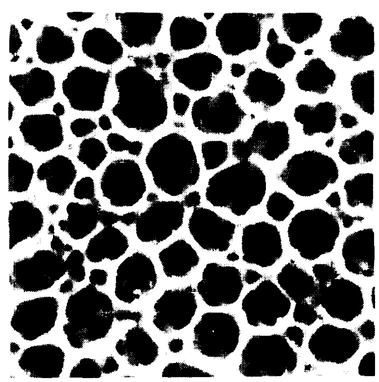
Biopolymer Research and Development in the United States 4

In recent years, there has been a steady expansion of biopolymer research activities in both the private and the public sectors. Concerns about the environmental impacts of petroleum-based polymers have led many companies to investigate several different classes of biologically derived polymer materials. Advances in chemistry and the biological sciences have also stimulated research efforts in the biopolymer area. As illustrated in chapter 2, the potential applications of biopolymer materials are extremely diverse, ranging from packaging to food additives and industrial chemicals to pharmaceuticals. Novel biopolymer materials are being investigated by Government and university researchers, large agricultural and chemical firms, and small biotechnology enterprises. As in Europe and Japan, U.S. biopolymer technology is, for the most part, still in the early stages of development, and substantial commodity markets for these materials are not likely to appear for several years.



ACTIVITIES OF THE FEDERAL GOVERNMENT

One of the principal difficulties in describing the biopolymer research efforts of the U.S. Government is that biopolymer science is inherently interdisciplinary in nature. Broadly defined, biopolymer research covers a number of different areas, including materials science, chemistry, microbiology, biophysics, plant biology, and structural biology. Thus, basic research in any of these disciplines can accelerate advances in biopolymer technology. Indeed, in many cases, biopolymer researchers have been able to take advantage of innovations that have emerged from the broad-based U.S. programs in biotechnology (e.g., recombinant DNA research).

Table 4-1—Federal investment in Manufacturing/Bioprocessing Biotechnology[a] ($million)

	FY1991	FY1992	FY1993[b]
National Science Foundation	$29.5	$32,3	$430
U.S. Department of Agriculture	17.6	18,8	23.6
Department of Defense	12,7	17,4	18,4
Department of Health and Human Services	16.7	17.0	17.7
Department of Energy	5.3	6.4	13.2
National Aeronautics and Space Administration	2,6	2.6	3.7
Department of Commerce	3,5	3.5	3,5
Department of the Interior	1,0	0.8	0.7
Total	$88.9	$98.8	$123,8

[a]These programs cover research in the areas of biomolecular materials, medical materials, biosensors, bioelectronics, plant- and-insect-derived products, metabolic engineering (recombinant DNA research as it relates to Industrial microorganisms), bioreactor design, biocatalysis or enzyme engineering, separation and purification technology, process design, and process monitoring and control

[b]The proposed FY 1994 budget calls for increases of about 7 percent over FY 1993

SOURCES Federal Coordinating Council for Science, Engineering, and Technology, Committee on Life Sciences and Health, Biotechnology *for the 21st* Century (Washington, DC U S Government Printing Office, February 1992), Alicia Dustira, White House Office of Science and Technology Policy, personal communication, July 1993

By many measures, the United States is preeminent in biotechnology, with strong research programs in biomedicine and agriculture.[1] In FY 1993, the Federal Government is spending about $4 billion to support research and development (R&D) in biotechnology-related areas.[2] In relative and absolute terms, the United States supports more research relevant to biotechnology than any other country.[3] However, only about 3 percent ($124 million) of the total 1993 biotechnology budget is devoted to biologically derived compounds and industrial bioprocessing research[4] (see table 4-l). And a only a small fraction of that 3 percent is targeted specifically to biopolymer development. A number of different Government agencies sponsor biopolymer research:

- the Department of Defense (DOD),
- National Science Foundation (NSF),
- the Department of Health and Human Services (DHHS) and specifically the National Institutes of Health (NIH),
- the Department of Energy (DOE),
- the Department of Agriculture (USDA),
- the Department of Commerce (DOC),
- the Department of the Interior (DOI), and
- the National Aeronautics and Space Administration

The following sections describe those research activities that relate directly to the production of biopolymer materials or to the development of new biopolymer applications.

1 U.S. Congress, Office of Technology Assessment, *Biotechnology in a Global Economy, OTA-BA-494* (Washington DC: U.S. Government Printing Office, October 1991).

2 Federal Coordinating Council for Science, Engineering, and Technology, Committee on Life Sciences and Health, *Biotechnology for the 21st Century* (Washington, DC: U.S. Government Printing Office, February 1992).

3 U.S. Congress, Office of Technology Assessment, op. cit., footnote 1.

4 The term bioprocessing refers to the steps involved in producing a material or a chemical by using biological conversion processes such as fermentation or special enzymatic treatment. The proposed $124 million in funding for bioprocessing represents a 25 percent increase over fiscal 1992 levels (Federal Coordinating Council for Science, Engineering, and Technology, op. cit., footnote 2, p. 42).

Department of Defense

The main programs sponsored by DOD are funded by the Office of Naval Research (ONR) Molecular Biology Program; the Army Research, Development and Engineering (RD&E) Center (Natick, Massachusetts); and the Army Research Office (Research Triangle Park, North Carolina).

OFFICE OF NAVAL RESEARCH BIOPOLYMERIC MATERIALS PROGRAM

The ONR Biopolymers Materials Program is investigating biologically derived materials for possible use in marine environments. There is particular interest in materials that prevent biofouling and biocorrosion. Among the materials being studied are thermoplastics, coatings, adhesives, and elastomers. One aim of this research is to achieve a greater understanding of the relationship between the microscopic structure of polymers and their macroscopic physical properties, such as elasticity, adhesion, piezoelectricity, nonlinear optical properties, and tensile strength. The program is also attempting to develop a fundamental understanding of molecular assembly processes. Many of the projects involve the study of novel protein polymers (see chapter 2). Of the 19 ongoing projects, 17 are being carried out in universities and 2 are in-house. The total annual level of funding is around $1.8 millions

U.S. ARMY PROGRAMS RELATED TO BIOPOLYMER SCIENCE AND TECHNOLOGY

1. *U.S. Army Natick, RD&E Center:* The U.S. Army RD&E Center is exploring a variety of biologically derived materials, as well as the processing mechanisms of biological systems. The ability of biological systems to produce a vast range of materials under mild processing conditions (i.e., low temperature and pressure), without creating toxic byproducts, could lead to new, environmentally sensitive manufacturing methods. The program has three principal areas of focus: advanced bimolecular materials, biodegradable polymers, and "intelligent" materials. In-house research is funded at about $1.5 million, with additional supplemental funds provided for special programs such as a joint effort with the USDA on biodegradable polymers for packaging. A significant percentage of the funding supports university projects. Cooperative programs are also in place with a number of industrial partners.[6]

Research on bimolecular materials is concerned primarily with protein-based biopolymers, Work in this area includes isolation and characterization of natural structural proteins (e.g., silk), cloning and expression of genes encoding these materials, molecular modeling to understand structure-function relationships, elucidation of the processes involved in converting water-soluble polymers to water-insoluble materials, and formation of films and fibers.

The biodegradable polymer program is focusing on naturally occurring biodegradable polymers, including polysaccharides, polyesters, and proteins. Research covers numerous activities: fermentation production and plant sources, purification, chemical modification of natural polymers, blending, processing into blown films, injection molding, characterization of liquid cyrstalline phases, determination of biodegradation kinetics, evaluation of toxicity of materials in marine and soil environments, consumer acceptance studies, and product evaluation.[7] These activities are directed toward the development of biodegradable products for Army and Navy use.

Research in the area of intelligent materials involves investigation of the interfaces between biological materials and synthetic polymers. This work is directed toward the development of materials that sense and react to changes in their operating environment (e.g., materials that stiffen in response to turbulence, or change properties

[5] Michael Marron, Office of Naval Research Molecular Biology Program, personal communication, June 30, 1993

[6] David Kaplan, U.S. Army Natick RD&E Center, Biotechnology, personal communication, July 16, 1993.

[7] Ibid.

under different temperature and pressure conditions). Specific areas of investigation include the study of energy transduction from proteins to synthetic polymers, thin-film assemblies, biosensors, and nonlinear optical polymers generated through biocatalytic processes.[8]

2. *Army Research Office: The Army* Research Office is sponsoring biopolymer research in several different areas. Particular emphasis is being placed on understanding the mechanisms of complex biopolymeric function, the macromolecular structures supporting such function, and the biosynthetic pathways that lead to those structures. Current efforts involve the use of molecular genetics, protein engineering, and physicochemical characterization to clarify how higher-order structure is achieved in polymer materials, and how such structural features might be genetically or chemically manipulated for different applications. The program is funded at about $1 million annually, with most of the funds supporting university research.[9]

National Science Foundation

The National Science Foundation has many programs that directly or indirectly support biopolymer research. NSF is spending more than $30 million annually on bioprocessing and bioconversion research, and about $12 million on bimolecular materials research.[10] Although most of this funding is not directed specifically toward biopolymer development, these programs are likely to have many positive spillover effects. For example, NSF is supporting work in the areas of gene transfer, macromolecular structure and function, metabolic pathways, molecular self-assembly, biomimetic chemistry (processes that utilize or mimic biological systems), gels and microemulsions, and material properties of membranes, surfaces, and interfaces.

There are currently about a dozen specific projects investigating the properties of protein polymers and various methods for their production. This includes a pioneering project to produce synthetic polyamino acids by genetic techniques.[11] Funding for these projects amount to less than $1 million. In addition, NSF has sponsored studies of lignin copolymers, which potentially could be used for a variety of purposes, including degradable plastics.[12] Another area of emphasis is the field of tissue engineering, where biopolymer materials are being evaluated for their restorative properties and as potential substitutes for damaged tissue.[13]

Department of Agriculture

USDA supports a variety of biotechnology programs that bear on biopolymer research and development. Projects include gene cloning in microorganisms, nucleic acid hybridization, biological and biochemical synthesis of nucleic acids and proteins, improving the quality of woody plants (for the extraction of cellulose), and mapping genes of agronomic importance. Several programs are investigating the use of agricultural

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[8] Ibid.

9 Robert Campbell, U.S. Army Research Office, personal communication July 29, 1993.

10 U.S. Congress, Office of Technology Assessment op. cit., footnote 1; Federal Coordinating Council for Science, Engineering, and Technology, op. cit., footnote 2. A recent initiative includes NSF participation in the Federal Advanced Materials and Processing Program (AMPP). The AMPP is designed "to support multidisciplinary research and to encourage bold new advances" in the materials area. The program specifically focuses attention on polymers and biomolecular materials.

11 Norbert Bikales, National Science Foundation, personal communication, July 22, 1993. Also see D.A. Tirrell et al., "Genetic Synthesis of Periodic Protein Molecules," *Journal of Bioactive and Biocompatible Polymers,* vol. 6, October 1991, pp. 326-338,

12 U.S. Congress, Office of Technology Assessment, *Agricultural* Commodities *as Industrial Raw* Materials, OTA-F-476 (Washington, DC: U.S. Government Printing Office, May 1991).

13 Federal Coordinating Council for Science, Engineering, and Technology, op. cit., footnote 2; and Robert Langer and Joseph Vacanti, "Tissue Engineering," *Science, vol.* 260, May 14, 1993, pp. 920-925,

commodities for industrial purposes,[14] and one of the major projects involves the use of cornstarch for degradable plastics. Proposed funding for biodegradable materials research in FY 1993 is $4.4 million. Another program, *Advanced Materials from Renewable Resources* (total N 1993 funding, $10 million), will also direct resources to the development of biopolymers.[15]

In addition, the Cooperative State Research Service (CSRS) Office of Agricultural Materials and the Alternative Agriculture Research and Commercialization Center work with academia and industry in the development and commercialization of new industrial uses of crops, including biopolymers.[16]

National Institutes of Health

The National Institutes of Health has played a central role in advancing the fundamental understanding of biological processes at the molecular level. NIH supports basic biotechnology research in areas such as recombinant DNA techniques, gene mapping, and protein engineering. It also supports a broad range of research that supports biotechnology: genetics, cellular and molecular biology, biological chemistry, biophysics, immunology, virology, macromolecular structure, and pharmacology.[17] Funding for NIH biotechnology and related programs, in FY 1993, is approximately $3 billion.[18] As stated earlier, only a small percentage of these resources is allocated specifically to biopolymer research. The principal areas of biopolymer work are in drug delivery systems where biocompatible polymers are used in sustained-release applications, and in biohybrid devices where polymer materials are used as implants, prosthetic devices, and agents of tissue repair or regeneration. Because biopolymers have several potentially important applications in the biomedical field, there have been proposals calling for a dramatic increase in the level of NIH activity in this area (see box 4-A).

Department of Energy

DOE has a large general effort in biotechnology, including projects in mapping the human genome and in structural biology. Research in structural biology is directed toward understanding the structure-function relationships of biological molecules and the synthesis of proteins. A number of different DOE programs are more directly involved with biopolymer research. The National Renewable Energy Laboratory is exploring how cellulosic biomass can be converted into sugars that can then be fermented into ethanol.[19] Enzymes are being used to break down cellulose polymers without attacking the product sugars that are subsequently fermented. Other DOE programs are studying how biological feedstocks can be used to create high-value chemicals. Argonne National Laboratory, for example, is investigating lactic acid-based degradable plastics (see chapter 2).

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14 These include the use of traditional crops such as corn and soybeans, as well as new crops such as guayule (robber) and kenaf (pulp similar to wood) (U.S. Congress, Office of Technology Assessment, op. cit., footnote 12).

15 The two programs mentioned here are funded through U.S. Department of Defense appropriations and are Jointly administered by the U.S. Army Natick RD&E Laboratory and the U.S. Department of Agriculture, Cooperative State Research Service, Office of Agricultural Materials.

16 L, Davis Clements, Cooperative State Research Service, Office of Agricultural Materials, personal communication, July 28, 1993.

17 U.S. Congress, Office of Technology Assessment, op. cit., footnote 1.

18 Federal Coordinating Council for Science, Engineering, and Technology, op. cit., footnote 2. Proposed funding for FY 1994 is approximately 7 percent above FY 1993 levels (Alicia Dustira, White House Office of Science and Technology Policy, personal communication, July 28, 1993.)

19 Cellulose from woody and herbacious crops offers a low-cost alternative to cornstarch as the feedstock for ethanol. See U.S. Department of Energy, *Conservation and Renewable Energy Technologies for Transportation* (Washington, DC: U.S. Government Printing Office, 1990).

Box 4-A–A Proposed Research Agenda for Medical Biomaterials: Recommendations to the National Research Council

In 1990, the National Research Council sponsored four regional meetings with the aim of developing specific recommendations for a national materials science and research agenda. One outgrowth of these discussions was a detailed proposal calling for a national initiative in the area of biocompatible materials. The proposal identified several opportunities for health care cost reduction through the development of novel materials. For example, if an implantable artificial insulin delivery system could be designed, it is estimated that costs associated with the treatment of diabetes could be reduced by $2 to $4 billion annually. Since biomaterials research cuts across several different disciplines such as chemistry, microbiology, and materials science, many potentially innovative technologies may be overlooked by academia and the different Federal agencies. Consequently, the proposal calls for much greater coordination of Federal programs in the biomaterials area and a dramatic increase in overall funding. This 10-year, $2.5 -billion program would be designed to greatly expand scientific understanding of the interaction between materials and biological systems, and to accelerate biomedical commercialization efforts. The principal recommendations include the following:

- The establishment of a new national institute of medical technology, within the National Institute of Health (NIH), to act as a central coordinator and lead funding agency for biomaterials research. The new institute would encourage interaction among medical clinicians, academic scientists, and industrial researchers.
- The establishment of several regional biomaterials research centers that would be funded at $10 to $20 million each for 10 years. Total funding would be about $150 million per year. Such centers would be designed to promote interdisciplinary research and greater university-industry cooperation. Areas of focus would include: genetically engineered biopolymers, "smart" bioresponsive materials, polymer-tissue interaction, analytical surface science, in vitro testing (faster materials testing and elimination of animal testing), environmentally compatible materials, and nondestructive evaluation techniques.
- The creation within the National Science Foundation (NSF) of a biomaterials program, where biomaterials research is defined as "the study and knowledge of the interactions between living and nonliving materials." Funding levels for individual investigators would total $100 million annually, and projects would be coordinated with t he institute of medical technology described above.
- The establishment of a national information center to serve as a clearinghouse for data on the physical, surface, and biological properties of biomaterials. The center would also evaluate and create standard testing procedures for novel materials.
- The development of performance criteria for biomaterials to expedite the Food and Drug Administration product approval process.

These recommendations were presented to the National Academy of Sciences and forwarded to the White House Office of Science and Technology Policy (OSTP) in early 1991. In response, OSTP initiated a cross-agency study that cataloged all Federal activity in the biomaterials area, and opportunities for greater coordination among Federal agencies were identified. In addition, funding for NIH and NSF biomaterials programs was increased slightly.

SOURCES: Materials Research Society, *A National Agenda in Materials Science and Engineering: Implementing the* MS&E *Report*, February 1991, Southeast Regional Conference on Materials Science and Engineering, Final Report, September 1990; E.P. Mueller and S.A. Barenberg, "Biomaterials in an Emerging National Materials Science Agenda," *Materials Research Bulletin*, vol. XVI, No. 9, September 1991, pp. 86-87; Edward P. Mueller, Food and Drug Administration, personai communication, Aug. 16, 1993.

Other Agencies

Several other Government research programs pertain to biopolymers. NASA is investigating new separation processes for the purification of biological materials, and new fabrication methods for biopolymer films and matrices. One major effort is in the area of protein crystal growth. The microgravity biotechnology program is utilizing the space environment to gain a better understanding of protein structure and formation.[20]

The Food and Drug Administration (FDA) has a sizable biotechnology effort in order to deal with the regulatory issues affecting genetically engineered pharmaceuticals and food products. In addition, the FDA is evaluating the use of biopolymers in medical devices. This research is concerned principally with the degradation of biomaterials that are placed in the body.

Within the Department of Commerce, the National Oceanic and Atmospheric Administration (NOAA) is investigating polymer materials produced by marine organisms (e.g., mussel adhesives and chitosan) that could have a variety of commercial applications.[21] By studying how various organisms form polymeric films on surfaces, NOAA researchers are also attempting to develop methods of controlling biocorrosion and biofouling. Another Commerce agency, the National Institute of Standards and Technology, is developing new sensor technologies to measure complex biochemical substances, and is also studying protein structure and function.

PRIVATE SECTOR ACTIVITIES

As in Europe and Japan, American commercial activity in biopolymers can be divided into two major market categories: degradable polymers that can be used in lieu of traditional commodity plastics and materials that can be used for biomedical applications.

DEGRADABLE POLYMERS

When the frost materials containing biodegradable additives were introduced in the late 1980s, controversy erupted as to whether they were truly degradable.[22] The principal products involved were packaging materials and garbage bags. Most of these goods were either withdrawn from the market or no longer advertised as being biodegradable.[23] These first-generation products were made from oil-derived plastic resins such as polyethylene that contained a low percentage (4 to 6 percent) of starch.[24] Although starch itself readily degrades, various studies indicate that even under optimal conditions the starch composition of these plastic-starch blends has to exceed about 60 percent before significant material breakdown occurs.[25] Due to regulatory uncertainty and the absence of clear standards for evaluating degradable plastics, the production of

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20 Federal Coordinating Council for Science, Engineering, and Technology, Op. cit., footnote 2.

21 Most of this research is conducted at universities under the auspices of the National Sea Grant College Program (ibid).

22 Apart from questioning whether these products do in fact degrade, many environmental advocacy groups and some industry groups do not view biodegradation as a solution to solid waste problems. These organizations believe that the introduction of biodegradable products into the marketplace will undermine recycling efforts and, depending on the extent of their degradation, will exacerbate litter problems. In a previous study, the Office of Technology Assessment suggested that a national municipal solid waste policy should be based on "the dual strategies of waste prevention and better materials management. ' A comprehensive materials management perspective recognizes that recycling, comporting, and incineration are complementary objectives. See U.S. Congress, Office of Technology Assessment, *Facing America's Trash; What Next for Municipal Solid Waste*, OTA-O-424 (Washington, DC: U.S. Government Printing Office, October 1989).

23 Photodegradable materials, consisting of ethylene-carbon monoxide (E/CO) copolymers, were also introduced for use in garbage bags and beverage ring carriers. Currently, only beverage carriers are made from E/CO; 27 States have passed legislation prohibiting the use of nondegradable ring carriers. The main suppliers of photodegradable polymers are Union Carbide, Du Pont, and Dow Chemical.

24 Most of these products were produced by the companies Archer Daniels Midland and St. Lawrence Starch.

25 U.S. Congress, Office of Technology Assessment op. cit., footnote 12, P. 96.

materials with low starch content has declined dramatically. The remaining market for these materials is limited primarily to compostable bags.[26]

While the Federal Trade Commission has issued guidelines designed to prevent deceptive environmental marketing claims, scientifically based definitions and standards relating to degradability have yet to be formally established.[27] Up to now, the process of creating environmental measurement standards has proven to be an extremely difficult undertaking.[28] A nonprofit private sector group, the American Society for Testing and Materials (ASTM), has developed some standards for evaluating degradable materials in the laboratory .29 ASTM's work has helped to create a consensus on testing procedures for certain categories of degradable materials (e.g., photodegradable and compostable substances). Researchers at ASTM's Institute for Standards Research are currently attempting to determine the behavior of degradable polymeric materials in real disposal systems and are correlating these results with ASTM laboratory methods .30 This research could lead to a better understanding of how products degrade under different environmental conditions. Yet, even if more reliable information can be generated, consumer confidence in degradable products is not likely to be restored without the creation of coordinated systems of product disposal and waste management. If, for example, products are designed for comporting, but end up being landfilled or incinerated, the design improvements are effectively nullified.[31]

Despite market and regulatory uncertainties, some companies are proceeding with the development and introduction of a new generation of starch-based products—materials that have a starch content ranging from 40 to nearly 100 percent.[32] Agri-Tech Industries is developing a material that is up to 50 percent starch by weight, and is targeting applications such as personal hygiene and disposable medical products.[33] Warner-Lambert has recently opened a large production facility for its NOVON family of polymers—films that range from 40 to 98 percent starch by weight. Properties of these materials can be varied depending on the specific types of starches and other biodegradable materials used. Early appli-

26 It is unlikely that compostable bags will provide a sustainable market for the partially degradable starch-ethylene blends. Current and proposed compost quality standards suggest that compost producers will be very concerned with the ultimate fate of materials accepted into their facilities. Several studies have demonstrated that plastic fragments, that do not degrade, have a negative impact on the productivity of farming soil.

27 See Federal Trade Commission, ''Guides for the Use of Environmental Marketing Claims,'' July 1992. Congress has mandated the use of degradable materials for one product category: plastic ring carriers for bottles and cans. In the proposed rule for this law, EPA has set specific performance standards for degradable materials. See *Federal Register,* vol. 58, No. 65, Apr. 7, 1993.

28 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).

29 There are more than 170 members serving on the ASTM subcommittee on degradable plastics standards. Industry, government, academia, and consumer and public interest groups have representatives on the subcommittee. See Ramani Naryan, ''Development of Standards for Degradable Plastics by ASTM Subcommittee D-20.96 on Environmentally Degradable Plastics," 1992.

30 The USDA-CSRS Office of Agricultural Materials is also sponsoring work on compost utilization, in which biodegradable polymers are among the materials being evaluated.

31 Apart from compost, biodegradable materials could also be used as feedstocks for biogas generation. The biogas could then be used to produce electricity by fueling gas turbines. Wolf-Rüdiger Müller, Institut für Siedlungswasserbau, Wassergüte-und Abfallwirtschaft der University Stuttgart, Federal Republic of Germany, personal communication, July 26, 1993.

32 In addition t. the efforts of individual companies, the Degradable Plastics Council (DPC), a trade organization that includes both traditional chemical firms and agribusinesses, is promoting the use of materials derived from agricultural commodities and other renewable resources. The aims of the DPC are to "stimulate research and development, coordinate efforts and communicate facts regarding degradable plastic technologies and materials" (Degradable Plastics Council, Washington, DC).

33 This material was developed at the U.S. Department of Agriculture and has been licensed exclusively to Agri-Tech.

cations of these specialty polymers include degradable golf tees, loose-fill packaging, compost bags, cutlery, pharmaceutical capsules, and agricultural mulch films.

NOVON materials are being targeted for markets where the benefits of their biodegradability can be clearly demonstrated. In the near term these materials will most likely be limited to specialized applications because their cost is two to four times the price of commodity resins. Although these novel starch-based compounds are not positioned to compete with commodity synthetic polymers such as polystyrene, if production costs can be brought down, they might eventually find a number of applications in the food service, food packaging, personal health care, agricultural, and outdoor markets.

As highlighted in chapter 3, European companies are also trying to develop a new generation of biopolymer plastics that will compete with American products. Japanese companies have essentially ignored starch-based materials and are concentrating on materials derived principally from microbial sources, whose development increasingly employs the techniques of genetic engineering. There are some limited efforts by U.S. companies to develop "next-generation" polymers for degradable plastic applications (i.e., materials derived chiefly from agricultural and microbial sources). These efforts center on the development of polylactic acid (PLA) materials. Cargill and a Du Pont-ConAgra joint venture, EcoChem, have set up polylactide production facilities. These processes use fermentation technology to produce lactic acid monomers from potato skins and corn (see chapter 2). PLA materials have some of the same mechanical and physical properties as petroleum-based polymers, but degrade rapidly under a variety of conditions. However, as with other biopolymers, there is a considerable cost premium for PLA materials. Both Cargill and EcoChem are projecting prices between $2 to $3 per pound for their PLA products.[34] Polylactide polymers that are used for medical applications currently cost about $100 per pound.

Although there is considerable academic interest in the area of microbially derived polyesters, no American company is actively pursuing this line of research.[35] Zeneca, Inc. of the United Kingdom is actively developing U.S. market opportunities for its microbial polyester materials. A few companies are also pursuing the commercial development of bacterial cellulose products (chapter 2). Table 4-2 lists current and potential U.S. suppliers of advanced biopolymer plastics.

BIOMEDICAL MATERIALS

Biomedical polymer science is one of the most dynamic areas of materials research. Biologically compatible materials are increasingly being used in a broad range of medical treatments.[36] More than 2 billion pounds of polymeric materials are used annually in medical products. Although most of these polymer materials are traditional

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[34] Ramani Narayan, i% chigan Biotechnology Institute, personal communication, July 19, 1993.

[35] A recently formed group, the Bio/Environmentally Degradable Polymer Society, has a mission to increase awareness Of scientific advances in the field of degradable polymers, The organization intends to focus principally on technical issues and plans to work closely with ASTM, the Degradable Plastics Council (footnote 32), and similar Japanese and European organizations. (Grahm Swift, Rohm and Haas Co., personal communication, July 13, 1993).

[36] A distinction is made in this report between polymers that are derived from biological sources and polymers that are derived from petroleum sources. Here, the term *biopolymers* is used to refer to biologically derived materials. Because some petroleum-derived substances can be used for medical purposes, these substances are sometimes called biocompatible polymers even though they are not derived from natural sources. Polyurethane, for example, although synthetically derived, is inert and compatible with blood, and is used in catheters and drug delivery devices. Synthetic polyesters such as Dacron arc used in membranes, grafts, and sutures, and polycarbonate is often used in orthopedic implants. In many of these applications, however, biologically derived polymers offer superior biocompatibility (lower rejection response), and are thus beginning to replace synthetic polymers. See ''Biocompatiblc Polymers, " *Materials Technology,* vol. 8, Nos. 1/2, January/February 1993, p. 34.

Table 4-2-Current and Potential U.S. Suppliers of Next-Generation Biopolymer Plastics

Company	Location	Product	Potential applications	Likely entry date	Comments
Zeneca Bio Products	United Kingdom/United States	BIOPOL resin (microbial polyester)	Rigid and flexible packaging—film, moldings, paper coatings	Now	1990 pilot plant in England; assessing full production plant
EcoChem (Du Pont-ConAgra)	United States	Polylactic-polyglycolic acid copolymers	Packaging ;some medical products	Customer sampling now	100-million-pound production facility to open in 1995
Cargill, Inc.	United States	Polylactide	Packaging	Customer sampling now	10-million-pound production facility recently opened
Battelle Institute and Golden Technologies	United States	Polylactic acid from fermented corn	Packaging	Not known	Available for license
Argonne National Laboratory and Kyowa Hakko, USA	United States	Polylactic acid from fermented potato waste	Packaging	1995-96	Available for license
Archer Daniels Midland	United States	Lactic acid supplier	Packaging	Not known	Has not announced production plans
Warner-Lambert	United States	NOVON starch-based polymers	Multiple-use structural materials	Now	100-million-pound production facility opened in 1992
Weyerhaeuser	United States	Bacterial cellulose	Absorbent, thickener, and mating agent	Now	Limited commercial quantities

SOURCES BioInformation Associates, Boston, MA, and Ramani Narayan, Michigan Biotechnology Institute synthetic compounds, biologically derived polymers have captured significant shares of some medical markets and are rapidly expanding into new applications. A recent market survey estimates that the total U.S. market for *biopolymer* medical applications will grow from about $300 million in 1990 to about $1 billion in 1995.[37] As in Europe, the three main biomedical market segments are wound management products, polymeric drugs and drug delivery systems, and orthopedic repair products. The wound management segment is the most mature of the three markets, with both drug delivery technology and orthopedic devices only now beginning to establish a significant commercial presence.[38]

WOUND MANAGEMENT

The main products in the U.S. wound repair market are absorbable sutures, surgical mesh, clips, and staples. This market is dominated by a handful of companies including Ethicon (Johnson & Johnson), U.S. Surgical Corporation, Davis & Geck, Du Pont, and Pfizer. The main polymers used in these products are polylactic-poly glycolic acid and related compounds such as polydioxanone. Other biopolymer materials such as chitin and modified cellulose may also be used as sutures in the near future.[39] The principal advantage of biopolymer-based wound management products is that they form natural bonds with surrounding tissue and thereby facilitate the healing process.

Biopolymer based sutures (i.e., absorbable sutures) currently hold about 50 percent (about $225 million) of the entire U.S. suture market and are expected to grow at an annual rate of more than 10 percent for the next several years.[40] The major factor explaining this growth is the preference shown by physicians for absorbable wound repair products over nonabsorbable devices. Companies in the bioabsorbable surgical device market are rapidly expanding the range of applications for their polymer products. Hyaluronic acid, a polysaccharide, is being used for surgical repair of soft tissue (particularly eye and ear tissue), and some proteins, such as collagen, are being used as wound dressings and for tissue reconstruction.[41] Bioadhesives are a new class of materials that could serve as suture enhancements, and can be used for attaching prostheses, or for dental applications. Enzon Corporation and W.R. Grace have launched programs to develop bioadhesives that are based on recombinant protein polymers. Adheron Corp. is developing a bioadhesive that is an exopolysaccharide-peptide complex derived from marine bacteria. Other biodegradable polymers are being tested as aids in repairing damaged arteries.[42] In the future, biopolymers may be used to facilitate tissue and organ regeneration, and

37 The survey was conducted by BioInformation Associates of Boston, Massachusetts.

38 New opportunities for biopolymer medical applications may emerge, given the recent decisions of three traditional polymer suppliers (Dow Plastics, Dow Corning, Du Pent) to withdraw some of their products from the market. The products involved are polyurethane, silicone, polyester, polyacetal, polytetrafluoroethylene, and others. The products have been withdrawn because of concern over actual and potential legal liabilities, As a consequence, it is possible that shortages of some types of implantable medical devices could occur. These developments could give impetus to R&D activities involving new, biocompatible materials that are derived from natural sources. (Bernie Liebler, Health Industry Manufacturers Association, Washington, DC, personal communication Aug. 9, 1993).

39 Chitin, a polysaccharide that can be extracted from crab shells, maintains its high-strength characteristics for long periods and degrades without causing allergic reactions or tissue irritation.

40 Bioinformation Associates, op. Cit., footnote 37.

41 A recent study, however, has raised some questions about the possible side effects of collagen implants that are used to treat wrinkles and scars in plastic surgery. See "Study Links Collagen With Ailments, But Maker of Implants Disputes Report," *Wall Street Journal*, June 15, 1993, p. B6.

42 Degradable polymers can act as an 'internal scaffolding' that prevent arteries from reclosing after they have been opened by angioplasty. After an artery heals, the polymers dissolve. See "Patents," New York *Times*, June 14, 1993, p. D2.

serve **as** vascular support meshes for blood vessel regeneration .43

Drug Delivery Systems

Drug delivery systems (DDS) utilizing polymers that degrade in the body have attracted considerable attention in recent years. The use of biopolymers for drug delivery can minimize tissue reaction and allow for the administration of drugs by methods other than injection.[44] A controlled-release drug system is a combination of a biologically active agent (i.e., the drug) and a support vehicle. The support vehicle can be either a matrix or a reservoir device. In a matrix system, an active drug is dissolved or dispersed uniformly throughout a solid polymer. Drug release from the matrix can be controlled by either a diffusion or an erosion process. In a reservoir system, the polymer acts solely as a barrier that controls the rate of drug delivery by diffusion. Polylactic and polyglycolic acid copolymers are the most widely used drug vehicle materials. Other biopolymers being investigated include poly amino acids, derivatives of chitin, and some chemically modified starches.[45]

The U.S. market for biodegradable drug delivery systems is expected to grow from its 1990 level of about $30 million to nearly $490 million by 1995.[46] One reason for this rapid growth is the large number of genetically engineered protein drugs that are now being introduced,[47] Encapsulation of proteins in biopolymer materials prevents the proteins from being prematurely destroyed by attacking enzymes. Another factor contributing to the growth of drug delivery systems is that they provide a means for extending the patent life of drugs. The major area of application for these novel sustained-release systems is in the treatment of cancers and geriatric diseases.

For the most part, the industry leaders in drug delivery systems are relatively small, technologically sophisticated firms that frequently have close relationships with academic research centers. Since DDS development lies outside the traditional expertise of most pharmaceutical companies, large firms have typically acquired this technology through contracting, licensing, joint ventures, and acquisitions. In recent years, however, most large pharmaceutical companies have initiated modest in-house research efforts. Table 4-3 lists the current and potential suppliers of drug delivery systems.

Orthopedic Repair Products

The U.S. orthopedic implant market provides a number of potentially interesting applications for biodegradable polymers. Commercial opportunities exist in the areas of joint prostheses technology such as artificial ligament coatings, ligament attachment devices, and tendon implant materials and bone trauma fixation devices such as plates, screws, pins, and rods used to stabilize fractures. Although only a few biopolymer devices are currently on the market (mostly bone fixation pins), ongoing research and FDA testing are

43 The Protein collagen, for example, induces new blood vessel and tissue growth. See Robert I-anger and Joseph Vacanti, "Tissue Engineering," *Science*, vol. *260*, May 14, 1993, pp. 920-925.

44 Biopolymers are also being evaluated for oral delivery of vaccines in which the polymer may act as an adjuvant to further stimulate an immune response.

45 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, and starch-based capsules have recently been introduced into the market. These capsules are commonly used to deliver aspirin and antibiotics. The world market for simple biopolymer capsules is close to $400 million annually. (Ken Tracy, Warner-Lambert Company, personal communication, July 30, 1993).

46 The estimated market value of degradable drug delivery systems reflects the combined value of the drug and the delivery systems, because it was not possible to obtain separate estimates for the delivery systems. The estimate was provided by BioInforrnation Associates, Boston, Massachusetts. This estimate for DDS does not include the market figure for simple capsules that are made from biopolymer materials.

47 The growth of the drug delivery market, however, could be slowed by the FDA drug approval process.

Table 4-3—Current and Potential Suppliers in the U.S. Drug Delivery System Market

Company	Product	Application	Polymer of interest
Abbott Laboratories	Lupron Depot	Microsphere injectable for protein drugs	Polylactlc-poly glycolic acid
Alza Corp	Alzamet	Injectable delivery of anti-infective drugs and peptides; surgical implant products	Polyanhydrides (synthetic degradable polymer)
Scios Novo, Inc	Biodel	Targeted, time-released therapies for anticancer and antiinfective drugs	Polyanhydrides
Enzytech	Prolease	Microsphere encapsulation of interferons, growth hormones	Polylactic acid
Merck and Co	In development	Implant for release of gyrase inhibitor	Polylactic-poly glycolic acid
Syntex Inc	In development	Controlled release of beta-Interferon; microencapsulation of peptide hormones	Polylactic-poly glycolic acid
Battelle Corp	In development	Process for developing microsphere	Polylactic acid
American Cyanamid	In development	Implant for release of estradiol in livestock	Polylactic-poly glycolic acid
Emisphere Technologies	In development	Oral delivery system for heparin, Zadaxin (hepatitis), and poultry vaccines	Polyamino acid
Southern Research Institute	In development	Microsphere for encapsulation of DNA-RNA for stimulation of Interferon production	Polylactic-poly glycolic acid
Allergan	In development	Implant and Injectable devices	Not known

SOURCE Biolnformation Associates

expected to open the way for a number of new product introductions by 1995.

Orthopedic products face several technical challenges. In addition to high strength, biopolymers must also have prolonged, well-controlled rates of degradation[48] because complete ligament and tendon healing requires a 1-to 2-year time frame. In addition, the degraded end products must be absorbed safely by the body. Even though the end product in most biodegradable orthopedic devices is lactic acid, which is metabolized by the body, the FDA will be assessing whether these devices cause soft tissue irritation or have toxic side effects. These side effects are of more concern in orthopedic devices than in drug delivery systems, because of the significantly larger mass of polymer used in orthopedic systems.

In 1990, the U.S. market for biopolymer orthopedic devices was about $15 million, and it

48 It has been difficult to develop biopolymers that display both optimal strength and the required degradation properties. However, some progress is occurring in this area, Johnson& Johnson Orthopedics' researchers have developed a polylactide bone fixation plate that exhibits superior strength over that of conventional bone fixation plates. Animal testing of the device over a 2-year period has revealed no tissue irritation or toxic side effects.

is expected to grow to $80 million by 1995.[49] However, market growth will depend in large part on the speed of the FDA approval process. While two companies, Johnson & Johnson and Davis& Geck, presently dominate the orthopedic repair market, several other health care companies are expected to enter the field in the next few years: 3M, Bristol Meyers Squibb, Pfizer, Allied Signal, Smith and Nephew, and Du Pont all have medical implant development programs. Potentially novel applications include degradable bone screws that obviate the need for followup operations, and the use of biopolymers as scaffolding in the formation of new ligament and cartilage material.[50] Because more than 1 million operations a year involve cartilage replacement, this particular biopolymer application could grow dramatically in the future. As biopolymer science evolves, many more important advances in the area of orthopedic repair can be expected.

BIOPOLYMERS IN PERSPECTIVE

Biopolymers are a diverse and remarkably versatile class of materials that have potential applications in virtually all sectors of modern industrial economies. Currently, many biopolymers are still in the developmental stage, but important applications are beginning to emerge in the areas of packaging, food production, and biomedicine. Some biopolymers can directly replace synthetically derived materials in traditional applications, whereas others possess unique properties that could open up a range of new commercial opportunities. As a consequence, novel biopolymer materials are being investigated by established agricultural and chemical fins, as well as small biotechnology enterprises.

At present, government-sponsored research and development efforts in the biopolymer area are relatively small in scope, but many ongoing Federal activities have an indirect bearing on biopolymer science. Unlike Japan and the European Community, the United States does not have a well-defined biopolymer policy. The United States is, for the moment, well positioned in some areas of biopolymer development because of its strong agricultural base, expertise in polymer engineering, and active biotechnology sector. However, the relative competitive position of the United States could be enhanced by fostering greater collaboration among researchers in government, industry, and academia. Fundamental research barriers in the biopolymer field could also be better addressed by bringing greater coherence to the R&D efforts of various Federal agencies. In addition to the scientific and engineering hurdles that exist in the biopolymer area, formidable commercialization barriers remain. Even if some biopolymers are shown to have environmental characteristics that are preferable to conventional polymers, much work needs to be done to bring down the costs of biologically derived materials. In only a few specialized applications, such as biomedicine, are the relatively high costs of biopolymer materials not likely to impede market growth. These economic and technical obstacles, as well as the interdisciplinary nature of the biopolymer field itself, pose difficult challenges for policymakers and industry managers alike.

49 Bioinformation Associates, op. Cit., footnote 37.

50 Some researchers are using a collagen-glycan template to grow new cartilage (Langer and Vacanti, op. cit., footnote 43).