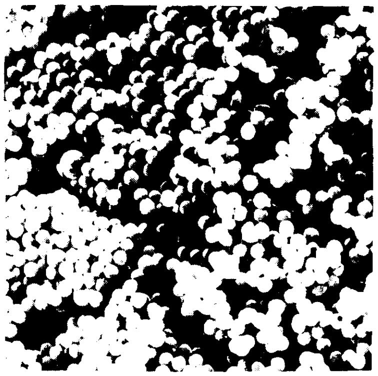
Biopolymer Research and Development in Europe and Japan 3

Significant biopolymer research efforts have been under way for many years in both Europe and Japan. In the European Community (EC), advances in biopolymer technology have been driven principally by the private sector. However, a number of basic and applied research programs have been initiated recently at the national and supranational (EC) levels. The Japanese Government, as it has done with other emerging technological fields, is actively sponsoring and coordinating biopolymer research among Japanese companies and scientific institutes. In both Europe and Japan, biopolymer research has two principal areas of focus: degradable materials that serve as substitutes for traditional commodity plastics and biomedical applications,

EUROPE

Several factors are stimulating European research and development (R&D) efforts in the biopolymer area. The emergence of a strong environmental movement has caused European governments to search for new methods and materials to address solid waste problems and other ecological concerns. As a consequence, there is considerable interest in developing biodegradable products that are derived from renewable resources.[1]



[1] Although about 15 percent of all materials used for commercial purposes are derived from petroleum, only about 3 percent of petroleum supplies are used as feedstocks for petrochemicals and synthetic resins. Thus, large-scale use of biopolymers for materials applications will not significantly affect oil consumption patterns. Biopolymers are important primarily because of their biodegradability and other physical properties. For more on petroleum feedstock applications, see U.S, Bureau of Mines, *Nonrenewable Organic Materials,* May 1993. For more on industrial energy use, see U.S. Congress, Office of Technology Assessment, *Industrial Energy Efficiency, OTA-E-560* (Washington, DC: U.S. Government Printing Office, August 1993).

The large agricultural surpluses that have resulted from the EC's Common Agricultural Policy (CAP)[2] potentially represent an abundant source of feedstocks that could be used for large-scale commercial production of biologically derived fuels and materials.[3]

Existing and proposed environmental regulations could provide a major impetus for the introduction of products containing biopolymers.[4] The proposed EC directive on a' 'Framework for Waste" provides regulatory guidance on how member states should handle the disposal of municipal waste. This framework embraces a hierarchy of waste management techniques, similar to that enunciated by the U.S. Environmental Protection Agency (EPA).[5] It will be left to individual governments to devise specific plans to implement this waste management strategy. The role of biodegradable materials is not delineated in this directive. However, the framework does call for the introduction of "environmentally safe" products, and it is proposed that such products be exempted from various environmental duties.[6] If biopolymer manufacturers can demonstrate that their products are environmentally safe, they could benefit from this proposed directive. However, no standards or evaluation methods have been established to determine what constitutes an environmentally safe product, and thus the ultimate commercial impact of the directive is uncertain. Moreover, many environmental advocacy groups do not view biodegradation as a solution to solid waste problems. Apart from medical products, these organizations believe that the introduction of biodegradable materials into the marketplace will undermine recycling efforts and, depending on the extent of their degradation, exacerbate litter problems.[7]

The development of labeling programs for environmentally preferred products could also promote the development of biopolymer materials. The European Commission has proposed a scheme whereby a single label would be granted to products that satisfy a range of ecological criteria. These criteria relate to all aspects of a product's manufacture, distribution, use, and disposal.[8] An eco-label will be granted to a product that has a clear environmental advantage over other products in its category. Commodity items such as packaging or plastics that contain biodegradable additives could become prime candidates for an eco-label. However, as mentioned previously, the methodologies for making such evaluations have yet to be developed. Up to now, the process of creating environmental measurement standards has proven to be an extremely

---

[2] The Common Agricultural Policy was devised to mitigate the impact of technological change on rural Europe. However, the CAP has led to enormous crop surpluses, massive public expenditures, higher food prices, and a net transfer of wealth from urban to rural regions. These surpluses have led to the dumping of European agricultural products in overseas markets and have, not surprisingly, exacerbated international trade tensions. See U.S. Congress, Office of Technology Assessment, *Biotechnology in a Global Economy*, OTA-BA-494 (Washington, DC: U.S. Government Printing Office, October 1991), p. 161.

[3] Biologically derived fuels such as ethanol and methanol and other bioenergy crops could potentially provide 10 to 20 percent of current energy needs, See U.S. Congress, Office of Technology Assessment *Environmental Impacts of Bioenergy Crop Production* (forthcoming).

[4] The EC has adopted more than 100 environmental directives on matters ringing from toxic emissions and the labeling of dangerous substances to the quality of drinkingwater. Many more directives are in draft form or are awaiting amendments.

[5] In order of priority, the hierarchy is: 1) waste prevention and reduction at the source;2) recycling and reuse (in energy, material, and chemical form); and 3) safe disposal of unavoidable waste. See *European Community Bulletin ''Framework* for Waste' Directive, document 375 L 0442, September 1989.

[6] Examples of products that could be subject to environmental taxes include nonreturnable bottles, gasoline, tropical wood, natural gas, and coal. Levies between 20 and 200 percent could be imposed on products deemed harmful to the environment. Ibid.

[7] See "Degradable Plastics Generate Controversy in Solid Waste Issues, " Chemical & Engineering News, June 25, 1990, pp. 7-14.

[8] These 'life-cycle" criteria would evaluate factors such as raw material usage, energy consumption, emissions from manufacture and use, and waste disposal impacts. For a detailed discussion of eco-labeling issues, see U.S. Congress, Office of Technology Assessment *Green Products by Design: Choices for a Cleaner Environment, OTA-E-541* (Washington DC: U.S. Government Printing Office, October 1992).

difficult undertaking.[9] At this writing, no date had been set for implementing the EC eco-label program.

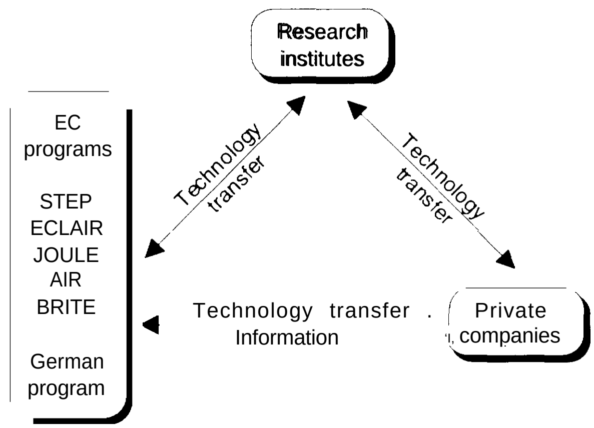
EC Research Programs

The European Community is currently funding several R&D programs that directly and indirectly involve biopolymer technology. These programs are attempting to develop new nonfood applications for agricultural commodities, alternative energy sources, and materials with superior environmental properties, Figure 3-1 outlines Europe's major biopolymer research programs.

The ECLAIR (European Collaborative Linkage of Agriculture and Industry Through Research) program (1988-93), with a budget of roughly $95 million, is designed to promote agroindustrial applications of new and improved varieties of plants and microorganisms. The program is concentrating on the extraction and transformation of biological materials such as sugars, starches, oils, and fats into useful commercial products. For example, ECLAIR is providing half of the $4.6-million research budget for a consortium consisting of Zeneca, Inc. (United Kingdom) and the universities of Hull (England), Ghent (Belgium), and Goettingen (Germany). The consortium is investigating microbial polyester production by the bacterium *Alcaligenes eutrophus (see* chapter 2). This program also includes research on genetically engineered plants for the production of natural polyester materials.

The AIR (Agricultural and Agro-Industry, Including Fisheries) program (1991-94) is focusing on "land and water-based biological resources, ' and has a planned 3-year budget of about $90 million. Research will focus on processes for transformingg materials from agriculture, horticulture, forestry, fisheries, and aquiculture into industrial products. One aspect of the program is to examine the biodegradability and larger ecological impacts of biopolymer materials.[10] As part of a wider effort in materials and polymer science, the Basic Research on Industrial Technologies in Europe (BRITE) program (1991-94) is examining polymeric materials with properties that ''minimize environmental impact, ' including a study of biodegradable packaging materials.[11]

Figure 3-l—European Initiatives and Programs in Biopolymers



SOURCES: BioInformation Associates, Boston, MA; Wolf-Rüdiger Miller, Institut für Siedlungswasserbau, Wassergüte-und Abfallwirtschaft der Universität Stuttgart, Federal Republic of Germany, personal communication, July 26, 1993.

Other efforts include the STEP (Science and Technology for Environmental Protection) and JOULE (Joint Opportunities for Unconventional or Long-Term Energy Supply) programs. STEP began in 1989 with a budget of $90 million. It is focusing on the development of technologies that safeguard environmental quality. One element of the program includes an assessment of biodegrad-

9 Product impacts on the environment are almost always multidimensional in character. Any given product 1S likely to have positive as well as negative environmental attributes. Existing methodologies for evaluating the ''environmental quality' of a product, such as life-cycle analysis, are in early stages of development and necessarily employ a great deal of subjective decisionmaking. Ibid.

10 Wolf-Rüdiger Müller, Institut für Siedlungswasserbau, Wassergüte-und Abfallwirtschaft der Universität Stuttgart, Federal Republic of Germany, personal communication, July 26, 1993.

11 Ibid.

able materials. The JOULE program, also begun in 1989, was given an initial budget of $145 million. The program is principally designed to improve long-term energy security by exploring ways of reducing the reliance on imported energy supplies. One part of the program is analyzing the potential of biomass as an energy source. Derivatives of cellulose and starch, for instance, can be used as transportation fuels.

These programs, with funding exceeding $400 million, demonstrate the EC's strong interest in developing new commercial products and energy supplies from renewable resources. Each program seeks academic and industrial participation. Research supporting the creation of ''next-generation' materials-materials derived principally from agricultural or microbial sources-is an important component of these collaborative programs.

Research in Germany

Among individual European states, Germany has launched a set of research initiatives that are specifically designed to advance biopolymer technology. Germany is being extremely aggressive in dealing with solid waste problems and other environmental issues.[12] These factors have led to the development of a 5-year biotechnology program that will focus on: conversion of biomass into alternative fuels and commodity plastics; new strains of plants to establish new routes for the development of nonfood renewable resources; fermentation technology for hydrogen production;[13] and new bioprocessing techniques.

The Federal Ministry of Research and Technology is coordinating and funding this program. Industry and academia are the principal recipients of research money. It has a substantial budget of DM 1 billion ($590 million) for the period 1990-95.[14] No other government in Europe has committed this level of funding to biotechnology R&D. Thus, German industry could be well positioned to exploit the expected demand for products that are derived from renewable resources (see table 3-l). German companies have the potential to become major players in the development of next-generation biopolymer materials.

Private Sector Activity

DEGRADABLE POLYMERS

A number of so-called biodegradable plastic products were marketed in Europe in the 1980s. These first-generation products were basically traditional oil-derived polymers, such as polyethylene, containing a low percentage (4 to 6 percent) of starch. Most of these products were made by the North American companies Archer Daniels Midland and St. Lawrence Starch. Controversy surrounding the degradability of these products has essentially stopped their production. A new generation of starch-based products is now being introduced by several fins. These materials have a cornstarch content ranging from 40 to nearly 100 percent. Manufacturers believe that by increasing the starch content of the polymer, the time for degradation will be reduced (see chapter 2).

12 For example, the German Government has instituted a mandatory ''take-back' program for several different types of product packaging. The take-back law requires manufacturers to recover and recycle various materials used in packaging. This scheme is likely to be applied to durable products, such as automobiles and electronics, in the near future. See U.S. Congress, Office of Technology Assessment, op. cit., footnote 8.

13 Hydrogen is an extremely clean fuel. Hydrogen-powered vehicles emit only water vapor and small amounts of nitrogen oxides. See U.S. Congress, Office of Technology Assessment, *Replacing Gasoline,* OTA-E-364 (Washington, DC: US Government Printing Office, September 1990),

14 The German biotechnology program is designed to promote research in the areas of the environment, public health, nutrition, energy, and natural resources. Another area of focus is pharmaceuticals. However, recent budgetary pressures associated with the costs of German unification could result in cutbacks in these efforts (Wolf-Rüdiger Müller, op. cit., footnote 10).

Table 3-I—Strengths and Weaknesses: Biotechnology Research in Germany

Strengths	Weaknesses
First nation to establish biotechnology program	Public opposition to genetic technology
Europe's highest concentration of biotechnology In pharmaceutical and chemical fields	Limited venture capital presence.
High-quality science training and research base	Dominance of large companies could limit small market opportunities typical in biotechnology.
Strong industry-university relationships	

SOURCE U S Congress, Office of Technology Assessment, Biotechnolgy in *a* Global Economy, OTA-BA-494 Washington, DC U S Government Printing Office, October 1991)

Companies are presently divulging little information about the functional properties, mechanical characteristics, degradation times, and final degradation products of these polymers. Ferruzzi, the parent company of Montedison, has developed a thermoplastic mixture of starch and a hydrocarbon in which the starch constitutes between 40 and 70 percent of the total weight. The hydrocarbon is described as a hydrophilic carbon-hydrogen-oxy gen polymer with a molecular weight low enough to accelerate degradation, but high enough to maintain the strength of the alloy. The company claims that the material behaves like polyethylene in its processing characteristics, but that the starch content reduces the tensile strength. The company contends that a 70-percent starch mixture takes about 3 weeks to degrade, but it does not provide details of the degradation conditions.[15] The starch-hydrocarbon blend is being used in packaging and diaper linings.

Battelle, an international research institute based in Switzerland, has also developed a starch-based technology that is able to incorporate up to 90 percent starch in its plastic. At present, however, there is likely to be limited application for this technology because of the polymer's susceptibility to moisture. Battelle has recently announced a plan to use vegetable oil-based polymers to overcome the moisture problem. Warner-Lambert of the United States has been marketing its NOVON starch-based materials (40- to 98-percent starch content) in Europe since 1991, with sales in the millions of pounds (see chapter 2). NOVON polymers are amenable to different plastic processing methods, including injection molding and film extrusion.

The entrance of companies making microbially derived products will also have an effect on the degradable polymer market. One company, Zeneca Bio Products (formerly ICI Biological Products, United Kingdom), has developed a microbially derived polymer with excellent degradation characteristics (chapter 2). The polymer, called BIOPOL, is produced through the bacterial fermentation of glucose and propionic acid.[16] The polymers derived from the fermentation process are linear polyesters that are true thermoplastics. Zeneca will have a production capacity of around 10 million pounds by 1995. The first commercial

[15] It should be noted that independent tests of polyethylene-starch blends show that although starch may biodegrade, the overall polymer formulation does not biodegrade at any significant rate. Distintegration of polyethylene-starch blends is not the same as biodegradation. The biodegradability of a particular material is determined by a set of complex factors such as material shape and surface-to-volume ratio, as well as environmental conditions such as nutrient concentration, bacterial-fungi inoculation pH, moisture level, and temperature. Any or all of these factors may vary from location to location.

[16] Glucose is derived from agricultural feedstocks such as sugar beets and cereal crops, while propionic acid can be produced from petroleum derivatives or by fermentation of wood pulp waste.

use of BIOPOL resin was in 1990, as consumer packaging. It has since entered other markets in Europe and Japan. The material is being targeted for use in moldings, films, and paper coatings for both rigid and flexible packaging, as well as a variety of specialty applications.[17] Some manufacturers are prepared to pay a premium price for BIOPOL because they believe that they will be able to market this product as an ' 'environmentally friendly" material. It currently sells for approximately $8 to 9 per pound, but Zeneca believes that with economies of scale in manufacturing, the price can be brought to around $4 a pound.

Other companies that are conducting research into microbial-based and agricultural-based polymers are Boehringer Ingelheim KG, Ems-Chemie AG, BASF, and Schering of Germany; Petrochemie Danubia of Austria; Montedison of Italy; and Tubize Plastics SA of Belgium. Some products are available now, whereas others are in the research stage and are not likely to enter the market until 1995. Table 3-2 summarizes the activities of firms currently developing or marketing next-generation biopolymers. Many of these companies have demonstrated considerable ability in incorporating synthetic processes into surrogate organisms and in improving their efficiency of production. European biotechnology firms will undoubtedly prove to be formidable competitors as markets for genetically engineered polymers begin to expand.

BIOMEDICAL MATERIALS

One industry survey estimates that the total European market for degradable biomedical materials will rise from $650 million in 1990 to $1.17 billion in 1995; this represents an average annual growth rate of 12.5 percent.[18] There are three principal market segments for biopolymers in Europe: wound management products, drug delivery systems (DDS), and orthopedic repair products. Each market is discussed in turn.

Wound Management: Absorbable wound closure products have represented a sizable portion of the European biomedical market for more than 15 years. The market size for wound management products is estimated to grow at an annual rate of 8.5 percent from $600 million in 1990 to $900 million in 1995.[19] This segment represented 100 percent of the total biomedical materials market in 1988, but will decrease to about 75 percent of the total market in 1995 as DDS and orthopedic repair product markets expand. The main polymers used in this market are polylactic-polyglycolic acid and related derivatives (see chapter 2).

The primary absorbable products in this market segment are sutures, ligation clips, and to a lesser extent, staples and wound meshes. Biodegradable polymers have been used in surgery for many years. Wound closure products (absorbable sutures) were introduced more than 20 years ago. The primary advantages of biopolymer sutures over catgut sutures are that they have a more predictable rate of absorption and produce less inflammation around wound sites. Two American fins, Ethicon and Davis& Geck, monopolize the European market for these products. Absorbable ligation clips and staples are also used during surgery and trauma care. In addition, biodegradable wound closure polymers are being used for other surgical applications, such as tissue and bone adhesives. Companies in the bioabsorbable surgical device market are rapidly expanding the range of applications for their polymer products. The introduction of vascular support meshes (for blood vessel regeneration) and other forms of wound dressing products is envisioned for the future.[20]

---

17 Zeneca has an agreement to sell BIOPOL to Wella of Germany for use in cosmetic bottles.

18 The survey was conducted by BioInformation Associates of Boston, MA.

19 Ibid.

20 See Robert Langer and Joseph Vacanti, "Tissue Engineering, " *Science,* vol. 260, May 14, 1993, pp. 920-925.

Table 3-2—Current and Potential Suppliers of Next Generation Biopolymers in Europe

Company	Location	Product/status	Potential application	Likely entry date	Comments
Zeneca Bio Products (formerly ICI)	United Kingdom	BIOPOL (microbial polyester)	Rigid and flexible packaging: films, moldings, paper coatings	Now	1990 pilot plant In England; assessing full production plant
BASF	Germany	Microbial- and agricultural-based polymers	Packaging	1995	In R&D stage
Schering	Germany	Same as above	Packaging	1995	In R&D stage
Boehringer Ingelheim KG	Germany	Polylactide polymers	Packaging, medical devices	Now	
Tubize Plastics SA	Belgium	BIOCELLAT (cellulose acetate)	Packaging	Now	
Ferruzzi (Montedison)	Italy	Agricultural polymers	Packaging	1995	In R&D stage
Petrochemie Danubia	Austria	Microbial polymers	Packaging	1995	In R&D stage
Battelle	Switzerland	Vegetable oil-based polymers; starch-based polymers	Packaging	Unknown	Working with German industrial partners
Warner-Lambert	United States	NOVON starch-based polymers (injection molding and various film grades)	Multiple use structural materials	Now	100-million-pound U.S production facility opened in 1992

SOURCE: BioInformation Associates, Boston, MA.

Drug Delivery Systems: For many years the major focus of drug research has been on the synthesis or discovery of new drugs. Although this continues to be important, increasing emphasis has been placed on the development of novel drug delivery systems. These systems first entered the European market in 1989; the total European market value for DDS in 1995 is estimated to be $250 million.[21] The principal materials being used for drug matrices in Europe are copolymers of polylactic acid (PLA) and polyglycolic acid (PGA). The use of biopolymer materials for drug delivery can minimize tissue reaction and allow drugs to be administered in nonconventional ways.

The use of biopolymers in these formulations has thus far been restricted to a narrow set of applications. There are several European companies developing products for this market, products that are technically comparable to those made by U.S. firms. Drug formulations incorporating polymer DDS are currently undergoing registration and are likely to make an impact on the market over the next 5 years.

21 The estimated market value of degradable DDS reflects the combined value of the drug and the delivery systems, because it was not possible to obtain separate estimates for the delivery system (BioInformation Associates, op. cit., footnote 18).

The major area of application for these novel sustained-release systems is in the treatment of cancers and diseases of the elderly. Some promising cancer treatment drugs are peptides or proteins, which are unsuitable for oral administration.[22] Similarly, products developed from genetic engineering may be toxic and thus may require nonconventional approaches for administration. Sustained delivery of a drug close to the site of action from an implanted or injected depot means that much smaller amounts of the drug need be used, thus reducing the possible side effects.[23] In the treatment of hormone disorders and geriatric diseases, biopolymer delivery systems allow drugs to be administered occasionally (even annually in some presentations). More importantly, these systems ensure patient compliance, which is often a problem for the elderly. Many of the drugs most suitable for presentation in a controlled fashion are for geriatric illnesses such as cancer and Parkinson's disease. It is in these markets that DDS will likely have the greatest impact.

European companies have an important strategic interest in DDS and have been instrumental in developing biopolymer technologies. The drug companies view biopolymer-based drug delivery as an important technological advance, because it can be applied to drugs that cannot be administered by conventional routes. Many companies also view this technology as an important tool for circumventing price restrictions that are being applied by European governments. Biopolymer-based drug delivery can offer important cost savings over conventional methods (e.g., injection) of drug administration.

The following European companies are currently developing products for the DDS market: Sanofi (France), Ciba Geigy (Switzerland), Capsugel[24] (Switzerland), Zeneca Bio Products (United Kingdom), Beam Tech (United Kingdom), and Innovative Biosciences (United Kingdom). Zeneca is hoping to develop DDS applications for its BIOPOL biopolymer discussed earlier. The other companies listed here would not divulge the products they are developing for this market, but did indicate strong interest in biopolymer drug delivery systems.

Orthopedic Repair Products: Biopolymer orthopedic repair products were expected to enter the biomedical market in 1992, with the introduction of absorbable pins and fixation devices from both Ethicon and Davis & Geck. The majority of biopolymers currently used for these applications are based on polyglycolide and polylactide polymers, with the latter being the most frequently used materials. There are a large number of lactic acid suppliers in Europe who provide this biological starting material to polymer manufacturers.[25] The manufacturers further purify the raw material

22 @I administration of protein drugs is not possible because digestive enzymes quickly break down proteins and thus destroy the drugs before they can be absorbed into the bloodstream. By encasing protein drugs in biopolymer materials such as polylactide, some researchers are trying to protect the proteins from the digestive enzymes in the stomach long enough for them to be absorbed into the bloodstream. However, this approach has had limited success in animals. Current biopolymer drug delivery systems are therefore used as implants. See "Stand and Deliver: Getting Peptide Drugs into the Body," *Science,* vol. 260, May 14, 1993, pp. 912-913.

23 Most cancer drugs are generally toxic to normal cells as well as cancerous cells. Delivery of anticancer drugs in polymers can help restrict drug activity to the site of the tumor and therefore protect normal tissue from exposure to toxicity. David Manyak, Adheron Corp., personal communication, Aug. 25, 1993.

24 Capsugel is a division of Warner-Lambert. Capsugel is producing starch-based capsules made from NOVON polymers. One of the oldest therapeutic applications of biopolymers has been in the area of pharmaceutical capsules. Gelatin (a protein polymer) capsules have been in widespread use for many years. Gelatin and starch-based capsules are commonly used to deliver aspirin and antibiotics. The worldwide market for simple biopolymer capsules is close to $400 million annually. Ken Tracy, Warner-Larnbert Co., personal communication, July 30, 1993.

25 Boehringer Ingelheim KG of Germany is one company that produces polylactide polymers for the orthopedic repair market. Croda Colloids markets lactic acid produced by a fermentation process. The other major European supplier of fermented lactic acid is C.C.A. Biochem in the Netherlands. Chemically synthesized lactic acid is marketed by Sterling Chemicals and Musachino Company of Japan. The price of this form of lactic acid is 20 percent higher than that of the fermented product.

to the required pharmaceutical standard (80 to 88 percent purity).

It is estimated that by 1995, the European market for biopolymer-based orthopedic repair products will reach $20 million.[26] Orthopedic repair products will probably represent only about 2 percent of the total market for medical biomaterials in 1995. Absorbable polyglycolide fixation devices for the treatment of porous bone fractures, joint reconstruction, and surgical alteration and realignment of bones are currently undergoing licensing. Fixation devices for the treatment of malleolar (leg and ankle) fractures are also undergoing licensing and should be available within 1 to 2 years. These devices are manufactured in Finland and are already used in some European countries. Orthopedic plates and screws are also likely to be developed within the next few years. A more speculative application is the use of biopolymer materials as scaffolding in the formation of new cartilage in the body.[27] With the advantage of biocompatibility, biopolymers are likely to be used in many more novel orthopedic applications.

JAPAN

Since the end of World War II, the Japanese Government has played an active role in encouraging the development of new technologies. The targeting of specific technologies for special government support has been part of a broader effort to influence the level and composition of Japan's national output. The central components of this national industrial policy have included financial aid, government sponsorship of pricing, investment, R&D cartels, and protection of the domestic market.[28] These initiatives have played an important role in enhancing the competitiveness of the automobile, steel, and semiconductor industries, In recent years, however, the efficacy of industrial targeting has been questioned both in Japan and elsewhere. While industrial policy has led to successes in some industries, there have been failures in others.[29] Nevertheless, it is still significant when the Japanese Government not only targets a sector, but also funds the initial research to stimulate its development. Two Japanese ministries, the Ministry of International Trade and Industry (MITI) and the Ministry of Health and Welfare (MHW), have committed funds and organizational support to the development of biologically derived materials. The different Japanese biopolymer programs are described below.

Government Biopolymer Programs

MITI is actively sponsoring and coordinating biopolymer research among Japanese companies, academic researchers, and scientific institutes. A major MITI initiative was the formation of the Japanese BioIndustry Association (JBA) in 1982.[30] A nonprofit organization designed to promote biotechnology and the bioprocessing industry, JBA serves as the principal coordinating agency for biopolymer activity in Japan. JBA's main function is to disseminate basic research information across industry, academia, and government. Its other roles are to define new directions for cooperative R&D programs, to assist in the formulation of product standards, and in some cases, to undertake biotechnology research projects directly. JBA is sponsoring a variety of development activities in the biopolymer materials area.

The most notable of these programs is an 8-year, 5 billion ($45 million) effort focusing on

---

[26] BioInformation Associates, op. cit., footnote 18.

[27] Robert Langer and Joseph Vacanti, op. cit., footnote 20.

[28] See U.S. Congress, Office of Technology Assessment, *Competing Economies: America, Europe, and the Pacific Rim,* OTA-ITE-499 (Washington. DC: U.S. Government Printing Office, October 1991).

[29] For example, the Japanese have not been able to develop a presence in the commercial aviation industry. Ibid.

[30] The original name of the organization was the BioIndustry Development Center (BIDEC).

the development of biodegradable polymers from microbial organisms.[31] This research program will concentrate on the following areas: developing probes for use in gene cloning; developing mass culture technology; improving natural polymer materials; developing technologies for molecular design and accurate polymerization of synthetic polymers; and testing and evaluation methods for biodegradable materials.

At the National Institute of Biosciences and Human Technology, a MITI laboratory in Tsukuba, researchers are working on biopolymer blends based on polyhydroxyalkanoates (PHAs) (microbial polyesters), starch, and polycaprolactone.[32] At MITI's Shikoku Laboratories in Takamatsu, biodegradable materials based on laminates of chitosan and cellulose are being investigated, and at the MITI research facility in Osaka, research on condensation polymers including polyesters and polyamides is being carried out.[33] In addition to research at its own facilities, the government is sponsoring biopolymer research at several universities.[34] MITI has also provided about 5 billion ($45 million) in funding to a multicompany venture in bacterial cellulose technology.[35]

Another program that could result in biopolymer advances is the Protein Engineering Research Institute (PERI) project. PERI, a consortium of 14 chemical, pharmaceutical, and food companies, will receive $150 million in government funding over a 10-year period. The focus of PERI's work is to develop a fundamental understanding of protein structure-function relationships, and thereby establish a competitive edge in protein engineering.[36] protein research is important to many areas of biotechnology, and could very well lead to new biopolymers with unique physical and functional properties, as well as basic improvements in the processes used to make biopolymers.

In addition to government-sponsored activities, several companies have formed an association called the Biodegradable Plastics Society (BPS) to help coordinate their research efforts. Activities of BPS include: determining the feasibility of making commodity plastics from biodegradable polymers; developing evaluation methods for biodegradable plastics; surveying market trends in plastics; and exchanging information with domestic and foreign organizations. Companies involved in this research are the more traditional chemical and plastics companies. About half of the 73 companies in BPS have also expressed considerable interest in the medical applications of biopolymers.[37]

The relationships among the various Japanese biopolymer research organizations are outlined in figure 3-2. The multifarious biopolymer research activities of Japanese Government and industry are designed to create new commercial opportunities in plastics and medical materials. MITI's sponsorship of biopolymer research is one indicator of the potential importance of this field. It is part of MITI's overall strategy to create a new, high-growth industry in biologically derived chem-

---

31 Yoshiharu Doi, Institute of Physical and Chemical Research (RIKEN) Japan, personal communication July 21, 1993.

32 Graham Swift, Rohm and Haas Co., personal communication July 13, 1993.

33 Ibid.

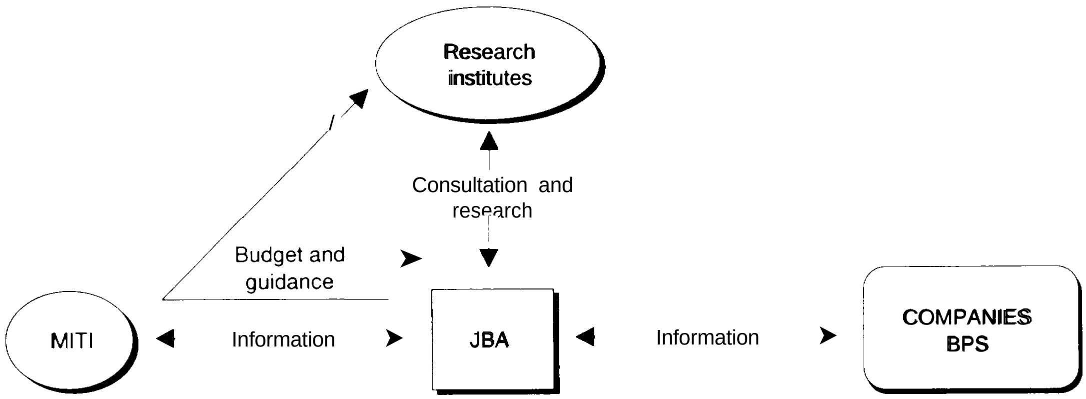
34 For ~-pie, scientists at the Tokyo Institute of Technology are working on genetic modification of PHA materials, and researchers at Keio University are investigating water-soluble polymers based on starch oxidation products and vinyl monomers.

35 The commercial venture in bacterial cellulose technology is financially supported by the Japan *Key Technology* Center, *a* joint organization under MITI and the Ministry of Post and Telecommunications, and six private sector companies: Ajinomoto, Shimizu Construction, Nikki, Mitsubishi Paper, Nikkiso, and Nakamori Vinegar. The venture is called Biopolymer Research Co., Ltd, and its principal focus will be the development of mass production techniques for cellulose that is made by fermentation (*Japan Chemical Daily*, Apr. 13, 1992).

36 U.S. Congress, Office of Technology Assessment, op. cit., footnote 2, p. 157.

37 In addition t. the 73 Japanese companies in BPS, a few foreign firms are also participating, including Zeneca Bio Products (United Kingdom) and Rohm and Haas (United States).

Figure 3-2-Japanese Initiatives and Programs in Biopolymers



SOURCES: BioInformation Associates, Boston, MA; Yoshiharu Doi, Institute of Physical and Chemical Research (RIKEN) Japan, personal communication, July 21, 1993.

icals and materials. Japan currently leads the world in microbial production of amino acids[38] and industrial enzymes, and thus is well positioned to take advantage of biopolymer advances that involve fermentation technology.

The Ministry of Health and Welfare is also supporting biopolymer research. MHW is encouraging private sector cooperation in the drug delivery systems field. Seven major pharmaceutical companies have joined together to sponsor DDS research. With support from MHW, the Drug Delivery Systems Institute has been capitalized at 1OO million ($900,000) and will focus on developing glycocarrier (sugars) drug delivery vehicles for central nervous system, bone, and kidney drugs. Although this amount is relatively small, the combined funding levels of programs sponsored by MITI and MHW make it clear that Japan is placing considerable emphasis on developing biomedical applications for biopolymers. Table 3-3 summarizes the work being performed at Japanese research institutions on biopolymers that could be used in the biomedical sector.

These collaborative programs are proceeding in earnest, although most companies interviewed in Japan did not think that the commercial potential for medical biomaterials would develop fully until after 1995. If current R&D efforts reach fruition, biopolymers could make significant inroads into the biomedical market by the end of the decade. Japan's multiyear research investment will likely result in both product innovations and a comprehensive review protocol against which biodegradable medical products can be tested.

Private Sector Activity

DEGRADABLE POLYMERS

In the area of degradable polymer research, Japanese companies are focusing primarily on the development of materials derived completely from microorganisms or agricultural feedstocks. The Japanese BioIndustry Association is the principal organization responsible for coordinating research in this area. MITI is also working with various research institutes and companies, including the Biodegradable Plastics Society, to establish evaluation methods, and to set up product specifications and standards for biude-

38 This commercial dominance may not last, because Archer Daniels Midland of the United States has recently entered this field and in only 1 to 2 years has captured 30 percent of the animal feed market for the amino acid lysine.

Table 3-3—Biopolymer Medical Research by Scientific Institutes in Japan

institution	Polymer	Potential	Comments
Tokyo Institute of Technology	Natural polyesters (i e., PHAs)	Sutures; orthopedic repair	Polymer similar to PHBV (BIOPOL); commercialization expected in 2 to 3 years
Kyoto University	Polyglycolic acid	Sutures; orthopedic repair	
Kyoto University	Gelatin (protein)	Drug carrier to deliver immunomodulators to tissue cells	Cells ingest gelatin
Industrial Products Research Institute	Leuclne-glutamine blomembrane (polyamino acids)	Drug delivery	Membrane reacts to acid-base changes by altering structure and admits or rejects different substances
Kansai University	Lactic acid-maleic acid copolymer	Slow release earners for anticancer drugs such as 5-fluorouracil	Injected into bloodstream; polymer is absorbed by cancer cells and releases drugs as it degrades
Japan Kokai Tokyo Koho	Copolymer amino acid (leuclne-benzyl glutamate)	Artificial blood vessels	Patented in 1986

SOURCE Bioinformation Associates Boston, MA

gradable products. This comprehensive program is being coordinated through JBA.

In addition to supporting biopolymer research in the areas of recombinant DNA technology and large-scale bioprocessing, JBA has completed a feasibility study evaluating the potential of biodegradable polymers as commodity materials. It is likely that biopolymer development efforts will receive additional impetus as a result of this study, with Japanese companies exploring a wide range of possible biopolymer applications. A partial listing of companies participating in BPS is provided in table 3-4.

Potential producers of next-generation biopolymer materials in Japan are listed in table 3-5. Scientists at the Tokyo Institute of Technology have produced a versatile polyester product from bacteria.[39] This ''bioplastic' is similar to the degradable material BIOPOL produced by Zeneca Bio Products in Europe. A copolymer of 3-hydroxybutyrate and 4-hydroxybutyrate (HB) has been extracted and fermented from *Alcaligenes eutrophus* under starvation conditions (chapter 2). This polymer is thought to have improved functional properties over BIOPOL, since it can be made more elastic by altering the ratio of the copolymers, Researchers expect this polymer material to be commercialized (probably by Mitsubishi Kasei) in 3 to 4 years; it will be targeted first at the mulch film, marine (nets and lines), and medical markets.[40]

Other companies such as Hayashibara Biochemical are interested in expanding the applications for their microbial polysaccharides (pullulans) into areas such as packaging (chapter 2). The company is already producing a pullulan derivative that is used as an edible protective film for

[39] See Yoshiharu Doi, "Microbial Synthesis and Properties of Polyhydroxyalkanoates,' *Materials Research Society Bulletin, vol. XVII, No.* 11, November 1992, pp. 39-42.

[40] Yoshiharu Doi, op. cit., .ootnote 31.

Table 3-4-Biodegradable Plastics Society Member Companies in Japan

Company	Core business	Company	Core business
Ajinomoto	Food processor, amino-acld producer	Mitsui Toatsu Chemicals	Chemicals, fertilizers
Asahi Chemical Industry Co	Synthetic resin producer	Nippon Kayaku	Pharmaceuticals, agrichemicals, special resins
Bridgestone Corp	Large rubber manufacturer	Nippon Shokubai Kagakku Kogyo Co.	Petrochemicals, industrial chemicals
Chou Kaguku Corp	Plastic containers	Sekisui Chemical Co.	Plastics processor
Dai Nippon Ink & Chemicals	Major producer of printing Ink	Sekisui Plastics Co	Largest producer of foam plastics
Dai Nippon Printing Co	Printing company	Shyowa Denko KK	Petrochemicals, industrial chemicals
Denki K K	Major chemical company	Sumitomo Bakelite	Integrated processor of synthetic resins
Idemitsu Petrochemical	Petrochemicals	Sumitomo Chemical Co.	Fine chemicals, agrlchemicals
Japan Steel West	Steelmaker	Sumitomo Metal Industries	Steelmaker
Kureha Chemical Industry Co	Leading fine chemical maker	Toagosei Chemical Industry Co.	Plastics
Mitsubishi Gas Chemical Co	Major chemical company	Toyo Ink Manufacturing	Printing ink materials
Mitsubishi Kasei	Largest all-around chemical company, mainline carbochemicals	Ube Industries	Petrochemicals, cement
Mitsubishi Petrochemicals	Large petrochemical enterprise	Unitika Ltd	Textiles, plastics

SOURCE Biolnformation Associates Boston, MA

food. The biodegradability of pullulan makes it an extremely attractive material. Japanese companies have developed sophisticated and advanced fermentation technologies that are ideally suited for developing biodegradable polymers from microbial metabolizes and polymer-producing microorganisms.[41] Thus, Japanesee companies could emerge as very strong competitors in the area of microbial biopolymers.

The British company Zeneca Bio Products, which has a subsidiary in Japan, is also a member of BPS. Zeneca is supplying 30 to 40 Japanese companies with research quantities of its BIOPOL polymer. Zeneca successfully introduced BIOPOL cosmetic bottles in Europe in 1990 and recently entered the Japanese market with another product—biodegradable golf tees.

BIOMEDICAL MATERIALS

Most Japanese companies do not believe that the medical biomaterials market will take off until after 1995. Since the use of biopolymers for therapeutic purposes is still in the exploratory stage, it is difficult to assess how the medical

[41] In addition t. the large chemical companies pursuing biopolymer production, some Japanese breweries are *retrofitting* their fermentation plants to produce new biological compounds (Norman Oblon and Karen Shannon, Oblon, Spivak, McClelland, Maier, & Neustadt, P. C., personal communication, Aug. 12, 1993).

Table 3-5—Current and Potential Suppliers of Next Generation Degradable Polymers in Japan

Company	Country	Product/Status	Potential application	Likely entry date	Comments
Mitsubishi Kasei and Tokyo Institute of Technology	Japan	Microbial polyesters poly(3HB)-(4HB) copolymer	Packaging	1994-96	Can biodegrade in 4 to 6 weeks; similar to Zeneca's PHBV copolymer
Hayashibara Biochemical	Japan	Microbial poly-saccharides (e.g., pullulan)	Pullulan packaging, edible/biodegradable food wrap	1993	Product available now
Kureha Chemical	Japan	Microbial-based polymers	Disposable packaging	Not known	Assessing government regulations
Kyowa Hakko Kogyo Co. Ltd	Japan	Microbial-based polymers	Packaging	Not known	Likely entrant
Kawasaki Steel	Japan	Microbial-based polymers	Packaging	Not known	Working with established biotechnology company—Clef-to research and develop biodegradable polymers
Showa Denko K.K	Japan	Microbial-based polymers	Mulch film; bags	1995	Assessing various polymer technologies
Showa High Polymers, Ltd.	Japan	BIONELLE—synthetic "biodegradable" polyester	Packaging; structural materials	1994	7-million-pound manufacturing facility in 1994
Zeneca Bio Products	United Kingdom	BIOPOL	Cosmetic bottles, other packaging materials	Now	Pilot plant in England; asessing full production plant

SOURCE: Biolnformation Associates, Boston, MA.

materials market in Japan will evolve. Table 3-6 provides information on companies that either have a product on the market or are known to have a product nearing introduction. Applications include artificial skin, sutures, orthopedic implants, and drug delivery vehicles. Many products are awaiting approval by the Ministry of Health and Welfare.

Many companies that are members of the Biodegradable Plastics Society are also expected to develop products for the biomedical market. However, it does not appear that these firms have clearly defined product strategies. Some of the companies listed in table 3-6 are traditional chemical companies that have expressed only a general interest in moving into the pharmaceutical, biochemical, and biomaterials sectors. Although it is unlikely that any of these companies will enter the biomaterials market before 1995, they may be presented with significant opportunities as the market develops over the long term.

Japanese Industrial Policy Revisited

MITI's sponsorship of biopolymer development has raised concerns among some U.S. researchers that leadership in yet another promising high-technology field might be ceded to the Japanese. For some observers, the past successes

Table 3-6-Current or Potential Suppliers of Biomedical Materials

Company	Core business	Polymer of interest	Comments
Ajinomoto Co.	Foods, amino acids	Biocellulose	Artificial skin
Terumo and Tokyo Toritsu University	Medical Instruments, pharmaceuticals	Collagen	Artificial skin (animal studies)
Chisso		Hyaluronic acid (HA)	Tissue repair, wound healing
Genzyme Japan	Medicinal products and botanical	HA	Tissue repair, wound healing
Kyowa Hakko Kyogo Co,	Chemicals, amino acids	HA	Tissue repair, wound healing
QP		HA	Wound healing
Riken Vitamen		HA	Wound healing
Seikagaku Kogyo		HA	Wound healing
Shiseido Co Ltd	Cosmetics	HA	Wound healing
Yakult Honsha Co.	Pharmaceuticals, cosmetics	HA	Wound healing
Mitsui Toatsu Chemicals	Chemicals, fertilizers	Polylactic-polyglycolic acid (PLA-PGA)	Sutures
Koken and Okayama University	Medical equipment	Collagen	Membrane to prevent adhesion after surgery
Johnson and Johnson Orthopedic Co	Healthcare products	PLA-PGA “Orthosorb”	Not yet commercial ;fixation plate, pins, etc.
Unitika	Textiles	Chitin/chitosan “Beschtin-W”	WiII be used for orthopedic surgery
Takeda Chemical Industries Ltd	Pharmaceuticals (drug delivery)	PLA-PGA Lupron Depot	Joint venture with Abbott Laboratories (United States)
Sumitomo Pharmaceutical & Koken	Pharmaceuticals, medical equipment	Collagen	Phase Ill trials for anticancer drug
Nitta Gelatin	Chemical preparations	Collagen	DDS for osteoplastic factors
Ajinomoto Co	Food Processor, amino acids	Glycocarriers	Member of Drug Delivery Institute (DDI)
Asahi Chemical Industry Co	Leading manufacturer of synthetic fibers	Glycocarriers	DDI
Dalichi Seiyaku	Pharmaceuticals: circulatory and respiratory	Glycocarriers	DDI
Eisai Co Ltd	Pharmaceuticals” nervous system	Glycocarriers	DDI
Meiji Selka	Pharmaceuticals” antibiotics; foods	Glycocarriers	DDI
Shionogi	Pharmaceuticals antibiotics	Glycocarriers	DDI
Tanabe Sekyaku	Pharmaceuticals circulatory and respiratory	Glycocarrier	DDI

SOURCE Biolnformation Associates, Boston, MA.

of MITI-initiated technology programs suggest that Japanese industry could be given a significant boost in its efforts to develop biopolymer products. Indeed, with their expertise in fermentation technology, Japanese companies are in an excellent position to exploit the market for some specific types of biodegradable polymers (e.g., microbial polyesters and polysaccharides). The 8-year MITI biopolymer program will undoubtedly lend momentum to initial Japanese commercialization efforts.

However, over the long term, the concerted attempt of the Japanese Government to promote biotechnology, and biopolymer applications in particular, could be impeded by a number of structural and institutional factors. In contrast to the United States, Japan has a weak basic research base in biotechnology, which has led many Japanese firms to send their personnel abroad for training and to set up foreign research facilities.[42] In addition, Japan's pharmaceutical industry has long been sheltered from international competition and is only now beginning to develop state-of-the-art skills in drug development, testing, and marketing.[43] This could inhibit the entry of Japanese companies into the lucrative global biomedical market. Because Japan is not a food-exporting country, its agricultural research enterprise is narrowly focused, and it may not be able to compete with the biopolymer programs of large U.S. and European agricultural firms.[44] Finally, the maturation of the Japanese economy has reduced the relative importance of government-sponsored R&D programs. Many segments of Japanese industry have become so successful that they are no longer willing to be guided into targeted investments. MITI, for example, recently abandoned a bioprocessing project because of the reluctance of industry to cooperate.[45] Nevertheless, the commitment of Japanese industry and government to biopolymer R&D is considerable, and it is therefore likely that in certain segments of the biopolymer field, Japanese companies will be formidable competitors.

---

42 U.S. Congress, Office of Technology Assessment, Op. cit., footnote 2.

43 Ibid.

44 Ibid.

45 over the past decade, the efforts of MITI to promote biotechnology as a key technology and to integrate it into existing industrial sectors, while bearing some fruit, have clearly been less successful than many observers anticipated. Ibid.