Joseph Kraft

Weinberger's One-Liner

"It is a system of destroying weapons rather than people," Cap Weinberger said of the Strategic Defense Initiative, or Star Wars proposal, at a lunch with this columnist and two other journalists on Sept. 4. Thirteen days later, at his press conference of Sept. 17, President Reagan said of SDI: "We're talking about a weapon that won't kill people, it'll kill weapons."

The near repetition testifies to the influence the secretary of defense enjoys with the president. The Pentagon boss has dominated public debate about the upcoming Big Two summit, and cast a dark shadow over its prospects. But analysis of his clout shows how little the Russians have to do if they really want to achieve progress on arms control at the November meeting in Geneva.

A strong personal rapport with Reagan is the starting point for Weinberger. Like the president, the secretary of defense is a man of grace and fluency. Like Reagan, Weinberger has a nice sense of humor, even about himself. At lunch the other day he joked about his "intransigence" and "stubbornness."

Strong powers of articulation enable the defense secretary to make even dubious arguments sound plausible. SDI, for example, is a dangerous enterprise given the context of nuclear stability. If the United States acts to perfect a strong defense, the Russians will counter with steps to improve their offense. To ensure penetration of some offensive missiles, Moscow would have to start things in an all-out attack. Thus, SDI presents the peril of a renewed arms race, and the threat of apocalypse if anything goes wrong.

The claim that the weapons do not kill people is truly irrelevant—a piece of utter sophistry. But it sounds good in a one-liner. And Reagan, perhaps even more than Weinberger, goes for what sounds good in one-liners.

Apart from personal rapport, the secretary of defense carries institutional power. Every previous secretary of defense supported efforts to reach accord with the Russians on limiting nuclear weapons. Some—notably Robert McNamara under Johnson, Mel Laird and James Schlesinger under Nixon and Ford, and Harold Brown under Carter—even forced the pace. Weinberger is the first secretary of defense opposed to arms control in principle.

The Pentagon weight in the country and the world is far greater than often recognized. Even if scheduled cuts in spending take effect, defense outlays will be around $300 billion annually. Well over half the amount spent on research and development in the country comes from the military budget. Virtually every state has a stake in a major weapons system, and big foreign firms are particularly keen to work on SDI, with its potential technological spinoffs. As a former Air Force secretary put it: "The Pentagon can buy off every constituency in the world."

Even that influence has not been decisive, however. For Reagan has repeatedly emphasized the need for achieving a "mix" of the offensive and defensive weapons systems in the arsenals of the Big Two. So have National Security Adviser Robert McFarlane and Secretary of State George Shultz. But the mix concept implies a trade whereby the United States and Russia both advance down the path of missile defense while cutting offensive forces.

Mikhail Gorbachev, the new Soviet leader, has repeatedly hinted at such a deal. Foreign Minister Eduard Shevardnadze took the theme a step further in speaking of "Star Peace" at the United Nations Tuesday.

But the Russians have not done much more than wiggle their eyebrows and nudge people in the ribs. They have not formally asserted how defense might be limited or offensive weapons reduced, or to what levels. That is why the president and Shultz and McFarlane all keep telling the Russians to make the hints official, to fill in the boxes with numbers.

As the summit draws closer, Moscow will almost surely move toward concrete proposals. That is what the private meetings of Shevardnadze with Shultz and Reagan this week are all about.

But probably the Russians will not move far enough to satisfy Reagan that they are dealing in good faith. After all, Moscow must find useful the propaganda gains scored in Western Europe and Japan by the Gorbachev peace offensive. There is even a risk that the Russians will be so mesmerized by the propaganda opportunities as to let genuine arms control progress drop through the cracks.

But the best bet is that the November summit will prevent such a sad outcome. There is every chance Reagan and Gorbachev will dance around the idea of an agreed mix of offensive and defensive missiles. They would then agree to discuss the matter further at a later summit. In the interim, they might also agree to abide by the provisions of the unratified SALT II treaty for another year, even though the treaty expires at the beginning of 1986.

Such an accord would not only assure a whittling down of the Weinberger clout. It would provide a start on arms control and ensure the one thing both leaders clearly want—a successful summit.

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Patrick J. Leah

A Count

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Miller Aides Follow Him To OMB



As wife Demaris holds Bible, Miller is sworn in as OMB chief by Vice President Bush; President Reagan looks on.

Former Federal Trade Commission Chairman **James C. Miller III** was sworn in yesterday as the new director of the **Office of Management and Budget**, where he'll be working with three former FTC bureau directors and its general counsel.

The day before, President Reagan named FTC Commissioner **Terry Calvani** as acting FTC chairman until a successor to Miller is nominated and confirmed. Calvani, 38, a former law professor at Vanderbilt University and a member of the commission for almost two years, moved quickly to fill some of the vacant slots:

- **Timothy J. Muris**, who had directed the FTC's **Bureau of Competition**, becomes executive associate director of OMB, while **Walter T. Winslow**, the bureau's deputy director, becomes acting director. Muris worked at OMB as an assistant to Miller when Miller was head of OMB's **Office of Information and Regulatory Affairs.**
- **Carol T. Crawford**, who headed the FTC's **Bureau of Consumer Protection**, becomes associate director of OMB for economics and government. **Amanda Pedersen**, the bureau's deputy director, becomes acting director.
- **Wendy Lee Gramm**, who directed the Bureau of Economics, takes over Miller's old job as administrator of the regulatory affairs office. **David T. Scheffman**, deputy director of the bureau, will serve as acting director.
- Former FTC general counsel **John H. Carley** becomes counselor to the OMB director. **Mary Tiffany**, executive assistant to the chairman, becomes acting general counsel.
- **Jeffrey A. Eisenach**, formerly special adviser to the FTC chairman for economic policy and operations, becomes executive assistant to the OMB director.

Karen Johnston, the FTC's director of congressional relations, is also leaving the FTC, but not joining the exodus to OMB. Johnston plans to leave Washington at the end of the month to work on the campaign of Rep. **James T. Broyhill** (R-N.C.) for the North Carolina Senate seat of Republican **John P. East**. She will be working alongside her husband, former Rep. **Eugene Johnston** (R-N.C.), who will serve as Broyhill's finance chairman.

Johnston previously had said she would stay on until Congress passed a bill reauthorizing the FTC, but she said yesterday that the bill is not expected to pass before her departure Nov. 1. But a House-Senate conference is expected before the end of the month, she said, and a final bill is expected to pass by the end of the congressional session.

Calvani has named one of his attorney advisers, **Randolf W. Tritell**, to serve as his executive assistant. Calvani also named three special assistants: **Neil W. Averitt**, former attorney adviser to former Commissioner **George W. Douglas** and former special assistant to Miller; **Donald S. Clark**, a former attorney adviser to Douglas; and **Cynthia E. Smith**, an attorney from the agency's Atlanta regional office.

Calvani's appointment may be a sign that the White House will not move quickly to nominate replacements for Miller and Douglas, a conservative Democrat who left the commission last month to return to Texas.

The president is expected to nominate **Agriculture Department** general counsel **Daniel Oliver** and Kenneth Elzinga, a University of Virginia economics professor, to fill the seats of Miller and Douglas, respectively.

Oliver, a Republican, also served as general counsel of the **Education Department** and is a former executive editor of National Review, as well as a former director of the American Conservative Union Inc. Elzinga, an independent, is an antitrust expert who writes mystery novels on the side. From 1970-71, he served as special economic adviser to the assistant attorney general for antitrust and from 1971-79 as a member of the **Nuclear Regulatory Commission's Atomic Safety and Licensing Board Panel.**

Although agency and congressional sources say the administration is close to a decision, Crawford, Muris and Gramm have also been mentioned as possible nominees.

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WAITING GAME . . . Rep. **James J. Florio** (D-N.J.), chairman of the House Energy and Commerce subcommittee on commerce, transportation and tourism, is still waiting for answers from the FTC to his questions about Gulf Corp.'s divestiture of certain assets in the Southeast.

In a Sept. 4 letter, Florio asked the agency to respond to complaints from gasoline retailers about the FTC's review of its consent agreement approving Chevron Corp's $13.2 billion takeover of Gulf. The agreement required the divestiture of 4,000 gas stations, including "the Gulf brand name and trademark." The retailers have complained that despite that, the FTC later approved the sale of Gulf stations that had only a temporary license to the Gulf trademarks. Florio requested a reply by Oct. 4, but his staff said yesterday that he has not yet received one.

—**Nell Henderson**

Spatially Regulated Expression of Homeotic Genes in *Drosophila*

Katherine Harding, Cathy Wedeen
William McGinnis, Michael Levine

Abstract. *The sites of transcript accumulation for six different homeotic loci of the Antennapedia and bithorax gene complexes (ANT-C and BX-C) were identified within embryo tissue sections by in situ hybridization. These six loci belong to the Antennapedia class of the homeo box gene family. Transcripts encoded by each locus are detected primarily in discrete, nonoverlapping regions of the embryonic central nervous system (CNS). The regions of the CNS that contain transcripts encoded by each of these loci correspond to the embryonic segments that are disrupted in mutants for these genes. The maintenance of spatially restricted expression of each ANT-C and BX-C locus could involve hierarchical, cross-regulatory interactions that are mediated by the homeo box protein domains encoded by these genes.*

A fundamental problem of development is how embryonic cells acquire their particular developmental fates as a result of their location within a developing embryo. A model system for analyzing the elaboration of this positional information during *Drosophila* development involves the morphogenesis of body segments. The adult fruit fly is composed of eight abdominal, three thoracic, and four to six head segments (*1*). Several of the constituent tissues of a given segment have morphological properties specific for that segment. For example, the epidermis elaborates cuticular structures, such as legs and antennae, that are distinct for a particular segment. In addition, the morphology of some of the mesodermal (*2*) and neural tissues (*3, 4*) may be specific for a given segment.

Homeotic genes are those that establish the diverse pathways by which each embryonic segment primordium develops a distinct adult phenotype (*5, 6*). Mutations of homeotic loci result in partial or complete transformations of the epidermal tissues of one segment into those of another. Homeotic transformations may include the neural and mesodermal tissues of the affected segment as well (*2, 3, 7*). For example, embryos that lack the *Antennapedia* (*Antp*) gene function display a transformation of the meso- and metathorax (T2 + T3) into homologous tissues of the prothorax (T1) (*8*).

Many homeotic genes appear within one of two clusters in the *Drosophila* genome, the bithorax complex (BX-C) (*5, 9*) or the Antennapedia complex (ANT-C) (*10, 11*). Genes of the BX-C are required for the specification of segments in the posterior regions of the fly (*5, 12, 13*). Lewis has identified a number of homeotic loci within the BX-C on the basis of embryonic and adult mutant phenotypes (*5*). Recently, a minimum of three essential domains of homeotic function within the BX-C have been identified by means of lethal complementation analyses: *Ultrabithorax (Ubx), Abdominal-A (abd-A), and Abdominal-B(Abd-B)* (*9*). The ANT-C is required for the specification of anterior body segments (*8, 14*). Several homeotic lethal complementation groups have been identified for the ANT-C (*8, 11, 14, 15*). These include the *Antp, Sex combs reduced (Scr), and Deformed* (*Dfd*) loci. Each ANT-C and BX-C homeotic lethal complementation group controls the development of a different subset of the embryonic segment primordia (Fig. 1a).

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A central problem in elucidating the genetic control of segment morphogenesis is how the different ANT-C and BX-C loci come to function in primarily nonoverlapping domains along the body axis of the fly. The molecular cloning of ANT-C and BX-C loci has permitted a direct assessment of the spatial and temporal limits of homeotic gene expression. The previous demonstration that *Ubx* and *Antp* share direct nucleotide sequence homology (*16-19*) facilitated the isolation of ANT-C and BX-C loci. This homology occurs within a conserved protein coding region designated the homeo box. A total of seven genomic DNA fragments cross-hybridizes strongly with the *Antp* and *Ubx* homeo boxes (*20*). These seven regions correspond to the Antennapedia class of the homeo box gene family, all of which are located within either the ANT-C or the BX-C (*20*). It appears that each of the six lethal complementation groups of the ANT-C and BX-C (Fig. 1) contains an Antennapedia class homeo box. However, there are additional homeotic loci within the BX-C that do not contain the homeo box (Fig. 1a) (*21*).

We show that each of the ANT-C and BX-C homeotic loci that contains a homeo box specifies transcripts that accumulate in discrete regions of the embryonic central nervous system (CNS). To a close approximation, the regions of the CNS that contain transcripts encoded by each of these loci correspond to the embryonic segments that are disrupted in mutants for these genes. We propose that spatially restricted expression of each ANT-C and BX-C locus involves hierarchical, cross-regulatory interactions that are mediated by the homeo box protein domains encoded by these genes. Support for this model is based on analysis of the distribution patterns of *Antp* transcripts in mutant embryos that lack BX-C loci.

Isolation of a new ANT-C homeo box locus. Molecular clones for the *Dfd, Antp, Ubx, iab-2*, and *iab-7* loci have been previously isolated (*16, 20, 22–25*). In order to determine the spatial limits of expression for each homeotic lethal complementation group within the ANT-C and BX-C by in situ hybridization, it was necessary to obtain a molecular probe for the *Scr* locus. A genomic DNA fragment that appears to derive from *Scr* was isolated on the basis of homeo box sequence homology as described below.

A total of 6×10^4 recombinants from a *Drosophila*–Charon 4 DNA library (approximately six genome equivalents) were screened with the homeo box se-

differ is in the type and amount of government support for the development of biotechnology. In Japan there is a clear effort by government to enhance the future commercial success of the pharmaceutical industry by assisting in the development of biotechnology. Although this support is administered by a few different agencies and is small in size (by U.S. standards), it is viewed both externally (*2, 25*) and internally (*16*) as a single cohesive effort with a high potential for success. The companies involved must create their own basic research and development programs; government assistance is at the next level, helping to foster commercialization of products, manufacturing, and generic support, such as gene banks (*18*). In the United States, federal support for biotechnology is ten times greater in magnitude and is aimed at basic research. Although support of basic research programs in biotechnology should be continued and expanded to ensure maintained leadership in basic research, support for more applied areas is also needed (*2, 16*).

Another contrast between the two countries is in the availability of basic researchers in biotechnology and bioprocess engineering. There was a reported shortage in the United States of basic researchers trained in genetic engineering, but this problem appears to have abated (*2, 30*). Due to strong academic programs in this and related areas, the availability of basic researchers should continue to be sufficient (*2*). However, a paucity of academic programs in bioprocess engineering continues (*2*). As more companies generate products of biotechnology for scale-up, it is expected that there will be a severe shortage of personnel trained in production technologies, which may hamper commercial success (*2*). Japan has the opposite problem—an adequate supply of fermentation engineers but too few basic researchers with training in molecular genetics (*16*). This is another reason why Japanese companies have been borrowing U.S. basic research, but are predicted to outpace the United States in commercialization (*2, 3*).

Outlook

In January 1984 the U.S. Congress Office of Technology Assessment (OTA) published a 612-page analysis on commercial biotechnology (*2*). The report noted the importance of biotechnology both for its basic scientific benefit and for its potential commercial development. In assessing the competitive position for the United States, the OTA report stated the following (*2*, p. 7):

> Japan is likely to be the leading competitor of the United States for two reasons. First, Japanese companies in a broad range of industrial sectors have extensive experience in bioprocess technology. Japan does not have superior bioprocess technology, but it does have relatively more industrial experience using old biotechnology, more established bioprocessing plants, and more bioprocess engineers than the United States. Second, the Japanese Government has targeted biotechnology as a key technology of the future, is funding its commercial development, and is coordinating interactions among representatives from industry, universities, and government.

When the focus of analysis is narrowed to the pharmaceutical industry, it can also be concluded that the Japanese have the potential to be a leading competitor. An important factor in their success has been the borrowing of basic biotechnological research by Japanese companies from U.S. biotechnology firms. Although biotechnology licensed by U.S. firms to Japanese companies generally involves marketing rights in Japan or Asia (*2*), the Japanese market for pharmaceuticals is the second largest in the world. When added to other Asian markets, it becomes two-thirds the size of the North American or European markets (*9*). U.S. pharmaceutical companies have gained 40 percent of their revenues from foreign sales, and the loss of a foreign market may represent lost income (*9*).

In addition to basic biotechnology borrowed from the United States, Japan has been simultaneously building its own strength in this field. There are more and more frequent reports of new developments in basic biotechnology and discoveries of new drugs from Japanese industrial laboratories (Table 3) (*12*). It is thus possible that Japan's predicted future strength in pharmaceutical biotechnology will come both from internal developments and strategic government programs (*16*).

This is not to imply that with Japanese strength in biotechnology will come U.S. weakness in this area. As stated earlier, pharmaceutical and other companies in the United States are expanding their efforts in biotechnology and are nearing their goals of bringing new therapeutics and diagnostics to market. However, an analysis of Japanese strategies may help to understand how U.S. industry can optimize this process. In addition, U.S. industry will be strengthened if the U.S. government makes the commercialization of biotechnology a high priority and funds specific academic and other programs leading to that goal (*2*). As stated in the OTA report (*2*): "The United States may compete very favorably with Japan if it can direct more attention to research problems associated with the scaling-up of bioprocesses for production."

In addition, government activities that enhance cooperation between companies, decrease regulation, or provide centers to assist in biotechnology would help meet this goal (*2, 6, 31*). However, in the period since the OTA report was made public, no broad program of support to strengthen the U.S. position in biotechnology has been announced by the federal government.

Steps in the Right Direction

A few recent developments should prove useful to the future development of biotechnology in the United States. The first is the opening of biotechnology centers to assist in the transfer of biotechnology expertise from academia to industry. Two of these centers are at Pennsylvania State University and in Research Triangle Park, North Carolina. The Penn State Biotechnology Institute has planned research and educational facilities and will allow member companies access to "application-oriented research" and to a pilot production facility for assistance in scale-up (*32*).

The North Carolina Biotechnology Center currently receives $2.5 million in annual funding from state, federal, and industrial sources. The center funds specific programs, such as its Monoclonal Lymphocyte Technology Center, which involves academic research at the University of North Carolina and Duke University, the participation of industry, and funding by the National Science Foundation. The five industrial members agree on priorities for directed research to be funded by specific grants to participating laboratories. Although still in its infancy, the Monoclonal Lymphocyte Technology Center is fostering cooperation between companies in a university environment that probably would not have otherwise occurred (*33*).

The Center for Advanced Research in Biotechnology (CARB), to be built in Gaithersburg, Maryland, will combine federal, state, county, and university efforts (*34*). With CARB, the National Bureau of Standards will add its analytical expertise to molecular biology expertise from the University of Maryland. A CARB research facility to be completed

Table 2. Equity purchased in firms with a major focus on biotechnology. Equity purchases selected from database (*12*).

Large company (purchaser)	Biotechnology firm	Year
Purchased by U.S. pharmaceutical companies		
Abbott	Amgen	1980
Baxter Travenol	Genetics Institute	1982
Becton Dickenson	Applied Biosystems	1984
Johnson & Johnson	Enzo Biochem	1982
Lederle	Molecular Genetics	1981
Lederle	Cytogen	1983
Lilly	Synergen	1984
Schering-Plough	Biogen	1982
Schering-Plough	DNAX Ltd.*	1982
SmithKline	Beckman*	1982
Syntex	Genetic Systems	1982
Purchased by other U.S. companies		
Dow	Collaborative Research	1981
Du Pont	New England Nuclear*	1981
Fluor	Genentech	1981
W. R. Grace	Amicon*	1983
Martin Marietta	Molecular Genetics	1982
Monsanto	Biogen	1980
Monsanto	Collagen Corporation	1980
Purchased by Japanese companies		
Green Cross	Collaborative Research	1981
Mitsubishi	BioVec	1984

*Acquisition. Each nonacquisition purchase involved an average of $8 million.

Table 3. Comparison of U.S. and Japanese pharmaceutical industries and involvement in biotechnology. All 1983 data, except as noted. [Sources: (*1*, *2*, *9*, *15*)]

Data category	United States	Japan
Population (millions)	234.5	119.2
Gross national product	$3.3 trillion	$1.2 trillion
Domestic pharmaceutical market (world rank)	$21.3 billion (1)	$13.4 billion (2)
Number of pharmaceutical companies with sales over $1 billion*	11	1
Total pharmaceutical sales of ten largest pharmaceutical companies†	$16.7 billion	$6 billion
Pharmaceutical sales as percent of total sales‡	50.1	74.1
Number of new pharmaceutical products introduced:		
1961–1980	353	155
1981–1983	24	41
R&D expenditures as percent of sales‡	6.8	9.2
Scientists and engineers in industrial R&D§:		
Total number	573,900	272,000
Percent of work force	0.58	0.50
Government-funded research in biotechnology:		
Total	$520 million	$60 million
Percent of basic research	>98	<50
Targets of funding in biotechnology	Basic research	Basic research, scale-up, industrial projects, government laboratory facilities, manufacturing technology

*Pharmaceutical sales only. †Total world pharmaceutical sales in 1983 were approximately $60 billion. ‡Average of top ten companies. §All industries, 1977 data.

the Ministry of Agriculture, Forestry and Fisheries (MAFF) (*2*, *18*). The total government support for biotechnology, $50 million to $60 million in 1984, is only about one-tenth of that spent by the U.S. government (Table 3) (*2*, *18*), but Japanese funding is much more focused on specific projects. For example, MITI, in a 10-year strategic program beginning in 1981, has targeted next-generation technologies to foster scale-up techniques, aimed at assisting in the commercialization of biotechnology (*2*). The STA is also funding applied research, such as the development of bioreactors (*2*). The latest announced budgets of STA, MAFF, and MITI are emphasizing national centers related to biotechnology research, including the development of cell line and gene banks (*18*). Very little of the Japanese government's support for biotechnology is for basic research (*2*). In contrast, the U.S. government's support of biotechnology is almost ten times more, but support of applied research makes up only 1 to 2 percent of this total, with far less specificity than in Japan (Table 3) (*2*).

Another emphasis in Japan is to foster cooperation between companies and between industry and academia. There are more than a dozen joint ventures on record involving two or more Japanese companies that are aimed at developing therapeutics through research in biotechnology (*2*, *19*). Similar cooperation between large U.S. companies does not (or cannot) exist (*2*).

In order to further foster cooperation between Japanese companies, a trade association, tentatively called the Society for Advanced Pharmaceutical Research, was formed in 1985 with 31 member companies and the support of Japan's Ministry of Health and Welfare (*19*). A trade group, the Industrial Biotechnology Association, exists in the United States with 46 member companies, but is not supported by the federal government (*20*).

Because government funding in Japan is focused on applied research, Japanese companies are also in the process of expanding in-house expertise in basic research and development in biotechnology. Many companies have announced the expansion of research facilities, such as Sankyo's new $53-million biotechnology laboratory to be completed by 1986 (*21*). The availability of personnel to staff basic research laboratories in Japan has been a problem, primarily owing to a paucity of university programs in molecular genetics (*2*, *16*). To fill the need for researchers, some Japanese companies

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Spatially Regulated Expression of Homeotic Genes in *Drosophila*

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Abstract. *The sites of transcript accumulation for six different homeotic loci of the Antennapedia and bithorax gene complexes (ANT-C and BX-C) were identified within embryo tissue sections by in situ hybridization. These six loci belong to the Antennapedia class of the homeo box gene family. Transcripts encoded by each locus are detected primarily in discrete, nonoverlapping regions of the embryonic central nervous system (CNS). The regions of the CNS that contain transcripts encoded by each of these loci correspond to the embryonic segments that are disrupted in mutants for these genes. The maintenance of spatially restricted expression of each ANT-C and BX-C locus could involve hierarchical, cross-regulatory interactions that are mediated by the homeo box protein domains encoded by these genes.*

A fundamental problem of development is how embryonic cells acquire their particular developmental fates as a result of their location within a developing embryo. A model system for analyzing the elaboration of this positional information during *Drosophila* development involves the morphogenesis of body segments. The adult fruit fly is composed of eight abdominal, three thoracic, and four to six head segments (*1*). Several of the constituent tissues of a given segment have morphological properties specific for that segment. For example, the epidermis elaborates cuticular structures, such as legs and antennae, that are distinct for a particular segment. In addition, the morphology of some of the mesodermal (*2*) and neural tissues (*3, 4*) may be specific for a given segment.

Homeotic genes are those that establish the diverse pathways by which each embryonic segment primordium develops a distinct adult phenotype (*5, 6*). Mutations of homeotic loci result in partial or complete transformations of the epidermal tissues of one segment into those of another. Homeotic transformations may include the neural and mesodermal tissues of the affected segment as well (*2, 3, 7*). For example, embryos that lack the *Antennapedia* (*Antp*) gene function display a transformation of the meso- and metathorax (T2 + T3) into homologous tissues of the prothorax (T1) (*8*).

Many homeotic genes appear within one of two clusters in the *Drosophila* genome, the bithorax complex (BX-C) (*5, 9*) or the Antennapedia complex (ANT-C) (*10, 11*). Genes of the BX-C are required for the specification of segments in the posterior regions of the fly (*5, 12, 13*). Lewis has identified a number of homeotic loci within the BX-C on the basis of embryonic and adult mutant phenotypes (*5*). Recently, a minimum of three essential domains of homeotic function within the BX-C have been identified by means of lethal complementation analyses: *Ultrabithorax (Ubx), Abdominal-A (abd-A), and Abdominal-B(Abd-B)* (*9*). The ANT-C is required for the specification of anterior body segments (*8, 14*). Several homeotic lethal complementation groups have been identified for the ANT-C (*8, 11, 14, 15*). These include the *Antp, Sex combs reduced (Scr), and Deformed* (*Dfd*) loci. Each ANT-C and BX-C homeotic lethal complementation group controls the development of a different subset of the embryonic segment primordia (Fig. 1a).

A central problem in elucidating the genetic control of segment morphogenesis is how the different ANT-C and BX-C loci come to function in primarily nonoverlapping domains along the body axis of the fly. The molecular cloning of ANT-C and BX-C loci has permitted a direct assessment of the spatial and temporal limits of homeotic gene expression. The previous demonstration that *Ubx* and *Antp* share direct nucleotide sequence homology (*16-19*) facilitated the isolation of ANT-C and BX-C loci. This homology occurs within a conserved protein coding region designated the homeo box. A total of seven genomic DNA fragments cross-hybridizes strongly with the *Antp* and *Ubx* homeo boxes (*20*). These seven regions correspond to the Antennapedia class of the homeo box gene family, all of which are located within either the ANT-C or the BX-C (*20*). It appears that each of the six lethal complementation groups of the ANT-C and BX-C (Fig. 1) contains an Antennapedia class homeo box. However, there are additional homeotic loci within the BX-C that do not contain the homeo box (Fig. 1a) (*21*).

We show that each of the ANT-C and BX-C homeotic loci that contains a homeo box specifies transcripts that accumulate in discrete regions of the embryonic central nervous system (CNS). To a close approximation, the regions of the CNS that contain transcripts encoded by each of these loci correspond to the embryonic segments that are disrupted in mutants for these genes. We propose that spatially restricted expression of each ANT-C and BX-C locus involves hierarchical, cross-regulatory interactions that are mediated by the homeo box protein domains encoded by these genes. Support for this model is based on analysis of the distribution patterns of *Antp* transcripts in mutant embryos that lack BX-C loci.

Isolation of a new ANT-C homeo box locus. Molecular clones for the *Dfd, Antp, Ubx, iab-2,* and *iab-7* loci have been previously isolated (*16, 20, 22–25*). In order to determine the spatial limits of expression for each homeotic lethal complementation group within the ANT-C and BX-C by in situ hybridization, it was necessary to obtain a molecular probe for the *Scr* locus. A genomic DNA fragment that appears to derive from *Scr* was isolated on the basis of homeo box sequence homology as described below.

A total of 6×10^4 recombinants from a *Drosophila*–Charon 4 DNA library (approximately six genome equivalents) were screened with the homeo box se-

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differ is in the type and amount of government support for the development of biotechnology. In Japan there is a clear effort by government to enhance the future commercial success of the pharmaceutical industry by assisting in the development of biotechnology. Although this support is administered by a few different agencies and is small in size (by U.S. standards), it is viewed both externally (*2, 25*) and internally (*16*) as a single cohesive effort with a high potential for success. The companies involved must create their own basic research and development programs; government assistance is at the next level, helping to foster commercialization of products, manufacturing, and generic support, such as gene banks (*18*). In the United States, federal support for biotechnology is ten times greater in magnitude and is aimed at basic research. Although support of basic research programs in biotechnology should be continued and expanded to ensure maintained leadership in basic research, support for more applied areas is also needed (*2, 16*).

Another contrast between the two countries is in the availability of basic researchers in biotechnology and bioprocess engineering. There was a reported shortage in the United States of basic researchers trained in genetic engineering, but this problem appears to have abated (*2, 30*). Due to strong academic programs in this and related areas, the availability of basic researchers should continue to be sufficient (*2*). However, a paucity of academic programs in bioprocess engineering continues (*2*). As more companies generate products of biotechnology for scale-up, it is expected that there will be a severe shortage of personnel trained in production technologies, which may hamper commercial success (*2*). Japan has the opposite problem—an adequate supply of fermentation engineers but too few basic researchers with training in molecular genetics (*16*). This is another reason why Japanese companies have been borrowing U.S. basic research, but are predicted to outpace the United States in commercialization (*2, 3*).

Outlook

In January 1984 the U.S. Congress Office of Technology Assessment (OTA) published a 612-page analysis on commercial biotechnology (*2*). The report noted the importance of biotechnology both for its basic scientific benefit and for its potential commercial development. In assessing the competitive position for the United States, the OTA report stated the following (*2*, p. 7):

> Japan is likely to be the leading competitor of the United States for two reasons. First, Japanese companies in a broad range of industrial sectors have extensive experience in bioprocess technology. Japan does not have superior bioprocess technology, but it does have relatively more industrial experience using old biotechnology, more established bioprocessing plants, and more bioprocess engineers than the United States. Second, the Japanese Government has targeted biotechnology as a key technology of the future, is funding its commercial development, and is coordinating interactions among representatives from industry, universities, and government.

When the focus of analysis is narrowed to the pharmaceutical industry, it can also be concluded that the Japanese have the potential to be a leading competitor. An important factor in their success has been the borrowing of basic biotechnological research by Japanese companies from U.S. biotechnology firms. Although biotechnology licensed by U.S. firms to Japanese companies generally involves marketing rights in Japan or Asia (*2*), the Japanese market for pharmaceuticals is the second largest in the world. When added to other Asian markets, it becomes two-thirds the size of the North American or European markets (*9*). U.S. pharmaceutical companies have gained 40 percent of their revenues from foreign sales, and the loss of a foreign market may represent lost income (*9*).

In addition to basic biotechnology borrowed from the United States, Japan has been simultaneously building its own strength in this field. There are more and more frequent reports of new developments in basic biotechnology and discoveries of new drugs from Japanese industrial laboratories (Table 3) (*12*). It is thus possible that Japan's predicted future strength in pharmaceutical biotechnology will come both from internal developments and strategic government programs (*16*).

This is not to imply that with Japanese strength in biotechnology will come U.S. weakness in this area. As stated earlier, pharmaceutical and other companies in the United States are expanding their efforts in biotechnology and are nearing their goals of bringing new therapeutics and diagnostics to market. However, an analysis of Japanese strategies may help to understand how U.S. industry can optimize this process. In addition, U.S. industry will be strengthened if the U.S. government makes the commercialization of biotechnology a high priority and funds specific academic and other programs leading to that goal (*2*). As stated in the OTA report (*2*): "The United States may compete very favorably with Japan if it can direct more attention to research problems associated with the scaling-up of bioprocesses for production."

In addition, government activities that enhance cooperation between companies, decrease regulation, or provide centers to assist in biotechnology would help meet this goal (*2, 6, 31*). However, in the period since the OTA report was made public, no broad program of support to strengthen the U.S. position in biotechnology has been announced by the federal government.

Steps in the Right Direction

A few recent developments should prove useful to the future development of biotechnology in the United States. The first is the opening of biotechnology centers to assist in the transfer of biotechnology expertise from academia to industry. Two of these centers are at Pennsylvania State University and in Research Triangle Park, North Carolina. The Penn State Biotechnology Institute has planned research and educational facilities and will allow member companies access to "application-oriented research" and to a pilot production facility for assistance in scale-up (*32*).

The North Carolina Biotechnology Center currently receives $2.5 million in annual funding from state, federal, and industrial sources. The center funds specific programs, such as its Monoclonal Lymphocyte Technology Center, which involves academic research at the University of North Carolina and Duke University, the participation of industry, and funding by the National Science Foundation. The five industrial members agree on priorities for directed research to be funded by specific grants to participating laboratories. Although still in its infancy, the Monoclonal Lymphocyte Technology Center is fostering cooperation between companies in a university environment that probably would not have otherwise occurred (*33*).

The Center for Advanced Research in Biotechnology (CARB), to be built in Gaithersburg, Maryland, will combine federal, state, county, and university efforts (*34*). With CARB, the National Bureau of Standards will add its analytical expertise to molecular biology expertise from the University of Maryland. A CARB research facility to be completed

Table 2. Equity purchased in firms with a major focus on biotechnology. Equity purchases selected from database (*12*).

Large company (purchaser)	Biotechnology firm	Year
Purchased by U.S. pharmaceutical companies		
Abbott	Amgen	1980
Baxter Travenol	Genetics Institute	1982
Becton Dickenson	Applied Biosystems	1984
Johnson & Johnson	Enzo Biochem	1982
Lederle	Molecular Genetics	1981
Lederle	Cytogen	1983
Lilly	Synergen	1984
Schering-Plough	Biogen	1982
Schering-Plough	DNAX Ltd.*	1982
SmithKline	Beckman*	1982
Syntex	Genetic Systems	1982
Purchased by other U.S. companies		
Dow	Collaborative Research	1981
Du Pont	New England Nuclear*	1981
Fluor	Genentech	1981
W. R. Grace	Amicon*	1983
Martin Marietta	Molecular Genetics	1982
Monsanto	Biogen	1980
Monsanto	Collagen Corporation	1980
Purchased by Japanese companies		
Green Cross	Collaborative Research	1981
Mitsubishi	BioVec	1984

*Acquisition. Each nonacquisition purchase involved an average of $8 million.

Table 3. Comparison of U.S. and Japanese pharmaceutical industries and involvement in biotechnology. All 1983 data, except as noted. [Sources: (*1*, *2*, *9*, *15*)]

Data category	United States	Japan
Population (millions)	234.5	119.2
Gross national product	$3.3 trillion	$1.2 trillion
Domestic pharmaceutical market (world rank)	$21.3 billion (1)	$13.4 billion (2)
Number of pharmaceutical companies with sales over $1 billion*	11	1
Total pharmaceutical sales of ten largest pharmaceutical companies†	$16.7 billion	$6 billion
Pharmaceutical sales as percent of total sales‡	50.1	74.1
Number of new pharmaceutical products introduced:		
1961–1980	353	155
1981–1983	24	41
R&D expenditures as percent of sales‡	6.8	9.2
Scientists and engineers in industrial R&D§:		
Total number	573,900	272,000
Percent of work force	0.58	0.50
Government-funded research in biotechnology:		
Total	$520 million	$60 million
Percent of basic research	>98	<50
Targets of funding in biotechnology	Basic research	Basic research, scale-up, industrial projects, government laboratory facilities, manufacturing technology

*Pharmaceutical sales only. †Total world pharmaceutical sales in 1983 were approximately $60 billion. ‡Average of top ten companies. §All industries, 1977 data.

the Ministry of Agriculture, Forestry and Fisheries (MAFF) (*2*, *18*). The total government support for biotechnology, $50 million to $60 million in 1984, is only about one-tenth of that spent by the U.S. government (Table 3) (*2*, *18*), but Japanese funding is much more focused on specific projects. For example, MITI, in a 10-year strategic program beginning in 1981, has targeted next-generation technologies to foster scale-up techniques, aimed at assisting in the commercialization of biotechnology (*2*). The STA is also funding applied research, such as the development of bioreactors (*2*). The latest announced budgets of STA, MAFF, and MITI are emphasizing national centers related to biotechnology research, including the development of cell line and gene banks (*18*). Very little of the Japanese government's support for biotechnology is for basic research (*2*). In contrast, the U.S. government's support of biotechnology is almost ten times more, but support of applied research makes up only 1 to 2 percent of this total, with far less specificity than in Japan (Table 3) (*2*).

Another emphasis in Japan is to foster cooperation between companies and between industry and academia. There are more than a dozen joint ventures on record involving two or more Japanese companies that are aimed at developing therapeutics through research in biotechnology (*2*, *19*). Similar cooperation between large U.S. companies does not (or cannot) exist (*2*).

In order to further foster cooperation between Japanese companies, a trade association, tentatively called the Society for Advanced Pharmaceutical Research, was formed in 1985 with 31 member companies and the support of Japan's Ministry of Health and Welfare (*19*). A trade group, the Industrial Biotechnology Association, exists in the United States with 46 member companies, but is not supported by the federal government (*20*).

Because government funding in Japan is focused on applied research, Japanese companies are also in the process of expanding in-house expertise in basic research and development in biotechnology. Many companies have announced the expansion of research facilities, such as Sankyo's new $53-million biotechnology laboratory to be completed by 1986 (*21*). The availability of personnel to staff basic research laboratories in Japan has been a problem, primarily owing to a paucity of university programs in molecular genetics (*2*, *16*). To fill the need for researchers, some Japanese companies

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Spatially Regulated Expression of Homeotic Genes in *Drosophila*

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Abstract. *The sites of transcript accumulation for six different homeotic loci of the Antennapedia and bithorax gene complexes (ANT-C and BX-C) were identified within embryo tissue sections by in situ hybridization. These six loci belong to the Antennapedia class of the homeo box gene family. Transcripts encoded by each locus are detected primarily in discrete, nonoverlapping regions of the embryonic central nervous system (CNS). The regions of the CNS that contain transcripts encoded by each of these loci correspond to the embryonic segments that are disrupted in mutants for these genes. The maintenance of spatially restricted expression of each ANT-C and BX-C locus could involve hierarchical, cross-regulatory interactions that are mediated by the homeo box protein domains encoded by these genes.*

A fundamental problem of development is how embryonic cells acquire their particular developmental fates as a result of their location within a developing embryo. A model system for analyzing the elaboration of this positional information during *Drosophila* development involves the morphogenesis of body segments. The adult fruit fly is composed of eight abdominal, three thoracic, and four to six head segments (*1*). Several of the constituent tissues of a given segment have morphological properties specific for that segment. For example, the epidermis elaborates cuticular structures, such as legs and antennae, that are distinct for a particular segment. In addition, the morphology of some of the mesodermal (*2*) and neural tissues (*3*, *4*) may be specific for a given segment.

Homeotic genes are those that establish the diverse pathways by which each embryonic segment primordium develops a distinct adult phenotype (*5*, *6*). Mutations of homeotic loci result in partial or complete transformations of the epidermal tissues of one segment into those of another. Homeotic transformations may include the neural and mesodermal tissues of the affected segment as well (*2*, *3*, *7*). For example, embryos that lack the *Antennapedia* (*Antp*) gene function display a transformation of the meso- and metathorax (T2 + T3) into homologous tissues of the prothorax (T1) (*8*).

Many homeotic genes appear within one of two clusters in the *Drosophila* genome, the bithorax complex (BX-C) (*5*, *9*) or the Antennapedia complex (ANT-C) (*10*, *11*). Genes of the BX-C are required for the specification of segments in the posterior regions of the fly (*5*, *12*, *13*). Lewis has identified a number of homeotic loci within the BX-C on the basis of embryonic and adult mutant phenotypes (*5*). Recently, a minimum of three essential domains of homeotic function within the BX-C have been identified by means of lethal complementation analyses: *Ultrabithorax (Ubx), Abdominal-A (abd-A), and Abdominal-B(Abd-B)* (*9*). The ANT-C is required for the specification of anterior body segments (*8*, *14*). Several homeotic lethal complementation groups have been identified for the ANT-C (*8*, *11*, *14*, *15*). These include the *Antp*, *Sex combs reduced (Scr), and Deformed* (*Dfd*) loci. Each ANT-C and BX-C homeotic lethal complementation group controls the development of a different subset of the embryonic segment primordia (Fig. 1a).

A central problem in elucidating the genetic control of segment morphogenesis is how the different ANT-C and BX-C loci come to function in primarily nonoverlapping domains along the body axis of the fly. The molecular cloning of ANT-C and BX-C loci has permitted a direct assessment of the spatial and temporal limits of homeotic gene expression. The previous demonstration that *Ubx* and *Antp* share direct nucleotide sequence homology (*16-19*) facilitated the isolation of ANT-C and BX-C loci. This homology occurs within a conserved protein coding region designated the homeo box. A total of seven genomic DNA fragments cross-hybridizes strongly with the *Antp* and *Ubx* homeo boxes (*20*). These seven regions correspond to the Antennapedia class of the homeo box gene family, all of which are located within either the ANT-C or the BX-C (*20*). It appears that each of the six lethal complementation groups of the ANT-C and BX-C (Fig. 1) contains an Antennapedia class homeo box. However, there are additional homeotic loci within the BX-C that do not contain the homeo box (Fig. 1a) (*21*).

We show that each of the ANT-C and BX-C homeotic loci that contains a homeo box specifies transcripts that accumulate in discrete regions of the embryonic central nervous system (CNS). To a close approximation, the regions of the CNS that contain transcripts encoded by each of these loci correspond to the embryonic segments that are disrupted in mutants for these genes. We propose that spatially restricted expression of each ANT-C and BX-C locus involves hierarchical, cross-regulatory interactions that are mediated by the homeo box protein domains encoded by these genes. Support for this model is based on analysis of the distribution patterns of *Antp* transcripts in mutant embryos that lack BX-C loci.

Isolation of a new ANT-C homeo box locus. Molecular clones for the *Dfd*, *Antp*, *Ubx*, *iab-2*, and *iab-7* loci have been previously isolated (*16*, *20*, *22–25*). In order to determine the spatial limits of expression for each homeotic lethal complementation group within the ANT-C and BX-C by in situ hybridization, it was necessary to obtain a molecular probe for the *Scr* locus. A genomic DNA fragment that appears to derive from *Scr* was isolated on the basis of homeo box sequence homology as described below.

A total of 6×10^4 recombinants from a *Drosophila*–Charon 4 DNA library (approximately six genome equivalents) were screened with the homeo box se-

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differ is in the type and amount of government support for the development of biotechnology. In Japan there is a clear effort by government to enhance the future commercial success of the pharmaceutical industry by assisting in the development of biotechnology. Although this support is administered by a few different agencies and is small in size (by U.S. standards), it is viewed both externally (*2, 25*) and internally (*16*) as a single cohesive effort with a high potential for success. The companies involved must create their own basic research and development programs; government assistance is at the next level, helping to foster commercialization of products, manufacturing, and generic support, such as gene banks (*18*). In the United States, federal support for biotechnology is ten times greater in magnitude and is aimed at basic research. Although support of basic research programs in biotechnology should be continued and expanded to ensure maintained leadership in basic research, support for more applied areas is also needed (*2, 16*).

Another contrast between the two countries is in the availability of basic researchers in biotechnology and bioprocess engineering. There was a reported shortage in the United States of basic researchers trained in genetic engineering, but this problem appears to have abated (*2, 30*). Due to strong academic programs in this and related areas, the availability of basic researchers should continue to be sufficient (*2*). However, a paucity of academic programs in bioprocess engineering continues (*2*). As more companies generate products of biotechnology for scale-up, it is expected that there will be a severe shortage of personnel trained in production technologies, which may hamper commercial success (*2*). Japan has the opposite problem—an adequate supply of fermentation engineers but too few basic researchers with training in molecular genetics (*16*). This is another reason why Japanese companies have been borrowing U.S. basic research, but are predicted to outpace the United States in commercialization (*2, 3*).

Outlook

In January 1984 the U.S. Congress Office of Technology Assessment (OTA) published a 612-page analysis on commercial biotechnology (*2*). The report noted the importance of biotechnology both for its basic scientific benefit and for its potential commercial development. In assessing the competitive position for the United States, the OTA report stated the following (*2*, p. 7):

> Japan is likely to be the leading competitor of the United States for two reasons. First, Japanese companies in a broad range of industrial sectors have extensive experience in bioprocess technology. Japan does not have superior bioprocess technology, but it does have relatively more industrial experience using old biotechnology, more established bioprocessing plants, and more bioprocess engineers than the United States. Second, the Japanese Government has targeted biotechnology as a key technology of the future, is funding its commercial development, and is coordinating interactions among representatives from industry, universities, and government.

When the focus of analysis is narrowed to the pharmaceutical industry, it can also be concluded that the Japanese have the potential to be a leading competitor. An important factor in their success has been the borrowing of basic biotechnological research by Japanese companies from U.S. biotechnology firms. Although biotechnology licensed by U.S. firms to Japanese companies generally involves marketing rights in Japan or Asia (*2*), the Japanese market for pharmaceuticals is the second largest in the world. When added to other Asian markets, it becomes two-thirds the size of the North American or European markets (*9*). U.S. pharmaceutical companies have gained 40 percent of their revenues from foreign sales, and the loss of a foreign market may represent lost income (*9*).

In addition to basic biotechnology borrowed from the United States, Japan has been simultaneously building its own strength in this field. There are more and more frequent reports of new developments in basic biotechnology and discoveries of new drugs from Japanese industrial laboratories (Table 3) (*12*). It is thus possible that Japan's predicted future strength in pharmaceutical biotechnology will come both from internal developments and strategic government programs (*16*).

This is not to imply that with Japanese strength in biotechnology will come U.S. weakness in this area. As stated earlier, pharmaceutical and other companies in the United States are expanding their efforts in biotechnology and are nearing their goals of bringing new therapeutics and diagnostics to market. However, an analysis of Japanese strategies may help to understand how U.S. industry can optimize this process. In addition, U.S. industry will be strengthened if the U.S. government makes the commercialization of biotechnology a high priority and funds specific academic and other programs leading to that goal (*2*). As stated in the OTA report (*2*): "The United States may compete very favorably with Japan if it can direct more attention to research problems associated with the scaling-up of bioprocesses for production."

In addition, government activities that enhance cooperation between companies, decrease regulation, or provide centers to assist in biotechnology would help meet this goal (*2, 6, 31*). However, in the period since the OTA report was made public, no broad program of support to strengthen the U.S. position in biotechnology has been announced by the federal government.

Steps in the Right Direction

A few recent developments should prove useful to the future development of biotechnology in the United States. The first is the opening of biotechnology centers to assist in the transfer of biotechnology expertise from academia to industry. Two of these centers are at Pennsylvania State University and in Research Triangle Park, North Carolina. The Penn State Biotechnology Institute has planned research and educational facilities and will allow member companies access to "application-oriented research" and to a pilot production facility for assistance in scale-up (*32*).

The North Carolina Biotechnology Center currently receives $2.5 million in annual funding from state, federal, and industrial sources. The center funds specific programs, such as its Monoclonal Lymphocyte Technology Center, which involves academic research at the University of North Carolina and Duke University, the participation of industry, and funding by the National Science Foundation. The five industrial members agree on priorities for directed research to be funded by specific grants to participating laboratories. Although still in its infancy, the Monoclonal Lymphocyte Technology Center is fostering cooperation between companies in a university environment that probably would not have otherwise occurred (*33*).

The Center for Advanced Research in Biotechnology (CARB), to be built in Gaithersburg, Maryland, will combine federal, state, county, and university efforts (*34*). With CARB, the National Bureau of Standards will add its analytical expertise to molecular biology expertise from the University of Maryland. A CARB research facility to be completed

Table 2. Equity purchased in firms with a major focus on biotechnology. Equity purchases selected from database (*12*).

Large company (purchaser)	Biotechnology firm	Year
Purchased by U.S. pharmaceutical companies		
Abbott	Amgen	1980
Baxter Travenol	Genetics Institute	1982
Becton Dickenson	Applied Biosystems	1984
Johnson & Johnson	Enzo Biochem	1982
Lederle	Molecular Genetics	1981
Lederle	Cytogen	1983
Lilly	Synergen	1984
Schering-Plough	Biogen	1982
Schering-Plough	DNAX Ltd.*	1982
SmithKline	Beckman*	1982
Syntex	Genetic Systems	1982
Purchased by other U.S. companies		
Dow	Collaborative Research	1981
Du Pont	New England Nuclear*	1981
Fluor	Genentech	1981
W. R. Grace	Amicon*	1983
Martin Marietta	Molecular Genetics	1982
Monsanto	Biogen	1980
Monsanto	Collagen Corporation	1980
Purchased by Japanese companies		
Green Cross	Collaborative Research	1981
Mitsubishi	BioVec	1984

*Acquisition. Each nonacquisition purchase involved an average of $8 million.

Table 3. Comparison of U.S. and Japanese pharmaceutical industries and involvement in biotechnology. All 1983 data, except as noted. [Sources: (*1*, *2*, *9*, *15*)]

Data category	United States	Japan
Population (millions)	234.5	119.2
Gross national product	$3.3 trillion	$1.2 trillion
Domestic pharmaceutical market (world rank)	$21.3 billion (1)	$13.4 billion (2)
Number of pharmaceutical companies with sales over $1 billion*	11	1
Total pharmaceutical sales of ten largest pharmaceutical companies†	$16.7 billion	$6 billion
Pharmaceutical sales as percent of total sales‡	50.1	74.1
Number of new pharmaceutical products introduced:		
1961–1980	353	155
1981–1983	24	41
R&D expenditures as percent of sales‡	6.8	9.2
Scientists and engineers in industrial R&D§:		
Total number	573,900	272,000
Percent of work force	0.58	0.50
Government-funded research in biotechnology:		
Total	$520 million	$60 million
Percent of basic research	>98	<50
Targets of funding in biotechnology	Basic research	Basic research, scale-up, industrial projects, government laboratory facilities, manufacturing technology

*Pharmaceutical sales only. †Total world pharmaceutical sales in 1983 were approximately $60 billion. ‡Average of top ten companies. §All industries, 1977 data.

the Ministry of Agriculture, Forestry and Fisheries (MAFF) (*2*, *18*). The total government support for biotechnology, $50 million to $60 million in 1984, is only about one-tenth of that spent by the U.S. government (Table 3) (*2*, *18*), but Japanese funding is much more focused on specific projects. For example, MITI, in a 10-year strategic program beginning in 1981, has targeted next-generation technologies to foster scale-up techniques, aimed at assisting in the commercialization of biotechnology (*2*). The STA is also funding applied research, such as the development of bioreactors (*2*). The latest announced budgets of STA, MAFF, and MITI are emphasizing national centers related to biotechnology research, including the development of cell line and gene banks (*18*). Very little of the Japanese government's support for biotechnology is for basic research (*2*). In contrast, the U.S. government's support of biotechnology is almost ten times more, but support of applied research makes up only 1 to 2 percent of this total, with far less specificity than in Japan (Table 3) (*2*).

Another emphasis in Japan is to foster cooperation between companies and between industry and academia. There are more than a dozen joint ventures on record involving two or more Japanese companies that are aimed at developing therapeutics through research in biotechnology (*2*, *19*). Similar cooperation between large U.S. companies does not (or cannot) exist (*2*).

In order to further foster cooperation between Japanese companies, a trade association, tentatively called the Society for Advanced Pharmaceutical Research, was formed in 1985 with 31 member companies and the support of Japan's Ministry of Health and Welfare (*19*). A trade group, the Industrial Biotechnology Association, exists in the United States with 46 member companies, but is not supported by the federal government (*20*).

Because government funding in Japan is focused on applied research, Japanese companies are also in the process of expanding in-house expertise in basic research and development in biotechnology. Many companies have announced the expansion of research facilities, such as Sankyo's new $53-million biotechnology laboratory to be completed by 1986 (*21*). The availability of personnel to staff basic research laboratories in Japan has been a problem, primarily owing to a paucity of university programs in molecular genetics (*2*, *16*). To fill the need for researchers, some Japanese companies

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Abstract. *The sites of transcript accumulation for six different homeotic loci of the Antennapedia and bithorax gene complexes (ANT-C and BX-C) were identified within embryo tissue sections by in situ hybridization. These six loci belong to the Antennapedia class of the homeo box gene family. Transcripts encoded by each locus are detected primarily in discrete, nonoverlapping regions of the embryonic central nervous system (CNS). The regions of the CNS that contain transcripts encoded by each of these loci correspond to the embryonic segments that are disrupted in mutants for these genes. The maintenance of spatially restricted expression of each ANT-C and BX-C locus could involve hierarchical, cross-regulatory interactions that are mediated by the homeo box protein domains encoded by these genes.*

A fundamental problem of development is how embryonic cells acquire their particular developmental fates as a result of their location within a developing embryo. A model system for analyzing the elaboration of this positional information during *Drosophila* development involves the morphogenesis of body segments. The adult fruit fly is composed of eight abdominal, three thoracic, and four to six head segments (*1*). Several of the constituent tissues of a given segment have morphological properties specific for that segment. For example, the epidermis elaborates cuticular structures, such as legs and antennae, that are distinct for a particular segment. In addition, the morphology of some of the mesodermal (*2*) and neural tissues (*3, 4*) may be specific for a given segment.

Homeotic genes are those that establish the diverse pathways by which each embryonic segment primordium develops a distinct adult phenotype (*5, 6*). Mutations of homeotic loci result in partial or complete transformations of the epidermal tissues of one segment into those of another. Homeotic transformations may include the neural and mesodermal tissues of the affected segment as well (*2, 3, 7*). For example, embryos that lack the *Antennapedia* (*Antp*) gene function display a transformation of the meso- and metathorax (T2 + T3) into homologous tissues of the prothorax (T1) (*8*).

Many homeotic genes appear within one of two clusters in the *Drosophila* genome, the bithorax complex (BX-C) (*5, 9*) or the Antennapedia complex (ANT-C) (*10, 11*). Genes of the BX-C are required for the specification of segments in the posterior regions of the fly (*5, 12, 13*). Lewis has identified a number of homeotic loci within the BX-C on the basis of embryonic and adult mutant phenotypes (*5*). Recently, a minimum of three essential domains of homeotic function within the BX-C have been identified by means of lethal complementation analyses: *Ultrabithorax (Ubx), Abdominal-A (abd-A), and Abdominal-B(Abd-B)* (*9*). The ANT-C is required for the specification of anterior body segments (*8, 14*). Several homeotic lethal complementation groups have been identified for the ANT-C (*8, 11, 14, 15*). These include the *Antp, Sex combs reduced (Scr), and Deformed* (*Dfd*) loci. Each ANT-C and BX-C homeotic lethal complementation group controls the development of a different subset of the embryonic segment primordia (Fig. 1a).

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A central problem in elucidating the genetic control of segment morphogenesis is how the different ANT-C and BX-C loci come to function in primarily nonoverlapping domains along the body axis of the fly. The molecular cloning of ANT-C and BX-C loci has permitted a direct assessment of the spatial and temporal limits of homeotic gene expression. The previous demonstration that *Ubx* and *Antp* share direct nucleotide sequence homology (*16-19*) facilitated the isolation of ANT-C and BX-C loci. This homology occurs within a conserved protein coding region designated the homeo box. A total of seven genomic DNA fragments cross-hybridizes strongly with the *Antp* and *Ubx* homeo boxes (*20*). These seven regions correspond to the Antennapedia class of the homeo box gene family, all of which are located within either the ANT-C or the BX-C (*20*). It appears that each of the six lethal complementation groups of the ANT-C and BX-C (Fig. 1) contains an Antennapedia class homeo box. However, there are additional homeotic loci within the BX-C that do not contain the homeo box (Fig. 1a) (*21*).

We show that each of the ANT-C and BX-C homeotic loci that contains a homeo box specifies transcripts that accumulate in discrete regions of the embryonic central nervous system (CNS). To a close approximation, the regions of the CNS that contain transcripts encoded by each of these loci correspond to the embryonic segments that are disrupted in mutants for these genes. We propose that spatially restricted expression of each ANT-C and BX-C locus involves hierarchical, cross-regulatory interactions that are mediated by the homeo box protein domains encoded by these genes. Support for this model is based on analysis of the distribution patterns of *Antp* transcripts in mutant embryos that lack BX-C loci.

Isolation of a new ANT-C homeo box locus. Molecular clones for the *Dfd, Antp, Ubx, iab-2*, and *iab-7* loci have been previously isolated (*16, 20, 22–25*). In order to determine the spatial limits of expression for each homeotic lethal complementation group within the ANT-C and BX-C by in situ hybridization, it was necessary to obtain a molecular probe for the *Scr* locus. A genomic DNA fragment that appears to derive from *Scr* was isolated on the basis of homeo box sequence homology as described below.

A total of 6×10^4 recombinants from a *Drosophila*–Charon 4 DNA library (approximately six genome equivalents) were screened with the homeo box se-

differ is in the type and amount of government support for the development of biotechnology. In Japan there is a clear effort by government to enhance the future commercial success of the pharmaceutical industry by assisting in the development of biotechnology. Although this support is administered by a few different agencies and is small in size (by U.S. standards), it is viewed both externally (*2, 25*) and internally (*16*) as a single cohesive effort with a high potential for success. The companies involved must create their own basic research and development programs; government assistance is at the next level, helping to foster commercialization of products, manufacturing, and generic support, such as gene banks (*18*). In the United States, federal support for biotechnology is ten times greater in magnitude and is aimed at basic research. Although support of basic research programs in biotechnology should be continued and expanded to ensure maintained leadership in basic research, support for more applied areas is also needed (*2, 16*).

Another contrast between the two countries is in the availability of basic researchers in biotechnology and bioprocess engineering. There was a reported shortage in the United States of basic researchers trained in genetic engineering, but this problem appears to have abated (*2, 30*). Due to strong academic programs in this and related areas, the availability of basic researchers should continue to be sufficient (*2*). However, a paucity of academic programs in bioprocess engineering continues (*2*). As more companies generate products of biotechnology for scale-up, it is expected that there will be a severe shortage of personnel trained in production technologies, which may hamper commercial success (*2*). Japan has the opposite problem—an adequate supply of fermentation engineers but too few basic researchers with training in molecular genetics (*16*). This is another reason why Japanese companies have been borrowing U.S. basic research, but are predicted to outpace the United States in commercialization (*2, 3*).

Outlook

In January 1984 the U.S. Congress Office of Technology Assessment (OTA) published a 612-page analysis on commercial biotechnology (*2*). The report noted the importance of biotechnology both for its basic scientific benefit and for its potential commercial development. In assessing the competitive position for the United States, the OTA report stated the following (*2*, p. 7):

> Japan is likely to be the leading competitor of the United States for two reasons. First, Japanese companies in a broad range of industrial sectors have extensive experience in bioprocess technology. Japan does not have superior bioprocess technology, but it does have relatively more industrial experience using old biotechnology, more established bioprocessing plants, and more bioprocess engineers than the United States. Second, the Japanese Government has targeted biotechnology as a key technology of the future, is funding its commercial development, and is coordinating interactions among representatives from industry, universities, and government.

When the focus of analysis is narrowed to the pharmaceutical industry, it can also be concluded that the Japanese have the potential to be a leading competitor. An important factor in their success has been the borrowing of basic biotechnological research by Japanese companies from U.S. biotechnology firms. Although biotechnology licensed by U.S. firms to Japanese companies generally involves marketing rights in Japan or Asia (*2*), the Japanese market for pharmaceuticals is the second largest in the world. When added to other Asian markets, it becomes two-thirds the size of the North American or European markets (*9*). U.S. pharmaceutical companies have gained 40 percent of their revenues from foreign sales, and the loss of a foreign market may represent lost income (*9*).

In addition to basic biotechnology borrowed from the United States, Japan has been simultaneously building its own strength in this field. There are more and more frequent reports of new developments in basic biotechnology and discoveries of new drugs from Japanese industrial laboratories (Table 3) (*12*). It is thus possible that Japan's predicted future strength in pharmaceutical biotechnology will come both from internal developments and strategic government programs (*16*).

This is not to imply that with Japanese strength in biotechnology will come U.S. weakness in this area. As stated earlier, pharmaceutical and other companies in the United States are expanding their efforts in biotechnology and are nearing their goals of bringing new therapeutics and diagnostics to market. However, an analysis of Japanese strategies may help to understand how U.S. industry can optimize this process. In addition, U.S. industry will be strengthened if the U.S. government makes the commercialization of biotechnology a high priority and funds specific academic and other programs leading to that goal (*2*). As stated in the OTA report (*2*): "The United States may compete very favorably with Japan if it can direct more attention to research problems associated with the scaling-up of bioprocesses for production."

In addition, government activities that enhance cooperation between companies, decrease regulation, or provide centers to assist in biotechnology would help meet this goal (*2, 6, 31*). However, in the period since the OTA report was made public, no broad program of support to strengthen the U.S. position in biotechnology has been announced by the federal government.

Steps in the Right Direction

A few recent developments should prove useful to the future development of biotechnology in the United States. The first is the opening of biotechnology centers to assist in the transfer of biotechnology expertise from academia to industry. Two of these centers are at Pennsylvania State University and in Research Triangle Park, North Carolina. The Penn State Biotechnology Institute has planned research and educational facilities and will allow member companies access to "application-oriented research" and to a pilot production facility for assistance in scale-up (*32*).

The North Carolina Biotechnology Center currently receives $2.5 million in annual funding from state, federal, and industrial sources. The center funds specific programs, such as its Monoclonal Lymphocyte Technology Center, which involves academic research at the University of North Carolina and Duke University, the participation of industry, and funding by the National Science Foundation. The five industrial members agree on priorities for directed research to be funded by specific grants to participating laboratories. Although still in its infancy, the Monoclonal Lymphocyte Technology Center is fostering cooperation between companies in a university environment that probably would not have otherwise occurred (*33*).

The Center for Advanced Research in Biotechnology (CARB), to be built in Gaithersburg, Maryland, will combine federal, state, county, and university efforts (*34*). With CARB, the National Bureau of Standards will add its analytical expertise to molecular biology expertise from the University of Maryland. A CARB research facility to be completed

Table 2. Equity purchased in firms with a major focus on biotechnology. Equity purchases selected from database (*12*).

Large company (purchaser)	Biotechnology firm	Year
Purchased by U.S. pharmaceutical companies		
Abbott	Amgen	1980
Baxter Travenol	Genetics Institute	1982
Becton Dickenson	Applied Biosystems	1984
Johnson & Johnson	Enzo Biochem	1982
Lederle	Molecular Genetics	1981
Lederle	Cytogen	1983
Lilly	Synergen	1984
Schering-Plough	Biogen	1982
Schering-Plough	DNAX Ltd.*	1982
SmithKline	Beckman*	1982
Syntex	Genetic Systems	1982
Purchased by other U.S. companies		
Dow	Collaborative Research	1981
Du Pont	New England Nuclear*	1981
Fluor	Genentech	1981
W. R. Grace	Amicon*	1983
Martin Marietta	Molecular Genetics	1982
Monsanto	Biogen	1980
Monsanto	Collagen Corporation	1980
Purchased by Japanese companies		
Green Cross	Collaborative Research	1981
Mitsubishi	BioVec	1984

*Acquisition. Each nonacquisition purchase involved an average of $8 million.

Table 3. Comparison of U.S. and Japanese pharmaceutical industries and involvement in biotechnology. All 1983 data, except as noted. [Sources: (*1, 2, 9, 15*)]

Data category	United States	Japan
Population (millions)	234.5	119.2
Gross national product	$3.3 trillion	$1.2 trillion
Domestic pharmaceutical market (world rank)	$21.3 billion (1)	$13.4 billion (2)
Number of pharmaceutical companies with sales over $1 billion*	11	1
Total pharmaceutical sales of ten largest pharmaceutical companies†	$16.7 billion	$6 billion
Pharmaceutical sales as percent of total sales‡	50.1	74.1
Number of new pharmaceutical products introduced:		
1961–1980	353	155
1981–1983	24	41
R&D expenditures as percent of sales‡	6.8	9.2
Scientists and engineers in industrial R&D§:		
Total number	573,900	272,000
Percent of work force	0.58	0.50
Government-funded research in biotechnology:		
Total	$520 million	$60 million
Percent of basic research	>98	<50
Targets of funding in biotechnology	Basic research	Basic research, scale-up, industrial projects, government laboratory facilities, manufacturing technology

*Pharmaceutical sales only. †Total world pharmaceutical sales in 1983 were approximately $60 billion. ‡Average of top ten companies. §All industries, 1977 data.

the Ministry of Agriculture, Forestry and Fisheries (MAFF) (*2, 18*). The total government support for biotechnology, $50 million to $60 million in 1984, is only about one-tenth of that spent by the U.S. government (Table 3) (*2, 18*), but Japanese funding is much more focused on specific projects. For example, MITI, in a 10-year strategic program beginning in 1981, has targeted next-generation technologies to foster scale-up techniques, aimed at assisting in the commercialization of biotechnology (*2*). The STA is also funding applied research, such as the development of bioreactors (*2*). The latest announced budgets of STA, MAFF, and MITI are emphasizing national centers related to biotechnology research, including the development of cell line and gene banks (*18*). Very little of the Japanese government's support for biotechnology is for basic research (*2*). In contrast, the U.S. government's support of biotechnology is almost ten times more, but support of applied research makes up only 1 to 2 percent of this total, with far less specificity than in Japan (Table 3) (*2*).

Another emphasis in Japan is to foster cooperation between companies and between industry and academia. There are more than a dozen joint ventures on record involving two or more Japanese companies that are aimed at developing therapeutics through research in biotechnology (*2, 19*). Similar cooperation between large U.S. companies does not (or cannot) exist (*2*).

In order to further foster cooperation between Japanese companies, a trade association, tentatively called the Society for Advanced Pharmaceutical Research, was formed in 1985 with 31 member companies and the support of Japan's Ministry of Health and Welfare (*19*). A trade group, the Industrial Biotechnology Association, exists in the United States with 46 member companies, but is not supported by the federal government (*20*).

Because government funding in Japan is focused on applied research, Japanese companies are also in the process of expanding in-house expertise in basic research and development in biotechnology. Many companies have announced the expansion of research facilities, such as Sankyo's new $53-million biotechnology laboratory to be completed by 1986 (*21*). The availability of personnel to staff basic research laboratories in Japan has been a problem, primarily owing to a paucity of university programs in molecular genetics (*2, 16*). To fill the need for researchers, some Japanese companies

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Space Arms Scientists in U.S. Selling Rights to Discoveries

By WILLIAM J. BROAD

A handful of Federal scientists quietly at work in their laboratories have touched off a heated national debate.

These inventors are selling their research on President Reagan's proposed system of missile defense for their private gain. They are being encouraged to do so by the Administration and hundreds of their scientific colleagues are expected to follow suit.

First of two articles.

White House officials strongly defend the practice, which is permitted under the law and has grown rapidly since Mr. Reagan took office in 1981. The officials say the public interest is best served when Federal scientists can commercialize aspects of their work. This is particularly true, they say, of research on the Strategic Defense Initiative, known popularly as "Star Wars."

These officials say the policy spurs scientific incentive, industrial productivity and the realization of Government goals. Under previous Federal practice, Government inventions often went unused and undeveloped, they assert.

But critics, increasingly angry about the new approach, say conflicts of interests can arise when Federal scientists seek private gain from publicly financed research, resulting in distorted judgments and skewed aims.

Dr. Hugh DeWitt, a physicist at the Lawrence Livermore National Laboratory, said in an interview: "You're being asked to serve two masters. The temptation is to conduct your research in such a way that it satisfies monetary goals."

In response, Dr. Jack B. Marling, a Livermore physicist who has sold the

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NY Times 11-4-85

Scientists Selling Space Arms Work

Continued From Page 1

rights of his laser invention to a private concern, said "serving two masters" was not the right way to look at Federal scientists who are engaged in commercial ventures.

"They're really serving one master, the human race," he said. "It doesn't matter whether they're working for the Government, the private sector, or both. The ultimate beneficiary will be the people, one way or another."

Patents and Industry

The debate is aggravated by two trends, according to both defenders and detractors of the commercialization of the missile defense research.

The first is the widening search for all kinds of spinoffs at the nation's Federal labs — a network of 755 facilities that spend about $15 billion a year. Instead of retaining all rights to inventions, as it did in the past, the Government today is encouraging Federal scientists to sell patents to industry, to accept private funds for research projects, to work with industry scientists in exchange programs and to found business ventures.

The second trend involves the expansion of research on missile defenses. Since Mr. Reagan's speech in March 1983 outlining his missile defense initiative, his vision has grown into a five-year, $26 billion program in which Federal laboratories play a pivotal role. Government scientists are pursuing not only exotic weapons but also advanced computers, optics, sensors, microcircuits, mirror coatings, nuclear reactors, rocket engines and industrial processes in dozens of areas. Last week the Pentagon disclosed that the plan for the missile shield, developed after a year of design work, calls for thousands of space satellites in a system with seven layers of weapons.

The debate is likely to intensify as more Federal scientists seek to profit from commercial spinoffs of missile defense research. In September, the director of the Strategic Defense Initiative Organization, Lieut. Gen. James A. Abrahamson of the Air Force, created a new office to encourage civilian spinoffs from the military program. On Oct. 8 he told a Congressional committee that missile-defense scientists have a "splendid opportunity to capitalize on the results of the research of the S.D.I. and apply it across all facets of our economy and society."



The New York Times/Jose R. Lopez

Dr. John P. McTague, a White House science official, said that Federal scientists today seldom commercialized their ideas.

Livermore Is Key Site

Although commercialization of missile defense research is still in its early stages, Federal scientists are excitedly planning to capitalize on their Government research and in some cases have already made financial gains. One center for such spinoffs is the Livermore laboratory in California, a facility for the design of nuclear weapons that was founded in the 1950's. Today the weapons laboratory, which employs 8,000 workers, is creating some of the most advanced technologies for the missile defense program.

According to Livermore scientists, one defensive technology with potential for spinoffs is a supercomputer known as S-1. In April 1983, shortly after Mr. Reagan's missile defense speech, Dr. Edward Teller, a founder of the Livermore laboratory, told Congress that the Livermore's S-1 supercomputer project was a key to making a defense against enemy missiles. "By using these upcoming supercomputers," he said, "we can make decisions in proper time so that we can orchestrate our defenses, and we can make sure that we do the best possible job in shielding ourselves from any strategic attack."

In addition to its defensive role, Livermore scientists say S-1 technology has wide commercial applications. One is a technique by which a laser can etch the circuitry of a room-sized supercomputer onto a single wafer of silicon. According to S-1 project scientists who are pioneering the process, such American companies as Magnavox are negotiating with Livermore scientists for the rights to commercial applications of the technology. The miniaturization goal is generically known as wafer-scale integration.

Potential for Industry

"The big companies realize they're going to have to go this way or be out of the business in 10 years," said Dr. Bruce M. McWilliams, who heads Livermore's laser approach to wafer-scale integration. He added that he and other members of his Livermore team had patented parts of the laser process.

Weapons, like lasers, that direct concentrated beams of energy are another missile defense technology being evaluated for commercial application. For instance, Livermore physicists have developed a powerful miniature accelerator to fire subatomic particles into special lasers that use electrons freed from atomic substance, potentially one of the Pentagon's most powerful space weapons.

The accelerator is also being promoted by its developer, Dr. Stephen M. Matthews, a physicist at Livermore, for use as a commercial radiation source for sterilizing fruits, vegetables, and processed food products. It would be safer than the chemicals used on many crops, according to Dr. Matthews.

The accelerator is six feet long and could be manufactured to sell for about $1.5 million, Dr. Matthews said, adding that its commercial utility is being evaluated by the Food Science Department of the University of California at Davis and that industrial contractors have shown interest.

"The benefits of big science should be channeled back to the taxpayer," he said. "The best way to do that is through the commercialization of the technology."

Communications Laser

A device related to the missile defense project from which Federal scientists have already profited is the blue-green laser, which is meant to beam messages from orbiting satellites to submerged submarines. The device is viewed by Livermore scientists as crucial for strategic defense because of its ability to transmit large amounts of information with great speed. Blue-green lasers could relay urgent messages about the size, direction and speed of a Soviet attack, allowing submarines to quickly fire interceptor weapons into space to try to knock out enemy missiles.

Last year, Dr. Marling, a key researcher, sold the rights for a blue-green laser detector to Helionetics Inc. of Irvine, Calif., which has contracts with the Navy for developing the communications system. The money Helionetics has paid for the rights to the laser will undoubtably be passed on to the Navy in increased costs for the communications system.

"The really good inventions have a wide impact only after they enter the commercial sector," Dr. Marling said. He added that in such highly productive countries as Japan there has been more interaction between the public and private sectors than in the United States.

Until 1980, the American Government tended to discourage Federal scientists from seeking private financial gains from their work, according to Government officials. It did this by issuing nonexclusive licenses for ideas patented at national laboratories and returning any profits to the treasury. Nearly anyone could pay a fee and receive rights to a Federal invention.

U.S. Holds Patents

Over the years the Government came to own 25,000 patents, but only 5 percent of them were commercially licensed. Policymakers in Washington said the problem was risk: No entrepreneur was willing to perfect a process that anybody could copy.

The emphasis on increased commercialization started around 1980 when two laws were passed encouraging the transfer of Government technology into the private sector by allowing Federal laboratories and employees to retain title to inventions and by encouraging the issuing of exclusive licenses to patents. This practice varies from the situation in private industry, where researchers normally retain no rights to their inventions.

Regulations are being written for recent amendments to the acts. There are also wide differences in how policies are applied at various Federal laboratories, since they are managed by universities, private contractors, and the Government itself under different sets of rules. In some cases, a researcher may receive nearly all the profits from the sale of the rights to a government invention. Other times, the sponsoring institution may retain much of the profit.

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Arms Work

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According to its proponents, commercialization has only recently come under fire because of its association with the politically sensitive missile defense program. They say potential problems have been exaggerated. They insist, for instance, that it is difficult for discoveries to be instantly profitable — a financial barrier that helps keep research from being skewed.

"One of the illusions of technology transfer is that there's a stock of technology on the shelf," said Albert H. Teich, head of public sector programs at the American Association for the Advancement of Science. "Most often there isn't a dual use — both 'Star Wars' and the corner store, for instance. It takes a lot of work to adapt something. It's not a widget that gets transfered. It's a much broader kind of thing."

Chance of Abuse

The potential for abuse is very small, according to Dr. Eugene Stark, director of the industrial liaison office at the Los Alamos National Laboratory in New Mexico. He said one protection was the tiny amount of money to be made. At the Los Alamos National Laboratory in New Mexico, he said, officials estimate that five years from now, after the revolution in commercialization has become routine, royalties from the private licensing of patents might amount to $2 to $3 million a year spread among 7,000 scientists. Currently, he noted, Los Alamos has an annual budget of about $600 million.

Dr. John P. McTague, deputy director of President's Office of Science and Technology Policy, said the Government had to finish the job of opening the Federal labs before turning its attention to potential conflicts of interests.

"In principle there might be a problem if we had a large number of people engaged in garage-type ventures," he said. He added, however, that Federal scientists currently fail to commercialize enough of their ideas. "We clearly need greater linkages to the private sector. If that leads to other problems, so be it. I would like to have too much technology transfer. There are certainly ways to deal with problems when they come along, such as having local managers look into conflicts. But we need to deal with the first problem first."

In contrast, critics say commercialization has serious potential pitfalls that should be addressed from the start. "Federal servants are paid to be impartial," said Dr. Charles Schwartz, a physicist at the University of California at Berkeley. "If there are financial interests or conflicts, it raises questions of whether it's really disinterested advice coming from the labs."

One danger, critics say, is the great disparity in the evaluation of different kinds of projects. They say commercial spinoffs are easy to test — they work or they don't. But short of actual war, a missile defense system is too complex to ever be thoroughly assessed. The result, they say, is that a researcher making private profits might be tempted to cut corners in evaluating the feasibility of complex public projects.

"Who's to say whether this stuff works?" asked John E. Pike, head of space policy at the Federation of American Scientists, a private, nonprofit group in Washington that has opposed the missile defense program. "With a vaccine it's really clear. But with 'Star Wars' there's not much opportunity for consumer feedback. You have to take somebody's word on it."

Previous Government policy, the critics say, served the public interest much better than is often claimed. It avoided the risk of diminished Federal efforts as Government scientists pursue monetary goals. Moreover, critics say the engines of commercialization may eventually run low on fuel. Some Government patents, they assert, are essentially worthless, having been filed defensively or as status symbols.

A final objection of the critics is that public monitoring of conflicts of interest under the new policy may be difficult or nearly impossible because of antiquated laws and regulations. A Federal researcher who sells the rights of an invention, for instance, might not have to reveal publicly whether he also owns stock in the recipient company.

"No one objects to technology transfer in general," said Albert H. Meyerhoff, an attorney at the Natural Resources Defense Council in San Francisco. "But you want it in a way that protects the public trust. At a minimum there should be full disclosure of any financial benefits accruing to government scientists from the for-profit use of their work products."

He added: "In general you're playing with fire when you mix the goals of the private sector, which is for profit, with the goals of the public sector, which should be devoted to finding new knowledge and benefiting society as a whole."

Next: Contractor's potential conflicts.



Associated Press

Albert H. Meyerhoff, a lawyer at the Natural Resources Defense Council in San Francisco, said, "We rely on these scientists to be our brain trusts."

Inside the Administration

An Inside Washington Publication

An exclusive report on the Reagan Administration's economic, regulatory and management policies

Vol. 4 No. 38, September 19, 1985 Vol. 4

With costs exceeding $100-billion annually

OMB DRAFTS EXECUTIVE ORDER TO CRACK DOWN ON ABUSES IN FEDERAL GRANTS

The Office of Management & Budget is attempting to crackdown on abuses in the $100-billion federal grants program and has drafted an Executive Order that will prohibit government agencies and states receiving federal aid from issuing public funds to parties involved in "illegal" grant activities. Sources said the draft OMB order would create a consolidated federal list of all parties that have been "debarred, suspended or deemed ineligible" to participate in federal assistance programs, a prospect that is raising concerns from state and local groups who are the major recipients of federal grant money. State sources said they fear OMB may attempt to use the contemplated order for political purposes to cut-off assistance for grants that OMB does not want to fund. However, one OMB source denied this accusation maintaining the Executive Order would only be used in cases where a court or administrative law judge

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DRAFT OF REAGAN TRADE PLAN WOULD FIGHT UNFAIR TRADE, SUBSIDIZE EXPORTS

An internal policy paper prepared by the Reagan Administration's Trade Policy Review Group (TPRG), and made available to *Inside the Administration*, says the White House is considering a trade bill, expected to be formally announced by President Reagan this week, that would fight unfair trade practices by proposing major changes to U.S. trade remedy laws. At the same time, the paper pushes aggressive promotion of U.S. exports with subsidized financing and proposes the creation of a new export promotion agency. The paper proposes trade remedy law changes covering sections 201 and 301 of the trade act, as well as antidumping and countervailing duty laws. Administration proposals to change sections 201 and 302 of the trade act have been carefully avoided by the White House up to now because

(continued on page 5)

DOD LIKELY TO WITHDRAW TECHNICAL DATA REGS UNDER PRESSURE FROM INDUSTRY

The Dept. of Defense, under intense industry pressure, is likely to withdraw technical data regulations it proposed only last week to govern the ownership of proprietary technical data, computer software and copyrights used in billions of dollars worth of defense contracts, according to a Pentagon source, who said an onslaught of industry complaints may prompt DOD to rewrite the rules. The technical data regulations are significant to the Defense Dept. because they enable defense agencies to purchase spare parts on a competitive basis. Industry is concerned the proposed rules will require DOD contractors to give up virtually all of their rights to technical data. Industry complaints about the regulations were so intense last week that DOD called a select group of defense industry officials to the Pentagon to discuss the regulations. Source said after the meeting, DOD appeared to be ready to "start over" and redraft the rules.

The defense industry asserted the proposed regulations are so "flawed as to be unworkable [and]

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WHITE HOUSE REJECTS FDA POWER PLAY FOR EXPANDED ROLE IN BIOTECHNOLOGY

A White House work group recently rejected a request by the Food & Drug Administration to expand the role of the proposed Biotechnology Science Board (BSB) by usurping the National Institutes of Health's oversight authority for human gene therapy, one of biotechnology's newest frontiers. White House insiders explain that FDA would benefit from vesting greater biotechnology authority in the BSB since, under the most recent Administration draft plan for the board, FDA is slated to chair the board.

The Reagan Administration plans to establish the board as an interagency oversight mechanism to coordinate federal policy on biotechnology research but has not yet finalized the proposed make-up of the board. The work group, chaired by the Office of Science & Technology Policy (OSTP), has been grappling with how to incorporate the role of NIH's recombinant DNA advisory committee (RAC), which is the longest standing federal entity to review the safety of biotechnology research. Administration sources said the decision to reject BSB authority over human gene therapy may "have settled the question of where to

FULL TEXT OF REAGAN TRADE PROPOSAL, SEE PAGE 6

4. **Section 301.**

Two amendments to section 301 would include:

— enactment of a 24-month deadline on dispute settlement; and

— provision of extensions at petitioner's request.

5. **Section 201***

We could usefully amend section 201 in two ways:

— provision of some type of "fast track" procedure for perishable agricultural items; and

— promotion of structural adjustment, by requiring the International Trade Commission to assess the petitioning industry's prospects for adjustment to changing conditions of competition.

* Some in the TPRG noted that proposing amendments to section 201 in particular may aggravate the risk (already inherent in any Administration trade package) of inviting protectionist riders.

6. **Export Promotion Activities.**

An Administration bill would promote U.S. exports through, for example:

— authorization and appropriation of funds to enable the Administration to offer $1 billion in mixed credit loans, to enable U.S. exports to compete in third country markets until we can eliminate predatory mixed credit competition through negotiations; and

— creation of a semiprivate, non-profit U.S. export promotion organization funded by private contributions and user fees, and managed by business representatives with the support of state and local government trade development groups.

We could also include in an Administration bill two proposals of the House Republican leadership that we support, although the goals are already being achieved and do not require legislation:

— review of Foreign Commercial Service personnel to ensure their maximum effectiveness; and

— a requirement for U.S. ambassadors to provide annual reports on their embassies' export expansion strategy and accomplishments.

7. **Reduction of Export Disincentives.**

An Administration bill would include a longstanding proposal also supported by House Republican leadership, as well as a House proposal whose implementation does not require legislation, but which we could support. They are, respectively:

— clarification of the accounting provisions and of the liabilities of foreign agents under the Foreign Corrupt Practices Act of 1977; and

— improvement of the export licensing process for small business.

8. **Statement of National Trade Policy Objectives.**

The preface to any Administration trade bill would be a clear, forceful statement of the Administration's trade policy objectives.

DOD LIKELY TO WITHDRAW TECH DATA REGS. . . begins on page 1

would violate rather than implement" a 1984 procurement law that directed DOD to draft the regulations by October 19. But now because of the flap over the regulations, DOD is likely to ask Congress to extend the deadline so it can draft new regulations to meet the concerns of defense contractors. The proposed regulations have angered Commerce Dept. officials with sources saying the agency may appeal to Congress for oversight hearings. DOD and Commerce have had a long standing disagreement over the degree to which a government contractor should be required to relinguish technical data rights to DOD. Traditionally, DOD has sought more access to the data than Commerce thought was warranted.

To address the spare parts issue, Congress last year passed the Defense Procurement Act of 1984 (DPA) to authorize DOD to broaden, and in many cases require, access to technical data generated under federal contracts. But critics said DOD, in proposing the regulations, has gone far beyond the intent of Congress. A chief critic complained that DOD has "gone so far as to make awarding a contract contingent on a contractor giving up all rights to technical data."

DOD's deputy under secretary for acquisition management Eleanor Specter last week called key industry officials to the Pentagon to discuss their complaints according to informed sources who said she indicated a willingness to work with industry in revising the regulations. The defense industry, in a number of "marathon" sessions, has prepared a working response to the proposed regulations which sources said includes the following points:

Industry officials said DOD appears to be using government access to technical data rights as a bribe, pointing to the regulations' inclusion of a provision to allow the government to consider how much a contractor is willing to give up rights in data when awarding a contract. The officials charged this is in blatant disregard of Congress' intent to create a "balance of interest" between the government's need for access to technical data and a contractor's proprietary rights to keep that data, as stipulated in the DPA. The DPA does not permit the government to make that consideration.

The definitions used in the proposed regulations do not coincide with those of the statute, according to industry sources. For example, the DPA uses "commercial" to mean "offered for sale to the public" while DOD broadened its meaning to include "used regularly for other than government purposes." Similarly, DOD excludes technical data that has been developed with both federal and private funds from its definition of "developed at private expense" even though the DPA makes it clear that such data is included in this definition.

DOD's new policy statement appears to make broad demands for access to technical data according to industry sources who said the proposed regulations require access to data needed to meet the "government's mission" rather than limiting access to that data needed to meet "DOD's needs" as expressed in the contract. Industry sources also said the policy statement preceding the proposed regulations fails to include statements contained in the DPA pertaining to preserving the contractors' rights and restricting access only to form, fit and function data when possible or avoiding the acquisition of unnecessary data.

A key Administration official, conceding that DOD "probably went too far with the" proposed regulations, attributed the broad scope of the regulations to DOD's "natural response" to recent spare parts scandals. This official predicted that DOD would withdraw its Sept. 10 proposal, issue temporary regulations and, at the same time, ask Congress to extend the Oct. 19 deadline for implementing final regulations.

FIVE SECTION 301 TRADE INVESTIGATIONS AT CENTER OF NEW REAGAN POLICY

Preident Reagan, as part of his tougher trade policy stance, plans to use the broad authority vested to him under the trade act to inititate three investigations of alleged unfair trade practices to retaliate against countries that are closing their markets to the U.S. Reagan is calling for expedited resolution of two pending cases, but cautioned that while he will use the 301 powers, "as a lever to open closed doors abroad, we will continue to resist protectionist measures that would only raise prices, lock out trade and destroy the jobs and prosperity trade brings to all."

The three new cases mark the first time the President has inititated a 301 investigation under the trade act. The three cases allege unfair restrictions against foreign computers and related products from Brazil, tobacco trade restrictions in Japan, and access barriers in the Korean insurance market that lock out U.S. firms. They are joined by the two previous cases on European Community (EC) canned fruit subsidies and efforts to open the Japanese leather and leather footwear markets. While five cases are being investigated now, U.S. Trade Representative Clayton Yeutter also said the list is not inclusive and more cases could be added to it.

Under section 301, Reagan has the authority to take any "appropriate and feasible actions within his power to obtain elimination of unfair trade practices," said a White House spokesman. Specifically, he may impose duties, fees or restrictions on products and services of the offending country, and not necessarily ones related to those under investigation. Reagan may also deny licenses issued by federal regulatory agencies to foreign service suppliers. The degree and duration of these actions are up to the President, and he is even allowed to initiate them summarily without any investigation at all. However, Yeutter ruled out Reagan's use of the authority under 301 to impose trade sanctions without an investigation. "You do not treat trading partners this way," he said.

Brazilian informatics. The Office of the U.S. Trade Representative (USTR) will initiate 301 proceedings against "Brazil's unfair trade practices in informatics." According to a White House spokesman, Brazil's new "informatics policy" has tightly restricted imports over an eight-year period while allowing only wholly owned Brazilian firms to sell computers and computer products in the domestic market. This, the spokesman said, has unfairly locked out U.S. imports and forced several U.S. firms in Brazil to shut down and leave the country. Before a 1984 Brazilian law took effect, the Brazilian market increased by 30% annually between 1980-82, primarily due to the microcomputer segment, and U.S. exports only increased by 14% annually.

Japanese restrictions on U.S. tobacco exports. Tight Japanese restrictions against foreign imports of tobacco products will be the subject of this new 301 investigation. According to the White House, "U.S. cigarette exporters have faced significant barriers in the Japanese market, including high tariffs and excise taxes, a prohibition on manufacturing by foreign firms . . . and restrictions on distribution." In spite of "intensive efforts" by U.S. officials and exporters, the U.S. share in the $10-billion Japanese cigarette market has only risen from 1.4% in 1979 to 2.1% this year. Repeated promises by Japanese officials for an increase in the market share have not been acted upon.

Korean restrictions on U.S. insurance firms. The third new case will attempt to find ways for U.S. insurance companies to break into the Korean market. Private and diplomatic efforts over the past six years have "had only limited success," a White House spokesman said. Korean law still prohibits foreign firms from writing life insurance for Korean nationals as well as the most lucrative types of fire insurance. This is true despite Korea's "obligation to provide national (non-discriminatory) treatment to foreign firms under the Treaty of Friendship, Commerce and Navigation," he said. In 1984, the total value of premiums for insurance other than life was over $1-billion, and for life insurance, nearly $4-billion.

Stepped up negotiations on canned fruit and Japanese leather cases. Besides initiating three cases, the