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THE EFFECTS OF THE NEW BIOTECHNOLOGIES

ON THE

INTERNATIONAL AGRICULTURAL RESEARCH SYSTEM

Prepared by:

John H. Barton
International Technology Management
1340 Harwalt Drive
Los Altos, CA 94022
415-961-6171

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John H. Barton
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Study of the Effects of the New Biotechnologies on the International Agricultural Research System

FINAL REPORT

The Green Revolution had an enormous effect on developing world agriculture. The new biotechnologies may have as great an effect -- and not only on the developing world farmer, but also on the way that developed world technologies are brought to the assistance of that farmer and particularly on the interplay between public and private institutions.

These changes will pose new policy questions for the Consultative Group on International Agricultural Researce (CGIAR) and for the design of United States research assistance to developing world agriculture. This study, as a first effort, estimates which of these new policy questions are most likely to be important and highlights the key issues affecting their answer.

INTRODUCTION AND SUMMARY OF CONCLUSIONS

In the traditional plant breeding structure, public institutions -- the United States land grant colleges and analogous developed-world institutions, along with the CGIAR system -- conducted a large portion of the basic breeding research. Commercial firms in the developed world and commercial firms or public agencies in the developing world frequently concentrated their efforts on working with strains derived from this public system and on the multiplication and preparation of seeds for farmers' use.

The rapid evolution of biotechnologies -- defined, loosely for this report, as including tissue culture as well as the genetic manipulation technologies emphasized by David Baltimore (1) -- is changing this linear relation. Even when these new

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(1) D. Baltimore, "Priorities in Biotechnology," in Priorities in Biotechnology Research for International

technologies are applied only at the basic research level so that varieties are released for seed multiplication as before, new commercial firms and new developing nation research groups have emerged to compete with and work at roughly the same intellectual level as the public institutions. The new technologies will also sometimes require close integration of high-technology work with field application. Thus tissue culture may bring sophisticated propagation methods directly to the farm or nursery; molecular genetics may permit the tailoring of cultivars or microbials to highly individual field situations. Moreover, the costs of these technologies are significantly higher than those of traditional breeding technologies.

This evolution poses three kinds of questions for the Agency for International Development (AID) and the CGIAR system:

(1) It puts these entities in a position of competing more sharply with private enterprise and perhaps with developing world public enterprise. It also gives them additional opportunity to cooperate with these new institutions.

(2) It requires new patterns of communications, as the new institutions with new expertise are brought into agricultural research.

(3) Because the regulatory and intellectual property systems are radically different from those relating to traditional breeding methods, it may also require a reconsideration of patenting strategies.

The private agricultural biotechnology industry is likely to shape the public structure much more than vice-versa; this paper therefore attempts to estimate the evolution of that industry as it affects the developing world. The pattern may differ radically for different technologies; the analysis is therefore carried out separately for different groups of technologies.

Building on this analysis, which defines the environment within in which CGIAR and AID can expect to operate, the paper then develops a variety of implications: implications for the new research areas and needs that might most usefully be met by public funds, suggestions for possible new ways for public and private institutions to cooperate, directions for developing nation patent systems, and directions for CGIAR and AID patent policy.

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(1)(continued) Development; Proceedings of a Workshop, p. 30 (1982). This entire workshop is an excellent introduction to the topic as are the two Office of Technology Assessment reports, Commercial Biotechnology; An International Analysis (OTA-BA-218, January 1984) [hereinafter OTA 1984] and Impacts of Applied Genetics: Micro-Organisms, Plants, and Animals (OTA-HR-132, April, 1981), and the special issues of Science including particularly v. 219, no. 4585, p. 609 (11 February 1983).

Summary of Key Conclusions

The international agricultural research system should strongly encourage application of the new biotechnologies to developing nation agriculture. As a strategy is defined, the following four directions should be considered for special emphasis:

1. Basic research on developing world cultivars and pathogens will be essential; the new technologies will permit accelerated application of new discoveries.

2. Developing nations should be assisted and encouraged to work with the new technologies themselves; the new technologies are widely accessible.

3. Communications among public and private researchers and developed and developing nation researchers should be fostered; those traditionally working in the area and the new institutions and actors now entering the area can then gain from one another's ideas.

4. Ecological and safety issues of the new technology should be explored early and cooperatively; they may otherwise seriously slow all applications.

Supporting conclusions

1. The new technologies are almost certain to bring enormous benefits to the developing nations. Not only can these technologies help increase yield or avoid disease; they are also likely to be appropriate in the sense of requiring relatively small investment and relatively little centralization or change in the social structure. There will be social costs -- land speculation in areas made arable by new stress resistant cultivars or balance of trade difficulties in competing with new cultivars introduced more rapidly in the developed world -- but these costs will be transitional and can sometimes be avoided by careful planning.

2. The new technologies also pose important regulatory problems. The containment and ecological issues have already received public and legal community attention; in the long run, it may be harder to resolve the health and safety questions of using varieties incorporating new genetic properties (e.g. animals with modified hormone balances or plants that obtain disease resistance through biological manufacture of chemicals that may affect human consumers).

3. A variety of developing nations already have substantial programs in tissue culture -- some public, some private, and some parastatal. These programs appear to emphasize export crops, and are generally oriented toward large-scale production of

vegetative propagating material or toward meristem culture for the removal of pathogens from propagating material.

4. AID, directly or working through its missions, may want to consider expanding its efforts to encourage these national programs through programs such as scholarship and exchange grants, loans or a bank approach for new projects, or assistance in programs for national planning and application of the technology.

5. In nearly all the developing-world agricultural biotechnologies, however, the risk of underinvestment is almost certainly greater than that of overinvestment. In many fields and for many nations, the International Agricultural Research Centers (IARCs) will be essential to technology development and application.

6. The first applications of genetic engineering, which may affect the developing world farmer by sometime in the 1990s, will be primarily in the animal, fermentation, microbial, and diagnostic areas rather than in the plant areas. Many of these technologies will be developed privately in the developed world, but will be available directly to the farmer in the form of finished products in current marketing channels, or be available for IARC use and application through licensing arrangements.

7. For plants, the first genetical-engineering applications will probably be single-gene disease, herbicide, or stress resistance -- possibly by sometime in the 1990s, possibly by the turn of the century. The more complex and multi-gene developments (like transfer of nitrogen fixation capability to new plants) will probably come later.

8. Although this point and the next are among the most important and most uncertain -- the privately developed plant technologies will usually be available on a research contract basis. Hence, the IARC's will usually be able to work in essentially a traditional fashion, perhaps, for example, contracting on occasion to have a specific gene inserted in a particular crop line.

9. For a few crops, however, and it is perhaps most likely to happen with those that have great economic importance in both the developed and the developing worlds (e.g. maize, wheat, rice, soybeans, and sorghum), the new technologies may encourage the evolution of global vertically-integrated seed firms. Such firms might compete in the entire world market and be willing to sell their technology only in seed form. Probably, they will charge a cost premium, but it will be only a fraction of the benefit of the new varieties to the farmer.

10. For these crops, the public sector may eventually want to consider refocussing its attention. The issue will not be posed for many years, but when it is posed, the public sector might place greater emphasis on germ-plasm maintenance, or do

more research on specific tropical pathogens, or applications technologies. It might also want to ensure that some advanced public releases are available to contribute to competition in the market. Moreover, nations which are too small or poor to afford their own large-scale research programs or to offer a large-enough market to encourage private research will continue to require breeding assistance or assistance in establishing cooperative programs.

11. The CGIAR and AID may also want to consider new kinds of missions arising from the new technologies, e.g. help in designing and training the new bureaucracies needed for some of the new regulatory tasks, or perhaps taking the lead in developing streamlined procedures to avoid replication of the regulatory structure from nation to nation.

12. The Plant Variety Protection Acts and breeders' rights generally will become relatively less important in this area, while the regular patent system, will become critical.

13. The IARCs will want to consider much wider use of the regular patent system, less to avoid someone elses' patenting of an innovation made at an IARC than to assist in commercialization of innovations and to obtain "bargaining chips" to help in working out practical conflicts. It is likely that most practical applications of the new technology willl require practice of a number of patents held by a number of different firms. Possession of some of those patents is likely to help in negotiating a cross-license.

14. The new technologies will require and benefit from even greater emphasis on basic research. The need for research on a plant or a pathogen's action is likely often to be the critical step in applying the new technologies -- and the new technologies will also be able to help in obtaining this knowledge.

Acknowledgements

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BACKGROUND

Agricultural research expenditures themselves are uncertain; the numbers for public biotechnology research have not been carefully assembled; those for private biotechnology research and for the division between agricultural and other goals are even less well known.

The numbers of Chart I (page 7) are therefore to be taken only as indications of order of magnitude relationships. The new biotechnology, although very important, is still absorbing only a fraction of the resources being devoted to agricultural research. For both types of research, the public sector is still doing much more than the private sector. And for both types, the resources devoted to developed world concerns greatly outweigh those devoted to the developing world.

Public-Private Pattern Within United States

In the United States plant breeding system, public institutions such as the land-grant schools have traditionally conducted most of the basic research underlying the introduction of new varieties. Private firms have then developed finished varieties, using germ plasm obtained directly from the universities or indirectly through a state crop improvement association.

This pattern has changed somewhat since the introduction of the Plant Variety Protection Act (PVPA) of 1970 (amended in 1980), which authorized a patent-like protection of sexually reproduced plants. According to the leading studies of the effects of this act, the act has encouraged private research in a number of crops. (2) Such research had previously been concentrated on corn (maize), where the use of hybrids permitted an effective form of property right. It now expanded to a number of other crops, and particularly soybeans. There was also a seed

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(2) L.J. Butler & B.W. Marion, "An Economic Evaluation of the Plant Variety Protection Act," p. 106, (University of Wisconsin), December 1983; R.K. Perrin et al, "Some Effects of the U.S. Plant Variety Protection Act of 1970," (Economics Research Report No. 46, North Carolina State University), August 1983; R.E. Evenson, "Intellectual Property Rights and Agribusiness Research and Development: Implications for the Public Agricultural Research System," Amer. J. Agr. Econ., v. 65, p. 967 (1983).

CHART I

ESTIMATED RESEARCH EXPENDITURES AND TRENDS

AGRICULTURAL RESEARCH AND BIOTECHNOLOGY - 1983

(All expenditures in millions of 1983 dollars)

ITEM	EXPENDITURE	TREND	COMMENTS & SOURCE
			Total Agriculture Research
Public - World	13,000	+7%	Trend line fitted to OTA, An Assessment of the United States Agricultural Research System, Table 14, p. 162 (1981).
Private - DC	1340	+7%	Estimated as 20.1 % of above, using factor calculated from Boyce & Evenson, National and International Agricultural Research and Extension Programs, Table 1.1, p. 3 (Ag. Dev. Coun. 1975).
Public - LDC	1780	+10%	Oram & Bindlish, Resource Allocations to National Agricultural Research: Trends in the 1970's, Table 16, p. 60 (ISNAR & IFPRI, Nov. 1981), adjusted to 1983 dollars.
Private - LDC	50	+10%	Estimated as 2.82 % of above, using factor calculated from Boyce & Evenson supra, and adjusted to 1983 dollars.
			Biotechnological Agriculture Research
Public - DC	300 ?	?	Very rough estimate, assembled and extrapolated from charts in Chapter 13 of OTA, Commercial Biotechnology: An International Analysis, p. 307 (January, 1984).
Private - DC	70 ?	?	Very rough estimate, based on the United States expenditures reported in J. Murray, "Patterns of Investment in Biotechnology II," Bio/technology 2, p. 332 (April, 1984) and assuming that foreign expenditures are comparable to those of United States. Murray's numbers show an 8% decline from 1982 to 1983; there may have been an upturn since. See A. Klausner, "Agriculture and Supply Attract Biotech Startups," Bio/technology, v. 2, p. 774 (September 1984).
Public - LDC	30 ?	+10% ?	Very rough estimate, based on existence of major programs in several nations and estimates of $10 million to $100 millionfor several years in total Brazilian program quoted in Rosillo-Calle & Rothman, "The Brazilian National Biotechnology Programme," Bio/technology, 2, p. 421 (May, 1984).
Private - LDC	10 ??	+10% ?	Absolutely intuitive personal estimate extrapolated from programs learned about in Columbia and the Philippines.

price increase, but this increase amounted to only about 30 percent of the value of the increased yield. (3)

Even without taking the new biotechnologies into account, this research structure was under pressure by the early 1980's, deriving from arguments by some private firms for increased control over the development and marketing of finished varieties. This was partly a simple division of labor argument that public funds should properly be concentrated on the longer range, riskier, lower payoff, more basic studies. But marketing considerations went nearly as far: a firm could market much more effectively if it had a monopoly on the particular variety it was selling -- otherwise its sales efforts could be offset by a competitor the following season. The counterarguments -- made by some of the smaller seed firms as well as by many in the land grant schools -- were that competition within a variety or among varieties would help hold down prices, and that public sales may be important in maintaining this competition. (4)

The new biotechnologies intensified these trends (5) -- for these technologies were based, at least in part, on research carried out in publicly financed laboratories, but commercialization took place through private firms which held regular patents on inventions to which university research had often contributed. These private firms were typically start-up firms that, at first, had little trouble raising significant sums of venture capital, and often later developed ties with chemical, pharmaceutical, or seed companies. The rate of formation of these firms may have peaked around 1981-82; they tended, later on, to have somewhat more difficulty raising capital. Nevertheless, many very capable people continued to move from the public to the private sector and there appeared to be another upturn in financing in 1983. (6)

Some other developed nations saw a similar growth of small firms. But in all such nations, this growth was paralleled by increasing interest among large chemical and pharmaceutical

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(3) Butler at 85-86.

(4) See, e.g. Butler, supra, at 110.

(5) See L. J. Butler & A. A. Schmid, "Genetic Engineering & the Future of the Farm and Food System in the U.S." Michigan State University Cooperative Extension Service, The Farm and Food System in Transition No. 15 (undated); National Association of State Universities and Land-Grant Colleges, Division of Agriculture, Committee on Biotechnology, Emerging Biotechnologies in Agriculture: Issues and Policies; Progress Report II (November 1983).

(6) See OTA 1984, Chapter 4, "Firms Commericializing Biotechnology," p. 61; A. Klausner, "R & D Limited Partnerships -- A Fading Rainbow?" Bio/technology, v. 2, p. 676 (August 1984).

firms, which created their own biotechnology laboratories, or entered contracts with or acquired small firms. The larger firms tended to have a longer range view than the small ones for they were under less immediate pressures from their capital souces. Ultimately, the structure of the industry would depend on the economic competition and balance between these two types of firm. Both, however, urged strong intellectual property protection and continued public support for basic research.

Environmental regulation of agricultural biotechnology also raised questions about the future of the technology and the relationship between public and private sectors. Some agricultural uses of biotechnology involve placing modified agents in the environment, and thus present ecological risks. Under United States law, the authority over such action when conducted by a private individual or firm is still somewhat unclear. The government may impose control on its own actions and, by contract, on those it supports; it has been enjoined from permitting a release before filing an environmental impact statement. (7) Private firms are not formally covered, but may accept the same restriction out of a combination of public relations reasons and the fear of litigation and liabilities. Many aspects of the issue were being debated within Congress and the executive during 1984. (8)

Public-Private Relations on the International Level

This pattern was a microcosm of the global one -- a situation in which the international public sector was facing pressures similar to those of the land-grant schools, in which the role of intellectual property systems was possibly increasing, and certainly controversial. In addition, there were deep divisions over the benefits and implications of the new technologies for the developing world. There were concerns that the new plant breeding technologies would create significant economic costs for the developing nations, or create significant social disruption (of the pattern envisioned by critics of the Green Revolution), and also concerns that these technologies might only slowly become available to the developing world at all. (9) An estimate of the role of private enterprise will be

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(7) Foundation on Economic Trends v. Heckler, 14 ELR 20467 (DDC, May 16, 1984).

(8) E.g. Staff Report to the House Committee on Science and Technology, The Environmental Implications of Genetic Engineering, 98th Cong., 2d. Sess., Serial V, February, 1984.

(9) See F. Buttel, "Biotechnology and Agricultural Research Policy: Emergent Issues," Cornell Rural Sociology Bulletin No. 140 (July 1984); M. Kenney & F. Buttel, "Biotechnology: Prospects and Dilemmas for Third World Development," Development and Change (forthcoming as of March, 1984); W. Roca, "Biotechnology:

presented in the following section of this report; other factors are noted here.

The roles of the CGIAR network and other public international research institutions have been, in the developing world, very similar to those of the land grant universities within the United States. In general, these centers take new cultivars to the level of seeds essentially ready to multiply and release. Developing world national governments then take the cultivars and multiply and release them according to their own domestic institutional preferences -- typically through their Ministries of Agriculture, sometimes using commercial seed multiplication farms. Moreover, like the land grant schools, these centers play an important educational function. And they have long exchanged germplasm freely and generally avoided seeking breeders' rights protection for their cultivars.

Again, just as with the land grant universities, the CGIAR centers are being urged to restrict themselves to more basic research. This time, the pressure is derived from their clients, the developing nation ministries which are becoming more and more sophisticated and capable, and are eager to take on various steps of breeding. Presumably, the motivation is not (at least in the short term) so much economic as it is these ministries' enthusiasm to develop the technology themselves -- the CGIAR system does not charge the developing nations for the new varieties. There might, however, be a long-term economic motivation based on the developing nations' interest in developing a domestic capability to hold up against foreign seed firms.

In addition, there are a surprising number of new developing world biotechnology programs. Some of these would be elaborate international efforts such as a proposal for Latin American cooperation (10) or the center proposed by the United Nations Industrial Development Organization (UNIDO), which has since led to an Indian-Italian initiative. (11) There are already unilateral national programs in a variety of nations such as

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(9) (continued) Opportunities for Agricultural Research in Latin America," (Presentation at the BID/CIMMYT Workshop of Latin American Agricultural Research Institutes; CIMMYT, Mexico, September 1984).

(10) C. Orrego, "New Cooperative Effort Planned for Latin American Biotechnology," Bio/technology, v. 1, p. 413 (July, 1983); W. Sawyer, "Interciencia Symposium 'Biotechnology in the Americas: Prospects for Developing Countries,'" Interciencia, v. 8, p. 420 (Nov.-Dec. 1983).

(11) D. Dickson, "UNIDO Hopes for Biotechnology Center," Science, v. 221, p. 1351 (30 Sept. 1984); B. Zimmerman, "The International Center for Genetic Engineering and Biotechnology," Bio/technology, v. 2, p. 55 (January 1984); B. Zimmerman, "India

Brazil and India. (12) Instead of setting up new centers, some nations are seeking national coordination of their university programs or considering research contracts with existing developed world firms. In several nations, indigenous developing nation firms have started their own biotechnology programs, sometimes alone, sometimes in cooperation with developed nation firms. (13)

Some of these programs will undoubtedly fail. Their very number poses new questions of coordination of research efforts and of competition for resources and personnel. There programs may also intensify the temptation for national governments to protect their own biotechnology establishments against foreign competition. Far more important, however, the programs can make a major contribution to development for the opportunities are enormous. And success in these programs is the ultimate way to alleviate developing nation concerns about technological dependence.

Publicly-funded international agricultural research will thus have to steer a course defined by a new interplay between public and private enterprise -- not just in the developed world, but, in an analogous form, in the developing world too. The AID and CGIAR system will, like the United States land grant institutions, move away from the areas being developed by private enterprise and its private and public analogues in the developing world. The move back toward basic research, however, will not be so clear a direction as for the land grant schools, for the CGIAR institutions have prided themselves on their interest in actual application. Moreover these development institutions must take into account the roles of the new agricultural and biotechnology research programs in the developing world as well as those of the new programs in the developed world.

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(11) (continued) and Italy Force Compromise on International Biotech Center Site," Genetic Engr. News, p. 3 (May/June 1984).

(12) See, for example, F. Rosillo-Calle, "The Brazilian National Biotechnology Program, Bio/Technology, v. 2, p. 421 (May, 1984).

(13) For an example in the pharmaceutical area, see "Meeting of Minds; Two South Korean firms hope joint ventures with US-based partners will give them a flying start in genetic engineering," Far Eastern Economic Review, p. 96 (8 March 1984).

DETERMINANTS OF PRIVATE BIOTECHNOLOGY DEVELOPMENT

As suggested at the beginning of this paper, AID and the CGIAR system will be in an environment shaped in large part by private agricultural biotechology. The rate and manner in which the private biotechnology firms will move into developing-world agricultural markets thus becomes a crucial question.

Officers of the smaller United States firms, along with some academics, usually argue that the developed world private firms will long be unable to reach the developing world. They might like to reach this market, but they expect it to be so small that it cannot attract much investment. Moreover, with an eye on the debt crisis, they fear that they would be unable to receive a hard currency return on any investment.

They do admit some special cases. If a technology is developed for the developed world market and directly applicable to developing nations without additional research, it will readily be marketed in developing nations as well as developed. Plantation companies, which typically earn hard currency, are also able to invest in the new technologies; there are already a number of examples. (14) Save for these special cases, they argue, the new technologies will not be made available to the developing world for a long time without some form of public subsidy.

The barriers may be even stronger than careful economic analysis would suggest. The smaller private firms are attempting to raise capital in a market that seeks a short-term return and has its own swings and moods. Those who grant funds to smaller companies (whether in the form of venture capital or of research contracts from chemical or pharmaceutical firms) tend to look primarily to the developed world market in analysing return on investment. The risks there appear big enough, so that these investors may not even consider a developing nation market, unless they have especially good information about an especially promising opportunity.

Thus, they may be missing potentially profitable markets in the developing nations and may be leaving opportunity open to indigenous firms in developing nations. Such firms are already emerging in areas like tissue culture, where the technology is relatively accessible -- and perhaps even labor-intensive enough to give developing nations a comparative advantage. Moreover, many developing-nation governments may be interested in helping such firms emerge and find these markets.

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(14) See the list in Kenny & Buttel, supra n. 9. The crops involved are unlikely to be of interest to CGIAR.

For a large firm that already has a marketing network there, developing world may look very different. As is often strongly argued by critics of these firms, such a firm might be interested in the biotechnology complementary to its current product line. Thus, a seed firm might apply the new technologies to develop new hybrids, or an agrichemical firm might introduce a crop resistant to its herbicide. The first is happening -- in the Philippines, for example, new hybrids are already being produced (albeit with traditional methods). For the agrichemical firm, the arguments are less clear. The developing world market is a relatively small part of the world market for these firms. Moreover, the most probable early product is a herbicide resistant crop, and the economics of herbicide use are relatively unfavorable in a nation with a foreign exchange crisis or a relatively low wage rate.

Perhaps of greater importance, the larger firm sometimes has a longer-term viewpoint and is more willing to make large investments that will yield a return only after a number of years. This is practical only if the firm can recover its investment through sales in a large market, such as that for seeds. These firms, therefore, may attempt to integrate a capability in the technology with a capability in the marketing, and, in order to protect their technology, seek to sell it only as embodied in finished products.

This question of vertical integration is critical for the public development institutions. When a smaller firm succeeds with an important innovation, it might be willing to supply the technology to public or private entities under contract or license. In at least some cases, larger firms may be unwilling to do so.

It is very early to estimate which pattern will dominate -- no company officer interviewed said that his or her firm had yet taken a clear marketing decision in favor of vertical integration. The patterns may exist side by side, or one pattern may prove significantly more efficient and be forced on all firms by competition. Among the relevant factors are the degree of competition in the markets for technology and for the finished product, the relative risks in the two markets, the need to integrate management of the two levels, and the extent to which the technology can be protected by patent law rather than vertical integration.

Most of these factors vary from biotechnology to biotechnology -- and the estimates must be made on a technology by technology basis. But the patent structure is so important in shaping the incentives to vertical integration and the regulatory issues so important to market access and timing that they deserve initial discussion.

The Patent Structure

There are foreign analogues to the United States PVPA, all coordinated by an international convention, the Union pour la protection des obtentions végétales (UPOV), under which nations commit themselves to provide breeders' rights protection roughly comparable to that of the United States PVPA. Most West European nations are members, along with the United States and South Africa; many others, including developing nations, have been strongly lobbyed to participate, but have generally rejected the concept. (15)

This approach, of providing what amounts to industrial property protection for plants, has evoked serious opposition in the form of a populist movement that is fearful of the power of international seed firms as well as of a possible loss of genetic diversity. The arguments are fundamentally that corporations holding breeders' rights might misuse their monopoly power and charge exorbitant prices to developing nations. Moreover, they argue that it is inequitable for a corporation to be able to charge a monopoly rent for a seed derived in part from germplasm obtained from a developing nation without fee. (The breeders' rights proponents respond that the monopoly rent is intended to encourage the breeding process and that the germplasm is still available for others for breeding purposes.) Supplementing these patent-monopoly based arguments is a less-sharply argued fear that intellectual property rights in this area will discourage free exchange of germplasm and cause a loss of genetic diversity. (16)

While this political attention is focussed on breeders' rights, private firms in the developed world are moving quite quickly toward use of the regular patent system to protect biotechnological advances, and many biotechnology firms appear to regard these patent laws as more important than the breeders' rights laws. Partly, this is a matter of what can be covered under the exclusive right. Although each nation has its own detailed rules, a number allow the patenting of novel life forms, of chemicals and processes of biotechnological importance,

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(15) See generally OTA, 1984 at 564-74; J. Barton, "The International Breeder's Rights System and Crop Plant Innovation," Science, v. 216, p. 1071 (4 June 1982); N. Byrne, "The Agritechnical Criteria in Plant Breeders' Rights Law," Industrial Property, v. 22, p. 293 (October, 1983); S. Williams, "Protection of Plant Varieties and Parts as Intellectual Property," Science, v. 225, p. 18 (6 July 1984).

(16) See P. R. Mooney, "The Law of the Seed," development dialogue 1983:1-2, p. 1; and Seeds of the Earth (1979). Breeders' rights are also one of the issues underlying the proposed International Undertaking on Plant Genetic Resources. See, for example, Plant Genetic Resources; Report of the Director-General, ¶¶ 28-32 (FAO document C 83/25, August, 1983).

and of the use of specific strains of microorganisms for the conduct of biological fermentations. Building on Diamond v. Chakrabarty, (17) United States firms are seeking regular patents for novel genes and plasmids as well as for plants that would also be protectable under the PVPA. (18) The law will not be clear until these patents have been tested in court, but the probability is that at least those genes or plasmids and organisms modified from nature will be patentable.

The Chakrabarty language gives United States patent laws a broad scope. Many other nations, especially developing nations, offer much less extensive patent rights in the biological area. Nevertheless, some offer patent protection to chemicals of biological interest. And some of the nations that refuse patents to pharmaceuticals or to microorganisms may offer protection to methods of producing the pharmaceuticals or using the microorganisms. There are much greater differences with respect to the mechanics of patenting, the relationships between publication and patenting, and the precise scope of the duty to provide samples of microorganisms as a form of disclosure of the way to practice the invention. (19)

When a firm has the choice, it would usually prefer the regular patent law over breeders' rights. There are several reasons beyond familiarity and the fact that the regular patent laws cover innovations not covered by the plant variety acts. The regular patent provides broader rights and easier enforcement. For example, a breeders' rights certificate is not generally infringed by use of the protected variety in research or by reuse of the seed by the farmer. In contrast, a utility patent on a gene or the plant containing it confers, at least theoretically, the rights to prevent another from using the plant in research and to prevent a farmer from reusing the harvested crop as seed. The patent law contains a limited research exception, (20)

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(17) 447 U.S. 303 (1980).

(18) OTA, 1984, pp. 383-407; Neagley, Jeffrey et al, "Section 101 Plant Patents-Panacea or Pitfall?" AIPLA Select Legal Papers, Vol. II, No. 2 (January 1984).

(19) See OTA, 1984, pp. 564-73; D. Chudnovsky, "Patentes y marcas registradas en la actividad farmacéutica," comercio exterior, México, 33, p. 497 (1984).

(20) The exemption is more likely to be applied to non-commercial that to commercial experimentation. Its expansion was recently rejected in a case whose importance was probably overstated in the scientific press. See Roche Prod. Inc. v. Bolar Pharmaceutical Co., Inc., 733 F.2d 858 (Fed. Cir. 1984); J. Fox, "Patents Encroaching on Research Freedom," Science, v. 224, p. 1080 (8 June 1984); K. Berkowitz (Hoffman-La Roche), Letter, "Patents and Research Freedom," Science, v. 225, p. 366 (27 July 1984). Reflecting European trends, the United Kingdom Patents Act

and a firm would usually hesitate to sue its customer for infringement, but these scope differences are still enough that firms would prefer the utility patent coverage.

The effective scopes of coverage also differ. There is controversy as to whether the United States plant patent system for asexually reproduced plants permits a United States grower of a protected flower variety to prohibit import of cut flowers grown abroad from protected materials. (21) A regular patent would almost certainly be held to confer parallel protection; but the total sweep of that protection is not yet clear and may be nearly as important as the definition of what can be patented. Thus, a patent on a gene will almost certainly be regarded as infringed by selling seed containing the gene; much harder issues are raised by the question whether sale of food grown from the seed should be regarded as an infringement. (22) The patent system also contains intrinsic limitations on the ability to claim analogous applications of a new idea, for patent disclosure has to enable others to practice the invention. An important recent case thus rejected an effort to extend rights on specific bacterial strains for producing a new antibiotic to attempt to reach all bacteria of the same species that produced the antibiotic. The court found an enabling disclosure only with

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(20) (continued) 1977 provides a broader exemption, § 16-60 (5).

(21) Industry has been urging clarification for some time. See, for example, American Bar Association Section of Patent Trademark and Copyright Law Resolution No. 24 of 1976 (1976SP95-R24), reproduced in 1984 Committee Reports, p. 71; a parallel United Kingdom controversy is reported in G. Dworkin, "The Plant Varieties Act 1983," 10 EIPR 270 (1983).

(22) The issue was raised in the British debates surrounding 1983 amendments to the Plant Varieties and Seeds Act, 1964. Dworkin, supra n. 21, argues that the plant protection right was never meant to stretch to products such as tinned or frozen fruits and juices. He also regards the fruits themselves as not meant to be covered; some private United States proposed revisions, however, would reach fruits as well as cut flowers. In the regular patent context, the issue typically arises from the use of a patented process to make goods that are imported. British law once gave the patent holder extensive rights but has begun to narrow those rights. Thus, Patents Act 1977 gives protection only against a "product obtained directly" by means of the patented process, § 16-60 (1)(c) and Beecham Group Ltd. v. Bristol Laboratories Ltd, [1978] R.P.C. 153 (H of L) includes dicta suggesting that a patent on a pharmaceutical intermediate would be infringed by use of that intermediate ""in the manufacture of a semi-synthetic penicillin, but not of a wholly different product like, say, glue," p. 204.

respect to the strains that were actually used and placed in a depository. (23)

Even when the law of infringement is clear, it may be hard to show that a particular seed is actually derived from one's own protected variety. Regular patent protection of a particular gene, for example, might be easier to enforce in practice. The regular patent on a process, however, is regarded as less effective than one on a product. It may be easier to design around a patents on a process, (24) and, in United States law, the legal procedures for responding to imports made through an infringing process are more complex that those for responding to imports that infringe a product patent. Nevertheless, the contrast with PVPA favors the regular patent.

A final reason why the regular patent system will become relatively more important is the fact that it is more global. A patent, plant or utility, normally confers rights only within the nation issuing the patent. Thus, patenting in the United States protects against competition within the United States and may also protect against import of products made abroad in infringement of the patent. To protect foreign markets, it is necessary to obtain national patents in the nations involved. In spite of the relatively narrow scope of biotechnology patent protection in many nations, the network of rights available is much stronger than that under the breeders' rights laws.

The foreign coverage must, however, be sought at essentially the same time as domestic coverage. Under the law of some nations, the filing of a patent application anywhere in the world constitutes a publication, which would prevent the issuance of a patent, save for a priority period (generally one year) set by treaty. (25)

These patent laws, and their exact scope, are likely to be critical to firms' decisions whether or not to license their technology to third parties, and therefore critical to the structure of the industry. Presumably, profit incentives will push a firm to sell its technology in as applied a form as possible, i.e. to sell seeds rather than research -- but the need for capital and the realties of competition in the product markets, may force it instead to license the technology for a fee which comes as close as possible to the total profit available from the technology. The greater the patent rights, the greater the chance that firms can achieve that profit through licensing rather than through direct participation in the product market.

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(23) Ex parte Jackson, 217 U.S.P.Q. 804 (1983).

(24) See "Patent Issues Cloud Biotechnology's Future," Bio/Technology, May 1984, p. 385.

(25) For an introduction to this very complex area, see OTA 1984, pp. 394-95.

Should patent laws appear too weak, firms may attempt to protect their technology less formally, as through trade secrecy or "biological protection." The trade secret approach will sometimes be attractive: the firm will seek actually to control the information. It does not then have to reveal the technology as required by the enabling disclosure that is part of a patent application. Nevertheless, it risks litigation should a competitor make the same discovery and file for patent protection. Moreover, it is unprotected against the possibility that a competitor can examine its finished product and "back-engineer" to the trade secret. (26) And all firms, whether or not they are emphasizing a trade secrecy approach, will be concerned about the distribution of cell lines and other "tangible research property," for commercial reasons, and in some cases out of privacy concerns. (27)

The "biological protection" alternative has proven very difficult to evaluate. The idea, whose reality is most strongly supported by those very committed for or against the role of private enterprise in biotechnology, is that a firm could design a plant so that the second generation could not be used. Hybrids already have this property, forms of second generation sterility might be envisioned, and there might be ways of building in a lethal gene which would be repressed by an additive sold with the seed. Which of these will actually be used is not at all clear. Firms are likely to prefer to offer their innovations in the form of hybrids. With some of the other techniques, however, seed production might be so much more expensive that the approach would be economically unwise. Moreover, the market available with these approaches is always limited by the farmer's ability to choose traditional (but probably lower yield) seed, and a firm using these approaches is vulnerable to a competitor who offers a comparable product without the built-in protection.

Health and Environmental Regulation

Questions of health and environmental regulation may become pacing issues in the development of some agricultural biotechnologies. Application of the new technologies to human medicine fits fairly easily into existing regulatory frameworks for medicines and vaccines; the same may be true for veterinary medicine. In other areas, however, regulatory concerns may significantly slow development. Moreover, the costs of satisfying regulatory requirements will, in some areas, give large firms a comparative advantage over smaller ones, which cannot as easily raise the capital for extensive testing programs.

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(26) See generally OTA 1984 at 391-92, 398-99, and Appendix G.

(27) Several universities including Stanford and Wisconsin have already developed policies in this area, OTA 1984, p. 420.

Initial efforts at biotechnology regulation sought to ensure containment of experiments in order to decrease the risk that a harmful new organism might inadvertently be spread throughout the world. Many nations have enacted such rules. (28)

Many agricultural applications, however, pose a much more difficult question: which modified organisms should be released? A balancing of risks and benefits is therefore needed. The current ability to predict the ecological risk is quite limited. (29) Moreover, the balances cut across traditional jurisdictional boundaries. They may, for example, involve a balance of, on the one side, environmental risks or human health risks derived from a modified crop plant, and, on the other side, important increases in yield and perhaps benefits to the safety of agricultural workers. These different concerns and benefits have traditionally been the province of a variety of different agencies. Even when jurisdiction is resolved, it will not always be clear which are the more conservative approaches to the uncertainties.

In the United States, in 1984, Congress and the Executive were attempting to deal with the jurisdictional issues. (30) But the question of what standards to apply was likely to turn out to be harder to handle and more likely to produce litigation. Allocation of responsibility among different agencies would neither clarify the standard nor avert litigation based on the differences in the various statutes that might be applicable. The first controlled release, of a microorganism conferring frost resistance, was being held up by court order. (31) Fear of damage suits by private individuals might also deter particular experiments or the development of particular products.

Although the United States is uniquely litigious, similar legal uncertainties are likely to arise in many nations; the

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(28) OTA, 1984, pp 550-555.

(29) See, for example, Sharples, "Spread of Organisms with Novel Genotypes: Thoughts from an Ecological Perspective," printed in House Committee on Science and Technology, Hearing on Environmental Implications of Genetic Engineering, 98th Cong. 1st Sess., No. 36, p. 157 (1983); Giles & Whitehead, "Reassociation of a Modified Mycorrhiza with the Host Plant Roots (Pinus Radiata) and the Transfer of Actylene Reduction Activity," reprinted in House Committee on Science and Technology, Staff Report, supra n. 8, p. 53 (unanticipated pathogenic combination of nonpathogenic organisms)(1984).

(30) House Committee on Science and Technology, Hearings, supra n. 29 and Staff Report, supra, n. 8; White House Memorandum on "Cabinet Council on Natural Resources and Environment Working Group on Biotechnology," (April 30, 1984).

(31) Foundation on Economic Trends v. Heckler, supra n. 7.

issues really are new and complex. But, everywhere, the legal issues will slow some agricultural technologies -- and, as will be seen below, some much more than others.

TECHNOLOGY BY TECHNOLOGY ANALYSIS

With this background, it is possible to estimate the extent and the economic pattern in which each of the new techologies will be applied in the developing world. Chart II, on page 22, presents an outline summary of the time the various technologies are estimated to be available and briefly notes the policy questions expected to be raised for developing nations along with those raised for the international agricultural research structure.

Animal Technologies

The various new animal technologies present a bewildering array of alternatives. Moreover, the institutional pattern for animal research is quite different from that for plant research, which is the central focus of this paper. There are a number of international animal research centers, and some work is being done under CGIAR, such as that at the International Laboratory for Research on Animal Diseases (ILRAD). In general, however, in comparison with plant research, private organizations have played a relatively larger role, particularly in areas like the manufacture and distribution of vaccines or the application of artificial insemination. Moreover, the intellectual property pattern is quite different. Many nations have long allowed patents on animal pharmaceuticals or processes to make them; but there is no animal analogue to breeders' rights.

Chemicals and pharmaceuticals

A wide variety of sophisticated chemicals and pharmaceutical products for animal agriculture are receiving significant research attention and some are already becoming available -- this is an area where single-cell manipulation is usually all that is needed, where the regulatory difficulties are minor, where the market potentials are relatively clear, and where the time requirements for testing and application are relatively limited. Hence, it is one of the first likely to benefit from the new technologies.

Thus, biotechnically-based vaccines are already on the market against scours, and the vaccine area is widely recognized as offering especial promise. (32) Monoclonal antibodies may serve a variety of purposes such as research, diagnosis, embryo

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(32) OTA, 1984, pp. 163-67; Priorities in Biotechnology Research for International Development, supra n. 1, p 67-86.

CHART II

EXPECTED AVAILABILITY AND SPECIAL POLICY ISSUES FOR VARIOUS AGRICULTURAL BIOTECHNOLOGIES

TECHNOLOGY	TIME TECHNICALLY AVAILABLE	TIME COMMERCIALLY AVAILABLE	SPECIAL POLICY ISSUES
ANIMAL TECHNOLOGIES			
Vaccines, BGH, diagnostic, etc.	1984	1984-85	Need for health & safety regulation; reaching smallholder as well as large farmer; need for new basic research on specific diseases.
MICROORGANISM TECHNOLOGIES			
Bioprocessing	?	?	Unpredictable changes in commodity demands.
Innoculants & microbials	1984	1986	Ecological questions; need for basic soil and pest research.
PLANT TECHNOLOGIES			
Gametocides, growth regulators	1984	1985	Market effects of hybridization; question whether chemicals will be sold separately; opportunity to incorporate into breeding programs.
Tissue culture	long since available		Developing world comparative advantage; opportunity to use the technique.
Plant genetic manipulation			For a few crops, suppliers may be willing to sell only seeds, as opposed to technology; for all, additional basic research will be beneficial; for some, ecological issues.
Disease resistance	1985-90	1990-95	Health and safety issues.
Stress resistance	1985-90	1990-95	Change in land use patterns.
Herbicide resistance	1985-90	1990-95	Economic and environmental concerns.
Protein balance change	1990-95 ?	1995-2000	
Nitrogen fixation	1995-2000	2000-2005	Major balance of payments benefit possible.

and spermatazoan sexing, and organic contaminant detection. (33) Genetically modified microorganisms are being used to produce bovine growth hormone -- now in field trials -- and bovine interferon is already being marketed. (34) Other possibilities include new feed additives, and perhaps the development of single cell protein (SCP) for feed purposes.

Many of these materials are being developed by private industry and are likely to be directly usable in developing nations. This would be the case for vaccines against diseases common to the developed and developing world; it would also be the case for various feed additives and such new products as bovine growth hormone. The market will almost certainly ensure that these new products will be made available to developing nations as the local costs (allowing for the debt crisis and the effective costs of hard currency) fall below the expected value of the benefits such as animal lives saved through a vaccine or increased milk production from bovine growth hormone.

The calculation must naturally allow for the costs of adapting the pharmaceutical to the local market, which almost certainly requires some testing and may require a regulatory review. For chemicals for human use or for initial applications of chemicals for animal use, these costs are generally much higher than those of basic research -- but, after the first approval, testing for use in new animal markets is likely to be much less expensive. Distribution and infrastructure will also be important factors, and perhaps nearly prohibitive in some nations. Some of the products, for example, are best used following a veterinary diagnosis; some require refrigeration.

Not all of the new animal technologies will be directly applicable to the developing world, nor is the market likely to support research oriented specifically to developing nation needs. As with the "orphan disease" problem for humans, subsidies or new public research are the only possible approach in these cases, and will sometimes be critical. One key example is the work on foot and mouth disease, a disease that is prevalent in many parts of the developing world and is being studied in a number of public laboratories, some of which are using cloning procedures in their research. (35) Another is ILRAD's work toward

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(33) R. Gatz et al, "Monoclonal Antibodies: Emerging Product Concepts for Agriculture and Food," Bio/technology, v. 1, p. 337 (June, 1983).

(34) R. Kalter, "Biotechnology: Economic Implications for the Dairy Industry," Dairy Marketing Notes, v. 3 (Cornell, Fall 1983); A. Klausner, "IML Introduces Interferon Product for Cattle," Bio/technology, v. 2, p. 841 (October 1984).

(35) OTA, 1984, pp. 162-65; L. McCauley, Animal Diseases in Developing Countries; Technical and Economic Aspects of their

the conquest of specific parasitic diseases -- and it appears likely that the new research tools offerred by biotechnology will be especially important in the study of parasitic diseases generally. (36)

Clearly, AID and the centers should consider research in these areas, but only when the biotechnological approach is likely to be more cost-effective than more traditional approaches to improve the health of developing world livestock. Moreover, when the centers do work in these areas, they will probably expect to apply the research through arrangments with commercial firms, which bring production experience and knowhow, and sometimes a marketing network as well. To the extent that production assistance is needed, the public entities can simply contract for manufacture of the chemical or vaccine (as has been done in some cases in the procurement of oral contraceptives). If a marketing network is needed as well, the entire distribution might be turned over to a firm.

As will be discussed below, in these cases, the public entity will probably want to obtain patent protection for the product, so that it can grant a license to a private firm. Even so, the terms of commercialization are likely to be controversial, as exemplified by the controversy which has already arisen over license terms for development of a malaria vaccine. (37) The contractor wants as exclusive a package of rights as possible, particularly if it is supplying important production knowledge; the donors want to keep the developing world price as low as possible, while still maintaining incentives to make the new product available.

There may be other new roles for the centers in the animal biotechnology area. One is to assist in the wise application of the range of technologies just described. In some cases, for example, disease can be prevented by feed additives rather than by vaccines. (38) The choice poses health and ecological questions; the implementation of either for smallholders poses difficult extension questions.

A related group of issues may emerge with respect to the development of new animal feeds. Although their economic feasibility is controversial, microbial engineering is likely to produce new fermentations that can upgrade feeds or provide

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(35) (continued) Impact and Control, p. 12 (World Bank AGR Technical Note No. 7, Jan, 1983).

(36) See L. Thomas, "A New Agenda for Science," in SIPIscope, pp. 5-6 (Spring 1984).

(37) E. Marshall, "NYU's Malaria Vaccine: Orphan at Birth?" Science, vol. 219, p. 466 (4 February 1983).

(38) OTA, 1984, pp. 167-68.

protein supplements such as SCP. (39) The choice of specific technology is likely to vary from feedstock to feedstock, and from agricultural system to agricultural system; even aquaculture is encompassed. Much of the technology is held by private firms, including some relatively small ones, (40) and there are many different processes, so it may prove quite difficult to match needs and technical capabilities or to define a useful work program for a center or a national biotechnology program. Considering the protein shortages in many areas, the effort, however, may be very important.

Other animal technologies

Technologies for artificial insemination and embryo transfer are widely used in much of the developed world, and are being used in at least some developing nations. (41) Of particular importance to the developing world, these technologies can help propagate a new strain more quickly from a limited number of breeding parents, can offer greater ease in moving breeding stock through quarantine restrictions, and can free a strain from some vertically-transmitted diseases. (42) Thus, they could support more rapid upgrading of a nations' livestock.

Genetic engineering technologies may also be used. In several cases, modified genes have already been introduced into animals. (43) And breeding for disease resistance would benefit from the availability of genetic assays. (44)

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(39) OTA, 1984, pp 202-05. For an example of the economic problems, see M. Sherwood, "The Case of the Money-Hungry Microbe," Bio/technology, v. 2, p. 606 (July, 1984).

(40) J. Litchfield, "Single-Cell Proteins," Science, 219, p. 740 (11 February 1983).

(41) See, e.g., the description of Trans World Genetics, a firm specializing in shipping livestock embryos to Asia, but in some economic difficulty, A. Klausner, "UGEN to Acquire Trans World Genetics," Bio/technology, v. 2, p. 844 (October, 1984).

(42) See Priorities in Biotechnology Research for International Development, supra n. 1, pp. 87-96.

(43) E.g. Palmiter et. al., "Metallothionein-Human GH Fusion Genes Stimulate Growth of Mice," Science, Vol. 222, p. 809 (18 November 1983); see also "Human genes injected into pigs; Critics brand tests cruelty to animals," Washington Post News Service, (San Jose Mercury-News, October 1, 1984)(insertion of growth hormone genes).

(44) McCauley, supra n. 35, p. 30.

The possible economic applications are obvious, and some of the technology will probably be applied by private firms and marketed in the form of breeding stock (or artificial insemination or embryo transplant services). The price would probably reflect the likelihood that some of the resulting animals might be used for further breeding. Moreover, private enterprise would probably concentrate on large herding or poultry operations. The public roles will therefore tend to emphasize the transfer of genetically modified breeding stock to smallholders and to the poorer developing nations and the support of research oriented toward characteristics (such as particular disease resistances) of economic importance only to developing nations.

Microorganism Technologies

Bioprocesses

The new technologies assist the design and optimization of microorganisms for a wide variety of industrial processes ranging from very specific chemical production to biomass conversion into energy. (45) Like the processes involved in the production of vaccines or bovine growth hormone, these technologies are not fundamentally new; they are extensions of the kinds of fermentations practiced in many cultures. What is new is the ability to design and modify microorganisms to use such technology in a much more planned way and with a much greater variety of applications.

There are many possible applications. The feed additive and SCP areas have been discussed in connection with animals. Another important one is large scale energy production, where the processes are probably at best marginal for developing nations; this is, of course, a function of the price of alternative sources of energy and of the effective cost of the foreign exchange needed to import that energy. (46)

However, more specific products may be highly feasible, may require significant crop pattern changes, and may even attract breeding research to optimize the crop for the process. This may already have happened in areas like brewery supply, where there is an obvious source of private funds for advanced technology. In

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(45) OTA, 1984, pp. 194-214, 236-50; C. Haber et al, "Methylotrophic Bacteria: Biochemical Diversity and Genetics," Science, v. 221, p. 1147 (16 September 1983); A. Klibanov, "Immobilized Enzymes and Cells as Practical Catalysts," Science, v. 219, p. 722 (11 February 1983); T. Maugh III, "A Renewed Interest in Immobilized Enzymes," Science, v. 223, p. 474 (3 February 1984).

(46) Consider the tables in H. Bungay, "Overview of New Biomass Industries," in Priorities in Biotechnology Research for International Development, supra n. 1, p. 159.

general, the variety of bioprocess opportunities is so great that the implications for the developing nations are impossible to predict. There will probably be cases in which a new bioprocess makes a crop economical and creates a new export industry for a developing nation. There will probably also be examples in which such a process creates a developed world industry and undercuts a developing world export. The development of high fructose corn syrup (HFCS) as a substitute for sugar examplifies this possibility.

The economic feasibility of these techniques is heavily dependent on the market for the product and the precise costs; the areas are likely to be left to private enterprise and to national research entities working in areas such as traditional fermented foods. The situations in which global public funds might be wisely used are those in which many nations might benefit from a development unlikely to be financially feasible on the basis of a single project. Energy is the obvious example; whether or not there are others is not yet clear. Global funds might also be wisely used here (and perhaps in the SCP and feed enhancement area) to support a central databank of processes.

Microbials and inoculants

For some time, microorganisms have been available to help protect plants against pathogens. Other microorganisms, such as Anabaena (in symbiosis with Azolla) and Rhizobium have been used in nitrogen fixation. Other systems may be developed such as those to confer frost resistance. Many of these organisms are single-celled and thus easier to manipulate than more complex organisms. Genetic modifications of these systems are therefore likely to be among the first agricultural applications of full DNA manipulation. Many firms are looking at such modifications, and over half the agricultural research goals listed by the OTA for new biotechnology firms involved microorganisms. (47)

For this research area, however, regulatory issues become particularly serious, as exemplified by the frost resistance case. The microorganisms may be easier to work with than plants; they are also more difficult to control after their release. (48)

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(47) OTA, 1984, p. 82; For additional information, see L. Miller et al, "Bacterial, Viral and Fungal Insecticides," Science, 219, p. 715 (11 February 1983); B. Dixon, "New Viral Weapons Against Plant Infections," Bio/technology, v. 2, p. 202 (March 1984); A. Klausner, "Microbial Insect Control; Using Bugs to Kill Bugs," Bio/technology, v. 2, p. 408 (May 1984); Priorities in Biotechnology Research for International Development, supra n. 1, pp. 119-130.

(48) Testimony of R. Hardy, House Committee on Science and Technology, Hearings, supra n. 29, p. 93 and letter by W. Alexander, id at 209.

Hence, it is important to be careful, in spite of the great potential benefits. Under current United States law, public entities will probably be unable to release such changed organisms until an Environmental Impact Statement has been prepared.

Although few developing nations will be interested in frost resistance, many will be interested in other applications of genetically modified microorganisms -- the potential benefits of biological pest control or improved nitrogen fixation are enormous. The new organisms or inoculants would have to be regularly distributed to the farmer, but the farmer would almost certainly be eager to use them if their benefits exceed their cost. Because soil conditions, climate, and the pathogens and crops involved may all differ, microorganisms used in the developed world will probably have to be modified for application in developing nations. In some cases, private enterprise may find a market that supports such modification; in many important cases, however, the adaptation will not be made unless the necessary research is subsidized or carried out at a public or international center. This is the pattern for research already underway with Azolla-Anabaena and Rhizobium.

Thus, AID and the centers may well want to expand their research in this area, particularly with respect to microorganisms relevant only to tropical pathogens or cultivars. And beyond research oriented toward developing microorganisms, they may want to consider additional study on complementary cultivars, and possibly work on helping nations in evaluating the agricultural benefits and ecological risks of specific microorganisms.

There will be patent issues with respect to some of the microorganisms. In the developed world, these new biological materials will more likely be cultured and distributed through private channels than through public ones. The modified organisms will probably be patented in the United States under regular patent laws; patents may also be sought in some other nations, and sometimes even in developing nations.

Because patents apply only in national territory, research centers and public and private national institutions are free to use the microorganism in nations where no patent has been sought. (49) When the microorganism is covered by a local patent however (and granting patents of this type will appear to some developing nations to be a useful way to encourage private investment in applying new microorganisms to local needs), a license will be needed, at least for work beyond the local version of the research exemption. A research center's improvement and

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(49) They may want a license if the microorganism is used in producing a commodity exported to a nation in which the microorganism is patented, but as discussed in note 22, supra, the trend is away from giving a patent such sweep.

adaptation of the microorganism may itself be patentable -- an improvement patent on the underlying invention. In such a case, the center would be wise to obtain the improvement patent, and bargain with the holder of the underlying patent for a cross-licence under which both parties can use both inventions, either royalty-free or with a negotiated division of royalties.

Plant Technologies

The new technologies will contribute to plant improvement in a wide variety of ways. (50) The following analysis is organized to reflect different economic patterns: first, new chemicals, such as those used to induce male sterility, that will be used in breeding or sold as commodities; second, tissue culture processes that will be available to many laboratories for use in breeding or asexual propagation; and third, full genetic engineering to introduce novel genes into plants. There will be other applications -- which may be even more important -- of assisting regular breeding through deeper insight into plant physiology and through providing new tests and probes for more rapid evaluation of breeding material.

New chemicals, as for induction of male sterility

Both European and United States firms are testing new gametocides that chemically create male sterility. With this technology, commercial production of hybrids becomes economically feasible in a wide range of crops for which cytoplasmic male sterility is unavailable or uneconomic.

Apparently, tests have not so far demonstrated yield increases large enough to make the technique more than marginally marketable. However, the method appears likely to offer a way to produce hybrids at lower cost. Moreover, as new strains are developed more specifically for their hybrid combining ability, one might expect greater yield increase. In the case of hybrid wheat, a male sterility technique was developed in the mid-60s, but it was not until the early 80s that this technique translated into significant yield increases (20-30 percent) and sales. (51)

The commercial use of hybrids will probably therefore move to new crops and eventually to developing nations as well. This

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(50) See, for example, in addition to the materials cited in note 1, supra: P. Ammirato et al, "Biotechnology and agricultural improvement," Trends in Biotechnology, v. 2, p. 53 (May/June 1984); National Academy of Sciences, Genetic Engineering of Plants (1984); K. Rachie & J. Lyman, Genetic Engineering for Crop Improvement (The Rockefeller Foundation, August 1981).

(51) Bishop, "Seed Firms Hope Hybrid Wheat Will Increase Harvests and Sales," Wall Street Journal, (July 5, 1984).

naturally poses questions of increases in seed prices and of the cost to the farmer of buying new seed each season rather than being able to reuse seed for several generations. This risk is probably not so severe as frequently argued. The farmer does have the choice of using traditional varieties, and will presumably not shift to hybrids unless the yield increase more than covers the seed cost, after allowing for changes in chemical and cultivation costs. Moreover, there is likely to be competition. Several firms offer the gametocide; probably at least as many will offer seeds. Even in the developing world, competition has already begun in traditional hybrid crops; in the Philippines, for example, several firms are producing hybrid corn, some using lines developed (at least in part) within the Philippines.

This combination of alternatives and competition will probably keep prices from going too high (as has been argued to be the case with pharmaceuticals, where the purchaser has fewer alternatives). In the United States, the seed firm has usually, as noted above, been able to gain about 30 percent of the value of the yield increase. (52) Similarly, the Technical Advisory Committee Workshop on Plant Breeders' Rights and the IARCs was told of a 5 to 10 percent seed price increase resulting from plant breeders' rights. (53) Even if hybridization produces a somewhat greater price increase, the value of the yield increase is likely to be a comparable percentage of a much bigger base. Thus, although the issue will deserve monitoring, one can be optimistic, assuming that this developed world experience can be extrapolated to the developing world.

What may be more important for the developing world is whether the gametocides themselves are marketed for use by a variety of firms and institutions. Conceivably, the inventors will attempt to keep the gametocides to themselves and market only the new hybrids. The technology, however, is probably too well known to be controlled by trade secrecy; use of a patent would require disclosure and still leave breeders practically and legally free to experiment with the technology in nations where no patent has been sought. In the face of these uncertainties, and of the facts that several different firms are pursuing the gametocides, and that the different gametocides use different biological principles and derive from different chemical families, it seems likely that at least some of the gametocides chemicals will be marketed for third party use.

For the AID and CGIAR systems, assuming the new gametocides are marketed, there are then new opportunities for breeding; and these opportunities will probably not be very expensive. These chemicals may not be the only new ones. Firms and public research centers, for example, are also experimenting with the production

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(52) See Butler, as cited supra n. 3.

(53) CGIAR Doc AGD/TAC:IAR/82/34, p. 13 (October, 1982).

of plant growth regulators. (54) These may bring significant benefits in yield or conceivably in protein quality. Again, it will pose new opportunities for breeding and experimentation in application to developing nation cropping systems.

Tissue Culture, Directed Mutation and In vitro screening

Tissue culture is an essential component of almost every form of new plant biotechnology. Tissue culture can be used as a method of propagation and to remove virus infections from propagating material; it can assist germplasm exchange and conservation; it is part of the process of somoclonal variation and selection; it is essential for the reconstitution of many forms of genetically modified organisms. Moreover, it is a labor-intensive technology in which developing nations may have a comparative advantage.

In large part as the result of previous AID and CGIAR programs, this technology is already one of the basic working procedures of plant breeding laboratories throughout the world. (55) A wide variety of IARCs, developing world universities, and developing world public and private institutions are already using the technology. Examples of indigenous programs range from Vietnam, where local farmers (motivated by a profit incentive!) are using tissue culture to propagate potato germ plasm, (56) to Mexico, where clonal propagation is being used in research to develop salt-tolerant tropical cultivars. In these areas, the intellectual flow will not always be from North to South.

The impact of commercialization in this area will depend on the strategy of the innovators, which, in turn, is likely to depend on the innovation itself. There will be proprietary innovations. Thus, patent protection is being sought for the gel and polymer formulations used to encapsulate somatic embryos to produce what amount to artificial seeds. (57) Similarly, firms will probably develop proprietary chemicals that help in the

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(54) E.g. OTA, 1984, p. 82; H. Yokoyama et al, "Bioregulation of Lipid and Protein Synthesis in Soybean by 2-diethylaminoethyl-3,4-dichlorophenylether," Bio/technology, v. 2, p. 712 (August 1984).

(55) W. Rockwood, "'New' Biotechnology in International Agricultural Development," AID Horizons, v. 2, p. 21 (November 1983).

(56) P. Zaag, "One potato, two potato," Far Eastern Economic Review, p. 64 (23 August 1984).

(57) F. Gebhart, "Plant Genetics Inc. Reports Successful Vegetable Harvest from 'Synthetic Seeds'," Genetic Engineering News, v. 4, No. 1 (January/February 1984).

culture of a wide variety of plants. In cases like these, particularly if the inventors are small firms, it is likely that the technology will be made broadly available, either by sale or by licensing. In contrast, however, an integrated firm with a technology relevant only to a specific crop might prefer to keep its information confidential and instead market the products of the technology. To the extent that firms choose this strategy, information flow will be slowed. Patents, however, may help encourage disclosure, and, even when the information is kept confidential, farmers may still receive the benefit of its application.

The key AID and CGIAR tasks in this area are to use the research as appropriate in breeding and research programs and to continue to provide the training and communication to assist other developing nation laboratories, public and private, to do so. It may be especially valuable to strengthen networks by which those working on a particular cultivar can trade their experiences.

The public system may want also to think beyond this technology to the next "building block" technologies that should be spread widely as was this one. The issue should be analyzed by scientists, but assay techniques such as those available through monoclonal antibodies deserve to be considered. Like tissue culture, these techniques can be readily made available, and are both stepping stones to full genetic engineering and tools independently useful in a variety of breeding and research programs. (58)

Full genetic manipulation

Technologies for genetically modifying plants have long appeared likely to lag those for other forms of genetic modification. The procedures for gene transfer, as through Ti-plasmids, are, so far, limited to some species; the ability to regenerate a plant (a tissue culture problem) is also limited to some species; most important, many of the economically important genetic structures, such as those involved in nitrogen-fixation or in shaping the protein composition of a grain, are still poorly understood.

There may, however, be recent reason for greater optimism. The structure of the Ti-plasmid is being rather fully elaborated, (59) creating the possibility that it might be itself genetically modified for greater usefulness. Moreover, it appears likely that

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(58) See Progress in Biotechnology Research for International Development, supra n. 1, pp. 96-111.

(59) A. Caplan et al, "Introduction of Genetic Material into Plant Cells," Science, v. 222, p. 815 (18 November 1983).

the genetic basis of some forms of herbicide resistance and stress resistance may prove relatively straightforward, and thus subject to relatively straightforward manipulation. (60) It therefore seems possible that such traits may be transferred into cultivars within a few years.

There might still, however, be regulatory problems. Moreover, almost any application would require perhaps five years of regular breeding, testing, certification, and seed multiplication for the products to be available. The genetic engineering does not replace the regular breeding process; it rather permits gene insertions that species boundaries might make very difficult with more conventional means and permits a precision in selecting the genes to be transferred that might require many generations with conventional approaches.

The dates estimated in Chart II reflect this combination of technical feasibility and the practical breeding that must come after a modified gene is inserted in the laboratory. They also reflect the expected relative complexity of the different tasks, ranging from single genes for some disease resistances to elaborate systems for nitrogen fixation or photosynthesis. Dates will vary as well from crop to crop.

From a social viewpoint, the hope of an agricultural revolution within even a generation is exciting. For business, however, the implications of these estimates are that profits are quite far in the future, that the effective rate of return on investment is low, and that small firms are likely to have difficulty raising capital for this market. The rate of research investment in the field does seem low -- somewhere between 1/2 and 2 1/2 percent of sales, as compared to the pharmaceutical industry's 10 percent. And some analysts argue that the market size and plausible markups, particularly for seeds, are unlikely to justify even the levels of investment now being made.

If these analysts are correct, private industry will succeed in making the technologies available only for the largest markets or with the assistance of subsidies. Developing nations, with smaller markets, will benefit only when a technology created for the developed world market is directly applicable for them as well. This may be the case, but there is another side to the argument: the value of increasing the yield of a major crop by a few percentage points is enormous; the technology is accessible to the developing world; and there are many ways to combine public research and private application. The new technology may

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(60) See, for example, LeRudulier et al, "Molecular Biology of Osmoregulation," Science, vol. 224, p. 1064 (8 June 1984); J. Marx, "Plants' Resistance to Herbicide Pinpointed," Id., v. 220, p. 41 (1 April 1983). See also the somewhat different evaluation in B. Miflin & P. Lea, "The genetic manipulation of crop plants," Nature, v. 308, p. 498 (5 April 1984).

not telescope the last several years of breeding; but it will greatly shrink the time between a university breakthough in understanding a genetic pathway and the incorporation of changes in that pathway into breeding material. With all these favorable conditions, there should be at least a reasonable return available!

Although the issue is not at all clear, it seems likely that some of the leading firms will be vertically integrated and be willing to sell only seeds and not technology. Through a careful combination of biotechnology research on the one hand, with large gene pools and seed marketing experience on the other, such a firm might manage to protect itself from less integrated competitors. From a financial viewpoint, selling seeds is viewed as better than selling research contracts to those who sell seeds:

> "Royalty and licensing income ... appreciably benefit cash flow .. and generally help a company endure the development stage, but we believe that only profits from fully integrated products will provide sustainable growth ..." (61)

There are factors cutting each way. If an intellectual property system is available, innovators will be more able to license the technology rather than apply it through an integrated operation. Likewise, if there are many applications for the technology, the greater flexibility of licensing is favored. It is also favored by the relative ease of entry into both the biotechnology and seed industries. The management style of <u>some</u> seed firms is quite different from that of <u>some</u> biotechnology firms, a factor cutting against integration -- but there are firms for which the styles are much more similar. Also favoring integration, a long time horizon is more feasible for an integrated firm. And close management integration of breeding with biotechnology research seems likely to be desirable and efficient.

On balance, it is likely that there will be some firms in each pattern. Vertical integration appears most likely for major crops like wheat, rice, maize, soybeans, and sorghum. This approach matches the strategy of the larger firms which have a longer range view and tend to look only to large markets. Such firms may well attempt to achieve global coverage, but there will probably be several of them and they will risk being undercut by small firms with new ideas willing to do research with public or private breeders in the developing world. Hence, even if there is global vertical integration, there may be a competitive fringe.

The smaller markets, e.g. vegetable seeds and perhaps some developing world varieties, are likely to be relatively more

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(61) Dean Witter Reynolds, Inc., <u>Bioscience and Biotechnology</u>, p.3 (1984).

appealing to the smaller biotechnology firms. These firms will have to apply their technology to a number of markets and they talk of their ability to conduct a research program to insert a particular gene into another firm's plants. The formal legal structure may sometimes involve a contract and sometimes a joint venture, but this pattern has become typical of many arrangements between U.S. biotechnology firms and a number of sponsors: developing-world plantation agriculture firms, some developing nations, and some seed and chemical firms.

When the new seed industry is vertically integrated, the economics will be somewhat like that of hybrid seeds. The developing world farmer will have, effectively, to pay a royalty for the higher quality seeds (which may even be sold in hybrid form). As with the hybrid, it is unlikely that this royalty will total more than a fraction of the gain realized from the improved seed, for the farmer has the alternative of traditional seed, and it is almost certain that there would be competition among the global integrated seed firms. The technologies available in this way would probably be those that look valuable in developed world markets; resistances for developing-nation pathogens, for example, will be only slowly developed.

To the extent that this pattern emerges for a crop of CGIAR interest, there will be a risk of duplication between the private firms and the IARCs or developing nation seed ministries. The issues will be similar to those being faced by land grant universities in the United States. Some seed firms will urge that the centers should avoid release of finished varieties and should concentrate instead on germplasm conservation and fundamental research. The smaller firms and smaller nations, will urge that the centers continue to release finished varieties, and perhaps build their own competitive genetic engineering capabilities. The issue will be complicated by the possibility that some national governments -- in the developed and developing world -- may be eager to help the competitive positions of their national seed firms. Some nations might also revise their patent system so as to ensure their freedom to use and reuse the seeds without royalty, but may face problems in gaining access to the latest and highest quality seeds.

Even if the international seed industry becomes very highly integrated, firms may want to enter into arrangements with an IARC to combine their patented and protected cultivars with the center's knowedge of particular local conditions or diseases. Such accomodations may become the practical way to apply the new technologies to needs that would not otherwise attract private investment.

If the industry is less integrated, there is much less impact on the IARCs. They might have to buy patented genes or use lines protected by a breeders' rights certificate, but in both cases, they could, in principle, breed and multiply modified lines, subject only to any royalties required in the particular legal context. They would thus be able to obtain breeding

materials, work them into their cultivars, develop and insert genes themselves, or contract with existing firms for insertion of genes that are of importance only in the developing world. The legal structure and scientific content might change drastically; the fundamental working structure would change only a little. Moreover, no matter which industry pattern dominates, the centers would have extensive roles in basic research -- which could be brought to the direct benefit of the farmer much more quickly -- and might also have extensive roles in areas like cropping patterns, environmental safety, and even consumer safety.

IMPLICATIONS FOR THE DEVELOPING NATIONS

The new biotechnologies are in many respects the ultimately appropriate technologies for developing nations. Equipment and technology costs may appear high, but they are small compared to those of manufacturing industries. The technologies can be practiced in a rural setting and thus need not imply rural-urban migration. (62) They can almost certainly be made ecologically sound -- and can probably even help make up for past environmental errors. Most important, they are potentially very specific and adaptive; in the long run, they will help transcend barriers of disease, climate, and soil quality and tend to permit a crop of choice to be grown in a location of choice at a technological level of choice.

These benefits are largely for the future. Within the next five years or so, the most important products for developing nations will probably be growth hormones, vaccines, new hybrids, innoculants, and microbials, and new industrial microorganisms, . In the five years following that, one can also expect genetically engineered disease and herbicide resistance in a number of plants. By the turn of the century, genetic engineering is likely to bring the greater flexibility to agriculture described above. And the product benefits are likely to be dwarfed by the research benefits of the new technologies, particularly as applied to conventional breeding.

Special concerns

These benefits will also bring their costs. The most obvious costs are those of the technology and the new products -- but these costs will probably be small compared with the benefits. The data is, of course, not in yet on biotechnology, but the costs of the last generation of agricultural research have been small compared with the benefits. Historically, public agricultural research has offered a dramatically high rate of return, typically 20 to 60 percent. (63) And these benefits can reach the farmer; the experience cited above with respect to seeds in the developed world suggests that the private entrepreneurs will typically recoup about a third of the benefit of the technology, and the farmers the rest. (64) Hence, even if a portion of the technology must be paid for in hard currency,

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(62) See Baltimore, supra n. 1.

(63) V. Ruttan, "Toward a Global Agricultural Research System,", Table 2, prepared for "Workshop on Agricultural Research Policy and Organization in Small Countries," Wageningen, Neth., Sept. 12-14, 1984.

(64) See Butler, supra n. 3 and discussion on p. 30 supra.

the benefits for a developing nation are likely far to exceed the costs, particularly if food imports can be avoided.

The most direct effects on the balance of payments are the cost of imported technology and the benefit of increased agricultural exports or avoided food imports. There will also be indirect effects resulting from price changes. Assuming that the technology is applied more rapidly in the developed world, developed-world agricultural costs and prices will fall (relatively) and place developing nation agriculture at a competitive disadvantage. Likewise, commodity prices might fall generally as a result of the new technology. These effects, however, are unlikely to be any larger than those associated with exchange rate fluctuations; and some developing nations will be helped at the same time others are hurt. And there will be a very unpredictable pattern as production technology modifications change the optimal locations for growing particular crops and as bioprocessing technology modifications change the demand pattern for different commodities. Specific developing nations will thus find their export patterns and balance of payments radically affected.

Certain of the new technologies will have more predictable special economic effects. Extension of nitrogen fixation to new crops could help reduce the cost of importing fertilizer. Crop yield will probably fall somewhat as photosynthetic energy is diverted to fix nitrogen; assuming that this loss does not lead to a compensating foreign exchange cost, the developing nation is likly to be better off. It has been argued that agricultural chemical firms are likely to attempt to slow this technology in order to protect their fertilizer profits. Undoubtedly, they will not be eager to allocate research funds in such a direction, but they risk the possibility that competitors, public or private, will offer the farmer a more economical way of fixing nitrogen. The difficulties of actually developing the technology are almost certainly more important than any short-term perverse incentives.

Herbicide resistance technology also raises special economic issues. Agrichemical firms are investing in the new biotechnology firms; herbicide resistance is likely to be one of the first plant applications of the new biotechnology; and the agrichemical firms already have a global marketing network. Hence, one can visualize early marketing of a package of herbicides and seeds resistant to the herbicide. This will probably happen in the developed world, and may happen in part of the developing world. The operation is subject to the usual constraint that the costs must be less than the benefits, or farmers will use alternate technologies -- but the costs in foreign exchange may be somewhat larger than for use of improved seeds that do not require complementary imported technology.

The social questions posed by biotechnology in the developing world will probably be much more complex than the Green Revolution's differential adoption rates and often-alleged favoritism for the wealthier developing world farmer. Although it

is very early for such estimates, the key issues may be those of changes in land use patterns. New stress resistant crops, for example, will permit the working of land once not usable at all or usable only for grazing. This will radically change some village social systems -- and at a much more mundane level, the risks of land speculation and corruption are obvious. In the longer run, this technology may lead to continuous change in developing world agriculture, and frequent and regular transitions like those in developed world high technology industry. Governments will have to work very hard to combine equity and efficiency in such circumstances -- but would certainly not want to forego the opportunity to do so!

There will be major ecological questions, which will require careful analysis by appropriate institutions, possibly including CGIAR centers. The balances involved in releasing genetically modified organisms have already been noted. The possibility of greatly increased use of herbicides raises natural hesitations -- but there will be arguments cutting both ways. Genetic incorporation of herbicide resistance, for example, might permit cultivation patterns that bring other benefits, e.g. conservation tillage, or use of less herbicide than is likely under other cropping patterns. Ecological issues might also be posed by wide use of newly-incorporated single genes to confer disease resistance. The risks undoubtedly depend on the specific disease resistance mechanism, but it is important to consider the depth of defense against pathogen mutations. Finally, the transfer of marginal lands to (hopefully sustainable) production patterns may, with all its implications for soil conservation, water use, and planning, prove to pose the most important of the new ecological effects.

The possible effects on genetic diversity deserve special note, and will continue to deserve special attention. There are arguments that private application of the new technologies is likely to lead to increased homozygosity. If only a few firms end up producing the world's seeds and use a limited range of genes, this could be a significant risk. One could also be reasonably concerned if new innoculants and microbials lead to increased uniformity of soil microorganisms or if the same genes for disease resistance are incorporated in a large portion of the world's cultivars. Nevertheless, private firms (who, admittedly, are interested in the outcome) make the strong counterargument that there are typically several ways of reaching most of the biological results. The new gametocides come from several different chemical families, and it is conceivable that a specific disease resistance might be incorporated in several different ways. Moreover, the new gametocides permit hybridization using a wide variety of breeding stock. Thus, although the issue must be watched as it develops, the trend may be in the opposite direction. And, as gene modification becomes easier, it may become possible to devise new genes to increase diversity.

Supporting indigenous programs

Many of the larger developing nations have already concluded that they want to encourage creation of a substantial national biotechnology program, and, as noted above, this technology offers that potential. Some areas may be most efficiently developed by multinationals. Some, however, can be most efficiently and effectively developed by public or private institutions within the developing world. This approach offers special promise, both for actual development and for the alleviation of developing nation concerns about technological dependence.

Nevertheless, the task is also difficult. At the very mundane level, capital is often hard to obtain, obtaining reagents and maintaining equipment may be even harder. Moreover, it is much easier to do academic research than to apply that research to the benefit of the farmer, a process that raises hard questions of internal technology transfer, of the patent systems, relations between the public and the private sector, and relations among different parts of the bureaucracy. These are politically difficult questions, and their answers will vary with the national tradition.

In the face of this combination of benefits and problems, AID, its missions, and CGIAR may want to intensify those programs that help the developing nations master and apply the new technologies themselves. Among the areas to consider or expand are:

(1) Scholarship, travel, and exchange grants to allow developing nation researchers to pursue advanced degrees in the developed world and to attend scientific meetings, and to encourage developed world scholars to undertake teaching or research stints in developing nation laboratories. The IARC's may be able to help evaluate possible students and also to serve as host laboratories for research.

(2) Training programs carried out through the IARC's to accomplish rapid diffusion and sharing of knowledge in areas like monoclonal antibody applications.

(3) Loan programs, or even a special purpose development fund, to help developing nation researchers and institutions without access to venture capital (or perhaps to business expertise) to bring their innovations to reality.

(4) Assistance in planning for and carrying out national programs. A number of nations already have such programs, particularly to coordinate education and research at the university level with that in ministries and the private sector. Nations vary in their approach to such planning -- but it may sometimes help in defining realistic goals, shaping educational support, utilizing major equipment efficiently, and coordinating assistance commitments.

Patent systems

The new technologies raise a variety of issues of general patent law; the political arguments raging over breeders' rights are likely to be eclipsed by questions about the evolution of the utility patent system now spread through the world. In facing these questions, the developing nations have substantial autonomy with respect to their own patent system (although they may face political pressures toward both stronger and weaker patent coverage); they have a much more limited opportunity to affect developed nation positions through international negotiations.

Patents bring the advantages of providing a decentralized incentive for economically responsive research, but it is important to be sensitive to the social costs of the patent monopoly. One United States analyst, for example, suggests that patent practices should be encouraged to the extent that the profit derived from the practice (the incentive) is large compared with the costs to the public of the patent monopoly. (75) This principle is particularly important for and difficult to apply to developing nations. On the one side, the social costs of the patent monopoly will sometimes be very high in such nations particularly if there is little competition. Moreover, firms may only rarely take these profits into account when planning research. On the other side, barriers to the investor's ability to appropriate a portion of the economic benefit of the new technology make it still less likely that the investor -- foreign or national -- will conduct the research needed for a specific developing world application.

Biotechnology is special in a number of ways, beyond being an area in which the patent law is especially flexible and uncertain. First of all, in this area, research is needed and a patent system may actually encourage local research, rather than just serving as part of an international technology transfer mechanism. The bigger and more advanced the nation, the more likely it is that there will be local innovation and that the social costs of the monopoly will be restricted by competition. Second, the flow of information is especially important in biotechnology. Patent systems probably favor this flow. Privatization is unavoidable and the information involved has commercial value in any event. Patenting requires disclosure and permits greater freedom in communication than does the trade secrecy approach that is the likely actual alternative. Third, the stronger the patent system, the less the likelihood that the international biotechnology industry will be vertically integrated, and the greater the likelihood that technology will be available through licenses. These factors favor the use of a patent system. The strongest counteargument is that, because of

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(75) L. Kaplow, The Patent-Antitrust Intersection: A Reappraisal (Harvard Program in Law and Economics, Discussion Paper No. 2, December, 1983.)

the territorial limitation of patent coverage a firm or entity does not violate a foreign patent by practicing the innovation locally. Thus, a developing nation might choose not to have a patent law and simply to encourage use of whatever technologies can be acquired. The approach reduces both royalty costs and incentive benefits.

Assuming that most developing nations will retain their patent systems and apply them to some forms of biotechnology innovations, the analysis of this paper suggests several desirable specific directions for that law:

(1) In biotechnology nearly everyone will be better off if the research exemption (76) is kept relatively broad. Most biotechnology research will involve so many actions arguably infringing so many patents that the nuisance costs would otherwise be quite serious.

(2) Although the policy balance requires a case by case analysis of incentive effects and monopoly costs, the developing nations would be best off if the effective scope of a patent right is not too expansive. It seems reasonable, for example, for a patent on a gene to permit prohibition of the sale for seed purposes of a variety containing that gene; one hesitates at extending the right to permit prohibition of sale of the product for food purposes.

(3) If a patent law really is valuable for encouraging innovation in biotechnology, abuses -- and they are possible -- are better dealt with by specific law than by eliminating patent coverage. For example, it may be reasonable to permit the inventor of a genetically modified microorganism to prohibit import of a specialty chemical made abroad with an infringing microorganism. But an antitrust principle may have to be added to keep this legal right form being used as a way to divide up global markets for the chemical. Similarly, the risk that an inventor bottles up patented technology might be better faced by creating a legal right to compel reasonable-royalty licensing under specified conditions rather than by making the technology unpatentable.

(4) Treaty negotiations may be wise for some of these issues as the likely fact and legal patterns become more clear. Such negotiations would not be easy for there are strong political pressures and difficult arguments on all sides of these issues. Legal uncertainty, however, will be a barrier to international trade and innovation, and is likely to be particularly harmful to the developing nations.

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(76) See note 20, supra.

IMPLICATIONS FOR INTERNATIONAL RESEARCH PROGRAMS

The more applied international biotechnology research programs should be focused on those areas complementary to private and national programs. Typical situations include: improvements in crops grown only in the tropics, in smaller nations, or in poorer areas, e.g. to cassava or perhaps to upland rice, new vaccines or resistant strains for diseases found only in poorer nations, or microorganisms adapted to certain tropical soils.

But there should also be major basic research programs -- a direction sought by practically every public or private actor in biotechnology. If the analysis of genetic engineering presented above (77) is correct, basic research will still be a public sector responsibility; what will change is the rate at which and confidence with which a fundamental breakthrough can be applied to the benefit of the farmer. A large block of traditionally basic research will be encompassed within the IARCs' traditional emphasis on foreseeable benefit to the farmer. Moreover, particular areas, like soil microbiology, may begin to offer so much more promise that they should be allocated increased research attention.

Public funding should be applied to biotechnology only when the new biotechnology approaches are cost-effective in comparison with other alternatives. Most analysts seem to have a long list of relatively straightforward activities that, they say, would greatly improve developing world agriculture. If these activities offer a higher benefit-cost ratio, it is, in general, better to subsidize them rather than biotechnology. This point must, of course, be balanced with the lead-time arguments that favor of beginning some exploratory biotechnology research. The lead time needed to build up personnel teams, communication networks, and laboratories suggests moving early, sometimes even when the ultimate benefit cost ratio is unclear.

New relations between the public and private sectors

Areas in which public sector is central

In some cases, the new technology will have to be developed entirely by public institutions, just as plant varieties once were. This is the situation for ILRAD's animal disease program, using very advanced technology on a category of problems being relatively neglected by private firms. A full scale research program is needed; that program is likely to benefit only

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(77) Page 33, *supra*.

indirectly from private research; it is likely to be useful for a number of developing nations. In such cases, biotechnology produces few institutional changes for the IARC; its key structural impact is to increase the need for close cooperation and communication with developed world public research institutions.

Areas in which private sector is central

At the other extreme, private firms or independent national programs will sometimes be able to produce a product directly applicable to developing nation needs. Thus, a developed world firm may produce an improved maize that is already adapted to a developing nation market, or a developing nation research program may develop disease resistant stock for vegetative propagation. These patterns will be most likely for vaccines, for new agricultural chemicals, and for improvements to plantation crops and to global crops such as wheat, maize, rice, soybeans, or sorghum.

Often, such developments will pose no new issues for the public agricultural research system; in a few situations, they may create pressure on the system to modify its missions in order most effectively to complement the unsubsidized activities. If the judgments of this study are correct, this pressure, if it ever evolves, is unlikely to be strong for at least a decade, for it would arise only with global crops. Even under those circumstances, there will be pressures in all directions. Some nations may urge the centers to avoid duplicating the efforts of private firms or national programs. But even if big developing nation markets attract globally integrated high-tech seed firms, there will be smaller nations and smaller seed firms crying out for a continued CGIAR presence in even the most global and technologically advanced crops.

When these issues do have to be faced, there are many directions for the IARCs to consider, for example:

(1) to continue to produce finished varieties in order to help smaller nations, to decrease the risk of possible monopoly, and to present an example to help indirectly in keeping costs down. (78)

(2) to emphasize the applications research needed to use the new varieties as effectively as possible in developing nations. There will probably be enormous needs to redesign cropping practices.

(3) to strengthen the underlying research and germplasm collection needed to help continue to improve new varieties for developing nations. Considering the short time-horizon

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(78) See page 8, supra, for the analogous arguments with respect to the land grant universities.

imposed on business investment, these tasks are likely to need substantial public support.

Moreover, although no international public research program is needed, other international assistance agencies might be called on to ensure widespread distribution. Thus, donors might subsidize purchase of a quantity of vaccine or seeds for distribution to poorer farmers -- and the material might have been produced in a developed or a developing nation, perhaps under license.

Mixed patterns

The more common patterns will probably lie between these extremes: limited public funds might be needed to support application of a proprietary technology to an otherwise unprofitable developing world market. A private firm might, for example, have formulated a way to insert a gene conferring resistance to a particular category of diseases -- but new research is needed for application to the tropical variants of the disease.

Such situations may require new cooperative arrangements between the centers and private firms; such arrangements may sometimes be the simplest way to give the developing nation farmer the benefit of a technology that might not be applied in a purely commercial context. Using the example of the prior paragraph, the firm might perhaps be funded to conduct the research and apply its proprietary technology to the tropical disease, using breeding material provided by a center. In essence, just as the centers now buy reagents or laboratory equipment from private firms, they may in the future buy genes or advanced research services from private institutions.

New arrangements may also be needed for distribution. In the situation just described, the center might then use the cultivar containing the new disease resistance in its regular breeding program and distribute the product through its normal channels; alternatively, the private firm might be permitted to distribute the new cultivar. The latter pattern may also become common for animal vaccines and perhaps a variety of chemicals and inoculants; the centers may provide materials for private firms (or, in some nations, specific ministries or public entities) to carry out the final production and distribution -- just as they now provide materials for seed production under a variety of national procedures.

The negotiation of such integrated research arrangements will pose important management questions of selecting the contractor fairly and of ensuring technical coordination of the research. It will also pose important economic questions of overall costs to the public and to the farmer. Beyond these, there are legal issues of allocating patent rights to any new inventions that are made -- an allocation which must recognize the bargaining positions of the two parties and must balance the

public interest in making the technology broadly available with the public interest in maintaining the contractor's incentives to develop and apply such inventions. (79)

The distribution arrangements pose further issues. If public agencies are to distribute the new product, the private firm will be reasonably concerned about protecting its unsubsidized developed world market. If the private firm does the distribution, the public agencies may want to give it exclusive rights to ensure that it has a strong marketing incentive; alternatively, depending on the economics, they may want to give much weaker rights or even impose a price limitation in order to protect the farmer.

CGIAR patent policy

Many aspects of the new technologies will be patented in the developed world and possibly in much of the developing world as well. Hence, the IARCs will be faced with a number of new patent issues. The key issues, presented in roughly the order in which they will be posed, are probably as follows:

(1) Given the fact that the new technologies are unlikely to rely on breeders' rights and the fact that developing nations have not enacted such rights, there is little reason to modify the traditional policy of not seeking such rights. Likewise, insofar as possible, the centers should continue to make new cultivars freely available and to exchange germ plasm on an essentially free basis.

(2) The centers should probably continue to place low emphasis on the fear that a private firm will use CGIAR germplasm in a variety patented under the breeders' rights laws. Since there are so few breeders' rights laws in developing nations, such action is unlikely to impose serious costs on the developing world. Moreover, it seems unlikely that any nation

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(79) The traditional United States policy, enunciated in 1971, is to give the government principal rights when the contract goal is to develop new processes and particularly mentions areas such as public health. The balance swings the other way when the contractor's retention of rights would help ensure application of the innovation or when the contractor already has substantial expertise in the area. In most cases, whichever party retains rights is to give the other a non-exclusive, royalty-free license. 41 C.F.R. § 1-9.107-3. In 1980, however, PL 96-517 gave non-profit organizations and smalll business a stronger position. See OTA, 1984, p. 419. In contrast, by resolution WHA35.14 of 12 May 1982, the World Health Organization adopted a policy balanced more toward its own obtaining of patent rights. See J-P Cailloux, "La Politique de L'O.M.S. en Matière de Brevets," 1982 Ann. Fran. de Droit Int'l. 739.

would knowingly grant a firm rights over materials acquired from a center. (80) The proof of such identity might be difficult, but the firm would be in a very weak position to keep CGIAR from making available to others the germplasm it had earlier been given! With respect to a private firm's use of the germplasm as breeding material, it should be remembered that the policy balance incarnated in the typical breeders' rights act permits a firm to use even a patented variety as breeding material for another patented variety. The IARCs' current approach to this issue through making material freely available and emphasizing publication is probably still correct.

(3) The centers should be somewhat more concerned, however, about the possibility that an innovation is appropriated and protected by a regular patent. The implications to the developing nations, which typically have regular patent laws, are much greater than with breeders' rights. Assuming that the facts can be shown, a person who stole an idea cannot patent it. Nevertheless, at least under United States law, when several persons invent something independently, even the later inventor can still obtain a patent if the first did not publish, make the invention public, or file a patent application. For the centers, the most straightforward response is to publish as rapidly as possible, and to maintain careful records and laboratory notebooks, etc. (and perhaps employee patent agreements) to protect against direct theft of an idea.

(4) For a number of types of technology, the centers should seriously consider routine acquisition of regular patents. There are negatives -- the costs of the legal expenditures, the need for employee patent agreements, and the fact that some will view this direction as inconsistent with the public mandate of the centers. Nevertheless, there may be major benefits in two situations:

(a) As noted in the previous section, a patent and exclusive license approach may sometimes help in building incentives for a private firm to disseminate a technology. This will particularly be the case for new vaccines, chemicals, and microbials that are likely to be most easily distributed through commercial channels. In this context, it is developing world patents that are most important. Moreover, it is appropriate to follow national policy here -- obtaining patents in nations emphasizing the patent system, and not doing so elsewhere.

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(80) Thus, under United States law, a "breeder" is entitled to PVPA protection, 7 U.S.C. § 2402 (a), and is defined as "the person who-- (1) directs the final breeding ... or (2) discovers the novel variety," 7 U.S.C. § 2401 (d). The UPOV Convention requires that a protectable variety be distinguishable from "a variety whose existence is a matter of common knowledge," which may be shown by "cultivation ... already in progress" or "inclusion in a reference collection." Article 6.

(b) As the centers work closer and closer to areas in which private firms are already obtaining patents, they should consider patenting their own technological innovations. This will help protect inventions from appropriation and patenting by a private firm. More important, it will give the centers a quid pro quo in dealing with private firms that hold underlying or improvement patents -- and a greater chance of negotiating cross-licenses that will protect the centers from any infringement claims and also give the centers a chance to affect the terms on which varieties incorporating patented features are marketed. For these purposes, the centers will be most interested in developed world patents.

(5) As the centers move closer and closer to the new biotechnologies, they will also have to consider ways to avoid infringing other's rights. At first, the risk will be small, because of the research exception and because few of the new biotechnological inventions will be patented in the developing nations where most of the centers are located. Later on, however, the problem will become more serious. For example, a center might use a patented vector or gene to improve a plant that turns out unexpectedly useful in the developed world. Or, a center might contract with a private firm to use a patented gene, and have to commit itself to make the resulting varieties available to developing nations only. If the centers do accept such contracts, they may have to develop what amounts to an intellectual property accounting system, and impose appropriate restrictions on use of their research results and germplasm.

New CGIAR and AID missions and tasks

Certain of the new technologies may bring new, but traditionally-defined, tasks to the CGIAR system, e.g. the application of various forms of microbials to tropical soils, design of new cropping patterns, rebreeding of cultivars for new goals such as improved symbiosis with a particular microorganism. Several specific lists of tasks have been proposed. (81) And new technologies will be integrated into the centers' research approaches.

But there will also be new types of tasks. One of the most important goes to the regulation of the new technologies. As noted above, these technologies pose both ecological and human safety concerns. Establishment of reasonable standards might well require enormous human resources and pose severe political confrontations within and between nations. It may be wise to explore these issues early and in a cooperative fashion. Thus,

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(81) See, for example, International Rice Research Institute, Report of Inter-Center Seminar on IARCs and Biotechnology (1984); Priorities in Biotechnoogy Research for International Development, supra n. 1.

the centers or AID might support the development of expertise, provide research and analysis to national governments and other international organizations, or offer training for the staffs of national agencies.

The maintenance of genetic diversity is one of these ecological issues, and one that clearly falls within the CGIAR's expertise. As noted above, this paper's analysis suggests that genetic diversity will not shrink as a result of the new technologies, but recognizes that this is an uncertain point and that the issue deserves monitoring. If genetic diversity does shrink, the CGIAR system will certainly want to focus research on ways to broaden diversity, as through seeking alternatives to a very widely used gene or exploring policies to encourage use of seed mixtures and diversified cropping patterns. Moreover, as genes become more fully known and more fully manipulable, the germ-plasm conservation task may fundamentally change to become one of information managment rather than one of collection management. (The in situ components of germ-plasm conservation would not change.)

The more sociological issues will also deserve analysis; whether these are issues for the centers is much less clear. For example, should the centers work on the sociological aspects of this generation of agricultural change or on ways to ensure that the adoption of the technologies is as equitable as possible? What about assistance in reshaping the roles of extension services? Or in planning for land use change? (82)

Finally, the new technologies pose several highly pragmatic issues for the centers and for international agricultural research. The centers will have to establish and follow wise standards in their own actions with respect to containment and the release of genetically modified varieties into the environment. Moreover, the new technology requires ability to move equipment, specimens, and reagents (some perishable or radioactively labelled with limited half lives) in and out of nations. Combinations of customs traditions, debt crises, and phytosanitary rules thus seriously complicate research. The International Rice Research Institute and perhaps other centers have immunized themselves legally from such problems. (83) Such legal arrangements may be important for other research institutions to emulate -- but nations can grant such exemptions only in very special situations. It may be better, for the sake of all researchers in the area, to consider defining model laws

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(82) See F. Buttel, "Biotechnology in the World Agricultural System: A New Technological Order for the New Biology?", paper prepared for delivery at the American Association for the Advancement of Science Annual Meeting, 27 May 1984.

(83) R. Chandler, An Adventure in Applied Science; A History of the International Rice Research Institute, p. 196 (1982).

for import of scientifically sensitive goods and possibly reexamining phytosanitary treaty provisions. (84)

Less focussed implications

An analysis like that of this paper necessarily emphasizes problems. That focus is needed, but the balance is needed too. The new technologies offer enormous potential, not just for feeding people but for improving the life of farmers throughout the world. The international system can help provide the communications and the needed increment of research.

This communications task may be the most important one and it is becoming much more difficult. The traditional network of land-grant schools, their developing world analogues, developing nation ministries, and the CGIAR community will be expanded. The most advanced research work is often being carried out in universities that have traditionally been outside the land-grant and agricultural network. The new developing world biotechnology institutions will be attempting to define their own relations to national ministries, national firms, and international institutions at the same time that CGIAR centers are thinking out their role. Much of the new research is being done privately, albeit by persons whose publications and communications traditions are closer to those of the university than to those of the industry of the past.

In this world, precise centralized research planning will be impossible; what will be needed is thoughtful decentralized planning based on increased opportunities for scientific communication. (85) It is wise that the CGIAR system is considering the addition of biotechnologists to advisory groups. There will need to be much more: exchange of personnel, support of education for developing world plant breeders and biotechnologists, conferences to bring together people from the international agricultural assistance community, the universities, the new developing-world biotechnology centers, and developed and developing world private industry. The opportunities are enormous and the benefits of communication are bound to outweigh the costs of competition and disclosure.

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(84) Genetic Engineering for Crop Improvement, supra, n. 50, p. 139.

(85) See D. Plucknett & N. Smith, "Networking in International Agricultural Research," Science, v. 225, p. 989 (7 September 1984); V. Ruttan, "Agricultural Research Policy Issues," HortScience v. 18(6), p. 809 (December 1983); M.S. Swaminathan, "Biotechnology Research and Third World Agriculture," Science, v. 218, p. 967 (3 December 1982).