a test tube of such marrow will attract only the cells attached to magnetized beads, which can then be isolated.

Folks infected some of the precursor cells with HIV. The cells survived instead of clumping together and dying, as would happen if HIV were mixed with mature T cells. This suggests that, in the body, these cells might form a reservoir of infection and could be an explanation for the long latency of HIV.

Folks speculates that mature blood cells such as lymphocytes passing through the bone marrow may pick up virus from the infected precursor cells, which sometimes burst from the number of viral particles inside them. Or, he adds, the precursors may mature into monocytes, and then into macrophages, while still infected. This fits in with what scientists already know, that the virus seems to be less efficient at killing mature macrophages.

Perhaps the most surprising finding of this study, is that the precursor cells do not possess the CD4 receptor, the protein which scientists have, up till now, believed was essential for the virus to lock onto the cell.

Folks and his colleagues will now look for infected precursor cells in marrow from patients infected with H.V. (Source: New Scientist, 12 May 1988)

UV light can activate the latent virus

American and Belgian researchers have found that ultraviolet light, including sunlight, can activate the latent genetic material of the human immunodeficiency virus in infected cells. The scientists raise the question of whether sunlight on the skin of an infected person may play a role in activating the virus.

The study also has important implications for researchers who want to isolate the virus from infected people, a time consuming task. The scientists found that it was possible to greatly shorten the time needed to detect the virus if the first exposed cells to ultraviolet light.

The team of researchers, from the research arm of the pharmaceuticals company, SmithKline Beckman in the US and Belgium, started out when they had found that both ultraviolet light and a drug which damages DNA, called mitomycin C, dramatically activated the viral gene that contains HIV's genetic material.

This effect led the team to look at the influence of ultraviolet light in an experiment which more closely resembled conditions in the body. They irradiated human T cells, infected them with HIV, and then tested for signs of viral growth. Whereas it took seven to eight days to detect virus in untreated cells, the team found virus in the irradiated cells within four to five days.

With the genetically engineered cells, just half an hour of exposure to sunlight resulted in activation of the viral genetic material. This finding may be particularly relevant as HIV is known to infect certain cells in the epidermis of the skin. However, no one knows whether enough ultraviolet light penetrates the skin from sunlight to have any effect on the activity of the virus. (Source: New Scientist, 12 May 1988)

Interferon can stimulate cells to "kill the virus"

British scientists say that they have managed to activate specific cells of the immune system in two patients with AIDS. The researchers claim that the activated cells were able to kill both virus and cells infected with HIV in the body. The condition of both patients has improved, the researchers say, since the treatment six months ago.

The technique the research team used is called "adoptive immunotherapy". The therapy involves separating the patients' lymphocytes from the blood, and incubating these with interferon alpha, a natural chemical normally produced by cells of the immune system. According to James Sharp, a haematologist who founded a private research company, in London called Brownings, the interferon activates the body's killer cells. These cells seem to kill virus when they are injected back into the body.

Sharp and his colleague, Jabar Gotch, also added zidovudine (formerly known as AZT) to the lymphocytes while these were incubating. This was to prevent HIV present in the cells from replicating.

The two patients, both at an early stage of the disease, received this therapy on five

[illegible] a period of three weeks. Sharp said [illegible] that both patients had recovered from [illegible] enlarged lymph nodes following the [illegible] and lost weight. They are still well, [illegible].

[illegible] interleukin 2 as the [illegible] lymphocytes because this [illegible] activates T-killer cells rather [illegible] T-helper cells that harbour HIV. To [illegible] researchers add interleukin 2 as the [illegible] activator. It is not appropriate to use [illegible] people with AIDS because it [illegible] T helper cells. This, in [illegible] replication of the virus. [illegible] 2 May 1988)

[illegible] provide clues to the biology of [illegible]

[illegible] strains that produce unusual [illegible] disease are illuminating our [illegible] of HIV. Brigitte Barre-Sinoussi, of [illegible] Paris, reported two case [illegible] with AIDS whose illnesses had [illegible] atypical patterns. She and her [illegible] that the Zairean strain of the [illegible], called HIV NDK, was a hundred to a [illegible] T killing cells than a [illegible]. Further tests showed that [illegible] with many different [illegible] protein on the [illegible]. However, HIV NDK closely [illegible] strain of HIV also isolated from [illegible].

[illegible] all the isolates [illegible] Africa, mainly from Zaire and [illegible] Republic, seemed to be highly [illegible] viruses isolated from [illegible] The reasons for this [illegible] [illegible] a given variety of this [illegible] the virus per se". [illegible] whether African [illegible] got HIV in general be more [illegible]

[illegible] a little-noticed report of a [illegible] pathway (AIDS [illegible] apparently recovered [illegible] when he was ill, the [illegible] to take the virus from [illegible] but from the [illegible] to cancer, they [illegible] the virus from either body [illegible] Antibodies were present, however, in [illegible] spinal fluid.

[illegible] study the [illegible] of this virus, they were [illegible] that they were not able to grow it [illegible] was that HIV normally grows in. They [illegible] in immature cells such as [illegible]

[illegible] was, though apparently [illegible] with HIV. Barré-Sinoussi suggested [illegible] be the example of someone whose defences [illegible] the infection.

[illegible] factor in protecting such cases [illegible] to be very, however. [illegible] suggest that the virus's genetic [illegible] present in the cells of these [illegible]

[illegible] Johns Hopkins [illegible] Baltimore, Maryland, found four men (0.4 per cent) who lost antibodies out of 1,000 tested. The men are part of the American Multicenter AIDS Cohort Study, which includes almost 5,000 homosexual and bisexual men in four cities, and aims to examine the natural progression of infection with HIV-1.

The researchers, led by Homayoon Farzadegan, assistant professor of epidemiology, reported last year that four men in the cohort study had lost detectable antibodies. They tried to culture the virus from the men's white blood cells, which the virus normally attacks, but without success.

More recently, they tried to find traces of the virus using a new and sophisticated test called the polymerase chain reaction. This test can find a single molecule of viral DNA among the DNA in someone's cells, and amplify it to a level at which scientists can detect it.

The team at Johns Hopkins was testing blood samples from patients in the cohort at six month intervals over a period of two years. Five men had antibodies at their first or second visit, but later tests failed to detect these. Exhaustive checks by the researchers excluded the possibility of the initial results being false positives, and of the blood samples being mixed up or contaminated.

The polymerase chain reaction found HIV-1's genetic material six to 18 months after the last positive test for antibodies in four of the five men. All four men were well. They had no symptoms such as swollen lymph glands. They also had normal counts of T helper lymphocytes, which usually decline in number in AIDS.

The chain reaction failed to find genetic material from the virus in the fifth man. The researchers concluded that he may not be infected with HIV-1 after all.

Oddly, later tests on two of the four men, in whom the polymerase chain reaction had been positive, were negative. The virus might might still be present in these individuals, perhaps sequestered somewhere such as the brain, where tests carried out on circulating blood cannot detect it.

The researchers say that the risk posed by these findings to the safety of the blood supply is extremely small. This is partly because loss of antibodies appears to be extremely rare. In addition, the blood transfusion service in the US, as in Britain, asks people who are at high risk of being infected not to give blood.

Farzadegan and his colleagues now plan to follow up the four men to see whether their antibodies eventually return. (Source: New Scientist, 26 May 1988 and 9 June 1988)

New technique reveals extent of viral variations

Researchers are finding that the human immunodeficiency virus is far more genetically variable than once supposed. Individuals can be infected with several unique strains of HIV. Some babies of infected women are born with quite different strains of HIV than those found in their mothers. A single infected cell can harbour as many as seven genetic variants of HIV.

These startling findings have only been possible using polymerase chain reaction (PCR), which scientists from Cetus Corporation in California helped to develop over the past year.

Steven Wolinsky, from the Northwestern University Medical School in Chicago, told the conference that he has been able to detect about six molecules of DNA in 150,000 cells - equivalent to finding a needle in a haystack.

He and his colleagues from Cetus have used the technique to identify the presence of viral DNA in newborn babies. Previously, scientists had only been able to detect the presence of antibodies to HIV in these infants. The antibodies could have come from either the child or its infected mother. The child itself could actually be free of HIV even though it carried its mother's antibodies.

Maternal antibodies can persist for up to 15 months after birth, Wolinsky said, but this does not necessarily mean that the virus has travelled across the placenta and infected the baby in utero. Hospitals in the US and Europe treat babies with HIV antibodies as if they are infected. This can be clinically and emotionally traumatic in the early days of life.

In a group of 15 babies, Wolinsky and co-workers isolated HIV and analysed the genetic sequence of the viral DNA to discover the similarity of the viruses infecting the babies to those infecting their mothers. Wolinsky found that in two cases, quite different strains of HIV infected the baby and the mother. There are two possibilities. One is that the virus has mutated radically in the foetus. The other is that Wolinsky has found a viral strain in the baby that also occurs in the mother, but which has not been identified - perhaps because it is present at very low concentrations in the mother.

Other researchers, such as Simon Wain-Hobson and Maureen Goodenow from the Pasteur Institute in Paris, have confirmed - again using the PCR technique - that a person can be infected with several strains of HIV, although some variants have only minor differences.

One of the most interesting findings to emerge from Goodenow and Wain-Hobson's work is the discovery of viruses that are defective. Such viruses have mutated to produce short sequences, called "stop codons", inserted in places that once coded for amino acids. Stop codons prevent the viral DNA from being expressed in the cell. Goodenow and Wain-Hobson have found a surprising number of these defective viruses in infected cells.

This research may shed light on what makes a virus cause disease. An HIV of one strain may turn out to be more pathogenic than an HIV of another strain. The research, however, underlines just how difficult it will be for researchers to design an effective vaccine against such a mobile target as HIV. (Extracted from New Scientist, 23 June 1988)

AIDS: even in vivo evolution persists

The AIDS virus, HIV 1, is notorious for its ability to mutate rapidly, making it a difficult, "moving target" for scientists trying to develop an effective AIDS vaccine. New research provides a genetic explanation for some of the clinical complexity of AIDS infection, and supports previous findings that rapid and significant HIV 1 mutation may be rampant within individuals even after initial infection.

Researchers at the University of Alabama at Birmingham and the University of Miami (Fla.) School of Medicine cloned and analysed the genetic makeup of AIDS viruses isolated from two infected patients over a 16 month period. In three samples, they found 7, 9 and 13 distinguishable varieties of the virus. The limited degree of difference among the varieties suggests the virus variants evolved after the patients were first infected.

Related work by the Alabama researchers in collaboration with scientists at the National Cancer Institute in Bethesda, Md., and the Walter Reed Army Institute of Research in Washington, D.C., indicates different HIV 1 clones may prefer to infect different types of white blood cells. This may account for the heretofore unexplained variation in HIV infectivity of T cells and monocyte-macrophages. (Source: Science News, Vol. 134, 13 August 1988)

AIDS and antibodies: a bad combination?

New findings depict "one of the worst possible scenarios" for developing an AIDS vaccine, according to a co-author of the study. The researchers report that the AIDS causing virus (HIV) can, by changing only one amino acid on its surface, thwart certain antibodies that prevent it from infecting cells. These "neutralising antibodies" are often the basis of effective vaccination.

A disturbing fact about HIV is that it frequently mutates, and neutralising antibodies against one genetic strain of HIV will not necessarily work against a second strain. Since each AIDS patient may harbour a slightly different variety of HIV, one vaccine may not suffice in halting AIDS. Also, studies show that HIV cultures isolated periodically from a single AIDS patient may reveal changes, becoming more virulent with time.

Now, a study suggests that AIDS viruses that differ by only one of two amino acids elicit drastically different responses from neutralising antibodies. David Ho, of the Walter Reed Army Institute of Research in Washington, D.C., and his colleagues tested viruses that varied in the amino acids of their protein coverage, the HIV shell. To the viruses they added a variety of blood serum samples that previous tests had indicated contained HIV antibodies. They then recorded each sample's geometric mean titer (GMT), a measure of its ability to neutralize a virus. They discovered that the various viruses, though almost identical, varied considerably in the degree to which the sera could neutralize them. A single amino acid change in the protein coat of a virus with a GMT of 2,000 for a particular serum sample could make the GMT drop to almost zero with the same serum.

According to the investigators, the study accords with AIDS researchers' that their carefully cloned strain of virus may contain a mixture of HIV variants and that it only takes one amino acid change to abolish a virus' ability to be neutralized by a particular set of antibodies. (Source: Science News, Vol. 134, 16 July 1988)

Children and AIDS

The vast majority of paediatric AIDS cases in the USA are now acquired perinatally - that is, from early pregnancy through the time of birth - through infection of the mothers with the human immunodeficiency virus (HIV), not because they are drug users, but because they were exposed to high risk males. As approximately half the children born to HIV carriers are expected to develop fatal AIDS, this represents an area of great concern. Previously, blood transfusions accounted for the majority of paediatric AIDS cases nationwide.

Although perinatal AIDS cases reported to the Centers for Disease Control represent just a tiny fraction of total cases, the latest CDC figures reflect almost a doubling in one year. Of the 816 perinatal cases cumulatively reported through January, 38% were reported in the previous 6 months.

By 1991 the cumulative number of infected children will range from 10,000 to 20,000, most with symptoms, and one of every 50 to 75 US hospital beds will be occupied by a child with HIV infection. (Source: Science News, Vol. 134, 30 July 1988)

HIV anomaly traced in family tree

The AIDS virus and its family tree are providing a new view of the virus' disease-causing ability.

Japanese researchers have reported that an apparently harmless virus found in African monkeys is not a distant relative of the virus that causes AIDS in humans and probably is not to blame for the AIDS epidemic. Their findings contrast with earlier predictions that the AIDS-causing human immunodeficiency virus (HIV) is the result of a recent evolutionary "jump" from the monkey virus. That assumption was based in part on evidence from contaminated laboratory specimens.

Masami Hayami of the University of Tokyo and his co-workers analysed the entire DNA sequence of the simian immunodeficiency virus, SIV_{AGM}, that normally infects African green monkeys. The virus stimulates production of antibodies in green monkeys but causes no overt symptoms. By comparing its genetic sequence with those of related immunodeficiency viruses, the researchers found that SIV_{AGM} is equally and distantly related to the two human immunodeficiency viruses, HIV-1 and HIV-2. This indicates the human AIDS viruses evolved independently for "a long time", the researchers say.

Other scientists agree that a monkey origin is unlikely, but these researchers, led by Dwight P. Bolognesi at Duke Comprehensive Cancer Institute in Durham, dispute several of the Japanese conclusions. On the basis of his group's own sequencing experiments, plus their analysis of the virus used by the Japanese, Smith said that SIV_{AGM} is much more closely related to HIV-1 than to HIV-2. He also says all three virus groups appeared not later than 30 years ago, and probably are not more than a few years old. Smith and his co-workers looked at thousands of data points in their tree construction.

However, most of the differences found by the Japanese may reveal the mechanism behind HIV's extreme rate of variability. For example, a small, apparently "nonsense" sequence is encoded in the DNA of SIV_{AGM} in the region that codes for production of a protein component of the viral envelope. The presence and exact location of this "in frame stop codon" may change significantly the structure of an envelope protein and may affect virulence, the researchers note.

Perhaps more intriguing, the Japanese researchers found that SIV_{AGM} lacks a gene - the so-called "R" gene - found in both HIVs and in a related simian immunodeficiency virus, SIV_{MAC}, which causes an AIDS-like disease in macaque monkeys. Scientists still do not know the function of the "R" gene, but it may prove critical to an understanding of what makes SIV_{AGM} non-pathogenic or what makes the African green monkey resistant to the virus. (Source: Science News, Vol. 133, 11 June 1988)

British plan trials on cats

Researchers in Britain will know by the end of the year whether another approach to developing an AIDS vaccine is feasible. The plan is to insert genes for HIV into DNA taken from yeast. The resulting "cassette" of DNA then codes for proteins, including HIV antigens, which form spherical particles that resemble viruses. Biotechnologists hope to produce these virus-like particles in giant fermenters to make a cheap AIDS vaccine.

According to the scientist in charge of this work, Alan Kingsman of the University of Oxford, a human trial of the vaccine could take place "any time within the next two years". Meanwhile, he intends to test the pseudovirus this summer with a potential vaccine against another retrovirus, the feline leukaemia virus, which infects cats.

The aim of the experiment is to see which of these proteins is best at stimulating the production of antibodies in cats inoculated with the "vaccine". If the cats produce antibodies that are effective at neutralizing, or destroying, the feline virus in the laboratory, then Kingsman will challenge the cats with live virus. This will establish whether they can fend off the real thing. Kingsman has tried to make a vaccine against feline leukaemia virus but with limited success.

The Medical Research Council will fund the experiment on cats. Kingsman hopes that the trial will produce an effective vaccine against feline leukaemia virus, but more importantly, will show whether it is possible to make a vaccine with yeast particles.

The next stage is to prepare for a human trial with an AIDS vaccine made from yeast particles. Kingsman has already inoculated small animals, such as rabbits and rats, with particles carrying HIV proteins to see the level of the immune response. He is planning a similar trial with simian immunodeficiency virus, which appears to cause a type of AIDS in certain species of monkey. (Source: New Scientist, 21 April 1988)

New nomenclature for HIV genes proposed

Five of the major figures in research on the molecular biology of human retroviruses - Robert C. Gallo, Flossie Wong-Staal, Ian Mackintosh, William A. Haseltine, and Mitsuaki Yoshida - have proposed a unified nomenclature for the regulatory genes of HIV 1 and HIV 2.

As a consequence of the tremendous activity in this field and the fact that some of the genes were identified by several groups within short periods of time, very often more than one name has been used to designate a single gene. This can be very confusing, particularly to newcomers to the field.

The seven regulatory genes, one of which is found only in HIV 1 and one of which is found only in HIV 2, are:

- tat. Previously sometimes labelled tat 3 and TA, tat encodes a protein that amplifies the expression of all viral genes, including itself, through an interaction with the regulatory portion of the viral genome known as the long terminal repeat (LTR). The tat protein increases transcription of the viral genome, but it probably also acts post transcriptionally by, for instance, enhancing the stability of viral messenger RNA.

- rev. Previously called art or trs, rev stands for regulator of expression of virion proteins. The product of rev appears to promote the accumulation of the higher molecular weight viral mRNA sequences that encode structural proteins. HIV's complement of proteins are produced by reading and splicing the same genetic material in different ways. When the mRNA copy of the HIV genome is fully spliced, the small regulatory proteins are produced for small mRNA fragments. The rev gene appears to stabilize the unspliced mRNA to allow longer stretches of mRNA to be translated into structural proteins such as the virus envelope and core proteins. The rev gene also may act to direct transport of unspliced mRNA to cellular compartments where it is protected from normal cytoplasmic nucleic acid degradation processes.

- vif. Previously called sor, A, F', and Q, vif stands for virion infectivity factor. In the absence of vif, AIDS viruses are able to spread directly from an infected cell to an uninfected cell, but cell-free virions are greatly reduced in their ability to infect new cells. This gene is not present in other human retroviruses, and, according to Haseltine, it is possible the presence of vif in the HIVs "gives the AIDS epidemic its ability to spread rapidly in populations" compared with the human leukaemia retroviruses.

- nef. Previously called 3'-orf, B, B', and F, nef stands for negative regulatory factor. The product of nef alters the fundamental cellular machinery of infected cells in order to repress virus replication, a process that likely plays a role in HIV latency.

- vpr. Previously called R, a gene that encodes a protein the function of which remains unknown.

- vpx. A recently discovered gene found only in HIV-2 and simian immunodeficiency virus (SIV), the function of which remains unknown.

- vpu. Another recently discovered gene, vpu is found only in HIV 1. Preliminary research suggests it acts to suppress viral replication.

The names of vpr, vpx, and vpu are likely to change when their functions have been determined. (Reprinted with permission from Chemical Engineering News, 11 July 1988. Copyright (1988) American Chemical Society)

Research instrumentation

Particle accelerators to image proteins

Particle accelerators allow imaging proteins at speeds of billionths of a second. The technique could allow viewing protein structure changes that last only a millionth of a second as the protein undergoes chemical reactions. A technique that shows a protein's movement might also help determine protein shapes. Determining protein shapes might help the development of new drugs or otherwise treat disorders involving protein dysfunction. X ray crystallography has been the standard technique for trying to determine protein structure, but this has serious limitations. Cornell University researchers use an undulator to accelerate particles to produce X rays that last one trillionth of a second. The reflections of these X rays are bright enough to allow imaging. Researchers hope to be able to take movies of proteins using the new technique. Meanwhile, nuclear magnetic resonance spectroscopy is being adapted by researchers at the University of Pennsylvania to allow for atom by-atom information on the structure of proteins. (Extracted from New York Times, 5 July 1988)

2000 DNA Sequencer

The Genesis 2000 automated DNA sequencer from Du Pont takes an innovative approach to determining the exact structure of genetic material by using highly efficient fluorescent labels. The labels are covalently bonded to dideoxynucleotide terminators so that DNA fragments can be detected, and the sequence bases determined using a modified Sanger method. These fluorescent sequencing fragments are resolved temporally rather than spatially in a single lane by conventional polyacrylamide gel electrophoresis. Details from: Du Pont (UK) Ltd., Wedgwood Way, Stevenage, Hertfordshire SG1 4QN or ... 0438 734777. (Source: Biotechnology Bulletin, Vol. 7, No. 5, June 1988)

Hitachi launches DNA sequencer

Hitachi Ltd., Tokyo, will begin marketing its "Beta ray Type DNA Sequencer", which detects radioisotopes incorporated into nucleic acid fragments. Currently available sequencers employ the fluorescence detection system. The machine uses the dideoxy method, in conjunction with P^{32} isotope. Some 250 bp can be determined in just over seven hours, and four different samples may be run concurrently. (Source: McGraw Hill's Biotechnology Newswatch, 2 May 1988)

Sensor to detect molecules

Molecular devices has developed a light addressable potentiometric sensor that can detect different biological molecules. The simple semiconductor device responds to surface potentials at an electrolyte silicon interface through the effect of such potentials on electric fields within the semiconductor. Its high potentiometric stability enables it to make biochemical determinations with great sensitivity. The device has been used to measure enzyme concentrations in one nanoliter samples. Different sensing sites can be addressed with light instead of fixed wires or other current paths, enabling potentiometric measurements to be completed with a single device. (Abstracted with permission from Chemical Engineering News, 30 May 1988. Copyright (1988) American Chemical Society)

System for automatic sorting of monoclonal antibody-producing cells

Sumitomo Electric Industries, Ltd. has developed a system for the automatic sorting of cells which produce monoclonal antibodies.

The monoclonal antibody is a unitary antibody reproduced in large quantities by cell fusion. Since it characteristically discriminates and binds itself with only a specific type of substance, it is widely used for the diagnosis and treatment of various kinds of diseases. It has also been employed for the separation and purification of diverse physiologically active substances. High expectations have been placed on it for use in the research, diagnosis and treatment of cancer.

To obtain the monoclonal antibody, it is necessary to sort one cell producing the target antibody from among a group of over 100,000 cells subsequent to cell fusion. Previously this sorting task required a minimum of 2 - 3 months work by skilled researchers. Thus, there had been a limit to the number of processable cells, and this had posed the biggest obstacle to obtaining monoclonal antibodies for working with cancer. Research was intensively advanced to develop a system enabling automatic sorting of these cells with ease and in large quantities.

When sorting monoclonal antibody producing cells, the most vital precaution is to prevent the live cells from losing their activities. Consequently, it is necessary to constantly monitor the conditions of the cells and to provide them with the appropriate amount of nutrition depending on the situation and to proceed accurately to the next step.

To perform these operations automatically, operations which previously relied on the judgement of researchers, the company developed (i) a system for optically measuring the pH values of culturing liquids; and (ii) a system for measuring cell proliferation quickly without injuring the cells. Accordingly, it is now possible to measure the pH values of culturing liquids as quickly as one second and very accurately. The judgement of cell proliferation condition is performed by picture processing for extracting live cells while accurately discriminating live and dead cells.

A mechanism simulating the detailed handling procedures of skilled researchers was also developed for pipetting and other cell processing operations, with each of these operations designed for the non injury of cells. In addition, basic research was advanced on methods for discriminating individual cells without inflicting any injury. As a result, cell discrimination can now be accomplished very accurately, conveniently and with a higher probability than ever before.

This system enables schedules to be drafted automatically in conformance with input routine processes. All operations, from the setting of fusion cells onto the system to the final separation of monoclonal antibody-producing cells, can be performed automatically, around the clock, completely eliminating manual operations. This enables the processing work normally performed by several skilled researchers to be accomplished automatically with ease. Further details from Sumitomo Electric Industries Ltd., Administrative Department, 3-12, Moto Akasaka 1-chome, Minato-ku, Tokyo. Tel.: 03 423 5221, Telex: 28202 SEITOKJ. (Source: JPRS, February 1988)

Laser-based gene slicing machine

Hamamatsu Photonics (Japan) has developed a "semiautomatic", dual-beam argon laser based gene slicing machine that allows chromosome fragments of under 2.5 million pairs to be removed by hand. The system has a laser beam of only 0.4 micron in diameter and reportedly allows a novice to prepare chromosome parts by monitoring sample chromosome on a video display screen. When done by hand, an expert in cutting genes averages about 1 gene min. A prototype of Hamamatsu's system, used at the National Institute of Agrobiological Resources, speeds up the process to about one gene sec. (Extracted from Chemical Week, 23 March 1988)

Bioreactor increases cell growth x 10

Marketed by Sterilin, the Helico Bioreactor provides increased product mass from cell culture. Employing airlift fermenter technology, continuous culture and an alginate macrocarrier encapsulation system, the equipment is said to give a tenfold increase in animal cell density in comparison with traditional suspension culture. Other advantages include simple material handling, automatic reuse of biocatalysts, and control over medium and nutrient. The Bioreactor has applications in biotransformations, e.g. the isomerization of glucose to fructose, and the manufacture of antibody molecules.

Cell immobilization prevents washout or decrease in density during media exchanges, because the cells are physically entrapped. Perfusion of the culture medium sets up an homogeneous growth environment and thus optimizes culture conditions.

Contact: Sterilin, Lampton House, Lampton Rd., Hounslow, Middlesex, TW3 4EE; Tel.: 01-572 2468. (Source: Manufacturing Chemist, May 1988)

Molecular computer graphics

Chemical and pharmaceutical companies that struggle with time-consuming molecular and drug interaction studies in pursuit of new products may get some help from two new computer graphics systems developed by Ardent Computer (Sunnyvale, Calif.) and Stellar Computer (Newton, Mass.). The systems are based on computers that sell for $80,000 and $98,000, respectively. Moreover, the companies say, their systems can do jobs performed by supercomputers, which sell for as much as $20 million.

Several molecular graphics programs for personal computers (PCs) now on the market also can be used to manipulate atomic charges, bond lengths and other data, then display the results as a new molecular structure. However, PCs are generally too slow, with limited memories, and their resolution too low to handle increasingly sophisticated graphics programs.

Ardent and Stellar say their products use large, high resolution monitors to display simulated molecules that can be manipulated on screen. Stellar, which shipped its first Graphics Supercomputer Model GS1000 in March, has marketing agreements with producers of more than 12 molecular modeling programs. By August, Ardent will ship it's first system - The Molecular Simulator (TMS) - which comes with a choice of programs from BioDesign (Pasadena, Calif.).

About 15 molecular modeling packages are available from third party vendors. Genentech (South San Francisco) hopes to have a TMS system soon. (Source: Chemical Week, 25 May 1988)

General

Lightning makes nitrogen usable

Scientists appear to have finally answered one of those basic, simple questions about how the world works that has long eluded them: what is the source of the nitrogen compounds that living things need to survive?

Nitrogen comprises 78 per cent of the Earth's atmosphere, and all living things need it as all the fundamental molecules of life contain it, but, most living things cannot just take what they need out of the air. The nitrogen to be useful, must be "fixed", or combined with other atoms that allow it to be taken up and used by living cells.

Until now bacteria in the soil have been thought the chief heroes of nitrogen capture and

fixation, followed by the manufacture of fertilizer and the use of fossil fuel. All make usable nitrogen compounds. Edward Franzblau and Carl Popp of the New Mexico Institute of Mining and Technology reported at the recent meeting of the American Chemical Society in Las Vegas that lightning may be the number one source of fixed nitrogen in the world.

Dr. Franzblau and others have during the past two summers worked at Langmuir Laboratory for Atmospheric Research to measure the amount of nitrogen fixation produced by flashes of lightning. They measured the amount of lightning fixed by the 100 or so flashes that occur every second on the Earth, and came up with a huge quantity of fixed nitrogen, many times the previous estimates for lightning's contribution.

Earlier estimates had been made largely from laboratory work, not actual atmospheric measurement. (Source: International Herald Tribune, 21 April 1988)

DNA moves into the clinics

DNA analytical methods once confined to research laboratories are moving into clinical laboratories, and a whole flood of practical applications could soon begin. Moreover, that cascade will likely gather far greater momentum because of the US Government's growing resolve to map and systematically analyse all human genes. In addition, US researchers have been carefully preparing for the first clinical tests of gene replacement therapy, with the earliest efforts in seriously ill young patients soon to be formally reviewed.

The two federal agencies overseeing plans for such early therapeutic experiments, the Food and Drug Administration (FDA) and the National Institutes of Health (NIH), went through a "dry run" review of such a proposal late last year. The FDA has authority to review all research involving the use of drug and related products in humans. Besides taking an interest in the safety and efficacy of gene therapy procedures, the FDA will scrutinize materials to see whether they can be reliably produced from one trial to another.

Within NIH, the Recombinant DNA Advisory Committee (RAC) and its Human Gene Therapy Subcommittee are providing a forum for public discussions of the new technology developing general guidelines and promising to review proposals as RAC evaluated early gene splicing experiments. The committee has adopted a "points to consider" document, on ethical as well as scientific issues.

At a meeting last December, the RAC subcommittee evaluated a lengthy preclinical data document, prepared by French Anderson of NIH and his collaborators at NIH and Memorial Sloan Kettering Cancer Center in New York. They want to correct a rare hereditary disease that results from a deficiency of the catabolic enzyme, adenosine deaminase. Its absence leads to one form of severe combined immune deficiency disease, whose victims usually do not survive the first two years of life. The lengthy pre-clinical data document candidly outlines current gaps in scientific knowledge, some of which may be closed only by conducting limited clinical trials.

Even as ambitious federal initiatives are being put into a cohesive framework, clinical researchers are establishing a new variety of diagnostic tests for selected metabolic and other medical disorders using DNA based techniques. Acceleration on so many fronts will soon present a broadened array of social and ethical questions particularly as methods for prenatal diagnosis are developed long before therapies for treating such disorders become available.

Already, several hereditary disorders can be reasonably predicted by chromosomal analysis, as can several forms of malignancy. With some genetic disorders, including Duchenne's muscular dystrophy, several forms of haemophilia, and Huntington's disease, analysis of DNA patterns along with disease incidence within a family can lead to a remarkably accurate predictive diagnosis of disease. Other techniques, which also are based on DNA analysis, are leading to sensitive tests for certain forms of malignancy, such as chronic myelogenous leukaemia, and to infectious diseases.

Before 1985, the only available predictive test for Duchenne's muscular dystrophy was based on measuring the blood levels in carrier women of a muscle enzyme, but it was not accurate and had many false positives. Since then, DNA probes for detecting and cataloguing restriction length polymorphism patterns (RFLPs) in DNA linked to the crucial gene responsible for the disease became available to improve prenatal analysis.

That first set of probes, which were not ideal because of the large size of the critical Duchenne's gene, were replaced last year with new probes derived from messenger RNA (cDNA probes). Despite such technical improvements, however the test is by no means always accurate particularly because new mutations of the Duchenne's gene arise frequently in about one third of all cases.

Haemophilia A, which is caused by abnormalities in factor VIII of the blood clotting protein cascade, is another chromosome-linked disease that is not being followed by DNA analysis within families. Although the critical factor VIII is only about one tenth the size of the Duchenne's gene, it still is very large.

Some malignancies lend themselves to DNA based analysis because they are closely associated with chromosomal rearrangements in cells. In malignant cells of individuals with chronic myelogenous leukaemia, for example, a portion of chromosome 9 is moved onto chromosome 22. Although that event can be followed using traditional microscope based cytogenetic analysis, the analytical procedure is slow.

However, because the chromosomal translocation includes the movement of a particular oncogene, a more rapid alternative test is to detect altered RFLP patterns by DNA analysis using appropriate probes. The procedure is sensitive enough to pick up new junction fragments within peripheral blood cells. Moreover, because low frequency events are detectable, the technique may be useful not only for confirmatory diagnosis but also for monitoring therapy. An application to use this diagnostic procedure is pending before the FDA.

In another twist, the DNA based "fingerprint method" for analysing forensic laboratory samples, determining family relations in paternity suits, and conducting diagnostic tests of genetic diseases has recently been offered in the USA as a commercial service by ICI's Cellmark Diagnostics subsidiary.

The fingerprinting technology analyses short, highly variable, but "stuttered" sequences of DNA that are scattered throughout the genes of individuals. Because analysis depends on patterns throughout a genome, the Cetus PCR amplification cannot be readily applied to bail out investigators when they are given miniscule samples.

None the less, the technology has sufficient sensitivity to be useful for many forensic applications, particularly where its ability to illuminate differences in genetic patterns between individuals can be crucial evidence in establishing guilt or innocence.

This medley of diagnostic developments spanning a wide cross section of infectious and hereditary diseases, cancer, and forensic evidence for criminal activity - promises to stir activity not only in the biotechnology industry and throughout the biomedical community, but also in the courts. However, many perplexing legal and ethical issues must be faced. For instance, there is the very practical question of how insurance companies will deal with screening test information about hereditary disorders. As new practical diagnostic technology becomes available, private insurers could pressure employers not to hire individuals with predispositions to costly diseases, not only to Huntington's disease but also diabetes, hypertension, and other health conditions with strong genetic determinants. Typically, evidence of a pre existing condition is used now in limited ways to disqualify affected individuals from insurance coverage.

Ironically, such pressures could eventually move the US health care system towards adopting more federally mandated standards - a development that is currently disdained by the industry because of the alleged taint of "socialized medicine". (Extracted from Chemistry and Industry, 6 June 1988)

Culture media

If mammalian cells are to survive, divide, and grow outside the body, their environment must at least mimic their natural physiological surroundings. Cell culture media are responsible for carrying out most of that deception. Basal media supplemented with serum (usually foetal calf, newborn calf, horse, or human serum at concentrations from 2 to 20 per cent or greater) and other additives have been the traditional tools.

In general, transformed cell lines have simpler media requirements than untransformed cell lines; they are more likely to grow serum-free. They would seem to be ideal substitutes for serum requiring cultures. Unfortunately, cell lines transformed by oncoviruses and activated oncogenes have regulatory drawbacks.

Thus, there seem to be no simple or universal solutions for mammalian cell culture media. Successful specific formulations for large-scale cell culture production of recombinant proteins tend to be well kept industrial secrets; published work on the subject is scarce. What is evident as the scale of rDNA mammalian cell culture increases, however, is a rising demand for workable serum free media.

EXAMPLES OF CELL TYPE AND GROWTH MEDIA, WITH AND WITHOUT SERUM

CELL TYPE	MEDIA	
	with serum	without serum
BHK (Hamster kidney fibroblast	Glasgow MEM	(Maciage, et al. 1980)
Chick embryo fibroblast	Eagles MEM, M199	MCDB 202 (McKeenhan & Ham, 1977)
Chinese hamster ovary	Eagles MEM	Ham's F-12 Nutrient Media. HB CHO (Hana)
Epidermal keratinocytes, human	KGM (Clonetics)	MCDB 133 (Clonetics)
Heha	Eagles MEM	(Hutchings, Sato 1978)
Hybridoma, mouse	RPMI 1640, DMEM Hybrie Care (ATCC)	HB101, HB104, HI 1, ABC (protein-free, Cell-Enterprises), WRC 935, (Wolfe, et al. 1986)
Hybridoma, human	RPMI 1640	RPMI 1640+HB102, (Glassy, 1987), (Higuchi, 1977)
LAK Cells	LAK Medium (Whittaker)	X-VIVO 10 Whittaker, AIMV (GIBCO), HB 104
Lymphocytes, human	McCoys	HB 104
Melanoma	MEM, SF12	(Barnes Sato 1980)
Myeloma, human (needing LDLs)		HB 101, HB 104, HB 102
Mammary epithelial cells, human	MM Medium (Stampfer, 1982)	(Hammond, 1984)
TIL Cells	TIL Medium (Whitaker MA)	

Abbreviations: AIMV - Adaptive immunotherapy medium. DMEM - Dulbecco's modified Eagle's medium. HB - Hana Biologics. LAK - Lymphokine activated killer. MCDB - Colorado University Department of Molecular, Cellular, and Developmental Biology. MEM - Minimal essential medium. RPMI - Rosewell Park Memorial Institute. TIL Tumour-infiltrating lymphocyte.

The media requirements of the parent cell line are still the best guides to the care and feeding of recombinant cell cultures.

Media manufacturers are already focusing on the specialized market for recombinant pharmaceutical production. For culture of Chinese hamster ovary cells (CHO, strains of which are recognized producers of tissue plasminogen activator, for example), Hana Biologics (Alameda, CA) has just introduced HB CHO serum-free media. Companies are also targeting the needs of the National Cancer Institute sponsored adaptive immunotherapy cancer clinical trials. Whittaker Bioproducts (Walkersville, MD), Ventrex Laboratories (Portland, ME), and GIBCO BRL (Grand Island, NY) have serum-supplemented and serum free media for cultivating lymphokine activated killer (LAK) cells and tumour infiltrating lymphocytes (TIL).

Since the American Type Culture Collection (ATCC, Rockville, MD) began distributing cell lines from its two-year old hybridoma cell bank, it has also been meeting customers' requests for its house brand of hybridoma culture media. Serum-supplemented, this Hybri-Care medium will support growth of 80-90 per cent of hybridoma cell lines. Serum-free, the medium will still support most hybridomas for several passages.

Optimal media for hybridoma cell culture have been investigated by William Long's group at Merck, Sharp & Dohme (West Point, PA). He has determined that, among serum-supplemented media, Dulbecco's modified Eagle's medium (DMEM) based formulations support greater numbers of cells for longer periods than do RPMI 1640-based media. His group is currently comparing commercially available serum-free media over a range of cell lines. (Extracted from Bio/Technology, Vol. 6, May 1988)

D. APPLICATIONS

Pharmaceutical and medical applications

New drug delivery techniques

Technology for delivering drugs to the proper site in the body is rapidly advancing. Old methods such as pills and hypodermic needles have serious limitations. Biomedical engineers are now developing biodegradable plastics, glass beads, etc., to deliver drugs. Transdermal patches are now commonplace and are being adapted for new applications. Advanced Polymer Systems has developed microscopic polymer sponges that are rubbed into the skin like talcum powder to deliver drugs such as topical antibiotics. Each time the skin is rubbed, a bit more of the drug is released. The sponges can also be engineered to release drugs at a certain temperature or humidity.

Researchers in the Federal Republic of Germany have developed contact lenses that deliver antibiotics or drugs to treat glaucoma or other eye diseases. (Eyedrops deliver at most 5 to 6 per cent of a drug to the eye.) Nova Pharmaceutical and Johns Hopkins researchers are developing a biodegradable plastic wafer to deliver drugs to brain tumours. Researchers at MIT and the Deutsches Wollforschung Inst. (Aachen, Federal Republic of Germany) are developing plastic wafers containing insulin and a sugar sensitive enzyme. When blood sugar levels rise, the enzyme is activated, increasing acidity. This increases solubility of the insulin, which can then diffuse out into the bloodstream. Nasal sprays could also deliver some drugs directly to the bloodstream. Contraceptive hormones might be implanted under the skin in match sized capsules, or released from vaginal rings. Injectable microspheres or microcapsules might be injected into the bloodstream to release drugs for years. Liposomes are an especially attractive form of microcapsule for drug delivery. Attaching the liposomes to monoclonal antibodies might allow delivery of drugs directly to target cells. (Extracted from Science News, 4 June 1988)

FDA approves more trials of anti brain tumour bacterial-membrane vesicles

A particle extracted from the cell membrane of Serratia marcesens, and trade-marked ImuVert™, has been approved by the US Food and Drug Administration for expanding Phase II clinical trials in treating brain tumours

Cell Technology, Inc. (CTI), Boulder, Colorado, is now writing protocols to further extend its human studies from Phase II toward Phase III - which measures actual efficacy in brain-cancer therapy. How soon these trials begin, says immunologist microbiologist Richard Urban, who founded CTI in 1982, depends on how quickly patients can be enrolled to try the experimental treatment.

Phase II trials at the University of Utah School of Medicine and New York Medical College, Valhalla, N.Y., convinced the FDA to allow the firm to extend them to other cancer centres initially, the University of California medical schools. Unlike individually acting recombinant BRMs, such as interferon, interleukin and colony stimulating factors, Urban explains, ImuVert is thought to turn on a cascade of responses via the immune system as a whole, which chooses "the sequence, timing and defence systems for attacking a specific disease in synchrony with its total defence strategy". After courses of ImuVert injections over many months of 17 patients at Valhalla, one had no tumour at all, another experienced a 93 per cent reduction in tumour enhancement, and two stabilized. Five of the 17 are still alive, four to 11 months after treatment.

Early-phase trials of the Serratia substance in other human tumours have also shown promising results, but the FDA is authorizing further studies in brain cancer, because for this lethal disease there is no other known remedy, so the risk/benefit ratio is more favourable. Fewer than 5 per cent of brain-cancer victims live longer than five years

Despite ImuVert's striking clinical results, Urban cautions, "We have a long way to go yet to really see it". (Extracted from McGraw Hill's Biotechnology Newswatch, 2 May 1988)

Modified cancer drug could ease treatment

Studies on how compounds pass across the intestines of rats have unexpectedly suggested a way of improving the delivery of drugs to treat cancer. As a result, modifications to a drug commonly used against cancer, 5-fluorouracil, may make it possible to cut down some of its side-effects.

Ramsey Bronk and John Hastewell, at the University of York, made their chance discovery earlier this year when studying how the compounds that form the building blocks of DNA and RNA pass across the gut into the bloodstream. These compounds are called bases. During the manufacture of DNA and RNA, enzymes in the cell add a sugar to each base, which then becomes known as a nucleoside.

One of the bases, which appears in RNA but not DNA, is called uracil. In its nucleoside form, it becomes uridine. Bronk and Hastewell examined the

transport of uracil and uridine across the rat intestine. They found that more uracil appeared on the other side of the intestine (the equivalent to the blood stream) when uridine was in the lumen of the gut than when uracil alone was present.

Uracil, it seems, does not pass readily across the gut wall. Uridine is a different matter. The intestinal cells appear to metabolize this compound into uracil during its transport across the gut wall, with the result that more uracil appears in the bloodstream.

The next step is to find out whether the nucleoside part of the drug 5 fluorouracil, called 5 fluoruridine, is more readily transported across the gut wall. The Yorkshire Cancer Research Campaign has now given the two researchers a grant of 30,000 pounds sterling to investigate this possibility. (Source: New Scientist, 16 June 1988)

Plans for altered lymphocyte release in humans

Two researchers at the US National Institutes of Health (NIH) are seeking permission to perform a controversial experiment requiring the administration of genetically engineered cells to people. If authorized, it will be the first officially sanctioned experiment in which human cells altered by recombinant DNA techniques are returned to the body.

The experiment, proposed by Steven A. Rosenberg of the National Cancer Institute (NCI) and W. French Anderson of the National Heart, Lung and Blood Institute, will track lymphocytes which have been activated to fight cancer as part of the tumour infiltrating lymphocyte (TIL) therapy developed by Rosenberg.

In this technique for effective only in patients with skin and renal cancer, lymphocytes which have already proven their anti-cancer ability by invading a tumour are selectively stimulated to grow by excising the tumour and treating it with interleukin 2 (IL-2). The purified tumour invading lymphocytes are then returned to the patient with additional IL-2, on the hope that the activated lymphocytes will attack the remaining cancerous tissue.

Rosenberg and Anderson plan to introduce the gene for bacterial resistance into the activated lymphocytes before they are administered to the patient in order to follow their action in TIL therapy.

The basis of Anderson's research has been in developing a therapy for infants with severe combined immune deficiency (SCID) who lack a functional gene for the basic enzyme adenosine deaminase (ADA). Anderson and his co-workers are trying the groundwork to allow them to restore the normal operation of SCID patients' immune systems by inserting the ADA gene into cells from their bone marrow using a retroviral vector.

Before the marker experiment outlined by Rosenberg and Anderson can proceed, it must be approved by the Human Experimentation board at the NCI, the Gene Therapy Working Group of the Recombinant DNA Advisory Committee, and several other bodies. If the experiment is approved and proves successful, the next step would be to engineer the lymphocytes to produce larger quantities of their own IL-2, removing the necessity for follow up IL-2 injections which cause side effects. (Source: Nature, Vol. 333, 23 June 1988)

Doctors test biological therapy on patients

American cancer patients are helping to test a controversial new kind of treatment. Called "biological therapy", it involves removing blood cells from the body, treating them with a natural protein called interleukin 2, and then replacing them.

The University of Chicago Medical School, one of five centres for the trial - which is one of many in the US - set up a biological therapy unit in February. By the end of June, there should be enough patients to establish how well the treatment works. The pharmaceuticals company Hoffmann La Roche, which is providing the genetically engineered interleukin 2, is co-ordinating the study.

John Richards at Chicago, together with his colleagues, has treated 47 patients with interleukin 2 since September, 16 of them since the new unit opened. All patients entering the trial receive an infusion of the protein over five days.

The normal function of interleukin 2 is to cause other cells of the immune system that have been primed by an antigen to divide, and to help other types of cells to kill more effectively. It also induces lymphocytes to produce other lymphokines, such as gamma interferon.

The infusion of interleukin 2 causes a drop in the patient's number of lymphocytes. Once the infusion stops, the number of lymphocytes rebounds to levels far higher than before the therapy began. At this point, doctors take blood from the patient and filter out the lymphocytes before reinfusing it. In this way, they can harvest up to 50 billion cells in three hours.

The next step is to wash the lymphocytes into so-called "LAK cells" - lymphokine-activated killer cells, produced by incubating the patient's lymphocytes with interleukin 2 for several days in the laboratory. Unlike normal lymphocytes, cells grown in this way can kill tumour cells in laboratory tests.

While the LAK cells are being cultured, the patient has a break from treatment. This is important, as the therapy causes unpleasant and possibly dangerous side effects, including low blood pressure, diarrhoea, fever, itching, nausea and anxiety.

The treatment then continues with infusion of LAK cells on several consecutive days, and several more five day infusions of interleukin 2. The whole course lasts 11 days.

Patients taking part in the trial so far have been those with melanoma that has spread around the body or with a type of renal carcinoma.

Richards says that the trial is limited to these groups for two reasons. One is that the original work on treatment with interleukin 2, by Steven Rosenberg of the National Cancer Institute in Bethesda, Maryland, suggested that these two diseases responded well. Secondly, says Richards, both of these cancers are "notoriously resistant to chemotherapy so we have a lot of ethical justification for trying a new treatment".

Initial results show that around a quarter of patients with melanoma had a 50 per cent reduction in the amount of tumour in their bodies.

Ultimately, researchers would like to know what is changing in the immune system that translates into a therapeutic effect.

Established anticancer drugs often have unpleasant side-effects, such as nausea and loss of hair. Interleukin-2 can also cause severe complications. The problem is that the group of symptoms produced by the protein closely resembles sepsis - overall rampant infection throughout the body.

Richards and his colleagues have found that patients respond to careful handling of these symptoms. From the patient's point of view, Richards adds, the worst problem is probably depression and lethargy, but this is bearable because it rapidly stops when the therapy comes to an end. (Source: New Scientist, 26 May 1988)

Cancer therapeutics

Immunex (Seattle, WA) has identified, cloned, and expressed the gene for interleukin-7 (IL-7), a hormone that appears to stimulate early lymphoid responses to immune challenges by promoting the development of T-cells and B-cells from immature bone marrow cells.

Immunex also released data from clinical studies showing that its granulocyte macrophage colony stimulating factor (GM CSF) restores circulating white blood cells in cancer patients. Patients receiving GM CSF following bone marrow transplant surgery produced normal levels of white blood cells faster than control patients - in some cases, in as little as 14 days post-transplant.

Another related recombinant immune factor, Amgen's (Thousand Oaks, CA) granulocyte colony stimulating factor (G CSF), also boosted the white blood cell count of patients in test conducted at Memorial Sloan Kettering Cancer Center (New York). G CSF given to bladder cancer patients undergoing intensive chemotherapy stimulated the proliferation of neutrophils, reducing the incidence and severity of bacterial infections. (Source: Bio/Technology, Vol. 6, July 1988)

Another anti-AIDS drug

A new antiviral agent that is effective against human immunodeficiency virus (HIV) but is much less toxic, at least in animals, than AZT, is expected to enter clinical trials later this year. The compound, called CS 87, is a nucleoside - a class of compounds including other anti-AIDS drugs such as AZT, dideoxycytidine and ribavirin.

CS 87 has been developed by scientists at the University of Georgia (UG) and Emory University in Atlanta. According to Chung Chu of UG, an application for Investigational New Drug status in the USA is being made this summer in collaboration with Triton Biosciences.

CS 87's lower toxicity might be due to the fact that it is similar to a human nucleotide, uridine, that is not in DNA. It may therefore not interfere with normal human DNA, unlike other antiviral nucleosides including AZT that closely resemble chromosomal DNA nucleosides. (Source: Chemistry and Industry, 20 June 1988)

Synthetic AZT

Scientists at Hasegawa Koryo Inc., working in collaboration with Hiroshi Orui at Tohoku University, have developed a method for the complete chemical synthesis of the AIDS therapeutic AZT (azidothymidine). Currently, AZT is synthesized from deoxythymidine isolated from DNA, an expensive starting material. In contrast, the new method begins with D-xylose, an inexpensive sugar, cutting the cost of AZT synthesis by 50 per cent. (Source: Bio/Technology, Vol. 6, July 1988)

Glucose compound in tests

A long-chain polymer of glucose which contains sulphur, called dextran sulphate, can prevent HIV from binding to susceptible cells in the laboratory. Researchers in the US and Japan showed that the drug, which patients have taken for more than 20 years for its ability to prevent the blood clotting, can "exert a potent inhibitory effect" against HIV. The drug was able to prevent viral genetic material from becoming incorporated in the DNA of T-cells.

One drawback, however, is that similar concentrations of dextran sulphate also suppressed the activity of mammalian DNA polymerase, an enzyme important in normal cells in synthesizing and repairing DNA. In addition, when the researchers added a protein that is not an enzyme, called bovine serum albumin, this eliminated the drug's capacity to inactivate the viral enzyme reverse transcriptase. (Source: New Scientist, 12 May 1988)

Broader tests begin on antiviral drug

A drug that may be helpful in the treatment of people infected with HIV, dextran sulphate, will soon enter wider tests in the US. The Government's Food and Drug Administration (FDA) has approved clinical trials by the AIDS Clinical Trials Units monitored by the National Institutes of Health.

Dextran sulphate is in high demand on the underground market in therapies for AIDS. Over a dozen companies in Japan make the drug under licence to Meiji Seika Chemicals in Osaka. In Japan, dextran sulphate, sold for two decades as an anticoagulant and for its ability to lower lipids in the blood, is available without a prescription. It is not approved in the US.

One approved trial has already taken place in the US. Donald Abrams at San Francisco General Hospital carried out tests to establish the toxicity of dextran sulphate at Meiji's request. Thirty patients with either severe disease caused by HIV infection or AIDS took the drug. It seemed to have some antiviral activity at doses that did not appear to be dangerous.

Now, at least seven institutions are applying for permission to start trials on people who are infected with the virus, who have severe HIV-related disease, or who have AIDS. These are the University of California at San Francisco and at Los Angeles, State University of New York at Stony Brook, Case Western Reserve University, Memorial Sloan Kettering Cancer Center, the University of Massachusetts, and St. Luke's Hospital in New York.

The first round of trials, to determine the toxicity and efficacy of the drug, will involve 60 volunteers. They will receive three daily doses, totalling either 2,700 milligrams a day or 5,400 milligrams a day over 28 weeks. In the trial in San Francisco, subjects showed a slight increase in the number of some lymphocytes after eight weeks.

Some subjects suffered side effects, however, such as a drop in the numbers of other white blood

cells, diarrhoea, rashes, insomnia and higher levels of some liver enzymes that could indicate toxicity. However, the original Japanese report suggesting that dextran sulphate merited further investigation in the treatment of AIDS said that there is extensive evidence that the drug has low toxicity. (Source: New Scientist, 21 July 1988)

AIDS risk reducing drug

Imreg has announced the development of a drug that reduces the risk of developing AIDS when administered to patients with AIDS-related symptoms. Imreg-1 says the findings are preliminary but encouraging. The drug is said to bolster the immune system. Observers say the reports should be viewed with caution, since few experts outside the firm have seen any data, and little is known about the nature of the drug. Imreg will soon provide data to FDA and seek permission to market the drug. The preliminary trials at eight medical centres involved 141 patients with ARC and 17 with Kaposi's sarcoma. Only four of the 93 ARC patients who received Imreg-1 progressed to AIDS in a six-month follow-up, against 12 of the 46 on placebo. No toxicity was reported for the drug.

Some researchers in six countries now report that individual susceptibility may be more important than the frequency of sexual contacts in the heterosexual transmission of AIDS. (Extracted from New York Times, 14 June 1988)

Interferon A used against HIV

Interferon alpha can stimulate isolated lymphocytes to kill HIV and infected cells in the body, according to J. Sharp of research firm Brownlogs. The extracorporeal treatment of lymphocytes apparently stimulates killer cells. Dideoxidine was added to the lymphocytes being treated to prevent any HIV present from replicating. The treatment has been tested on two volunteers, who were at early stages of symptomatic infection. Both have recovered from fever and enlarged lymph nodes, and both remain healthy six months after a three week course of treatment. Interferon activates T-killer cells but not T helper cells, which may be infected by HIV. (Extracted from New Scientist, 26 May 1988)

Process to transplant pancreatic islet cells into diabetics

Hana Biologics has developed a process to treat foetal pancreatic islet cells for transplant into diabetics. The process removes substances that might trigger an immune response in the recipient. Islet cells treated in this way have now been implanted into 24 diabetics. Results of the trials will be known soon. Preliminary results are favourable, according to Hana's F. Voss. Other attempts at foetal or cadaver islet cell transplants have been disappointing. Transplantation of whole pancreases has achieved high success rates recently, and may be a viable option for severe cases of type I diabetes. But these transplants require life long immunosuppression. The newly developed treatment for foetal islet cells uses monoclonals to remove any cells capable of producing lymphokines. The treated cells are then grown in culture and implanted in an area under the kidney.

Another approach to preventing an immune response is encapsulation of the cells in alginate and poly-L-lysine, according to G. Eisenbarth of Joslin Diabetes Center (Boston). (Extracted from Medical World, 25 April 1988)

A tablet a year could conquer river blindness

A new drug for the treatment of onchocerciasis, the tropical disease also known as river blindness, appears to be safe. Preliminary results from the first large-scale trials of the drug, called ivermectin, suggest that countries could use it to treat whole populations at risk of the disease.

Hans Remme, a statistician with the Onchocerciasis Control Programme in West Africa, announced the results of the trials at a meeting in Geneva of the Tropical Disease Research Programme, which is run by the World Health Organization. The trials, currently under way in 12 tropical countries, involve 65,000 people.

WHO estimates that about 17 million people suffer from the disease, mainly in Africa but also in parts of Central and South America. Overall, 80 million people are at risk from the disease.

Only two drugs, diethylcarbamazine and suramin, have so far been available for the treatment of onchocerciasis. Both cause severe side-effects so they cannot be used safely to treat whole populations.

Ivermectin, which was discovered 14 years ago, seems to be much safer. Vets have used it successfully for several years to rid horses, sheep and cattle of worms. In humans, it produces only mild itching, swollen lymph nodes and, occasionally, dizziness for a few days. A single tablet kills virtually all the larvae in the body within two to three days. People need to take the drug only once a year.

Ivermectin prevents the blindness caused by the build-up of microfilariae in the eye. It will not, however, reverse severe eye disease and so will not restore sight to the 340,000 people already blinded by onchocerciasis.

Another drawback is that the drug does not seem to affect the adult worms, which live in copulating pairs within rubbery nodules under the skin or in deeper tissues of the body.

One of the most exciting findings reported by Remme last week came from a study in Ghana. There, the proportion of blackflies carrying microfilariae fell by three quarters within three months of health workers distributing an ivermectin tablet to each of 15,000 people in the area, suggesting that the drug might be able to control transmission without attempts to control the blackfly.

This approach has been successful in the past. The Onchocerciasis Control Programme has sprayed from helicopters chemicals that kill larvae in affected areas.

Ivermectin could offer a faster, cheaper method of controlling the disease. The manufacturer, pharmaceuticals company Merck Sharp & Dohme, announced last September that it would provide the drug free of charge, indefinitely. The next problem is making sure it reaches the people who need it most. (Source: New Scientist, 7 July 1988)

Successful treatment for hepatitis B

The most successful treatment yet for hepatitis B infection has been reported by a research team headed by Robert P. Perrillo at Washington University in St. Louis. The work could

have a major impact, because about 200 million people worldwide chronically carry the virus; the virus can lead to cirrhosis of the liver and liver cancer, with 5,000 deaths yearly in the United State alone attributed to these complications. No consistently effective treatment for the infection now exists.

Although a vaccine for hepatitis B became available in 1982, the incidence of infection has increased nationwide in the past decade. Public health experts blame in part a general unawareness of who is at high risk of infection and thus should receive the vaccine. In addition, the effectiveness of the vaccine appears to be limited.

The new treatment combines two approaches tried previously. One is the use of immune suppressing steroids. Administered long term, these drugs ultimately result in increased viral replication, but when given over a relatively short time in high dosages they can lead to "immunologic rebound" - enhanced immune activity shortly after the drug is withdrawn - and remission of the disease. This method alone does not eliminate the virus and in some cases can cause life threatening complications.

In the other approach, based on growing evidence that the development and persistence of chronic hepatitis B infection may be caused by insufficient production of alpha interferon by white blood cells called lymphocytes, researchers use the interferon itself - a small protein made by cells as a defence against viral infection and produced in quantity by laboratory recombinant techniques.

The investigators randomly assigned patients with proven chronic hepatitis B to two groups: 18 received the combination treatment and 21 were untreated. All patients were generally asymptomatic. Among those treated, replicating forms of the virus disappeared in nine. But the "most exciting" aspect of the work was an even greater response to treatment by four in the group, according to Richard D. Aach of Johns Hopkins University in Baltimore. In these patients, who had been infected for a shorter time than the others in the treated group, the remaining evidence of infection - the hepatitis B antigen HBsAg - also disappeared. These patients also developed hepatitis B antibodies, which the other patients in the study lacked.

The work does not prove absolutely that the combination treatment can cure chronic hepatitis B, but it has spurred a large-scale investigation of 185 patients, now under way, comparing patients treated with alpha interferon alone to those receiving the combination and to untreated controls. Researchers express hope for the outcome of these trials next spring. (Source: Science News, Vol. 134, 6 August 1988)

Effective antibiotic against many fungi

A novel polypeptide antibiotic that is effective against a wide variety of fungi has been discovered at the Biological Sciences Research Laboratories of Lion Corp. (Tokyo). Lion Corp., a major detergents and toiletries manufacturer, has recently diversified into pharmaceuticals. Isolated from a strain of Bacillus polymyxa, the new antibiotic is being studied by Lion researchers in collaboration with Tadashi Arai at the Eukaryotic Microbiology Research Centre at Chiba University. It has been shown to be effective against a wide range of fungi, including those that cause ringworm and athlete's foot, as well as species of Candida and Trichomonas. The product, designated LI F, kills fungi by causing their cell walls to lyse, but its exact mechanism is not known. (Source: Bio Technology, Vol. 6, June 1988)

Fungi produce biopharmaceuticals effectively

Filamentous fungi provide a very effective system to produce protein products by genetic engineering. Pioneering work to develop this system has been done in Canada. Work is now under way to transform the initial prototypes into full-scale production systems. Dr. Owen Ward and his co workers at the University of Waterloo have embarked on a programme to optimize the efficiency of an award winning fungal system developed by Allelix Biopharmaceuticals, a division of Allelix Inc. The work is partly supported by a three year grant from the National Research Council.

Allelix has spent several years developing filamentous fungi as a system to produce proteins The pioneering work to develop a prototype was recognized in 1986 by a Canada Award for Excellence in Invention. The system is now being developed to produce a number of pharmaceutical proteins which can be made effectively in the system. As part of the project, Allelix will be making a number of pharmaceutical proteins, especially EGF (epidermal growth factor), which can speed healing of wounds, including ulcers.

In collaboration with SOD Pharmaceuticals Inc., California, Allelix is also using its fungal system to produce SOD (superoxide dismutase), for the treatment of arthritis and heart attacks, as well as for preserving kidneys before transplantation. In addition, work is under way with another company to develop a vaccine product.

Allelix Biopharmaceuticals is a division of Allelix Inc., Canada's largest biotechnology company which has a staff of over 250. The Division is developing new pharmaceuticals that can be produced by genetic engineering and which can be designed using information on the structure of key molecules in the body.

The University of Waterloo has strong basic and applied research and development capabilities in fermentation and protein technology, molecular biology, biochemical engineering and other areas of microbial and industrial biotechnology. (Extracted from News Release, 25 August 1988)

New way to remove virus cells from blood

Researchers at the University of Michigan (Ann Arbor) have developed a novel method of removing viruses and virus infected cells from blood, using immobilized target cells. I-Fu Tsao, a graduate student working with Henry Y. Wang in the chemical engineering department, found that cultured human foreskin fibroblasts attached to polymer beads or membranes were able to remove human cytomegalovirus and herpes simplex viruses, both singly and in combination with one another, from blood serum without loss of important blood proteins. The key, according to Tsao, was cross linking the target cells to one another with glutaraldehyde, which stabilizes the cells without impeding virus binding. Besides purifying blood for transfusions, the method may also be used to remove viruses from patients with infections. (Source: Chemical Week, 15 June 1988)

A new class of antivirals

A promising family of antiviral agents developed by Sterling Winthrop (Rensselaer, N.Y.) kills viruses

by preventing them from releasing their genetic material into an infected cell. However, the viruses can counteract the action of the drugs through a simple mutation. Thomas D. Smith, a postdoctoral student at Purdue University (West Lafayette, Ind.), has reported that the antiviral compounds can work their way into a cavity present in one of the three proteins that make up the virus's capsid, the protein coat that encases its genetic material. By filling the cavity, the drug stabilizes the protein's three dimensional structure, which prevents the capsid from falling apart and releasing its genetic material into the target cell. Smith, working with scientists from the University of Wisconsin (Madison), elucidated the drug's mechanism of action by solving the crystal structure of rhinovirus 14, one of the many viruses known to cause colds in people. Using a series of nine of the sterling drugs, Smith also prepared a number of rhinovirus mutants affected by the drugs and found changes in the viral capsid in the susceptible proteins. The Sterling drugs are just entering human clinical trials. (Source: Chemical News, 16 June 1986)

Antibodies 'retooling' the cell's metabolism

Dr Frank Bennett is refocusing his strategy to develop a novel anti-bleeding heart drug. The drug's existing patent has given out of deals with Bristol and Eisai. Bristol for tissue plasminogen activator (tpa), and intends to concentrate on its collaboration with British Bio Technology, the Oxford based company.

Sankyo, meanwhile, will now concentrate on its collaboration with British Bio Technology to develop its second generation anti-bleeding drug. The two companies are pleased with the results of their efforts and plan to apply for patents soon. Sankyo will further develop patented compounds with the British receiving royalties.

Under the terms Will receive rights to tpa products and the patented manufacturing system. The two companies have agreed financial terms for the collaboration, but Sankyo Europe does not expect this to have a material effect on its fiscal 1986 operating results. Analysts predict Sankyo will report losses of $10 million this year compared with losses of $16.6 million in fiscal 1985.

Will the formation of the Anti-Bleeding Drug, Bio Tech is looking for a new partner to develop tpa. The company is already in negotiations with firms for a production release and new plans to sell tpa by the end. (Edited text from Business Chemical News, 16 July, 1986)

Chitin in artificial skin

Unitika Inc. (Osaka), another Japanese textiles based company diversifying into medical products, is now marketing an artificial skin containing chitin isolated from the shells of shrimp and crabs. Unitika researchers have developed a special process to convert chitin powder into long threads 2 microns in diameter. These threads are then used to fabricate a 250 micron-thick nonwoven cloth that provides a smooth, non pyrogenic surface for skin regeneration. The company expects annual sales in Japan to reach some $4 million within three years. (Source: Bio Technology, Vol. 4, June 1986)

Altered cells fool the immune system

Researchers at the John Radcliffe Hospital in Oxford have shown that it is possible to fool the immune system into ignoring a transplanted organ while retaining it's power to fight disease. At the moment, people receiving transplants must take drugs to suppress the activity of their immune systems and prevent their body from rejecting the organ.

The immune system recognizes tissues by the glycoproteins embedded in the cell membranes. These glycoproteins are manufactured in cells using genes from a number of genes, known collectively as the major histocompatibility complex (MHC). If these glycoproteins are not recognized as belonging to the body, then the immune system responds by attacking the cells that carry the foreign glycoproteins. It is this response that results in rejection of a transplanted organ.

The idea of the new technique is to introduce glycoproteins from the transplant donor into the recipient's body before the transplant operation. Soren Madsen and his colleagues have done this successfully for heart transplants in mice. They first took fibroblast cells from the mouse's connective tissues, introduced the gene that codes for a glycoprotein from the donor's MHC, and released the "altered" cells back into the patient's blood stream.

During the trials on mice, Madsen and his colleagues also discovered that some glycoproteins are more effective than others at desensitizing the immune system to donor tissue. There seems to be an order of dominance between them, whereby more dominant glycoproteins will suppress the immune response to less dominant glycoproteins as well.

Mice survive a heart transplant for a short time without the treatment. By introducing a donor glycoprotein before the transplant, the survival time increased to more than 20 days. One particular type protein, called H-2 Kb Product, extended the survival of the recipient mice indefinitely. The researchers believe that the glycoprotein is at the top of the dominance hierarchy.

If this technique proves as successful for transplants in humans, it might eliminate the danger of a rejection. It will also remove the need for exhaustive tissue matching, copious blood transfusions, and drug treatments that suppress the entire immune system and so lower the body's resistance to disease. (Source: New Scientist, 24 March 1988)

Kodak and Immunex expand pharmaceutical cooperation

Eastman Kodak Company and Immunex Corporation last week announced agreements which will expand the

drug discovery activities conducted by Immunology Ventures, the partnership created by the two companies in January 1988.

The two companies will work together in an effort to create conventional drugs which mimic or inhibit the activities of the proteins currently being developed through biotechnology, offering improvements that could yield greater therapeutic impact and market potential. These "second generation" pharmaceuticals may reduce or eliminate side-effects caused by biological products. Additionally, they have the potential for oral administration, the most convenient delivery route.

As envisioned in these agreements, the research programmes include rational drug design, a strategy for designing organic molecules which mimic or inhibit the biological action of natural proteins. Research into possible new therapeutics using this approach will be funded by Immunology Ventures, and will take place at both Immunex and Kodak.

The first target for this research will be a lymphokine antagonist, with potential as a treatment for auto immune disorders. (Extracted from Chemical Marketing Reporter, 16 May 1988)

Partnership expands drug discovery research

Expansion of drug discovery research is the aim of an agreement between Immunex (Seattle) and Kodak. The research - which will be conducted by Immunology Ventures, a two year old joint venture between the companies - will focus on development of conventional drugs that mimic or inhibit the activities of proteins now being developed through biotechnology. Those second generation drugs could reduce side effects caused by biological proteins and could have the potential for oral administration, the most convenient delivery route. The first drug targeted for development will be an antagonist to lymphokines, which are natural proteins that regulate the immune system. Such a drug could have potential for treatment of auto-immune disorders. (Source: Chemical Week, 25 May 1988)

Agreement to make engineered proteins

Production of genetically engineered proteins is the subject of a licensing agreement between Jacobsen and Kabigen (Stockholm). Genetech will license KabiGen's E-Coli System to manufacture Insulin like Growth Factor I (IGF 1), a human hormone that could treat wounds, burns and postmenopausal osteoporosis. The process involves use of Escherichia coli to produce genetically engineered proteins and secrete them directly into the surrounding culture medium. (Source: Chemical Week, 11 May 1988)

An agreement on ophthalmic drugs

Development of new ophthalmic drugs is the aim of an agreement between Alcon Laboratories (Fort Worth) and Creative BioMolecules (Hopkinton, Mass.). Alcon will screen genetically engineered growth factors produced by Creative BioMolecules. Such proteins - which are reported to play a crucial role in the healing and regeneration of damaged tissue - could help repair corneal ulcers and traumatic eye injuries, as well as aid such surgical procedures as corneal transplants. (Source: Chemical Week, 8 June 1988)

Bioglass: a sticky story

After years of legal wrangling, a material that shows promise for medical use in fixing hip and other implants, as well as repairing broken bones, may be on the verge of clinical application. Developed by scientists at the University of Florida, Bioglass actively bonds with living tissue, rather than filling it like plastic.

As Professor Larry Hench explained, Bioglass is a silicate in which certain amounts of sodium and phosphate are present in the same proportions as in bone. When placed in contact with living bone tissue, it gradually interacts with the tissue by allowing bone cells to grow on it and forms a bonded interface that is stronger than cement, metal screws or even the bone itself.

As a bioactive material, its characteristic lies in inducing the body into accepting the material as itself, unlike other inert materials which tend to be rejected, resorbed or have a toxic effect. "The body never sees that it is a foreign material," Hench said.

The new applications viewed to be offered by Bioglass will include small implants to fill gaps left by the roots of missing teeth, middle ear implants, and a ground powder for treating periodontal disease. If all goes well, regulatory agencies continue to find Bioglass safe, it could transform over the next decade. (Source: Chemistry and Industry, 4 May 1987)

Big hopes in vaccine development

The vaccine industry has been in a slump for a number of years, but biotechnology may better understanding of the immune system are breathing life into the industry. The technology has enabled researchers to get their sights on safer synthetic vaccines. It also has demonstrated promise in diseases thought to be resistant to vaccines, like genital herpes, malaria and tuberculosis. Numerous companies are deeply involved in vaccine development, such as Merck (the market leader) and smaller producers. New entrants including foreign companies as well as a number of biotechnology companies.

The stakes are certainly high. This year, the human vaccine market at the wholesale level was $710 million in the US and $4500 million worldwide, and predictions are that by 1997 the annual market could more than double, to $1.5 billion in the US and $12 billion worldwide.

A greater selection of vaccines will be available, too. Manny Patarca, president of Technology Management Group (New Haven), projects that by the year 2000, 30 new vaccines will have been introduced worldwide.

The new generation of vaccines will differ from most of those in current use. Conventional vaccines generally make use of actual pathogens, either viruses or bacteria, which are killed or genetically weakened so they will not cause disease. When a conventional vaccine is introduced into the body, it triggers a response from the immune system, which produces antibodies against the pathogen that protect against further exposure to the pathogen.

The problem with conventional vaccines is that they sometimes fail because the pathogen has not been killed or sufficiently weakened. Indeed, introducing a pathogen into the system can actually cause the disease that the vaccine is meant to prevent.

To get past that problem, the new vaccines will use only portions of viruses or bacteria. The segments, often surface proteins called antigens,

...ve cellular antibody production. However, they are far more likely than conventional vaccines to cause recurrent infection.

Two of the new vaccines have already reached the market. SmithKline Beckman and Merck are marketing a genetically engineered hepatitis B vaccine, and Praxis Biologics is selling a vaccine that uses bacterial polysaccharides to ward off meningitis in infants.

The hepatitis B vaccine of Merck and SmithKline typifies a common approach to vaccines these days. It uses an immunologically active antigen on the surface of the hepatitis virus. The antigen is made in large quantities by transplanting the genes that code for the antigen from the virus into the yeast Saccharomyces cerevisiae. The yeast is then fermented, churning out the antigen, which is purified for the vaccine.

SmithKline also is working on an influenza vaccine that may be safer than the older versions and could be used universally, without the constantly changing strains of the viruses. Typically, every year or so the flu virus changes its surface antigens, and a vaccine developed for one strain is ineffective against another. However, SmithKline researchers have isolated a particular surface antigen that seems to be common to all strains. Researchers have transplanted the genes that code for this antigen into the bacteria Escherichia coli and have made experimental quantities of the antigen.

Vaccination is also becoming a new vaccine technology. The latest standing search for a malaria vaccine, one of the world's deadliest diseases, has been stymied by the complex life cycle of the parasite that causes the disease. It is likely at least a multi-component vaccine, if it is to attack antigens against the several different stages through which the organism passes while in the human body.

Despite the need to develop vaccines against many diseases, the vaccine business is not booming. Many companies have dropped out of the field because of the failure of the pharmaceutical industry to provide adequate profits to them. They have complained that even immediately after it enters the body, the vaccine is usually absorbed. They have requested the government to provide tax breaks for basic research and to protect the patents for vaccines. The government has responded, somewhat slowly. SmithKline hopes to avoid these problems with the vaccine within years. If the work goes well, the commercial rights for the vaccine would probably be sold to an international company, to Africa, Asia and Latin America.

Similar techniques are being explored for other vaccines. For instance, Chiron Corporation, which helped Merck develop its hepatitis B vaccine, has identified the immunologically active surface antigen on the genital herpes virus and has transplanted the genes for that antigen into mammalian cells. The protein produced by those cells, once purified, has induced immunity to the herpes virus in guinea pigs. The vaccine, moreover, not only prevents initial herpes infections but can also be used after infection to stop recurrences or progression of the disease. Chiron plans to petition the Food and Drug Administration for permission to test the vaccine in people both before and after infection.

Other diseases exist but appear to demand a vaccine that produces both a humoral and cellular immune response. Tuberculosis and leprosy, for example, which are closely related, are caused by the bacteria Mycobacterium tuberculosis and leprae, respectively.

Applied Biotechnology (Cambridge, Mass.) is developing vaccines against the two diseases. Researchers have pinpointed antigens on both bacteria which they believe can cause humoral and cellular immunity. They have isolated the genes coding for the antigens and have transplanted them into vaccinia — the virus used in smallpox vaccines. When injected into the body, the engineered vaccinia virus is supposed to infect cells but not reproduce. It should, however, produce the bacterial antigens it is programmed to make. The antigens should then induce both humoral and cellular immunity. Live virus vaccines are controversial because of the widespread fear of side effects. Applied Biotechnology will seek approval for its tuberculosis vaccine in the US and overseas. Currently, both products are being tested in animals, with hopes for clinical trials under the auspices of the World Health Organization. (Extracted from Chemical Week, 19 June 1985)

An improved vaccinia vaccine to be developed

The vaccinia virus has been used since the late 1800s, as a vaccine to prevent against smallpox, but the virus can cause side effects in some individuals, principally those whose immune system has been suppressed through disease or as a result of chemotherapy, and people with eczema. Applied Biotechnology, (Cambridge, Mass.) says it has received a small business innovation research grant from the National Institutes of Health, which will bolster its effort to develop an improved strain of vaccinia virus for use in human and veterinary vaccines. The company plans eventually to insert into the virus genes coding for antigens of the bacteria that cause tuberculosis and leprosy, as well as genes coding for antigens of other infectious agents. Using recombinant technology, the company will identify the genes responsible for causing side effects and modify them to reduce the risk of those effects while retaining the vaccine's effectiveness. (Extracted from Chemical Week, 17 April 1985)

Private gets NIH vaccine testing contract

The National Institutes of Health will award Praxis Biologics Corp., Rochester, N.Y., nearly $1 million in initial development of a new vaccine to combat the bacteria "Staphylococcus pneumoniae" recently ranked by the US National Academy of Sciences among the top 10 priority vaccines for international use. The three-year project will study application of Praxis' bioconjugate vaccine technology.

The pneumococcal vaccine Praxis develops will be used in Phase I clinical studies to determine safety and immunogenicity. Following a successful outcome, Praxis would be awarded another contract to supply 20,000 doses of vaccine for use in an efficacy trial. (Source: Chemical Marketing Reporter, 13 May 1985)

Oral malaria vaccine

A vaccine has been developed against [illegible] malaria that can protect mice from a challenge infection with malaria parasites [illegible] unrelated to the disease ([illegible] bacterium) served as Trojan horse vector [illegible] attenuated (alive but not pa[illegible], genetically engineered to contain the malaria parasite's circumsporozoite antigen, and given orally to mice.

Jerald Sadoff and colleagues at the Walter Reed Army Institute of Research, Washington DC, hypothesize that the effectiveness of the vaccine might have been due to the proper presentation of the antigens to the host's immune system: if liver macrophages ingested the bacteria and displayed circumsporozoite antigens on their surfaces in the right context (in association with histocompatibility antigens), effective cellular immune responses might then be induced. The success of the animal vaccine suggests that it may be possible to develop oral vaccines for human malaria and for various diseases - leprosy, leishmaniasis, schistosomiasis, AIDS, and others - in which cellular immune responses appear to confer some protection. (Source: Science, Vol. 240, 15 April 1988)

Possible antimalarial drug

The artemether weed may contain a potent antimalarial drug, according to WHO. The drug is effective in killing the merozoite stage of the parasite in vitro and in animal experiments. The drug is not preventative, and would have to be taken several times a day after infection. The drug is expensive, but SAPEC (Switzerland) is hoping to develop a cheaper version. (Extracted from New Scientist, 31 March 1988)

Hepatitis breakthrough at Chiron points to possible vaccine

A diagnostic test for non A, non-B hepatitis and perhaps eventually a vaccine for the disease, are being developed by Chiron, the US biotechnology company, now that researchers have successfuly identified the virus responsible, and can produce the viral proteins using genetic engineering techniques.

The discovery of the elusive virus, responsible for some 150,000 cases of the disease in the USA - including 30,000 chronic liver disease cases through blood transfusion, was made by scientists at Chiron's joint venture with Ciba Geigy, Biocine.

Chiron is likely to ask for clinical trial approval for a diagnostic test in the autumn. The test would be marketed through its joint venture with Ortho Diagnostic Systems. If a vaccine is ever made, this will be sold through Biocine. (Source: Chemistry and Industry, 6 June 1988)

Experimental AIDS vaccine effectiveness prolonged

The effectiveness of an experimental AIDS vaccine has been prolonged by four booster shots administered over a period of one year, according to researchers led by I. Zagury of the Pierre & Marie Curie University (Paris, France). In March 1987 Zagury said he had inoculated himself and some African volunteers with an AIDS vaccine that consisted of a vaccinia virus modified to make gp 160, an AIDS virus protein. Zagury has now confirmed earlier reports that the vaccine caused his body's immune system to produce antibodies in addition to a special type of blood cell. Some 370 days after the initial vaccination signs of immune defences were still appearing, thanks to the four booster shots. The idea behind the test was to see if the vaccine was safe and determine whether it would produce the desired immune response. Zagury's report adds that in tests conducted with cells in laboratory dishes, immune factors in his blood actually prevented two strains of the AIDS virus from causing infection under certain conditions. (Extracted from The New York Times, 22 April 1988)

Receding hopes of AIDS vaccines

It would have been extraordinary if the first shots at making an AIDS vaccine had been effective, so there need not be too much despondency now that they seem likely to fail. Not that they have failed yet in human beings; indeed, the trials have only just got under way. But the lack of success of initial trials in chimpanzees and rhesus monkeys cast a dark shadow over the IVth International Conference on AIDS, held in Stockholm. The problems of producing a vaccine against the human immunodeficiency virus (HIV) are greater than for any other virus. One is that HIV is notoriously variable. No two isolates are identical. Each isolate contains many variants. Variation may be HIV's way of escaping destruction by the immune system, and may yield variants of increasing pathogenicity and preferences for one tissue over another in the course of disease. A successful vaccine would have to be able to deal with a wide and shifting variety of strains.

A second serious problem is that the virus lucks for cover shortly after infection. That is to say, once HIV has infected a cell, its RNA genome is transcribed into DNA by reverse transcription, which then becomes integrated into the chromosomal DNA of the infected cell. An effective vaccine would have to prevent the virus from infecting any cells, for no vaccine can attack the integrated DNA. Viruses subsequently made under the instructions of that DNA will be susceptible to attack if they leave the shelter of the cell. But there is growing evidence that some cells may transmit their HIVs directly to other cells, without releasing them. To make matters worse, it may be that the original infecting virus is largely within cells in the blood, semen or vaginal fluids, rather than free, and is also transmitted from cell to cell. In that case a vaccine would never get sight of HIV in the first place.

Had all this been known three years ago, when the first candidate vaccines were on the drawing board, it might have influenced their design. As it was they were hurriedly designed from what was most available at the time. In essence, that meant the envelope protein of the virus. This forms the external surface of the virus and therefore is most easily seen by the immune system. It is also the protein that varies most between strains.

At the latest count no chimpanzee vaccinated with the envelope protein has been protected against infection by HIV. This is true whether the vaccine is made from the protein itself, or whether it consists of vaccinia virus genetically engineered to contain the gene for HIV's envelope protein. The potential advantage of vaccines of this type is that live viruses activate parts of the immune system that proteins alone cannot reach. In doing so, they stimulate the production of immune cells that can recognize and kill virus infected cells, which may well be a more important defence system than the production of antibodies.

Because of the shortage of chimpanzees, it has not been possible to ring the various changes that might turn the initial failures into success. What makes it questionable whether any easy change in the vaccine will make a difference is the failure of a trial of passive immunization described by Jorg Eichberg of the South West Foundation for Medical Research in Texas.

Despite, or perhaps because of, these failures, four starts on vaccinating human beings have begun.

One uses envelope protein alone. Made by MicroGeneSys, the protein has been given in four different doses to homosexual volunteers, some of whom received a booster shot one month later. The higher doses sometimes, but not reliably, induced antibody production and a positive lymphocyte blast transformation test. A yet higher dose, 180 micrograms, will now be tested.

Another vaccine uses both an engineered vaccinia virus and cells taken from the vaccinated subject infected with virus, killed and given back by slow infusion. Daniel Zagury, who has used him self as a guinea pig for this complex procedure, is now seeking a simplified version. In a third trial, with very tentative beginnings, two patients in London have been given an (anti-idiotypic) antibody designed to prevent infection by HIV. The fourth trial involves giving killed HIV to people already infected with the virus in an attempt to boost their immune reaction against it. The virus, which is killed by gamma irradiation and then purified with the loss of envelope protein, was first given to nine people with Aids-related complex - the condition that precedes full-blown AIDS - last November. A second group of nine people joined the trial in March and 54 matched pairs of infected but asymptomatic volunteers have been recruited for the third stage.

The killed virus preparation has also been given to one uninfected and two HIV-1 infected chimpanzees, but they have yet to be tested for resistance to infection or reinfection. That humans greatly outnumber chimpanzees in the trials is a measure of the scarcity of the latter. Moreover, chimpanzees do not develop AIDS after infection. For both reasons the hunt for an alternative animal model is intense. Since some simian immunodeficiency viruses (SIV) will produce Aids in rhesus monkeys, this is a promising, if inexact model.

Unfortunately, the first attempt to vaccinate rhesus monkeys against SIV infection, using an inactivated virus vaccine at the New England Primate Center, has failed. Another hope is that HIV-2, the predominant Aids virus in western Africa, will infect rhesus monkeys and produce Aids, even though HIV-1 will do neither. Groups in France and Sweden have begun to test this possibility and are confident it will work on the basis of early trials. Finally there is a hint from separate laboratories in the United States and Italy that rabbits can be infected by HIV-1.

In the absence of a simple animal model, trials of AIDS vaccines are inevitable but present many problems. For safety reasons trials of candidate AIDS vaccines are at first restricted to healthy volunteers who are not at risk of HIV infection. Such trials will need careful scrutiny before approval and should not be implemented without fully informed consent as they are not without imaginable risk. But there is little option other than to allow the best of them to proceed. (Source: Nature, Vol. 333, 23 June 1988)

HIV Vaccine trial begins

Geneva University Hospital, Switzerland, has started phase one clinical trials of a vaccine against the human immunodeficiency virus. Biocine (US) is jointly developing the HIV vaccine with Chiron Corp. (US). The vaccine uses a genetically engineered antigen developed by Chiron and an adjuvant for enhancement of immune responsiveness developed by Biocine joint parent Ciba Geigy (Switzerland). In animal trials the vaccine stimulated anti-HIV antibodies and cell mediated immunity, which elicited an effective immune response in several species. The phase one trials will test the vaccine's safety in humans and measure its stimulation of antibodies to neutralize HIV and T-cells. HIV is the cause of AIDS and AIDS-related complex. (Extracted from Financial Times, 28 June 1988)

First trial of blocking antibody dispels safety fears

Research towards an anti-idiotype vaccine has progressed one step further with the first tests in humans of an antibody which recognizes part of the CD4 molecule, the protein on human cells to which HIV binds. Two patients infected with HIV have received low doses of the antibody with the aim of testing its safety.

Both patients, somewhat unexpectedly in view of the poor state of their immune systems, responded by making antibodies to the foreign antibody. Most surprisingly of all, one even made anti-idiotype antibodies: antibodies in the form of a mirror image of the injected antibody. In theory, these anti-idiotypes would recognize the part of the virus which binds to the site on CD4 recognized by the injected antibody.

Angus Dalgleish, from the Clinical Research Centre in Harrow, Middlesex, said that some scientists had feared that the antibody, called anti-Leu 3a, would cause the immune system to attack and kill the last few T cells left in the patients. This had not happened. The anti-Leu 3a had bound to the patients' T-helper cells, and fallen off within 24 hours of administration.

Dalgleish said that he had not expected the patients to make such a good response to the monoclonal antibody. The next step would be to give anti-Leu 3a along with an adjuvant, a substance that potentiates the immune response to the antigen administered with it.

Ultimately, this work could lead to the development of a component of a vaccine, or some kind of immunotherapy for infected people. If infected people could make anti-idiotype antibodies to anti-Leu 3a these could "mop up" free virus.

Dalgleish says he believes that some of the immune response to the envelope protein could be harmful. (Source: New Scientist, 7 July 1988)

FDA approves Hygeia Corp to test kit

Cetus Corp. and Eastman Kodak have licensed Cetus' highly sensitive AIDS virus detection procedure to two reference laboratories in California, Specialty Laboratories and Pathology Institute.

The procedure, which is based on Cetus' GeneAmp polymerase chain reaction (PCR) technology, detects the viral DNA in infected cells by amplifying AIDS viral DNA sequences by as many as one million times. Cetus says that its PCR method provides new information complementing the currently available antibody and antigen tests, which both have limitations. The companies expect that the reference laboratory licensing arrangement will provide information which will help in the development of kits. (Source: European Chemical News, 18 July 1988)

Diagnostic kit to detect blood clotting disorders

Teijin Ltd. (Osaka), a major textiles company that has diversified into health care, has started

selling a diagnostic kit for the early detection of blood clotting disorders such as disseminated intravascular coagulation. The enzyme linked immunosorbant assay (ELISA) uses a monoclonal antibody to detect the complex that forms between the enzyme plasmin and the peptide α-2 plasmin inhibitor. α-2 plasmin inhibitor controls blood clot dissolution by binding to and inhibiting plasmin, a protease that dissolves clots by cleaving fibrin. Believed to be the first commercially available kit of its kind, the new diagnostic was developed in collaboration with Nobuo Aoki at the Tokyo College of Dentistry and Medicine. The assay requires only 10 microlitres of serum, is very specific for the plasmin inhibitor complex, and is sufficiently sensitive to detect 0.5 to 40 micrograms of complex per millilitre. (Source: Bio/Technology, Vol. 6, June 1988)

Du Pont introduces a rapid test for herpes

Du Pont has introduced a rapid test for herpes simplex virus infection that it says is accurate enough to replace tissue culture tests. The Du Pont approach, known as Herpcheck, is an antigen test for herpes simplex virus that gives results within four hours. Tissue culture - currently the primary diagnostic test for herpes simplex virus - can take days. (Source: Chemical News, 4 May 1988)

FDA approves a test for cytomegalovirus

Enzo Biochem (New York City) has received approval from the Food and Drug Administration to market its nonradioactive, fluorescent DNA probe for detection of cytomegalovirus (CMV). A ubiquitous virus that belongs to the herpes virus family, CMV can cause fatal respiratory and neural disorders in newborn babies and immunosuppressed people. Enzo expects to ship the probe in early summer through its wholly-owned subsidiary, Enzo Diagnostics. (Source: Chemical Week, 4 May 1988)

Test to detect sickle cell anaemia

A monoclonal antibody test to detect sickle cell anaemia has been developed by researchers at Lawrence Livermore National Laboratory. The Joint Sickling Haemoglobin Universal Assay (Joshua) does not require trained technicians or electronic equipment. Some 200,000 babies per year are born with sickle cell. Death rates from infection are high among these children, but early treatment with prophylactic penicillin can reduce this risk. The new test cannot distinguish between persons who have the disease and those who are only carriers. A positive test result should be followed by electrophoresis to identify sickle cell victims. (Extracted from New Scientist, 31 March 1988)

Hereditary disorders predictable

Certain hereditary disorders can be predicted with reasonably good accuracy through chromosomal analysis. New DNA based analytical methods are also being used in forensic analysis. Analysis of DNA patterns combined with the medical history of a family can enable disorders such as Duchenne's muscular dystrophy, Huntington's disease and some forms of haemophilia to be predicted accurately. Some forms of malignancy, such as chronic myelogenous leukaemia, but unfortunately not Alzheimer's disease, are also being detected through DNA based analyses. These DNA tests are based on the polymerase chain reaction procedure developed by Cetus several years ago. Some malignancies are suitable for DNA based analysis because they involve chromosomal rearrangements, according to M. Furst of Oncogene Science. In patients with chronic myelogenous leukaemia, a portion of chromosome 9 is moved into chromosome 22 in malignant cells. The chromosomal translocation can also be detected with traditional microscope based cytogenetic analysis, but this is time consuming.

Jellmark Diagnostics is offering a molecular fingerprinting technique as a service to forensic and medical laboratories. The DNA based analytical technique detects short, highly variable but repeated DNA sequences that are found throughout a person's genes. The method may be useful in determining family relationships in paternity suits and in diagnostic tests for genetic diseases.

The British Government's plan to take mouth swabs from suspected terrorists for 'genetic profiling' cannot work in it's present form, according to scientists who use the technique. They say that genetic fingerprinting, which can identify individuals by the pattern of bands resulting from an analysis of their genetic material, requires more DNA than a mouth swab can provide.

The genetic fingerprinting of the DNA present in a mouth swab, however, can work by amplifying the DNA with polymerase chain reaction.

The possibility of using genetic fingerprinting on mouth swabs, provided that DNA is also used, is shown in a paper published in The Lancet. Researchers from St. Mary's Hospital in London examined a number of saliva samples produced by swilling the mouth with a saline solution for 10 seconds. This produces more salivary cells than are harvested on a swab. (Extracted from Bio/Technology, Vol. 6, May 1988 and New Scientist, 23 June 1988)

Europe getting into the HIV-testing act

Compared with the large number of US companies in the highly competitive business of blood-screening tests for human immunodeficiency virus (HIV), European firms are still few. In technical terms, however, they seem to be holding their own, especially when it comes to tests for HIV 2. Among recently introduced antibody tests under development in Europe are a three minute whole blood test and a saliva test. The blood test is a collaborative French-US project involving Genetic V Tech (Pomona, CA), and Syntro (San Diego, CA). The test uses an immunofiltration device, consisting of a synthetic polymer membrane. After a drop of sample is filtered through the membrane it is followed by an enzyme linked anti-immunoglobulin and substrate. With different peptides on different regions of the membrane, at least four different antibodies can be detected simultaneously. Syntro says that independent tests have confirmed that this three minute test can be 100 per cent specific for HIV 1 if the right peptide is used.

The saliva test is being developed at the UK Government's Central Public Health Laboratory (London), where many commercial tests have been evaluated (although official approval is not necessary for the UK sale of diagnostics). It is an antibody capture assay in which the sample is immunoglobulin G (or A) coated on polystyrene beads. Tenfold diluted (but otherwise untreated) saliva is incubated with the beads, after which they are further incubated first with HIV antigen and then with radiolabelled or peroxidase labelled HIV antibody. (Extracted from Bio/Technology, Vol. 6, July 1988)

New interleukin assay system

An interleukin-1(alpha) assay system is now available from Amersham International. This allows the precise detection and measurement of the lymphokine IL-1(alpha) in body fluids or cell culture media. The specificity of the assay allows the measurement of IL-1(alpha) in the presence of IL-1(beta), providing much improved results.

The discrimination of the two lymphokines will help research workers to define the specific role of IL-1(alpha) in the many areas in which IL-1 is known to be involved, including inflammation and immune response. Details from: Amersham International plc, Amersham Place, Little Chalfont, Buckinghamshire HP7 9NA or on 02404 4444. (Source: Biotechnology Bulletin, Vol. 1, No. 5, June 1988)

Xenova links up with Du Pont

Xenova, the two year old UK biotechnology firm, has entered into a collaborative research agreement with Du Pont. The collaboration will focus on the discovery and development of small molecules derived from micro organisms that can be used in cardiovascular therapy.

Under the terms of the deal, Du Pont will allow Xenova to use and develop one of its assay systems to screen compounds from microbes for therapeutic activity. Xenova will receive revenues and milestone payments during this programme. For this, Du Pont will have exclusive rights to develop and market drugs emerging from the collaboration.

Xenova is currently adopting a two-pronged approach to its development. The firm plans to do contract research for other companies and develop its own portfolio independently.

The UK firm has already developed a screening method to detect antagonists of interleukin 1 (IL 1) and is using it to screen its microbial collection. (Source: Biogen Chemical News, 25 July 1988)

Newer ping tests for the developing world

The testing of blood for infection with the human immunodeficiency virus is not always a perfect science. Even under the most sophisticated laboratory conditions, inaccurate results - false positives or false negatives - can and do occasionally occur. This is why the regime for testing blood donations in developed countries such as Britain includes at least two types of test, ending with a confirmatory test on positive samples.

A regime such as this, which can take several days, is not always possible in the developing world. The equipment needed is expensive and includes items, such as incubators, that require a reliable source of electricity. A further problem is that trained people are needed to interpret the results of the highly accurate but complicated confirmatory test, called the western blot.

A further difficulty is that blood from people living in Africa and other tropical areas where infectious diseases are common is loaded with antibodies that can "cross react" with the HIV tests to give false positives. The test kits, therefore, have to be extremely specific for antibodies to HIV, and yet be strongly sensitive so that the kit does not fail to detect the presence of antibodies to HIV.

According to Fred Mhalu, from the Muhimbili Medical Centre in Dar es Salaam in Tanzania, scientists have made "significant advances" in finding reliable blood tests that require no electricity, and little expertise. He identified a number of new tests that scientists are trying out on blood taken from people living in African countries.

One such test is made by Du Pont, an American chemicals company. The test, called Hivchek, takes minutes to carry out. It consists of a porous membrane stuck to the inside of a well in a plastic dish. The membrane is bound to proteins taken from the envelope of HIV.

A hospital worker adds a drop of blood to the dish and, after a few minutes, washes it away. Only antibodies to HIV's envelope, if present in the blood sample, will stick to the membrane and remain after washing.

The next stage is to add a special reagent that uses a gold pigment which turns red when HIV antibodies are present. Du Pont says that the test takes five minutes from start to finish and needs no refrigeration.

Greet Lauwereys from the Institute of Tropical Medicine in Antwerp has worked with another simple test for detecting antibodies to HIV. She has tested the technique on stored blood samples taken from 2,000 people living in Central Africa.

This technique is the haemagglutination assay. The manufacturer, Abbott in the US, attaches proteins of HIV to the membrane of red blood cells. When infected blood is added, these membranes bind to antibodies in the blood sample. This leads to the membranes clumping together, which can be seen with the naked eye.

Lauwereys compared this test with test kits used routinely in the west. These kits use the standard technique known as ELISA, enzyme linked immunosorbent assay. She found that provided the blood was not repeatedly frozen and thawed (which often occurs in African hospitals that store blood), the simple test proved to be extremely sensitive. However, she still advises that positive results should be confirmed at a central laboratory that can carry out a more sophisticated test.

There is another type of agglutination test that uses tiny latex beads rather than the membranes of red blood cells. Other researchers are evaluating this [illegible].

The need to [illegible] blood tests that can give accurate results [illegible] rather than hours is necessary in some [illegible] countries because the average time betw[illegible] a donor giving blood and a patient receiving it is 30 minutes. Research by Claire Kabeya of Project SIDA in Kinshasa, Zaire, suggests that fresh blood gives fewer false positives and negatives than stored blood.

A final problem remains, however. Any new test must be able to detect both types of HIV in order to ensure the safety of donated blood. (Source: New Scientist, 24 June 1988)

Biodhesives programme set up

Genex Corporation and W. R. Grace & Co. have launched a programme to develop and market protein based adhesives for medical and dental use. The firms say they are working together to develop bioadhesives based on recombinant proteins similar to those produced by the common sea mussel. The

firms expect the adhesives to be commercially available by the mid 1990s and have wide medical and dental applications including suture enhancement and replacement, bone and wound repair, and the bonding of caps and crowns.

Current research has focused on using bio-engineering to isolate the DNA used by the mussels and transfer it to yeast, which is used to mass-produce the precursor protein used in the suture adhesives. "We are now able to design these proteins and express them efficiently through microbial fermentation," a spokesman for Genex reports. "We have scaled up to a 250-litre fermentation and have the capacity to manufacture as much of the proteins as we want. Our emphasis has changed to how to make adhesives out of these proteins." (Source: Chemical Marketing Reporter, 29 August 1988)

Livestock applications

Seeking trials for a new rabies vaccine

The Wistar Institute (Philadelphia) has applied for approval from the US Department of Agriculture to conduct field trials of a new, genetically engineered rabies vaccine designed to immunize wildlife. Unlike traditional rabies vaccines, the new vaccine - developed by Wistar and Transgene, a French biotechnology company - is not made from the whole rabies virus. It is made, instead, by taking a gene from the rabies virus that codes for a protein on its viral coat and inserting that gene into the vaccinia virus, the virus used to eradicate smallpox in people. The genetically engineered virus - which can be administered orally - generates antibodies to rabies in the vaccinated animal but cannot cause the disease, because the disease causing parts of the rabies virus are not present. The genetically engineered vaccine would have encapsulated altered rabies vaccine hidden in bait. The vaccine would elicit an immune response in skunks, raccoons, rats, etc., who eat the bait, preventing them from becoming carriers of the disease. The technique worked in indoor trials, and is already in field trials in Europe. Wistar is considering several uninhabited islands off the coast of Virginia or South Carolina as potential sites for field trials, which are under way in Belgium and are expected to begin soon in France. (Source: Chemical Week, 18 May 1988 and Science News, 28 May 1988)

Three ways to make a transgenic pig

Researchers have devised three methods of transferring genes in mice, and animal breeders are now seeking to apply these techniques to livestock.

The most common approach is to inject DNA directly into fertilized eggs. Before harvesting the eggs, researchers feed hormones to the donor animals. This causes them to ovulate several eggs at a predictable time so that researchers can time matings and recover the fertilized eggs a few hours later. When the egg and sperm meet, each carries only one member of each pair of chromosomes present in the adult animal, and the chromosomes are tightly condensed. Soon after the sperm penetrates the egg, the chromosomes disperse and are contained within small bodies known as pronuclei. The pronuclei swell and migrate towards the centre of the egg.

The goal is to inject genes - sequences of DNA - into a pronucleus. To accomplish this delicate task, a researcher holds the egg on one pipette by gentle suction, and with another very fine pipette places copies of the gene in one pronucleus. Approximately 30 per cent of injected embryos degenerate within a few hours. Researchers transfer surviving eggs into the oviduct of recipient females. This is the only proven route for gene transfer in livestock.

But other techniques could work in farm animals. Certain viruses known as retroviruses can ferry genes into cells. They infect cells and insert their DNA into the chromosomes. They replicate in the infected cell and then spread to other cells in the animal. Genetic engineers can disable a retrovirus so that it can still incorporate into the chromosome but cannot replicate and spread.

Using retroviral vectors in livestock has disadvantages. The technique creates offspring that are usually "mosaic" - where some cells contain the transgene while others do not. Secondly, there is a limit to the size of the foreign DNA that a retrovirus can carry. Finally, we need to be sure that the modified viruses cannot leave the transgenic animals, perhaps regaining the ability to replicate through recombination with wild viruses. Given these difficulties, retroviruses may never be used routinely to transfer genes into livestock.

The third way of producing transgenic mice uses special cells from the embryo. The foetus develops from an inner part of a very young embryo (often referred to as a pre-embryo), called the inner cell mass. Martin Evans and Matt Kaufman at the University of Cambridge developed a method to isolate these cells and grow them in such a way that they continue to divide, but do not become specialized or "differentiated". When such "stem cells" are injected into the hollow cavity of another embryo that has reached the blastocyst stage the injected cells can join the embryo and participate in the formation of all of the tissues, including the germ cells from which sperm or eggs develop. Several groups have transferred genes into mice using stem cells.

Researchers use a number of methods to introduce foreign genes into the embryonic stem cells in the first place. Sometimes it is possible to detect transgenic cells in culture before the cells are transferred to another embryo. But even some of these cells retain the ability to colonize the embryo and to form germ cells, they provide a means of introducing foreign DNA into the mouse germline. As with retroviral infection of eggs, no transgenic chimeras are known to have died as a result. So far, researchers have grown chimeras only in mice and guinea pig embryos, but there is no reason to suppose that they cannot develop techniques for farm animals. (Source: New Scientist, 1 July 1988)

Toxicity tests - good for animal experiments

Animal cells grown in the laboratory are now used to test the toxicity of chemicals. Previously this information could only be obtained by testing the chemicals on animals. The test, developed by the In Vitro Toxicology Group of ICI's Pharmaceuticals Division, can see if drugs and cosmetics irritate the eyes, to cause liver toxicity, skin irritation and phototoxicity.

Animal welfare groups have long urged the chemical and pharmaceutical industries to develop "test tube" methods to replace animal experiments. Unfortunately, a layer of identical cells growing in a laboratory culture dish will never behave in the

same way as the highly structured communities of cells inside an animal and the result of in vitro toxicity tests are often very difficult to interpret. Paul Duffy, the research group's leader, says that this may now be changing.

A test for liver toxicity cannot just look at whether or not exposure kills liver cells, says Duffy, because even a small change in the behaviour of liver cells can cause serious side effects. It is not possible to give a culture dish a blood test but, with the right conditions, cultured liver cells do seem to react to toxic chemicals in a comparable way to the cells in the animal.

Damaged cells lose enzymes to the culture medium in the same way as they do to blood. Liver cells also show an increased activity of the P450 group of isoenzymes when they are exposed to toxic substances. Duffy can predict how a chemical will affect the liver of an animal by looking directly at the activity of these enzymes.

Duffy has developed a test for skin irritant using a line of cells derived from a mouse teratoma. These are cancer cells with many of the characteristics of skin cells. When grown in the right conditions, they organize themselves into layers like skin cells and produce many of the same proteins. Like all cancer cells, these cells can grow in culture indefinitely.

Chemicals that irritate the skin can have several toxic effects. They can damage and kill cells, but they often act more subtly. Duffy found that chemicals which are known to irritate the skin make the cell layers grown in the laboratory produce more keratin, a hard protein that toughens the skin.

Phototoxicity is a problem that is not always detected in safety tests on animals.

Because laboratory animals are not exposed to the levels of ultraviolet light found in sunlight, they may show some of the toxic effects later seen in humans. The hair of animals also protects them from the effects of light. Cultured cells are therefore better for phototoxicity.

The researchers performed the test on two cell lines, mouse fibroblasts and cells derived from a human epidermal carcinoma. They added a non-toxic concentration of the test substance to the culture media and exposed it to ultraviolet light. It took about 15 minutes before the light inhibited the growth of the culture.

All chemicals known to be phototoxic in humans reduced the safe exposure time in both cell lines.

It is hoping the tests to weed out the most toxic chemicals before much time and money is invested in them. (Source: New Scientist, 25 June 1988)

New hope for babies against AIDS infection

Cows could be a valuable source of antibodies for treating some infections common among people with AIDS. Vagn Faber, of the University of Copenhagen, says that if cows are vaccinated with a preparation of a fungus which commonly occurs in AIDS, they produce large quantities of antibodies in their milk.

It is the colostrum which the cow first produces after calving, that contains such high levels of antibodies. These antibodies protect the calf from infections during its early life when its own immune system is immature. A cow will produce 30 to 35 kilograms of colostrum after calving, although Faber says a calf receives all the antibodies it needs from only 5 kilograms.

He and his colleagues decided to vaccinate cows with a fungus called Candida, which causes oral candidosis, or thrush. In AIDS, severe thrush of the mouth and throat is common. Doctors can treat it with antifungal drugs but some of these are toxic; in particular, the drugs may interfere with the synthesis of steroids by the adrenal glands.

In people with AIDS, an infection of the adrenal glands with cytomegalovirus may make the problem worse. A less toxic treatment could be of great benefit.

The researchers vaccinated the cows and purified antibodies against Candida from their colostrum. They tried the treatment on 20 patients with oral thrush. The condition disappeared in half of them. A larger study is now under way. Faber believes that it may be possible to apply the same method to protect against other infectious agents. (Source: New Scientist, 17 March 1988)

Salmon diet supplement

Interesa Alimentos (Chile) and Igene Biotechnology (US) will jointly produce and sell astaxanthin diet supplement for salmon farms. Astaxanthin is found in shellfish and gives salmon flesh its red colour. Since farmed salmon eat less shellfish, their flesh is usually lighter. Interesa Alimentos, a salmon farmer and the largest yeast producer in Chile developed the pigment from yeast. The Astaxin product is all natural, and gives farmed salmon a nearly identical colour to wild salmon. Global sales should reach $75 100 million a year. LeferGen (Bermuda) has been jointly formed by the companies to market AstaXin worldwide. AstaXin plants will be built in Europe, the US, and perhaps South East Asia. (Extracted from Fish farming Industry, May 1988)

Animals for the tropics

The goats grazing in the open-air enclosure appear somewhat unusual. Their coats resemble those of sheep. There are also strange looking chickens among them a bald necked variety. The chickens, however, live in a covered building just next to the enclosure. Both species of animal have been specially bred to be able to live in the tropics.

The "Institute for Animal Research", which is responsible for the new varieties mentioned above, is part of the Technical University of Berlin and works primarily in the field of international animal research.

The institute's installations in the West Berlin district of Dahlem are well equipped for this kind of basic research. The institute's technical facilities include equipment for continually register the skin and body temperature of cattle, laboratories for serological and similar examinations as well as apparatus for carrying out comprehensive physiological analyses.

The stock of animals consists of 40 milk cows, 100 pigs, 1,400 laying hens and 8,000 mice. Nevertheless, these facilities are not always sufficient to be able to carry out research into new systems for new breeds. The institute's professors and research assistants then have to complement

their work with precise analyses and experiments in the field, for example, in South America, West Africa, South East Asia, in the Near East or in the People's Republic of China. Such work in the field is only possible because international institutes cooperate very closely in this area of research. The projects of the Berlin animal researchers are financed not only by the German Research Society (DFG), but also by the Federal Ministry for Economic Cooperation in Bonn and, of course, by the Society for Technical Cooperation (GTZ) in Eschborn.

Because of the biologically determined intervals between generations the research projects generally require a great deal of patience and a considerable amount of time. However, the institute now has a large amount of practical expertise which can flow directly into development work in the field.

In the case of chickens, for example, it was discovered that both body size and body weight directly influence their ability to adapt to conditions in tropical regions. This can be proved, say the scientists, by the productivity of laying hens. In Niger the GTZ is involved in several development projects aimed at improving poultry husbandry on small farms. For the GTZ's development workers the new ideas coming from west Berlin are just what they need. "As the indigenous village chicken is a poor producer of eggs and meat attempts were made to increase the genetic potential of this variety by crossing it with pedigree animals," writes Dr. Kappo of the GTZ. "By providing carefully directed support for poultry breeding the nutrition of the rural population is to be improved with animal protein and - at least in part - the money income of small farmers there will also be increased."

Experiments with dominant alleles, these are special genes also found in chickens, are also to contribute to making the animals more adaptable to tropical temperatures. They make it possible, for example, to influence the animal's plumage. As a rule of thumb, the fewer feathers, the better the heat regulation. The research programme as a whole offers favourable prospects for being able to improve the input/output relationship and productivity of chicken farming in tropical countries.

A further project is investigating questions of avian physiology, in relation to bioclimatic factors.

The combined effects of air temperature and air humidity are being tested on young cows, goats and sheep. The aim is to determine their effect on the productivity of these animals. It has been shown that generally the fall in output resulting from increased temperatures is all the more marked when the relative humidity also increases. As the result of combined investigations into the way in which feed and energy are converted within the animal's body in varying environmental conditions information is also being gained which will provide criteria to help determine the potential effectiveness of different feedstuffs.

In addition to this the institute's present research projects also include the cross breeding of different varieties of cattle. In Bangladesh, for example, farmers would like cattle which produce more milk and meat; the animals should also be able to draw heavier loads. In the Latin American States of Colombia, Brazil and Venezuela farmers would also like cattle with more flesh covering their ribs.

In Togo in Africa the animals often become ill and are very susceptible to different viruses. In addition to this, special breeds of laying hens are at present being tested in Israel, Egypt, Zambia and Malaysia; then again, in Turkey farmers are worried about the poor fertility of their angora goats. They are now being crossed with North American goats and since this began their numbers have again begun to increase. (Source: Scala, May 1985)

Agricultural applications

Controlling pests the non-chemical way and succeeding

Trichogramma is a tiny wasp that has found its original place in about 17 million hectares of cropland all over the world. The wasp "destroys" the eggs of certain butterflies and moths and prevents them from developing into caterpillars which damage crops. It is popular and effective in temperate and tropical countries.

The Biocontrol Research Laboratories in India supply farmers with Trichogramma to control sugarcane and cotton pests. The wasps come on a "Prism Card" of 20,000 wasps per card, complete with directions for their release. A minimum number of two cards is recommended per acre, at a cost of just 30 rupees ($US 2.75).

The Chinese rice industry depends on it to protect its crops of corn, cotton, rice, sugar cane and other crops. The Chinese, it appears, lead the world in the non-chemical methods of pest control.

"A commitment to break agriculture's chronic dependence on toxic chemicals is the first step toward realizing the potential of more ecologically sound, economically sustainable pest control methods," says Ms. Sandra Postel, a senior researcher with Worldwatch Institute, a Washington, D.C. based think tank.

Pesticides account for only a small share of the 70,000 chemicals used but they pose some of the greatest potential hazards, between 1 and 2 million pesticide poisonings occur worldwide every year, mostly among farmers in developing countries. Some 10,000 to 20,000 of these poisonings are thought to result in death each year.

"Unlike most industrial compounds, pesticides are purposely designed to alter or kill living organisms," writes Ms. Postel. "Since they are spread widely over the land, they pose risks to many farm workers but to the general population through residues in food crops and the widespread contamination of drinking water."

Ms. Postel believes, however, that with technologies and methods now available, pesticide use "could probably be halved and the creation of industrial waste cut by a third or more over the next decade".

One way to break the pesticide habit is by applying integrated pest management, or IPM. The system uses biological controls (like natural predators of pests), cultural practices (planting patterns), genetic manipulations (pest resistant crop varieties), and the application of chemicals selectively and only when necessary, rather than as the first and primary line of attack.

IPM's goal is not to eradicate insects and weeds but to keep them below the level at which

damaging economic losses occur. IPM has been strongly endorsed and supported by ESCAP, the United Nations Development Programme, the Food and Agricultural Organization of the United Nations and the United Nations Environment Programme.

For the last three decades, a nation wide pest forecasting system in China has helped farmers identify, track and control pest problems. Between 1979 and 1981, Chinese scientists have located organisms that could help farmers in pest control. Hundreds of natural control agents for pests of rice, soybeans, tea and other crops have been identified.

Natural insect enemies control pests on some 4.6 million hectares of farmland. In Guangdong province, the Trichogramma controls sugar cane stemborers at one third the cost of chemical controls. In Jiangsu province, farmers plant sorghum between cotton plants to attract the cotton pests' natural enemies. Pesticide use dropped 30 per cent, pest controls decreased 84 per cent and cotton yields increased.

One method of pest control is biological, either alone or as part of an IPM strategy. In biological control, a beneficial organism is introduced into a pest infested area. The pest and the introduced natural enemy reach a population balance keeping damage at a minimum.

Biological pest control was popular in the United States at the end of the 19th century. Worldwide, some 500 organisms have been introduced since the 1880s in control programmes. In the 1940s, a European beetle was introduced to control a toxic range weed in California. Accumulated savings made by the beetle control are estimated at more than US$ 100 million.

Because of heavy pesticide use, pests have developed resistance to chemicals designed to kill them. In 1938, there were just seven insect and mite species that developed resistance to pesticides. This figure increased to 447 by 1981, including most of the world's crop pests. Chemical resistance in weeds was virtually unknown before 1970. With increased herbicide use, at least 45 weed species have developed resistance.

Resistance problems threaten the soybean and rice crops in South-East Asia, corn in the United States, sugar beets in the United Kingdom, cotton in many parts of the world.

Examples of how effectively biological control methods can be pressed into service to combat agricultural pests have been accumulating for years. To cite just a few of these:

> In the late 1960s, when Sri Lanka's flourishing coconut groves were menaced by a plague of leaf mining hispides, a larval parasite imported from Singapore brought the pest under control.
>
> Neodumetia sangwani, a natural predator indigenous to India, was found useful in controlling the Rhodes grass scale insect that was devastating forage grass in many parts of America.
>
> The proliferation on Indian farmland of Spodeptera, a parasite with a liking for cotton, maize, tobacco, and tomatoes, was curbed by an egg eating parasite imported from New Guinea.

An important factor in effective biological control is the availability of required quantities of healthy natural enemies for timely and repeated release into the infested fields. This need has created a role for the commercial insectary, a sort of biofactory where parasites and predators are cultured with scientific expertise, mass-produced, and offered for sale.

In several countries around the world, such insectaries have made significant contributions to curbing pest depredations in agriculture in Canada and the United States alone. About 50 commercial insectaries are in operation, mass-producing a number of specific predators for a variety of harmful pests.

India entered this field in 1981 with the Biocontrol Research Laboratory (BCRL) at Bangalore. BCRL is the first commercial insectary of its kind in the country, selling beneficial insects to farmers and cultivators. BCRL identifies economic pests amenable to bio-control, selects promising natural enemies and develops suitable techniques for their rearing and mass production.

Of critical importance is the maintenance of pure and healthy cultures so that these beneficial insects will acquit themselves well in the fields once they are released. Thus far, BCRL has identified pests devouring such crops as sugar cane, coffee, citrus, mango, grapes, and cotton as susceptible to biological controls.

Meanwhile, the Indian Council of Agricultural Research (ICAR) has asked the Bangalore station of the Commonwealth Institute of Biological Control (CIBC) to prepare a feasibility study on bio-control of pests affecting many of these crops and others.

According to Dr. I. Charko, the entomologist in charge there, the Bangalore station has already introduced more than 100 natural enemies from different parts of the world for the control of pests and weeds in India.

At BCRL, annual production of parasites is estimated at 45 million, covering seven different species. "Even with this much production," says a senior BCRL official, "we would only be covering a fraction of the area and demand. Losses due to the pests are so widespread and colossal, it is difficult to meet the demand of growers for the supply of natural enemies."

He estimated India's cotton crop losses due to pests, over plantings calculated at 7.8 million hectares, at a staggering 40.5 per cent. Pest losses over 2.4 million hectares of sugar cane are computed to be about 20 per cent. In coffee, another important crop, the loss is about 10 per cent.

The beneficial insects are distributed through selected fertilizer and pesticide dealers who sell directly to farmers "tricho" cards, each containing 40,000 parasites. A single tricho card costs just 18 rupees. (Source: Agricultural Information Development Bulletin, Vol. 10, No. 1, March 1988)

Biopesticides: an $8 billion market potential

The gradual but relentless transition from chemical to biological pest control "is definitely coming," says William Marshall, president of the microbial genetics division of Pioneer Hi Bred International, one of the US's largest crop seed companies. A recent study by Frost & Sullivan (F&S), New York City, predicts that chemical

pesticide use will recede in importance in coming decades, with a corresponding growth in the market for microbiological and biochemical pest control products. By the end of the century the yearly western world market for microbial pesticides should grow from the current $33-45 million to between $6 & billion; US sales should amount to $1.2 billion/year.

Biopesticides' increasing attractiveness is keyed to several trends: government restrictions or bans on more chemical pesticides; increased insect resistance to chemical pesticides; and the time it takes to bring new chemical pesticides to market. Since 1964, when the federal Government banned the use of DDT and 15 other pesticides on Interior Department lands, several dozen other chemical pesticides have been banned or restricted nationwide.

Getting a new product on the market is increasingly time consuming and expensive. In its report, F&S estimates that it takes 8-12 years and costs $35-40 million to bring a new chemical pesticide from the research and development (R&D) stage to registration. During those years the patent -- and the commercial life -- of the product is running out. According to Jerry Caulder, president and chief executive officer of Mycogen (San Diego), an agricultural biotechnology company, the equivalent time and cost for a biopesticide is three years and less than $5 million.

Also, insect resistance to chemical pesticides is steadily rising. In 1955 only 25 species were known to be resistant to chemical pesticides then on the market. Today 447 species are resistant. And whereas insects took 60 years to develop resistance to arsenicals, it took only 7 years from DDT approval to the appearance of DDT resistance. Resistance to some products began showing up in the year they were introduced.

Spurred by those factors and others to find alternative methods of pest control, more than a dozen chemical pesticide manufacturers have either begun to look into biopesticides with increasing interest or have already taken the plunge into the nascent market. Biotechnology companies are also creating biopesticides, and firms specializing in biopesticides have sprung up as well.

Ecogen (Langhorne, Pa.), founded in 1983, which, in addition to working with American Cyanamid to develop a cotton bioinsecticide for the worldwide market, has already commercialized its first two biopesticides on its own. In March, Ecogen received registration from EPA for Dagger G, a cotton biofungicide that uses the naturally occurring micro-organism Pseudomonas fluorescens to control damping off, a fungal disease of cotton seedlings. Towards the end of March, Ecogen acquired from NOR-AM-Chemical (Wilmington, Del.) its Collego biopesticide, for use on jointvetch in rice and soybeans. Ecogen is looking for other joint-venture partners to help market its products, especially for products in big market sectors.

Also in March another biotechnology firm, Igene Biotechnology (Columbia, Md.), won EPA approval to make and market ClandoSan, a nematocide made from crab, shrimp and crawfish shells, and other shellfish, to kill the worm like microbes that feed on roots and cause more than $5 billion/year in crop damage. Igene Chairman Robert A. Milch pegs ClandoSan's potential market at $100 million/year.

Coming up with a biopesticide product does not always guarantee quick EPA approval. A case in point is Monsanto's experience with its genetically engineered strain of P. fluorescens bacteria, which incorporates the insect toxin gene from the common microbial pesticide Bacillus thuringiensis (BT).

In 1986, Monsanto unsuccessfully attempted to get EPA to approve a field trial of its BT-producing Pseudomonas. The organisms were expected to colonize plant roots and kill soil-dwelling insects such as corn cutworms. EPA's scientific advisory board recommended allowing the field trials, but agency officials delayed approval and continued to demand additional safety and migration data, despite the fact that natural strains of BT have a proven track record of safety.

Even with that long history of safe BT usage, EPA officials say that they were forced to act with extreme caution in 1986 when they reviewed Monsanto's application for testing a BT producing Pseudomonas because little was or is known about the migration of BT or any other species of bacteria. When Monsanto's BT organism came up for review, it closely followed the agency's cancellation of a previously approved field test of another genetically engineered bacterium known as the ice minus strain of Pseudomonas syringae, and called Frostban by Advanced Genetic Sciences (AGS), Oakland, Calif. EPA cancelled the Frostban tests on learning that AGS had conducted unauthorized outdoor tests.

The resulting negative publicity about Frostban had a chilling effect on Monsanto's proposed test. EPA officials, concerned about what would happen to BT in the environment, stalled approval.

Monsanto then devised a different experiment to see whether the micro-organisms would migrate from the site of application. Scientists engineered entirely new lactose-digesting P. fluorescens bacteria that left out the BT toxin gene but incorporated a readily observable genetic marker that turns bright blue in culture and would be easy to spot if the bacteria migrated off the corn rows on which they would be placed. EPA approved the experiment in four months.

Genetically engineered bacteria may not be the way to go, however, say some industry executives. There is "more opportunity in fungi and viruses than in BT," says Geoffrey Barnes, director of crop protection and improvement at Monsanto. Most of the company's microbial pesticide work, says Barnes, focuses on fungi and viruses. One such fungus is Alternaria cassiae, which can kill the jointvetch weed that commonly infests soybean fields, Barnes says. Monsanto is working with Mycogen, which hopes to market the fungus under the name Casst in 1990.

Despite Monsanto's interest, there is little commercial fungal pesticide use in the US. Temperature and humidity requirements, says F&S, are limiting factors in using fungus based pesticides.

Viral pesticides, first successfully used in 1946, present different problems and opportunities. Although at least 10 different virus families are known to be pathogenic to insects, one of them, baculoviruses, is considered uniquely safe. Viruses in this family, such as nucleopolyhedrosis virus (NPV) appear to have no effect on vertebrates, including people. Baculovirus pesticides also are compatible with chemical pesticides, do not build up insect resistance, and can target specific pests. Four strains of NPV have been registered with EPA.

A major disadvantage of insect viruses is that, like bacteria, they do not have the rapid "knockdown"

effect that farmers have come to expect. Farmers and home gardeners are used to putting a spray on "and seeing the bugs go belly up," says George Kidd of the Fowles Seed Report (Chicago). Viral pesticides, as do bacteria, work only after ingestion, usually during the larval stage, and thus fail to kill many leaf eating adult insects. Thus, says Kidd, "it is a problem to convince people that they are effective." Further, viruses are easily killed by ultraviolet radiation, so they lose their biological activity rapidly when sprayed on leaves.

"The big thing" coming in biopesticides, says Kidd, "is building biopesticides into seed" - incorporating pest resisting features directly into the genes of the plants. In effect, the plants become pesticides. "That is where everybody is headed," says Kidd.

Indeed, several companies, including Rohm and Haas, Monsanto and Sandoz have field tested tobacco that produces enough BT toxin to kill hornworms. Paul J. Kiefer, manager of business development for Monsanto's agricultural products, says BT genes have been successfully spliced into tomatoes, which hornworms also attack. And work continues on the more difficult monocot crops that comprise the bulk of American agriculture and therefore the real market for such plants.

Bioengineered plants have a significant advantage over both chemical pesticides and other biopesticides: they travel more smoothly down the regulatory trail because public concerns over genetically engineered plants are relatively small.

An even more intensive effort by Monsanto and other chemical companies that have successful herbicides on the market is to make crop plants resistant to chemicals that would otherwise kill them. This month in California, and then in June in Illinois, Monsanto will test tomato plants into which genes have been incorporated to produce extra amounts of an enzyme called EPSP synthase. Without the extra EPSP synthase, the plant would be destroyed by Roundup (glyphosate), the company's best selling herbicide. The new plant can be sprayed by farmers while the tomatoes are growing, rather than only before the seeds are planted.

This third generation of pest control has already arrived, though it has yet to make serious inroads against chemicals or even biopesticides. It includes hybrid seeds, plant chemicals and semiochemicals that act as sex attractants, developmental regulators, deterrents or poisons, and plants for different insects. At least 17 pesticides have received EPA approval.

Total pesticide restrictions since the first features of chemicals, IR pesticides and biopesticides, will grow in use primarily as parts of integrated pest management, IPM products. Integrated pest management is already coming into fashion, particularly as farmers see the waning effectiveness and variety of chemical pesticides and view their environmental effects firsthand. (Extracted from Chemical Week, 4 May 1988)

Agrocetus manipulates soya

Agrocetus, the joint venture between W. R. Grace and Petrofina Corporation, claims it has genetically engineered soya bean plants using a method potentially applicable to all plants.

The method differs from that used by Monsanto which uses a bacteria to gene splice soya. A finely tuned electric discharge is used to shoot very fine gold particles covered in genes into the plant. The target is the meristematic region which contains the germ of the seed. Once the genes enter the seed the plant can be grown without the tissue culture needed in Monsanto's method.

Agrocetus says that, unlike the Monsanto method, not only is the technique applicable to all varieties of soya bean, it could also be used to change genetically any type of plant. The company claims it has had some success with corn and had already incorporated genes for insect resistance into the soya. Researchers are now working on increasing plant resistance to fungal diseases and on improving oil quality and yield.

Agrocetus says it has been approached by several seed and chemical companies interested in the new process. (Source: European Chemical News, 27 June 1988)

New technique developed to convert cotton plant cells into fibre cells

A technique for converting isolated cotton plant cells into fibre cells and growing cotton fibres in solution has been developed by Texas Technological University biologists. The product could be used commercially as a microbe free fibre whose length, thickness and quality can be controlled. A patent for the process is pending. Commercialization is expected to be two to three years away. Research Corp. Technologies is handling licensing arrangements in exchange for 50 per cent of the royalties. Sonoptex (France), a textile company, may be interested in licensing the technology.

The biologists isolated cells from plant components immersed in water solutions. The cells were cultured in nutrient solutions containing a mixture of two plant hormones: auxins, cytokinins and gibberellins. A balance of these hormones causes cells to lose differentiation and further changes in the hormonal balance enabled the dedifferentiated cells to become fibre cells. Thousands of these cells on cotton seed surfaces form individual cotton fibres. The cells in culture elongate in two directions to form fibres with two smooth ends, instead of one smooth and one rough end, such as those from whole cotton plants. (Abstracted with permission from Chemical Engineering News, 6 June 1988. Copyright (1988) American Chemical Society)

Hormones called up to guard the grain

As grain pests become increasingly resistant to insecticides and public concern grows about pesticides in food, the search for alternative protection intensifies. After nine years of research, scientists at Britain's Agricultural Development Advisory Service (ADAS) at Slough, Berkshire are now convinced that the key to solving the problem of resistance and finding a foreign protectant lies in the corpora allata - a pair of glands in the head of an insect that produce a developmental hormone.

A promising substitute for pesticide protectants is a family of chemicals that mimic the action of insect juvenile hormones (JH analogues). JH analogues are specific for insects and arthropods and are believed to be completely harmless to mammals and other forms of life. Although they have proved efficient in controlling house pests such as cockroaches, Pharaoh's ant and cat fleas, there are special problems in their use as grain protectants.

Biochemical research at the ADAS aims to learn more about how insects make JH in order to control its actions exogenously.

Juvenile hormones regulate metamorphosis by controlling the time an insect spends in its various larval stages. When the level of juvenile hormone decreases to a critical concentration, physiological changes take place which prompt larvae further along the road to adulthood. JH analogues trick an insect into remaining in the larval stage even when the rest of its metabolic processes demand that it develops further. That disruption in development eventually kills the insect.

Such a mode of action is acceptable for killing cockroaches or other pests of buildings. However, many pests of stored grain are more damaging as larvae than as adults. Although the pest will eventually die the larvae, longer lived than they would normally be because of the action of a JH analogue, may still destroy large quantities of grain. More appropriate would be an anti JH, which would push larvae into premature development. Precocious insects would die much quicker.

JH is produced in specific glands, called the corpora allata, that have a direct nervous connection with the insects brain. Anti JH compounds are thought either to bind to the hormone as it is produced by the corpora allata or to compete with JH for binding sites on target cells. Another mode of action may be to disrupt the action of enzymes essential for making JH.

Attention has turned to a deeper study of the control of JH production within the corpora allata. The current idea is that JH production may be turned on or off by specific, as yet unidentified compounds. Researchers suggest that one chemical switches on production and another inhibits production. They are unable to say what this molecular switch might be or even to what class of compound the switch might belong.

The favourite at the moment, however, is that the switch is a neuropeptide. Once researchers get to grips with the control of JH production they will be in a much better position to attack insect pests where it matters most. (Source: New Scientist, 4 August 1988)

A plant product to help fight pests

American Cyanamid (Wayne, N.J.) and marine biotechnology company Ocean Genetics (Santa Cruz, Calif.) have teamed up to develop a range of products from cultured marine algae. The two-year pact calls for screening of marine microalgae for bioactive compounds that might be useful in pharmaceutical, veterinary and agricultural applications. Ocean Genetics will use its culture technology to supply Cyanamid's Lederle laboratories and Cyanamid Agricultural, with promising strains of marine algae. In return, Ocean Genetics will retain the right to produce any bioactive substance identified. (Source: Chemical week, 29 June 1988)

Insecticidal family boats pests

A new class of pesticides derived from the bark of the pawpaw tree will be one of several reports on attempts to find natural pesticides and make use of them. Such agents are an attractive possibility in the face of environmental worries and growing insect resistance to existing pesticides. Ideally, genes for the natural pesticides will be incorporated into other plants, eliminating the need for spraying chemicals on crops.

The pawpaw tree is native to North America. Scientists at Purdue University have found that extracts of the bark are active against a number of pests, including Mexican bean beetles, pea aphids, cabbage loopers, mosquito larvae and forest bugs. Jerry McLaughlin of Purdue said the active compounds were annonaceous acetogenins whose activity exceeded or equalled those of pyrethrins and rotenone, two other natural insecticides. However, its costs check if synthesis of the active ingredients is unlikely to be commercially viable, though the extract is effective.

Meanwhile, Anthony Hess of the US Department of Agriculture has found that a fat found in the tomato fruitworm, Heliothis zea, is also the reason why some plants in the wild, like potato, the tomato, gooseberry and the tomatillo, resist and others will now try to introduce some of the resistance genes from the tomatillo into food plants using protoplast fusion.

If the work is successful, it may be possible to use the tomato fruitworm fat to protect other crops like many vegetables, soybeans, cotton, tobacco, earworm, cotton bollworm, and Japanese beetles. (Source: Chemistry and Industry, 20 June 1988)

New applied organism tests the water

A new genetically engineered micro-organism was applied to a field of crops in the US for the first time early July. Unlike the first experiments with novel organisms in California strawberry fields, this one took place on a plot owned by the US government, and drew no protests from opponents of genetic engineering, because they doubt whether the new bug will survive.

The test pits a bacterium against the European corn borer. The former is a coryneform bacterium, an endophyte that lives inside plants. Although it is commonly found in Bermuda grass and is generally considered harmless to its hosts.

The corn borer is far from harmless. It infests about two thirds of the country's corn fields. In its larval stage, the borer eats its way inside the corn stalk and then up to the ear. The hollowed stalks can no longer support the ears, which drop off. Harvesters cannot pick them.

The borers' appetite costs American farmers about $4.5 billion a year. Despite the $5 billion they spend on chemical pesticides to fight it. These chemicals are among the most toxic used in agriculture.

Scientists at Crop Genetics International (CGI), a company in Hanover, Maryland, noticed a gene from a bug that produces (BT), a toxin that works if injected into a resistant corn stalk. The gene makes the endophyte, the researchers think, produce the toxin, which consumed by a borer would kill it. Theoretically, researchers have used it for decades to attack insect pests.

CGI, which holds a patent on what it calls its "in-vivo" technology, was prepared for a long fight to win permission to release its experiment.

The test took place in a fenced 10 acre field, the Department of Agriculture's Beltsville, Maryland farm. It marked the first time that any genetically altered micro-organism was released into the environment. The other test took place at Dekalb's plant in eastern Illinois.

Regardless of the novelty of the new technique, the test should determine whether it will

infect other plants outside the test site. CGI hopes to make Incide more toxic.

In the trial, workers used needles to insert the endophyte solution into plant stalks. Eventually, the engineered bacterium will be vacuum-sealed into seeds. The growing plant will then be protected throughout its lifetime, predict CGI's scientists. (Source: New Scientist, 7 July 1988)

Field test of nematacide

Igene Biotechnology will field test a nematacide based on plant meal. The product, intended for use on corn, cotton, peanuts, etc., could be ready for registration in 1989. Nematodes caused an estimated $3.7 billion in crop losses in 1985, according to the Society of Nematologists. Igene recently introduced a nematacide based on chitin from shellfish. The product is in limited supply, and so is marketed for high-cash value crops such as fruits and vegetables. (Extracted from Chemical Marketing Reporter, 2 May 1988)

An international agreement in biopesticide genes

Joint research and development and a world wide licensing pact covering insect resistant corn, sunflowers and potatoes is the subject of an agreement between EniChem and Ecogen (Langhorne, Pa.). Under the licensing pact, Ecogen will supply two proprietary genes derived from Bacillus thuringiensis that produce biopesticidal proteins effective against economically important caterpillar and beetle pests. EniChem will use the genes to produce plants that are resistant to insects. The R&D agreement calls for Ecogen to increase performance of the two licensed genes and to identify additional biopesticide genes from its library of more than 5,000 strains of B. thuringiensis. (Source: Chemical Week, 18 May 1988)

EPA approves a new biopesticide

The US Environmental Protection Agency has granted full registration to a new biopesticide that combats the Colorado potato beetle. Trademarked M One, the new insecticide was developed by Mycogen (San Diego) and received approval three years after it was discovered, rather than the customary seven to 10 years for a chemical pesticide. M One is based on a variety of Bacillus thuringiensis, which farmers have used for decades to control caterpillars. Initially, the product will be marketed for control of the Colorado potato beetle in the eastern US on such crops as potatoes, tomatoes and eggplant. (Source: Chemical Week, 25 May 1988)

[illegible] tested by Monsanto

Monsanto Canada and Alberta Pool, representing Saskatchewan and Manitoba pool co-operatives, have begun trial [illegible] field tests of genetically engineered canola, which has been improved to tolerate "Roundup" herbicide. Similar field tests with genetically engineered tomato plants were conducted last year in Illinois and are being conducted currently in the United States by Monsanto.

Engineered and controlled (non engineered) canola seeds were planted and the crops will be studied for comparison.

Monsanto and Alberta Pool were given permission to conduct the field test by the food production and inspection branches of Agriculture Canada.

The added trait for "Roundup" herbicide tolerance has the potential to significantly reduce the cost of growing canola, by allowing weeds such as wild mustard and stinkweed to be more efficiently controlled.

Canola, specific strains of rapeseed, was developed by Canadian researchers and is used primarily for cooking and salad oil, and in margarine and shortenings.

Monsanto researchers placed a gene from another plant species into canola, instructing it to make extra quantities of an essential enzyme it already produces - EPSP synthase. In non-engineered plants, this essential enzyme is inactivated by "Roundup" herbicide, which cause the plants to die.

In the genetically-engineered canola, the extra quantities of the enzyme and its decreased sensitivity allow the plants to grow normally despite the presence of "Roundup".

The improved canola was engineered using a naturally occurring bacterium known as Agrobacterium tumefaciens. In nature, agrobacteria are already capable of inserting genetic information into plants but the result is a type of injury to the plant known as crown gall. Monsanto scientists developed a way to stop agrobacteria from causing crown gall, while maintaining their ability to insert DNA into plant cells. Engineered canola cells are then developed to plant shoot stage and grown into healthy plants.

Field testing of the genetically engineered canola will continue over the summer. All research activities at the site will be carried out in accordance with protocols reviewed by Agriculture Canada.

If successful, the improved canola plants could eventually save Canadian growers millions of dollars in weed control costs. (Extracted from Chemical Marketing Reporter, 16 May 1988)

PGS develops herbicide resistant sugar beets

Brussels based biotechnology company Plant Genetic Systems (PGS) says it has developed herbicide resistance in sugar beet plants. The company says the plants survived treatment with Basta phosphinotricin broad spectrum herbicide from Federal Republic of Germany's Hoechst. Resistance has been achieved, PGS adds, by transferring to the plants a gene from bacteria of the genus Streptomyces, which produces an enzyme that renders phosphinotricin inactive. PGS says that development of herbicide resistant plants will bring savings to farmers, who will be able to use lower cost broad spectrum herbicides to protect crops. (Source: Chemical Week, 18 May 1988)

Atlantic Institute of Biotechnology and Endogro sign research agreement

The Atlantic Institute of Biotechnology has acquired 38 per cent of the common stock of Endogro Systems Inc., a Nova Scotia based biotechnology company.

In return for the stock, AIB is providing finance to enable Endogro to carry out its R&D programme aimed at developing a commercial production system for endomycorrhizal inoculum.

Endomycorrhizas are naturally occurring fungi which live symbiotically with, and impart benefits

to, higher plants. These fungi infect the roots of most crop plants and develop structures which enable the plant to much more efficiently explore large volumes of soil; consequently, the plant's nutrient uptake is increased especially for certain immobile elements such as phosphorus. The increased nutrient uptake can, under many circumstances, translate into increased crop yield coupled with lower fertilizer requirements. Through mechanisms that are still not completely understood, the mycorrhizas also enhance the plant's disease resistance, transplant survivability and drought tolerance.

There is considerable interest world-wide in the possibility of using such innocula to enhance the growth of crops and reduce fertilizer use and cost. AIB believes that very large markets may develop within the next five to 10 years. Endogro is developing unique technology which, it is hoped, will position the company as one of the leaders in this field.

The research is also being financially assisted by a $55,000 grant under the IRAP-M programme of the National Research Council of Canada and funding under the Nova Scotia Technology Assistance programme has been applied for. (Source: News Release, 13 May 1988)

New soil improvement material

Takasaki Chemical Corporation has come out with a new type of soil improvement agent that is a mixture of organic sludge discharged from paper manufacturing and food processing factories and Ohya stone powder. Ohya-stone is porous, features a high cation conversion capacity and makes organic sludge odourless when it is mixed into the sludge. This mixture enables the sludge to be handled with ease and constitutes an excellent soil improvement agent.

Currently, most paper manufacturing and food processing factories are being deluged with complaints regarding the disposal of organic sludge which has a highly offensive odour. Meanwhile, huge quantities of powder are generated in the processing of Ohya stone which is a speciality product of Tochigi Prefecture. Against this backdrop, the company succeeded in creating a moderately priced soil improvement agent, named "Futoru No. 5", by combining the sludge and powder. The mixture is then allowed to mature and compost, is dried and again allowed to compost.

In Japan, farmers are faced with the problem of deterioration of earth quality due to an insufficiency of organic substances and this situation is triggering serious chain obstacles especially in the cultivation of vegetables. Soil problems, which account for about 8% per cent of these chain obstacles, are regarded as being difficult to resolve simply by spraying agricultural medicines. However, an effective method is to mix an organic substance into the soil to proliferate microbes and diversify the soil through mutual reaction between the soil and the organic substance.

Cellulose is the principal component of the organic sludge used as the starting out material for producing the soil improvement agent. This cellulose is generated through high temperature, high pressure pulp digestion and washing in the paper manufacturing process, and therefore contains no undesirable substances such as phenol and tannin which are harmful to plants. Accordingly, cellulose serves as a readily digestible food for soil microbes.

As for Ohya stone powder, it displays excellent cation conversion (1.2 me/100 me) and low phosphoric acid absorption (174 mg/100 mg) characteristics comparable to those of zeolyte. In addition, it is porous and has an alkalescence (pH 8.0 - 8.5), making soil containing cellulose an ideal habitat for useful microbes which are compatible with alkalescent soils. Bacteria causing soil diseases are known to proliferate actively in acidic soil.

The main characteristics of the soil improvement agent Futoru No. 5 are that (1) it has the effect of upgrading produce yield rates by about 40 per cent, (2) it costs only about one sixth compared with straw compost and (3) it has a lasting fertilization effect that enables substantial savings in fertilizer costs. (Source: JETRO, June 1988)

Food production and processing

Chitin gives navy food for thought

The shells of crabs, lobsters and other crustaceans are 15 per cent chitin, the second most abundant biological material on Earth. Almost 100,000 million tons of chitin is synthesized worldwide each year, and not just by crustaceans: insects, fungi and yeast also make it.

In the USA, around three quarters of the 350 million kg of shellfish processing waste produced each year is disposed of. The practical use of chitin is hampered by its insolubility, though it can be acetylated to an acid soluble derivative, chitosan.

Potential applications for chitin or chitosan include use as a dietary supplement to sequester cholesterol, a slow release material for drug implants, or a source of feed-type. Existing uses include surgical sutures and burn wound treatments.

Chitin or ground shells as a dietary supplement to stimulate the growth of intestinal digestive bacteria in the gut is being studied by J. M. Gould of the University of Delaware. Lactose is the main constituent of whey, a major pollutant and waste product of the cheese industry. If this application comes to fruition, some of the 50,000 million kg of whey disposed of in the USA each year could become a useful nutritional source for animals and humans.

Meanwhile, Canadian scientists have developed a promising water soluble derivative of chitin: N,O carboxymethylchitosan, or NOCC. Ernest Hayes of Acadia University in Nova Scotia claims NOCC can be applied as a thin film to the surface of fruit and so keep it fresh. Active ingredients in fungicides could be added to NOCC, with the prospect of controlling a company, Nova Chem, to develop NOCC. Hayes is applying to the US authorities for approval for NOCC as fruit that is industrially processed - washed and peeled before it reaches the consumer.

The Canadian navy will also benefit from NOCC. In collaboration with the company Sparr on the S. Nova Scotia coast, Hayes has made a gel with NOCC that improves the performance of sonar instruments. The gel allows greater power output from the transducers before bubbles of air are released from the water. Sparr, which normally works in high technology fields, has been searching for some time for a gel which, like the NOCC gel, has a controllable consistency and a suitable setting time for fitting sonar transducers. (Source: Chemistry and Industry, 20 June 1988)

Insect trap

Japan Tobacco's new Fuji Trap 87 product uses sexual pheromones to attract and trap male insects. It is intended for use in warehouses to control insects that eat grain, dried foods, spices and medicinal herbs. The matchbox shaped trap contains a pheromone pill and an adhesive sheet. It will sell for ¥48,000 200 units. Japan Tobacco subsidiary Tama Trading will soon begin marketing it in foreign countries. (Extracted from Asian Wall Street Journal, 23 May 1988)

Bioreactor developed to produce erythritol

Researchers at Nikken Chemicals Co. Ltd. in Tokyo, working in collaboration with the Japanese General Food Research Institute, have developed a bioreactor for producing large quantities of the low calorie sweetener erythritol. A four carbon containing polyalcohol which is synthesized from glucose by certain strains of yeast, the white powder is similar to sucrose and is about 80 per cent as sweet. Nikken's new bioreactor allows the reuse of the special yeast cells developed by the company, thereby increasing the efficiency of production to a level that can bring the product's end cost to about three times the cost of table sugar. (Source: Bio Technology, Vol. 6, July 1988)

System for detecting micro organisms in draught beer

Suntory Limited has developed a new system that enables the rapid detection of micro organisms in draught beer to take place easily and with high sensitivity.

In this new detection method, adenosine tri phosphate (ATP) is reacted with an enzyme, and the bioluminescence generated in the process is measured.

ATP is a substance in which three phosphoric acid radicals are bonded into adenine, and energy is discharged when these phosphoric acid radical bonds are severed. Adding a luciferin compound to ATP and reacting this mixture with a luciferase enzyme will break the phosphoric acid radical bonds, causing the molecule to fluoresce.

Suntory, applied this to the detection of micro organisms in draught beer. After the beer was filtered and the collected micro organisms cultured, they were transferred from the filter into water and only ATP was extracted. The extracted ATP was mixed with reactive agents (such as luciferase in order to examine the bioluminescence behaviour). In these experiments, [illegible] enzyme [illegible] were employed.

As a result, [illegible] was found that between the quantity of ATP and the number of bacteria were [illegible] the quantity of bacteria can be measured, with [illegible] bacteria, the ATP quantity [illegible] with [illegible] per milliliter. From this, it was confirmed that detection sensitivity requires 25,000 cells per milliliter, and culturing time is 22.4 hours. For [illegible] method requires [illegible] 48 hours, [illegible] culturing time [illegible] 24 hours. [illegible] 2/3, the culturing time is [illegible] compared with the [illegible] by the [illegible] method. (Nikkei, February 1988)

Bioreactor developed for production of fructo oligosaccharide

Bio Science Laboratories (Japan) has jointly developed a trial bioreactor for the continuous manufacturing of fructo oligosaccharide with Process Engineering Laboratory, National Food Research Institute of the Ministry of Agriculture, Forestry, and Fisheries. The bioreactor features a porous ceramic membrane in which enzymes are immobilized, so that fructo oligosaccharides are made while the raw material is passed to the outer surface of the membrane. The reaction takes place in about 30 seconds, against the usual 24 hour reaction time for batch reactor production of large quantities of the oligosaccharide. The ceramic membrane has a 10 mm external diameter and 1 mm thickness; its pores have a mean diameter of 0.2 micron. (Extracted from New Technology Japan, May 1988)

New testing of Spirulina

The blue-green alga Spirulina can use up and convert carbon dioxide solutions generated by biogas generators. The methane from such generators can contain up to 40 per cent CO_2. This is dissolved in water to yield pure methane. The Spirulina can then be used as food for people or fish. It is up to 70 per cent protein dry weight, with vitamins A and E, and little saturated fat. The volunteer group Green Flamingo, which is developing the system, has set up prototypes of the biogas system in India, Togo and Peru. Babies on the edge of starvation can also easily digest Spirulina when they cannot digest more complex foods. The Chinese will test the system on 300 of their seven million biogas generators. (Extracted from New Scientist, 31 March 1988)

Cholesterol reducing food additive

Iowa State University researchers are testing a powdered food additive that can reduce the harmful effects of cholesterol. The project is modelled on a bacterium (called Eubacteria) that breaks down cholesterol naturally. Eubacteria lives in the large intestine, where it secretes an enzyme that converts cholesterol into coprostanol, a substance which is poorly absorbed and passes out of the body. Adding the bacterium to fat has reduced cholesterol by more than 80 per cent. The task now is to extract the enzyme responsible and produce it in large quantity through genetic engineering. The Wisconsin Milk Marketing Board is funding the research. (Extracted from Business week, 25 April 1988)

How to detect Salmonella [illegible] in processed foods

Foods often have bacterial counts of up to [illegible] cells per gram. The task is to find if any of these cells are Salmonella. The usual method of detecting these bacteria in dried processed foods is labour intensive, requires trained staff and is not guaranteed to pick up every type of Salmonella. It takes a minimum of five days and is done in five stages.

First, technicians grow [illegible] in "pre enrichment" broth, for [illegible] hours. [illegible] damaged by processing to recover. Then they are transferred to a "selective enrichment" broth for 18 to 24 hours. There, there is [illegible] the growth of other bacteria, but all Salmonella must grow to increase their relative [illegible] in the sample.

The bacterial culture is then transferred to selective agar for 24 hours. This media incorporates a biochemical test so that potential Salmonella colonies are highlighted.

The next step, biochemical identification, takes between 6 and 24 hours. Suspect cultures are identified by their reactions to up to 25 biochemical tests. Serological confirmation follows, in 6 to 24 hours. Suspect cultures are confirmed by reaction with specific antibodies raised in the blood of animals in response to Salmonella.

Faster, more sensitive techniques are badly needed. Research over the past 10 years has produced several promising approaches. In principle, these methods will also be applicable to Listeria. None of the new methods can yet accelerate the pre enrichment period, and the times noted below include 18 hours for this stage.

TEST	MINIMUM TIME	MECHANISM
Immune fluorescence	20 hours	Antigen-antibody reaction Antibody labelled with fluorescent dye which enables Salmonella to be seen in a liquid culture by direct microscopic observation. Snags are non specific reactions, high cell count requires and eye strain for the operator, unless the process is automated.
Enzyme linked immunosorbent assay (ELISA)	25 to 30 hours	Antigen antibody reaction. Antibody labelled with enzyme which will react with a chromogen to give a colour change. Can be automated.
DNA probes	48 hours	Recognition of Salmonella DNA. Highly specific test. Will need probes able to detect a wide range of strains. Uses radioactive DNA labels: alternative labels would be preferred for industrial use.
Motility and agglutination	28 hours	Salmonella migrate through a semi solid medium to a pool of antibodies. Will detect only motile strains.
Impedance	16 to 48 hours	Salmonella causes characteristic electrical changes in selective media during growth. Computer used to interpret results. Between two and four media needed to detect a wide range of strains. High false positive rate in heavily contaminated samples.
Enzyme conjugated phage attachment	20 hours	Labelled bacteriophage attaches to Salmonella. Enzyme reacts with a chromogen to give a coloured reaction. Automated. This technique is not on the market yet but claims for its sensitivity are impressive.

(Source: New Scientist, 9 June 1988)

Extraction of eicosapentaenoic acid from fish enteric bacteria

Sagami Chemical Research Center and Toso Corporation have jointly succeeded in extracting eicosapertaenoic acid (EPA) from enteric bacteria present in the intestines of fish with greenish blue backs, such as mackerel.

EPA is a fatty acid (vitamin F) that has a large market for use as an agent to treat diseases such as arteriosclerosis and hyperlipemia. Its chemical structure being highly complicated, EPA is extremely difficult to synthesize and is therefore extracted from fish oil. However, much time and costs are involved in eliminating the impurities which cause an offensive fish odour.

The bodies of this newly discovered bacteria consist essentially of fatty acids containing 25 - 40 per cent of EPA and are entirely free of impurities causing the offensive odour. The mass culture of this bacteria will enable EPA of high purity to be produced at a low cost.

Researcher K. Yazawa of Sagami Chemical Center separated about 1,000 kinds of microbes from the intestines of fish and marine animals and examined their EPA contents. As a result, it was confirmed that a high concentration of EPA is contained in the bacteria discovered in the intestines of mackerel and sardine.

Culturing the bacteria at a temperature of 20 - 25°C was found to increase their number to about 10 trillion litre in about a dozen hours, with roughly 250 mg of EPA contained in one litre of the culturing solution.

Toso, for its part, has developed a technology to increase productivity tenfold. Since there is no need to remove impurities causing the offensive fish odour, it will be possible to conspicuously lower the price of EPA synthesized by this process compared with that extracted from fish oil.

EPA has the effect of decreasing cholesterol existing in the body and also of inhibiting thrombocytes from coagulating which, in turn, suppresses the thrombosis that causes arteriosclerosis. (Source: JETRO, June 1988)

Chemical applications

Biotechnology's potential impact on the chemical industry

Biotechnology has the potential to bring about some vast changes in the chemical industry. Indeed, some analysts look to this emerging set of technologies to revitalize the US economy's mature chemical segment. Others envision dramatic new advances that will eventually transform the petrochemical process industry into a biochemical process industry.

It will entail the evolutionary development of specialty new products and processes as inevitable trends in economics, market needs and technologies have their reactions. For the near term, biotechnology will affect specialty chemicals rather than commodities. The broad spectrum of products in this category includes amino acids, enzymes, vitamins, oils, aromatic compounds, biopolymers and dyes. Some of these products, such as amino acids and enzymes, are already made by a biological route; some, such as polysaccharides, can only be made biosynthetically. For other products, like hydroxylated aromatic compounds, microbial production systems may offer the potential for substantial cost advantages over synthetic chemical pathways.

Amino acids and enzymes are two of the larger, rapidly growing specialty chemical segments that stand to benefit from biotechnology in the near term. The current world market for amino acids totals over $1 billion and is growing at nearly 10 per cent annually. Those compounds and their derivatives are most commonly used as food additives, such as monosodium glutamate (MSG) and aspartame (Nutra Sweet), and feed supplements. They are also used as additives in certain cosmetics, antibiotics and herbicides.

Intensive research is also being conducted towards developing and improving industrial enzymes, whose current world market is over $500 million a year. Important industrial enzymes on the market today include proteases (which are added to detergents) and amylases and glucose isomerases (which are used in converting starch into high fructose corn syrup).

Biotechnology is similarly being applied to improve processes for other types of specialty chemicals, including vitamins, steroids, lipids, aromatic compounds, dyes and biopolymers, as well as to create new products in these categories. Some companies are attempting to replace expensive synthetic chemical steps with naturally occurring bioconversions. For example, microorganisms can hydroxylate some steroids and aromatic compounds.

The current total US market for specialty chemicals is approximately $40 billion. Approximately two per cent of this conventional market will be susceptible to penetration by new biotechnology based specialty chemical products within the next decade.

Most high volume, low value "commodity chemicals" such as ethanol, glycerol, acetic acid, and acrylic acid can be manufactured biosynthetically. But the biological route using biomass feedstocks is usually far more expensive than the chemical route using petrochemical feed stocks. In fact, crude oil prices (and associated feedstock costs) would need to triple to make the biosynthetic route competitive. And the current infrastructure based on petrochemical synthetic processes has also acted to curtail interest in developing bioprocesses for producing commodity chemicals, especially in the United States.

Biotechnology, however, can improve the economics of current biosynthetic processes. Research has been conducted to genetically engineer more efficient microbial strains, as well as to design better bioprocesses for commodity chemical production.

Despite this longer term potential for improvement, the nearer term value of biotechnology R&D in the commodity chemicals segment remains questionable. Nevertheless, the threat of another oil crisis in the Middle East suggests that funding research in the commodity chemical area could be an excellent way for firms to keep their options open.

Biotechnology will have other impacts as well. For example, new monoclonal antibodies have been designed to bind hazardous chemicals. This development has made possible immunoassays that can detect chemical hazards in the environment. The relative ease of use, accuracy and cost effectiveness of these immunodiagnostic tests will put chemical monitoring technology literally in the hands of the individual consumer. This new technology may complement the recent growth in public concern over chemical hazards and have a profound, long term effect on the chemical industry. (Paraphrased from Bio Technology, Vol. 6, June 1988)

New route to batch synthesis of peptides

Chemists at Bio Mega, Laval, Quebec, have developed a solid-phase process capable of 1 kg syntheses of peptides of up to 50 amino acids long in 9h per cent purity in a matter of weeks per batch. The company has used the process to make commercial quantities of such naturally occurring hormones as atrial natriuretic factor and growth hormone releasing factor for human and veterinary drug research.

Jean Gauthier, who is group leader for peptide synthesis and who invented the technique, says that 50 amino acids is the maximum number for which it is economical. Above that number, fermentation of genetically engineered micro organisms may be preferred.

The Bio Mega approach is to produce large batches of relatively pure, chemically protected subunits, which are then cleaved from the resin, purified and reacted to make large batches of pure peptides. In this way, impurities resulting from incomplete or side reactions are minimized.

Traditional solid phase syntheses accumulate such impurities continuously as chemists couple amino acids from first to last without stopping. Products are then difficult to purify.

The key to the success of the subunit approach was Gauthier's development of photochemically reactive spacer molecules to attach each first amino acid to the resin. These photoactive compounds allow separation of subunit peptides from resin in high yield. Chemists can thus detach subunits from and reattach them to resin as each synthetic strategy requires without significant loss.

Gauthier stresses the importance of choosing subunits when planning syntheses. First, the BioMega research workers often join subunits in solution rather than on resins, so they design subunits to be

soluble compounds. Also, some sequences of amino acids are more susceptible to racemization than others and must be avoided in subunits.

One example of strategic subunit design was the Bio-Méga synthesis of human atrial natriuretic factor-(99-126). This hormone, secreted by the atrium of the heart, stimulates sodium excretion and urine formation, relaxes peripheral blood vessel walls, and lowers aldosterone and renin concentrations. It thus shows promise as a drug against hypertension. (Abstracted with permission from Chemical Engineering News, 18 July 1988. Copyright (1988) American Chemical Society)

Enzyme-fixing role found for silk

Research at the Tokyo University of Agriculture and Technology has found silk to be an excellent material for fixing enzymes used in bioreactors, while also prolonging their catalytic activity. Enzyme fixing is regarded as a crucial factor determining bioreactor performance.

Up until now, gelatin has been the common choice for fixing enzymes in such applications, but in experiments using glucose oxidase, the University's R&D group discovered that silk was in many ways superior as an immobilizing agent. Whereas "considerable elusion of the enzyme was seen for gelatin," the group's leader, Prof. Tadashi Matsunaga, pointed out, "scarcely any of the oxidase escaped when we used silk as the fixing agent".

In a performance comparison, moreover, he explained that, "enzymes fixed by this natural fibre showed substantially higher activity, standing up more strongly to variations in the temperature and acidity of the culture medium". (Source: Manufacturing Chemist, February 1988)

Direct monitoring of fungal oil synthesis

The use of micro-organisms as an alternative to seeds for the production of fats and oils is becoming increasingly attractive, particularly in countries where conventional starting material is in short supply. Researchers under the direction of R. Sankaran at the Defence Food Research Laboratory (Mysore, India) have developed a rapid and simple staining technique to detect the onset accumulation and termination of fat synthesis in the oil-producing fungus, Fusarium pallidoroseum. Using the lipid-soluble dye, Oil Red O (which darkly stains hydrophobic lipids, and only weakly interacts with phospholipids) and Trypan Blue as a counterstain, the scientists were able to monitor oil synthesis in the fungal mycelium as accurately as by standard gravimetric techniques. In contrast to gravimetric determinations - which require harvesting, drying, and extracting the mycelium, and consume 12 or more hours - colorimetric estimates can be made in 30 minutes. (Source: Bio/Technology, Vol. 6, June 1988)

Bioplastic with variable hardness and shape

Associate Professor Y. Doi and his research group at the Research Laboratory of Resources Utilization, Tokyo Institute of Technology, have succeeded in synthesizing bioplastic by using an inexpensive material called 1;4 butanediol to produce a plastic of variable hardness, flexibility and shape.

Prof. Doi and his research group earlier succeeded in synthesizing a flexible bioplastic by using 4 hydroxybutyric acid, but this raw material is costly and is not practical for commercial production. In this respect, 1;4-butanediol is available at a low cost so mass producing the bioplastic with this new raw material is possible at a cost that is only a few times higher than that of petroleum-derived plastics. Commercial production of the material is therefore also possible.

Utilized in its synthesis is the phenomenon of polyester polymerization, generated in bacteria (Alcaligenes eutrophus), supplied with a special type of nutrient. The bioplastic, being a microbial derivative, is degradable by bacteria existing in soil or water, thereby eliminating the environmental pollution problem associated with existing petroleum-derived plastics. In addition, it is highly biocompatible and may become usable for producing various kinds of biological materials.

The UK's Imperial Chemical Industries commercialized a bioplastic about eight years ago, but the company's product is a co-polyester of 3-hydroxybutyrate (3HB) and 3-hydroxy valerate (3HV) and is very hard and brittle, making its moulding difficult.

Prof. Doi and his research group found the production of a new co polyester of 3HB and a 4-hydroxybutyrate (4HB) by Alcaligenes eutrophus using 4-hydroxybutyric acid as the carbon source.

The 4HB component serves as the softening agent, so by regulating its ratio it will be possible to produce a wide variety of bioplastic plates: those which are hard or soft, pliable, transparent films, and threads and elastic rubber bands.

The problem is 4-hydroxybutyric acid's extremely high cost. Even with the most sophisticated synthesis techniques, the bioplastic material will be incapable of competing with inexpensive petroleum plastics if expensive raw materials have to be used.

To cope with this problem, the 4-hydroxybutyric acid was replaced with 1;4-butanediol as the nutrient source, and an attempt was made to synthesize a polyester co-polymer containing 4HB. As a result, the ratio of 4HB was varied up to 25 per cent and the substance was confirmed to be usable for obtaining very pliable films and threads.

The bioplastic material will be comparatively higher priced, but will become amply competitive with petroleum plastics depending on specific applications. (Source: JETRO, June 1988)

Energy and environmental applications

Algae put the tiger in your tank

Scientists in the US have shown that algae can be an economic source of oil and chemicals, and could supply 8 per cent of America's motor fuel by the year 2010. A research group at the Solar Energy Research Institute (SERI) at Golden, Colorado, is working on certain algae which produce a large amount of lipids which can be extracted and used to make diesel oil or petrol. The algae under investigation are Chaetoceros and Navicula, and the green alga Monoraphidium. Given the right conditions they multiply so rapidly that a pond 20 metres in diameter can produce over 4 tonnes of algae per year.

Paul Roessler, who heads the group at the SERI, said that the algae can thrive in water that is twice as salty as sea water, but the ponds need to be sited where sunshine can be guaranteed for at

least six months of the year. These are often areas where water is in short supply. But if local water is too salty for watering fields, algal ponds could come into their own.

To get the algae started, urea is added to the water along with a pinch of phosphate and other trace elements if these are missing from the local supply. The algae then grow rapidly, consuming carbon dioxide from the air. The scientists have found that if extra carbon dioxide is bubbled through the pond, then the algae can double their numbers up to five times within a day. This makes them several times more productive at generating biomass than a tropical rainforest. Waste gas from a coal- or oil fired power station could provide the carbon dioxide.

The secret of the process is in inducing the algae to use their energy to make lipids. This is done by controlling the supply of nitrogen and silicon during the process. In the laboratory the algae can convert over two thirds of their mass to lipids. It is also possible under the conditions to harvest 50 grams of algae per square metre of pond per day.

Given this, and an 80 per cent conversion of lipids to diesel oil, a pond 20 metres in diameter could produce over 3,000 litres of fuel per year at a cost of only 25 pence per litre.

The lipids from the algae can be turned into either diesel or petrol. Heating with a mixture of hydrochloric acid and methanol produces diesel, by a chemical reaction called transesterification.

This is a two step process in which the lipids first break down to release fatty acids, which then react with the methanol to form methyl esters that can be used as fuel. Such molecules, however, still contain two oxygen atoms, which must be got rid of if the oil is to be used for petrol. The SERI team has shown that this can be done by passing the oil over a zeolite catalyst, ZSM-5.

Roessler says that he is now focusing on molecular biology as a way of improving the algae to get them to produce more lipids. At the same time, other groups will be looking at pond design, and yet others at the non-lipid part of the algae as a source of chemicals. Carotenoids are one such algal by-product that could make vitamins, or be used as a natural food colouring. (Source: New Scientist, 2 June 1988)

Fungus fights mosquitoes

Fungi from a university's pond may help kill the world of disease carrying mosquitoes.

The fungus, Lagenidium giganteum, works its way into mosquito larvae and kills them. Now an entomologist has discovered a way to encapsulate the fungus and the pellets can be thrown into stagnant water and ditches where mosquitoes breed.

The fungus was discovered several decades ago in mosquito larvae in a pond by Richard Axtell, professor of entomology at North Carolina State University.

Axtell starts the process with the fungus in its mycelial stage, as a tangled mass of threads. He ferments and grows it in a mixture of grain and sunflower seed and water for four days, then combines it with an alginate, a substance from the cell walls of kelp that is used to make ice cream smooth.

Axtell forms his mixture into pellets about the size of buckshot. The alginate dissolves when placed in water as the fungus grows a sporangial shoot. The shoot culminates in a vesicle that in turn produces swimming zoospores. These only attack mosquito larvae, burrowing inside the egg and devouring the host within 48 hours.

Axtell expects that habitats of mosquitoes might need repeated inoculation with the fungus because changes in water temperature kill it, as does salt water. Axtell's fungal pellets can be stored at room temperature for two to three months, and he hopes to increase their shelf life for use in developing countries. (Source: New Scientist, 23 June 1988)

Bacteria show promise in soil clean up

Micro-organisms have cleaned up about 4,000 cubic yards of diesel- and gasoline-contaminated soil in a project undertaken by Biota (Los Angeles), an environmental consulting firm that specializes in the use of microbes. Employing bacteria saved an unidentified client about 75 per cent in costs, compared with the alternative of shipping the contaminated dirt to a landfill, says Keith Kaufman, president of Biota. The project was unusual in terms of its size as it took about three and a half months to reduce contaminant levels to those that are "significantly lower than" the legal requirement. The site was a non-operational Los Angeles distribution and trucking facility, where soil had been contaminated by leaking underground fuel tanks. After the tanks were removed, the soil was excavated, and the hydrocarbons were degraded by two naturally occurring bacteria: Pseudomonas pseudomallei and Serratia liquefaciens. Potassium nitrate was added to the soil, which had virtually no nitrogen, as were inorganics (mostly phosphate buffers), which were nutrients and also served to stabilize the pH. In another project with Hercules, Biota is planning to use bacteria to clean up soil residues of trinitrotoluene and other products of an explosives plant operated by Hercules at Hercules, Calif. The residues include dinitrotoluene and dinitrobenzene. (Source: Chemical Week, 4 May 1988)

Biomass gasification technology

Onsite*Offsite has licensed thermal biomass gasification technology from Battelle Pacific North west Laboratories. The Battelle reactor processes a 90 per cent water biomass slurry over a transition metal catalyst at 350-450°C. Pressures of 2,000-4,000 psi prevent the water from evaporating. The biomass is converted into gas that goes into solution, and the gases are then separated. Onsite hopes to offer commercial systems that will allow industries to process their waste and produce methane and carbon dioxide gas. A five-tons per day pilot plant should be ready by end 1988. Systems could be built to handle 100,000 gallons per day. (Extracted from Chemical Week, 20 April 1988)

Extraction industry applications

Microbial recovery field test raises stripper well crude output

A strain of Bacillus licheniformis dumped down an Oklahoma oilwell in March 1987 turned up 30 weeks later in other wells hundreds of feet away. "It was the first time to our knowledge that an injected microorganism has been shown to transport from an injection well to a producing well," Rebecca Smith Bryant told some 200 oilmen attending

the Sixth Symposium on Enhanced Oil Recovery. Her report on "Microbial Enhanced Water Flooding: Mink Unit Project," was the only presentation on the programme to deal with microbial enhanced oil recovery (MEOR), for reclaiming residual 'gets' oil from sluggish or played out wells.

Ms. Smith Bryant is microbial research project leader at NIPER - the National Institute for Petroleum and Energy Research, in Bartlesville, Okla., which operates under contract to the US Department of Energy.

The Mink Unit on which Smith Bryant reported is a low-acre oil lease in Nowata County, in Oklahoma's northeastern state line. With originally estimated reserves of 1,700,000 barrels, the site had yielded only 341,000 by 1982, after which its average output per well sank to 0.4 barrels a day.

Thirteen months ago, NIPER teamed up with two commercial companies in Bartlesville. **Microbial Systems Corp.** and **Injectech, Inc.**, to test whether adding bacteria plus nutrients to the flood-water could increase oil production.

"The injection of micro-organisms and molasses has improved the rate of oil production at the Mink Unit Project Site by approximately 1? per cent," Smith Bryant stated. Moreover, it "decreased the water oil ratio at all monitored producing wells ... by as much as 35 per cent."

Jack Watson, senior research engineer in the chemical technology division of Oak Ridge Nat. Nat. Lab. ratory, Tenn., noted that MEOR is "a low capital operation, so it is very interesting to small independent petroleum operators." (Source: McGraw Hill's Biotechnology Newswatch, 2 May 1988)

Microbes that eat sulphur

A microbial culture that can remove sulphur from organic material such as coal has been developed by researchers at the Institute of Gas Technology (Chicago). John Kilbane, the environmental microbiologist who heads the research, calls the development the first documented evidence that micro-organisms can be used to remove organic sulphur from coal without affecting the fuel value. The next step will be to use genetic engineering to enhance the desulphurization ability. (Source: Chemical Week, 9 June 1988)

Gold and biotechnology

Most of the world's remaining gold reserves - perhaps 30 per cent - is locked up in sulphide. Biotechnologists think they can now get it out more cheaply and easily. There are several time-honoured ways of getting the sulphur out of the ore, all of which have drawbacks. Some, such as roasting it, can produce arsenic, sulphur dioxide fumes and then acid rain; others - involving feats only high temperatures and pressures - can be prohibitively expensive. A gentler way is to exploit bacteria that eat the sulphur and - break down the ore. In principle, this approach to the problem is no tougher than making beer or cheese. The right bacteria for the job were identified long ago.

All that needs to be done is to crush the ore, and put it in a tank with plenty of bacteria and a few nutrients. The bacteria eat the nutrients and, in effect, from - a bigger expense will be to keep the tank at a constant temperature. With enough carbon dioxide and oxygen, the bacteria will degrade the sulphide ore into a form from which the gold can easily be extracted.

The Canadian mining firm, [illegible] is already building a plant to [illegible] An American firm [illegible] to have a plant that [illegible] day ready by early 1989. Mr. Dr. Brierley, president of [illegible], reckons that the cash cost of gold produced by biological methods will be $100 an ounce - not much more than the [illegible] it costs his firm to produce gold from its mine. The capital cost of the biotechnology [illegible] Mr. Brierley hopes, will be paid back in five months.

Both processes propose to exploit the bug *Thiobacillus ferrooxidans*, which works best at 30-35° C and cannot work at all above 40° C. That might prove to be a problem, though, because the reaction produces plenty of heat. Keeping the tank cool would be expensive: failing to do so would have the bacteria uncomfortable and slow down the process.

Luckily there is another bacterium which likes hot conditions. A heat-loving strain was first discovered independently by two scientists [illegible] oxidizes sulphide ores just as *T. ferrooxidans* does, but it works most happily at [illegible]. That is a double advantage: the mixing tank can take [illegible] cooling, and it can take the ore about the bacterium works at a quick no pace when [illegible] enough. Studies at the British Government's Warren Spring laboratory in Stevenage showed that, after almost a fortnight, *Sulfolobus* had recovered 80 per cent of the copper from a sulphide copper ore; *T. ferrooxidans* only managed to recover 10 per cent.

Two scientists at Warren Spring, Dr. Norman le Roux and Dr. Roger Dunn, are trying to promote bioleaching in the gold-mining industry. So far nobody uses it, although one multinational mining firm is interested. Dr. James Brierley, one of the two scientists who first isolated the bacterium, is now research director of Advanced Mineral Technology in Golden, Colorado. His firm has been awarded a patent for the use of *Sulfolobus* in gold mining, and it has set up a joint venture with a Canadian mining firm to investigate how best to take advantage of it. Why have things taken so long to make it into the gold business? Because, says Dr. Brierley patiently, "the mining industry is a trifle conservative." (Source: The Economist, 25 June 1988)

E. PATENTS AND INTELLECTUAL PROPERTY ISSUES

Drugs lead the biotech patent race

US inventors are ahead in the biotechnology race, but biology discoveries in the drug field are the analysis of 1987 US biotechnology patents shows that pharmaceuticals command the most advanced biotechnology research but that the "broad potential for such research. These were some of the conclusions drawn by the Pharmaceutical Manufacturers Association (PMA) of Washington, DC, in a survey it published in New York City.

Of the 1,425 biotechnology patents that were issued last year by the US Patents and Trademarks Office (PTO), 2% involve genetic engineering, says PMA, while the remainder use more traditional biotechnology techniques, such as fermentation of yeast and other micro-organisms. Genetic engineering, in PMA's definition, is when recombinant DNA, hybridoma and DNA probe techniques.

A breakdown of the [illegible] patents [illegible] patent shows that fully 30 per cent of the patents are for pharmaceutical research.

More over, [illegible] these [illegible] patents, [illegible] are of US origin; only [illegible] are of foreign origin. Outside the US, Japan leads, with 14 genetic engineering patents for this [illegible].

Of the 59 US pharmaceutical patents, 45 per cent, or 59 patents, are issued to companies. The remaining 41 patents are issued to universities, the Government and non profit organizations. (Extracted from Chemical Week, 30 July 1986)

US awards Factor VIII patent

The recent award of a US process patent for recombinant factor VIII to Genetics Institute could theoretically give the US biotechnology firm and its [illegible], Boston Biotech, a US monopoly for this important drug.

Rorer is [illegible] a US patent on all purified Factor VIII preparations, but may be obliged to take a sublicense on it to Genetics Institute under the doctrine of intervening rights. The US doctrine states that a company which has spent heavily developing a product has the right to sublicense any later of the patent from the company holding it.

However, a ethics institute is not obliged to sublicense its patent. The [illegible] could arise as both patents are required to make the Factor VIII. (Extracted from European Chemical News, 1 August 1986)

Ciba-Geigy gran's first patent on plants

The biotechnology company Agrigenetics of [illegible], Colorado, has had an application approved by the European Patent Office (EPO) in Munich for what is claimed to be the first european patent on plants.

According to [illegible] from the EPO, the patent in question involves a technique for increasing the protein content of forage crops such as alfalfa. The limitations of the patent is that it includes not only legal protection for the technique itself, but also for plants produced with the aid of the technique.

The Patent office's decision appears to open the way for the general acceptance in Europe of patents covering both plants and animals created through the application of genetic engineering. Until now, there has been general uncertainty over whether such patents are allowable under the European Patent Convention of 1973.

Article 53b of the Convention, which sets the general framework for patent law in most European countries, allows the patenting of micro-organisms but specifically excludes from patent protection "plant or animal varieties", as well as "essentially biological processes for the production of plants or animals".

Some argue that a limited interpretation of the criteria "animal and plant variety" is adopted, then the Convention still allows patents to be granted on new animals and plants, or on their [illegible], which are not considered a form of biology.

This approach, for example, has been adopted in the draft of a directive seeking to unify European patent law, which is currently being completed by the Commission of the European Economic Community (EEC) in Brussels. A final version of the directive is due to be presented to ministers representing the 12 member States of the EEC soon.

In its current form, the draft is said to argue that genetic manipulation should be characterized as a (patentable) "microbiological process", rather than as a (unpatentable) "essentially biological process", and that as such it should be legitimately considered a patentable invention.

The Commission intends to go on to claim that, since a basic principle of European patent law is that protection should cover both a process and the product that results from its application, a new plant or animal produced with the use of these genetic manipulation techniques should also be patentable.

Such patents can therefore be granted, it suggests, regardless of the ban on patents on new animal and plant varieties imposed by the 1973 Convention. In other words, the Commission intends to argue that the Convention does not exclude the patenting of plants and animals as such.

The European Patent Office appears to have adopted this interpretation of the current legislation in approving the Agrigenetics patent (which will be valid in all European countries that have signed the Convention).

It has yet to make a decision on whether the same principle should be applied to an application it has received from Harvard University for a patent on the so-called "oncomouse" developed by Philip Leder and Timothy Stewart, which carries the myc oncogene in its genome, and was recently awarded the first US patent on a living animal. Applications for patents on living organisms have also been filed by several European companies. (Adapted from Science, Nov. 14th, 27 May 1986)

PTO reports on meeting to align [illegible] patents in US, Europe, Japan

In 58 double spaced pages and 12 single spaced tables, the US Patent and Trademark Office (PTO) has summed up comparative policies and practices of the US, European and Japanese patent offices in dealing with biotechnology applications. The report was presented late in March to the Association of Biotechnology Companies (ABC) by Michael F. Kirk, assistant PTO commissioner for external affairs. It sums up data derived from several meetings of biotechnology trea examiners from the three national patent offices over recent years, aimed at harmonizing patents in the world. The next such tripartite encounter is set for July or August.

Entitled "Comparative study of patent practices in the field of biotechnology, related mainly to microbiological inventions", the report details similarities and differences in all aspects of patent prosecution, with special attention to deposition of micro-organisms, and comparative criteria for plant and animal patenting. Copies of the PTO report are available on request from ABC, 730 Vermont Avenue, Suite 600, Washington, D.C. 20 05. (Courtesy McGraw Hill's Biotechnology Newswatch, 2 May 1986)

Patent on mouse breaks new ground

A mouse has shaken the foundations of biotechnology in the US by earning the first patent for a genetically engineered animal. The Government's Patent and Trademark Office last week issued the patent to Harvard University and two of the university's scientists, Philip Leder and Timothy Stewart, who is now with Genentech.

The patent is broad, covering any "nonhuman eukaryotic (having nucleated cells) animal" into which scientists plant an active oncogene (a cancer-causing gene) or a sequence of DNA that induces cancer in the animal and its offspring. Leder and Stewart created a "transgenic" animal, a mouse, that carries the oncogene c-myc in both its sex and somatic cells. As a result, the mouse and its offspring are genetically predisposed to breast cancer. Harvard has deposited the plasmid, or genetic vector, carrying the oncogene with the American Type Culture Collection.

Such mice are valuable to researchers for testing the potency of carcinogens or substances that combat cancer, and as cell banks for cancer research. For example, tests of weak carcinogens normally require exposing mice to massive doses of the substance. Because such large doses almost never occur in nature, researchers often challenge the results. Harvard's mice will succumb to carcinogens at lower doses more commonly found in nature.

Patent officials found the application troublesome, according to Donald Quigg, commissioner of patents. Examiners took almost three times the normal 13 months to study Harvard's application.

The University of Washington, Seattle, had previously tried to patent an animal - oysters genetically engineered to have more than one set of chromosomes. The application failed because the Patent Office said that the technique was not novel. Companies are also trying to patent animals in Europe.

One agency deeply involved in genetic engineering, the Department of Agriculture's research branch, has chosen to sidestep any trouble by deciding not to get patent protection for higher vertebrate animals. Researchers, either at the US Department of Agriculture, or funded by it, are experimenting with several transgenic animals. They have developed a genetically altered chicken that is resistant to avian leukosis virus.

A decision is still awaited on 21 applications for patents on "higher" life forms, those more complicated than micro-organisms. The patent office will not discuss pending patents, but one application, by Integrated Genetics in Massachusetts, covers engineered rodents that secrete tissue plasminogen activator in the milk of lactating females. The company has also applied for patents in Europe.

Without the promise of patent protection, the few companies that sell rodents for research have had little incentive to produce transgenic animals. A senior official at the National Institutes of Health, which funds biomedical research involving millions of rodents each year, applauded the precedent set by the patent.

Du Pont, which has funded Leder's research since 1981, has an exclusive licence to breed the mice commercially. (Source: New Scientist, 21 April 1988)

The biotechnology patent track may be too fast

The US Patent and Trademark Office (PTO) is determined to cut the time it takes to make a decision on biotechnology patent applications from the current 28 or 29 months to just 18 months by the year 1994, at the latest. So the agency plans to hire 130 additional examiners during the next five years for its new Examining Group 180, which will handle only biotechnology patent applications. The backlog since 1985 has grown from about 5,700 applications to about 14,500 currently. Ironically, some industry officials are beginning to worry that patent examiners are now pushing applications through faster than they should - partly to counteract criticism about delays - and allowing overbroad patent claims. (Source: Chemical Week, 9 June 1988)

A genetic patent for an industrial enzyme

Genencor (South San Francisco), the industrial biotechnology joint venture of Genentech, Corning Glass Works, A.E. Staley and Eastman Kodak, says that it will soon get a patent on protein engineering of the enzyme subtilisin, a proteolytic enzyme currently used in cleaning products, metal-recovery processes, leather treatment and food processing. Using proprietary mutagenesis techniques, Genencor has been able to produce modified subtilisins with characteristics significantly different from those of the parent enzyme. Genencor says they can modify, among other things, the catalytic efficiency of the enzyme. (Source: Chemical Week, 15 June 1988)

A genetic route to superoxide dismutase

Aiming to tap an estimated $500 million market, Bio-Technology General (New York City) says that it has won a patent (U.S. 4,742,004) on a method for producing enzymatically active human copper-zinc superoxide dismutase (SOD), a substance that may reduce heart-attack tissue damage. The patent, which the company says is the first to be issued for genetically engineered human SOD, covers broadly the "cost efficient" production of human copper-zinc superoxide dismutase in bacteria. The company is moving to develop a commercial recombinant superoxide dismutase product with Bristol-Meyers, which is now sponsoring clinical trials. (Source: Chemical Week, 11 May 1988)

HTLV-I patent awarded by US

Cambridge Bioscience Corporation (CBC) of Worcester, Mass., has been issued a US patent covering the purified form of gp 61, the envelope glycoprotein found on the surface of Human T lymphotrophic virus type I (HTLV-I), a virus thought to cause adult T-cell leukaemia and lymphoma. The company is developing a test to detect exposure to the virus.

Harvard University granted the company an exclusive licence to its gp 61 patent, credited to the work of Dr. Myron Essex, a member of the CBC's Scientific Advisory Board, and his co workers at the Harvard School of Public Health, who first identified the gp 61 protein marker.

Cambridge Bioscience has successfully cloned, expressed and purified the critical immunoreactive fragments of gp 61 for use in its first test. The company has also succeeded in cloning, expressing and purifying the p24 protein, found in the core of the virus, which may also be useful in an HTLV-I test.

Epidemiological studies suggest the need to screen blood donors for HTLV-I virus, and to investigate the seroepidemiology of the disease. (Extracted from Chemical Marketing Reporter, 27 June 1988)

t PA patent issued

The first US tissue plasminogen activator (t PA) patent, based on research done at Oxford

University (PF), was issued to Monsanto (St. Louis, MO) in June. But this patent should not prevent Genentech or other companies from marketing first-generation t PA, according to Denise Gilbert of Montgomery Securities (San Francisco, CA). The patent only covers t PA isolated from human uterus cells; Genentech's t PA is a recombinant product produced in Chinese hamster ovary (CHO) cultures. However, the Monsanto Oxford patent may put a damper on second generation t-PAs, since it specifies the attachment of carbohydrate groups to the protein. If (as Gilbert expects) a series of Monsanto Oxford patents issues, each specifying a different carbohydrate profile, other companies involved in remodelling second generation t PAs will find their options limited. (Source: Bio Technology, Vol. 6, July 1988)

Canadian biotechnology company patents plant breeding process

A US patent has been issued to a Canadian company for a new method of plant breeding. The novel process provides an improved means of developing hybrid plants by overcoming traditional genetic barriers. The discovery, made by Dr. Larry Erickson, a plant geneticist, is a major landmark in this science. It provides a significant competitive advantage for Allelix Agriculture, the patent holder.

The patent covers a unique process of using pollen to transfer genetic material from one canola plant to another. It is notable because it challenges an established genetic principle of maternal inheritance. According to this principle, certain genetic material inside a cell (but outside the nucleus) is transferred to the offspring only from the mother. This has been a major obstacle to agriculture scientists trying to improve various plants using traditional crossing methods, especially when desirable traits are carried only outside the nucleus.

The process is used by Allelix to facilitate the development of hybrid canola. Canola is a high quality rapeseed used for food and feed. It is the third largest source of vegetable oil worldwide and the most widely planted oilseed in Canada and Europe. Canada alone has an annual production of $1 billion, making it Canada's second most valuable crop.

Allelix holds six US and four Canadian patents for devices and methods, and has filed many other applications in Canada, the US and Europe. For Allelix Agriculture, Dr. Erickson's discovery provides the first patent on in house research.

Allelix Agriculture develops improved crop seeds and microbial seed treatments using plant breeding, cell biology, molecular biology and agricultural microbiology. The canola research programme is believed to be the largest in the world and one of the few that encompasses all types of rapeseed. Allelix Agriculture is distributing two varieties of seed in Kentucky, Illinois, Indiana and Tennessee for planting in autumn 1988. (Source: News Release, 23 August 1988)

F. BIO INFORMATICS

$1 billion liposomes market by 21st century

A critical property of liposomes, their ability to be used as delivery systems, has found limited applications so far. The reason is that the extreme instability of liposomes results in a very short shelf life. A new research has developed a second generation liposome, a polymerized version, that remains stable indefinitely even in the presence of detergents and organic solvents.

According to a new report from Technical Insights, Polymerized Liposomes: Unique Carriers of Drugs, Catalysts, Other Agents, this extended shelf life means that almost any application for first generation non polymerized liposomes is not only subject to take-over by polymerized variety, but also that it is now feasible to develop new commercial applications. The company forecasts that liposomes will become a $1 trillion business by the year 2000.

Among the likely applications are human and animal pharmaceuticals, chemical and acoustic sensors, new microfiltration systems, gas separation membranes, catalyst delivery systems, agricultural chemicals (including pesticides and fertilizers), paints and coatings (including "self-healing" paints) and ceramic fibre reinforcements. Details of the report priced at $900 ($940 for non-US purchasers), from: Kristine Swain, Technical Insights Inc., P.O. Box 1304, Fort Lee, NJ 07024, USA or on ++ (201) 568-4744. (Source: Biotechnology Bulletin, Vol. 7, No. 6, July 1988)

Genetic Technology News (GTN) and Bioprocessing Technology (BT) have gathered 33 monthly market forecasts in one data-packed sourcebook Biomarkets: 33 Market Forecasts for Key Product Areas. Biomarkets outlines the breakthroughs and points out market opportunities in such key areas as:

- Recombinant DNA products
- Low temperature pyrolosis
- Monoclonal antibodies
- Cancer therapeutics
- Biopolymers
- AIDS diagnostics therapeutics
- Genetically altered animals
- Microbial insecticides
- Interferons
- Lymphokines
- Supercritical fluids processing
- Interleukin 1 and 2
- Bovine fertility
- Immune response enhancers
- Epidermal growth factor
- Herbicide-resistant plants

Biomarkets: 33 Market Forecasts for Key Product Areas. 285 pp; 1988, is available from Technical Insights, Inc., Dept. BMT188, P.O. Box 1304, Fort Lee, NJ 07024, USA. Price: $890; overseas buyers add $40 per copy for postage and handling.

Growth factors will find wound healing market

The Technology Management Group has published Growth Factors for Wound Healing II: Worldwide Markets for Surgical Healing, Wounds, Eye Cure, Bone Fractures and Other Applications. The report, based on telephone interviews of key individuals at over 50 leading organizations, predicts these markets are expected to be worth $1 billion in the US and $5 billion worldwide by 1997.

Early applications include ophthalmic surgery, burns and chronic non healing bedsores. Growth factors may, ultimately, be used for many or all forms of surgery. TMG suggests, for bone fractures and for dental applications. Thirteen clinical trials that are either under way or are expected by 1989 are discussed, including Chiron's joint venture with Ethicon (Johnson & Johnson) and trials being

[illegible] in Europe and Japan. [illegible] companies are [illegible] the [illegible] [illegible] with [illegible] [illegible]. Details of the report, priced at $[illegible], from [illegible] Technology Management Group, [illegible], New Haven, CT [illegible], USA [illegible] (203) [illegible]. (Source: Biotechnology Bulletin, Vol. 7, No. [illegible], July 1988)

The [illegible] [illegible] [illegible] [illegible] [illegible]

Analysts are [illegible] much more [illegible] at the market projections for Genentech's [illegible] tissue plasminogen activator (t-PA) [illegible] becomes clear that the US biotechnology company will enjoy a considerably [illegible] [illegible] [illegible] [illegible] than previously forecast. Emerging competitors to Genentech's Activase include streptokinase with aspirin, a combination which has performed well in broad scale European trials, and Beecham's Eminase.

The results of comparative [illegible] of the three new forms of thrombolytic therapy are unlikely to be in before late 1988 or 1989, although it is clear that all three represent major advances [illegible] conventional therapy. In what is [illegible] seen as a defensive ploy, Genentech has offered [illegible] free of charge to American patients not covered by health insurance or government reimbursement schemes.

But there is [illegible] [illegible] the potential [illegible] the market, as a new report from market analysts Frost & Sullivan points out. [illegible] drug [illegible] Market in the US projects an average [illegible] per cent rise in annual cardiovascular drug sales, with a $4 billion market in 1986 expected to expand to $[illegible] billion by 1991. However, the report [illegible] by [illegible] the growth rate will be [illegible] [illegible] more than [illegible] per cent annually. These drugs already make up the largest single [illegible] [illegible] per cent of [illegible] of the US pharmaceutical market, a share expected to grow to 18.4 per cent by [illegible].

The most important factor [illegible] the [illegible] cardiovascular product sales is the aging of the US population. The US [illegible] segment was [illegible] million people in 1975, [illegible] million in 198[illegible], [illegible] million in 1985 and is expected to reach [illegible] million by [illegible]. At the same time, the number of doctors prescribing cardiovascular drugs grew [illegible] to 174,000 in 1985.

Compared to someone in the [illegible] age group, a person aged 65 or more is nearly seven times more likely to suffer a heart condition [illegible], [illegible] times more likely to suffer from hypertension [illegible] and [illegible] times more likely to have [illegible] heart disease. Details of the report, numbered A[illegible] and priced at $[illegible], from: Customer [illegible], Frost & Sullivan Ltd., [illegible] House, 4 [illegible] Gardens, London [illegible] [illegible]. (Source: Biotechnology Bulletin, Vol. 7, No. [illegible], July 1988)

Fast growing US market for biotechnology media

Although a great deal of interest has been shown in the potential of genetic engineering products, relatively little attention has been given to the materials consumed in the processes used to make [illegible] products. This has been rectified for the US market by a new report from Business Communications Co. (BCC), The [illegible] Media, [illegible] and Reagent Markets in Biotechnology.

The US market for media, [illegible] and reagents used in biotechnology for cell culture totalled an estimated $407 million in 1987 and is expected to grow at an average rate of 12 per cent a year through 1995. The media portion for the US market

[illegible]

[illegible]

[illegible]

[illegible]

According to the [illegible] [illegible] market was an estimated $[illegible] [illegible] growing [illegible] per cent a year [illegible] [illegible]. The [illegible] market [illegible] [illegible] a year.

[illegible]

Recombinant [illegible]

[illegible] A new report from [illegible] [illegible] [illegible] $4.[illegible] billion by [illegible].

"The [illegible] demand for [illegible] [illegible] the third world," the report [illegible]. By contrast, "the greatest demand [illegible] will exist in more advanced countries". Details of the report, No. [illegible] ($[illegible]), from: Theta Corp., Theta Building, Middlefield, CT [illegible], USA. Tel. (203) [illegible]. (Source: Biotechnology Bulletin, Vol. 7, No. [illegible], June 1988)

Information [illegible] [illegible] and [illegible] [illegible]

The World [illegible] (WDC) [illegible] [illegible] collaborating information [illegible]. They are:

The World Data Centre on Microorganisms (WDC)

The Microbial Strain Data Network (MSDN).

MIRCEN Location	Title
Guatemala	Mushrooms: characteristics, physiology and growth, 12 pages $US 7.00
Nairobi	Nairobi MIRCEN Culture Collection Catalogue
	Biological Nitrogen-Fixation in Africa. Editors: Ssali, H. and Keya, S.O., 1985, pp. 540 $US 30
NifTAL	NifTAL Rhizobium Antisera Catalogue, $US
	NifTAL Rhizobium Germplasm Catalogue
	Methods in Legume-Rhizobium Technology by Somasegaran, P. and Hoben, H.J., 1985, pp. 367, $US 22
	The Legume-Rhizobium Symbiosis: A Continuing Bibliography
	Legume Inoculants and Their Use by J.C. Burton, FAO NifTAL, US$ 8
	10th North American Rhizobium Conference Book, US$ 5
	NifTAL MIRCEN Rhizobium Resource Catalogue, US$ 5
	Design and Analysis of an International Experimental Network: Legume Inoculation Trials in the NifTAL Project, the INLIT Experience by R.J. Davis, F.B. Cady, C.L. Wood and C.P.Y. Chan
Porto Alegre	Rhizobium Culture Collections of the World
	Brazilian Network of Rhizobium laboratories
	Colecoes de Estirpes de Rhizobium da Latina America
	Rhizobium Culture Collection Catalogue
Stockholm	Details on the Proceedings (available at US$ 20 per annum) of the Anaerobic Digestion MIRCEN Computer Conference Series
WDCC	World Directory of Collection of Cultures of Micro organisms, 2nd Edition, US$ 30
	World Directory of Collection of Cultures of Micro organisms, 3rd Edition
	World Catalogue of Rhizobium Collections, 2nd Edition, US$ 10
	World Catalogue of Rhizobium Collections, 3rd Edition.

(Source: MIRCEN News, July 1988)

In some cases, where available, the prices have been listed. In other cases, these can be supplied by the MIRCEN concerned. Readers desirous of obtaining priced publications are advised to utilize the UNESCO Coupons scheme in the event of foreign-exchange problems.

Living Resources for Biotechnology

This is an international initiative by the World Federation for Culture Collections with financial support from UNESCO.

This series of source books has been assembled with the needs of scientists using microbiological materials as tools in biotechnological investigations in mind. When starting to handle bacteria, filamentous fungi, yeasts, algae, viruses, animal and plant cells, research workers are faced with a number of questions. Where can the material be obtained and who will supply basic information about its use and preservation? Are there identification services available? How is material deposited in gene banks? How are patents taken out? Are there centres that will carry out contract work? What safety regulations should be taken into account and what organizations exist to help?

This is the first time that such data have been drawn together in single volumes and they will be valuable to workers all over the world in universities, research institutes and industry. Price: about Y12.50. (Source: MIRCEN News, July 1988)

Industrial Biotechnology International 1988 39

Industrial Biotechnology International provides a two-yearly review of major technological advances and corporate developments culled from boro meetings with senior personnel from many companies, and from computer searchers on European, Japanese and American literature.

The book is divided into two major parts: the first is on technological advances and market analyses. In its seven chapters many recent advances of biological origin used in the present-day food, health, waste treatment, and agricultural industries are described. The chapters are:

1. **Therapeutics** (includes sections on drug delivery, gene analysis and anti-cancer applications)

2. **Diagnostics** (includes screening for drug abuse and pathogenesis of AIDS)

3. **Agriculture and botany** (includes recombinant DNA technology, biocides and animal health care)

4. **Waste treatment** (antibiotics in waste treatment plants and steroids from pulp and paper waste)

5. **Marine and aquatic advances** (includes fuel oil from algae and chitin in cosmetics, toiletries and sutures)

6. **Food and beverages** (includes enzyme applications and looks at speciality ingredients such as preservatives and vitamins)

7. **Bioelectronics and biosensors** (includes utilization of fats, proteins and nerve cells in electronics and enzyme and microbial biosensors).

Part two is on Biotechnology and the Corporations. This looks at:

Industrial analyses, which consist of:

- **Biotechnology industry analysis** (includes developments affecting the industry as a whole and financial and stock market reports of biotechnology corporations), and
- **Pharmaceutical industry analysis** (includes developments affecting the pharmaceutical industry as a whole and financial and stock market reports of pharmaceutical corporations).

Corporate focus (includes a discussion of individual biotechnology and pharmaceutical corporations, companies discussed include Eastman, Kodak, Monsanto, Biogen, Cytogen, etc.).

Then follows a conclusion and glossary of terms, an organizations index, a subject index, and a personal name index.

Industrial Biotechnology International is edited by Laurence H. Bernath of Dr. Link Consultants in Vancouver. Price $35 plus $10 for airmail. Copies may be ordered from Promotion Department, Longman Group UK Ltd., Westgate House, The High, Harlow, Essex CM20 1NS, United Kingdom. Tel: 0279 442601.

WHEAT HERBICIDES: The Challenge of Emerging Resistance

In November 1987, Professor Jonathan Gressel of the Department of Plant Genetics at the Weizmann Institute of Science, warned the British Crop Protection Conference of the imminent possibility that major groups of herbicides currently used to control weeds in wheat would become ineffective due to the evolution of resistance by economically damaging weeds. Failure to control such weeds can cause yields to fall by 60 per cent. He stressed the fact that due to key biochemical differences between wheat and other crops there might soon be no effective weed control methods left.

Some of the most pernicious of these weeds, including blackgrass and wild oats, are not just evolving resistance to the cure but, very expensive herbicides but are developing a new and potentially, even more damaging characteristic, multiple resistance to virtually every chemical presently in use, and also to new herbicides to which they have never been exposed.

The result is a compounded, terrifying possibility, that for increased weeds, which have previously been relatively easy to control, will also become resistant to many of the new high potency herbicides. In addition, multiple resistance is just as likely to occur among broad leaved weeds as it is in grasses.

These changes could have dire consequences for production of the world's number one food crop.

Professor Gressel, one of the world's pre-eminent authorities on herbicide resistance, analyses both the problems and the possible solutions in a newly published multi-client study. In appropriate, possible answers to the industry and to growers he raises a strong case that the elite cure solutions may come from genetically engineering wheat to modify its basic biochemistry. In addition, he shows how these modifications to the wheat genome can also be used to reduce the cost of producing hybrid wheat seed making genetically engineered hybrid wheat profitable for agrochemical companies, biotechnology and seed companies, and farmers and consumers.

The study, WHEAT HERBICIDES: The Challenge of Emerging Resistance, is available from Biotechnology Affiliates, P.O. Box 8, Checkendon, Reading, Berkshire RG8 0BP, UK. Price: 1,000 pounds sterling.

Capsules for living

Space Biospheres provides a descriptive and analytical underpinning to the work now under way of the Arizona biospherians. The authors propose a concise integrative model of Biosphere I (Earth's biosphere) then describe the work under way to model Biosphere II, the extraordinary project to create biospheric systems to further humankind's ability to live in harmony with the sphere of life on Earth or in space. There is a compelling vision of a possible future which takes the dream of the space frontier into the practical domain of science and management.

For the first time, this book structures the grand geobio conceptual work of Vernadsky and his Russian successors, with the atmospheric microbiological achievements of Lovelock, Margulis, Folsome, and with the Institute of Ecotechnics' series of biomic and biospheric projects and modelling. The vast panorama of the extraordinary cultural agenda now opening to humanity through the synergy of biospherics and astronautics is explored. Biosphere II's enlightenments will have implications for development on Earth as well as for colonies on Mars. Space Biospheres by John Allen and Mark Nelson, Synergetic Press, 1986, $US 6.95 or Y4.95. In US: P.O. Box 689, Oracle, Arizona 85623. In UK: 24 Old Gloucester St., London WC1 3AB. (Source: Development Forum, Vol. 16, No. 4, July August 1988)

CAS and computer firm plan joint projects

Chemical Abstracts Service and Evans & Sutherland Computer Corp.'s interactive systems division have agreed to jointly develop and market computer based products for scientists and engineers. Evans & Sutherland designs and makes special purpose computers, interactive three dimensional display equipment, and software with science and engineering applications. Its Tripos Associates subsidiary develops software for molecular modelling and computational chemistry. CAS, a division of the American Chemical Society, produces scientific databases and software for searching, retrieving, and displaying scientific information. One joint effort already under way is aimed at tying CAS software for chemical structure and literature searching to Evans & Sutherland and Tripos software for three dimensional molecular modelling. The link would let scientists with personal computers combine on line searching of the CAS chemical registry database with manipulation of molecular models. (Source: Chemical and Engineering News, 20 June 1988, p. 20)

Herbs on line

Information on herbal preparations has mushroomed in the last 20 years. To facilitate access to it UNESCO established the Asian and Pacific Information Network for Medicinal and Aromatic Plants (APINMAP) in 1986 as part of the Regional Network for Exchange of Information and Experience in Science and Technology in Asia and the Pacific (ASTINFO). When operational, the network's computer data base will make available data received from member countries (Australia, China, India, Nepal, Pakistan, Papua New Guinea, the Philippines, Sri Lanka, Thailand and Viet Nam). Technical discussions of hardware configuration and software are proceeding. (Source: Development Forum, Vol. 16, No. 4, July August 1988)

NEBIS Information Services

A new online newsletter is offered by NEBIS Information Services, a joint project between the Microbiology Department and the Computing Laboratory of the University of Newcastle upon Tyne. Academics can access the newsletter from terminals with links to the JANET network. Details from: Julie Glanville, Information Officer, NEBIS Information Services Department of Microbiology, Medical School, Framlington... ace, Newcastle-upon-Tyne NE2 4HH or on 091 232 8511. (Source: Biotechnology Bulletin, Vol. 7, July 1988)

Pharmacia's new version of DNASIS and PROSIS software

The DNASIS and PROSIS software packages are designed to enable quick, easy and total analysis of genes and proteins. DNASIS is used in DNA sequencing results and molecular weight separations and PROSIS for structure analysis of amino acid sequences. Primary results are entered directly into the software by digitalizing the gel images. Hundreds of routines may be used to form a hypothesis about gene function and regulation. The DNA and protein databases are all directly accessible online from a laser disk. Details from: Pharmacia LKB Biotechnology, Box 305, S-161 26 Bromma, Sweden or on +46 8 98 63 64. (Source: Biotechnology Bulletin, Vol. 7, No. 6, July 1988)

Bio process management package for IBM compatible PCs

LH Fermentation is now marketing a fermentation management package developed by Biotechnology Computer Systems (BCS), another Porton International Group member. Called BIO-pc, the programme is a single user system, designed for use with up to four bioreactors and associated on line ancillary equipment. The programme was developed by BCS to complement its powerful multi-user process management system, BIO-i.

Configured for an IBM AT or compatible computer, BIO-pc uses the standard MS-DOS 3.1 operating system and is capable of performing data monitoring, logging and feedback control "in background mode". Consequently, the complete SMART applications package, incorporated into the system, can be assessed at any time during operation. The facilities offered by this package include full word processing, spreadsheet with graphics, database manager, communications and time manager programs.

Management of the databases, batches and graphics is achieved through an applications program incorporating much of the philosophy behind the comprehensive BIO-i process management software. Written specifically for bioreactors and fermentation systems, the BIO-pc software allows comprehensive process management in numerous applications and is both convenient and simple to operate. (Source: International Industrial Biotechnology, 8 February 1988)

G. MEETINGS

1989

5 - 9 February	Perth, Australia. Advances in Biomedical Polymers. Further information from D.G. Richardson, Chemistry Centre, 125 Hay Street, Perth, Western Australia.
6 - 9 February	Sydney, New South Wales, Australia. 8th Australian Biotechnology Conference. Further information from P.F. Gray, Department of Biotechnology, University of New South Wales, P.O. Box 1, Kensington, New South Wales 2033, Australia.
6 - 10 February	International Center, Miami, Florida. Bio-Technology Winter Symposia: Advances in Gene Technology - Molecular Neurobiology and Neuropharmacology. Further information from Bio-Technology, 65 Bleecker Street, New York, N.Y. 10012, USA.
12 - 17 February	Canberra, Australia. Summer Workshop in Immunological Methods. Further information from Peggy Horn, School of Applied Science, P.O. Box 1, Belconnen, ACT, 2616, Australia.
20 - 24 February	Stuttgart, FRG. Biotechnology and Food (IUFOST). Further information from University of Hohenheim, Institut fur Lebensmittel Technologie, Attn. Frau Ursula Hess, Grabenstrasse 25, D 7000 Stuttgart 70, FRG.
14 - 17 March	Interlaken, Switzerland. First Conference on Advances in Purification of Recombinant Proteins. Further information from AKM Congress Service, P.O. Box, CH-4005 Basel, Switzerland.
19 - 21 April	Athens, Greece. Workshop entitled "What are the Initial Lesions in Atherosclerosis?" (Part of the 23rd Scientific Meeting of the European Society for Clinical Investigation) Further information from Drs. J.F. Martin and R.F.G. Booth, Department of Medicine, King's College Hospital Medical School, Denmark Hill, London SE5 8RX, UK.
14 - 19 May	New Orleans, USA. 89th Annual Meeting of the American Society of Microbiology. Further information from R.A. Bray, ASM, 1913 I Street, N.W., Washington DC., 20006, USA.
15 - 18 May	London, UK. Biotech '89. Further information from Blenheim Online Ltd., Blenheim House, Ash Hill Drive, Pinner, Middlesex HA5 2AE, UK.
30 July - 5 August	Berlin, FRG. 7th International Congress on Immunology. Further information from Dr. H. Kirchner Deutsches Krebsforschungszentrum, Institut für Virusforschung, Im Neuenheimer Feld 280, D 6900 Heidelberg, FRG.

21 - 25 August	Utrecht, The Netherlands. 11th International Congress of the International Society of Developmental Biologists. Further information from Congress Secretariat, 11th Congress (Holland), Keizersgracht 74a, 1017 EC Amsterdam, The Netherlands.
24 - 26 August	International Conference Centre, Kobe, Japan. Protein Engineering '89. Further information from IRL Press Ltd., P.O. Box 1, Eynsham, Oxford OX8 1JJ, UK.
28 August - 3 September	University of York, UK. Conference on Insulin: Structure, Chemistry and Biology. Further information from Prof. Guy Dodson, Department of Chemistry, University of York, Heslington, York, YO1 5DD, UK.
11 - 17 October	Beijing, China. ACHEMASIA '89. International Meeting on Chemical Engineering and Biotechnology in the Far East. Further information from DECHEMA, P.O. Box 970146, D-6000 Frankfurt am Main 97, FRG.

1990

11 - 15 February	Massey University, Palmerston North, New Zealand. An International Conference on Fermentation Technologies: Industrial Applications. Further information from The Conference Director, Biotechnology Department, Massey University, Palmerston North, New Zealand.
13 - 18 May	Anaheim, California, USA. 90th Annual Meeting of the American Society of Microbiology. Further information from R.A. Bray, ASM, 1913 I Street, NW., Washington DC. 20006, USA.
8 - 13 July	Copenhagen, Denmark. 5th European Congress on Biotechnology. Further information from Secretariat ECB5, DIS Congress Service, Linde Allee 45, DK 2720 Vanlose, Copenhagen, Denmark.
July	Amsterdam, The Netherlands. 11th International Congress on Pharmacology. Further information from J.M. van Ree, Dutch Pharmaceutical Society, c/o Rudolf Magnis Institute, Vondellaan 6, Utrecht, The Netherlands.

1991

August	Jerusalem, Israel. 15th International Congress on Biochemistry. Further information from N. de Groot, Department for Biological Chemistry, The Hebrew University, Jerusalem 91904, Israel.

H. REPRINTED ARTICLES

Biotechnology and the Third World: the missing link between research and applications 1 by
Raymond A. Zilinskas, Ph.D.,* Program for Public Issues in Biotechnology, University of Maryland, Baltimore County, Catonsville, MD 21228.
27 October 1988.

Abstract

A United Nations University study investigated the activities of four major UN agencies that focused on helping developing countries gain advanced capabilities in biotechnology. Relevant programme and project documents were scrutinized at agency headquarters and managers were interviewed, after which projects under way in three case countries (Egypt, Thailand and Venezuela) were examined to assess these countries' needs and/or advances in biotechnology capability.

The findings revealed that the available UN-originated assistance was directed solely towards increasing capabilities in research and thereby benefiting bioscientists and their institutes. However, as virtually no links exist between research establishments and the industrial marketing sector, results from indigenous research does not reach industrialists, farmers or health workers. Consequently, in the case countries biotechnology is largely irrelevant to their economic and social development. This situation is likely to persist as corrective systematic changes will be difficult to implement. Major implications of these findings are discussed.

INTRODUCTION

This article is based on a study undertaken to investigate the activities four United Nations (UN) agencies are undertaking to help developing countries attain advanced capabilities in biotechnology (Zilinskas, 1987b). The author initially researched the concept development process in industrialized countries, after which three developing countries were selected for case studies (Egypt, Thailand and Venezuela). These countries were visited in order to scrutinize their biotechnology related activities vis à vis health and planned industry or were already under way. 2 Information from the case countries was used to assess the concept development process as it takes place in these countries. Information on relevant projects was also obtained at the headquarters of the UN agencies of the United Nations Development Programme (UNDP), the United Nations Educational, Scientific and Cultural Organization (UNESCO), the United Nations Industrial Development Organization (UNIDO), and the World Health Organization (WHO). The two information sets were analysed to clarify major gaps in the assistance being provided by agencies and to assess whether the UN sponsored projects are indeed augmenting and advancing the case countries' capabilities in biotechnology.

1. The "ideal" concept development process

Fermentation industries using traditional techniques have a long history in both developed and

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* Dr. Zilinskas is an associate staff scientist with the Program for Public Issues in Biotechnology, Maryland Biotechnology Institute, University of Maryland, Baltimore County.

developing countries. However, from about 10 years ago, advanced biotechnology R&D has given rise to a rapidly growing bioscience based industry which is now beginning to market its first products. With this development, it is possible to chart the progression of events whereby an idea or concept becomes a marketable product (i.e. the concept development process) in order to identify its important components and the forces that act on it. Furthermore, it is possible to distinguish and evaluate the elements essential for capability building in its research and applications sectors. Hence, the concept development process may be schematically presented (see figure 1).

Fundamental to the process is the easily accessed knowledge base. In science, the most important contributions to the knowledge base come from basic research, but only a small fraction of this base has the potential for practical applications. This fraction, accessed by innovators, inventors and entrepreneurs, is further researched in an applied research facility. If the concept is demonstrated as having the potential for meeting a need and of being workable, it enters advanced research and development. In a developed country, advanced R&D usually takes place at one of three types of facilities: a national laboratory, a defence establishment laboratory, or an industrial laboratory. If development is successful, a product or process results. To lay the technical basis for its large-scale manufacture and to determine its economics, the product is scaled up at a pilot plant facility. Pilot plant operations and down stream processing may occasionally be done at development laboratories, but generally takes place at the industrial plant. If the feasibility of the product is proven, the industrial plant scales up for the commercial manufacture of the product, while the marketing and sales division ensures the product reaches those for whom it is intended. The educational system produces the scientists, technicians and managers who operate the process.

2. Biotechnology related activities in the case countries

The "ideal" concept development process provided a framework for analysing biotechnology related activities in the case countries surveyed (Egypt, Thailand and Venezuela). The major findings were as follows:

Knowledge base

The knowledge base is theoretically as accessible to educators, scientists and industrialists in developing countries as it is to anyone else. However, from a practical point of view, severe impediments prevent the third world researcher from access to important information sources. These are due to the relatively high expenditures involved, the scarcity of funds and at times the lack of hard currency. Only a few libraries in the case countries have book and journal collections adequate to support strong research efforts in biotechnology and these are located in the countries' capital cities; researchers elsewhere in the countries are as a rule not adequately served by libraries. Access to data banks is limited or is not available, due to lack of funds, poor communication lines and lack of technical expertise. Person to person contacts between researchers from developed and developing countries are relatively infrequent because third world researchers have few opportunities to travel, while scientists from industrialized countries do not usually travel to developing countries. It may be concluded that apart from the fortunate scientists who work in the capital cities, the knowledge base is neither readily nor easily accessible to bioscientists in the case countries. Limited accessibility to the knowledge base is thus a principal barrier hindering the advancement of biotechnology.

Basic research

Wide ranging basic research in the traditional areas of bioscience is being carried out at universities and government institutes in the case countries, with a strong emphasis in Venezuela and Thailand. Thus a substantial scientific base does exist from which research in biotechnology could expand. None the less, before such research can be undertaken on a larger scale certain barriers have to be overcome. One was mentioned above - access to the knowledge base must be improved. Secondly, there is a pervasive shortage or lack of rare chemicals - enzymes and radioisotopes are particularly difficult to procure. The barrier presented by the unavailability of rare chemicals is very serious since some of them, particularly the endonucleases, are the indispensable tools of the modern biotechnologist. Without an assured and adequate supply of these substances it is not practicable to expand a biotechnology research programme, nor is it possible to lay a basis for a bioscience based industry.

Research laboratories in the case countries in general lack modern equipment, especially major pieces of hardware such as mass spectrometers, gamma counters, ultracentrifuges, automatic DNA sequencers and flow cytometers. The relatively small sums of money allocated by governments for research does not allow for the purchase of these "big ticket" items. Without major equipment, researchers performing advanced biotechnology research will sooner or later reach limits that cannot be surmounted. Sophisticated research cannot be undertaken. Therefore, the lack of such essential equipment presents a serious barrier to the development of biotechnology in the countries surveyed.

Even if the equipment and instruments were available, other problems could prevent their full utilization. Spare parts are often unavailable, so when equipment breaks down, it stays down for lengthy periods of time while the request for needed parts is processed through official channels and funds are procured for the unexpected expense.

The problem of breakdowns is compounded by instrument and repair technicians who do not have the training or the motivation to clean and perform preventive maintenance of equipment. This situation is very difficult to correct because it often stems from systematic reasons: low wages, job security despite poor performance, minimum or non existing criteria for licensing of technicians and lack of incentives for superior job performance. The net effect of equipment being down, whether from normal wear and tear or to careless maintenance, is that the productivity of the affected research laboratory decreases through researchers being forced to spend precious time away from the bench on frustrating and intransigent tasks. Projects under way are stopped and some may have to be redone altogether while planned projects are delayed, sometimes indefinitely.

Frequently, third world scientists face difficulties rarely encountered by their colleagues in developed countries on a daily basis, such as

power cuts or shortages, interrupted water supplies, supplies of vital reagents running out with little chance of their timely replacement, equipment breakdowns that take long periods of time to repair, lengthy delays in communications caused by poor telephone systems, and so on. The net effect of these factors on research productivity is without doubt negative.

Scientists and technicians are civil servants in the case countries, compensated according to scales set for government employees. As part of austerity measures, governments have for the last five years or so refused or limited pay raises to civil servants. The wages in the public sector have accordingly not kept pace with increases in the cost of living, nor with the wages in the private sector. Scientists and technicians are poorly compensated when compared to equivalent employees in the private sector. Furthermore, the possibilities for earning supplemental income are severely restricted for scientists. This situation stems from the lack of alternative employment opportunities for scientists as no research and little development is done in the private sector.

Applied research

In the countries reviewed, the amount of applied research being done at universities is rather low. There appear to be two reasons for this. First of all the traditional role of scientists in universities is to teach and instil an enthusiasm for learning among students and to perform basic research. A university scientist would find it trying to take up applied research projects since there is minimal appreciation for such work among colleagues (some may actually denigrate it), and at the professional level there are no, or very few, contacts between professors and industrialists or health providers.

Secondly, with few exceptions, there are no contractors for applied research or consumers for research results in the case countries. As a result, it would make little sense for university researchers to perform applied research since results, even if potentially useful, will not be developed. The exceptions tend to prove the rule. The few applied projects under way in Thailand and Venezuela are being carried out by groups who through strong efforts in basic research have developed expertise in narrow areas pertaining to various disease agents. The expertise allows the groups to take on projects supported by international organizations or funding organizations in developed countries, who may then use the results for their own purposes.

Outside the universities, a certain amount of applied research does take place at public research institutes in the three case countries. In Egypt it is quite significant - more than 75 per cent of research carried out by its science and technology organizations is applied (El Nokrashy, et al., 1982). Only a small percentage of research results is eventually used as either the work is inappropriate, of low quality, or because there is little association between the research units and potential users of results in agriculture and industry. No applied biotechnology research funded by indigenous industry is done in either of the countries.

Advanced research and development

No units capable of advanced research and development in biotechnology, whether at universities, national laboratories or industries exist in the case countries. The advanced research and development component so strategically located in the ideal concept development process (see figure 1) is missing in the case countries. As a result it is difficult, if not impossible, to effect the transfer of knowledge and technology from research units to indigenous industry. This absent component presents a fundamental barrier to the development of biotechnology.

Industry

The industrial unit in the case countries takes one of two forms, neither of which has a research capability. In its first form the enterprise is merely a packaging and marketing unit of bulk products produced elsewhere and imported. This is probably the most common form of transnational corporations' subsidiaries. The second form is the indigenous industry which can have a development capability, but is in the main a manufacturing facility. When either form needs a technology, it is imported. The importing industry's development capability, at the maximum, allows the industry to adapt the imported technology to meet its own requirements.

In industrialized countries, the acquisition of scientific knowledge and new technology may enable the recipient industry to become more competitive in local or international markets. At times changing markets create conditions whereby a continuous flow of new technologies is required by industry. Industrial managers rely on science and technology providers to respond quickly and appropriately to meet such demands. This the research sectors in the case countries cannot do, so indigenous industry habitually turns to foreign technology suppliers for these needs. For example, in Thailand it was noted that a local industry was interested in acquiring a technology for processing palm oil. Although appropriate R&D was taking place at a Thai university the firm chose to buy the technology from an enterprise in the United Kingdom.

The two major reasons why industrialists in the case countries do not turn to the research sector for a needed technology are that scientists in the public institutions are perceived as having little appreciation of real life problems and that their services are difficult to secure because of bureaucratic restrictions. Consequently, industrialists as a rule have no professional contacts with the research establishment in the country in which they are located. Therefore industry is unable to access the knowledge base, cannot assimilate results from basic or applied research and is incapable of independently performing research to solve problems or to develop new products or processes. The absence of research consumers in the industrial sector is a serious barrier to the development of biotechnology.

"Technology push" and "demand pull"

In the ideal scheme of concept development, technology push and demand pull exert forces that act at every point along the 'concept development' process. Thus, the push of a powerful technology is likely, for better or for worse, to result in the delivery of new products and processes to customers. Conversely, the pull generated by customer demand can, and does, give rise to applied research. However, the 'concept development' process in the case countries is different to the ideal because of the breach between the research sector and the industry marketing component. As a result, differing push and pull forces act on the two elements. With reference to the research sector,

technology push in the case countries results from proponents of biotechnology (bioscientists and officials who support them in the government), striving to include biotechnology research in the universities' and institutes' programmes. Such is accomplished when biotechnology research programmes are taken up by universities and institutions, and even more so when the field is designated by a government as having high priority, with commensurate funding made available for its expansion. On the other hand, there is no demand pull for biotechnology research since there are no consumers of research results.

In the industry marketing component, a technology is pushed by an industry for much the same reasons as in the industrialized countries: i.e. the technology has led to the development of improved or new products or processes, so the industry, whether indigenous or multinational, attempts to market them.

Consumers in the third world are apparently considered only marginally important in economic terms by research directors in the industrialized countries, as is demonstrated by the findings of a study carried out by the Science Policy Research Unit at Sussex University which shows that less than one per cent of research in the developed world has relevance to developing countries (Freeman-Seers, 1979). Hence, products and processes developed and marketed for consumers in the industrialized world are also marketed in developing countries without much regard for their populations' needs. Demand pull possibly exerts a more telling force on indigenous industry than on the multinationals, but since this industry lacks capabilities in applied research and advanced research and development, it cannot be well accommodated.

From my survey of activities in biotechnology in the three countries under investigation, I determined that nearly all the designed to increase capabilities in research, practically none are designated for the purpose of increasing capability in biotechnology development or industry. The relatively new local support for the biotechnology research in these countries results from bioscientists formed into vociferous, organized themselves to form political pressure groups to lobby for the support they want. Close and continuous relations exist between scientists and the policy makers who look after scientific technical matters in a permanent way. This "normal" political activity in democracies cannot be criticized, except that the bioscientists appear myopic in their neglecting to establish relations with the industrialists and health providers. Although several of the interviewed scientists acknowledged and deplored this lack of communications, neither they, as individual scientists, nor their interest groups had made meaningful attempts to begin a dialogue between the two groups. The sentiment prevalent among scientists appears to be that they are not interested in helping to turn their research into profit making enterprises for others and that their governments, rather than themselves, should take the necessary steps whereby their research findings are applied. As long as this attitude prevails among bioscientists, it is unlikely that attempts will be made by them to bridge the gap between the research sector and the industrial marketing component.

Efforts by bioscientists are leading to an increase in their countries' research capabilities; possibly the research sector's productivity will go up and more remarkable results could be generated from improved research units. But even if research productivity increases, its results are likely to be rejected by industry, a health problem. As a consequence, if the favourable impact of biotechnology is unlikely, [illegible] research to advance national self reliance. Conversely, it is entirely possible that if scientists in the case countries started "best present course of action they may in the end weaken their own position since the public and its representatives could come to the realization that the bioscientists, while real, [illegible] scarce funds from many sectors to further their research interests, [illegible] worth to their host nations. The disparity between the great expectations for biotechnology and the actual lack of a tangible product in the third world countries [illegible] proposals to shift [illegible] scientists.

3. Different perceptions by the actors

The [illegible] can be seen as a result of a scheme of the concept development process in the case countries (see figure). For [illegible] to be different to the ideal depicted in figure .

The first difference is that a [illegible] knowledge base by researchers in the case countries is often difficult. [illegible] and may be expensive.

[illegible] countries where a [illegible] perceived to be [illegible] which have arisen in applied research [illegible] development, in the case of [illegible] is basic research to its fullest extent. In other words, results from basic research [illegible] the knowledge base [illegible] applied [illegible] about for product solution.

Thirdly, an [illegible] applied research. In [illegible] industrialized countries, where up [illegible] are usually supplied [illegible] industry, in the case countries [illegible] strong basic research [illegible] is just starting to [illegible] applied research [illegible]

Fourthly, a [illegible] between [illegible] industrial marketing components. In the [illegible] problems, [illegible] by the [illegible] research and be of great [illegible] part of the research [illegible] situations. These [illegible] countries.

A fifth difference is that [illegible] case countries to inject a technology, readily imported, directly into the industrial component without involving the research sector in any way.

Sixthly, the types of industrial units prevalent in the case countries may be grouped under two headings. The first is a subsidiary of a multinational corporation; its major function is to package and market bulk products manufactured abroad by the multinationals. The second type is indigenous industry that may import a technology as the best arises. In contrast to industry in developed countries, neither of these two types possess advanced research or development capabilities.

4. UN sponsored activities in biotechnology

A survey was made of past, ongoing and planned biotechnology related activities sponsored by UNIDO,

barriers are found in the ministries under whose auspices or authority researchers work. Simply put, large quantities of general and technical information is routinely sent by international organizations to the ministries they liaise with; very little of it is forwarded to anyone outside these ministries. Apparently, information dissemination is poorly practised by governments of the case countries.

Other information is provided by international organizations directly to scientists upon request, yet few of them take advantage of this facility. Even in those few cases where the issuing organization has a programme for the active, direct forwarding of information to scientists, the potential recipients rarely benefit. Thus, for example, the International Network of Biotechnology (INB), through its member governments' diplomatic missions in developing countries, exerts much effort in sending information circulars directly to scientific societies, university departments, institute research units and individual scientists. Yet, it was only the rare researcher in the case countries who had heard of the INB. 4

Clearly, this method of information dissemination is not optimal and more active mechanisms ought to be devised to ensure that technical information gets to the intended recipients.

(b) Training opportunities

The provision of training opportunities by international organizations is a major, widely practised activity and the one most requested by scientists in the case countries. By providing training opportunities, international organizations augment existing capabilities of scientists to perform research and make it possible to introduce new techniques to research units. Sometimes the beneficial effects of training can be readily observed, such as the joint, co operative UNIDO project between the Universities of Lahore and Guelph demonstrates. As part of that project, the Pakistani principal investigator received hands-on training in cloning and sequencing. After completing his training and return to Pakistan, this scientist was the first to do cloning in that country. Furthermore, he quickly set up a local two week workshop during which 20 other Pakistanis received training in this technique.

Unfortunately, it is more usual that resources spent on training are wasted. Many scientists from developing countries who receive advanced training cannot use it in their home institutions due to lack of facilities, equipment and expendable supplies. Some respond by allowing their skills to languish. Others leave their home countries and use their new knowledge in developed country laboratories.

(c) Funds to purchase major equipment

With the possible exception of WHO (through its Research Capability Strengthening programme), international organizations are wary of financing projects when the equipment component adds up to more than 50 per cent of the project's budget, for a number of reasons:

First, since a piece of major equipment is usually shared, because it remains with the supported research unit after a project ends, and because very few projects would by themselves necessitate its sole use, it could be considered part of the infrastructure. Thus, in the international organization's view, the apparatus should be purchased by the institute running the project or by the home government.

Second, it can be difficult for a funding agency to evaluate requests for major equipment. The need for some can be measured; for example, that of a fermenter can be calculated by considering the value of its output over a period of time. Requests for other instruments can present problems: for example, on what grounds could a UN agency justify giving support for the purchase of an automatic DNA synthesizer? It may be justified when a project has institution building as its prime aim. Thus, when a national or regional centre is being established, equipping it with sophisticated, expensive equipment is reasonable because it will serve as a reference and training centre for an entire nation or region. But its purchase for a particular research project may be questionable since only the rare project would have need of that sophisticated equipment, few researchers would know how to use it, backup support by its manufacturer is often unavailable, and few, if any, technicians are able to maintain it.

Third, every international organization project manager is aware of expensive equipment that has been unnecessarily purchased with the organizations' funds.

Nevertheless, leaving aside the questions of waste and inefficiency, the amount of major equipment being provided by international organizations to research institutions in developing countries is minute when compared to the need.

(d) Funds to purchase chemicals

Rare chemicals, and other expendable supplies, are vital to research and to bioscience based industry. Thus, all biotechnology related research projects supported by international organizations include provisions for their purchase. While such funding helps carry individual projects forward, it does nothing to help solve the overriding problem, namely, that no dependable manufacturers of rare chemicals exist in the case countries or, with the rare exception, in the third world. In order to secure these chemicals, researchers have to use up much time and spend scarce hard currency, and even so they are usually in short supply. Clearly, the shortage of rare chemicals limits the growth of biotechnology R&D and places what may be a fundamental barrier to the establishment of bioscience based industry in the third world.

(iii) International organizations and international networks

International organizations have the important function of acting as a catalyzing force in the setting up and operation of networks having international reach. Two networks have the longest history; the Consultative Group on International Agricultural Research (CGIAR) and the Microbiological Resource Centres (MIRCENs). The two are quite different: CGIAR, although an informal organization without constitution or charter, fully funds its 13 member institutions, and its research activities are in a general sense co ordinated by the network secretariat (located at the World Bank's headquarters in Washington D.C.). Its focus is on tropical agriculture and animal diseases prevalent in the tropics (UNDP, 1986). The 16 MIRCEN institutions are independent units only loosely

connected through networking and minimally funded by UNESCO. Initially MIRCEN's interest was focused on research pertaining to gene pools; now its scope is wider, including both agriculture and industry (DaSilva and Taguchi, 1986). Despite differences, both networks facilitate communications between widely dispersed units so they may work in unison towards achieving certain general objectives by sharing expertise, undertaking co operative research, integrating training of scientific personnel and sharing certain resources. Occasionally, research results from a network have had dramatic effects on the third world; for instance, the highly productive dwarf rice developed by CGIAR's International Rice Research Institute has been adopted by farmers throughout the world, resulting in a marked increase in rice production.

New networks which concentrate on biotechnology are in the process of being set up by international organizations. Thus, three international organizations (UNESCO, UNDP and UNIDO) are helping in the establishment of the Regional Biotechnology Programme for Latin America and the Caribbean (UNDP, 1986); UNIDO is setting up the International Centre for Genetic Engineering and Biotechnology (ICGEB) and its network of affiliated centres (Zilinskas, 1987a); and the United Nations University is formulating a network for international co operation in biotechnology (UNU, 1985). The functions of the new networks will be similar to those of the older ones; i.e. they will seek to integrate the work and training programmes of participating institutes, share expertise, pool resources and perform co operative research. By doing so, individual institutes in the network can take on projects which they would otherwise have had to forsake, perhaps because they would be too expensive, too large, or too difficult. As a group, network institutes should be more productive than they would have been if working independently.

5. Major gaps in assistance by UN agencies

The major gap in assistance being provided by UN agencies is related to applying results arising from research. Three problem areas are particularly noteworthy: disseminating findings to industry; funding projects pertaining to advanced research, development and industry; and the promoting of research for consumers.

(i) Dissemination of research results

International organization sponsored projects usually include measures for the dissemination of the results they generate to industry, usually through a workshop or symposium and publications. In actuality, these approaches do not work for five reasons. First, information about the holding of workshops or symposia, or of the availability of publications, most often does not reach those who would be interested. Second, the described results may be in a narrow scientific area of interest to few people in industry or to health providers. Third, since industries as a rule do not have a research or development capability, they cannot take advantage of the presented results. Fourth, even if results could be usable, the adaptive capabilities of the affected industry would most likely be so low that it would be unable to utilize findings without making major new investments in manpower and equipment. Five, capital needed for making investments in development, scale-up and manufacture is difficult to raise in the developing countries.

(ii) Advanced research, development and industry

The scrutiny of UN activities indicates that no resources have been expended on biotechnology advanced research, development or industry, except perhaps indirectly, and no resources have been allocated for this purpose in projects being planned. As a result, there is no natural outlet for the results and findings generated by UN-supported basic and applied research.

(iii) International organizations and research consumers

The lack of consumers for research is largely due to systemic reasons, which are best solved by Governments. Yet, international organizations can help improve the situation by funding projects that involve industrialists and health providers from beginning to end. Some projects do in fact contain such clauses. In addition, UN agencies can provide counsel on how changes can best be accomplished and what steps governments can take to encourage indigenous industry to contract with local research establishments for needed research or to develop customized biotechnology. No such international organizations projects are, however, active or planned.

To sum up the findings of the preceding analysis:

- The number of biotechnology related projects, whether completed, under way or planned, is small when compared to the total number of projects being undertaken by the UN agencies, and the resources being committed to them are also minute.

- No general policy in regard to biotechnology has been formulated among the international organizations, or indeed within any individual agency. However, even without a policy, or policies, and whichever the executing agency, the activities pertaining to biotechnology are remarkably similar in that they can be grouped under one of three types of activities; either rendering assistance to policy-makers (informing them about biotechnology and its promises, and organizing forums to delineate national programmes in biotechnology); promoting capability building in biotechnology research (supporting research and training projects at the national and international levels); or helping in establishing international biotechnology networks.

- No active or planned international organization project appears to have as its aim to improve either the biotechnology capabilities of advanced research and development units or the industrial sector.

- No instance of wasteful overlap between activities of different international organizations is noted. Possibly, the small number of projects being done in a large technological field occasions few barriers for overlaps.

- International organization biotechnology projects have created opportunities for productive co-operation between agencies. Specifically, UNDP, UNESCO and UNIDO co-operate in the Latin American regional programme; and ICGEB is expected to work closely with FAO, UNESCO, UNIDO and WHO. Future regional projects involving Africa and Asia are likely to provide additional possibilities for international organization co-operation. Collaboration on policy-related issues has barely begun. For example, UNEP, UNIDO and WHO have recently formed a joint working group on biotechnology safety issues.

b. A cohesive approach by UN agencies

For the reasons already discussed, international organization biotechnology projects are almost entirely aimed at increasing capabilities in research, while little effort is given to making certain research results are applied. Unless a more balanced approach is taken, i.e. that the applications side receives at least equal attention to that given to the research side, biotechnology for the foreseeable future is not likely to be a factor in helping solve pressing problems facing the third world or to contribute to its economic development. This should not be allowed to happen, and international organizations could take the lead, in fact, to prevent it.

The first step in designing a coherent action plan for making certain that biotechnology is deployed for the benefit of the developing countries would be to hold a workshop for international organization managers. One of the more policy-oriented international organizations, perhaps the UNU or the United Nations Centre for Science and Technology for Development, should organize a workshop comprised of managers responsible for funding and executing biotechnology related projects by major UN agencies. The workshop would have four objectives:

- To develop a broad consensus among the UN agencies on concepts, ideas and issues pertaining to capability building in biotechnology research and applications by developing countries.

- To identify key policy and institutional constraints that prevent capability building in biotechnology by developing countries, especially in their health delivery, industrial and agricultural sectors.

- To identify promising approaches that may be taken by the UN agencies to assist developing countries help overcome these constraints and to otherwise facilitate capability building in biotechnology.

- To delineate in general terms areas of responsibilities for the various UN agencies in future efforts to overcome constraints and to facilitate capability building.

Once UN programme managers have a good perspective of the problems hindering the advancement of biotechnology in the third world and how to deal with them, corrective measures can be taken. An initial measure could be for them to make certain that industrialists or health providers participate in a certain proportion of UN sponsored research, from inception to completion. In fact, this principle should be able to be obtained to clarify in concrete and practical terms how the findings they generate will be applied.

Conclusion

It can be seen that the resources allocated by developing country governments and by international organizations to biotechnology related activities have been, and are, almost exclusively aimed at developing or augmenting capabilities in research. But research without development and application is a luxury few developing countries can afford for long. Thus, a more balanced approach needs to be taken; more effort has to go into making certain research results can and will be applied.

Of course, the problem of transferring knowledge and results from research to applications is one that is present to a greater or lesser extent in every country and every economic system. The problem is accentuated when capital for investment is in short supply, a common situation in the third world. So one should think that the problem of technology transfer is anything but difficult. Nevertheless, national and international agencies can help make the process work. In the short term, these organizations can designate a proportion of available funding to projects that include industrialists and health providers from the very beginning: from the instance when the project is conceptualized to its end. A clear, unbroken continuum from research to application has to be evident, otherwise the project does not get funded. Perforce, this type of project brings together researchers with those who can and will use the products of their research, hopefully leading to a new, working ethos. As its effects are accepted and spread, the number of these projects can be allowed to increase.

In the long term, agencies can attempt to identify the key policy and institutional constraints that prevent capability building in the development and industry sectors of developing countries. Undoubtedly, constraints will stem from the legal economic political environment in which these institutions function. These types of systematic hindrances are best tackled by governments, but international agencies, on the basis of good managerial practice, can suggest remedial actions. Presented with tact, persistently delivered, such suggestions would have an educative effect. Eventually, some would be adopted.

Notes

1/ An oral version of this paper was presented at the XVIth International Congress of Genetics, Toronto, Canada, on 26 August 1988.

2/ Due to project limitations, agriculture and other fields were not included.

3/ The many biotechnology related activities and initiatives in the case countries were described in the original UNU study. Due to their large number, only the findings from the analysis of them can be presented here.

4/ The INB is jointly co-ordinated by the UK and France. In addition, Canada, the Federal Republic of Germany and Japan belong to it. The INB provides financial aid and training opportunities in biotechnology for third world students at universities in member countries.

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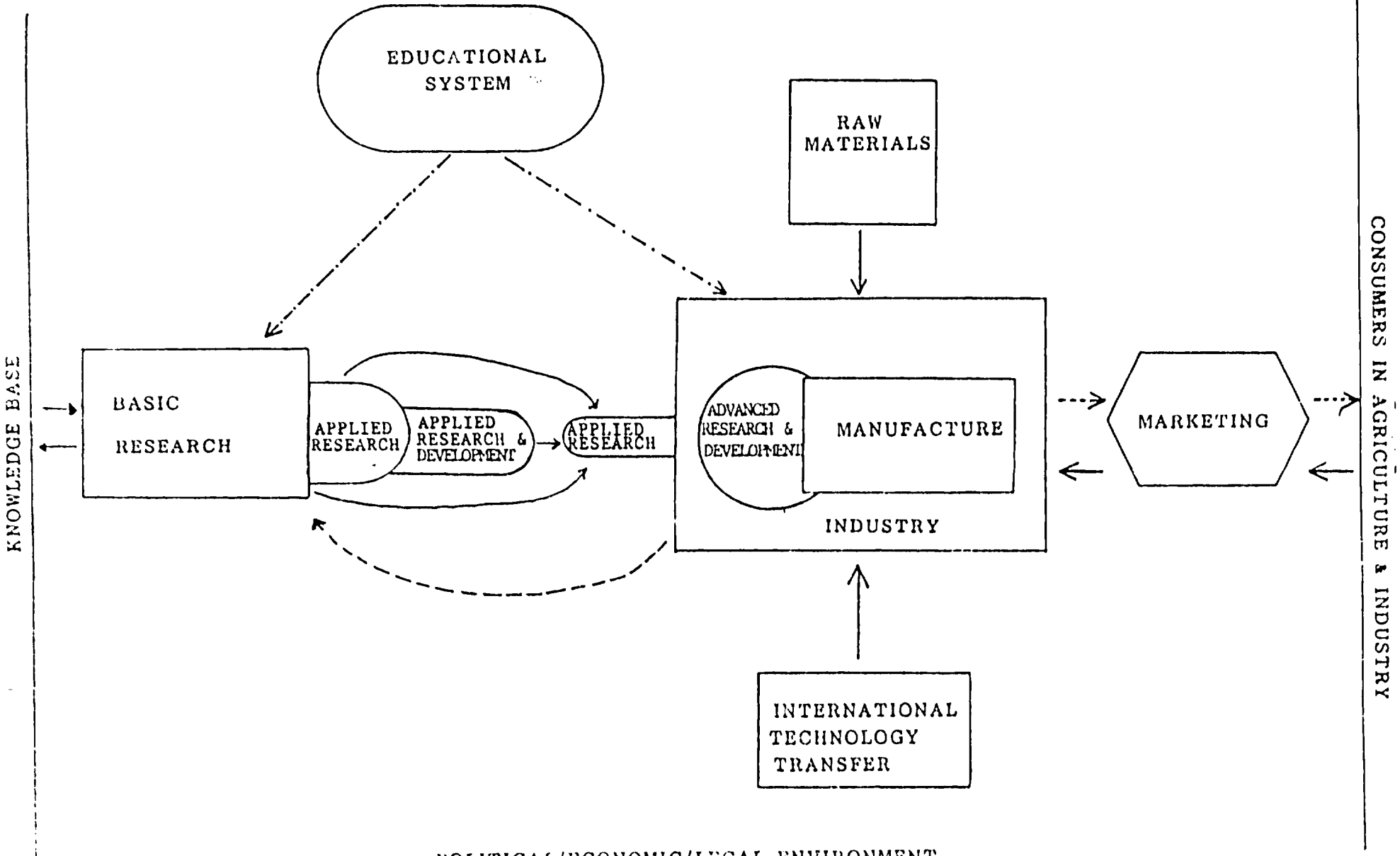
FIGURE 1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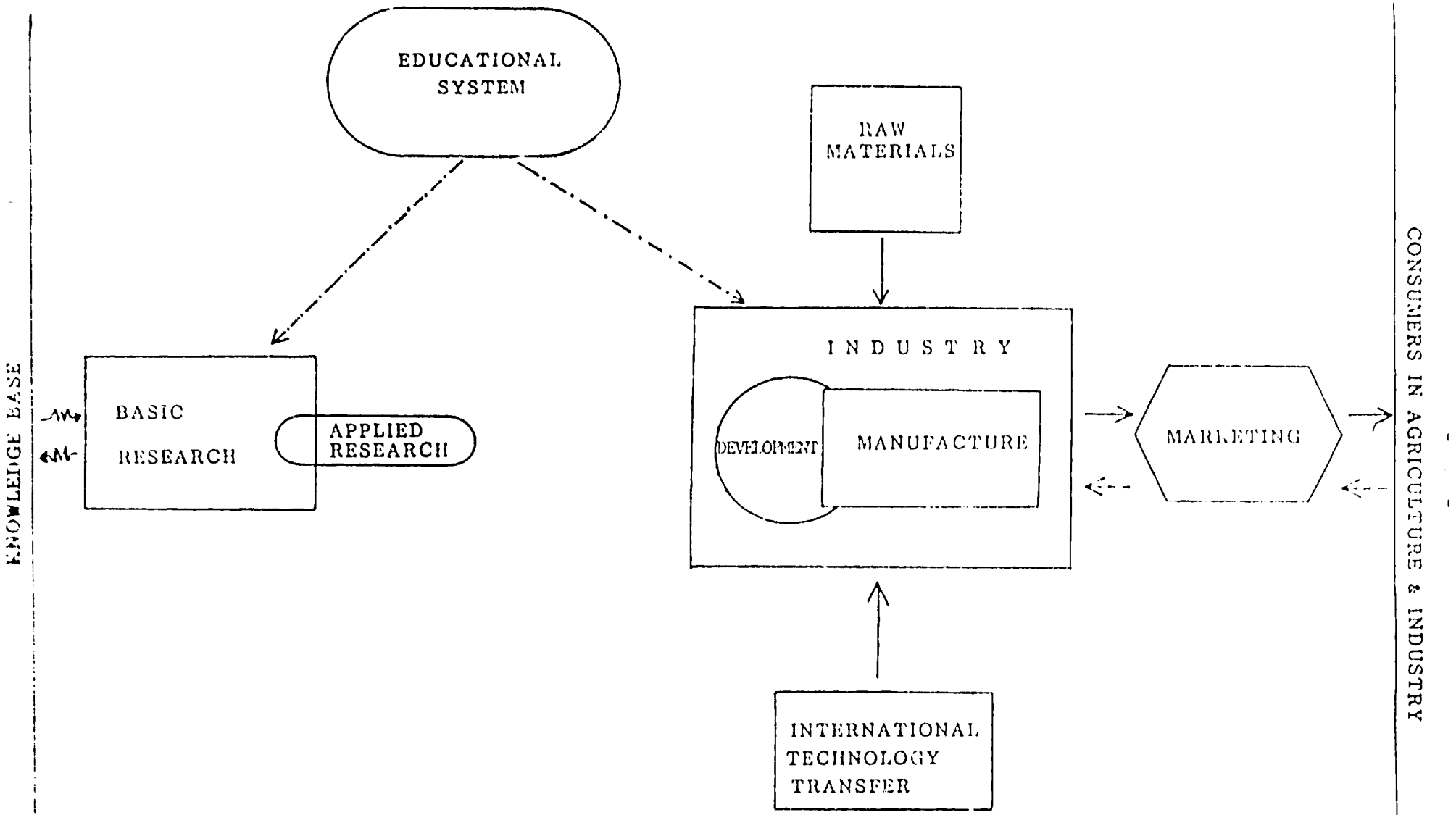
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