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NATIONAL INSTITUTIONS AND TECHNOLOGICAL INNOVATION:

A CASE STUDY OF JAPANESE BIOTECHNOLOGY

Steven W. Collins

MITJP 95-06

Center for International Studies
Massachusetts Institute of Technology

E38-754
Center for International Studies
77 Massachusetts Avenue, Cambridge, MA 02139

Tel: 617-253-2839
Fax: 617-258-7432
Email: <robart@mit.edu>

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NATIONAL INSTITUTIONS AND TECHNOLOGICAL INNOVATION: A CASE STUDY OF JAPANESE BIOTECHNOLOGY

I. INTRODUCTION

The relationship between technological innovation and the larger social, economic, and political environment is the subject of increasing attention. One approach gaining currency uses the concept of "national innovation systems" (NIS) to explain how and why patterns of technological performance and change differ among nations.[1] Though it can be interpreted in a number of ways, the concept refers to the networks of institutions--firms, universities, research institutes, scientific and technical societies, national, state and local governments--that support technological innovation as a means of advancing the economic interests of industry and the broader military, developmental, and welfare interests of the nation-state.[2] Its usefulness as an analytical framework derives from the importance it attaches to the networks of relationships among supporting institutions, public policy and the political process, and the role of path-dependence in limiting the range of viable technological outcomes within a state. Put simply, technological innovation is embedded in a community of institutions whose systemic integrity is manifest at the national level.

Although scholars increasingly acknowledge the importance of contextual and systemic influences in shaping technological change, identifying precisely which institutions comprise an NIS is no simple task. Among the main points of contention is the degree to which systems of innovation remain distinctly national given the increasing complexity and geographic extent of

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[1] Representative works include David Mowery, "The U.S. National Innovation System: Origins and Prospects for Change," Research Policy 21 (1992): 125-144; Nathan Reingold, "The Peculiarities of the Americans or Are There National Styles in the Sciences? Science in Context 4 (1991): 347-366; Henry Ergas, "Does Technology Policy Matter?" in Technology and Global Industry, eds. Bruce Guile and Harvey Brooks (Washington, DC: National Academy Press, 1987); and Richard Nelson, ed., National Innovation Systems: A Comparative Analysis (New York: Oxford University Press, 1993).

[2] This definition draws from insights found in Christopher Freeman, Technology Policy and Economic Performance: Lessons from Japan (New York: Pinter, 1987); Richard Nelson, "Institutions Supporting Technical Change in the United States," in Technical Change and Economic Theory, eds. Giovanni Dosi, et al (London: Pinter, 1988); and Richard Samuels, "Rich Nation, Strong Army:" National Security and the Technological Transformation of Japan (Ithaca: Cornell University Press, 1994), chapter 9.

innovative activity.[3] On one hand, the proliferation of cross-border alliances, joint ventures, and foreign direct investment makes it increasingly difficult to determine where one national system ends and another begins.[4] On the other hand, many studies point to the increasing localization of production and innovation systems, examples of which include Silicon Valley and Route 128 in the United States and the Keihanna region in Japan.[5] Regional innovation systems develop around a major research university, research park, large firm, or a cluster of firms bound together in extended networks of long-term relationships; public policies often aim to catalyze their formation, though the presence of an abundant supply of highly specialized factor inputs drives the process.[6]

In what ways do national institutions shape the process of technological development? To what extent does the NIS approach retain explanatory power given the increasingly global scope of technology and business activity? This paper seeks to shed light on these questions through a detailed case study of the emergence of commercial biotechnology in Japan. Since the techniques of recombinant DNA and cell fusion came into practical use in Japan ten years ago, biotechnology has had enormous impact on the discovery and manufacture of pharmaceuticals, agricultural, and specialty chemical products. Although still small--580 billion yen in 1994 (roughly 5.8 billion dollars), or about one-tenth the size of the domestic pharmaceutical industry--the market for biotechnology products has exploded since the middle 1980's, growing on average between 30 and 50 percent annually. To date, fifteen physiologically important proteins and peptides of human origin, including interferons, growth hormones, blood cell growth factors, plasminogen activators, and hepatitis B vaccines have been successfully brought to market, as well as numerous monoclonal antibodies and specialty chemical products. Among leading economies,

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[3] For a thoughtful discussion of these limitations, see Nelson, National Innovation Systems, chapter 16.

[4] See, for example, Robert Reich, The Work of Nations (New York: Vintage, 1992); Peter Dicken, Global Shift: The Internationalization of Economic Activity, second edition (New York: Guilford Press, 1992); John Dunning, Multinational Enterprises and the Global Economy (Reading, MA: Addison-Wesley, 1993); R.D. Pearce, The Internationalization of Research and Development by Multinational Enterprises (London: MacMillan, 1989), chapter 7; Peter Cowhey and Jonathan Aronson, Managing the World Economy: The Consequences of Global Alliances (New York: Council on Foreign Relations, 1993).

[5] Giacomo Becattini, "The Marshallian Industrial District as a Socio-Economic Notion," in Industrial Districts and Interfirm Cooperation in Italy, eds. F. Pyke, et al (Geneva: International Institute for Labor Studies, 1990); AnnaLee Saxenian, "The Origins and Dynamics of Production Networks in Silicon Valley," Research Policy 20 (1991): 423-437; Allen Scott, Technopolis: High-Technology Industry and Regional Development in Southern California (Berkeley: University of California Press, 1993).

[6] Paul Krugman, Geography and Trade (Cambridge, MA: MIT Press, 1991); Michael Storper and Bennett Harrison, "Flexibility, Hierarchy and Regional Development: The Changing Structure of Industrial Production Systems and their Forms of Governance in the 1990's," Research Policy 20 (1991): 407-422.

only America's 7.2 billion dollar market surpasses Japan's. And yet the road to commercializing biotechnology has been strewn with boulders. Caught off guard in the late 1970's by the rapid diffusion of recombinant DNA techniques in the United States, Japanese industry faced a wall of regulations that severely restricted the use of genetically engineered organisms. After a bout of collective hand wringing, the political process was mobilized in an effort to launch a "bioindustry." In the middle 1980s, commercialization took off, fizzled, then rebounded as firms imported and indigenized foreign technology, in many cases "fusing" the new techniques with existing know-how to yield a distinctive set of technological trajectories. From the point of view of this paper, national institutions, policies, and stocks of knowledge and experience embodied in firms that had long served local markets had a powerful orienting effect on commercial development. In other words, the evidence makes a strong case for the national innovation systems approach. However, recent shifts by firms toward global and local networking strategies underscore the limitations of the model.

The next section of the paper recounts the story of biotechnology's evolution in Japan. I distinguish three phases: In the first phase, from the 1920's until 1980, Japanese industry developed world-class expertise in fermentation and industrial microbiology. When commercialization of biotechnology commenced in the 1970's, it was primarily these established firms, not new dedicated companies as in the United States, that shouldered the bulk of innovative activity. The second phase was marked by the birth and rapid growth of the American biotechnology industry and Japan's frantic effort to catch up. Finally, the late 1980's marked the beginning of a third phase as products began to reach the market, market entry trailed off, and the catch-up phase concluded. The paper ends with a reconsideration of the national systems approach in light of contradictory trends taking place in the third phase.

II. THE ORIGINS OF JAPAN'S BIOINDUSTRY: 1920-1980

Whereas molecular biology and genetics defined technological trajectories in the U.S., the impetus for innovation in Japan came from industrial applications. In the U.S., science paved the way for commercial development; in Japan, commercial need determined relevant fields for subsequent scientific inquiry. Generally, private firms were the center of action, though they enjoyed a steady stream of highly capable new researchers from engineering and agricultural science departments of the national universities. Rather than probe scientific frontiers, firms concentrated on shoring up areas close to their own traditional technological strengths in food processing and fine chemicals. Institutional linkages were few, government policy weak or absent entirely. Nevertheless, food and chemical companies undertook a series of innovations that established Japan as a the global leader in modern industrial fermentation and bioprocess engineering. On the basis of accumulated skills in conventional process technologies, these firms would later spearhead Japan's thrust into genetic engineering and cell fusion-based biotechnology in the early 1980's.

A. Industrial Fermentation and Japan's Traditional Industries

Commercial biotechnology in Japan dates back to a centuries old tradition of craft-based fermentation, brewing, and applied microbiology. Historical accounts attribute Japanese strengths in bioprocessing to centuries of food and agricultural practices which emphasized tinkering with biological phenomena. The production of sake (nihon-shu), an alcoholic beverage derived from fermented rice, is documented as early as 712 AD in the ancient historical text Kojiki; today, more than 200 companies carry on the tradition, many using processes dating back hundreds of years.[7] In addition, production of traditional cuisine such as soy sauce, miso (soy bean paste, often used as a soup base), tofu (bean curd), natto (fermented soy bean paste), and murin (a sake-like substance used in food preservation) gave Japan's food processing industry early experience with microbial fermentation. One of Japan's oldest extant corporations, Yamasa Shoyu, began as a producer of soy sauce in 1645; in the 1980's it was one of scores of food processing companies that diversified into biopharmaceuticals. Initially, contributions from theoretical science were few; technology was mostly in the form of experiential or tacit knowledge embodied in craftsmen.[8] And although other countries, especially in Europe, had also mastered craft-based fermentation by the middle of the nineteenth century, none approached the level of sophistication commonly found in Japan.[9] According to Karube, this early experience in applied microbiology provided a solid foundation on which Japanese firms would later build world-class expertise in antibiotics and amino acid production.[10]

Crucial to the mastery of fermentation techniques were the new schools of agriculture attached to the imperial universities, which the government had established as a means of promoting absorption of foreign technology.[11] Like their counterparts in modern times, these schools housed departments of applied microbiology (or in some cases departments of biochemistry), whose original faculty had been trained largely by German organic chemists, and whose focus was, and remains, fermentation engineering. Graduates often moved directly into industries that manufactured traditional food and beverage products. Working through the Nihon

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[7] Hongo Motoyoshi, Nihon no baiteku choryu: shindai kara gendai o koete [Trends in Japan's Biotechnology: From the Age of the Gods to Modern Times] (Tokyo: HBJ Shuppankyoku, 1988), pp. 4-6.

[8] The modern science of microbiology emerged only after the pathbreaking experiments of the French scientist Louis Pasteur in the mid nineteenth century.

[9] According to one source, Japan was the only country at that time capable of carrying out fermentation using more than one type of micro-organism. Indeed, there is evidence that brewers and fermentors used quite elaborate mixtures of organisms, which they could vary depending on characteristics desired in the final product. See Hongo, Nihon no baiteku, p. 51.

[10] Karube Isao, Baio no hanashi: nogyo kara erekutoronikusu made nyu baiogijutsu ga hiraku kanosei [The Biotechnology Story: The Potential of New Biotechnology From Agriculture to Electronics] (Tokyo: Nihon Jitsugyo Shuppansha, 1991), pp. 20-21.

[11] The Commission on the History of Science and Technology Policy, ed., Historical Review of Japanese Science & Technology Policy (Tokyo: National Institute of Science and Technology Policy, 1991), pp. 20-21, 25.

Nogei Kagakukai (Japan Agricultural Chemistry Society), which was formed in 1927, these scientists contributed to several key product and process innovations. The most significant of these was the food flavor enhancer monosodium glutamate (MSG), which in the 1930's became one of Japan's major export products.[12] Given the nearly complete absence of modern research capabilities in the private sector, firms relied strongly on infusions of such newly trained scientists into their organizational structures.[13]

Process innovations in fermentation and microbiology helped revive Japanese industry in the early post-war period. Two early beneficiaries were the drug and food processing industries. In 1948, the U.S. Occupation forces introduced strains of penicillin into Japan for the first time. More than seventy companies rushed headlong into the new industry; by one author's estimate, virtually the entire class of 1942 of the department of applied microbiology of Tokyo University became chief executive officers of these new companies.[14] Although only four of the original 70 firms survived, Japan quickly emerged as the world's foremost producer and exporter of antibiotics, for which it now supplies roughly 60 percent of global demand.[15] One reason was the development of large, enclosed fermentors that employed new techniques of agitation and aeration (the kokiseihakko process). Though the first large-scale, aerated fermentation was carried out in the U.S. and Europe, the improvements contributed by Japanese firms actuated the shift to mass production.[16] Many of the processes pioneered in Japanese firms in the early post-war period remain standard practice worldwide in the production of antibiotics.[17]

Process innovation in the drug industry trickled down to chemical and food processing firms. In the 1950's and 1960's, Japanese firms achieved breakthrough innovations in the manufacture of amino and nucleic acids for food and specialty chemical applications. Perhaps the most important of these was Yoshiro Kinoshita's discovery in 1955 of an organism that permits efficient, single-step synthesis of the amino acid glutamate, which gives MSG its distinctive flavor. Commercialized in 1909 by Ajinomoto Corporation, MSG originally required costly extraction of glutamic acid first from seaweed, then from Chinese soy bean.[18] Capitalizing on Kinoshita's

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[12] For a discussion of the Nihon Nogei Kagakukai, see Malcolm Brock, Biotechnology in Japan (London: Routledge, 1989), p. 30.

[13] Hongo, Nihon no baiteku, pp. 102-103.

[14] Herman Lewis, "Biotechnology in Japan," Scientific Bulletin 10 (April-June 1985), Department of the Navy, Office of Naval Research Far East, p. 13.

[15] Hans Katayama, "Biotech Unbound," Business Tokyo (September 1991), p. 23.

[16] Hongo, Nihon no baiteku choryu, pp. 105-106; Karube, Baio no hanashi, p. 14.

[17] Today, roughly 50 antibiotic compounds, including penicillins, tetracyclines, and streptomycins, are produced in commercial amounts, mostly by submerged-culture methods introduced and refined in Japan. They are used not only to treat human disease and infection, but as growth-enhancing additives in animal stock feeds. See James Bailey and David Ollis, Biochemical Engineering Fundamentals (New York: McGraw Hill, 1981), pp. 605-607.

[18] Though inefficient, extraction of glutamate from plant protein left amino acid residues which were sold as fertilizer and as flavor-enhancing additives for use in soy sauce manufacturing. This

discovery, the chemical company Kyowa Hakko in 1956 conducted the world's first large-scale production of glutamic acid by fermentation. By 1960, advances in metabolic suppression techniques had made possible mass production of a variety of commercially important amino and nucleic acids, hormones, and vitamins.[19] Intense competition fueled technological change: Ajinomoto, determined not to surrender market share to Kyowa Hakko, fought back by quickly developing an even more efficient process for making MSG. In addition, in a move reflecting the crucial importance of fermentation in shaping subsequent technological trajectories, Ajinomoto began using byproducts from glutamic acid production as starting materials for making a new generation of pharmaceutical products. The company now supplies more than half of world demand for amino acid-based drug products.[20]

B. The Emergence of Modern Biochemical Process Technology

By 1970 Japan was firmly established as the world leader in bioprocess technology applied to production of commodity chemicals. In addition, its laboratories had on hand the world's greatest variety of microorganisms which had been screened, mutated, and cultured for industrial use. Its most lasting contributions, however, came in the late 1960's and early 1970's in a cluster of innovations that vastly improved the performance and range of application of industrial bioreactors.[21] Though lacking the high drama of research in molecular genetics then underway in the U.S., Japan's process innovations not only facilitated catch-up, albeit a decade later, they provided the hardware necessary to scale up and commercialize the new products made possible by the new genetic engineering techniques.

The breakthrough innovation came in 1969, when Tanabe Seiyaku, a mid-size drug maker, pioneered the immobilized enzyme technique for production of L-glutamic acid. Tanabe's breakthrough involved isolating the necessary enzyme and then depositing it onto a sticky solid

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represents an early example in Japan of a single process innovation yielding product and process innovations in other areas. In the 1940's, U.S. companies began producing MSG using the glutamate extraction process; however, the absence of markets for by-products made it impossible for companies to defray high production costs. See Hongo, Nihon no baiteku, pp. 127-128.

[19] For details, see Kogyogijutsuin somubu gijutsu chosakai, hen, Baioindasutorii: sono kanosei o saguru [Probing the Potential of Bioindustry] (Tokyo: Tsushosangyochosakai, 1982), pp. 16-17.

[20] Nikkan kogyo shimbunsha, hen, Nihon no kenkyujo yoran [Survey of Japanese Research Laboratories] (Tokyo: Nikkan shobo, 1991), pp. 6-7, 56-57.

[21] Generally, a bioreactor is a large tank in which nutrients, cultured microbes, and enzymes interact chemically to yield a desired final product. Structurally, however, it differs from a simple fermentor in that it contains "immobilized" (koteika) enzyme or microbial cultures, usually fastened to a solid support, whose function is to catalyze or otherwise quicken the pace of the desired reaction. Glass beads, roller bottles, and flat plates are among the materials used to support the catalyst, thereby immobilizing it. See Katsuki Yoshitaro, "Kogyo bunya ni okeru baio no oyo: biaoriakutaa o chushin toshite," [Biotechnology Applications in Manufacturing: Focus on Bioreactors] Purometiusu 57 (March-April 1987): pp. 40-43.

support immersed in the reaction vessel, hence immobilizing it. Through continuous contact with the vessel's liquid contents, the immobilized enzyme hastened conversion of starting materials to desired final product. Though simple in principle, the technique had revolutionary consequences. By consuming less enzyme and energy than conventional methods, Tanabe's technique slashed the cost of producing amino acids by 30 to 40 percent.[22] A few years later, researchers applied the concept to microbes, whose immobilization in ceramic packing or other suspension greatly broadened the scope of applications for the bioreactor. By the mid 1970's, it had become the standard process in the production of syrups and oils, glucose and other sugars, enzymes, detergents, nutritional supplements, specialty chemicals, antibiotics, and even cosmetics.[23] The bioreactor's importance was acknowledged by MITI when, in 1981, it incorporated the technology as one of four targets in its Next Generation Biotechnology project.

These early advances in the areas of fermentation, bioreactors, and large-scale cell culture placed Japan in a favorable position to exploit recombinant DNA technology that emerged in the U.S. after 1972. Genetically engineered drugs and vaccines depended strongly on processing technologies; efforts on the part of American firms to access complementary assets in scale-up and manufacture attest to their significance.[24]

On the other hand, there were clear limits on the extent to which process technologies could drive technological change, given the maturity of markets for fine chemical products. Perversely, bioreactors may have even deterred subsequent innovation by driving down prices: glutamic acid in 1980 was selling at its 1950 price, despite the more than six-fold increase in consumer prices. Many companies after the twin oil shocks moved production overseas. On the eve of the genetic engineering revolution, the fear was that productivity gains from recombinant DNA technology would destroy, not rejuvenate, Japan's traditional fine chemicals industry.[25]

Also weakening Japan's position after 1970 was the surprising ambivalence of Japanese companies toward the new genetic technologies, even as they were beginning to take off in the U.S. The only major firm to undertake a substantial commitment to research in the life sciences was Mitsubishi Kasei, which in 1971 established one of Japan's first private laboratories dedicated solely to research in the life sciences. The extent of Japan's nonparticipation was subtly criticized

[22] Hongo, Nihon no baiteku, pp. 144-145. Tanabe's process involved mounting in the reactor vessel a resin on which a precise quantity of enzyme needed to control the reaction (in this case amino acylase) had been affixed. In older methods, large quantities of costly enzyme had to be added continuously to the process.

[23] Karube, Baio no hanashi, pp. 108-109.

[24] Amgen, the world's leading producer of biopharmaceutical products recognized Japan's strengths in bioprocessing early on. In the middle 1980s, it formed a joint venture with Kirin Beer to scale up and mass produce its erythropoetin and granulocyte macrophage colony stimulating factor, which today are the world's best selling genetically engineered products.

[25] "Baiotekunorojii no shogeki: aminosan shijo ijo ari" [Biotechnology shock: disorder in amino acid markets] Nikkei Sangyo Shimbun (16 July 1981).

in an early MITI study, which noted that of the 40 key research breakthroughs in molecular biology stretching from 1665 to 1981, Japanese researchers were credited with only four.[26] When the actions of Genentech and other American start-ups finally galvanized Japanese companies into action in the early 1980's, they were so far behind as to render catch up a nearly impossible task, even with a head start in process technology. Nevertheless, Japan's strengths in bioprocessing must not be downplayed.[27] After all, most firms that acquired new product technology from the U.S. in the 1980's quickly commercialized the results, often before the product reached the market in the U.S.

C. Rumblings in the Laboratory

The relative absence of basic research in biomedical science must be understood in the context of Japan's post war development needs. Given the destruction of much of Japan's physical infrastructure, industrial reconstruction and modernization naturally took precedence over pushing back frontiers of basic science. Through the 1960's, virtually all new drugs and biologicals introduced in Japan were developed by foreign companies; few firms could afford to undertake the massive R&D required to develop a new drug on their own. Fermentors, bioreactors, and other process innovations also flowed largely out of incremental applied research--in essence, tinkering--carried out on production floors and corporate R&D laboratories. Japan's push into biotechnology had thus been up to this point almost entirely industry-driven.

In terms of policy, the Ministry of International Trade and Industry (MITI) maintained exclusive jurisdiction over matters pertaining to industrial science and technology. The Ministry of Education (Monbusho), though reorganized under the U.S. Occupation, quickly re-centralized administration of university research under its tight jurisdiction. Scientists themselves were polarized ideologically between the "minka" group, which resisted the industrial orientation of science and dependence on imports of foreign technology, and the "technocratic group," which went along with the status-quo--a schism whose influence still reverberates through the academy.[28] The creation of the Science and Technology Agency (Kagaku gijutsucho) in the mid 1950's was aimed at unifying science policy within a single administrative unit; yet the practical effect was to add yet another competitor for relatively scarce science funding.[29] The resulting

[26] Kogyogijutsuin, Baioindasutorii, pp. 25-30.

[27] See in particular the recent report of the Japanese Technology Evaluation Center (JTEC). JTEC, Bioprocess Engineering in Japan (Springfield, VA: National Technical Information Service, 1992).

[28] Interview with Nambu Hiroyuki, Professor of Economics, Gakushuin University, Summer 1995. Nambu, who has studied the history of the pharmaceutical industry in Japan, contends that the arms-length relationship between academic researchers and drug firms has hobbled commercial development, especially in the area of clinical trials.

[29] The STA has two roles: it administers six national laboratories and seven special public corporations, and it formulates and administers science policy along lines proposed by the Prime Minister's Council on Science and Technology (CST). Although it is often said that STA "coordinates" interministerial science policies, that in fact is too strong a term. STA officials

institutional structure produced a schizophrenic policy environment in which research in the universities--with a few notable exceptions--became almost completely disconnected from applied research and development in industry, while different ministries wondered off in different directions--a problem that still evokes much hand-wringing in Japan's science policy community. Although steps have been taken to increase joint research between universities and industries, there simply has been no counterpart in Japan to the tight institutional nexus between biotechnology firms, universities, and the National Institutes of Health (NIH) that so powerfully underpins the dynamism of American science.

Not until the early 1970's did references to molecular biology begin to appear widely in science policy discourse. The turning point came in 1971, when the Council on Science and Technology (CST), which officially advises the Prime Minister and Cabinet on science policy, issued the fifth in a series of broad policy statements on science and technology. It noted Japan's lagging investment in R&D as a proportion of national income, which at less than 2 percent, was roughly half that of the U.S. and one-third that of West Germany. Most significantly, the report called for application of the principles of molecular biology in five areas: treating cancer, improving animal and plant breeds, developing information processing devices, engineering of microorganisms, and environmental preservation.[30] A few years later, the Council's newly formed Committee on the Life Sciences (raifusaiensu bukai) issued an interim report that linked elucidation of life phenomena on the molecular level to applications in preventive medicine, treatment of the elderly, cancer therapy, animal agriculture, and development of new food resources.[31] Although, curiously, the interim report failed to acknowledge the recombinant DNA process which had been demonstrated in the U.S. a year earlier, it galvanized the scientific community to the potential importance of this new and expanding field of inquiry.

Initially, only the Science and Technology Agency moved aggressively on the CST's recommendations. In 1974, it established the Center for Promotion of the Life Sciences in its leading laboratory, the Institute of Chemical and Physical Research (RIKEN). The new center initiated projects grouped under five themes: control of aging, engineered enzymes and bioreactors, the biology of thinking, artificial organs, and physiologically active substances.[32] Three years later, it was elevated into a full-fledged institute within RIKEN. Elsewhere, mission-

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themselves use the phrase kokuzentai toshite seigosei o tamotsu, which might be translated as "keeping the parts of the machine in adjustment." See Kagaku gijutsucho, Kagaku gijutsu hakusho, heisei yonen han [Science and Technology White Paper, 1992 edition], p. 241.

[30] Kagaku gijutsu kaigi, Komon dai 5 go: "1970 nendai ni okeru sogoteki kagakugijutsu seisaku no kihon ni tsuite" ni taisuru toshin [The basis for science and technology policy for the 1970's], 21 April 1971, pp. 3-6., pp. 38-39. The report uses the term "life sciences" (raifusaiensu) rather than biotechnology, which would not gain currency for another decade.

[31] Kagaku gijutsu kaigi, raifusaiensu bukai chukan hokoku [Interim Report of the Committee on the Life Sciences], December 1974.

[32] Kagaku gijutsucho, Kagaku gijutsucho nenpo, showa 52 nendo [Annual bulletin of the Science and Technology Agency, 1977], p. 77.

oriented research related to life sciences slowly increased in prominence, especially in the national laboratories of the Ministry of Health and Welfare and in research institutes of public universities associated with Monbusho's anti-cancer research program.[33]

Astonishingly, not until the CST's "Sixth Recommendation" in May, 1977, did science policy officially respond to the first experiments on recombinant DNA that had been taking place in the U.S. since the early 1970's. While the policy statement echoed old themes, it for the first time called for a policy promoting research in recombinant DNA and proposed guidelines for its safe conduct.[34] This set in motion a chain of events by which both CST and Monbusho drew up separate guidelines for regulating research using genetically modified organisms. A year earlier, in 1976, the Recombinant DNA Advisory Committee of the American NIH had issued the world's first comprehensive guidelines. Using the NIH's guidelines as a blueprint, the Science Council of the Ministry of Education (gakujutsu shingikai) issued its policy in March, 1979--but only after more than two years of intense lobbying by Japanese scientists. The guidelines covered only research conducted in universities or affiliated institutes, or with grant funds obtained from Monbusho. Five months later, the CST, in response to a Cabinet request, issued its own set of guidelines covering research in government institutes not associated with Monbusho.[35] These were somewhat less restrictive than those of Monbusho, an indication of industry's participation in drawing them up.[36]

Delay in setting up a regulatory framework and responding to developments in the U.S. cost Japan dearly. In the first place, the reaction began a full four years after Cohen and Boyer had first spliced foreign DNA into a bacterial host cell. During that interval, public and private research in the U.S. had boomed, giving American researchers a virtually insurmountable lead. To make things worse, few Japanese firms showed any interest at all in applications of the new techniques, squandering any advantages attributable to their strengths in bioprocessing.

Finally, by the time Japan's regulatory framework coalesced, America's NIH had already eased or eliminated 90 percent of the restrictions in its original draft.[37] This left Japanese researchers encumbered with regulations with which American researchers did not have to contend. Though these were eased in 1982, and again in 1983 under intense pressure from

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[33] Kagaku gijutsucho, Raifusaiensu no genjo to tenbo: showa 49 nen han [Current Conditions of Life Science, 1974], p. 8.

[34] Kagaku gijutsu kaigi, komon dai 6 go "chokiteki tanbo ni tatta sogoteki kagakugijutsu seisaku no kihon ni tsuite" ni taisuru toshin [The Fundamentals of Comprehensive Science and Technology Policy with a View to the Long Term: A Report Made in Response to the Prime Minister's Inquiry No. 6], 25 May 1977, pp. 95-97.

[35] Kogyogijutsuin, Baioindasutorii, pp. 101-105.

[36] In particular, the CST's guidelines broadened the range of bacterial hosts that could be used in recombinant DNA experiments. Brock, Biotechnology in Japan, p. 87.

[37] Kogyogijutsuin, Baioindasutorii, p. 107; "Seimei o ayatsuru: kikendo ni ooji shishin" [Manipulating Life: Guidelines to Deal with the Dangers," Asahi Shimbun (15 January 1981).

industry, many companies by that time had already invested in costly safety facilities that suddenly became obsolete.[38] Without the flexibility to respond nimbly as knowledge accumulated--NIH had revised its guidelines five times by 1982, compared to the Japanese government's single revision--Japanese firms limped into the commercialization stage at a severe disadvantage.

III. BIOTECHNOLOGY FEVER HITS JAPAN (1980-1985)

A. Barriers to Commercializing New Biotechnology

Industry's leadership in bioprocess technology, coupled with the government's failure to move expeditiously on new scientific advances, left Japan's biotechnology effort in an awkwardly ambiguous position. On the one hand, Japan had garnered 60 percent of the 2400 biotechnology-related patents awarded worldwide between 1977 and 1981, though the vast majority covered innovations related to bioreactors and other so-called "old" biotechnologies.[39] Beginning in 1980, moreover, the new regulatory framework unleashed a flurry of activity in the nation's university, public, and private research laboratories: the number of registered experiments involving recombinant DNA rose from 284 in 1980 to more than 3500 in 1986.[40]

On the other hand, Japan remained far behind the U.S. and Europe in terms of resources committed to research related to the life sciences, even correcting for differences in GNP. Though estimates varied, one source suggested that Japan had fallen as far as ten years behind the U.S.[41] In 1980, total funds committed to biotechnology research in public research institutes amounted to only 13 percent of those in the U.S. and one-third of those in West Germany; funding for biomedical research, of which biotechnology was a component, amounted to a mere 1/30 the level in the U.S. The private sector, too, lagged far behind: funding of biotechnology R&D in Japan's five leading firms amounted to only 14 percent of that being spent in the five leading western companies, which also had more than 17 times the number of researchers (Tables 1 and 2).[42]

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38 JEI Report (24 February 1984), pp. 7-9.

39 Tsushosangyosho, kisosangyokyoku hen [Basic Industry Bureau of MITI], 21seiki o hiraku biaoindasutorii: sono tenbo to kadai [Bio-Industry: Making way for the 21st Century] (Tokyo: Tsushosangyochosakai, 1984), p. 248.

40 Tsushosangyosho, Baioindasutoriishitsu hen [Bio-industry Office of MITI], Baioindasutorii bijion: sekai ni koken suru nihon no baioindasutorii [Vision for the Bio-industry: Japanese Bio-industry's Contribution to the World] (Tokyo: Tsushosangyochosakai, 1988), p. 74.

41 Nihon Kogyo Ginko [Industrial Bank of Japan], "Baiotekunorojii no shintenkai to kadai," [New developments and problems in biotechnology], Ginko chosa No. 4 (1984), p. 28.

42 "Baiotekunorojii," Kogyo gijutsu [Industrial Technology] 22 (November 1981), p. 28.

TABLE 1

Conditions in Government Laboratories at the Beginning of the 1980's

Country	Expenditures in Life Sciences (billions of yen)	Of Which was Bio-Technology-Related (billions of yen)
Japan	25.1 (1980)	1.6 (1980)
U.S.	771 (1979)	12 (1979)
U.K.	---	2.5 (1980)
W. Germany	---	5.3 (1980)

TABLE 2

Conditions in Five Leading Private Firms at the Beginning of the 1980's

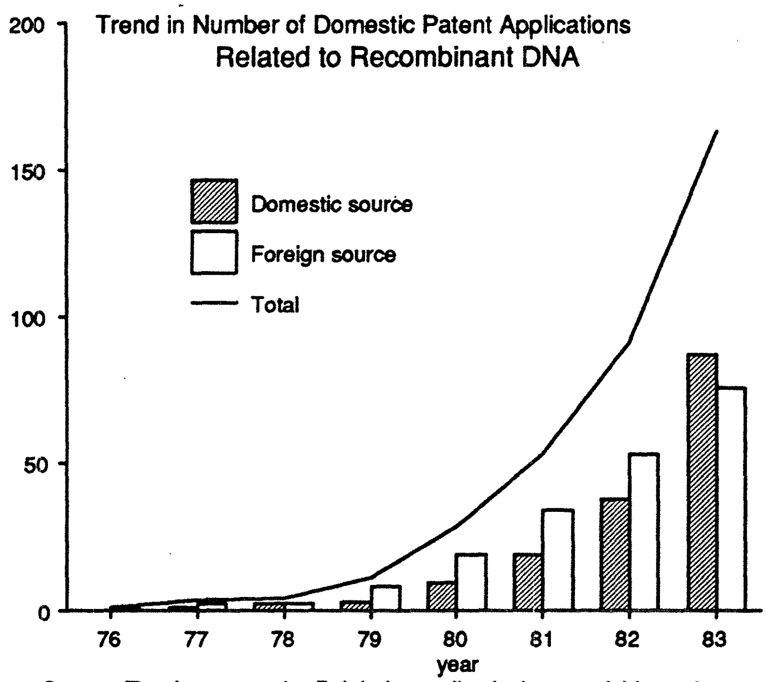
	R&D Expenditures (billions of yen)		Number of Researchers	
Country	Total	Life Science	Total	Life Science
Japan	53.2	9.9	6,600	845
U.S./Europe	370	124	42,200	14,900

Source: "Baiotekunorojii," Kogyo gijutsu [Industrial Technology] 22 (November 1981), p. 28.

The effects of relatively low levels of research appear in Japan's patent data for the period, which show a high level of foreign ownership of key patents related to recombinant DNA. In 1978, foreigners received two of six rDNA patents, six of nine in 1979, and 10 of 11 in 1980, after which the proportion awarded to Japanese parties gradually began to take off; overall from 1973 to 1981 foreigners filed for more than three-fourths of all patents in fields related to the life sciences.[43] Only after 1983 do Japanese applications even begin to outnumber those of foreigners (Figure 1). Such foreign penetration of Japanese patenting is striking considering that

[43] Kiban gijutsu kenkyu sokushin sentaa [Key Technology Center], Baiotekunorojii kenkyuukaihatsu kiban ni kakaru chosa hokokusho [Survey report on base research and development in biotechnology] (Tokyo: Baioindasutorii kyokai, 1987), p. 100.

FIGURE I



Source: Tsushosangyosho, Baioindasutorii seisaku no suishin, p. 31

the proportion of foreign ownership of all patents awarded in Japan during this period ranged from 13 to 15 percent.[44]

Japan thus found itself in a position quite different from that of the U.S. Large chemical, food, and pharmaceutical companies, though strong in downstream process technologies and distribution networks, had little access to relevant knowledge bases; there were literally no researchers working in genetic engineering in private industry. Nor was there a pot of venture capital awaiting potential investors not already affiliated with an established company. Not that such funds would have mattered, for Japanese universities, which had only just received permission to conduct experiments using recombinant DNA, fielded few scientists whose research offered meaningful commercial prospects. In addition, restrictions on formal faculty contacts with industry and taboos on professors leaving university posts blocked the university-industry channel which was at the heart of America's success.[45]

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[44] Kagaku gijutsu cho, Kagaku gijutsu hakusho, 1992, p. 398.

[45] Indeed, such faculty in the U.S. drew ridicule in the Japanese media, which referred to them as gakusha shonin (scholar-merchants), whose sell-out to business threatened the free flow of scientific information and corrupted the mission of the basic research enterprise. Nikkei Sangyo

The U.S. had demonstrated that mastery of the new technology required the marriage of excellent basic research, risk capital, and visionary entrepreneurship. This had been accomplished through creation of a specialized institution--the dedicated biotechnology firm ("DBC")--which pulled together the complementary assets needed to move new ideas into the product development stage. An institutional adaptation to highly mobile financial, knowledge, and human resources uniquely abundant in the American national system, DBC-style enterprises were ill suited to conditions in Japan. Yet Japanese firms faced the same technical challenges as those in the U.S. The problem, therefore, was to craft an institutional response that could overcome the technical hurdles, while capitalizing on the distinct market conditions and resources available in the Japanese national system. Because high uncertainty and risk deterred most firms from entering the market--a classic case of market failure--the role of formulating a response fell to the government. Before that could happen, however, a consensus on the importance of mounting a commercial thrust had to obtain.

B. The Public Policy Response

In 1980, biotechnology burst into the national limelight. That year, the Japanese term for biotechnology (baiotekunorojii), along with references to a distinct biotechnology industry (baioindasutorii), began to appear in government and private sector reports. Newspapers ran glossy spreads on the "genetic revolution" underway in the life sciences, noting in particular the degree to which Japan had fallen behind. Biotechnology, all but ignored by industry during the 1970's, suddenly was hailed as a "base technology" (kiban gijutsu) that would underpin the future industrial economy. As one journalist put it, Japan was about to "catch the biotech wave" rolling in from the U.S.

The surge of interest in biotechnology grew out of a sense of panic that a new technological revolution was beginning without Japan's participation. Several developments raised this concern to the level of national policy. First was the growing chorus of criticism from the scientific community concerning the severity of restrictions on research using recombinant DNA and general ambivalence with which the government appeared to be responding to new breakthroughs in the U.S.[46] The Japan Society for Bioscience, Biotechnology, and Agrochemistry and the Chemical Society of Japan led the lobbying effort, arguing that unless the government took action, the nation would be rendered irrelevant as a meaningful contributor to the global scientific effort.[47]

Shimbun, Seimei sangyo jidai: Baiotekunorojii no shogeki [The Era of Bio-Industry: Biotechnology Shock] (Tokyo: Nihonkeizai shimbunsha, 1981), p. 164.

[46] "Jikken de usureta kikenshi: Bei de wa Teppai, Nihon de wa okureru" [Japan lags U.S. in abolishing tough restrictions on experimentation] Nikkei Sangyo Shimbun (8 August 1981).

[47] Interview with Dr. Kinji Gonda, Director in Research, National Institute of Science and Technology Policy, Fall 1991, Summer 1995. According to Dr. Gonda, scientific organizations play a crucial role in gathering information from abroad and diffusing it within the scientific and public policy community.

Second, commercial take-off in the U.S., especially the record-shattering initial public offering of Genentech in the fall, 1980, and the subsequent rapid-fire emergence of American DBCs, caught experts in Japan by surprise.[48] For the Japanese, Genentech embodied the ethos of American capitalism; indeed, Genentech's CEO and co-founder Robert Swanson became a media sensation when he visited Japan late in 1980, prompting one observer to comment: "Whether biotechnology has the promise of semiconductors remains to be seen; nevertheless, Genentech will be the world's next Sony."[49] Reinforcing these fears was a flurry of patent activity by DBCs in Japan; as noted above, in no other industry were Japanese companies ceding the lion's of intellectual property on their own turf to foreigners. In addition, the granting of an important patent in the U.S. covering part of the original Cohen-Boyer recombinant DNA process, coupled with the U.S. Supreme Court's landmark decision to uphold the right to patent a genetically altered organism, added to the fear that Japan might be entirely shut out of the new genetic technologies. Warning of dire consequences should that happen, Keidanren, Japan's prestigious peak industry association, brought its influence to bear on urging a decisive policy response.[50] A MITI official summed up the emerging consensus: "We're as far behind the U.S. in biotechnology as we are in rocket technology... For a country with no natural resources, technology is the only means of survival. Consequently, government and industry must work together to develop biotechnology."[51]

Finally, though seemingly unrelated to biotechnology, there was deepening concern over how to deal with Japan's struggling chemical industry. Since the mid 1970's, MITI and the industry had tried various attempts at reducing capacity to no avail. The twin oil shocks of the 1970's had abruptly halted two decades of stable growth. The tripling of prices of petroleum-based feedstocks from 1972 to 1975, and again from 1978 to 1980 sent firms reeling; thereafter, ruinous competition and surging imports of chemical intermediates from the U.S., amid declining demand in the domestic market, wreaked further havoc, especially among the "Big 12" oil companies. Growing concern over pollution and a number of high profile accidents at large processing plants, moreover, had cast a pall over the industry.[52] As the new decade began, MITI and industry were groping toward measures that would encourage firms both to reduce capacity and shift resources away from petroleum-based commodity chemicals to fine and specialty chemical products.

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[48] "Kigyoka sareru seimei: joho ga kigyo no shimei o sei suru" [Commercializing Life: Company's at the Mercy of Information] Asahi Jyaanaru (19 December 1980), pp. 22-25.

[49] "Idenshi de dai ni no Sonii ni" [Becoming the second Sony by way of the gene], Asahi Shimbun (6 January 1981), p. 22.

[50] "Nigasu na san cho en sangyo" [Don't miss out on 3 trillion yen industry!], Asahi Shimbun (7 January 1981), p. 18.

[51] "Gijutsu rikkoku e kan-zai-ro ittai de" [Technological leadership through government-finance-labor cooperation], Asahi Shimbun (11 January 1981).

[52] Itami Hiroyuki, Nihon no kagaku sangyo: naze sekai ni tachiokureta no ka [Japan's Chemical Industry: Why It Lags the Rest of the World] (Tokyo: NTT Shuppansha, 1991), pp. 83-85

For MITI, this convergence of policy demands provided an extraordinary opportunity: why not fuse structural adjustment and high technology policies by persuading chemical companies to lead Japanese commercial entry into the new biotechnology in return for adjustment assistance?[53] Consequently, MITI secured funding for its Next Generation Industries Base Technology (Jisedai) project, which targeted biotechnology, electronic devices, and new functional materials as three core technologies which would "adjust" Japan's industrial structure (sangyo kozo chosei) for competition in the upcoming decade. MITI took the lead in the program by organizing the Research Association in Biotechnology (RAB), which brought together eleven of Japan's top chemical companies, along with two pharmaceutical and one food company, to work jointly on projects related to commercial applications in genetic engineering, mass cell culture, and large-scale bioreactors. MITI's first foray into biotechnology, the program mobilized industry's interest, thus helping to launch Japan's commercial biotechnology boom.[54] That MITI managed the project from its newly established Bioindustry Office in the Basic Industries Bureau, which oversees the chemical and heavy industries, gave clear indication of its aim to link high technology promotion with structural adjustment.[55]

C. Commercial Take-Off and the Consequences of Government Policy

Judging from the acceleration in rate of market entry into biotechnology after 1980, MITI's initiation of a biotechnology policy certainly could qualify as a success. It is quite possible, however, that firms would have become active regardless of MITI's action. Indeed, my interviews with industry participants in the initial RAB projects suggest that MITI's policy helped, though only at the margins: firms viewed the seriousness with which MITI approached biotechnology as validation of the technology's potential but also as an indication that onerous regulations would soon be loosened. By 1985, at the peak of the "bio-boom," an average of 30 firms were entering the biotechnology market each year, six times the rate of the late 1970's. Between the late 1970's and 1985, more than 200 companies started major biotechnology development programs.[56] Not only did companies rush into the market, other government agencies quickly began promoting biotechnology policies for their client firms, broadening the extent of participation into agriculture and pharmaceuticals. The next few years ushered in what one analyst called the "explosive rise to power" (bokkoki) of government leadership (seifushudogata) over the fledgling industry.[57]

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[53] For a discussion of the process by which this policy was arrived at, see Brock, Biotechnology in Japan.

[54] "'Tsusan ni Tsuzuke' issai ni," Nikkei sangyo shimbun (12 August 1981).

[55] Interview, Mr. Yuuichi Sakamoto, Director, Coordination Division, Japan Bioindustry Association, Fall, 1991.

[56] "10 shunen kinen tokushu: Baio/ 1981 nen/ 1991 nen/ 2001 nen," Nikkei Baio-interijiensu (7 October 1991), p. BI-4.

[57] Nikkei Baio-interijensu, (7 October 1991), p. b16.

The speed with which MITI had implemented its program and the prestige surrounding the promotion of a national strategic technology were lessons not lost on other ministries. In 1983, the Central Pharmaceutical Affairs Bureau of the Ministry of Health and Welfare (MHW), concerned about stagnating profits in the pharmaceutical industry, convened a biotechnology study group. The group's final report, issued in the Fall of 1984, called for, among other things, improvement of basic research and establishment of a "Biotechnology Research Exchange Center." In April 1985, on the recommendation of the Pharmaceutical Industry Policy Forum, the Japan Association for Advanced Research of Pharmaceuticals was formed and charged with the task of applying advanced technologies such as genetic engineering to human health care and catalyzing cooperation among drug firms, universities, and public research institutes.[58] Fast on its heels, the Ministry of Agriculture, Forestry, and Fisheries (MAFF) set up its Biotechnology Division and government-industry consultative committee, the Cooperation Group for Promoting R&D in Biotechnology. Unlike MHW or MITI, MAFF has no single organization that promotes commercialization of biotechnology across the spectrum of industries falling under its jurisdiction. Instead, it has established a number of small RAs to promote cooperative research in the many sub-fields under its jurisdiction. These include the areas of enzyme function, bioreactors, agrochemical, and genetic analysis of agricultural organisms. Two aspects of MAFF's activities would have an important bearing on later commercial trends. First, more than other ministries, it has had to deal intensively with public concerns about the release of genetically altered organisms in the environment. Secondly, by virtue of the organization of MAFF's research into a large network of regional research institutes, it has become an important, if debatably effective, channel for technology transfer into rural areas.[59]

The results of government policies were mixed. On the one hand, a wide variety and number of firms entered the industry, many of which did not participate in formal RAs (see Table 3). Competition, therefore, was intense: no less than six companies vied to commercialize cancer-killer interferon alpha; TPA, Genentech's blockbuster anti-clotting agent, drew seven Japanese competitors, including firms from the textile, dairy, chemical, and food industries.[60]

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[58] Koseikagaku kaigi, "Koseikagaku kenkyu no kiban kakuritsu to bureikusuruu no tameni" [Establishing breakthrough-oriented welfare scientific research base], September 1987. "Hyuman Saiensu Shinko Zaidan", Hyuman Saiensu Nyusu 5 (August 1989). The association was later renamed as the Japan Health Sciences Foundation.

[59] Interviews with Dr. Yoshiaki Ui, Director of the Biotechnology Division, Ministry of Agriculture, Forestry, and Fisheries, Fall, 1991.

[60] Nikkei Baioteku, Baio-Interijensu (8 October 1989), p. BI-1.

TABLE 3
Sampling of Firms Developing New Products
in Biotechnology in 1985 (by primary sector)

Synthetic Fibers	Pharmaceuticals	Food/Spirits	Chemicals
Toyobo	Yamanouchi	Suntory	Mitsui Toatsu
Kuraray	Dai-ichi	Takara shuzo	Mitsui Seika
Toray	Takeda	Toyo Jozo	Mitsubishi Kasei
Teijin	Sankyo	Ajinomoto	Mitsubishi Yuka
Asahi Kasei	Dai Nippon	Yamasu shoyu	Sumitomo Kagaku
	Chugai		
	Meiji Seika	Snow Brand	Showa Denko
	Yoshitomi		Kyowa Hakko
	Green Cross		
	Fujisawa		
	Shionogi		

Source: Itami, Nihon no kagaku sangyo, p. 199

On the other hand, not all firms regarded the government's role in a positive light; some even resisted its prodding. When MITI convened its first research association in biotechnology, for example, Kyowa Hakko, widely recognized as a leader in genetic engineering at the time, declined to participate in that portion of the project for fear of losing control of proprietary technology. For the same reason, Tanabe, a mid-size pharmaceutical firm, refused to participate in the bioreactor program.[61] One anonymous participant in the project conceded that the association was merely symbolic (tatemae); the majority of participants in reality (honne) wanted the project to be discontinued.[62] Others have mentioned that firms rarely send their best researchers to joint laboratories. While I documented no such pessimism, it did appear that criticisms were more substantive from firms who saw themselves at the cutting edge in a

[61] Interviews, Mr. Kazuaki Manabe, Project Coordinator, Life Science Business Development Department, Mitsui Toatsu Chemicals, Fall, 1991.

[62] Baio 21 Guruppu, Baioindasutorii: yume to genjitsu (Tokyo: Baio 21 Guruppu, 1988), p. 38.

particular area; firms whose competitive position was weak, especially the chemical industry, tend to speak more positively about their relationship with MITI.[63]

Second, MITI's crash program ultimately failed to deliver on the explicit goal of restoring the chemical industry to health. Although profits of chemical makers staged a comeback after the 1982 recession, they plummeted again after 1985. In addition, after 1981, Japan's trade balance in chemicals swung into deficit for the first time since the mid 1960's. Since that time, American and German chemical firms have far outpaced Japanese rivals in diversifying into more lucrative fine and specialty chemicals.[64]

Nor did the pharmaceutical industry, many of whose firms had their main activities in food or chemical, receive the expected boost from new recombinant DNA-based drugs. For reasons discussed earlier, Japan's major drug firms had built dominant positions in world markets for antibiotics, partly because of their experience making them: because far more antibiotics are consumed per capita in Japan than elsewhere, Japanese pharmaceutical makers naturally specialized in their manufacture. Antibiotics, however, had become a commodities business. Worse, the reimbursement system by which the government administers the national health care system not only kept existing drug prices low, it forced them lower almost every year, even as reimbursement rates for medical treatment were rising.[65] Indeed, nothing more clearly underlines the dramatic difference between health care delivery systems in Japan and the U.S. than the trend in drug prices: in the U.S. prices in 1986 were 251 percent of 1975 levels; in Japan, by contrast, drug prices by 1986 had *fallen* to 54 percent of their 1975 level![66] Inability to raise margins severely crimped spending on R&D, which in the mid 1980's averaged only 8 percent of sales, or nearly half the amount spent by major American firms.[67] The only way for firms to increase

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[63] Interviews, Mr. Kazuaki Manabe, Project Coordinator, Life Science Business Development Department, Mitsui Toatsu Chemicals, Fall, 1991.

[64] Itami, Nihon no kagaku sangyo, pp. 195-197.

[65] Drug makers in Japan often find themselves caught between two often (though not always!) contradictory missions of the Ministry of Health and Welfare--promoting competitiveness while setting prices through the national health insurance reimbursement price system.

[66] Prices plunged in the early 1980's as a result of revisions in MHW's method of calculating list prices for drugs in order to narrow the discrepancy between regulated and market prices. Firms accustomed to bi- or triennial cuts in list prices of 1.6-5.8 percent every two to three years in the 1970s had to swallow cuts of 18.6 percent in 1981, 4.9 percent in 1983, 16.6 percent in 1985, and 6 percent in 1986. Hasegawa Hisashi, Iyakuhin (Tokyo: Nihon Keizai Hyoronsha, 1986), pp. 148-149. It is tempting to think that such a pricing system would destroy the profitability of the industry. It does not. Regulators permit premium pricing on new, innovative drugs, while holding down prices on me-too products; by cutting prices across the board every two years, they ensure that competition turns on the ability to pump out a continuous stream of novel new drugs. See Tsuruhiko Nambu, "Characteristics of the Pharmaceutical Industry in Japan: Mechanisms of Regulation and Competition," Review of Social Policy (March 1994): 19-34.

[67] "Prescription for Drug Makers: More R&D," Nikkei Weekly (23 May 1992), p. 17.

profits and hence R&D was to pump out a continual stream of new, innovative drugs--which they did. This made biotechnology especially attractive and accounts for the numerous entries under pharmaceuticals in Table 2. For Japanese drug firms, joint R&D to build pre-commercial capabilities was not a choice, it was a matter of survival.

Although markets were slow to develop, firms soon began turning out a wide range of innovative products uniquely adapted to domestic demand.[68] Cosmetics drew early attention: Kanebo's "Bio-lipstick," derived from a fungus whose rearranged genes produce a rich red pigment, took the market by storm during the "bio-boom" of the mid 1980's. MITI's National Laboratory for Chemical Technology devised a way of cheaply mass-producing lanolinic acid using mass cell culture; Shiseido, which licensed the technology from MITI, used it produce a popular line of cosmetics (Shiseido "seltz" and "revital").[69] Ajinomoto developed a biocellulose product that it sells to Sony for use in audio speakers. Plant agriculture also attracted interest. Using cell fusion technology, Mitsui Toatsu developed a high-yield hybrid strain of rice. Mitsui Petrochemical and Suntory introduced colorful virus-free flowers, based on large-scale tissue culture; they are used in miniature flower arrangements, a lucrative market in Japan. Continuing in the rich tradition of innovation in bioprocess technology, Nitto Chemical, in conjunction with a Kyoto University researcher, in the mid 1980's developed an immobilized enzyme bioreactor to mass produce acrylamide, a key raw material in the production of industrial polymers. Finally, Japan's biggest selling biotechnology product to date is laundry detergent containing a genetically engineered protein purchased "off-the-shelf" from a European firm. Though lacking the glamour of "blockbuster" drugs being developed in the U.S., these products nonetheless illustrate the novel ways in which biotechnology was adapted to the domestic market.

IV. FROM BIO-BOOM TO BIO-REALITY: ALLIANCE STRATEGIES AND THE SHIFT TO BASIC RESEARCH (1986-PRESENT)

As the 1980's progressed, it was clear that research and commercialization were driven by national goals, domestic patterns of demand, national policy, and the stock of technological knowledge available to innovators within the national system. In particular, development acquired a character and momentum notably different from that found in the United States. The development of the technology can be understood only within the context of the network of

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[68] The following examples are taken from Karube, Baio no hanashi and from company reports found in Nikkei Baioteku, Sekai no baio kigyo 800 sha [World's 800 Biotechnology Companies] (Tokyo: Nikkei Baioteku, 1989). Also

[69] Kao Soap recently released new additions to its Sofina line of lipstick, "trumpeting the microcrystalline structure of the base ingredients and a new moisture-retaining component developed using biotechnology." See "Spring Cosmetic Lines Stress Function Over Color," Nikkei Weekly (8 March 1993), p. 12. It is difficult to imagine biotechnology being used to market cosmetics here in the U.S.

national institutions and the sequence of events that constitute the history of Japan's biochemical and pharmaceutical industry.

By the second half of the decade, however, the picture had become more complicated. On the private level, firms stepped up pursuit of alliance strategies, entering into partnerships with foreign firms on more equal terms than before. On the public level, the government shifted attention from promoting commercialization to shoring up weaknesses in basic research. In addition, regional governments, hoping to tap local sources of competitive advantage, began targeting biotechnology as a means of revitalizing local economies. While the verdict is still out on the significance of these trends, they lend some credence to the arguments of *localists* and *globalists* alike.

A. Changes in Industry

By the end of the 1980's, the private sector had entered a period of rapid flux. Most notably, companies that diversified into biotechnology in the early 1980's became more aggressive at expanding their boundaries to take advantage of complementary assets both within the domestic innovation system and abroad. At the same time, the flood of new entrants into biotechnology which characterized the "bio-boom" years slowed to a trickle. Though partly the result of the strengthening yen, it also reflected sobering realization of the long lead times between research and return on a new product.[70] Still, the market retained its dynamism; sales of new products derived from recombinant DNA more than doubled from 1988 to 1989, and again from 1989 to 1990.[71]

Two trends distinguished the evolution of commercial biotechnology trajectories in Japan during this period. First was the application to biotechnology of what Fumio Kodama terms "technology fusion" (gijutsu yugo).[72] This occurs when different types of technology, often originating in different industries, are combined into a hybrid technology to yield novel products. Commonly cited as examples are robotics (fusion of mechanical engineering and electronics) and liquid crystal displays (electronic, crystal, and optical technologies). Fusion involves a process Kodama calls "demand articulation," which takes place when users transmit wants and needs to producers; networks of relationships among companies in keiretsu and between contractors and subcontractors drive the process.

The "fusion" concept was not new. In biotechnology, fusion began in 1974 when a triangular pattern of demand emerged among food, drugs, and industrial chemicals makers. Food and drugs had been connected for decades through common use of fermentation technology; it

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[70] "Japan Cools Biotech Spending," Bio/Technology (May 1992), p. 505.

[71] Nikkei Baioteku Nenkan 89/90, p. 13; Nikkei Baioteku Baiointerijensu (2 December 1991), p. BI-1.

[72] Kodama lays out his theory, though without reference to biotechnology, in Kodama, "Technology Fusion and the New R&D," Harvard Business Review (July-August 1992), pp. 70-78.

was the opening of a channel to chemicals that turned old bioprocessing into new biotechnology. The process has been accelerated through the growth in number of cross-industry research associations. According to a survey by Kodama, the ten research associations related to biotechnology and founded between 1964 and 1988 involved on average companies from 3.3 different industries. Most likely to be represented were firms from the food, chemical, and textile industries.[73]

Fusion has recently taken a striking variety of forms. One example is the field of biosensors, which fuses semiconductor, molecular biology, and, occasionally, optical technology. A biosensor is a biochemical transducer that sends out an electrical signal when it comes into contact with a biologically active substance. Developed serendipitously when Isao Karube and his team of researchers at Tokyo University tried and failed to build an organic battery powered by glucose, biosensors now command a market in excess of 2.2 billion yen ($ 21 million using today's exchange rate).[74] Applications include monitoring of wastewater and detection of biological hazards in environments unsuitable for conventional instrumentation. More recently, tiny enzyme sensors have been developed to measure concentrations of organic acids and sugars in the human body. Among products that have been commercialized in this category is the toilet sensor, which is a conventional toilet equipped with molecular sensors that monitor various chemicals in the urine; the sensors feed a transmitter inside the toilet which provides a real-time output on an attached LCD readout. Another example is the "wristwatch fatigue sensor" in which a tiny sensor mounted on a wristwatch provides continuous measurement of the concentration of lactic acid in body sweat.[75]

Another fascinating example of technology fusion is in the area of "nutriceuticals," a hybrid of food and pharmaceutical technologies. Building on accumulated expertise in fine chemicals and food processing companies such as Hayashibara, Suntory, Meiji Seika, and Taiyo Kagaku, nutriceuticals involves the use of genetic engineering to boost nutritional value, while lowering caloric content, of a variety of foodstuffs.[76] Targeted products include wheat bran and corn fiber, dextrin, and erythritol, a low calorie sweetener used in various chocolates and sweets in Japan. At the cutting edge are the so-called "physiologically functional foods," whose introduction has just received approval from the Ministry of Health and Welfare. These include Morinaga Dairy's low-phosphate milk intended for patients with chronic kidney disorders. Most striking of all perhaps is the cosmetic giant Shiseido's engineered rice, whose production employs a special enzyme that deactivates an allergen responsible for severe skin lesions on thousands of

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[73] Kodama Fumio, Kyodo kenkyu ni okeru sanka kigyo ni kansuru chosakenkyu [Survey Research of Companies Participating in Cooperative Research] Kenkyu gijutsu keikaku 5 (1990), pp. 30-50.

[74] Tsuyuchika Kaminuma and Gen Matsumoto, Biocomputers: The Next Generation from Japan (New York: Chapman & Hall, 1991), pp. 114-116; Nikkei Baitekunorojii, Baiointerijensu (2 December 1991), p. BI-2.

[75] For these and other examples, see Karube, Baio no hanashi, pp. 196-205.

[76] "The Perfect Food," Bio/Technology (10 September 1992), pp. 952-953.

Japanese afflicted with rice allergy.[77] That Shiseido's primary field is cosmetics exemplifies the extent to which firms use biotechnology to create hybrid technological trajectories. Such a phenomenon, to my knowledge, has not yet been seen in the U.S.

The second trend to emerge in this period was the growth in numbers of strategic alliances between Japanese and foreign firms. Like large American firms, large firms in Japan have pursued strategic alliances as a means of accessing new products and technologies, especially from the U.S. Small American DBCs, conversely, have sought out Japanese partners both as a source of capital and as means of penetrating markets in Japan and East Asia.

Although a wide variety of linkages has been employed, the predominant strategy reflects prevailing technological and institutional capabilities and needs at a given point in time. In the early 1980's, licensing agreements proliferated as Japanese companies rushed to acquire new products and technology from American companies and, in some cases, universities.[78] Later in the decade, marketing agreements and joint product development supplanted licensing as the most popular strategy. By 1991, Japanese companies had negotiated at least 282 alliances with American biotechnology companies and 27 tie-ups with large American companies active in biotechnology.[79] Interestingly, an examination of 231 of the former found eleven cases of technology transfer from Japan to the U.S. and only eight cases of two-way technology flow. Perhaps for these reasons, American firms prefer partnering with each other or with Europeans: according to a recent survey, in only 13 percent of worldwide alliances involving an American DBC is the DBC paired with a Japanese partner.[80] Recently, however, recession at home has sharply curtailed the number Japanese firms seeking foreign partners in biotechnology, even as the total number of deals worldwide continues to soar.[81]

Japanese firms have also sought to compensate for weaknesses in infrastructure for basic research by tapping into the intellectual resources of American universities and research institutes. Shiseido made waves in 1989 when it pledged $85 million to Massachusetts General Hospital and Harvard University to support basic research in dermatology.[82] At the same time, Kirin set up a non-profit research center, the La Jolla Institute for Allergy and Immunology, in close proximity to the University of California, San Diego. And Hitachi Chemical built a 20 million dollar

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[77] "Japan Explores the Boundary between Food and Medicine," Nature (15 July 1993), p. 180.

[78] Edward Roberts and Ryosuke Mizouchi, "Inter-firm Technological Collaboration: The Case of Japanese Biotechnology," International Journal of Technology Management 4 (1989): 43-61.

[79] National Research Council, U.S.-Japan Technology Linkages in Biotechnology (Washington, DC: National Academy Press, 1992).

[80] Of the remainder, 38 percent were with larger American firms, 29 percent were with European firms, and 21 percent were with other DBCs. "International Strategic Alliances," Bio/Technology (May 1992), pp. 528-533.

[81] "European Pharmaceuticals Hungry to Do Deals; Japanese Sitting on the M&A Sidelines, PR Newswire (8 December 1994).

[82] "Shiseido Grant: More than Skin Deep," Science (25 August 1989), pp. 810-811.

research center in the same building as the biochemistry department at the University of California, Irvine.[83] Together with expanded corporate tie-ups, these investments have drawn widespread criticism that American biotechnology is heading down the same road as the electronics industry a generation earlier. Such fears have proved unfounded. Japan's investment in American basic research has generated little return to date.[84] Furthermore, according to one study, European firms are more a cause for concern, accounting for 450 biotechnology-related collaborations with U.S. universities and companies, compared to only 50 for the Japanese.[85]

The prevalence of licensing and other forms of collaborative research might be construed as undermining the national systems framework. That would be a mistake. Far from supporting the technoglobalist position, dependence on alliance strategies underscores the centrality of licensing and technology imports in the Japanese NIS. It also affirms the extent to which institutions designed for technological catch-up continue to drive the process of technological change.

B. Changes in Public Policies

Public policies impacting on biotechnology have also changed. By the middle 1980's, interest groups that had pressed government into action five years earlier were once again calling for action. This time the demand was for greater spending on basic research to put the Japanese innovation system on a more equal footing with those of the United States and Europe. Among the more strident voices was that of Keidanren, which issued a special report on biotechnology in February, 1985.[86] Echoing criticisms made elsewhere, the report singled out deteriorating conditions in university and national laboratories, and it urged that these institutions fulfill their role in promoting basic R&D, cultivating human resources, and strengthening the diffusion of information. Most importantly, it stressed that there were clear limits to what industry alone could achieve. The government could contribute most effectively through provision of tax and financial incentives, a unified regulatory structure, improved mechanisms of personnel exchange, and more effective regional policies. Interestingly, MITI's new vision for biotechnology, released in 1988, echoed many of these recommendations.

To some extent, the thrust of science and technology policy had already begun to change. Since the early 1980s, the Science and Technology Agency had been leading the charge toward greater levels of spending on basic research and a higher profile for science in the national budget. The efforts have borne fruit in the life sciences, which experienced double digit increases in government R&D funding in four of eight years since 1986. Expenditures by nine ministries on

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[83] "In Biotechnology, Japanese Yen for American Expertise," Science (27 November 1992), pp. 1431-1433.

[84] "Academic Biotech Deals Offer More Promise than Product," Science (14 January 1994), pp. 168-169.

[85] "Away from Home: U.S. Sites of European and Japanese Biotech R&D," Bio/Technology (December 1992), pp. 1535-1538.

[86] Keidanren, Kaihatsubu, Raifu saiensu no suishin ni kansuru kenkai (February 1985).

biotechnology reached 170 billion yen in 1994. Among the most active areas is genome research, in which human, dog, and rice genome projects today fetch 5 billion yen, up 24 percent over 1993. Still, biotechnology pales in comparison with budgets for space development, atomic energy, and environmental protection.[87] Notably, MITI's portion of the biotechnology research budget has steadily declined, reflecting the growing importance of basic research and quality of life issues outside of narrow industrial applications.

Finally, in recent years the Japanese innovation system has evolved an increasingly dynamic regional component. Because of its widespread application in local agriculture and food processing, biotechnology has generated high hopes as a means of energizing local economies and upgrading productivity and the pace of innovation in local industry.[88] Initially, the impetus came from the central government. As part of its Technopolis Plan, MITI has established a Regional Biotechnology Association Network, whose centers in each region facilitate information exchange. Not to be outdone, MAFF has set up more than 20 regional R&D projects emphasizing agricultural biotechnology.[89] Centrally administered initiatives, however, have played to mixed reviews. The Technopolis program as a whole has done little to ease the excessive concentration of high technology activities in big cities, which was one of its primary goals.[90] Toyama prefecture, one of 26 regions awarded the technopolis distinction, has fared well, having induced a total of 40 high technology enterprises to relocate there since 1984; Hakodate, by contrast, has attracted only eight over the same period. In biotechnology, Aomori, Toyama, and Kumamoto technopoli have become noteworthy centers of biotechnology research.

Yet the technopolis phenomenon is only one of several types of regional agglomerations. I've identified at least five other patterns of clustering of science and technology resources, specification of which is the subject of my current research. Among the most interesting trends is the growing involvement of local and prefectural governments in supporting science and technology as part of regional economic development policies. In accordance with the Fourth Comprehensive Development Plan and the Council on Science and Technology's recommendations, 14 of 47 prefectures have set up their own science and technology promotion

[87] Nikkei Baiointerijensu (28 February 1994), p. BI-1.

[88] Hakko kogyo kyokai, Baioindasutorii shinko jigyobu, Baiotekunorojii no chushokigyo e no shinto jokyo oyobi donyu doko ni kakaru chosa (1983). See also "Chiiki ni okeru kagaku gijutsu shinko," Kankai (March 1991), pp. 150-158. For a comprehensive review of recent initiatives, see "Ganbare! Chiho no kenkyujo," Trigger (September 1990), pp. 8-31. The entire 1992 edition of the Science and Technology White Paper was devoted to the topic of science and technology for regional development.

[89] Bio-oriented Technology Research Advancement Institution: A Challenge to the 21st Century, undated brochure.

[90] As of 1994, 26 regions had won the distinction of being designated as technopolis zones. For an upbeat assessment of early accomplishments, see Sheridan Tatsuno, Japan's Technopolis Strategy. On the disappointments that characterize more recent years, see Ito Tsunatoshi, et al, Kensho: Nihon no Tekunoporisu (Tokyo: Nihon Hyoronsha, 1995).

councils, 13 or which have issued policy directives.[91] Regional governments, moreover, are applying increasing pressure on the central government to decentralize the science policy making process.[92] Although only 2.4 percent of the nation's total R&D expenditures are borne by local and prefectural governments, the amount comes to 29 percent of the central government's share--a far higher percentage than in the U.S.[93]

In terms of biotechnology, local and regional governments in 1993 spent nearly 8.3 billion yen to promote regional innovation, about 5 percent of the amount spent by the central government. In addition, one prefectural government has fleshed out a comprehensive biotechnology policy while eight others are poised to follow suit.[94] Aomori prefecture leads the nation in expenditures, followed by Kagoshima and Toyama, each of whose policy makers aim to use biotechnology as a means of stimulating local economies and exploiting locally based resources. In all cases, local groupings of small and medium-sized firms, agricultural cooperatives, and local research institutes are closely involved in planning and execution of research activities.

National and local initiatives, in conjunction with market forces, have produced a distinctive spatial distribution of biotechnology resources. The Osaka region, the birthplace of the pharmaceutical industry, fields the most formidable agglomeration of biotechnology research. Comprising a dense network of linkages among the National Cardiovascular Disease Institute, the Protein Engineering Research Institute, the Osaka Bioscience Research Institute, Senri Life Science Center, and five other research centers associated with Osaka University, the Osaka region is literally an innovation system in its own right.[95] Across Japan, smaller networks of prefectural research institutes, small firms, and universities are attempting to distinguish themselves by capitalizing on products peculiar to their regions. For example, a Nagano prefecture-based research network recently used genetic engineering to develop a higher quality variant of its home-grown lettuce. Networks in Miyazaki and Tokushima prefectures, which produce rival strains of sweet potatoes, are each using biotechnology to give its product an edge over the other. Finally, prefectural-based collaborative projects in Hokkaido, Osaka, Ehime, and

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[91] Kagaku gijutsucho, Kagaku gijutsu hakusho, heisei nana nen han [1995 Science and Technology White Paper], pp. 352-353.

[92] Interview with Dr. Kinji Gonda, Director of Research, National Institute of Science and Technology Policy, August 1995. That the Ministry of Home Affairs has recently added science and technology policy to its agenda is indicative of growing interest in incorporating local and regional input in science and technology policy.

[93] Kagaku gijutsucho, Kagaku gijutsu shihyo, 1994 nen han (Science and Technology Indicators, 1994).

[94] Nikkei Baioteku, Chosa: Zenkoku todofuken baiotekunorojii kaihatsu jokyo, 1993 (Tokyo: Nikkei BP sha, 1993), p. 12.

[95] Sankei Shimbun, eds. "Cho Kansai": Sengen hakko suru toshi no subete (Osaka: Brain Center, 1994; Tsushosangyosho, Higashi kara nishi e takyoku-ka o sendo suru kinki (Tokyo: MITI, 1989)

Okayama prefectures are developing new diagnostic kits using Polymerase Chain Reaction technology. In sum, prefectures have sponsored formation of 25 special joint research corporations in biotechnology. In addition, 46 cooperative research ventures have been established between prefectural research institutes and private firms. Although it is difficult to assess the impacts, prefectures report eleven cases of large corporations moving into their regions as a result of their policy initiatives.

V. CONCLUSIONS

Technological development is by nature a path dependent process. The dynamic pattern of innovation and commercial development of Japanese biotechnology cannot be understood apart from its historical and institutional roots. The findings here are thus in agreement with conclusions reached by Mowery and Rosenberg in their study of the chemical industry and Samuels in his study of Japan's defense industry.[96]

As argued above, by the time the techniques of genetic engineering and cell fusion became widely available, the only companies capable of responding were locked into a set of technological trajectories oriented around industrial fermentation and bioreactor technology. Drug firms, burdened by a centrally administered pricing system and heavily dependent on imported foreign technology, were unable to set the pace. The immobility of researchers across sectors, lack of venture capital, and proscriptions on research using genetically engineered organisms ruled out the creation of new forms of enterprise like the American DBC. Firms thus faced a narrow range of options in attempting to catch up with the U.S. The important point, however, is that all these factors derive from the particular historical experiences of institutions that comprise a national system of innovation.

Once the transformative power of the new techniques became clear, the government, under relentless pressure from researchers and firms, eased regulations; bureaucrats cobbled together programs to spur market entry and rally firms to catch up with sprinting American DBCs. Through the middle 1980s, firms from diverse industries, often participating in or following the leads of research associations sponsored by the government, fused the new techniques into existing product lines, then bombarded markets with a variety of new products. Again, the possibilities open to innovators were largely set by national institutional factors--in this case, the industrial policy making process, regulatory regimes in drug pricing and research, and national developmental goals stressing importation and indiginization of foreign technology.

More recently, innovation strategies have become embedded in local and regional economies; local initiatives are replacing national ones as firms and research centers attempt to

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[96] Ralph Landau and Nathan Rosenberg, "Successful Commercialization in the Chemical Process Industries," in Technology and the Wealth of Nations, eds. Nathan Rosenberg, et al (Stanford: Stanford University Press, 1992); Samuels, "Rich Nation, Strong Army."

capitalize on local sources of competitive advantage. Though this trend partly reflects the wide range of technological opportunities posed by biotechnology, political factors are accelerating the process: pressures for decentralization combine with long-standing interministerial jealousies to set the tone for public policies promoting biotechnology.

Does the localization of innovative activity undermine the national systems framework? Probably not. It has become quite fashionable to sound the death knell of the nation state as national borders yield to transnational business activity. "Region states," "global webs," and "agglomerated production networks" have come to dominate the discourse on economic geography and political economy. Yet such conceptions appear to confuse wishful thinking with empirical reality. Worse, they reflect continued misguided attempts to interpret the Japanese economy through the lens of western liberal ideology. Certainly, the withering away of the state would be surprising news to Japanese, many of whom no doubt would welcome a diminution of the influence of the central government. If anything, however, localization and--to the extent it is taking place--globalization of innovation are proceeding within the institutional framework of the nation-state and in accordance with national developmental goals.

That is not to deny that the national systems approach needs to be modified. Cross-border alliances and localized production networks increasingly reflect the reality of economic activity--a fact that needs to be accommodated within the NIS framework. Technology and competitive pressures are ushering in a "borderless" economy, but the boundaries that are dissolving belong to firms, not to states. Firms shift their boundaries outward in an effort to internalize new technology and exploit external economies, and in so doing create new organizational forms. Yet they do so because of, not in spite of, the political, developmental, and institutional imperatives embedded in the community of institutions comprising the NIS. What is needed is a theory of the firm that more effectively links internal strategy with external political and institutional factors, a goal that is part of the author's ongoing research.