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Trends in biotechnology development and transfer*

by

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Summary

As with other advanced technologies, there are three main actors involved in research, development and marketing of products and processes based on biotechnology: industrial companies, universities and other research institutions and government agencies. The extent of their involvement, their relative importance and their links differ from country to country. This paper seeks to explain this involvement in terms of research and manufacture, financial commitment and the government's role, both financial and regulatory.

Applied research and product and process development in biotechnology is being undertaken by both small specialized biotechnology companies and large transnational corporations in a variety of industrial sectors, and they have developed a wide variety of arrangements with others involved in research and development. These arrangements are examined, as well as the financial considerations motivating them. Also covered are the manufacturing and marketing practices and firm strategies of biotechnology companies and transnational corporations, the biotechnology supply industry and international technology flows and collaboration.

The roles of some of the key actors in the international movement of biotechnology is discussed, including those of the developing countries, and the need for accurate intelligence in relation to new technologies through a variety of links ranging from patent office submissions, universities and R&D institutions to industries and TNCs. In this respect the importance of the establishment of the International Centre for Genetic Engineering and Biotechnology is underlined.

CONTENTS

Chapter I

I. EVOLVING GOVERNMENT-INDUSTRY-UNIVERSITY RELATIONSHIPS

1. The developments in biotechnology, including tissue culture technology, advances in fermentation technology and genetic engineering,1/ have not created totally new relationships between universities, governments and industrial companies. Such relationships have, however, in many cases gone far beyond those established in the development of other frontier technologies in terms of numbers of persons, departments and institutions involved, extent of financial commitment, and government participation, both financial and regulatory. In this section the actors developing biotechnology and their inter-relations are examined, especially the potential these relationships will have in affecting the impact of biotechnology on developing countries.

2. As with other advanced technologies, there are three main actors involved in research, development and marketing of products and processes based on biotechnology: industrial companies, universities and other research institutions and government agencies. The extent of involvement of each of these actors, the importance of categories within each division and the links between the actors differ from country to country, and relations in industrialized countries differ significantly (in magnitude and extent) from developing countries. Before examining some of these links and their implications for the development of biotechnology, a brief look at the three categories of actors and their roles in developing biotechnology is required.

A. Government

3. Governments in industrialized and developing countries are becoming increasingly involved in the development of biotechnology for several reasons. One is the perceived importance of biotechnology through its potential impact across a number of industrial sectors such as pharmaceuticals, chemicals, energy and food. Another is its potential role in international commercial competition.2/ Also of concern are some of the potential side effects of biotechnology - medical, environmental, social and economic.

4. Government involvement comes primarily through financing and regulation and is wide ranging. Substantial sums of public monies which in some countries are spent on basic research, direct support of industrial biology4/, regulations guarding against damage to human health and the environment and export and import restrictions or encouragement, are among the forms of government involvement. Others include incentives to industry to encourage R&D (both direct subsidies and tax incentives such as investment tax credits and limited investment partnerships) and programmes sponsored by government institutions for the training of scientists and others involved in the development of biotechnology.

5. Several governments have pronounced biotechnology R&D to be a national priority or have otherwise devoted substantial resources to its development (for example, Brazil, Canada, France, India, Japan, Mexico and the U.S.A.).5/ Some have gone as far as drawing up national plans for biotechnology (India and Mexico, amongst others) and some have established national biotechnology companies to increase links between research and development and production (e.g., France, Mexico and the U.K.).

6. Estimates of government funding of biotechnology have recently been made by the U.S. Office of Technology Assessment.6/ An estimated US$51 million per year in funds for basic research7/ are provided by the U.S. government (in addition to programmes by the U.S. Department of Agriculture and Department of Energy for generic applied biotechnology and by the U.S. Army, funding amounts for which are not known).

7. The Japanese government's funding levels are approximately US$60 million a year for biotechnology, broadly defined, while those for the Federal Republic of Germany, France and the United Kingdom range from US$60 to US$100 million. These countries spend relatively more (the OTA estimates almost equal amounts for the latter three) on generic applied research than the U.S.

B. Universities

8. In several of the countries most advanced in biotechnology R&D, universities and other research institutions have played the primary role in carrying out the basic research from which biotechnology techniques and processes were developed. Often the departments undertaking such basic research are funded at least in part (and often primarily) by public monies.8/

9. In addition to support of departmental research, support has been provided from government sources for the education and training of scientists at such institutions. Universities have typically benefitted from, and taken part in, a free flow of information on basic and applied research among peers, through the publication of papers, visits, conferences, etc. Often these scientists also provide a resource pool from which governments can draw on for help in determining appropriate policies regarding biotechnology.

10. As with governments, the extent of involvement of universities and other research institutions in biotechnology and their importance vis-à-vis other actors differ from country to country. In some developing countries, these institutions have carried the primary responsibility for developing national plans for biotechnology development. In the U.K. and the United States, for example, universities have played the most important role in developing the basic science and continue to be relied on heavily for such research. In some other countries (e.g., Japan and to some extent the Federal Republic of Germany), large corporations have performed this role to a greater extent.

11. Universities are now (especially in the U.S.A.) engaged in a "race" for patents on biotechnology processes and products in addition to active financial and programatic links with industrial partners. Such practices have raised many questions regarding the free flow of information and access to publicly-sponsored research at universities which would be of great importance to developing countries. These are further discussed below.

C. Industry

12. In the U.S.A. and several other industrialized countries (including Canada, France and the U.K.) there are two distinguishable types of industrial actors in biotechnology - although the importance of each varies, namely the transnational corporations and speciality biotechnology companies.

13. Transnational corporations have played an important role and are becoming increasingly involved in the development and marketing of products and processes based on biotechnology. In the United States and a few other industrialized countries, TNCs first entered the field cautiously, by funding other R&D programmes at universities and small companies in exchange for "windows" on the developing technology, and then by creating their own in-house R&D capabilities. Some of these risk-minimizing strategies are described later in this paper when the links between TNCs and other actors are discussed. With the growing need to market products as these are developed - as well as to get them through often extensive regulatory mechanisms - and as the impact of biotechnology becomes increasingly evident to a greater number of TNCs, these companies are beginning to play a more active role, both through in-house efforts and through the acquisition of other companies and the funding of research in universities and other institutions.9/

14. In some other industrialized countries (e.g., the Federal Republic of Germany and Japan), TNCs have played the primary role in both basic and applied research leading to biotechnology-related products and processes, both through in-house programmes and links with companies and universities in other industrialized countries. For developing countries, TNCs may well provide the primary means, at least initially, for the products and processes of biotechnology to be disseminated. Whether this will also involve dissemination of the technology will, however, depend on the relative bargaining strengths and capabilities of the two groups of parties.

15. The second major group of industrial actors are the smaller, often venture capital-financed, specialty biotechnology companies which are most numerous in the U.S.A., but also extant in Canada, France, the U.K., and a few other industrialized countries. In the U.S.A. alone, there are some 200-300 such companies. Some distinguishing features differentiating these companies (most of which have appeared only in the last ten years) are already apparent.

16. There are differences in terms of financial resources, types of R&D links with other actors, and another group of companies which has been set up specifically to supply the biotechnology industry.

17. In addition to companies set up as consultants and suppliers to biotechnology companies, those active in R&D differ in the extent of operations they undertake (some are only research companies doing contract research, often for TNCs, while others perform a full range of activities from research through development of products and processes, and even marketing and licensing), and the fields of activity. Some undertake R&D in only one area while others (e.g., Genentech, and Genex especially in its earlier stages) are exploring a wide range of products and processes.

18. These companies also differ in the extent to which they are involved with other actors. Most of these companies were set up by university-based scientists in collaboration with entrepreneurs and venture capitalists and they often maintain active links with these universities (see below). These companies are increasingly developing ties with TNCs, especially as they come closer to having marketable products and need TNC experience and resources for production and marketing.

19. These companies are also distinguished by their financing arrangements. Many were set up as venture capital companies by private investors, universities and TNCs, but often they have moved beyond their initial financial bases by seeking to mobilize capital through the public sale of shares or by forming joint ventures and limited partnerships (see below). Some have been taken over by TNCs or other biotechnology companies, and, of course, as with any technology where the yields are often far removed in time from the initial investment, some have gone bankrupt, have significantly curtailed operations, or have been merged with other financially stronger companies.

20. A small, but growing number of these companies, however, is now becoming increasingly self-supporting through the sale of products, licensing agreements and research contracts with other companies. Some companies (e.g., Hybritech) were successful in quickly developing products (diagnostic kits in

Hybritech's case), sales of which helped to finance other research in biotechnology.10/ These arrangements are examined in more detail in Chapter III below.

21. As has been noted, the links between the major actors are often as important as what the actors are doing independently. These links are also of major concern to the Third World's access to biotechnology. In some cases they provide a means for access to the technology (i.e., through the formation of such links between Third World institutions and industrialized country partners, or through access based on links in industrialized countries themselves - e.g., arrangements between biotechnology companies and TNCs for testing, production and/or marketing in Third World countries). However these links may also encourage (and there is increasing evidence that they do) privatization of the technology and a resulting decrease in access - at least to the technology, if not the products - for Third World countries, as well as a deflection of the technology from products and processes of special interest and utility to Third World countries.

22. The following are some examples of links which have been established between the major actors, followed by a discussion of some of the concerns and opportunities raised by these links.

23. There are two major categories of linkages which are examined here: links between industrial actors and universities and other research institutes and government interactions with these actors. Links between TNCs and smaller biotechnology companies are discussed in Chapters II., III. and IV., below.

D. Industry/university links in biotechnology

24. As indicated above, one of the features which differentiates the development of biotechnology products and processes from that of other frontier technologies is the extent of interaction between industry and academia, both through direct funding of R&D programmes and institutes, through the setting up of separate companies by university-based researchers, often with the support of larger corporations, and through agreements with industrial scientists.

Table 1. University/industry/government biotechnology agreements

Country (ies)	University (ies)	TNC/biotechnology company/government	Type	Amount (US$)
United States	Stanford University	Engenics/Center for Biotechnology Research (CBR) (Elf Technologies, General Foods, Koppers, Bendix, Mead, McLaren Power and Paper)	The six sponsors set up Eugenics and CBR, the former as a for-profit company, the latter to fund university research	2.5 million for CBR for four years, 7.5 million for 30% equity in Engenics
United States	Michigan State University (MSU)	Neogen and Doan Resources	Neogen was founded by Michigan State to provide limited partnership funds for faculty and research results	230,000 in stock purchases by MSU, 250,000 by Doan Resources
United States	Rockefeller University	Monsanto	Five-year agreement on photosynthesis research	4 million
United States	Washington University	Monsanto	Support for faculty research in hybridomas	1.5 million
United States	Harvard University	Monsanto	Support of basic research on cancer	long-term agreement
United Kingdom/ United States	Oxford University	Monsanto	Five-year research project on oligosaccharides	£ 1.2 million
United Kingdom	Bristol, Birkbeck College, Oxford, Imperial College, Leeds, York	Celltech, Glaxo, ICI, RTZ Chemicals/Sturge, Science and Engineering Research Council (SERC)	The parties have agreed to a four-year research "club" to study protein engineering and produce novel proteins	£ 2 million
Federal Republic of Germany/United States	Massachusetts General Hospital (Harvard University)	Hoechst A.G.	Research in molecular biology	70 million
United States	University of Illinois	Standard Oil of Ohio	Five-year grant establishing a centre in Crop Molecular Genetics and Genetic Engineering	2 million
United States	Massachusetts Institute of Technology	National Science Foundation	Establishing centre for biochemical engineering including research in genetics and molecular biology	20 million
United States/ Israel	Rockefeller University and the Weizman Institute	Rapid-American Corporation	Research on cancer biology, neurosciences, molecular genetics, immunology	5 million
United States	Northern Illinois University	Argonne National Laboratory, State of Illinois	Project on crop plant growth rates, pest-resistant and chemical synthesizing plant strains	1 million for first year

Table I. (cont'd)

Country (ies)	University (ies)	TNC/biotechnology company/government	Type	Amount (US$)
United States	Washington University	Monsanto	Five-year contract for research projects including fundamental research (30%) and research into human disease	23.5 million
United States	Massachusetts Institute of Technology	Whitehead Institute (head is President of Technicon Corporation)	Institute to be built and funded, including funding of MIT's biology department's faculty, graduate students and research assistance	20 million for structure, 5 million, to operate, 100 million to Institute upon death of Whitehead, 7.5 million to MIT, plus 1 million annually
United Kingdom	University of Leicester	John Brown Engineers, Dalgety-Spillers, Gallahers and Whitbread and the Science and Engineering Research Council	Five-year research programme	£ 1 million from the four companies, £ 133,000 from the Research Council to equip laboratories.
United States	Cornell University	Union Carbide, Corning, Eastman Kodak	Establishment of biotechnology institute	2.5 million each over 6 years by the companies, 4 million by Cornell
United States	Massachusetts Institute of Technology	W.R. Grace	Research on micro-organisns	8.5 million
United States	Columbia University	Bristol-Myers	Investment in work of molecular biologist involved in gene cloning and rDNA technology	2.3 million
France	University of Compiegne	Elf Acquitaine	Enzyme engineering	N.A.
United States	Harvard	Du Pont	Five-year grant to head of new department at medical school	6 million
United States	Yale	Celanese	Three-year R&D in enzymes	1.1 million
United States	Washington University	Mallinckrodt	Three-year hybridoma research programme	3.88 million

Table 1. (cont'd)

Country (ies)	University (ies)	TNC/biotechnology company/government	Type	Amount (US$)
Federal Republic of Germany	University of Heidelberg	BASF, FRG	Ten-year support of research	1 million DM from BASF, 18 million DM three year grant by the government
Federal Republic of Germany	Max Planck Institute, University of Cologne	Bayer	Support	1 million DM per year
Federal Republic of Germany	Max Planck Institute of Immunology, University of Munich	Hoechst	Collaborative project	n/a
Federal Republic of Germany	National Centres of Excellence at Cologne, Heidelberg, Munich and Berlin	BMFT (Federal Ministry of Science and Technology)	Support of biotechnology projects in universities and government institutes .	1.05 million DM in 1983, 1.15 million DM in 1984
United Kingdom/ United States	Universities of Oxford and Cambridge, Imperial College, London	Monsanto, Nuffield Foundation	Advent Eurofund to finance biotechnology (among other) projects	£ 10 million initial capital, half from Monsanto
United States	Brigham Young, California Institute of Technology, Colorado State, Emory, Illinois Institute of Technology, Iowa, MIT, Purdue, State State University of NY at Albany, Texas A&M, Tulane, Universities of California, California at Davis, Cincinnati, Connecticut, Georgia, Idaho, Kansas, Kentucky, Maryland, Massachusetts, Minnesota, North Carolina, Utah	U.S. Pentagon	Funding of genetic engineering research for biological warfare	42 million in 1986 for 57 projects (including six private res- research institutes and four corporations - see below)
United States	Agouron Institute	U.S. Pentagon	Research into applications of genetic engineering to biological warfare	-
United States	N.Y. State Department of Health	U.S. Pentagon	Research into applications of genetic engineering to biological warfare	-

Table I. (cont'd)

Country (ies)	University (ies)	TNC/biotechnology company/government	Type	Amount (US$)
United States	Salk Institute	U.S. Pentagon	Research into applications of genetic engineering to biological warfare	-
United States	Scripps Clinic	U.S. Pentagon	Research into applications of genetic engineering to biological warfare	-
United States/ United Kingdom	National Environment Research Council	U.S. Pentagon	Reserach into applications of genetic engineering to biological warfare	-
United States/ Israel	Weizman Institute	U.S. Pentagon	Research into applications of genetic engineering to biological warfare	-

Sources: "Industry and Universities Prepare to Study Proteins", New Scientist, 20 June 1985: "Foreign Funding of Research", New York Times, 5 August 1985; "Eight Universities Get Industrial Grants", New York Times, 4 April 1985; "Industrialist Gives $5 Million Grant for Biomedical Research", New York Times, 24 March 1985; Bio/Technology, June 1985: Commercial Biotechnology: An International Analysis (Washington: GPO, January 1985) Appendix H: "Monsanto's External Investments and/or Contracts", Monsanto Public Relations Department; "Monsanto Inks R&D Pact with Oxford University", European Chemical News, 19/26 December 1983; "Monsanto Act", Nature, 5 August 1982; International Review Service, Trade and Economic Development, 1 September 1982; "$2.3 Million Fund for Gene Research", New York Times, 13 September 1983; "Oil Firm Pins Its Hopes on Genetic Research", New Scientist, 11 March 1982; "DuPont Gives Harvard Gene Research Grant", Chemical and Engineering News, 6 July 1981; "Celanese, Yale Set Biotechnology Agreement", Chemical and Engineering News, 22 February 1982; "Company Funds University Hybridoma Research", Chemical and Engineering News, 7 September 1981; "Biotechnology Taking Root in West Germany", Bio/Technology, April 1984; "German Firms Move into Biotechnology", Science, 24 December 1982; "Controversy Grows Over Pentagon's Work on Biological Agents", Wall Street Journal, 17 September 1986.

25. Table 1. provides examples of 27 of the largest agreements between universities and TNCs, smaller biotechnology companies, and/or governments both within and between industrialized countries.

26. Many of these agreements set precedents for the dollar amounts concerned and several of the earlier ones raised several issues concerning academic freedom which is discussed in greater detail below. The agreement between Hoechst and Massachusetts General Hospital (an institution affiliated with Harvard University) posed different sorts of issues for TNCs and especially their home countries. When Hoechst announced the US$70 million agreement, FRG universities, research institutes and regional governments questioned the need for an FRG-based TNC to go abroad for research in biotechnology. A result was a commitment by FRG's largest TNC to fund R&D within that country.11/

27. Funding of academic research is not the full extent of the industry/university interface. In the U.S.A. especially, several universities and local governments have gone to great lengths to attract industrial financing through other means. The setting up of industrial parks adjacent to universities is one such attempt. Among the universities involved thus far are the University of Missouri, Yale, the Polytechnic Institute of New York, Princeton and Stamford. Such parks provide universities with monies to support their programmes, and give industry access to university research departments.12/

28. In France as well, corporations are choosing to locate new biotechnology facilities near university centres to benefit from improved access. Elf Aquitaine at Toulouse and Transgene at Strasbourg are two examples.13/

E. Trends in industry-university-government arrangements

29. As the number of countries pursuing national programmes in biotechnology has increased, attempts to enhance their competitive positions have led countries to encourage industry-university links. In the U.S.A., where such links are perhaps most numerous, for example nearly half of the companies engaged in biotechnology R&D, or who support such R&D, have arrangements with universities. A recent study indicates that as much as one-fourth of all biotechnology research at universities is supported by industry in the U.S.14/

30. Such support occurs at the same time as funding of basic research at universities in the U.S. has increased - over 60 per cent in the last five years to $4 billion in 1986.15/ Industry-sponsored research appears, however, to be increasingly restricted to specific projects with end goals in sight. While some of the initial large grants made to universities (see Table 1.) were unrestricted, it appears that most grants have had restrictions.

31. One result is that biotechnology faculties at U.S. universities working with industry funds are much more likely to claim that their research has resulted in trade secrets and that their research directions have been more influenced by industry priorities than those not receiving funds.16/

32. The impacts which such trends are having are discussed below. While the U.S. probably leads in the number and importance of such links it is, however, possible that as other countries continue to encourage such links similar trends and impacts will emerge.

F. Concerns regarding university/industry links

33. Since 1980, concerns over the extent of industry/university links have been expressed in a number of ways, especially in the United States.17/ Several conferences18/, articles and reports by government and private institutions have discussed the implications of such links, as well as the benefits arising from them.

34. The first well publicized such conference was the so-called Pajara Dunes Conference. Heads of five universities and 11 corporations met in early 1982 to discuss issues relating to university/industry ties. Concern focused on whether contracts between the two should be public19/, whether universities should grant exclusive licenses to companies which support research leading to a marketable product, what university policy should be regarding patenting and whether agreements should be made between a university and a company in which a university researcher or administrator has a significant equity interest and/or is on the board of directors.

35. While those who attended the conference were able to agree that these were all problems which needed to be addressed in drawing up such agreements, consensus was not reached on such issues and several persons attending (especially university members) expressed concern over the impact of these issues on academic freedom and conflict of interest.20/

36. These concerns are, in part, a reflection of actual events in the development of biotechnology, several of which have been the subject of recent articles and reports. In the winter of 1982, the Brookings Institution published an article which looked at conflicts arising between private interests and academic research in the interferon field over the past 20 years or so.21/

37. That article pointed to a number of occasions where concerns with secrecy (including agreements with companies not to divulge information and competitions between scientists at universities to develop a product first for a company) resulted in the refusal not only to share research results, but also in refusals to share interferon for further research.

38. Also in 1982, David Noble published a now well-known article in The Nation on "The Selling of the University" in which he examined the agreement between the Massachusetts Institute of Technology and Whitehead for the formation of the Whitehead Institute (see Table 1.).22/ The article goes beyond the concerns already mentioned regarding academic freedom, possible distortion of a university's primary functions in teaching and advancing knowledge, and open dissemination of that knowledge to discuss a larger public interest.

39. As was mentioned earlier, much of the basic research which led to the development of biotechnology took place, not in corporate laboratories, but in universities and other research institutes with a very significant infusion of government (i.e., public) money. That such public-supported research should now lead to private profit for a few is another major concern in the development of biotechnology.

40. A somewhat more recent and related concern involves the numerous agreements between industry in one country and universities in another. The Hoechst agreement with Harvard mentioned earlier (see Table 1.) is one example. Recently, a number of foreign companies have sought agreements with U.S. universities to provide them with access to research not being done (or to which they have no access) in their home countries.23/ This has raised the question whether it is proper for foreign companies without reciprocal arrangements to gain access to research paid for by another country's taxpayers.

41. The study by the U.S. Congressional Office of Technology Assessment on commercial biotechnology24/ identifies five types of university/industry arrangements in biotechnology (consulting arrangements, industrial associates' programmes, research contracts, research partnerships and private corporations) and looks at problems relating to such arrangements, with a special concern for implications for international competitive positions in biotechnology.

42. The OTA notes four areas of concern in such relationships: increased secrecy on the part of university faculties; a deflection of research towards profitable lines of inquiry; lawsuits for damages from products developed from university research; and a change in emphasis from universities competing for the best faculty to competing for the most lucrative lines of inquiry.25/

43. In addition to the concerns raised by the above mentioned studies, articles and conferences, an additional concern raised by a professor at Tufts University is that the number of ties between university-based researchers and industry has a bearing on the existance of an independent, "impartial" community of scientists on whom government and the public can rely for opinions regarding safety and environmental issues related to biotechnology.

44. A U.S. report on a preliminary study of scientists involved with industry who are also relied on for government and scientific bodies shows that there is a substantial basis for concern. A sample of 291 biotechnology firms showed 362 academic scientists serving on scientific advisory boards of the companies. Of these, 64 were members of the National Academy of Sciences, 48 served on the U.S. National Institutes for Health (NIH) Public Advisory

Committees or Study Panel from 1982-1984, 235 were National Science Foundation research proposal reviewers from 1983-1984 and 19 served as U.S. Department of Agriculture proposal reviewers.26/

45. The extent of overlap of those scientists who work for industry and are expected to provide various scientific bodies with objective opinions is viewed by several scientists as a basis for concern over the reliability of decisions made by these bodies affecting the public's interest and safety.

G. Impacts on Third World access to appropriate biotechnology

46. The developments regarding university-industry-government relationships in biotechnology are of special concern to developing countries. These concerns fall into two broad areas: (1) access of Third World countries to research and development carried out in industrialized countries; and (2) development in industrialized countries of appropriate biotechnology to meet Third World needs.

47. The first of these concerns encompasses some of the same issues discussed above such as the free flow of information among scientists and universities and research institutions and restrictions placed on this flow when scientists seek to privatize research results in order to maximize profit from their research. This can lead to decisions to withhold findings as well as inputs into research (including strains of micro-organisms, process developments, etc.) until contracts have been made with companies on decisions reached on patenting by companies or universities.

48. The specific agreements between scientists or universities and/or university departments and companies might also provide another obstacle to the free flow of information. Companies may demand that results of scientific inquiry be kept secret long enough to file for patents, or if secrecy is being relied on instead of patent protection, then for a period long enough to allow the company to gain a competitive edge in the market.

49. These concerns are not hypothetical. Examples of the detrimental impacts of commercial interests on scientific discourse are examined in a number of

sources as indicated above, and in a study by Nicholas Wade for the Twentieth Century Fund Task Force on the impacts of business on science. Wade investigates examples of these impacts, including the contests over the commercialization of insulin, trends towards what he terms "press conference science" (i.e., timing scientific disclosures to sales of company stock), problems in lending cells for investigation which might lead to commercial products (in this case dead KG-1 cells for cloning of the interferon gene), methods for making synthetic vaccines (in this case one researcher failed to disclose conversations with another which led to a commercial synthetic vaccine process, etc.)29/

50. Yet another set of concerns directly related to the above involves agreements between universities and governments or international organizations. An example of the conflicts which may arise and the obstacles to access by Third World countries (in this case, the primary beneficiaries) is illustrated by the case of malaria vaccine. Research by Ruth and Victor Nussenzweig at New York University was funded by the U.S. Agency for International Development and by the World Health Organization. Genentech had expressed interest in marketing the vaccine, but in 1983, because the company was unable to obtain an exclusive license, it withdrew from the project.30/

51. The clash of interests is evident in the explanation offered by a New York Times article reporting on the project:

> Most experts believe a "cocktail" of vaccines is the answer - but even that would face a clash of commercial and political interests. The World Health Organization, which finances much of the vaccine research, generally demands that discoveries be widely available, while drug companies consider profit margins on vaccines unattractive, especially vaccines aimed at poor areas.31/

52. Whether Third World scientists will have continued access to research in biotechnology being carried out in universities of a industrialized country will depend, in part, on the types of agreements made between these universities and companies, and by the number of university-based researchers who develop ties with TNCs or smaller biotechnology companies. The attention given to some of the larger arrangements (e.g., the

Whitehead-MIT agreement and the Whitehead-MIT and Hoechst-Harvard agreements) has created some concern over these issues among university administrators.32/ Some of the recent agreements (e.g., Monsanto/ Washington University, Harvard/Biogen patent agreement, etc.) have taken some of these conflicts of interest into account in drawing up the contracts33/ and others (e.g., the Hoechst/MIT agreement) have been re-examined in the light of such concerns.34/

53. The second, and equally important area of concern over growing industry/ university ties involves the potential turning of research and development away from products and processes of direct benefit to most of the people in developing countries (who happen to be poor and lack significant purchasing power) and towards products and processes which provide high profit margins for the companies involved. (The malaria vaccine case discussed above is but one good example.) As companies gain influence over academic research - either by providing funds earmarked for specific applied projects or by their choice of departments or scientists for funding - it is increasingly likely that such a change in emphasis will take place.

54. A recent study of biotechnology research, for example, indicates that of the DNA-based studies listed in 1982 by the Smithsonian Science Information Exchange, only one per cent were directed towards any type of vaccine development.35/

55. The impact which the strategic goals of commercial enterprises (e.g., profit maximization, risk minimization) has on university research is of direct concern to developing countries. To the extent that government funding continues to be available for basic research at universities and other research institutes in industrialized countries and enables scientists to pursue research interests for their intrinsic potential to advance human knowledge and not their commercial potential, this may not develop into a significant constraint on access to appropriate technology. But to the extent that ties between industry and universities continue to grow and redirect R&D towards readily exploitable commercial results, and to the extent that governments concerned with fiscal restraints (e.g., the U.S. government under the Gramm-Rudman legislation) cut back on such funding, Third World countries, and indeed, the public in industrialized nations, have cause for concern.

Notes on Chapter I

1. For the purpose of this study, biotechnology is defined as a set of techniques, both "new" and "old," that involves the use of biological processes and living organisms in industry, agriculture and other areas of applied activity. ("Old" techniques are traditional or established methods such as fermentation and use of enzymes in biological reactions. "New" techniques involve novel biological processes such as recombinant DNA and cell fusion.)

For various definitions of biotechnology, see, e.g., A. Bull, G. Holt and M. Lilly, Biotechnology: International Trends and Perspectives, Paris, OECD, 1982, pp. 21 and 67; Government of India, Department of Science and Technology, National Biotechnology Board, Long Term Plan in Biotechnology for India, April 1983, p. 1; Monsanto Europe-Africa, Biotechnology at Monsanto: An Overview, June 1983; European Federation of Biotechnology, Announcement of Federation Congress, 1983; U.S. Congress, Office of Technology Assessment, Impacts of Applied Genetics: Microorganisms, Plants, and Animals, Washington: GPO, April 1981, p. 4 and "New Biotechnology: Potential Problems, Likely Promises", Politics and the Life Sciences, August 1983, p. 42.

2. See, e.g., "Draft Report by a U.S. Government Interagency Working Group on Competitive and Transfer Aspects of Biotechnology", Washington, D.C., McGraw Hill Publications, 1983 and OTA, Commercial Biotechnology: An International Analysis, Washington: U.S. Government Printing Office, January 1984.

3. For example, U.K. support of Celltech and French support of Transgene as well as support in developing countries for national biotechnology companies.

4. See, for example, OTA, op. cit., p. 415, for analysis of various countries' governnmental support of biotechnology.

5. OTA, Commercial Biotechnology: An International Analysis, Washington: GPO, January 1984, p. 323.

6. The OTA believes that the U.S. government does not provide sufficient funds for generic applied research compared with other industrialized nations - especially Japan, ibid., p. 323.

7. See the discussion, by way of illustration, of lessons to be learned from development of microelectronics in OTA, ibid., p.415.

8. As of 1983, for example, some 83 of the 500 largest U.S. corporations and 62 of the largest non-U.S. corporations were active in biotechnology (Ward Morehouse and David Dembo, Transnational Corporations in Biotechnology (Draft Report prepared for the United Nations Centre for Transnational Corporations (New York), December 1983. Revised Draft, October 1984. pp. II-10 to II-19).

9. It should be mentioned, however, that Hybritech was recently acquired by Eli Lilly. ("Hybritech Agrees to Bid by Lilly", New York Times, 19 September 1985.)

10. "Biotechnology Taking Root in West Germany", Bio/Technology, April 1984.

11. "Attracting the Research Dollar", New York Times, 9 March 1983.

12. OTA, op. cit., p. 427.

13. David Blumenthal, et al, "Industrial Support of University Research in Biotechnology", Science, 17 January 1986.

14. David Sanger, "Research Sponsorship Soaring at Universities", New York Times, 8 September 1986.

15. David Blumenthal, et al, "University-Industry Research Relationships in Biotechnology: Implications for the University", Science, 13 June 1986.

16. In other countries, the concern is often the opposite. The U.K., the Federal Republic of Germany and France, for example, have been equally concerned with how to improve and increase ties between universities and industry. In these countries it is often felt that the university-based researchers would be "contaminated" through contact with industry. For such reasons governments in these countries have become actively involved in pushing such links, either through setting up biotechnology companies to bring the two together (e.g., Celltech) or through funding joint research programmes (e.g., the research "club" formed between six universities and five companies (including Celltech) and the Science and Engineering Council in the U.K. or the BMFT/corporate funding of national centres of excellence in the Federal Republic of Germany). "Biotechnology Taking Root in West Germany", Bio/Technology, April 1984; "Industry and Universities Prepare to Study Proteins", New Scientist, 20 June 1985; "German Firms Move into Biotechnology", Science, 24 December 1982; "France Seeks a Biotechnology Payoff", Chemical Week, March 10, 1982; "France Entices Its Biotechnologists into Industry", New Scientist, 25 March 1982; "Oil Firm Pins Its Hopes on Genetic Research", New Scientist, 11 March 1982.

17. In addition to the Pajaro Dunes Conference discussed earlier, similar topics have been discussed at the University of Pennsylvania December 1982 conference on university-corporate relations in science, at the New York Academy of Sciences in 1983 and at hearings before the U.S. Congress. "University-Academic Ties: Profit Over Progress", New York Times, 1 February 1983.

18. The Hoechst-Massachusetts General Hospital agreement was made public through U.S. Congressional pressure. While Harvard generally does not make such documents public, Stamford University, also represented at the conference, does. "Pajaro Dunes: The Search for Consensus", Science, 9 April 1982.

19. Ibid., and "Biotechnology Firms and Academics Meet on Research Accords", Wall Street Journal, 29 March 1982; and "Conflict of Interest on the American Campus", The Economist, 22 May 1982.

20. "The Interferon Dilemma: Secrecy v. Open Exchange", The Brookings Review, Winter 1982.

21. David Noble, "The Selling of the University", The Nation, 6 February 1982.

22. For example, in countries where much of the basic research is undertaken by corporations (e.g., Japan), it can be easier for other companies to gain access to foreign research. "Foreign Funding of Research", New York Times, 5 August 1985.

23. OTA, Commercial Biotechnology, op. cit., Chapter 17.

24. Ibid., p. 412. The OTA presents the recommendations of the Subcommittee on Investigations and Oversight and the Subcommittee on Science, Research, and Technology joint hearings on these issues: (1) universities should prepare guidelines for industrially sponsored research that require open disclosure of all faculty consulting and contractural agreements; and (2) full-time faculty should be discouraged from holding equity or directing such firms. The subcommittee further recommended that there be continued review by universities, industry, and the Federal Government of the benefits and problems resulting from large-scale corporate support for and involvement in university research programmes in biotechnology.

25. "Corporate-Academic Ties in Biotechnology", Genewatch, September-December 1984.

26. Nicholas Wade, The Science Business, New York: Priority Press, 1984.

27. "NYU's Malaria Vaccine: Orphan at Birth?" Science, 4 February 1983.

28. "Vaccine Is Elusive Weapon in New War on Malaria", New York Times, 26 August 1984.

29. The debate surrounding the Whitehead arrangement is discussed in Noble, op. cit. The Harvard-Biogen patent arrangement has also initiated such debate. "Harvard Biogen in Patent Deal", New York Times, 29 November 1983.

30. OTA, op. cit., p. 574.

31. "Industry-Academic Ties: Profit Over Progress?" New York Times, 1 February 1983.

32. Marc Lappe, "Recombinant DNA: Prospects for Health", Genewatch, September-December 1984. See also Marc Lappe, Broken Code, (San Francisco: Sierra Club Books, 1984).

II. ALTERNATIVE RESEARCH AND DEVELOPMENT ARRANGEMENTS

A. Four methods of financing R&D

56. Applied research and product and process development in biotechnology is being carried out by both the smaller specialized biotechnology companies and by large transnational corporations in a variety of industrial sectors such as food and beverages, energy, chemicals and pharmaceuticals and in agriculture. These two major actors have, in turn, developed a wide variety of arrangements with others involved in research and development, some of which were discussed in Chapter I above.

57. In this chapter some of these R&D arrangements are examined. While such arrangements are not necessarily limited to biotechnology they appear to be more frequent in biotechnology than in other areas of development of "frontier" or advanced technologies such as microelectronics.1/

58. As the biotechnology industry has developed, the smaller biotechnology companies have adopted a number of strategies, largely in response to financial constraints. Such considerations have influenced the determination of whether or not to seek partners or develop new products independently as well as the choice of partners if the former course is pursued and the types and ranges of products, processes and research projects undertaken.

59. Thus, some companies have adopted the strategy of providing services to the emerging industry while building a resource base from which to fund R&D in biotechnology-related fields (e.g., Applied Biosystems, Inc.). Other companies *(see paragraphs 75-81 in section D. below) have relied on development and marketing of diagnostic kits to provide revenue for more complex and long-range biotechnology R&D.

60. The range of projects has also been affected by financial considerations. One of the largest and oldest of the biotechnology companies (Genex) began R&D into a wide variety of possible applications, but was recently forced to curtail many projects because of falling revenue. Other companies (e.g., Genentech) chose a smaller number of projects in order to get products onto the market quickly so as to provide a financial base for longer range projects.

61. Because financing of R&D has played such a central role in determining the structure and function of the specialty biotechnology companies, a brief look at the various types of financing is necessary. Initially four methods of financing R&D in these companies have emerged. In the U.S. particularly, but also in some other industrialized countries, venture capital has played an important role in starting up new biotechnology companies. Within the last ten years dozens of biotechnology companies have been launched with venture capital, both from independent funds or groups and through venture capital funds of TNCs. Advent Eurofund is an example of the latter, funding European ventures through major financial support from a U.S.-based TNC (50 per cent by Monsanto).2/

62. Public stock offerings are a second means of funding biotechnology companies. This option has fluctuated in importance depending on the public (or more importantly, the investment community's) perception of the short-term potential of biotechnology. Currently, interest seems to be picking up, although after the initial surge of interest in the early 1980s, there were a couple of years when public offerings were not well received and biotechnology companies were forced to seek other means of financing.

63. Transnational corporations provide a third means of obtaining financing for these companies through at least four different arrangements: outright purchase; purchase of equity positions; joint ventures; the above mentioned TNC- managed or financed venture capital funds; and contracts and/or licensing arrangements between TNCs and specialty companies for R&D on specific products. Examples of the latter two methods of financing are given in Table 2 below.

64. The fourth method through which biotechnology companies have been initially funded is government support. A number of these arrangements are listed in Table 1 above, and include the governments of the U.K. (e.g., Celltech, Agricultural Genetics Corp. and Leiscester Biocentre), France (e.g.,Transgene), and Mexico (where a company is now being set up with support from the Mexican government, a foreign TNC and domestic pharmaceutical companies).

B. Research development limited partnerships (RDLPs)

65. One of the more innovative financing strategies used by biotechnology companies and some TNCs in the U.S. involves research and development limited partnerships (RDLPs). Under U.S. tax law, RDLPs provide a means by which investors can finance selected R&D projects while functioning as tax shelters which bring substantial advantages in tax reduction to the investors. The returns on such projects come either from royalties on product sales, or arrangements made when the RDLPs are bought out (as they frequently are) by either the original biotechnology company or as part of a buyout of that company by a TNC. In October 1986, for example, Genentech announced the buyout of two of its RDLPs for US$400 million after the RDLPs had developed growth hormone, interferon and blood clot dissolving products.3/

66. California Biotechnology, Inc., is another example. The company was originally financed through a limited partnership. Now that several potentially lucrative products are approaching the commercialization stage, the company's officers are planning on buying out the partnership to retain more of the royalties for the company.4/

67. Table 3 indicates the amount of funds generated by such partnerships, the products or projects involved, and the current status, where known. The ten RDLPs listed amounted to US$361.4 million in funding and most have begun to pay royalties to investors. According to a New York University study, biotechnology RDLPs account for 27 per cent of all RDLPs, with a total investment of US$663 million by the end of 1985.5/

C. Trends in R&D arrangements

68. The specialty companies have relied on a number of financing arrangements in order to support both short- and long-term R&D in biotechnology. Table 2. provides a list of some of the recent R&D arrangements between TNCs and the biotechnology companies. Such arrangements are used not only to finance the projects described, but also to allow the smaller companies to continue long-term R&D, often while positioning themselves for other financing alternatives (e.g., public offerings or support through product sales). The

Table 2. Some recent research and development arrangements

Research & development company or university	Transnational corporation	Type of arrangement	Amount (US$)
Joint Venture	Corning Glass Works	Joint venture to develop medical diagnostic products	
Creative Biomolecules	Stryker Corp.	Long-term agreement covering R&D and supply of human osteogenic protein	
Centocor	Hoffman La Roche	Joint venture. Roche will do clinical testing on non-human cell line-derived monoclonals. Roche will then develop and market products based on these antibodies.	
Centocor	FMC Corp.	Joint venture covering development of human cell line-derived antibodies, production of human monoclonals and development of immuno-regulatory therapeutics and diagnostics.	
Calgene and Phytogen		Joint development between two specialty bio-technology companies of herbicide-tolerant cotton varieties	
Biotechnica International	Seagram	Five-year research contract and purchase of 11 per cent equity	10 million
Biotechnica International	Uniroyal	Four-year programme on applying genetic engineering and nitrogen fixation technology to increase crop plant yields	
DNA Plant Technology	Campbell Soup	Funding of high solid tomato development in return for exclusive rights to varieties developed	
Intellicorp	Amoco Corp.	Joint venture to develop and market artificial intelligence-based software products for molecular biology	Additional 4 million for controlling interest in Intellicorp's genetic engineering software subsidiary
Nova Pharmaceutical Corp.	Celanese Corp.	Joint venture to develop drug delivery systems in Nova	Also, 10 million for 4% interest
Applied Biosystems	Rothschild Inc.	Two-year research funding through several venture capital funds	3.1 million
Imperial Biotechnology Ltd.	U.K. Dairy Industry Research Policy Committee	Three-year agreement for development of an enzymatic system for maturation of cheddar cheese	£100,000

Table 2 (cont'd)

Research & development company or university	Transnational corporation	Type of arrangement	Amount (US$)
Calgene	Rhône Poulenc Agrochimie	Contract to develop sunflower varieties tolerant to Bromoxynil (herbicide)	
Calgene	Kemira (Japan)	Contract to develop herbicide-tolerant rapeseed and turnip rape	
Calgene	Nestle Products Technical Assistance Co.	Joint development of herbicide-tolerant soybeans for third parties	
Hybritech	Teijin Ltd. (Japan)	Ten-year joint venture to develop human monoclonals against cancer	Up to 7.5 million for three years
Cetus	Eastman Kodak	Development of in-vitro human diagnostics	
Immunex	Eastman Kodak	Joint venture (Immunology Ventures) to research, develop and manufacture lymphokine therapeutics	
Cold Spring Harbor Laboratory	Pioneer Hi-Bred	Five-year joint research agreement on genetic manipulation of corn	2.5 million
Amgen	Johnson & Johnson	Develop, manufacture and market erythropoietin hepatitis B vaccine and interleukin-2	
Louisiana State University	Helix International Corp.	Joint research programme (University Ag[illegible]tics) into viral diseases in animals and plant and animal improvement	
Amgen	SmithKline Beckman	Joint programme into commercializing porcine somatotropin	5 million investment by SmithKline in Amgen
Chiron Corp.	Ciba-Geigy	Joint venture to develop vaccines against infecsious diseases	
DNA Plant Technology	Du Pont	Project to develop value-added plant varieties	
Calgene	Ciba-Geigy	Agreement for Calgene to develop disease-resistant crop plants	
NeoRx Corp.	Eastman Kodak	Joint development of monoclonals for cancer treatment and diagnostics	Kodak now holds over 20 per cent of NeoRx.

Table 2 (cont'd)

Research & development company or university	Transnational corporation	Type of arrangement	Amount (US$)
Endotronics	Celanese Corp.	T cell adoptive immunotherapy programme	Additional 2 million in return for 120,000 shares of Endotronic.
Nova Pharmaceuticals	Celanese	Drug delivery systems joint venture	Celanese will acquire 10 million (4%) of Nova.
Monoclonal Antibodies Inc.	Alcan Laboratories	Development and Manufacture of external ocular infection detection tests..	

Sources: "Hybritech: Portrait of a Monoclonal Specialist," Bio/Technology, April 1983; "Turbulent Times for Kodak," New York Times, 13 February 1986; "Down to Earth Biotechnology," New Scientist, 25 April 1985; "Calgene, Phytogen Sign Pact on Herbicide Tolerant Cotton Seed," Genetic Engineering Letter, 24 November 1984; "Centocor: Cashing in on Serendipity," Bio/Technology, February 1985; "Calgene Strives to Lead in Plant Biotechnology," Chemical & Engineering News, 29 April 1985; "Chronicle," Bio/Technology, January, September, October and November 1985 and January, March, April, August, and November 1986; "Biotechnology Firms Record Substantial Revenue Increases," Chemical & Engineering News, 1 September 1986.

Table 3. Research and development limited partnerships

Biotechnology Company	Product	Amount of initial funding (US$)	Current status
Genetic Systems	Diagnostic tests for a variety of diseases (including AIDS)	17 million	Genetic Systems acquired by Bristol Myers. RDLP bought out at a profit of $5 per warrant for the investors.
Hybritech	Tests for various cancers	70 million	Hybritech bought by Eli Lilly with significant gains to investors once purchase is complete - royalty payments expected this year (1986).
California Biotechnology	7-8 projects including two already licensed	27.5 million	Paybacks to investors began last year on licenses by Wyeth Labs and American Home Products for two products
Genentech	Recombinant human growth hormone and gamma interferon	55 million	Royalty payments to begin this year
Genentech	Tissue type plasminogen activator	34 million	Clinical trials
Genentech	Tumor necrosis factor	33 million	Clinical trials
Agrigenetics	Plant breeding, cell tissue culture, molecular biology	55 million	Acquired last year by Lubrizol. Royalties since 1984. Purchase of technology by Lubrizol for US$5.5 million.
Centocor	Diagnostic applications of oncogene research	5 million (2.9 million contributed before buyout)	Switched to therapeutics and bought out partnership for US$4.1 million.
Centocor	Cardiovascular imaging product (Myoscint)	23 million	Royalties began in 1986
Becton Dickinson	Immunodiagnostics, microbiology, cellular analysis	44 million	Two products already paying royalties

Source: "R&D Limited Partnerships Start to Pay Off", Bio/Technology, April 1986.

arrangements listed often cut across national boundaries and are not limited to research and development. While TNCs (as discussed below) are sometimes only looking for a "window" on the emerging technology, they are often interested directly in the product being developed for production and marketing because it is potentially competitive with an existing product (e.g., biological pesticides) or because it might complement sales of an existing product (e.g., herbicide tolerant seeds or plants).

69. The impacts on R&D programmes of such concerns are increasingly evident. The time when biotechnology companies could depend on long-term external financing (through venture capital or public offerings) without demonstrating the possibility of shorter-term profits is probably past. In the next section, a few of the R&D programmes of the more prominent biotechnology companies are examined by way of illustrating the impact of these factors on research and development in biotechnology in industrialized countries.

D. Case studies of R&D arrangements

Genentech

70. Genentech is one of the largest of the biotechnology companies. It was organized in California in 1976. The company aims at becoming a major independent pharmaceutical company and has structured its operations to allow for this longer-term development. The company has four core products on which it is focusing its development, manufacturing and marketing efforts. The company performs basic research in human health products and has a number of projects funded by outside sources.

71. Genentech spent US$65 million on research and development in 1985 (up from US$55 million in 1984 and US$37 million in 1983). Of this expenditure, some 36 per cent in 1985 was financed by the company out of its own resources.6/ Its "core" products are a direct result of its own R&D. One of those - human insulin - was the first DNA pharmaceutical product to receive U.S. FDA approval.

72. Genentech currently has three research and development limited partnerships (RDLPs). Genentech Clinical Partners funded trials of recombinant human growth hormone, for which the company received approval in 1985 and is now marketing. The company's other RDLPs are funding clinical trials of tissue-type plasminogen activator and tumor necrosis factor.7/

73. In addition to developing the "core" products based on its internalresearch, Genentech licenses the results of some of its research to other companies for testing and/or manufacture and marketing. Monsanto, Ciba-Geigy, Hoffman-La Roche, Miles Laboratories, Cutter Group, and Mitsubishi Chemical Industries are each licensed to test the company's products.

Calgene

74. Calgene (Davis, California), one of the better-known biotechnology companies in the field of agriculture, demonstrates a different approach to R&D funding. Because products from more advanced plant biotechnology are further in the future than some of the medical applications of biotechnology, there is less of a possibility of relying on product sales and licensing agreements.

75. Thus Calgene depends on a wide variety of R&D contracts to support research in its fields of interest, realizing that such contracts are not as lucrative as marketing arrangements would be and that they take the company in directions not necessarily of its own choosing.

76. For example, Calgene is now best known for developments in the area of herbicide tolerance - a technology that has limited applications and that may compete with the company's products down the line.8/

77. Calgene currently has R&D contracts with Campbell Soup for the development of high solids tomatoes, Rhône-Poulenc Agrochimie for herbicide-tolerant sunflowers, Roussel-Uclaf for increasing crop yields and Kemira for herbicide-tolerant rapeseed and turnip rape.9/

78. R&D joint ventures have been formed with Nèstle for the development of new soyabean varieties, DeKalb-Pfizer for herbicide-tolerant corn, Phytogen for herbicide-tolerant cotton, Kuraray for plant disease resistence and the U.S. Department of Agriculture Forest Service for herbicide-tolerant trees.10/

79. Calgene is one of the few examples of an independent biotechnology company which has chosen not to rely on public stock offerings. The effect of this on its R&D projects is evident and to some extent keeps the company from pursuing its own R&D interests in specialty vegetable oils.

Centocor

80. Centocor (Malvern, Pennsylvania) is an example of a very specialized biotechnology company in the health care field. The company depends to a large extent on short-term product development to fund its research efforts. The company also attempts to minimize financial risk by selecting a narrow range of products which do not require long time periods or development costs.

81. Cancer diagnostics are the company's main interest. The company has contacts with academic laboratories from which it licenses monoclonals, develops diagnostic products, markets the products initially and then licenses them to transnational pharmaceutical companies for production, marketing and/or distribution.

82. The company is involved in two major research and development joint ventures with Hoffman-La Roche and the FMC Corporation. The ventures call for the two TNCs to test and develop antibodies and products based on antibodies (Hoffman-La Roche for non-human cell lines and FMC for human cell lines).11/

Cetus

83. Founded in 1972 in Berkeley, California, Cetus is one of the oldest biotechnology companies and has research projects in a larger number of areas than most others. The company is involved in developing products and processes in the areas of human health care, agriculture and industrial markets.

84. Cetus's health care R&D is funded, in part, through its RDLP, Cetus Healthcare Limited Partnership. That arrangement allows Cetus to perform R&D for the Partnership in return for reimbursement of costs. The Partnership retains manufacturing and marketing rights, but Cetus has an option to purchase Partnership interests.

85. An agreement with W.R. Grace & Co. formed a partnership (Agracetus) to fund R&D in agriculture. Grace agreed to fund Agracetus for at least four years and Cetus contributed (through its Cetus Madison subsidiary) licenses to some of its technology.

86. Cetus has R&D agreements or joint ventures to fund a number of its other projects. The Nabisco/Cetus Food Biotechnology Research Partnership is a 1984 joint venture for R&D into foods and food processing technology. Cetus and Weyerhaeuser have a 1983 research agreement into wood-use technology. Weyerhaeuser has marketing rights in return for funding the research and royalty payments. From 1977 to 1985, Cetus and National Distillers and Chemical Corporation had a series of agreements for alcohol production technology.

87. In 1985, Cetus had R&D expenses of US$40 million, of which US$7.3 million was for its own projects and US$33 million was for client-sponsored R&D.

E. The emerging role of transnational corporations

88. Many biotechnology companies have survived longer than was thought probable only two or three years ago. At that time some believed there would be a shakeout in the industry, with many companies going bankrupt. That has not happened, due in part to the diversity of available funding sources. Yet the other side of the shakeout has been occurring - biotechnology companies both large and small, established and just beginning, profitable or otherwise, have been bought out entirely or in part by TNCs in a variety of industrial sectors.

89. Initially, TNCs were anxious to obtain a "window" on the technology and purchased equity interest in biotechnology companies. As these companies increasingly are bringing products to market (see Chapter III below), they are being acquired for their product lines.

90. TNCs have also greatly expanded their own in-house R&D programmes in biotechnology, often to complement existing product lines, but also in an attempt to diversify existing operations.

91. Many TNCs, including several of the Japanese companies, have had long-standing programmes in biotechnology or at least in technologies closely related to the newer biotechnologies (e.g., fermentation technology). Monsanto and W.R. Grace are examples of TNCs which gained "windows" on the technology and have then become more involved internally in the technology. Joint ventures provide one of the most numerous avenues for TNCs to take part in R&D in biotechnology both domestically and abroad. Many Japanese TNCs, for example, have R&D arrangements with biotechnology companies in the U.S.A. and Europe which provide them with the technology in return for royalties and initial project funding. (TNC R&D agreements with universities are numerous and were discussed in Chapter I above.) Table 2 provides some recent examples of research and development arrangements, often between biotechnology companies and TNCs, with the amount of funding from the TNC indicated where available.

92. Monsanto is one of the largest TNCs in the chemical industry worldwide. Examination of its experience in developing R&D in biotechnology is particularly useful because it illustrates a number of different possible strategies.

93. In 1979 Monsanto initiated a major programme in the biological sciences, including a major emphasis in biotechnology, as Monsanto's traditional business biotechnology promises to increase the possibilities for use of chemical pesticides and herbicides, but clearly the company is looking beyond that - not only at applications of biological pest controls which may compete with its traditional product lines, but also at other areas, including the human health field.

94. Monsanto has invested in biotechnology R&D through the variety of mechanisms discussed earlier, and over a broad spectrum. This capability differentiates this TNC from the smaller biotechnology companies which have been forced to choose carefully and look to short-term product development in order to support ongoing efforts.

95. Monsanto has invested in several biotechnology companies through venture captial funds as well as directly, both in the U.S.A. and abroad. The company holds or has held equity positions in Biogen, Genex, Genentech and Collagen among others, and through its major stake in Advent Eurofund, in Agricultural Genetics Company (U.K.).

96. The company's university agreements include the US$23.5 million programme with Washington University for immunology, cardiovascular and central nervous system research; an agreement with Harvard University discussed in Chapter I; with Oxford University on sequencing oligosaccharides; with Rockefeller University on gene regulation of photosynthetically activated plant genes; with the California Institute of Technology and at the University of California.12/

97. In addition to its equity positions in biotechnology, Monsanto has two R&D agreements with BioTechnica International on microbial pesticides and Bacillus subtilis expression systems.

98. There are also many external arrangements and linkages which allow the company to follow developments in biotechnology in a number of areas. On top of this, Monsanto has built up one of the largest in-house biotechnology R&D programmes in the world. In 1986 alone, the company will spend US$450 million on R&D. Of this amount, US$100 million is to be devoted to biotechnology. At Monsanto's $250 million life sciences facility over 700 persons do research in agriculture, animal health and nutrition and human health.13/

99. Much of the R&D work in biotechnology has, as indicated above, focused on short-term projects largely for financial reasons. Such projects tend to be in health care and agriculture, there has been some experience with attempts to develop products in other fields, especially by TNCs involved in other sectors such as energy. Several of the large energy-related TNCs have become

involved in various aspects of biotechnol R&D. Because of their ability to finance long-term R&D projects they have already had some experience with other types of products or processes based on biotechnology. While there are few, if any, cases where the economic and social environment has been appropriate for success with such experiments, the experience gained in one area - the manufacture of single-cell protein from natural gas - is instructive in such long-term experiments.14/

100. British Petroleum, Shell Oil, Phillips Petroleum, Dai Nippon, and Kanegafuchi are among the TNCs which attempted to produce single-cell protein (SCP) from a variety of sources. Most of these have discontinued their R&D projects in this area, either due to economic reasons or lack of a well-defined market - in some cases due to adverse public perceptions of the safety of the products based on the technology.15/ Imperial Chemical Industries (ICI) in the United Kingdom has had the most experience with SCP and has actually reached the commercialization stage with its process. Its failure to profit financially offers an insight into the difficulties experienced by even the largest TNCs in biotechnology, but also offers an example of the ways in which companies will gain experience and adapt the technologies and processes involved.

101. ICI's single-cell protein product, Pruteen, was the result of a US$150 million project, including construction of a plant to produce the product. Pruteen is produced from micro-organisms feeding off methanol, an oxidation product of methane. ICI's process, like that of most of the other TNCs involved, was based on the economics of cheap oil in the 1960s and early 1970s. With the rise in the price of oil, SCP, in most cases, is not competitive with substitute products: protein from soya and fish meal.

102. The markets for SCP include animal feed and possibly protein supplements for humans. The most likely current markets, due to the availability of the raw material, are oil-rich countries in the Middle East with few alternative sources for protein-rich feeds, the Soviet Union and Mexico.

103. In the process of developing Pruteen, ICI has gained considerable experience in operating fermentation plants - especially large-scale sterile

plants which will be of use in its ongoing projects. ICI hopes to get back some of its investment in the technology through licensing and continues some production at its domestic plant.

104. The company has also decided to utilize other companies in testing other products. ICI's second major project, polyhydroxybutyrate, will be developed by Marlborough Biopolymers, a small company in which ICI is the majority shareholder.

105. While ICI will probably not get back its investment in Pruteen, the company's US$150 million expenditure in this area may well have provided it with a competitive position for its future projects involving biotechnology.

F. Trends in construction for scale-up and production

106. Several years ago, stories abounded of small biotechnology companies set up with little more than a laboratory in a garage and a couple of scientists. That is rarely the case now, as the types of research and development projects outlined above move beyond the initial stages into the product and process scale-up and production stages.

107. We have discussed some of the strategies followed by companies in funding and carrying out their research and development projects. In the next section, some of the strategies and trends relating to manufacture and marketing of products are discussed. It is appropriate here to discuss some of the aspects of the commercialization of biotechnology relating to scale-up and production, especially the experiences of companies involved in biotechnology with the construction of both laboratories and production facilities.16/

108. Design and construction engineering firms were among the first to benefit and see the potential for future business from biotechnology. As early as the 1970s, some of these firms were benefitting from their experience with fermentation technology, including design and construction of breweries, experience with alcohol production, corn sweeteners, antibiotics, enzyme production and yeast production facilities. Coppee, the French firm has, for example, had

experience since 1974 in biotechnology engineering and construction. Coppee was given a contract for architecture, engineering, procurement and construction management services for an L-lysine plant in France.17/

109. During the early 1980s, several of the design engineering and construction firms were among the early investors in the smaller biotechnology companies. In January 1981, for example, Fluor Corporation, one of the largest construction companies in the world, announced the purchase of an undisclosed number of shares of Genentech.18/ In 1982, Stone & Webster, a U.S.-based contractor, announced a collaborative agreement with Biogen to speed up commercial development of Biogen's products.19/

110. Construction and design engineering companies have been eager to undertake contracts related to biotechnology in this early stage to gain experience for the larger, more numerous opportunities in the future. While there has been considerable experience with fermentation technology, there is not as much experience with large-scale sterile processes, such as those involved in SCP production. As ICI has pointed out (see discussion of single cell protein production elsewhere), while their process has not been profitable in the short run, they have gained more experience (perhaps more than any any other company) with design and construction of sterile process plants on a large scale to benefit them with future products, as well as to enable them to license their process to others.

111. By the mid-1980s, there had been considerable activity among construction and design engineering firms for design and construction of laboratories, pilot plants and manufacturing facilities for biotechnology-related products and processes. In 1984 alone, a review of projects announced in journals showed over US$960 million-worth of projects either completed or begun in the field. Of this total, some US$45 million was for pilot plant construction. Production facilities accounted for US$467 million and research facilities for the balance of US$457 million.20/

112. Continued activity in this area around the world is indicated in Table 4. This table shows some of the projects underway or announced in 1985 and 1986. Among the projects are research facilities, manufacturing plants and even a laboratory to conduct safety tests of products.

113. As more and more products are brought to the scale-up stage, these initial experiences with construction and design engineering relating to biotechnology will be learned from and expanded. According to several of the firms involved, the design and engineering of such facilities will not be a major constraint. These firms point to economic and social constraints, discussed elsewhere in this study, as being more important than problems in design engineering.21/

Table 4. Some recent examples of construction agreements for biotechnology-related facilities

Biotechnology company	Construction company	Plans	Amount (in US$)
WelGen Manufacturing (Cambridge, Massachusetts/U.K.)	N/A	50-50 joint venture of Wellcome Biotechnology and Genetics Institute to build plant in New England by 1989 for production of proprietary products, products developed by the venture and products of Burroughs Wellcome.	$30 million
Novo Biochemical Industry Japan, Ltd. (Tokyo)	N/A	Subsidiary of Novo Industri has opened an industrial enzyme production plant in Hokkaido.	N/A
Damon Biotech (Needham Heights, Massachusetts	N/A	Manufacturing facility under construction in Scotland (Damon Biotechnology Centre).	40 million
Scripps Clinic/ PPG Industries (LaJolla, California)	N/A	Expansion of laboratories at Scripps Clinic for US$120 million joint venture.	N/A
Hayashibara Biomedical Labs (Japan)	N/A	Factory for interferon and anti-cancer agent production under construction.	11 billion Yen
Yabult Honsha Co. (Minato-Ku)	N/A	Completion of facility with testing and research laboratories.	3 billion Yen
Oriental Yeast Co. (Tokyo)	N/A	Construction of biological research laboratory.	800 million Yen
Yamanouchi Pharmaceutical Co. (Tokyo)	N/A	Bulk pharmaceutical plant under construction at Irish subsidiary, Yamanouchi Ireland (Dublin)	N/A
Fujisawa Pharmaceutical Co. (Osaka)	N/A	Assisting Sri Lanka in construction of pharmaceutical formulation centre	2.6 billion Yen
Toyo Soda Manufacturing Co. (Tokyo)/Dutch Chemical Group DSM	N/A	Joint venture (Holland Sweetener Company) plant for production of Aspertame	N/A
Sumitomo Chemical Co. (Osaka)	N/A	Construction of safety laboratory for checking safety of chemical products	8 billion Yen

Source: "Wellcome, Genetics Institute Join Forces", Chemical & Engineering News, 15 September 1986; "Japan Roundup", Bio/Technology, October 1985 and May, June and November 1986; "Chronicle", Bio/Technology, November 1985.

Notes on Chapter II

1. Companies engaged in biotechnology R&D do not constitute an industry in the conventional sense, but rather cut across several industrial sectors. By biotechnology industry, we refer to those companies engaged in biotechnology R&D from a number of industrial sectors.

2. "W.R. Grace, Monsanto in Major Biotechnology Cash Boosts", European Chemical News, 9 August 1982.

3. "Partnership Buyout by Genentech", New York Times, 28 Octobre 1986.

4. "A Biotech Maverick with a Head for Business", Business Week, 21 July 1986.

5. New York University Center for Science and Technology Policy study for the National Science Foundation, cited in "R&D Limited Partnerships Start to Pay Off", Bio/Technology, April 1986.

6. Genentech 1985 10-K Report.

7. "R&D Limited Partnerships Start to Pay Off", Bio/Technology, April 1986.

8. "Calgene Strives to Lead in Plant Biotechnology", Chemical & Engineering News, 29 April 1985.

9. Ibid.

10. Ibid.

11. "Centocor: Cashing in on Serendipity", Bio/Technology, February 1985.

12. "Monsanto: Betting a Giant on Biotechnology", Bio/Technology, May 1986.

13. Ibid.

14. This section is based on "The Money-Hungry Microbe", Bio/Technology, July 1984.

15. Phillips has continued its R&D in this area, however, and has delayed some of its other R&D in biotechnology, including enhancement of tertiary oil recovery, until oil becomes scarce enough to change its costs significantly. "Phillips: Wildcatting in Biotech", Bio/Technology, October 1984.

16. Because there is often little difference between laboratory facilities and those used in manufacturing in biotechnology, we discuss the two together. Often, the facilities developed to carry out R&D products and processes in biotechnology have proved sufficient, initially to carry out commercial production as well. Similarly, some of the pilot plants set up have met current needs for some products and further expansion has not proved necessary.

17. "Engineering Contractors Look to Biotechnology", European Chemical News, May 1983.

18. "Activity Swelling at Gene-Splicing Firms", Chemical & Engineering News, January 19, 1981.

19. "Stone & Webster Teams Up with Biogen for Biotech Scale-Ups", European Chemical News, 8 November 1982.

20. "Trends in Construction and Planning", Bio/Technology, March 1985.

21. "Engineering Contractors Look to Biotechnology", European Chemical News, May 1983.

III. MANUFACTURING AND MARKETING PRACTICES AND FIRM STRATEGIES OF BIOTECHNOLOGY COMPANIES INCLUDING TRANSNATIONAL CORPORATIONS

114. Most of the products of biotechnology relying on the more advanced techniques of genetic engineering continue at the research stage. For those products further along in development, the regulatory process - especially in the United States where much of the more advanced development is occurring - has significantly dictated the types of products developed and processes relied on as well as the speed at which products pass through the development stage into scale-up, manufacturing and marketing.

115. On 18 June 1986, for example, the U.S. Food and Drug Administration approved the first therapeutic use of a monoclonal antibody for the treatment of kidney transplants. The treatment, developed by Ortho Pharmaceutical Corporation, is the first of what is expected to be a large number of uses for monoclonal antibodies in treating diseases and other transplant rejection therapies.1/

116. Another example, which has had the opposite effect, was the approval by the U.S. Department of Agriculture for marketing of a genetically altered virus. By 8 April 1986, the USDA had to review its approval process after widespread public criticism for it. The vaccine to prevent pseudorabies in pigs was developed by Novagene, Inc. and marketed under license by TechAmerica Group Inc.

117. A second recent setback in the production and marketing of genetically altered organisms is the case of Advanced Genetic Sciences, Inc.'s frost damage-prevention testing. In this case, after receiving approval for testing from the U.S. Environmental Protection Agency in November 1985, it was discovered that the company had violated Federal guidelines in testing the product in an open-air roof test. This disclosure led to a series of attacks on the company and is expected to set back open-air testing of genetically altered micro-organisms.2/

118. A recent example of these setbacks is the EPA decision of 20 May 1986, not to permit Monsanto to conduct field tests of a genetically engineered pesticide until further safety tests had been conducted. Monsanto originally

estimated the delay caused by this decision at one year,3/ but has since drastically cut back on this project and months after the decision had still not announced plans to attempt testing again.4/

119. TNCs and smaller biotechnology companies are responding to negative public perception of biotechnology (as well as potential negative publicity) in a number of ways. In addition to attempting to influence directly (through corporate public relations, lobbying and advertising) such companies have also set up associations to promote their interests. In the U.S.A., the Industrial Biotechnology Association was set up as the industry was just beginning. In 1985, in the United Kingdom, the Association for the Advancement of British Biotechnology was established by 20 corporate members. The association was formed to promote the interests of its members with government and regulatory agencies.5/ Similarly, the U.S. group has worked, along with the Pharmaceutical Manufacturers Association, to lessen restrictions on exports of products not yet approved in the U.S. to other countries.6/

120. In Japan, the Association for the Promotion of Advanced Technology on Pharmaceuticals was formed in 1985. The 120 member company organization was formed to promote relations between manufacturers, government and academia.7/

121. The examples in paras 115 to 120 have resulted in delays in bringing into the market products resulting from genetically altered micro-organisms when released into the environment. Yet these developments have not adversely affected other biotechnology-related products. Many of the smaller biotechnology companies, realizing the potential delays in regulatory approval, have designed products which would allow them to circumvent this process or minimize possible delays. These companies have typically continued research and development into the more controversial products while awaiting further clarification of the regulatory process before seeking approval for these products.

122. The difference is evident in a recent approval by the U.S. EPA which came just over two weeks after their denial to Monsanto. Ecogen, Inc. sought, and was granted permission to conduct field tests in eight states of a microbial pesticide made from genetically altered strains of a common bacterium. The difference is that the product is not a result of DNA genes from different species, but the enhancement of a natural process of genetic manipulation.8/

123. More common to this point, however, is the production and marketing of products which do not enter such a complex regulatory process. Diagnostic kits developed from monoclonal antibodies were among the first products developed through the new biotechnology-related processes. Hybritech is an example of a company whose strategy was to quickly develop a variety of such kits to fund future R&D work while most biotechnology companies depended almost totally on external R&D contracts to support themselves initially.

124. The success of some of the smaller biotechnology companies is evident in their very recent financial performance. Genentech, considered the industry leader, had product sales amounting to 29 per cent of total revenues in the second quarter of 1986. Protopin, the human growth hormone, had sales of US$9.5 million during the quarter. Centocor also had significant product sales of US$8.7 million during the second quarter.9/

A. Patterns and trends in production and marketing

125. There are several different approaches to production and marketing used by biotechnology companies and TNCs active in biotechnology. The smaller companies may complete the R&D work and then license the production and/or marketing to other biotechnology companies, or to TNCs with established production facilities and marketing outlets.

126. Alternatively, these smaller companies may attempt production and marketing themselves, at least in their home countries and arrange with other companies (usually TNCs) for marketing abroad. Typically, under such an arrangement, an American company might license production and/or marketing to a Japanese TNC for marketing in Japan and/or other Asian countries and reserve North American rights to itself. A second or even third TNC might also have rights to other geographic areas.

127. A third and more unusual approach, that has at least in one case already been arranged, is for a larger corporation to license a biotechnology company to do marketing and take care of regulatory problems. In such a case, it is the ability of a smaller company to focus its energies on one product or product line and to develop a marketing system specific to that particular line desired by the larger corporation.

128. Transnational corporations have well established production and marketing systems as well as departments to handle regulatory hurdles which may be utilized for biotechnology products alongside their traditional product lines. Such transnational systems also provide these companies with means of circumventing U.S. restrictions on dumping unapproved products on other countries. Companies such as Genentech have, however, complained that these restrictions work against small biotechnology companies wishing to produce products in the U.S.A. and then export them. There are cases now where even these smaller companies set up subsidiaries in other countries (especially Europe) to deal with product approval in those countries and to avoid U.S. restrictions. While Genentech's strategy is to get passage of a bill (the Hatch Bill - S.1848) lowering restrictions on exporting unapproved products, companies like Centocor opt for setting up plants abroad - in this case a US$25 million R&D facility in the Netherlands and another operation in Asia.10/

129. Damon Biotech, Inc. (Boston) provides another example of how international production and marketing might take place. In this case, it is the British government that will build the largest monoclonal antibody factory in the world for US$42 million in Scotland. Damon will own 80 per cent of the equity in the plant and will operate it.11/

130. In another U.S./European agreement, Schering-Plough, the U.S.-based TNC, through its 10.8 per cent equity in Biogen, the Swiss-based biotechnology company, will begin manufacture of interferon in a US$54 million plant in Ireland. This move will allow Schering-Plough to compete with Hoffman La Roche for the European interferon market.12/

131. Table 5 provides examples of 41 recent agreements in production and marketing of biotechnology-related products and processes. These examples range from acquisition of a company to improve marketing capabilities or to market the acquired company's products (e.g., the Monsanto acquisition of G.D. Searle and the equity position of Syntex in Genetic Systems) to all of the options outlined above. Some of the strategies biotechnology companies or TNCs are following in bringing products to market are reviewed in the paragraphs following the table.

132. Diagnostic products were among the first biotechnology-related products to be marketed. Several companies have begun marketing diagnostics. One of the first, Liposome Technology (California) formed a joint venture with Cooper Laboratories (Cooper-Lipotech). Lipotech has developed modified agglutination tests and Cooper is responsible for the marketing.

133. Cooper Laboratories, prior to the formation of the joint venture, marketed several of the conventional agglutination assays. Liposome Technology is using the joint venture to test the market for the new assays. Due to competition in the field, both from the conventional assays and the newer ones based on liposomes, there is doubt about the success of any new product in the market. As discussed in Chapter II above, these first products are used to establish the potential of the technology in order to make the companies more attractive to the investment community.13/

134. Also among the first companies active in biotechnology to bring products to market is Hybritech. Originally one of the most successful of the smaller biotechnology companies, it has since been acquired by Eli Lilly. Hybritech was founded in 1978 to produce and market monoclonal antibodies. Within three years, the company had received approval for TANDEM IgE, a disgnostic used by allergy patients. By 1983, Hybritech had marketed nine other TANDEM radioimmunoassay diagnostic products and had two lines of clinical diagnostic products.

135. Hybritech's initial strategy was to bring several products to market quickly to support continued R&D work and to attract additional investors. The company emphasized replacement products based on the new technology. This meant creating products that were cheaper or more effective. This strategy has been questioned by a number of people who feel it is not a creative way of using the new technology and who believe it will be very hard to displace existing products.14/

136. The company's marketing strategy - of improving on existing products with known markets - simplified the search for short-term products and helped to develop their reputation with customers and the FDA. The company marketed the diagnostic product through advertising in journals, direct mail and the symposium programme in the U.S.A.

Table 5. Some recent marketing and production agreements in biotechnology

Product	Research & Development company/university	Marketing company	Type of agreement
Pharmaceutical biotechnology products	Monsanto	G.D. Searle	1985 acquisiton of G.D. Searle to help Monsanto market its biotechnology related products
Animal health care (including interferon products)	Genentech	Ciba-Geigy	US$42 million for exclusive rights
Monoclonal antibody feline leukemia virus diagnostic kits	Cambridge BioScience Corp.	Norden Laboratories	Cambridge will supply Norden with kits for sale to veterinarians
AIDS blood screening tests	Cellular Products	Technogenics	International marketing rights
VegiSnax	DNA Plant Technology	Kraft	Kraft will market the snacks developed by DNAP
Omnivac (pseudo-rabies vaccine)	Novagene	Biologics	In return for marketing rights, Biologics will pay Novagene 50% of any profits from sales of product
Serum hepatitis *in vitro* radio-immunoassay	Centocor	Warner-Lambert and Toray-Fuji	Worldwide marketing rights. Centocor gets 20% royalties for non-exclusive marketing rights.
Animal health care products, including $Genecol_{99}$ (for calf scours prevention)	Molecular Genetics	Upjohn Co.	Distribution of products to 57 international markets
Animal health care products, including $Genecol_{99}$ (for calf scours prevention)	Centre for Applied Micro-Research at Porton	Porton International	13-year exclusive commercializing agent agreement
Animal health care products, including $Genecol_{99}$ (for calf scours prevention)	Nova Pharmaceutical Corp.	Mitsubishi Corporation	Exclusive marketing rights for Japan
Urine test for lutinizing hormone	Hygenia Sciences	Hoffman-La Roche	Marketing agreement
Pregnancy test	Hygenia Sciences	Zer Science (Israel)	Distribution agreement
DNA probes	Amgen	Abbott Labs	US$19 million funding of kit development. Abbott will sell kits.

Table 5 (cont'd)

Product	Research & Development company/university	Marketing company	Type of agreement
DNA probes	Enzo	Ortho Diagnostic Systems (Johnson & Johnson)	Exclusive worldwide marketing rights to probes in return for US$20 million investment
Erythropoietin (EPO)	Amgen	Kirin Brewery	US$24 million contract to make hormone for worldwide marketing
AIDS diagnostics	Genetic Systems Corp.	Syntex	Agreed to buy 18% of Genetic Systems in exchange for distribution rights for products developed in five years
Cattle ovulation cycle diagnostic	Boots-Celltech	Bayer AG and Sumihito and Sankyo	Bayer will manufacture and market kit worldwide except China and Japan where Sumihito and Sankyo will distribute it
Generic anticancer drugs	Ben Venue Laboratories	Cetus Corp.	50-50 joint venture for Cetus to get approval to market drugs
Immunological and biological products	Serotec Ltd. (U.K.)	Bioproducts for Science, Inc.	Exclusive U.S. distribution rights
Agricultural products	Plant Genetics	Kirin Brewery	Licensing and joint research arrangement with Kirin marketing some of Plant Genetics' products in Asia
Cardiovascular and diuretic therapeutic agents	California Biotechnology	Wyeth Laboratories (American Home Products)	Exclusive worldwide marketing license developed under a joint programme
Malaria vaccine	Biogen	Behringwerke A.G. (Heochst)	Development and marketing
Platelet-derived growth factor	Bioprocessing Ltd. (U.K.)	Bethesda Research Lab.	Distribution in the U.S.A. and Canada
Monoclonal antibody kits to detect turfgrass diseases	Agri-Diagnostics	O.M. Scott & Sons	Marketing of kits developed by DNAP and Koppers' joint venture
Human growth hormone	Biotechnology General Corp.	ABI Biotechnology (Canada)	Exclusive rights to distribute product
Monoclonal antibodies	Ube Industries Ltd. (Japan)	Wako Pure Chemical Industries Ltd. (Japan)	Marketing agreement
Diagnostics	Liposome Technology Ind.	Cooper Laboratories	Joint marketing venture (Cooper-Lipotech)

Table 5 (cont'd)

Product	Research & Development company/university	Marketing company	Type of agreement
Liposome-based assay kits	Collaborative Research	Sterling Drugs	Marketing to over-the-counter markets
Monoclonal antibody treatment of mastitis in cows	Molecular Genetics	Eastman Kodak	Development and marketing
Human granulocyte colony stimulating factor	Amgen	Memorial Sloan-Kettering	Production and distribution
Hepatitis B test	Organon Teknika Corp.	Electro-Nucleonics	Marketing in the U.S.A. and Canada
Alpha interferon	Biogen	Schering-Plough	Licensing agreement--Schering-Plough has a 10.8% share of Biogen. Manufacturing of the drug is in Biogen's US$54 million plant in Ireland.
Chemotherapeutic drugs	Cetus Corp./Ben Venue Laboratories	Cetus-Ben Venue Therapeutics	Joint venture to market anti-cancer products. Methotrexate is its first product.
Salinomycin antibiotic	Kaken Pharmaceutical Co.	Kaken in China, Robins in the U.S., Hoechst in Europe and Pfizer in Canada and South America	Worldwide marketing of Kaken's product
Snomax	Advanced Genetic Sciences	Eastman Kodak	Production of AGS's ice formation product.
Snomax	Advanced Genetic Sciences	Karlshamns Oljefabriker A.B.	Marketing of Snomax in Sweden and expansion into Europe.
Lung surfactant	California Biotechnology	Byk Gulden Lomberg Chemische Fabrik GmbH	European marketing rights
Growth factors	Chiron	Johnson & Johnson	Distribution and marketing
Semposai	Kirin Brewery	Tokita Seed	Marketing of new vegetable hybrid.
Hepatitis B vaccine	Chiron Corp.	Merck Sharp & Dohme	Marketing of gene-splicing vaccine
Human tumor necrosis factor-producing bacterium	Biogen	Suntory Ltd.	Suntory will produce and sell products in Japan and South East Asia

Sources: "New Commercial Opportunities for Liposomes Emerge", Bio/Technology, April 1983; "Biotech Breakthroughs in Detecting Disease", Fortune, 9 July 1984; "Interferon Lifts Schering-Plough Hopes", New York Times, 13 January 1986; "Syntex to Acquire 18% of Genetics", New York Times, 20 August 1985; "Japan Roundup", Bio/Technology, January and September 1985 and April, July and November 1986; DNA Plant Technology 1985 10-K Report; "Biologics' Historic Product", New York Times, 27 May 1986; "Small U.S. Biotech Firm Testing Products with Commercial Potential", Chemical & Engineering News, 25 March 1985; "Growing Pains Give Biotechnology Firms Mixed Results in Quarter", Chemical & Engineering News, 10 June 1985; "Cetus-Ben Venue: A Deal with a Twist", Bio/Technology, November 1985; "Chronicle", Biotechnology, May, September, November and December 1985 and January, March, April, August and November 1986; "Biotechnology Deal at Eastman Kodak", New York Times, 7 October 1986; "A Shot in the Arm for Vaccine Makers", Business Week, 4 August 1986.

137. Internationally, Hybritech markets products through Hybritech Europe S.A. (established in Belgium in 1981); Mitsubishi Chemical Industries in Japan; and American Hospital Supply Corp. in Canada and Australia. These independent companies (and in the case of Europe, Hybritech's subsidiary) are responsible for obtaining government approval and for supporting product distribution in their marketing areas. The company's products are marketed through local distributors. Packaging and promotion is geared toward the local market. Hybritech carries out its own production and packaging of the diagnostic kits. The company has a separate production facility.

138. In addition to Hybritech and Cooper-Liposome, other companies manufacturing and marketing disgnostics include Cetus, Amgen, Genentech, Enzo Biochem, and Genetic Systems. Larger corporations include Abbott, Syntex and Johnson & Johnson. These latter companies are active especially through joint ventures with the smaller companies. The market for these new diagnostics based on biotechnology is expected to add US$900 million to the US$4 billion market by 1987.15/

139. The entrance into the field by the larger companies threatens the ability of smaller biotechnology companies to compete. For example, Abbott is working on at least three projects - one in-house, one with the University of Colorado, and one with Amgen. Because of the marketing strength of Abbott, many smaller companies are seeking ventures with other companies to improve their marketing capability. Enzo Biochem, for example, has agreed to give a subsidiary of Johnson & Johnson (Ortho Diagnostic Systems) exclusive worldwide marketing rights (except for Israel and Japan) for DNA probes developed by Enzo. In return, Johnson & Johnson and Ortho have invested US$20 million in Enzo.16/

140. In September 1985, Hybritech agreed to be acquired by Eli Lilly & Co. for US$300 million. The acquisition provides the TNC with "immediate entry into the diagnostics market" and provides Hybritech with access to Lilly's substantial marketing networks for complementary products.17/

141. Although buyouts and joint ventures seem to be more likely as these first products are developed, some of the smaller companies are fashioning strategies to avoid this. Integrated Genetics in Massachusetts is an

example. The company developed a probe to diagnose contaminants in food rather than humans to avoid the FDA approval process. The market is a $50 million per year salmonella test market. The company hopes to avoid competition with the larger companies by exploiting markets small enough not to be of great interest to them.18/

142. Another company active in the diagnostics field is the most active of the U.K.'s biotechnology companies: Celltech. Ninety per cent of Celltech's sales come from outside the U.K. The company has formed a joint venture in Slough (U.K.) called Boots-Celltech Diagnostics Ltd. That venture has a newly formed joint venture in the U.S.A. (Boots-Celltech Diagnostics, Inc.) to focus on marketing Celltech's diagnostics in the U.S.A. The American subsidiary will market three monoclonal products initially: chlamydia, respiratory syncytial virus and thyroid stimulating hormone diagnostic tests. The subsidiary, which currently works exclusively on marketing but may get into R&D work, is to be financed through equity offerings, both public and private.

143. Only ten per cent of Celltech's sales are currently in the U.S.A. The company now has ten kits on sale and has an FDA inspected and approved bulk culture manufacturing plant for monoclonal antibodies with a 1,000-litre deep-tank fermenter. Celltech has an agreement with Ortho Diagnostics for the manufacture and sale of blood-grouping reagents. A recently developed kit to determine when dairy cows come into oestrus is to be manufactured and marketed worldwide this year (1986) by Bayer AG, except in China and Japan, where Sumihito and Sankyo will handle distribution.19/

144. Thus far the discussion has been of companies, both TNCs and the smaller biotechnology companies, involved in marketing of diagnostic products for the former. The decision to develop and market such products has usually been a strategy to allow companies to bring products to market quickly, either to produce revenues from sales or to make the company more attractive to investors.

145. This strategy has, however, been one of several followed by companies developing biotechnology-related products. As Table 5 demonstrates, there have been many agreements made between companies regarding production and/or marketing. Many of these were agreements made in order to obtain financing for R&D projects as discussed in Chapter II or to allow TNCs to control

distribution of products' competitive with or complementary to existing products. In most cases, the products have not yet reached the production and marketing stage (often still awaiting regulatory clearance), but a look at some of the agreements reached provides an understanding of what marketing arrangements will develop later.

146. Monsanto, one of the largest chemical TNCs based in the U.S.A. (see description in Chapter II above) has perhaps gone furthest among the TNCs in building up a marketing network for products (in this case pharmaceuticals) to come from its R&D activities in biotechnology. In 1983, Monsanto acquired Continental Pharma, S.A. (Belgium) to begin the process of building a marketing and distribution network.20/ In 1985, Monsanto announced the acquisition of G.D. Searle for US$2.7 billion. Searle, a pharmaceutical company best known for its sweetener, Aspartame, was purchased largely because of its marketing skills in the pharmaceutical area. Searle provides Monsanto with a sales force and expertise in dealing with the U.S. Food and Drug Administration's regulatory process.21/

147. Another of Monsanto's projects demonstrates the use of biotechnology-related products in enhancing sales of traditional products. Monsanto produces Roundup - the largest-selling herbicide in the world. The company is working to develop plants resistant to the herbicide both to increase sales of Roundup and at the same time creating a market for the "improved" seeds. A competitor in the plant-improvement area is currently developing such a seed.22/ Calgene also has an agreement with Phytogen to develop and market cotton varieties resistant to Roundup.

148. In addition to Monsanto, at least 25 other companies are working on producing herbicide-tolerant crops, including American Cyanamid and Du Pont.23/ Partly because of this potential for marketing complimentary products, but also to control technology for substitute products, TNCs have been very active in buying seed companies to control the outlets for "improved" crops. Ciba-Geigy, for example, has a new US$7.5 million facility for agricultural biotechnology and a seed subsidiary - Funk Seeds International - to market its products.24/

B. Trends in property rights in biotechnology

149. Of much concern to scientists, universities, companies involved in research, development and marketing of products and processes based on biotechnology, as well as to others concerned with technology development and dissemination, is the whole arena of intellectual property rights and intellectual property law. Concerns relate to how best to ensure development of technology; how to protect the interests of individual scientists and promote their efforts; how to protect products and processes being marketed, often following large R&D expense; and how to ensure dissemination of technological know-how, either within a country or between countries.

150. The means by which such concerns are addressed take a variety of forms. In this section we examine some trends, especially among industrialized countries, and conclude with some observations regarding related concerns of developing countries.

151. The three main forms for protection of intellectual property rights in biotechnology in industrialized countries are trade secrets, patents and plant breeders' rights. Trade secrets refers to a body of law which protects companies who choose not to patent products or processes, but instead to rely on secrecy to protect their interests. In biotechnology, this course is sometimes preferable because of the speed of introduction of new products and processes and some of the difficulties experienced with patents in protecting property. Most industrialized countries (with the important exception of Japan and to a lesser extent France) have well developed laws protecting trade secrets.25/

152. Patent law regarding biotechnology has become a much contested field in industrialized countries where companies and universities in the 1980s, (especially since patenting of live organisms was permitted in the U.S.A. following the 1980 Supreme Court decision in the case of Diamond v. Chakrabarty)26/ have rushed to file patent applications on all aspects of the developing technology.

153. Patents on live organisms have proved problematic for a number of reasons. In order to obtain a patent under U.S. law, it must be proven that the process or product is capable of being classified as a process, machine, manufacture, or composition of matter; is new, useful, and not obvious; and is disclosed to the public in sufficient detail to enable reproduction.27/ For live organisms, however, it is not clear at what point an organism or process is different enough from another to be patentable.

154. Many of the issues regarding patenting in biotechnology will be resolved as patent offices gain more experience. There have already been some procedural refinements in patent law (such as the requirement of a deposit of the item along with a description to fulfill the reproducability requirement) to adapt it to biotechnology. The subject of patent law in biotechnology is complex and evolving rapidly. It has been discussed at length in several of the references included in the notes to this chapter.28/

155. Plant breeders' rights also have a major role to play in the development and dissemination of biotechnology. In the U.S.A. and Europe laws exist to protect breeders of plants much as patents protect those who develop other types of products. Since much of the new biotechnology will be directed at new types of crops and modified varieties, plant breeders' rights will loom large in determining patterns of development of the technology in industrialized countries, with a strong orientation toward increasing privatization of the results of plant breeding work, much of which used to be in the public domain.

156. For biotechnology, with the emergence of genetic engineering, the two systems - patents and plant breeders' rights - now overlap. In the U.S.A., for example, novel living organisms can be patented and new varieties of plants are covered under the Plant Variety Protection Act (PVPA). Since April 1986 new varieties can be protected under either.29/ (Previous government policy held that if a product was covered under PVPA, it could not be patented.)

157. Perhaps as important, however, for the protection of new varieties of plants is that provided through hybridization. Hybrid plants have their own built-in protection, as farmers must repurchase the seed each year - seed from the present year's crop will not breed true the next year.

158. The whole area of protection of property rights in biotechnology is developing rapidly along with developments in the technology itself. It is still not clear to what extent some of the original, broader patents will be upheld in court, or to what extent patents on processes or similar products developed by more than one company will be upheld. Because the technology is developing so rapidly, and because several companies are often simultaneously developing similar products, the strength of protection afforded by patents remains unclear.

159. In the United States, probably the country with the most activity in biotechnology patents, the review for patent applications in biotechnology is currently approximately 26 months.30/ The U.S. Patent Office has received thousands of patent applications in biotechnology, but has processed few of these and of those few, many are being contested. Some examples follow.

160. Hybritech, now a subsidiary of Eli Lilly, had filed for and been granted one of the original patents for monoclonal antibody-based diagnostic kit technologies. That patent was invalidated in 1985 and that invalidation was overturned in September 1986 on appeal. Hybritech will now continue its almost three year old infringement suit against Monoclonal Antibodies.31/

161. Two patents covering some of the basic processes in genetic engineering were granted to Stanford University in 1980 and 1984. These patents have been the subject of much controversy and licensing revenues based on the patents have provided far less revenue than originally expected (notwithstanding that over 60 companies had licensed the technology as of 1984).32/

162. More recently, in August 1986, Amgen (based in Thousand Oaks, California) filed a suit against Cetus Corporation (Emeryville, California) to declare invalid Cetus' patents for interleukin-2. Cetus, in return, is suing Amgen for infringement of those patents.33/

163. Hoffman-La Roche (Nutley, New Jersey) is suing Genentech (South San Francisco, California) for infringement of a patent La Roche licensed from the Hormone Research Foundation (Berkeley, California) for recombinant human growth hormone.34/

164. An out-of-court settlement was reached by Johnson & Johnson (New Brunswick, New Jersey) and Becton Dickinson (Paramus, New Jersey) in the former's patent infringement case. Becton will pay US$5 million to Johnson & Johnson and receive a license for use of the monoclonal antibodies covered by the patent.35/

165. These patent litigation cases, and costs of filing patents themselves, are proving quite a burden for the smaller biotechnology companies. While TNCs already have the capability and resources to protect their patents, it is unclear that patent filings will be the primary means relied on in this field. Patent filings are, however, one of the means by which universities and other research institutes can continue to disclose results of research but at the same time inhibit publication of research findings until patent applications have been filed. The concerns raised in the first chapter of this study regarding secrecy are very much connected with the types of protection of property chosen by companies in their efforts to commercialize products and processes based on biotechnology.

166. Patents, trade secrets and plant breeders' rights are often primarily of benefit to those with the most advanced technology who are able to bring products to the market fastest. Developing countries interested in building up their own capabilities in biotechnology and benefitting from products or processes developed domestically or in co-operation with others should be wary of setting up structures which will allow TNCs to be the primary beneficiaries.

167. There are other means to reward and encourage scientific and technological efforts in this area. Regarding plant breeders, for example, alternative systems of reward to include rewards for the breeder (as in the U.S.S.R.), inventor's certificates, seed certification schemes, civil law contracts or agreements, legislation providing for trademarks, creation of brand images, or producer levies.36/

168. Of the patents filed in the United States, for example, most are filed by corporations, and with one or two exceptions (of centrally planned economies), all are from countries in North America, Europe, Japan and Israel. Of the 374 patents granted from 1963 to 1984 in genetic engineering in the U.S.A., 222 were to U.S. corporations, government or individuals. Of these, 188 (85 per

cent) were to corporations. Of patents granted to non-U.S. entities during this period, 123 (87 per cent of foreign owned U.S. patents) were to foreign corporations. Of the 152 of foreign origin, Japan, the Federal Republic of Germany, France, and the United Kingdom accounted for 72 per cent.37/

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IV. THE BIOTECHNOLOGY SUPPLY INDUSTRY

A. The topography of the supply industry

169. The biotechnology supply industry is large, diverse and growing rapidly. The authoritative Guide to Scientific Instruments produced each year by the American Association for the Advancement of Science (as a special issue of its periodical Science) is in 1986 entitled "Biotechnology Products and Instruments". It contains products of over 1,800 manufacturers in North America alone and lists literally thousands of products and instruments.1/

170. The broad contours of the biotechnology supply industry are reflected in the 21 sections into which the 1986 Guide to Biotechnology Products and Instruments of the American Association for the Advancement of Science is divided:

1. Animals, housing, handling
2. Cell culture, fusion, manipulation
3. Centrifuges, physical separation
4. Computers, data handling
5. Chromatography
6. Electrochemistry
7. Electrophoresis
8. Environmental chambers, freezers, hoods, ovens
9. Fermentation
10. Genetic engineering
11. Glassware, furnaces, labware
12. Laboratory chemicals
13. Laboratory furnishings
14. Liquid handling
15. Microscopy
16. Monoclonal antibodies
17. Nuclear instruments, isotopes
18. Rec ders, plotting
19. Physiology and in vivo instrumentation
20. Spectroscopy
21. Technical materials; scientific apparatus2/

171. That this premiere interdisciplinary guide to scientific equipment and supplies should have chosen to focus its 1986 volume on biotechnology is a reflection of changing priorities and interests in the research community, both academic and industrial, in a country that invests substantially more than any other in seeking to advance the frontiers of scientific knowledge and apply that knowledge to the market place for products and services. It also reflects, as the Editor of the AAAS Guide to Scientific Instruments is candid enough to admit, a more pragmatic consideration: The scientific supply industry is shifting its emphasis in response to changing interests and priorities within the research community, and the AAAS needs advertising revenue to assure continued publication of its annual guides.

172. This shift of emphasis cuts across many different aspects of the scientific supply industry, bringing about a marriage of the old and the new under the rubric of biotechnology. As the Guide's Editor comments on the 1986 edition on biotechnology, "the subsections on genetic engineering, cell manipulation, monoclonal antibodies, laboratory chemicals, and physiology and in vivo instrumentation achieve new prominence in addition to such analytical standbys as chromatography, electrophoresis, microscopy and spectroscopy."3/

173. This marriage of the old and new is even better reflected in the list of some 210 categories for biotechnology included in the AAAS 1984-85 Guide to Scientific Instruments, which is reproduced in Table 6. The biotechnology supply industry covers a wide spectrum of instruments and other apparatus as well as supplies and consumable materials such as restriction enzymes, monoclonal antibodies and other biochemicals.4/ This list is, however, too detailed to be a useful analytical tool in determining the likely impact of the biotechnology supply industry on the development of research work in, and commercial production based on, biotechnology in developing countries. Differentiation in broader categories is needed to assess the varying impacts of these categories on such countries, a point further discussed in the concluding paragraphs to this chapter.

174. Not only does the supply industry loom large today in the rapidly emerging arena of industrial activity and related research work in biotechnology, but its importance is likely to grow in the years ahead as new developments in instrumentation make possible new achievements in the

Table 6. Categories for biotechnology supplies and equipment for annual American Association for Advancement of Science guide to scientific instruments

[illegible]

Source: American Association for Advancement of Science, 1984-85 *Guide to Scientific Instruments*, Washington, The Association, 1984.

laboratory or in manufacturing products based on laboratory work. This will apply, of course, not just to biotechnology but to other areas of advanced science and technology as well. Consider this observation by a senior U.S. laboratory scientist in an article on "Instrumentation in the Next Decade: "The progress of instrumentation and measurement science in the next decade will be marked by three major trends. First, as the average instrument achieves a rather considerable level of intelligence, "dumb" systems will become the exception, and we will eventually begin to become proficient in exploiting the resulting capabilities. Second, more sophisticated understanding of measurement science and of actual measurement needs will drive instrumentation design advances such as miniaturized sensors and yet more "hyphenated" instruments and "mapping" instruments. Third, the combination of sensor-based instrumentation and microminiaturization will make possible distributed measurement by allowing point-of-use measurements by nonexperts."5/

B. A shifting and expanding market

175. In a field as new and rapidly changing as the biotechnology supply industry, precise and comprehensive data on the size of the market, let alone which companies have how much market share for particular categories of products, are extremely difficult to come by. Yet we have a picture of sorts, even if it is not fully up to date, from two market studies conducted at the beginning of this decade.

176. One of these by TAG Marketing Associates of Erie, Pennsylvania, calculated that the U.S. market was about US$90 million in 1981 and should have reached at least US$140 million by 1985. This study, focusing largely on equipment and apparently little on supplies, estimated 1985 sales for the largest categories of equipment as follows:

	US$ million
Fermentors	37
Centrifuges	20
Final isolation and purification apparatus and consumables	20
Tissue-culture devices	15
Filters and membranes	15
Freeze driers	7
Freezers and refrigerators	5
Autoclaves and sterilizers	5
Water purification equipment	4.5 6/

177. The other study of the biotechnology supply industry is more comprehensive in scope, covering both hardware and supplies such as biochemicals. This study by International Resource Development, Inc., entitled Biotechnology Equipment and Supplies, concludes that the biotechnology industry (including universities and other non-profit institutions) is spending about US$190 million a year worldwide on biotechnology equipment and supplies and the supply industry expects to see an annual growth in the range of 15-25 per cent over the decade of the 1980s. Indeed, it is a reflection of the embryonic state of products based on advanced biotechnology that we are confronted with an anomoly. Jamie Banks, an IRD researcher who worked on the above study, observes that "the current biotech equipment/supplies market is much bigger in terms of annual shipments, than the current output of genetically engineered products." Her study suggests that biotechnology equipment and supplies offer major short-term profit opportunities to the scientific equipment and supply industry.7/

178. As more products are brought to the production stage, there will be two discernible markets for the biotechnology supply industry. One market, already existing, is for laboratory equipment such as DNA synthesizers. The second, emerging market, is for equipment used in scaled-up production - for example, fermentors. As the latter market develops, it will be important to follow trends in the supply industry, and the relative ability of the TNCs and biotechnology companies to afford such supplies.

179. The IRD study forecasts significant growth in all major categories of biotechnology equipment and supplies. Top performing sectors are likely to be fermenters, synthesizers/sequencers and membranes/filters - findings that thus parallel the TAG Marketing Associates study previously mentioned. A summary of the major findings of the IRD study is given in Table 7.

180. The companies that service this shifting and expanding market are varied in size and character. Many are small and privately held. Others are subsidiaries of such large corporations as Du Pont, Hewlett Packard, Digital Equipment Corporation and Harris Manufacturing Company. Some companies that produce equipment and supplies are also themselves active in the emerging biotechnology industry, such as Biogen and Genentech. To make these

Table 7. Outlook for biotechnology equipment and supplies 1982-1992

Equipment Type	Usage growth in rDNA research and production	Usage growth in monoclonal antibody industry	Example of current suppliers
Freezers	Strong, particularly in non-profit sector	Steady	Linde, Revco, Forma, Kelvinator
Incubators	Growth from increased *in vitro* research and production	Some expansion	Napco, Forma, Bellco, New Brunswick
Ultracentrifuges	Stimulus from scale-up activities	Market may saturate in late 1980s	Beckman, Sorvall, International Equipment
Electrophores'	Stagnation after mid-decade	Modest prospects	LKB, Bio-Rad, Hoeffer, Pharmacia
Synthesis/ Sequencers	Revived interest in protein sequencing will stimulate market	'.A.	Bio Logicals, Beckman, Merck, Biosearch
Fermentation Equipment	Strong growth in medium and l·rge scale equipment	Boost from therapeutic substance prod.	Chemapak, Assoc. Bioeng., New Brunswick
Chromatography	Strong growth added boost from accessories	Growth will taper off	Waters, Pharmacia, Bio-Rad, Beckman, IBM
Cell and Tissue Culture ware & Glassware	May level off by mid-decade	Steady market little major growth	Corning, Costar, Falcon, Bellco, Kimble
Membranes and Filters	Excellent growth prospects	Significant growth expected	Millipore, Nalgene, Pall, Gelman

Source: International Resource Development Inc., Biotechnology Equipment and Supplies, as given in Biotechnology Bulletin (London), December 1982.

generalized observations more concrete, here is a sample of some firms and the products they put on display at a Nature conference on microbiology in Boston a couple of years ago:

American Bionuclear of Emeryville, California, makes fine organic and biochemical compounds, with a special focus on raw materials for biotechnology. The two-year old firm produces "the purest materials" for various biotechnology synthesis and DNA reagents. Says president Martin Marks: "Our goal is to become the benchmark supplier of biotechnology materials, the resource for the biotechnology industry."

Jordan Scientific Products of Philadelphia produces a broad range of "controlled temperature equipment" that include biological refrigerators, blood plasma freezers, blood bank refrigerators and incubators.

Gibco Laboratories, a division of the Dexter Corporation, makes products for molecular genetics. They range from beef extract powders ("a source of nutrients replacing meat infusions,") that sell for US$36.50 per pound, to a nutrient broth used for cultivation of micro-organisms at US$29.75 per pound.

Worthington Diagnostic Systems of Worthington, N.J. specializes in diagnostic products, marketing components or complete systems. The firm aims at the clinical market. One of its major achievements was the launching of "UV enzyme measurement as a rapid means for diagnosis of myocardial infarction" - as a diagnostic tool for heart attacks.

The Zymark Corporation of Hopkinton, Massachusetts, markets laboratory automation equipment that "combines robotics and state-of-the-art microprocessor technology to perform common laboratory operations." These include weighing, diluting, mixing and transferring samples to test tubes; homogenizing, centrifuging and extracting samples for biological testing.

New England Nuclear, a division of Du Pont, markets a broad range of reagents used in research on major disease from AIDS to cancer, leukemia, thymus and rheumatoid disorders, and in research on aging.

Pharmacia P-L Biochemicals of Milwaukee provides highly purified, "base specific" ribonucleases for RNA structure analysis and sequencing procedures.8/

181. Another concrete illustration is Applied Biosystems which currently holds some 80 per cent of the automated DNA synthesizer market. The outlook for this small company's performance (annual sales in 1985 were US$35 million) is, in the eyes of the company's management, very bullish. According to Sam H. Eleter, Chairman and Chief Executive Officer of Applied Biosystems, the company's growth over the next several years will be limited only by its ability to hire and train qualified new personnel. He looks for a 40 per cent annual increase in both sales and staff during this period. The company's most insistent need is to bolster its worldwide service network. Service is the critical element in this kind of business and the sale of 20 new complex machines such as DNA synthesizers means bringing on an additional service person. Eleter concludes that "if you are going to sell twice as many machines, you are going to need twice as many people to manufacture them, twice as many people to install them, and twice as many to service them."9/

182. Another form of activity in the biotechnology supply industry involves joint ventures between TNCs and smaller R&D companies or other TNCs. One example is a joint venture formed from Alfa-Laval's biotechnology centre in Sweden, its design and engineering resources and Chemap, its Swiss subsidiary, and Pharmacia, a Swedish pharmaceutical group. This venture, announced in April 1986, is to supply equipment and systems for scale-up manufacturing of biotechnology-related products. The venture, claimed to be the first biotechnology joint venture with the express aim of "designing processes and systems for the large-scale manufacture of biotechnological products,"10/ is expected to have annual sales of US$68 million within two years. Sweden, in fact, is encouraging such joint ventures especially with American companies, to capitalize on its efforts in biotechnology.11/

183. How long the numerous small and privatly held companies in the biotechnology supply industry will remain that way is unclear. Those that survive and become successful also become tempting targets for acquisition by larger companies with far more substantial capital resources necessary for further expansion. If the trend in other fields of high technology in the

industrialized countries holds for this segment of industrial activity, we can anticipate a process of acquisition and consolidation during the balance of this decade and into the next. How much of this will represent vertical integration - i.e., major transnational pharmaceutical and petrochemical companies that are moving aggressively into biotechnology seeking to acquire a dominant position through acquisition of smaller companies in the biotechnology supply industry - is not yet clear. However, as a corporate strategy, such an effort has obvious attractions, paralleling the large-scale movement of such transnational companies into the seed business, another TNC strategy involving vertical integration.

C. A case in point - gene machines

184. Microprocessor-based DNA synthesizers automatically string together pre-programmed sequences of nucleotides into DNA strands. Their cost ranges from US20,000 to US$50,000. Users of such machines credit them with boosting output among laboratory scientists and R&D workers as much as ten-fold. If indeed they do have this kind of impact on productivity, they obviously enjoy a rapid payback period in terms of saving on expensive research personnel time.

185. As of March 1984 there were seven fully automated DNA synthesizers on the market. (There are also numerous semi-automatic instruments available but they offer relatively few advantages over manual methods, the principal alternative.) Users of these machines are university and government research laboratories, large chemical and drug companies and genetic engineering firms. Some 60 per cent of the market is in the U.S.A., with the remaining 40 per cent elsewhere in the world, principally Japan and Western Europe.

186. Automated DNA synthesizing machines are far from perfect. The most widely sold machine - manufactured by Applied Biosystems - has an error rate of one in every 500 nucleotides. Other, more advanced machines which will hopefully reduce this error rate are being developed, including one by the transnational pharmaceutical company, Hoffman-La Roche, headquartered in Switzerland.

187. In addition to Applied Biosystems with, by its estimate 80 per cent of the market, there are five other U.S. companies:

Vega Biotechnologies (Tucson, Arizona)
Biosearch (San Rafael, California)
Systec (Minneapolis, Minnescta)
Genetic Design Sequemat (Watertown, Massachusetts)
SmithKline Beckman (Philadelphia, Pennsylvania)

European manufacturers include Sweden's Analysteknik, the F.R.G.'s Biochemische Synthesetechnik and the U.K.'s Celltech.12/

188. The outlook for the market for gene machines is, in the view of some analysts, limited even though it is presently expanding at a rapid rate. They calculate that there are less than 7,000 potential users worldwide - genetic engineering firms, pharmaceutical and other industrial companies, and universities - and once these users have been supplied the market will reach a plateau, if not decline. Others however see continuing improvements in gene machines as assuring a lively replacement market as companies and research laboratories seek to upgrade their equipment. Beyond that, according to Eleter of Applied Biosystems, sales of the chemicals that gene machines use are very likely to generate the bulk of profits in future years. One financial analyst observed that "It's the old razor-razor blade analogy. The margins on consumables such as reagents are always much higher than on an instrument."13/

189. The president of another important biotechnology equipment company, Leon Barstow of Vega Biotechnologies, emphasizes that while gene machines may bolster earnings over the short term, "their primary role is in helping us establish a customer base among the biotechnology community. The companies buying them may also have applications for some of our other products."14/

D. Implications for developing countries

190. Virtually all of the really critical biotechnology equipment and supplies needed by developing countries come from industrialized countries. It is not that developing countries do not make extensive use of local raw materials and even when they are available, more sophisticated scientific instrumentation.

Indeed one Mexican biotechnology company estimates that some 90 per cent of its raw materials come from Mexican sources. However, the remaining 10 per cent that do come from outside - principally the United States - are absolutely vital to maintaining production volumes and product quality and keeping costs manageable.15/

191. Thus, developing country biotechnology officials - both in industry and government - are apprehensive about their vulnerability in the event that access to such vital equipment and supplies is restricted. A Latin American biotechnology company, for example, has had no difficulty with supplies of biochemicals and other biotechnological raw materials but it has had difficulty from time to time with equipment suppliers, especially scientific instruments. The company wanted the latest version of a particular item of equipment which it sought to acquire from the Mexican subsidiary of a large United States scientific equipment manufacturer. Eventually it did succeed in obtaining the equipment it desired, but only after considerable additional effort. In other words, this was not treated as a routine transaction, as it almost certainly would have been had the Mexican biotechnology company been U.S.-based.16/

192. Other developing countries are developing anticipatory strategies. A good illustration is India, where a lead institution such as the Centre for Biochemicals of the Council for Scientific and Industrial Research undertakes co-ordinated procurement from abroad of a wide range of biochemicals such as restriction enzymes needed by several different research institutions within the country. Efforts are also being made to produce at least some of the most widely needed biochemicals within the country, and indeed, CSIR's Centre for Biochemicals began production of six restriction enzymes in April 1984.17/

193. While co-ordinated "buying trips" undertaken by Indian scientists in industrialized countries to assure high quality and uninterrupted supplies of crucial biochemicals are an essential element of India's short-term strategy, for the long term it plans to develop the capacity to make enzymes and other biochemicals within the country, principally through the Centre for Biochemicals. One part of this Centre is located at the University of Delhi in the Patel Chess Institute. Another part of the Centre will be based at Madurai University in South India. Within a few years, if current plans are

realized, India will be 75 per cent self-sufficient in biotechnological raw materials - about as much as any other country in the world, including those most advanced in biotechnology such as the U.S.A. or Japan.18/

194. This last example of efforts at self-sufficiency in the production of consumable supplies raises issues critical to understanding the prospects of developing countries in significantly reducing their dependence on industrialized countries for equipment and supplies essential for their research work in and commercial production based on biotechnology. It is quite conceivable that countries like India, Brazil or Mexico which have a relatively advanced scientific infrastructure, will achieve a significant measure of self-sufficiency in consumable supplies, but that degree of self-sufficiency is quite unlikely in the case of scientific instruments and other essential equipment. In the latter situation efforts are continuing to improve existing instruments and develop new ones by the scientific instrument industry in industrialized countries (which is, of course, much larger in those countries because of much larger R&D activity than in developing countries, even the most advanced ones).

195. As already indicated, there are examples of developing country-based companies already experiencing difficulties in obtaining equipment for R&D in biotechnology. This is one of the areas where the current administration in the U.S.A., for example, has considered the possibility of taking action to protect the U.S. competitive position in biotechnology.19/

196. A very rough indication of the relative diversity of these two markets (equipment versus raw materials and supplies) can be obtained from the listing of categories in the biotechnology supply industry in Table 6, above. Of the 112 categories, some 75 per cent are equipment-related. While many of these products are readily available, some effort should be made to determine the accessibility of developing countries to the more advanced and complex equipment.

197. A second area of differentiated access by developing countries is that of equipment for research and manufacturing. All things being equal, developing countries are likely to find it somewhat easier - even though they may still encounter difficulties such as those mentioned - to gain access to equipment

for research in biotechnology than for the capital goods necessary to scale up biotechnological processes and move them into commercial production. In some instances industrialized countries may limit access in an effort to protect their international competitive position in biotechnology. In other instances they may justify such limitations on national security grounds. In still other instances, there may in fact be access but on financial terms so difficult that no developing country will be able to afford to acquire the capital goods necessary to establish its own biotechnology industry.

198. There is very little actual experience as yet in these matters because industrial production based on modern or advanced techniques in biotechnology is extremely limited, even in the industrialized countries. However, experience of developing countries with access to critical inputs for biotechnology, whether they be consumable supplies, scientific instruments, or capital goods for industrial production, should be carefully monitored in the years ahead to identify any recurring problems that arise. This is a potential problem area which an international facility such as the International Centre for Genetic Engineering and Biotechnology set up to enhance capacity-building in biotechnology in developing countries should address by trying to facilitate access on equitable terms while simultaneously assisting developing countries in strengthening their own capabilities.

199. It is clear that if developing countries want to be assured of continued access on reasonable terms to biotechnology equipment and supplies, they will need to undertake steps such as those being pursued by India. They also have important opportunities for sharing among themselves, particularly if access to these supplies and equipment are restricted in some industrialized countries.

Notes on Chapter IV

1. American Association for the Advancement of Science, Guide to Scientific Instruments, May 1986.

2. Ibid., p. 3.

3. Ibid., p. 5.

4. American Association for the Advancement of Science, 1984-85 Guide to Scientific Instruments, p. 159.

5. Tomas Hirschfield, "Instrumentation in the Next Decade", Science, 18 October 1985, p. 286.

6. "Biotechnology Equipment Sales Rising", Chemical & Engineering News, 6 September 1982, p. 22.

7. As quoted in Biotechnology Bulletin (London), December 1982, p. 3.

8. Research Institute of America, "Suppliers for the Biotechnology Market", High Technology, November 1983, p. 5.

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10. "Alfa-Laval, Pharmacia in Joint Venture", Financial Times, 3 April 1986.

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13. As quoted in "Business Outlook", High Technology, ibid.

14. As quoted in ibid.

15. Interview with Mexican biotechnology company official, November 1985.

16. Ibid.

17. Government of India, Department of Science and Technology, Annual Report 1985, New Delhi: The Department.

18. Interview with senior Indian scientist active in developing that country's national programme in biotechnology, New Delhi, February 1983.

19. See Draft Report by a U.S. Government Interagency Working Group on Competitive and Transfer Aspects of Biotechnology, Competitive and Transfer Aspects of Biotechnology (New York: McGraw-Hill, 1983) p. C-3.

V. INTERNATIONAL TECHNOLOGY FLOWS AND COLLABORATION

200. Because so much of the global effort in biotechnology is concentrated in the industrialized countries, the developing countries have a vital interest in international flows of this technology from one country to another. They have an equally vital interest in different patterns of international co-operation that will help to increase their access on more equitable terms to emerging biotechnologies that have significant potential for application in their economies. This chapter explores the roles of some of the key actors in the international movement of biotechnology, including the initiative of what is undoubtedly the greatest potential significance to developing countries - namely, the creation of the International Centre for Genetic Engineering and Biotechnology under the auspices of UNIDO.

A. Transnational corporations and other industrialized country-based companies

201. TNCs active in biotechnology maintain a variety of linkages with other companies and agencies outside of their home country. The forms which these links take include financing, joint ventures, technology licensing, equity ownership, and research contracts.*/

202. In addition to financial and contractual links between TNCs, there are other less formal linkages through several networks and associations being formed worldwide. In Japan some 100 companies formed a trade group to avoid duplication in R&D, hold symposia and train personnel. The charter members of the group include some of Japan's largest TNCs such as Ajinomoto, Toray Industries, Kyowa Hakko Kogyo, Suntory, Sumitomo Chemical, Mitsubishi Chemical Industries and Hitachi.1/

203. One major characteristic of international activity of biotechnology companies is reflected in their access to major capital markets worldwide. Novo Industri, a Danish-based biotechnology company, has raised more than US$100 million in the last three years on both the London and New York stock exchanges. This internationalization of its equity base has meant that Novo

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*/ International links between universities and TNCs were discussed in Chapter I. Patterns of R&D activity involving TNCs were examined in Chapter II.

has been able to expand despite a sluggish domestic stock market. Novo has not restricted its internationalization to its equity base. It is also internationalizing its manufacturing operations by building an enzyme plant in North Carolina in the U.S.A. and another plant in Japan.

204. Biogen is an example of a publicly held company with an international equity base in addition to transnational biotechnology activities. The Geneva-based company's initial funding was through investments by Inco, a Canadian mining company, Schering-Plough, a U.S.-based pharmaceutical TNC, Monsanto, a U.S.-based chemical TNC and Grand Metropolitan, an hotel, food processing and catering group based in the U.K. Biogen has laboratories in Cambridge, Massachusetts and in Switzerland. A subsidiary in the Netherlands handles marketing and licensing activities.

205. Monsanto is a good illustration of a TNC with many "windows", both in the U.S.A. and abroad, on the emerging industrial interest in biotechnology. Monsanto holds equity positions in several biotechnology companies in the U.S.A. and elsewhere, including Geneva-based Biogen (see above) and has also been active in funding venture capital firms in the U.S.A. (InnoVen) and abroad. A venture capital fund, Advent Eurofund, provides Monsanto (50 per cent funded by Monsanto) not only with investment returns on foreign high-technology companies, but also with a means of observing new developments abroad in biotechnology. Monsanto, as one of the largest TNCs, has subsidiaries worldwide including R&D facilities.

206. Japanese company links with Western-based biotechnology companies, are extensive, particularly in the U.S.A. Japanese companies seek greater access to a perceived superior U.S. position in basic biotechnology research; conversely, U.S. companies hope to gain from Japanese experience with fermentation.2/ These links include stock purchases (for example, Japanese organizations purchased US$4.5 million of Genentech Inc. stock in 1981), licensing agreements (Hoffman-La Roche Inc. licenses its interferon technology to Takeda Chemical Industries Ltd. and Morchida Pharmaceutical Co.), and joint technology development agreements (Genentech and Sumitomo Chemical Co. reached an agreement to have Genentech's growth hormone clinically tested by Sumitomo).

207. Another illustration is the Japanese company Green Cross Corporation which is based in Osaka. It is one of the most active Japanese companies in establishing international links with smaller biotechnology companies in other countries (e.g., Collaborative Research Inc., Genex Corp. and Biogen).3/

208. In addition to corporate linkages for biotechnology R&D, numerous university/corporate and government/corporate agreements cut across national political boundaries. In its efforts to enhance biotechnology activity in Belgium, for example, the regional government of Waloon has funded Hybritech (United States) for research and development of diagnostics at the University of Liege and has formed a joint venture with Chiron of San Francisco for R&D on vaccines. The Federal Republic of Germany-based pharmaceutical TNC, Hoechst, has given Massachusetts General Hospital, an affiliate of the Harvard University Medical School, $50 million for biotechnology R&D. In a similar manner, Bayer has an agreement with the University of Geneva for research into the application of microbiological processes to wastewater purification.4/

209. There are numerous additional illustrations of linkages between biotechnology companies or in some cases between a company and a foreign government or a foreign university. Thus, two U.S.-based venture capital-funded biotechnology companies, Genentech and Cetus, were reported to be negotiating with the Dutch government's industrial projects company, MIP, to set up subsidiaries in the Netherlands. Both companies have indicated that their decision to create subsidiaries in the Netherlands will be dependent upon the nature and extent of government financial support.5/

210. Another illustration involves the genetic engineering firm, Biogen, which already spans the Atlantic with laboratories in Cambridge, Massachusetts, and Geneva, Switzerland. It recently signed a licensing agreement with BASF, the FRG TNC, for further development and marketing of a product known as tumor necrosis factor (TNF) which is based on recombinant-DNA technology.6/

211. Yet another illustration concerns a subsidiary of the U.S. chemical TNC, Monsanto, through its subsidiary Hybritech Seed International and a French agricultural company, Cooperative de Pau. Plans were announced in late 1984 for the creation of a new research-oriented joint venture in seeds, which will

seek to develop and commercialize new and improved wheat and barley varieties and hybrids. Both companies have already been collaborating in joint trials on genetically engineered corn or maize.7/

212. Another example involving a French company is an international cement group, Lafarge Coppee, which is currently expanding into food and agriculture-linked biotechnology activities through a recent series of acquisitions and expansion moves in France and the U.S.A. Lafarge's biotechnology initiatives are concentrated in a subsidiary, Orsan, which has its roots in sugar refining. In the 1960s Orsan withdrew from sugar refining and ventured into fermentation. Orsan is now one of the world's leading producers of monosodium glutamate, and under a collaboration agreement signed in 1974, with a Japanese company, Ajinomoto, controls about one-third of the world market for lysine.

213. The parent of Orsan, Lafarge, wanted to move its biotechnology efforts beyond work in amino acids. It thus began acquisition of U.S. businesses including the Illinois-based maize seed company, Wilson Hybrids, and in late 1974 the seed production business of the U.S. chemical TNC, Celanese. 8/

214. Other European-based companies are also involved in transatlantic expansion. Celltech Ltd., the U.K.'s major biotechnology company, recently formed an American subsidiary, Boots-Celltech Diagnostics, Inc. This subsidiary is located in Morristown, New Jersey, and will focus on marketing its parent company's diagnostics products in the U.S.A. Celltech, originally formed as a public sector company funded and owned entirely by the U.K. government, now expects to go "public" through the sale of its shares to private investors sometime in 1987.9/

215. The close interaction between government and industry in developing biotechnology in the industrialized countries is, of course, reflected in a government-funded and owned industrial venture like Celltech or in the insistence by U.S. companies that they will establish subsidiaries in the Netherlands only if there is significant Dutch government financial support. Yet another illustration involves the U.K. government and a Boston-based biotechnology company which in 1985 announced plans to build the world's largest factory to produce monoclonal antibodies. A US$42 million plant will

be built in Scotland where it is expected to create some 300 jobs in an area of high unemployment. The U.K. government will built the plant. Damon Biotech Inc., of Boston will have an 80 per cent equity stake in the plant and operate it.10/

216. Several agreements have been reached between developed country-based biotechnology companies and developing countries, particularly for testing of drugs developed in industrialized countries in the Third World. One example is the agreement between the Shaanxi Pharmaceutical Bureau in the People's Republic of China and Biogen, based in Switzerland, for clinical trials of Biogen's gamma interferon. Other agreements between China and industrialized country-based companies for production of biotechnology-related products include an agreement by Biotech Research Laboratories (Maryland, U.S.A.) to develop monoclonal antibody technology and related products in China (through training of Chinese scientists in the U.S.A.) further discussed below.11/ In Malaysia, a joint venture was formed between the International Plant Research Institute, a privately held commercial company based in California (U.S.A.) and Sime Darby for the introduction of plant genetic engineering products into Indonesia, Malaysia, the Philippines, Singapore and Thailand through land owned by Darby in those countries.12/

217. Other linkages between industrialized country-based corporations and China in biotechnology and closely related fields of industrial activity have begun to multiply. By 1983, three joint ventures in the pharmaceutical field had been initiated, involving the Swedish company ASTRA, Japan's Otsuka Pharmaceuticals, and the U.S. transnational, Squibb. In the case of Otsuka, the Japanese company is analyzing some 5,000 traditional Chinese herbs and medicines to see which ones can be exploited for the international market. Squibb's relationship with China is said to be a trade-off of skills and training (presumably provided by Squibb to its Chinese collaborators) for access to the Chinese market.13/

218. While the foregoing collaborations are in the pharmaceutical sector and not in biotechnology as such (albeit closely allied to biotechnology applications in that sector), by 1985 what was hailed as the first R&D agreement between China and a Japanese biotechnology company, Nippon Zeon Co.

Ltd., had been signed. This five-year pact involving China's Biotechnology Development Center in Beijing will undertake joint R&D on animal cell culture aimed at pharmaceuticals and fragrances.15/

219. In a related initiative, also announced in 1985, China has formed its first company for manufacturing products and supplies for biotechnology research and genetic engineering through a joint venture with U.S. and Canadian firms. The Sino-American Biotechnology Company will receive advanced technology from Promega Biotec in Madison, Wisconsin, under the first agreement, according to Promega, for technology transfer to China in this field. Nine senior scientists will receive training at Promega in the U.S.A. Another partner in the venture is SinoGenetik, a consulting firm in Vancouver, British Columbia, in Canada. Production was scheduled to start within a year of the agreement and to expand over the next three years to include human and animal diagnostics research, instrumentation and agricultural applications of biotechnology.16/

220. These links - whether industry-industry, industry-university, or industry-government - stimulate the international movement of biotechnology in a variety of ways. In some instances the movement of technology is explicit and a central objective of the linkage - for example, when a large manufacturing corporation with worldwide marketing capabilities in one country contracts with a smaller venture capital-funded biotechnology company in another country to undertake R&D that the larger corporation expects will yield a marketable product. In other instances the movement of technology may be implicit, as when a corporation based in one country makes a substantial equity investment in an R&D company in another country, typically with the understanding that a substantial equity investment will give the investor preferential access to the emerging results of R&D work.

221. Regardless of the character of the linkage or the ways in which it stimulates international technology flows, most such links exist between industrialized countries. While there is no generally accepted way to measure the international movement of technology, making meaningful quantification difficult, if not impossible, there is little doubt that most of the international movement of biotechnology [illegible] North among industrialized countries. North-South links [illegible] very m[illegible] limited and not much

technology flows through those links, save in the case of biotechnology supplies and equipment which have been identified by developing country industrial managers as key points of access for developing countries to technology being developed in the industrialized countries.

B. Transnational corporation activities in biotechnology in developing countries

222. Notwithstanding the fact that most movement of biotechnology is among industrialized countries, transnational corporations based in industrialized countries do have a number of activities involving biotechnology which do occur in developing countries. Some have already been mentioned, particularly in the case of China. TNCs have numerous manufacturing and marketing operations in developing countries in industrial sectors such as pharmaceuticals and chemicals where the potential for biotechnology is very substantial. However, because very little biotechnology, certainly that based on the most advanced techniques, has actually been commercialized, there are - so far - relatively few TNC operations involving biotechnology of this character currently under way in developing countries.

223. It is clear however, that if present trends continue, more and more industrial processes of TNCs in pharmaceuticals, chemicals and other fields will become based upon biotechnology. As that occurs, there will be substantial TNC marketing and probably manufacturing operations in developing countries in the future. Even now there are several aspects TNC operations in biotechnology that involve developing countries.

224. One existing path for TNC involvement in developing countries in biotechnology is through the acquisition of marketing rights. For example, Genentech has contracts with Toray Industries Inc., and Dauchi Seiyaku Co. to market gamma-type interferon in Asia. Biogen, based in Switzerland, has an agreement with Shinogi & Co. for the same substance, giving the Japanese company marketing rights in exchange for royalties. A similar agreement exists between Biogen and Suntory Ltd. for a cancer drug.18/ Genentech has an agreement with three other companies for marketing tissue plasminogen activator (an anti-clotting agent). Genentech retains marketing rights in

North America, Boehringer Ingelheim International has marketing rights in Europe, the Middle East, South America and parts of Australia, while Mitsubishi Chemical Industries and Kyowa Hakko Kogyo will market the agent in Japan.19/

225. One key sector in which TNCs are assuming active roles in biotech- nology R&D and already occupy a major position in many developing countries is the pharmaceutical industry.20/ As these companies begin to develop and market products in their home countries and other industrialized countries, based on biotechnology generally and genetic engineering more specifically, these products will begin to find their way into developing countries as well.

226. Pharmaceutical products based on biotechnology will not only be marketed in developing countries, but even before they are marketed, will be tested in these countries. Such tests are indeed already underway. For example, China has a joint venture with Biogen for marketing and production of gamma interferon as well as an agreement with Biogen to supply the drug for clinical trials of cancer patients in Chinese hospitals.21/

227. Another major sector of existing TNC involvement in developing countries closely related to biotechnology is agriculture generally and seeds more specifically. According to a recent study by Teweles (a major broker of seed companies) of the seed industry, the U.S. seed industry is already a US$5 billion annual market and it is expected to grow to US$11.8 billion annually by the end of the century due to advances in genetic manipulation techniques.22/

228. Large numbers of seed companies have been acquired in recent years by transnational corporations, particularly pharmaceutical and petrochemical companies. This process of acquisition has now penetrated developing country seed markets. According to one recent study, significant segments of the developing country vegetable seed market are already substantially in TNC hands. Suttons (owned by Cardo), Ohlsenn Enke (owned by Svalof), Daehenfeld of Denmark, and Zaadunie of Holland (owned by Sandoz) are among principal suppliers of vegetable seeds to Africa and Western Asia. Japanese breeders such as Takii and others linked to Sumitomo and Mitsubishi occupy a leading position in the vegetable seed market in South East Asia. In Latin America

and the Philippines, vegetable seed is marketed by American companies such as Dessert Seeds (owned by Atlantic-Richfield, the petroleum company) and Ferry-Morse (once owned by Purex and now controlled by Limagrain of France).23/

229. There are various other seed-related activities in developing countries involving TNCs and their subsidiaries. For example, a Cardo subsidiary, Hilleshog, is working with Swedish Match to breed Acacia Mangium trees for the Philippines. Campbell Soup, a U.S. food processing company, has linked up with an American genetic engineering company and Brazilian interests to breed new tomatoes in Brazil. Among vegetable varieties being grown in Kenya are cabbages from Ohlsenn's of Denmark (a subsidiary of Svalof of Sweden mentioned above), cauliflowers and carrots from Dutch and American subsidiaries of the Swiss pharmaceutical TNC, Sandoz, and lettuces from ARCO's seed subsidiary.24/

230. TNCs are getting more actively involved not only in vegetable seeds but seeds for cereals and other food grains as well. The initial thrust has been directed towards industrialized country markets but more recently attention has been directed towards developing country markets as well. The relationship to biotechnology stems from the circumstances that many of these same transnational corporations have both active in-house biotechnology R&D programmes and close links with the smaller biotechnology R&D companies. Biotechnology techniques are already beginning to be applied in plant breeding programmes, with very great potential for the future.

231. TNCs and smaller venture capital-funded biotechnology companies (in which TNCs often hold major equity positions) will need a marketing system for newly developed seeds based on plant breeding through genetic manipulation. One obvious approach to marketing these new varieties of seeds is through the acquisition of existing seed companies. Thus, a company based on advanced biotechnology such as the Agrigenetics Corporation of Colorado has purchased over ten seed companies since 1975.

232. Biotechnology applications in agriculture offer a number of opportunities to TNCs. Perhaps most important is the ability, through biotechnology, to link the use of fertilizers and pesticides to new varieties of seeds. Thus it is possible to develop seeds which require increased applications of certain chemicals to receive the benefits of improved yields and stress tolerance.

Through those seeds with such characteristics, TNCs can build a market for other agricultural imputs which they manufacture and market. In a similar manner, food TNCs are interested in seed companies because of their ability to develop and market new varieties of seeds through biotechnology that will produce not only greater yields but products better adapted to commercial harvesting, storage, transportation and preparation.

C. Biotechnology supply and equipment companies

233. The biotechnology supply and equipment industry, already examined in the preceding chapter, is mentioned again here only because equipment and supplies represent such an important form of the international movement of biotechnology. Interviews with a senior government official co-ordinating a major national programme in biotechnology and a senior management official of a private industrial company involved in biotechnology (one located in Latin America and the other in Asia) suggest that one of the most significant sources of information on advanced technologies in biotechnology with the potential for industrial application is through suppliers of equipment and raw materials. These firms are overwhelmingly based in the industrialized countries and many of them are relatively small companies. Experience in both countries is that smaller biotechnology companies in industrialized countries are more flexible and open than larger companies. The officials mentioned above felt that this was the case because, at least in part, smaller companies have no markets to protect while bigger concerns, especially TNCs, do. Indeed, smaller companies which are primarily engaged in the provision of equipment and supplies in biotechnology are in fact building markets for their products and services by sharing information about advances in technology embedded in or utilizing the products and services they supply.

D. International organizations

234. Because of the limited flows of biotechnology from industrialized to developing countries, the efforts of international organizations to promote collaborative activities across national boundaries assume all the greater

importance. Even among industrialized countries, collaboration at the intergovernmental level is significant and could become even more so if a major new undertaking proposed by Japan becomes operational.

235. One of the most substantial existing initiatives of intergovernmental co-operation in biotechnology among industrialized countries is that of the European Economic Community. The Commission of the European Communities has developed a five-year Biotechnology Action Programme (1985-89) with six major elements - research and training, co-ordination and communications, access to raw materials, regulatory regimes, protection of intellectual property, demonstration projects and other forms of collaboration with industry. This programme is an outgrowth of and continues an earlier effort, begun in 1982, involving Commission co-financing of research contracts in six key areas, all oriented towards agriculture and the food industry:

1. Development of advanced bioreactors for agriculture and the food industry.
2. Improved production of materials for stock breeding and for agriculture and the food industry through application of biomolecular engineering techniques.
3. Improvement of plant products.
4. Development of methods for identifying and transferring new genetic information in plants.
5. Improvement of the symbiotic relations between cultivated plants and soil micro-organisms.
6. Development of methods for cell selection and regeneration in other plants.26/

236. The new five-year programme is broad in scope, moving well beyond the earlier focus on research and training. To have a major impact on the development of biotechnology within the member countries of the Community will require substantial resources. But already difficulties have been encountered on the level of funding, when the European Council of Research Ministers recently approved only US$40 million spread over five years, a sharp cut from the US$64 million that the EC biotechnology officials had originally proposed. Funding at this level will not be able to do much more than maintain the research and training programmes already initiated earlier in the decade.27/

237. Even at this reduced level of funding, the European Community programme in biotechnology constitutes one of the largest, perhaps the largest, among efforts at intergovernmental co-operation in biotechnology. And that effort is focused on strengthening the position of the EC member countries vis-à-vis what these countries see as their two principal industrialized country competitors - namely, Japan and the United States. There is little of direct relevance to developing country needs in this effort, nor are developing countries likely to have any kind of special access to the results of these activities, except to the extent that the results of some of the EC-sponsored research are published and thereby enter the public domain.

238. Considerably more ambitious in substantive scope is a propsoal being mounted by the government of Japan to finance a new research programme which it calls "Human Frontiers". While details about this initiative are still lacking, it appears to be heavily oriented towards the biological sciences and would take up questions about such matters as the functioning of the human brain and body, cancer, protein engineering, artificial photosynthesis, and the whole field of genetic sciences. The programme would have a much more substantial funding level than the European Community initiative - some US$5 billion over the next decade. These funds would go to support research at universities and other scientific institutions in the other leading industrialized countries which participate in the annual Economic Summit - namely, Canada, Federal Republic of Germany, France, Italy, the United Kingdom and the United States. The results of this research would then be shared among all of the foregoing countries together with its sponsor, Japan.28/

239. Much more oriented toward the needs of developing countries are various initiatives within the United Nations system. In a system as large and diverse as the United Nations, efforts specifically related to biotechnology are widely scattered and all quite modest in scope. Among the agencies concerned in one way or another with the development and application of biotechnology to the needs of developing countries are the Food and Agriculture Organization (FAO), World Health Organization (WHO), UNESCO (particularly through its network of MIRCENs or Microbiology Centres for Training and Research which are located throughout the world), the UN Conference on Trade and Development (UNCTAD) (through its Technology Division, which has a long standing concern with the pharmaceutical industry and is

currently examining advanced renewable energy technologies, including biomass), the UN Centre for Science and Technology for Development (through its Advanced Technology Alert System and related initiatives), and the UN Industrial Development Organization (UNIDO) with its Programme on Advanced Technologies.

E. International Centre for Genetic Engineering and Biotechnology

240. Almost certainly the most substantial among these various initiatives within the UN system is the International Centre for Genetic Engineering and Biotechnology (ICGEB), which has grown out of UNIDO's Programme on Advanced Technologies. The ICGEB programme has now been initiated, with two major components being set up - one in Italy (at Trieste) and the other in India (at New Delhi). The basic objectives of the ICGEB are to enhance biotechnology capabilities among developing countries and to focus this technology on the solution of problems specific to these countries. The Centre's activities will encompass basic and applied research, training of scientists from developing countries and development and delivery of technology to developing countries suitable for application in those countries. In addition, centres in member countries may be "affiliated" to the ICGEB to facilitate close co-operation with the ICGEB.

241. Each of the two major centres in Italy and India will have complementary foci. The Indian centre will focus on human health and fertility, animal health and productivity, and agriculture, while the Italian centre will concentrate on energy, industrial technology and pollution abatement.

242. Steps have been taken in recent months to move the ICGEB from the planning stage into actual operation. Some 39 countries, primarily but not exclusively from the developing world are members of the ICGEB. An interim programme involving the expenditure of over US$18 million over three years, financed by the Italian and Indian governments, has been approved.29/

243. The question of safety guidelines for biotechnology research, manufacture and release into the environment is also an important issue and has relevance

to the operations of the ICGEB and its members. After analysing the issues involved in this respect, the UNIDO secretariat has formed an informal working group with the secretariats of the World Health Organization (WHO) and the United Nations Environment Programme (UNEP) to work further on this subject.

244. While such efforts at international collaboration, particularly when focused on the specific needs of developing countries, are very important to those countries in ensuring that the positive potential of biotechnology for these countries is realized, the major endeavour will of necessity have to be made by the developing countries themselves. Indeed, the stronger the national effort in biotechnology, the greater will be the ability of these countries to take advantage of international efforts such as the ICGEB.

F. Implications for developing countries

245. Several developing countries are pursuing national strategies to enhance their capabilities in biotechnology - for example, Argentina, Brazil, India, Mexico and Thailand. Because of the concentration of most of the world's activity in biotechnology in the industrialized countries these national strategies, if they are to be effective, will require a variety of links to the industrialized world. One of the most important and continuing needs is for accurate intelligence about what is going on in relation to new technologies through the monitoring of patent office submissions, data on what TNCs and other biotechnology companies are doing and the kinds of linkages among them, as well as information on socio-economic and environmental impacts of technology.30/

246. The growing privatization of much work on biotechnology in industrialized countries means that established channels between developing countries and universities and government R&D institutions in industrialized countries may prove to be less useful than in the past. These channels nonetheless remain important and there is a very substantial amount of data on biotechnology available in the public domain in many industrialized countries that developing countries should make a more systematic effort to gather and analyze. A particular effort should be made to establish ties with some of the smaller biotechnology R&D companies which are working on the leading edge

of the technology. A number of these were established by scientists who were previously university-based and who carry with them into the industrial world many of the values and orientations of university-based scientists, including the sharing of data with colleagues elsewhere and the open publication of the results of their work. Of course, when information is considered to have proprietary significance, it will ordinarily become available only through some kind of established commercial relationship.31/

247. Transnational corporations represent a major potential source of biotechnology for developing countries. Where TNCs already have established operations in a particular country, the country concerned may find it useful to determine just what kind of work on biotechnology is being undertaken by the TNCs elsewhere in the world and explore with the corporation terms under which this technology might become available to the country within the framework of overall relationships between the host country and the TNC. The importance of maintaining accurate and up-to-date intelligence about what different TNCs are doing in biotechnology applies with particular force here because the number of TNCs involved in biotechnology is growing substantially and the range of their activities is also increasing. Developing countries have a number of quid pro quos to offer in return for access to key biotechnologies especially related to their own needs, including continuing access to markets and raw materials which may be important to TNCs in other areas than those most immediately related to the biotechnologies in question.

248. The growing government-industry-university relationships in industrialized countries mentioned above pose an especially significant challenge to developing countries in biotechnology. Results of scientific research which in the past would be published and thereby freely available in the world body of scientific literature may be withheld from publication for fear of undermining future patent claims or because of arrangements between universities and private industry which give the industry the right of prior access to the results of research supported financially by that industry. Still, the door is far from closed, and developing countries are exploring a variety of devices to gain access to work on biotechnology being carried out in industrialized countries relevant to developing country needs.

249. It is precisely because traditional forms of access are becoming restricted that the establishment of the International Centre for Genetic Engineering and Biotechnology discussed above assumes so much importance. The Centre will seek not to privatize knowledge but rather to do whatever it can to make knowledge based on the work it undertakes at its two centres in Italy and India as readily available as possible to scientists and other research workers in developing countries. Since one wing of the Centre will be established in an industrialized country, this also represents a major collaborative effort between industrialized and developing countries.

250. There are numerous developing country scientists and technologists working in universities and industrial establishments in the developed countries. Such persons represent a potentially very important channel for developing countries to keep abreast of work relevant to their needs being undertaken in the industrialized countries. India, by way of illustration, is taking several initiatives to expand information flows and sharing of experience through such channels.

251. One is a programme of the National Biotechnology Board which involves inviting leading scientists working abroad in biotechnology to visit India for relatively short periods of between three to six months. The Visiting Scientist Programme, which may involve both Indian and non-Indian scientists working abroad, facilitates a rapid exchange of current knowledge and latest techniques through personal contact and discussion with Indian scientists working in India.

252. A related scheme involves the creation of National Biotechnology Board Associateships for Indian scientists overseas. In 1984-85 there were 11 Overseas Associates (9 Junior and 2 Senior) who will undertake training (in the case of the Junior Associates) and research work (in the case of the Senior Associates) in Indian scientific institutions.

253. Yet another initiative on India's part is the creation of the Standing Advisory Committee for North America. This Committee includes well established scientists of Indian origin working in North America who by virtue of their own scientific standing and experience are providing valuable inputs of knowledge for short- and long-term R&D planning, evaluation and assessment

of R&D work in progress in India. Members of the Committee will also participate from time to time in conducting workshops and training courses and giving lectures.

254. R&D activities in biotechnology in the industrialized countries, as previously discussed, follow one or more of three basic patterns:

1. R&D work in existing, expanded, or newly created R&D facilities of transnational corporations, particularly in (but not limited to) the pharmaceutical, agricultural chemical and food products fields.
2. R&D work undertaken by smaller, more specialized biotechnology firms funded through venture capital markets or with government support. (TNCs are linked to these biotechnology companies in a variety of ways, including the conduct of R&D projects under contract and equity investment by the TNC in the biotechnology company.)
3. Research in universities and government R&D institutions. (TNCs are related to such research activities, especially in universities, through the provision of financial contributions, which sometimes give the TNCs the opportunity for preferential access to the results of such research.)

255. Very little of the mainstream R&D in biotechnology encompassed by these three types of arrangements is undertaken in developing countries or is related to their needs. However, there are some exceptions. Thus a Swedish company, A.B. Astra, is seeking approval from the government of India for the establishment of a research and development centre at Bangalore. The proposal was considered by the National Biotechnology Board of the Department of Science and Technology in March 1984 and has since been cleared by the Cabinet Committee on Economic Affairs and the Foreign Investment Board. Under the agreement with the Swedish company, the government of India has nominated five of its leading scientists in biotechnology as members of the Board of Governors of the Centre.32/

256. Another important initiative outside the prevailing patterns for R&D work in biotechnology of special interest to developing countries is the International Centre for Genetic Engineering and Biotechnology, which has been

discussed previously. In addition, a handful of scientifically and industrially more advanced developing countries are beginning to develop their own R&D facilities independent of those that are emerging in the industrialized countries. Two good examples are India and Mexico, where substantial efforts have been made in recent years to strengthen and expand R&D work related to biotechnology in government research laboratories and universities.

257. In India, as already mentioned, a National Biotechnology Board has been created to co-ordinate these efforts and promote the development of biotechnology in the country. Among the activities undertaken under the auspices of the Board are manpower development (including short- and long-term training courses), sponsorship of university and industry-based R&D projects (e.g., development of biological pesticides, tissue culture propagation of bamboo, production and procurement of enzymes and biochemicals for [illegible]etic engineering research, etc.), creation of infrastructural facilities (including at least two major R&D centres) and as R&D work progresses, establishment of biotechnology manufacturing units. Progress on all of these fronts [illegible] been significant since the National Biotechnology Board was establis[illegible] in January 1982, and it is expected that work on establishing the manufac[illegible]g units will get underway in 1986-87, leading to the production of vacci[illegible]r human and animal use, hormones and peptides, agriculturally important micro-organisms and plants for biological nitrogen fixation, a[illegible]ell as biocides and other biological pesticides.

258. Currently, the National Biotechnology Board is engaged in reformulating its programmes and plans within the framework of newly articulated mission goals for the Board, as part of a government-wide effort to sharpen the focus and increase the effectiveness of research and related government activities. It is anticipated that this process of redefinition and reorganization of effort will be largely completed by mid-1986.33/

259. Comparable kinds of initiatives are being made and similar problems encountered in Mexico, as well as in the other developing countries that have made a major commitment to strengthening their capacity in biotechnology. All of these efforts are affected to varying degrees by a variety of issues on the agenda of the international community that involve biotechnology. For

example, international conventions for the protection of intellectual property such as the Paris Convention on industrial patents (which in some countries now include the pâtenting of life forms and are therefore of special importance to biotechnology) and the Union for the Protection of New Varieties of Plants (UPOV) are periodically renegotiated and constitute an important opportunity for developing countries to increase their access to biotechnology that may be protected by patents or their equivalent (in the case of UPOV and plant varieties).

260. The question of conservation of, and access to, the world's genetic resources constitutes another key set of international issues. There is a growing need for a number of internationally organized and supported facilities, including Biosphere Reserves, a system of village-level landrace custodians which might be called the farmer curator system, an international gene bank system, and national conservation centres. There is also a need for new and revised international structures, including an international convention on the preservation of genetic resources open to all countries under the auspices of the Food and Agriculture Organization, a conservation and development fund within the framework of the convention, and a restructured International Board for Plant Genetic Resources directly under the control of the FAO and the International Convention. The International Convention on the Preservation of Genetic Resources, which is now officially on the agenda of FAO, should encompass all categories of germplasm and ensure that privately held germplasm collections are safely stored, publicly documented and freely available.34/

261. There are still other issues and initiatives important to developing countries in biotechnology. The fact that several developing countries such as those mentioned above have already achieved a considerable level of competence in fields closely related to or involved in biotechnology opens up important possibilities for co-operation among developing countries. The growing significance of the genetic supply industry suggests that it should be carefully and systematically studied through an investigation involving such international bodies as the FAO or the World Food Council, UNCTAD, UNIDO and the UN Centre on Transnational Corporations.

262. Biotechnology has the potential for enormous impact, both for good and for ill, on developing countries and their peoples. If the good is to be maximized and the ill minimized, these and other initiatives at the national, regional and international level must be pursued with increasing effort and determination.

Notes on Chapter V

1. "Bioindustry Firms Plan Trade Group", Asian Wall Street Journal, 31 January 1982.

2. "Biotechnology Links the U.S.and Japan", Business Week, 19 October 1981, p. 62.

3. Ibid., pp. 62-64.

4. "Holland, Germany Move Slowly into Biotech", European Chemical News, 2 May 1983, p.17.

5. Manufacturing Chemists, April 1985, as cited in UNIDO: Genetic Engineering and Biotechnology Monitor, June/July 1985, p. 14.

6. Chemical Week, 19 December 1985, as cited in UNIDO: Genetic Engineering and Biotechnology Monitor, April/May 1985, p. 27.

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16. "Biotech Comes of Age", Business Week, 23 January 1984.

17. "Genentech's Triple Play", Chemical Week, 4 January 1984.

18. For data on TNCs in the pharmaceutical industry in developing countries see United Nations, Centre on Transnational Corporations, Transnational Corporations in the Pharmaceutical Industry of Developing Countries: A Technical Paper, New York: United Nations, 1983 (advance text of forthcoming sales publication).

19. "Joint Bioventures in China", Chemical Week, 11 January 1984, p. 16.

20. "The Biotech Big Shots Snapping Up Small Seed Companies", Business Week, 11 June 1984, p. 59.

21. Pat Roy Mooney, "The Law of the Seed: Another Development and Plant Genetic Resources", Development Dialogue, 1983, Nos. 1-2, pp. 105-106.

22. Ibid., p. 106.

23. Interviews with a senior government official and a private sector industrial company manager in Mexico and India, November and December 1985.

24. UNIDO, Genetic Engineering and Biotechnology Monitor, June/July 1985, p. 6. See also Commission of the European Communities, Biotechnology in the Community, Brussels: The Commission, 3 October 1983 (COM-83) 672 Final/2-Annex.

25. Chemical Week, 2-9 January 1985, as cited in UNIDO, Genetic Engineering and Biotechnology Monitor, March/April 1985, p. 22.

26. "Science Proposal Pressed by Japan", New York Times, 9 April 1986.

27. "International Biotechnology Centre Takes Shape", Chemical & Engineering News, 13 October 1986. See also the reports of the Preparatory Committee on the Establishment of the International Centre for Genetic Engineering and Biotechnology - e.g., Report of the Meeting of the Panel of Scientific Advisors (Vienna, 11-13 February 1985) issued as ICGEB/Prep.Comm.6/9, (sixth session, New Delhi, 1-3 April 1985) and Conclusions and Decisions, issued as ICGEB/Prep.Comm./6/13 (sixth session, New Delhi, 1-3 April 1985). Also relevant in tracing the formation of ICGEB are various issues of UNIDO's Genetic Engineering and Biotechnology Monitor.

28. Ravi Chopra and Ward Morehouse, Frontier Technologies, Developing Countries, and the United Nations System After Vienna: Analysis of the Impact of Technological Trends in Developed Countries on Developing Countries, the UNCSTD Programme of Action and United Nations Science and Technology Policies, New York: UNITAR, Science and Technology Working Paper Series No. 12, 1981, pp. 60-63; UNIDO, Genetic Engineering and Biotechnology Monitor, March/April 1985, p. 2. See also UNESCO/United Nations Environment Programme/International Cell Research Organization, MIRCEN News, occasional; E.J. DaSilva, "The Rennaisance of Biotechnology: Man, Microbe, Biomass and Industry", Acta Biotechnologica, 1981, pp. 207-246. MIRCENs have now been established by UNESCO in Bangkok, Nairobi, Porto Allegre, Guatemala City, Cairo, Hawaii, and Stockholm.

29. For a proposal for sharing of intelligence on biotechnology, see Carl-Goran Hedén, "Networking the Biodevelopment Community", in von Weizsaecker, Swaminathan and Lemma, op. cit., pp. 224-231.

30. A good illustration of the possibilities of the collaboration involving indusrialized country universities and government research institutes with developing country institutions is a co-operative programme to use cloning rather than chemical spraying in combating a fungal infection of Mexican coffee plantations; involved have been Purdue University in the United States, the Coffee Rust Research Institute in Lisbon, and the University of Chapingo in Mexico. (UNIDO, Genetic Engineering and Biotechnology Monitor, August 1982, p. 54.)

31. Government of India, Department of Science and Technology, Annual Report, 1984-85, New Delhi: The Department, pp. 198-211; interview with a senior government official, New Delhi, December 1985.

32. Mooney, op. cit., pp. 167-170.