Biopolymers: Making Materials Nature's Way

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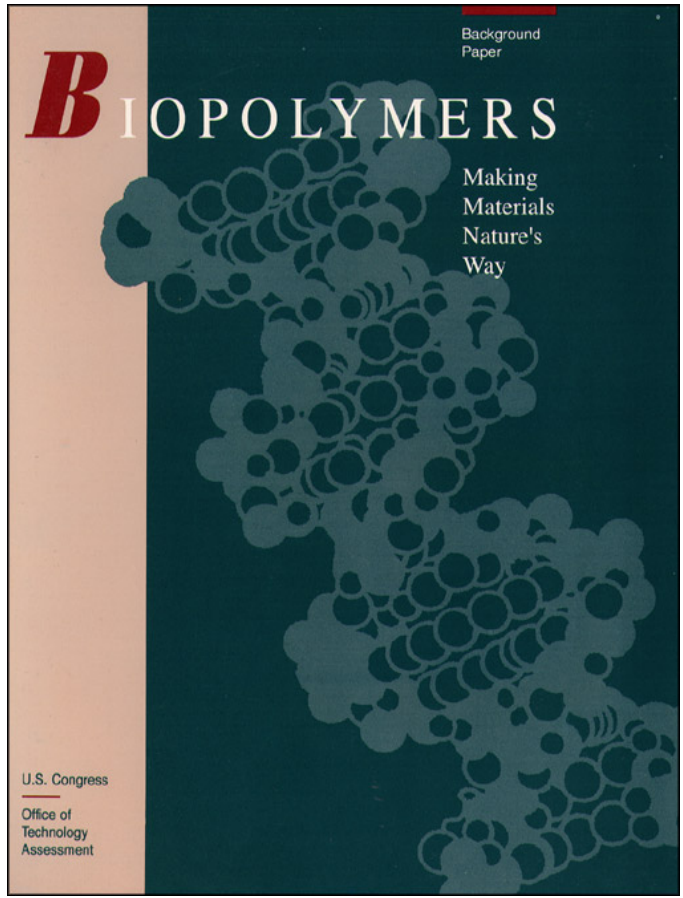

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Foreword

Over the past century, global economic activities have increased more than fifty-fold. This extraordinary growth has raised serious concerns about current patterns of production and consumption. As society has increased its understanding of the environmental implications of its industrial practices, greater attention has *been* given to the concept of sustainable economic systems that rely on renewable sources of energy and materials. The use of biologically derived polymers—biopoly - mers-could emerge as an important component of this new paradigm of economic development.

By transforming agricultural or marine feedstocks, or harnessing the enzymes found in nature, a new class of renewable, biodegradable, and biocompatible materials is being introduced. Emerging applications of biopolymers range from packaging to industrial chemicals, to medical implant devices, to computer storage media. In addition to producing "green" materials with unique physicaI and functional properties, the processes used to create biopolymers could lead to new manufacturing approaches that minimize energy consumption and waste generation.

As the United States and other countries address a growing list of environmental problems, the possibility of using proteins, carbohydrates, and other biopolymers to meet the materials requirements of an expanding economy is likely to receive increasing attention. However, as with other nascent technologies, difficult engineering and economic hurdles stand in the way of biopolymer commercialization efforts. With its current areas of emphasis, the extensive U.S. public investment in agricultural science and biotechnology can only be expected to provide modest assistance in overcoming some of these barriers. Advances in biopolymer technology have been driven principally by industry and academia, with Federal programs being relatively limited in scope. Because biopolymers have applications in many different sectors of the economy, their widespread use could have important competitive implications. At present, Japan and the European Community are sponsoring major programs in biopolymer science and manufacturing. Due to the potential importance of biopolymer technology, the Federal role in this interdisciplinary field warrants closer scrutiny.

This Background Paper was requested by the Senate Committee on Energy and Natural Resources. The study provides a basic introduction to biopolymer technology; profiles some of the more promising polymer materials; reviews research activities in the United States, Europe, and Japan; and describes the principal technical challenges and regulatory issues that may affect biopolymer commercialization efforts.

OTA appreciates the assistance provided by its contractors and the many reviewers whose comments helped to ensure the accuracy of the study.



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Introduction 1

Throughout history, humans have relied extensively on biological materials like wool, leather, silk, and cellulose.[1] Today, such natural polymers can be tailored to meet specific needs. The advent of modern biotechnology has fundamentally transformed the way scientists view organisms and the materials they produce. For example, the genetic manipulation of some plant species could give rise to a new source of structural polymers that supplant traditional commodity plastics. By harnessing the enzymes found in nature, or transforming agricultural or marine feedstocks, a new class of biodegradable, biocompatible, and renewable materials is on the horizon.

Polymers play a central role both in the natural world and in modern industrial economies. Some natural polymers, such as nucleic acids and proteins, carry and manipulate essential biological information, while other polymers such as the polysaccharides—nature's family of sugars-provide fuel for cell activity and serve as structural elements in living systems. With advances in chemistry and materials science, a vast array of novel synthetic polymers has been introduced over the past century. Synthetic polymers such as nylon, polyethylene, and



1 These four materials are natural polymers. Polymers are substances composed of repeating structural units that are linked together to form long chains.

polyurethane have transformed daily life.[2] From automobile bodies to packaging, compact discs to clothing, and food additives to medicine, man-made polymers pervade virtually every aspect of modern society.[3]

However, the growing reliance on synthetic polymers has raised a number of environmental and human health concerns. Most plastic materials, for instance, are not biodegradable and are derived from nonrenewable resources.[4] The very properties of durability and strength that make these materials so useful also ensure their persistence in the environment and complicate their disposal. In addition, the synthesis of some polymeric materials involves the use of toxic compounds or the generation of toxic byproducts.[5]

These problems have focused increased attention on polymers that are derived from biological precursors or are produced by using the methods of modern biotechnology.[6] Such *biopolymers* may prove to have a variety of environmental benefits. Possible applications range from agriculturally or bacterially derived thermoplastics that are truly biodegradable, to novel medical materials that are biocompatible, to water treatment compounds that prevent mineral buildup and corrosion.[7] However, because materials typically have many different properties, in certain applications biopolymers may not necessarily provide environmental advantages over conventional polymers.[8] In practice, it is extremely difficult to develop testing methods that assess the environmental characteristics of materials.[9]

In recent years, a number of significant technical developments, particularly in the area of genetic engineering, have enhanced the commer-

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[2] These materials have been widely adopted because they are lightweight, strong, versatile, damage-resistant and chemically inert.

[3] In 1990, the United States produced 46.8 billion pounds of thermoplastics (e.g., polypropylene, polystyrene, polyethylene), 8,6 billion pounds of thermosetting plastics (e.g., urethanes and epoxy compounds), 8.1 billion pounds of synthetic fibers (e.g., nylon and polyester), and 0.5 billion pounds of cellulosic fibers (e.g., rayon) (data compiled by BioInformation Associates, Boston, MA).

[4] A biodegradable material is a material in which degradation results from the action of naturally occurring microorganisms such as bacteria, fungi, and algae.

[5] Although toxic intermediatcs are sometimes used in the manufacture of polymers, *the* final polymer products themselves are rarely toxic. Few commercially important polymers have any toxicity at all, thus they are used in a broad range of applications from food packaging to medical care. It is important to note that toxicity is often determined by the dose or concentration of a substance, so many compounds that pose health or ecological risks at very high concentrations may pose little risk at low concentration.

[6] Biotechnology, broadly defined, includes any technique that uses living organisms (or parts of organisms) to make or modify products, improve plants or animals, or develop micro-organisms for specific uses. Biotechnology also includes the development of materials that emulate the molecular structures or functions of living systems. For a comprehensive discussion of developments in this emerging field, see U.S. Congress, Office of Technology Assessment, *Commercial Biotechnology:* An International Analysis, OTA-BA-218 (Washington, DC: U.S. Government Printing Office, January 1984); U.S. Congress, Office of Technology Assessment, *Biotechnology in a Global Economy,* OTA-BA-494 (Washington, DC: U.S. Government Printing Office, October 1991); and Federal Coordinating Council for Science, Engineering, and Technology, Committee on Life Sciences and Health, Biotechnology~or *the* 21st *Century* (Washington DC: U.S. Government Printing Office, February 1992).

[7] Conventional water treatment chemicals employed as flocculants, corrosion inhibitors, and antiscalants are generally used at very low concentrations where they are not known to produce toxic effects. However, these compounds are not typically biodegradable.

[8] Little research has been done concerning the potential environmental impacts of biopolymers that are used in large quantities, It is possible that the widespread use of some biopolymers may have unanticipated effects on ecosystems or waste streams. It should be noted that some naturally occurring polymers have varying degrees of toxicit y. Some examples of natural toxicants include the protein toxins from pathogenic bacteria, and certain plant proteins that act as natural pesticides. *See Regulatory Toxicology and Pharmacology,* vol. 12, No. 3, December 1990, pp. S11-s77.

[9] For example, 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. For a discussion of the problems associated with environmental evaluation methods, 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).

cial prospects of biologically derived polymers .10 The advent of recombinant DNA technology has allowed researchers to exercise unprecedented control over the purity and specific properties of polymers. [11] Advances in genetic engineering have also enabled scientists to study how biological systems produce complex polymers. It is remarkable that living organisms are able to create sophisticated materials (e.g., spider silk) at normal temperature and pressure, without causing environmental disruption. This is certainly not the case for many man-made materials. *2 Thus, biopolymer research could also lead to the development of new environmentally sensitive manufacturing methods.

Biopolymers area diverse and versatile class of materials that have potential applications in virtually all sectors of the economy. For example, they can be used as adhesives, absorbents, lubricants, soil conditioners, cosmetics, drug delivery vehicles, textiles, high-strength structural materials, and even computational switching devices. Currently, many biopolymers are still in the developmental stage, but important applications are beginning to emerge in the areas of packaging, food production, and medicine. Some biopoly - mers can directly replace synthetically derived materials in traditional applications, whereas others possess unique properties that could open up a range of new commercial opportunities. Novel biopolymer compounds are being investigated by established agricultural and chemical firms, as well as small biotechnology enterprises.

Yet despite the promise of these new materials, a series of economic and engineering hurdles may impede their introduction to the market in the near term. 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. Commercially available biopolymers are typically two to five times more expensive than synthetic resins. In only a few specialized applications, such as biomedicine, are the relatively high costs of biopolymer materials not likely to impede market growth. Since many biopolymers are in the early phases of development, it is difficult to determine whether economy-of-scale manufacturing will be able to bring down their current high production costs. The commercialization difficulties facing biopolymers in many ways resemble the problems confronting other emerging technologies such as photovoltaic cells and fuel cells.[13]

At present, government-sponsored research and development efforts in the biopolymer area are relatively small in scope, but many ongoing Federal activities in biotechnology and agriculture 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

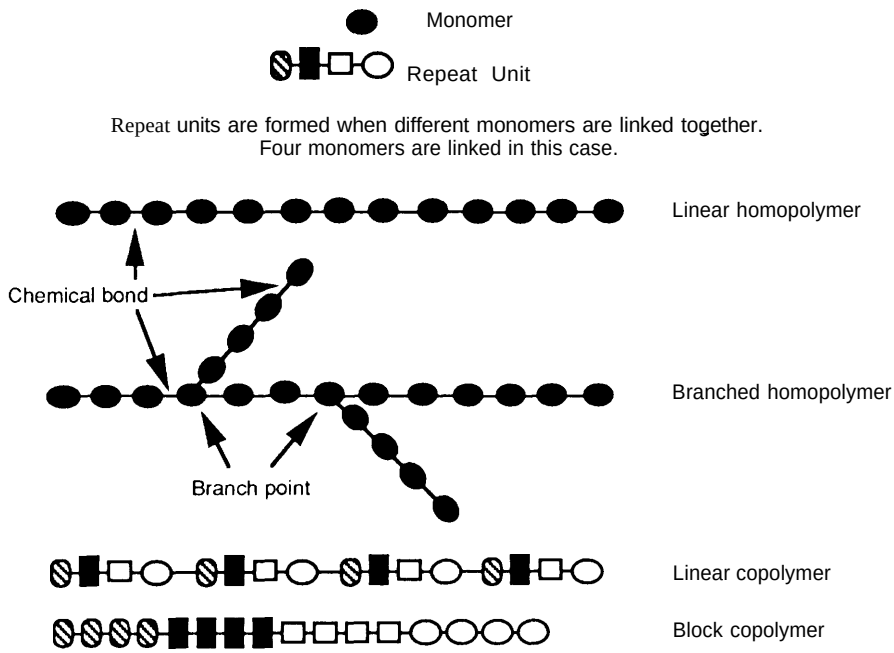
[10] Advances have also occurred in the development of chemical analogues of natural polymers (see Ch. 2).

11 Recombinant DNA technology allows direct manipulation of the *genetic material* of individual *cells. The* ability to direct which genes arc used by cells permits extraordinary control over the production of biological molecules. See discussion below.

[12] Many advanced materials are synthesized at extremely high temperature and pressure, and require toxic substances at various stages of processing.

[13] Technologies that convert or use renewable energy face a number of commercialization barriers. Some barriers are technical, while others relate to the high costs of production. There is a ‘ ‘chicken and egg’ problem of developing a market. Lower costs might be achieved through economy-of-scale manufacturing, but without market demand, it is not possible to make the investments necessary to achieve those low costs. Since fossil fuels are relatively inexpensive, it has been difficult for renewable energy technologies to make significant commercial inroads.

Figure 1-1—Some Basic Structural Features of Polymers



SOURCE: Office of Technology Assessment.

the research and development (R&D) efforts of different Federal agencies. The formidable economic and technical obstacles facing biopolymers, as well as the interdisciplinary nature of the biopolymer field itself, pose difficult challenges for policymakers and industry managers alike.

POLYMERS: A PRIMER

Polymers are a class of "giant" molecules consisting of discrete building blocks linked together to form long chains. Simple building blocks are called monomers, while more complicated building blocks are sometimes referred to as ''repeat units' (see figure l-l). When only one type of monomer is present, the polymer is referred to as a homopolymer. Polyethylene—the material commonly used in plastic bags—is a homopolymer that is composed of ethylene building blocks. A copolymer is formed when two or more different monomers are linked together. The process by which the monomers are assembled into polymers, either chemically or biologically, is referred to as polymerization. Polymers can **be** either linear or branched (figure l-l).

The distinguishing features of a polymer are determined by the chemical properties of the monomeric units (i.e., what the polymer is specifically composed of), the way in which the monomeric units are linked together, and the size or molecular weight of the polymer. (The size of the polymer is determined by the number of monomers linked together.) Each of these parameters contributes to the physical properties of the polymer product. Understanding the relationship between polymer structure and physical properties remains one of the most active and challenging areas of current research. In practice, polymers that are created by conventional chemical approaches lack uniformity in length, composition, and spatial orientation. Thus, a central aspect of polymerization techniques is statistical

Table 1-1—Biopolymers Found in Nature and Their Functions

Polymer	Monomers	Function(s)
Nucleic acids (DNA and RNA)	Nucleotides	Carriers of genetic information universally recognized in all organisms
Proteins	Alpha-ammo acids	Biological catalysts (enzymes), growth factors, receptors, structural materials (wool, leather, silk, hair, connective tissue); hormones (insulin); toxins; antibodies
Polysaccharides (carbohydrates)	Sugars	Structural materials in plants and some higher organisms (cellulose, chitin); energy storage materials (starch, glycogen); molecular recognition (blood types), bacterial secretions
Polyhydroxyalkanoates	Fatty acids	Microbial energy reserve materials.
Polyphenols	Phenols	Structural materials in plants (lignin), soil structure (humics, peat), plant defense mechanisms (tannins)
Polyphosphates	Phosphates	Inorganic energy storage materials
Polysulfates	Sulfates	Inorganic energy storage materials

SOURCE BloInformatlon Associates, contractor report prepared for the Office of Technology Assessment, April 1993

control of key polymer characteristics. Much of modern polymer science is concerned with reducing this variation in polymer properties.[14]

BIOPOLYMERS

The term “biopolymers’ is used to describe a variety of materials. In general, however, biopolymers fall into two principal categories:

- polymers that are produced by biological systems such as microorganisms, plants, and animals; and
- polymers that are synthesized chemically but are derived from biological starting materials such as amino acids, sugars, natural fats, or oils.[15]

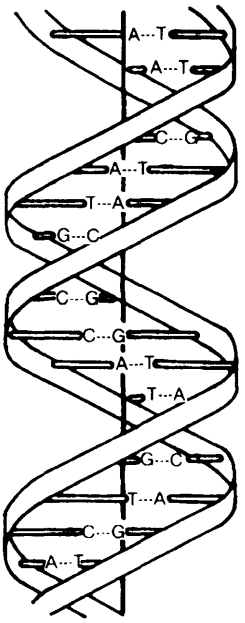
Table 1-1 lists various types of naturally occurring biopolymers defined on the basis of the chemical structure of their monomeric units, and indicates the functions that these polymers serve in living organisms. For example, DNA (deoxyribonucleic acid), which carries the essential genetic information of living systems, is a linear copolymer composed of four monomer nucleotides. [16]The nucleotides are linked together along

[14] Curtis Frank, ‘‘Polmer Materials Science: Novel Synthesis and Characterization of Supermolecular *Structures,* ” *Materials Research Society Bulletin,* vol. 16, No. 7, July 1991.

[15] Polyamides (nylons), some epoxies, and other polymers can be synthesized from naturally occurring fatty acids and oils. For example, ‘*nylon 11, ’ which is derived from castor oil, is now available commerically. The U.S. Department of Agriculture has sponsored a great deal of work in this area (L. Davis Clements, U.S. Department of Agriculture, Cooperative State Research Service, Office of Agricultural Materials, personal communication, July 27, 1993).

[16] The amount of DNA present in a cell is proportional to the complexity of the cell. This was one of the clues that led scientists to confirm that DNA is the bearer of genetic information. DNA can be thought of as a library that contains the complete plan for an organism. If the plan were for a human, the library would contain 3,000 volumes of 1,000 pages each. Each page would represent one gene or unit of heredity and be specified by 1,000 letters. The four nucleotide bases—adenine, cytosine, guanine, and thymine—are the letters of the chemical language. A gene is an ordered sequence of these letters. Any particular sequence specifies the information necessary to create a protein.

Figure 1-2—Structure of DNA



Schematic **diagram of the DNA double helix.**

The DNA molecule is a double helix composed of two chains. Sugar-phosphate backbones twist around around the outside, with paired bases on the inside serving to hold the chains together.

SOURCE: U.S. Congress, Office of Technology Assessment, Com-*mercial Biotechnology:* An International*Analysis,* OTA-BA-218 (Washington, DC: U.S. Government Printing Office, January 1984).

a pair of helical sugar-phosphate backbones (see figure 1-2). As an industrial polymer, DNA is currently not of commercial interest, although some researchers are beginning to examine this biopolymer for the purpose of assembling nanostructural materials, as well as for its electrical properties. [17]

Proteins-also referred to as polypeptides—are complex copolymers composed of up to 20 different amino acid building blocks. There are virtually a limitless number of proteins that can be formed from these 20 monomers, just as there are a vast number of words that can be made from the 26 letters of the alphabet (see box l-A). Proteins can contain a few hundred amino-acid units or thousands of units. Each protein has a specific chemical composition and three-dimensional shape. The amino-acid building blocks are linked by amide bonds in specific sequences determined by the DNA code of the corresponding gene.[18] Protein polymers are unique in that the sequence of the monomers in the polymer chain is predetermined by the template specific reamer of the polymerization process (i.e., they are copied from a genetic blueprint.)19 The sequence diversity of proteins is responsible for the wide array of functions performed by these materials in living organisms. Proteins typically account for more than 50 percent of the dry weight of cells, and are the primary means of expressing the genetic information coded in DNA. In recent years, researchers have been able to synthesize various polypeptides that are similar to natural proteins found, for example, in biominerals such as shells or bones. Synthetic polypeptides are usually created from amino-acid precursors (e.g., aspartic acid).

Polysaccharides are polymers or macromolecules composed of simple sugars. The polysaccharides have two principal functions. Some, such as starch, store energy for cell activity, and others, such as cellulose, serve as structural

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17 Researchers have used the twisting strands of DNA to construct simple three-dimensional structures. These DNA structures could conceivably be used to encase other molecules or to serve as a molecular scaffolding to which other molecules could be attached. See J. Chen and N. Seeman, ''Synthesis from DNA of a Molecule with the Connectivity of a Cube, " *Nature, vol.* 350, Apr. 18, 1991, pp. 631-633.

18 The term ''gene " is defined as the basic unit of heredity-an ordered sequence of nucleotide bases, constituting a distinct segment of DNA.

19 Each amino acid in a protein chain is represented *by three* nucleotides from the DNA. Thus, different nucleotide combinations give rise to different amino-acid sequences, which give rise to different proteins.

20 Unlike proteins, polysaccharides do not have an information-carrying function. However, when polysaccharides are connected to proteins, they guide proteins to correct locations within a cell—a property that is useful in drug delivery. For more detail on the respective functions of these biopolymers, see Albert Lehninger, *Biochemistry (New* York, NY: Worth Publishers, 1975).

Box I-A–Probability and the "Miracle" of Life

How is it that biological systems are able to produce the polymers that are needed to sustain life? Stated another way, how can a particular kind of polymeric structure be created out of the extraordinarily vast number of structures that are possible? If, for example, a polymer consists of k types of monomers and has a total length N, the number of possible polymeric structures that can be generated is k^N. This number becomes extremely large when the polymer is of even moderate length. For instance, proteins consist of 20 different types of amino acids and are about 100 units long. Therefore, 20^{100} (about 10^{130}, or 1 followed by 130 zeros) possible polymeric configurations exist. For DNA, k = 4 (four types of nucleotides), and N = 1 million, so 4^{106} (about $10^{600,000}$, or 1 followed by 600,000 zeros) structures are possible. Thus, the probability of the right polymer being created by chance alone is fantastically small. However, biological systems are able to generate the desired polymer with a probability virtually equal to 1 (i.e., there is basically a 100 percent chance that the correct polymer will be created). This high probability is due principally to the presence of biological catalysts (enzymes) that eliminate the randomness associated with chemical transformations and thereby ensure the "uniqueness" of biochemical processes. Enzymes play a central role in DNA replication and protein production, as well as in polysaccharide biosynthesis. It should also be noted that some biological monomers have certain chemical tendencies to form "nonrandom" polymers even under simple conditions of formation (e.g., simple thermal polymerization of amino acids gives rise to compounds that have a relatively high degree of order).

SOURCES: V. Averisov et al., "Handedness, Origin of Life, and Evolution," Physics Today, July 1991, pp. 33-41; S. Fox and A. Pappelis, "Synthetic Molecular Evolution and Photocells," The *Quarterly Review of Biology*, vol. 68, No. 1, March 1993.

materials in living systems.[20] After proteins, polysaccharides are among the most diverse and complex group of biopolymers. This is because the bonds linking the sugar monomers can be formed at different positions on the sugar units (illustrated in figure 1-3 for homopolymers of glucose). By simply linking glucose monomers together at different positions, polymers with very different properties are produced (see chapter 2). At least 20 different sugars have been identified in a variety of polysaccharides from biological sources, and thus a great range of polymer structures can be created (see box l-A).

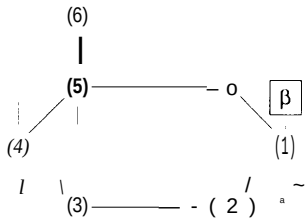
Many polysaccharides contain branched structures and are chemically modified by the addition of other molecules. The monomeric or repeat units are often made up of more than one sugar molecule and consequently can be quite complex. The xanthan gum repeat unit, for example, contains five sugars. The assembly of polysaccharide repeat units and the associated polymerization processes are not dependent on a template or genetic blueprint, but are specified by the enzymes (biological catalysts) involved in an organism's "biosynthetic pathway."[21] This process in biological systems is often referred to as contemplate polymerization.

Other biopolymers include polyhydroxyalkanoates (PHAs), nature's biodegradable thermoplastics[22] (chapter 2); polyphenols, a class of structural materials; and inorganic polyphosphates and

21 The term "biosynthetic pathway" is used to describe the step-by-step conversion of precursor molecules into a final product, with each step in the process being carried out by a specific biological catalyst (enzyme), A pathway consists of a sequence of reactions leading to a final product that is usually quite different from the starting materials.

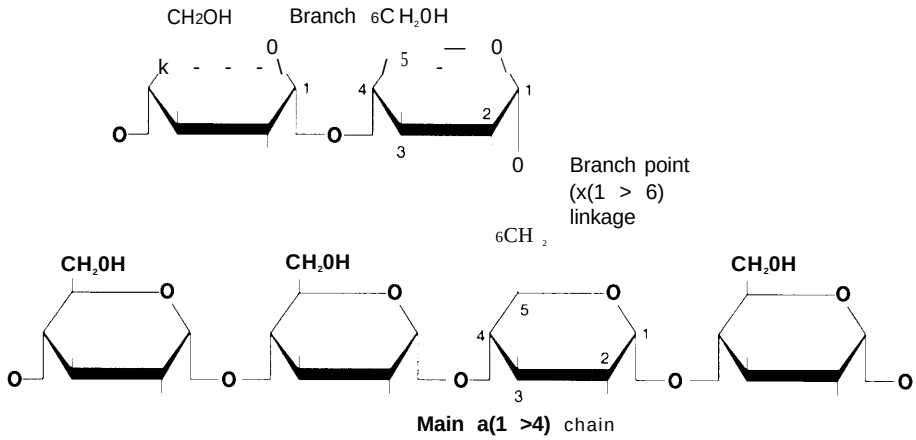
22 Thermoplastics are polymers that will repeatedly soften when heated and harden when cooled.

Figure 1-3-Anatomy of a Natural Sugar



Bond(s)	Polymer
B(1-4)	**Cellulose**
B(1-3), B(1-6)	Yeast glucan
a(l-4), a(1 -6)	Starch

The different types of linkages found in some glucose homopolymers are illustrated. The glucose monomer (above) is made up of six linked carbon atoms. The bond that joins two different sugar units is described by the respective numbers of the carbon atoms that are linked. For example, if the "B1" position of the first sugar monomer is linked to position 4 of the second sugar monomer, the bond would be described as B(1-4). In amylopectin (depicted below), a form of starch, the main polymer chain consists of a(l-4) bonds and the branched chain is connected by a(l-6) bonds.



Amylopectin (a form of starch)

SOURCE: BioInformation Associates, contractor report prepared for the Office of Technology Assessment, April 1993.

polysulfates, which are not discussed in this report.[23]

IMPACT OF GENETIC ENGINEERING ON BIOPOLYMER TECHNOLOGY

Modern biotechnology has given scientists revolutionary tools to probe and manipulate living systems. Genetic engineering permits extraordinary control over the time, place, level, and type of ''gene expression. ''[24] The simplest case applies to protein polymers. Having access to the genetic blueprint (gene) of a particular protein polymer allows one to change both the system that produces the polymer and the composition of

23 These ''inorganic'' polymers have structural backbones that do not contain carbon atoms. However, the polymer side groups often do contain carbon. One type of inorganic polymer family is the polyphosphazenes. These compounds have unique elastic properties.

24 Gene expression is the mechanism whereby the genetic instructions in any particular cell are decoded and processed into a final functioning product, usually a protein. This involves several steps: In a process called transcription, the DNA double helix is locally unzipped near the gene of interest, and an intermediate product, known as ''messenger' RNA, is synthesized. The messenger RNA transmits the instructions found in the DNA code to the protein-synthesizing machinery of the cell, and a protein is created. Proteins are composed of amino acids. Each amino acid in a protein chain is represented by three nucleotides from the DNA. See *Commercial Biotechnology,* op. cit., footnote 6, pp. 34-35.



COURTESY OF DISCOVER MAGAZINE (JULY 1990)

Some bacteria can store energy in polymer-bearing granules (polyhydroxyalkanoates) that can be collected and made into truly biodegradable packaging like these plastic bottles made from Alcaligenes bacteria by Zeneca Bio Products.

the polymer itself. Recombinant DNA techniques permit the creation of polymer chains that are virtually uniform in length, composition, and stereochemistry or spatial orientation[25] (see box l-B). For example, the protein polymer silk that is produced commercially by silkworms can now be made in recombinant microorganisms.[26] The advantage of this new approach is not that the recombinant DNA method is necessarily more economical, but that it is possible to generate polymers of exceptional structural purity, as well as manipulate the biopolymer production system to create new materials. In addition, the recently developed ability to chemically synthesize DNA allows scientists to construct entirely new genes

[25] The three-dimensional arrangement of a biological polymer gives rise to specific types of biochemical activity. For example, the Spatial arrangement of an enzyme results in some reactions being greatly favored over others. It turns out that natural proteins are constructed only from ''left-handed'' amino acids, and nucleic acids are made up only of "right-handed" sugars. Their mirror image structures (e.g., right-handed proteins) are not found in living systems. Although 'left-handed' and 'right-handed' versions (so-called stereoisomers) of any given compound have identical chemical composition and physical properties, they react quite differently biologically and with some reagents. Traditional chemical synthesis techniques usually produce left- and right-handed versions of a polymer, which is undesirable from the perspective of production efficiency.

[26] See David L. Kaplan et al., "Biosynthesis and Processing of Silk Proteins, ' *Materials Research Society Bulletin*, vol. 17, No. 10, October 1992, pp. 41-47.

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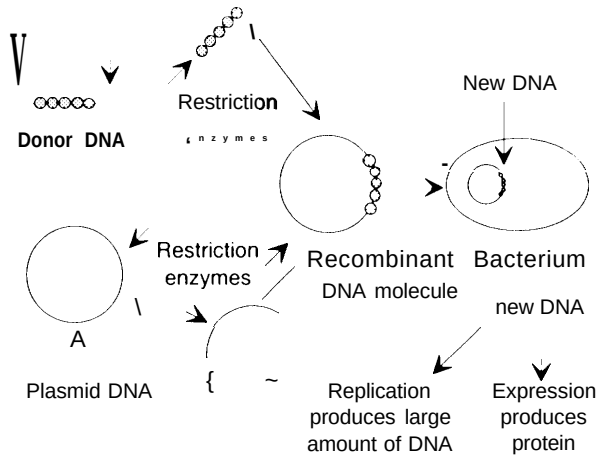
Box l-B–The New Alchemy: Recombinant DNA Technology

Recombinant DNA is formed when **pieces of DNA f from different organisms** are joined together. The basic tech**nique of preparing recombinant** DNA is illustrated in the **diagram shown. Special biological catalysts known as "restric**tion enzymes" are used to cut donor DNA (usually from a higher organism) into fragments, one of which contains the gene of interest. Restriction enzymes recognize certain sites along t he DNA and can chemically cut the DNA at those sites. The resulting DNA fragments are t hen inserted into a "vector,"- a DNA molecule used to introduce foreign genes into host cells. Plasmids, circular segments of DNA **that are not part of chromosomal** DNA, are t he most common types of vectors used. Thus, selected genes from donor DNA molecules are inserted into plasm id DNA molecules to form the hybrid or recombinant DNA. Each plasm id vector **contains a different donor** DNA fragment. These recombinant DNA plasm ids are introduced into host cells in a process called "transformation." When the transformed host cells grow and divide, the plasm ids replicate and partition with the host daughter cells, ultimately providing many host cells that carry the same donor DNA fragment. This process of replication is known as cloning. The cloned genes can then be "switched on, " resulting in the creation of large quantities of the desired protein. Recombinant DNA is grown principally in simple microorganisms such as bacteria and yeast. In recent years, scientists have also developed methods of introducing genetic material into higher plants and animals.



SOURCE: U.S. Congress, Office of Technology Assessment, Commercial *Biotechnology: An /nternationa/* Analysis, OTA-BA-218 (Washington, DC: U.S. Government Printing Office, January 1984).

SOURCE: U.S. Congress, Office of Technology Assessment, *Commercia/Biotechno/ogy:An Internationa/Ana/ysis,* OTA-BA-218 (Washington, DC: U.S. Government Printing Office, January 1984).

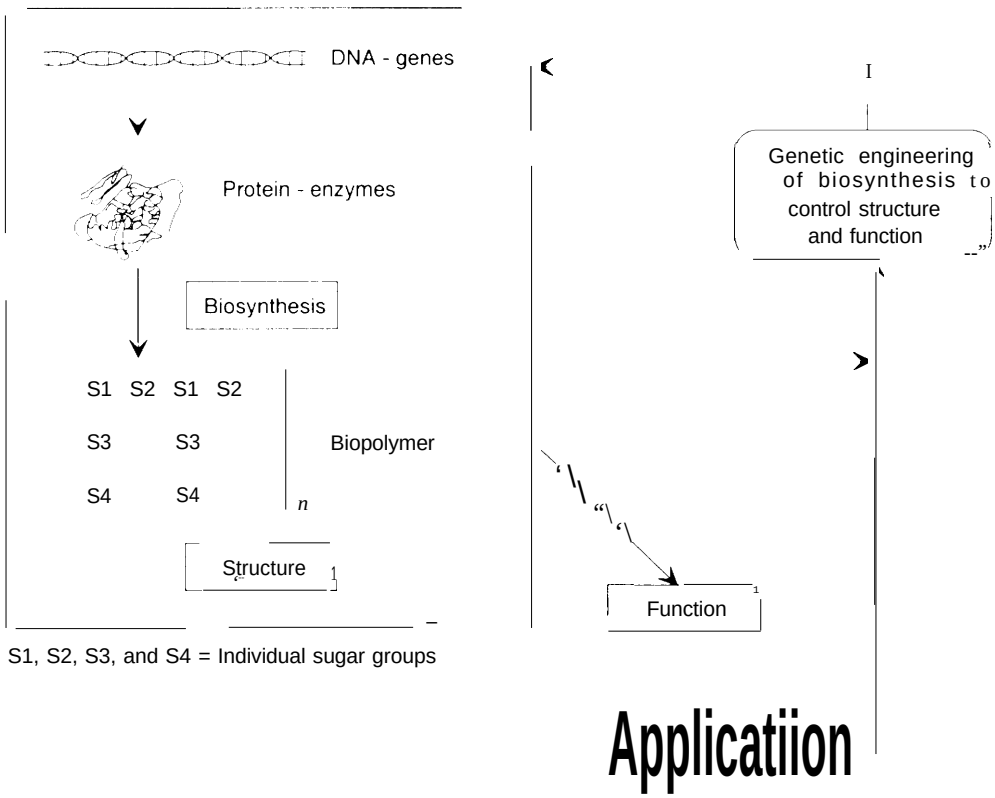
that encode unique protein polymers .27 Researchers are now modifying genes to improve the mechanical and chemical properties of structural proteins such as silk, elastin, and various adhesive polymers.[28]

For biopolymers other than proteins, such as polysaccharides and polyhydroxyalkanoates, the situation is more complicated. In these cases, genetic manipulation permits control of the production of biological catalysts (proteins known as enzymes), which are in turn responsible for the production and polymerization of the building blocks that make up the final polymer products (see figure 1-4). A useful analogy is to view

27 A gene can be synthesized or created directly since the nucleotide sequence of the gene can be deduced from the amino-acid sequence of its protein product.

28 David Tirrell et al., "Genetic Engineering of Polymeric Materials, " *Material sResearch Society Bulletin,* vol. 16, No. 7, July 1991, pp. 23-28.

Figure 1-4-A Genetically Engineered Biopolymer Production System



S1, S2, S3, and S4 = Individual sugar groups

Unlike proteins, polysaccharides and other natural polymers are not created by following a genetic blueprint; rather, an organism outlines a "pathway" of synthesis in which each step of the pathway is carried out by a specific enzyme. Some polysaccharide pathways can have more than ten steps and sometimes as many as a hundred steps. By using recombinant **DNA techniques, enzymes from different** biological sources (i.e. species) can be introduced into host organisms, thereby creating entirely new biosynthetic pathways or polymer assembly lines. These new biological assembly lines could be used to produce greater quantities of a particular polymer, or to design novel polymers with unique physical and functional properties.

SOURCE: BioInformation Associates, contractor report prepared for the Office of Technology Assessment, April 1993.

enzymes as being machines that carry out different steps on a biological assembly line. Throughout the biological world there exists an extraordinary army of different machines (enzymes), all encoded by specific genes. Many of these enzymes are present in only one species or strain of organism. The genes for these enzymes are then the blueprints for the individual pieces of machinery, and remarkably, these blueprints are recognized and translated in the same way in all organisms. By adding the appropriate signals and transferring the gene into a new organism, the organism can then produce a new enzyme, thereby giving the organism the capacity to carry out a particular step in the assembly line process. Genetic engineers now have the ability to add new machines, or remove old ones, in practically any system.

The implications of these genetic techniques are quite profound. It is now possible to genetically modify an organism so that it produces greater quantities of a particular polymer. As an example, the introduction of a specific enzyme has allowed researchers to increase starch produc-

tion in genetically engineered plants.[29] It is also possible to transfer an entire assembly line into a new host organism to improve a production process. One illustration of this procedure is the production of the bacterial thermoplastic polyhydroxybutyrate (PHB) in transgenic plant species.[30] Finally, these new techniques allow organisms to be modified so that truly novel materials can be produced. For instance, a series of genetically engineered xanthan gums has been developed by removing specific enzymes from the xanthan assembly line (ch. 2). Ultimately, it may be possible to construct biological systems for the production of entirely new classes of polymers. This could be accomplished by creating new assembly lines using enzymes from diverse sources and then introducing the correct blueprints into an appropriate host. The long-term objective of this type of research is to design biological systems that produce specific polymers for specific applications. For example, materials might be genetically ''customized' to have a unique combination of mechanical, chemical, and degradative properties.

THE ROLE OF CHEMISTRY IN BIOPOLYMER TECHNOLOGY

Given the advances in genetic engineering, what is the role of traditional chemical synthesis in creating biopolymers? The most widely used polymers, such as polypropylene and polyester, are produced by standard chemical means. But as mentioned previously, the processes used to manufacture these synthetic polymers can sometimes have a number of drawbacks. Although technologies for producing proteins by chemical synthesis have been developed, they are extremely costly. Such methods are used primarily for the production of research chemicals or for very high-value applications such as pharmaceuticals. There is no existing chemical technology capable of producing the complex polysaccharide structures made so readily by biological systems. Because of their structural and chemical specificity, enzymes are extremely efficient at producing polymer compounds with high yield.[31]

Yet, chemistry still has an important role to play in the development of biopolymers. Chemical techniques can be used to modify the properties of biopolymers to expand their range of applications, to polymerize biological starting materials, or to create new gene sequences that can lead to novel protein polymers through the application of recombinant DNA methods. Examples of such chemical methods are presented in chapter 2.

THE POLICY CONTEXT

As noted in previous sections, there have been significant advances in basic biopolymer science, with a wide range of new applications on the horizon. Due to the versatility and potential environmental benefits of biopolymer materials, R&D activities are likely to expand considerably in coming years. While technical progress in the biopolymer field is, for the most part, being driven by academia and industry, the Federal Government directly and indirectly affects biopolymer development. In the following sections, the role of federally funded research and various regulatory issues are discussed.

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29 See David M, Stark et al., ''Regulation of the Amount of Starch in Plant Tissues by ADP Glucose Pyrophosphorylase,' *Science*, vol. 258, Oct. 9, 1992, pp. 287-292.

30 While early work in this area is encouraging, many technical challenges remain. See Yves Poirier et al., ''Polyhydroxybutyrate, a Biodegradable Thermoplastic, Produced in Transgenic Plants,' *Science*, vol. *256*, Apr. 24, 1992, pp. 520-523. Transgenic plants are plants whose hereditary DNA has been augmented by the addition of DNA from other species.

31 However, polymers that are created by biological processes such as fermentation may require further purification before they are suitable for a particular application.

Role of Federal R&D Programs

Although there is not a well-defined biopolymer research program in the United States, many ongoing Federal activities have a bearing on biopolymer science. Several Federal agencies are sponsoring efforts in biopolymer research, as well as related areas such as bioprocessing and genetic engineering (see ch. 4). In February 1992, the White House Office of Science and Technology Policy announced the Biotechnology Research Initiative—a coordinated interagency effort to strengthen and diversify Federal research activities in biotechnology .32 This initiative is designed to extend the ''scientific and technical foundations' of biotechnology, to "accelerate the transfer of biotechnology research" to applications in the commercial sector, and to expand interdisciplinary research between biology and other fields, such as chemistry, physics, or materials science .33 The initiative calls for greater attention to be paid to bioprocessing and manufacturing, including bimolecular materials, biocompatible materials, and metabolic engineering, and thus addresses many aspects of biopolyrner science.

However, the amount of funding specifically targeted for biopolymer programs is relatively small. In FY 1993, only about 3 percent ($124 million) of the total biotechnology budget ($4 billion) is devoted to biologically derived compounds and industrial processing research (see ch. 4); and only a small fraction of that 3 percent goes directly to biopolymer development. Some members of the research community have called for more explicit Federal goals in the biopolymer area, particularly in the biomedical field (see box 4-A). For example, the creation of a national center for biomaterials research at the National Institutes of Health (NIH), as some observers have called for, could lend greater focus to biopolymer programs in the medical area.

It is important to recognize, though, that while many important biopolymer applications are emerging in the medical field, there are also promising applications in the industrial, agricultural, and waste management sectors. As noted in a previous Office of Technology Assessment report, Federal funding for biotechnology in the area of medicine dwarfs the funding directed toward agriculture, chemicals, energy, and other biotechnology applications.[34] To ensure that promising nonmedical biopolymer applications are not ignored, Federal programs could give greater emphasis to areas such as the conversion of agricultural or aquatic materials into useful industrial feedstocks and the production of environmentally sensitive materials .35

Despite the promise of new biopolymer production technologies, this nascent field faces the same problems that have confronted other new technologies: development periods of 5 years or longer, poor prospects for short-term gains, and uncertain demand in the marketplace because of inexpensive alternatives (synthetic polymers are currently much less expensive than agriculturally or microbially derived materials). Although some materials are being used now, many biopolymers face a variety of technical and economic barriers that will take several years to overcome. The efforts of the private sector to overcome some of these barriers might be aided by such Federal

32 *Biotechnology for the 21st Century,* Op. cit., footnote 6.

33 Ibid.

34 Biotechnology in *a Global Economy,* op. Cit., footnote 6.

35 Nonmedical research in the biopolymer area is being carried out or sponsored by the office of Naval Research, the U.S. Army Natick Research, Development and Engineering Center, the U.S. Army Research Office, the U.S. Department of Agriculture's Office of Agricultural Materials, the National Science Foundation, and the National Oceanic and Atmospheric Administration (see ch. 4).

programs as the Advanced Technology Program[36] of the Department of Commerce, or the cooperative research and development programs (CRADAs) of the U.S. Department of Agriculture (USDA) and the various Department of Energy national laboratories.[37]

At present, Federal biopolymer research activities are diffuse and for the most part, not well coordinated. Yet, given that biopolymer materials have an extraordinarily broad range of possible uses, the decentralized structure of the Federal research system should not necessarily be regarded as a barrier to biopolymer development. Many biopolymer applications fall neatly into the research agendas of individual Federal agencies and are already the subject of focused attention. On the other hand, a large number of biopolymer applications involve a range of different scientific disciplines, and thus some areas of biopolymer research could no doubt benefit from increased coordination of Government resources.

The recent White House initiative to classify biotechnology research across the Federal research system is beginning to address this situation and is intended to lead to greater cross-agency cooperation.[38] Creating opportunities for increased collaboration among academic, industrial, and Government researchers is an explicit objective of the initiative. These efforts, even without increased levels of funding, should benefit ongoing biopolymer research activities. Over the long term, Federal R&D programs in the biopolymer area might focus on:

- exploratory work on biopolymer materials that are genetically engineered to have unique physical and functional properties or that could be used as substitutes for the commodity resins currently derived from petroleum sources;
- utilization of agricultural or marine products and byproducts;
- biopolymer processing technologies that could potentially lead to new environmentally sensitive manufacturing methods;
- approaches to lower the costs of production associated with various biopolymer manufacturing technologies;
- research on the environmental impacts (positive or negative) of biopolymers that are introduced into solid and aqueous waste streams or natural ecosystems.

As with other areas of technology development, the challenge for policymakers is to determine where Government can best use its R&D resources to complement, rather than replicate, the activities of the private sector.

Regulatory Issues

A number of existing or potential regulatory factors could affect biopolymer development and commercialization efforts. These include the Food and Drug Administration (FDA) approval process for medical applications that use biopolymers; the development of legal definitions for biodegradable materials, or regulations mandating the use of biodegradable materials for

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36 The Advanced Technology Program (ATP) has granted a small number of awards to companies working in the biotechnology Mm. Some of the recent ATP grants have included biopolymer applications in the medical field. For example, Tissue Engineering, Inc., is developing biopolymers derived from animal and marine sources that can be used as prosthetic devices or vascular grafts (Les Garrick, Tissue Engineering, Inc., personal communication, Aug. 23, 1993).

37 The Agricultural Research Service of the USDA has more active CRADAs than any other Government agency. In addition, the USDA's Alternative Agriculture Research and Commercialization Center works with private industry to promote the commercialization of promising new materials. The Department of Energy has a large general effort in biotechnology at its national laboratories, including projects in mapping the human genome and in structural biology.

38 Another White House initiative that relates to biopolymer research is the Federal Advanced Materials and Processing Program (AMPP). AMPP is designed to encourage multidisciplinary research and new advances in materials science. For example, as part of AMPP, the National Science Foundation is supporting work in ceramics, composites, electronic and magnetic materials, superconductors, and biomaterials and bimolecular materials. See "NSF's Participation in Advanced Materials and Processing program (AMPP)," NSF document 93-68, May 7, 1993.

applications such as packaging; regulations affecting the use of genetically engineered systems for producing biopolymers; and requirements regarding the introduction of new industrial chemicals.

FOOD AND DRUG ADMINISTRATION

The FDA is a regulatory agency responsible for the safety of the Nation's foods, cosmetics, drugs, medical devices, biological products, and radiological products. Since biopolymers have potential uses in virtually all of these areas, the market introduction of many biopolymer compounds will be governed by FDA guidelines.[39] For example, biopolymer crystallization inhibitors such as polyaspartate (see chapter 2) could be used in oral health care as tartar control agents. However, toothpaste and mouthwash additives are considered "drugs," and therefore require FDA approval. The principal biopolymer applications affected, however, will be drug delivery systems and medical devices .40

To enter the U.S. market with a new drug or an advanced drug delivery system that is being packaged with a new or existing drug, an application must be filed with the FDA before a manufacturer can begin human clinical trials.[41] Following this step, a new drug application (NDA) is submitted with supporting evidence as to both safety and efficacy. Even if a proven drug delivery system is packaged with a proven drug, anew application is required. Such safeguards are necessary because a new delivery system-drug combination will have new pharmacological properties. This requirement can obviously affect the rate at which various biopolymer drug delivery systems are introduced into the market.

Medical device implants are also subject to FDA review through the Medical Device Amendments Act of 1976.42 The FDA evaluates the safety and effectiveness of medical devices, but does not necessarily approve biomaterials per se. There is not an FDA list of approved medical materials, but if a material is itself a product, such as bone cement, the material does receive certification. However, the evaluation of materials in medical devices is obviously an important part of the overall review process.[43]

In recent years, medical device manufacturers have expressed considerable concern about the length of time required for FDA approval of medical products.[44] This has resulted in calls to streamline FDA evaluation procedures. In 1989, the Biomaterials Industry Subpanel of the Na-

39 FDA evaluation efforts focus on the development of in vitro (outside the body) assessment methods. This includes the evaluation of cellular and molecular mechanisms of biomedical materials degradation and performance, as well as assessment of host system-medical device interactions. *Biotechnology for the 21st Century,* op. cit., footnote 6.

40 The three main biomedical market segments for biopolymers 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 just beginning to establish a significant commercial presence.

41 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 device 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. Polylactide and some polyamino-acid polymers are currently being evaluated as drug vehicle materials (see ch. 2).

42 In 1990 Congress passed the Safe Medical Device Act, which modified the 1976 act. The 1990 law requires manufacturers to take steps to evaluate medical device performance after a device has been approved and distributed in the marketplace.

43 E. Mueller et al., " 'Regulation of 'Biomaterials' and Medical Devices, ' *Materials Research Society Bulletin, vol.* 16, No. 9, September 1991, pp. 39-41. Also see U.S. Department of Health and Human Services, Tripartite Biocompatibility Guidance for Medical Devices (Washington, DC: 1986).

44 See "FDA Foot. Dragging Stymies Medical Device Makers, " *Wall Street Journal*, June *4, 1993,* p. B2.

tional Research Council made several recommendations[45] for improving the FDA approval process:

- A biomaterials evaluation process should be established to facilitate the use of new materials in medical devices. The material itself, once proven safe and effective, should not be subject to further testing in the event of its use with additional medical devices.
- The FDA should establish a biomaterials advisory committee.
- The FDA should establish biomaterials guidelines and standard test protocols.

Regardless of whether these proposals are adopted, the introduction of procedures that ensure product safety, while reducing evaluation times and costs, will bean important objective of the FDA in years to come.[46]

BIODEGRADABLE MATERIALS

Scientifically based definitions and standards relating to degradability have yet to be legally established. While some studies on degradability have been performed by the Environmental Protection Agency (EPA) and the USDA, Congress has not yet mandated technical standards in this area. However, in Public Law 100-556, Congress required that plastic ring carriers for bottles and cans be made of degradable material. In the proposed rule for this law, EPA does not specify that particular materials be used, but has instead set performance standards for degradable materials.[47] The performance criteria include three factors: a physical endpoint for degradation, a time limit for degradation, and marine environmental conditions.[48] By specifying performance goals rather than particular materials, EPA hopes that industry will have sufficient flexibility to develop new classes of degradable polymers. Currently, beverage ring containers are made only from photodegradable materials, consisting of ethylene-carbon monoxide copolymers.[49] In addition to this Federal action, 27 States have passed legislation prohibiting the use of nondegradable ring carriers.

Although this EPA rule applies to a narrow product category, the precedent of setting performance standards for degradable substances could facilitate the introduction of biopolymer materials. If Federal or State action is taken to expand the range of mandated degradable products (e.g., personal hygiene products or diapers), market opportunities could develop for the new starch, polylactic acid, and microbial polyester biopolymers. However, precise technical definitions and testing methods will be needed to convince both manufacturers and consumers that such new materials are indeed environmentally

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45 See "Report of the Committee to Survey Needs and Opportunities for the Biomaterials Industry," *Materials Research Society Bulletin*, vol. 16, No. 9, September 1991, pp. 26-32.

46 The FDA has taken some steps in this direction with its recently announced "expedited review' process for innovative medical devices. The new procedures are intended to give administrative priority to potential 'breakthrough devices," and to better classify products submitted for FDA approval. In the past, every product submitted for approval was subject to the same administrative procedures. The new procedures will eliminate some of the review steps for relatively simple devices and give greater attention to more complex medical devices (see "Promising Medical Devices To Be Speeded to Market," *Washington Post,* June 25, 1993, p. A2).

47 The proposed EPA rule states that the term "biodegradable plastic" is used to "describe any plastic that is intended to completely assimilate into the environment regardless of the derivation of the material or the combination of degradation processes involved in assimilation" (see *Federal Register,* vol. 58, No. 65, Apr. 7, 1993).

48 Ibid.

49 Scientists are still concerned that these "dqp&ble' materials may seine only to substitute one hazard for another in marine waters. That is, with the use of degradable plastics, the hazard of ingesting plastic fragments may replace the hazard of entanglement in nondegradable plastics. 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), pp. 180-183.

superior and do not affect product integrity.[50] In this regard, the efforts of the American Society for Testing and Materials (ASTM) to develop scientific definitions and evaluation methods for degradable materials may serve to allay public concerns.[51]

GENETICALLY ENGINEERED BIOPOLYMER PRODUCTION SYSTEMS

The principal Federal regulatory guidelines dealing with biotechnology were formulated in the 1986 White House Office of Science and Technology Policy report "Coordinated Framework for Regulation of Biotechnology. ' The document describes how novel chemicals, materials, and organisms, produced by the methods of biotechnology, fit into the existing corpus of Federal legislation and regulation. In general, genetically engineered products are regulated on the basis of their intended use, rather than the method or process by which they are made. For example, under current FDA rules, genetically engineered foods are treated the same way as conventional products. The FDA does not require that new products be approved or labeled, as long as such products are essentially similar in composition, structure, and function to food items already available on the market.[52] However, USDA and EPA do regulate field tests of genetically modified plants.[53] As of 1993, more than 400 permits have been granted for the field testing of genetically altered plants and other organisms.[54]

For the short term, genetically engineered biopolymers will be produced in "contained" fermentation systems where standard safety procedures are well established.[55] Thus, microbially derived biopolymer materials are unlikely to face any significant regulatory obstacles.[56] In the future, however, schemes that involve the production of biopolymers through the genetic modification of crops could face greater regulatory scru-

50 For example, the FDA is concerned about the possibility of a shortened shelf life of degradable food-packaging material. In evaluating the safety of new additives in food-contact materials, the FDA must consider potential problems such as enhanced migration of food-packaging components as a consequence of accelerated degradation of a polymer. In the case of some proposed biopolymer packaging materials such as pullulan (ch. 2), there would have to be evidence that the food product is adequately protected. Ibid.

51 The ASTM Degradable Plastics Subcommittee is examining various degradation pathways, including photodegradation, oxidation, chemical degradation, and biological degradation. It has developed standard laboratory test methods that measure the rate and extent of degradation for different materials, and is in the process of establishing a classification and marking system for polymer compounds. ASTM researchers are currently attempting to determine the behavior of degradable polymeric materials in real disposal systems and are correlating these results with ASTM laboratory methods. This work could very well become the de facto industry baseline for defining and evaluating new polymer materials, Already, EPA has used some of ASTM's work in developing proposed performance standards for degradable beverage ring carriers (op. cit., footnote 47; and see Ramani Naryan, "Development of Standards for Degradable Plastics by ASTM Subcommittee D-20.96 on Environmentally Degradable Plastics, ' 1992).

52 Some consumer groups have expressed concerns that genetically engineered foods may be subject to microbial contamination, possess higher levels of toxins, or expose consumers to allergy-producing compounds that are not naturally present in foods. The present consensus among scientists is that the risks associated with genetically altered organisms are similar to those associated with nonengineered organisms or organisms genetically modified by traditional methods (Biotechnology *in a Global Economy*, op. cit, footnote 6).

53 Currently, researchers are required to give 30 days notice to the USDA before beginning field tests. During that time, a determination is made as to whether additional review or inspection is necessary. See *Federal Register,* "Genetically Engineered Organisms and Products; Notification Procedures for the Introduction of Certain Regulated Articles; and Petition for Nonregulated Status, " vol. 58, No. 60, Mar. 31, 1993. Also, EPA considers microorganisms that are released into the environment to be chemical substances subject to the Toxic Substances Control Act of 1976. EPA is currently developing guidelines governing genetically engineered pesticides and other microbes.

54 For a discussion on how scientists are assessing the ecological impacts of genetically altered plants, see M.J. Crawley et al., ''fiolo8Y of Transgenic Oilseed Rape in Natural Habitats, ' *Nature,* vol. 363, June 17, 1993, pp. 620-623.

55 NIH has developed guidelines that prescribe various procedures of containment for genetic experiments. See *Federal Register,* "Guidelines for Research Involving Recombinant DNA Molecules, " vol. 51, No. 88, May 7, 1986.

56 Whether a biopolymer is regulated will to a large degree depend on the application. For example, medical products that contain microbially-derived biopolymers will still be subject to FDA review.

tiny. Several researchers, for instance, are exploring the possibility of producing natural polyesters such as PHB by altering the enzyme machinery of corn or potatoes.[57] Such approaches to biopolymer manufacture will be subject to existing Federal rules governing genetically engineered agricultural organisms.

REGULATIONS RELATING TO INDUSTRIAL CHEMICALS

In response to public concerns over the possible health and environmental implications of widespread chemical use, Congress passed the Toxic Substances Control Act (TSCA) in 1976, Under the provisions of TSCA, EPA is charged with assembling basic data on chemicals, reviewing industry tests of new and existing compounds, and reducing public risk. There are more than 60,000 chemicals currently on the TSCA inventory, and roughly 1,000 new chemicals are proposed for manufacture each year.[58] Before manufacturers can begin production of a new chemical, they must submit a Premanufacture Notice to EPA. Only a small number of the premanufacture notices submitted to EPA are held up for extended review.[59] In the vast majority of cases, manufacturers can begin production of a chemical 90 days after notifying EPA.

Since some of the more interesting biopolymer compounds are new chemical formulations, they will also be subject to TSCA provisions.[60] Yet, given that biopolymers are derived from natural precursors, most biopolymer *products* should not have difficulty meeting current TSCA requirements.[61] For instance, this should be the case for biopolymers that are created by the chemical polymerization of naturally occurring monomers, such as polylactide and the polyamino acids.[62] However, as indicated previously, some of the *processes* used to produce genetically engineered biopolymers may be subject to more detailed regulatory review (e.g., genetic modification of plants).

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57 See "In Search of the Plastic potato, " *Science,* vol. 245, Sept. 15, 1989, pp. 1187-1189.

58 Michael Shapiro, "Toxics Substances Policy, " Paul Portney (cd.), *Public Policies for Environmental Protection* (Washington, DC: Resources for the Future, 1990), p. 208.

59 Often, new chemicals are simply slight modifications of existing substances and are therefore not subjected to a rigorous review. However, if EPA is concerned about a particular chemical, it can take years before definitive toxicity data can be developed. This has led to calls for new procedures in the TSCA chemical evalution process. Ibid.

60 Depending on the types Of applications involved, biopolymers could also be subject to the provisions of the Clean Water Act and the Safe Water Drinking Act. The Clean Water Act regulates contaminants discharged into surface waters, and the Safe Water Drinking Act safeguards drinking water sources and prescribes drinking water standards. For a general discussion of the regulation of water pollutants and treatment chemicals, see "Water Treatment Chemicals: Tighter Rules Drive Demand, " *Chemical & Engineering News,* Mar. 26, 1990, pp. 17-34.

61 However, for most biopolymers, the presumption that they pose little risk to human health and the environment has yet to be conclusively proven.

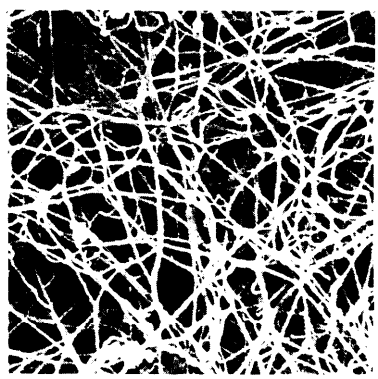
62 Polyamino acids such as the polyaspartates show considerable promise as water treatment additives. Biodegradable polyaspartate compounds could be used to replace petroleum-derived polymers such as polyacrylate and polyacrylamide. However, it is not known whether the use of large quantities of natural polymers will have any adverse ecological effects.

Technical Overview of Biopolymer Field 2

Biopolymers can be produced through a variety of mechanisms. They can be derived from microbial systems, extracted from higher organisms such as plants, or synthesized chemically from basic biological building blocks. A wide range of emerging applications rely on all three of these production techniques. Biopolymers are being developed for use as medical materials, packaging, cosmetics, food additives, clothing fabrics, water treatment chemicals, industrial plastics, absorbents, biosensors, and even data storage elements. This chapter identifies the possible commercial applications and describes the various methods of production of some of the more promising materials. Table 2-1 provides a partial list of the biopolymers now in use. [1]

SELECTED POLYMERS PRODUCED BY MICROBIAL SYSTEMS

In recent years, considerable attention has been given to biopolymers produced by microbes. It is on the microbial level where the tools of genetic engineering can be most readily applied. A number of novel materials are now being developed or introduced into the market. In the following sections, three



[1] A comprehensive treatment of biopolymer compounds is beyond the scope of this Background Paper. The categories of biopolymers described here are designed to illustrate the diverse physical characteristics and the broad application range of these materials. For a more detailed discussion of biopolymers, see David Byrom (cd.), *Biomaterials: Novel Materials from Biological Sources (New* York, NY: Stockton Press, 199 1); Roger Rowell, Tor Schultz, and Ramani Narayan (eds.), *Emerging Technologies for Materials and Chemicals from Biomass* (Washington, DC: American Chemical Society, 1992); David Kaplan et al., ''Nahmally Occurring Biodegradable Polymers,' G. Swift and R. Narayan (eds.), *Polymer Systems—Synthesis and Utility (New* York, NY: Hanser Publishing, forthcoming 1994).

Table 2-l—A Snapshot of the Biopolymer Family

Polyesters	**Polysaccharides (plant/algal)**
Polyhydroxyalka noates	**Starch (amylose/amylopectin)**
Polylactic acid	**Cellulose**
Proteins	**Agar**
Silks	**Alginate**
Collagen/gelatin	**Carrageenan**
Elastin	**Pectin**
Resilin	**Konjac**
Adhesives	**Various gums (e.g., guar)**
Polyamino acids	**Polysaccharides (animal)**
Soy, zein, wheat gluten, casein,	Chitin/chitosan
Serum albumin	Hyaluronic acid
Polysaccharides (bacterial)	Lipids/s urfactants
Xanthan	Acetoglycerides, waxes, surfactants
Dextran	Emulsan
Gellan	Polyphenols
Levan	Lignin
Curd lan	Tannin
Polygalactosamine	Humic acid
Cellulose (bacterial)	Specialty polymers
Polysaccharides (fungal)	Shellac
Pullulan	Poly-gamma-glutamic acid
Elsinan	Natural rubber
Yeast glucans	Synthetic polymers from natural fats and oils (e.g., nylon from castor oil)

SOURCE David L Kaplan et al , "Naturally Occurring Biodegradable Polymers," G Swift and R Narayan (eds), ***Po/ymer .Systems-Synthesis*** and ***Utility (New*** York, NY Hanser Publishing, forthcoming 1994)

different classes of microbially derived biopolymers are profiled: polyesters, proteins, and polysaccharides.

Microbial Polyesters: Polyhydroxyalka noates

Much of the current interest in biopolymers stems from the growing concern about the environmental impacts of synthetically produced materials. In particular, the highly publicized disposal problem of traditional oil-based thermoplastics has promoted the search for biodegradable alternatives (about 17 billion pounds of thermoplastic packaging material was produced in the United States in 1991). Apart from the agriculturally derived biopolymers (e.g., starch) being investigated for their biodegradable properties, there is a class of natural thermoplastic materials that is drawing much attention. Polyhydroxyalkanoates (PHAs) area family of microbial energy reserve **materials that accumulate as granules** within the cytoplasm of cells. They are genuine polyester thermoplastics with properties similar to oil-derived polymers (melting temperatures between 50 to 180"C). Their mechanical characteristics can be tailored to resemble elastic rubber or hard crystalline plastic.[3] The prototype of this family, polyhydroxybutyrate (PHB), was frost discovered in 1927 at the Pasteur Institute in Paris. Commercialization of PHB was first attempted by W.R. Grace Co. in the 1950s. More recently, a British company, Zeneca Bio Products (formerly ICI Bio Products), initiated commercial production of a series of PHA copolymers under the trade name BIOPOL™. Several companies and government research organizations, particularly in Europe and Japan, have active research and development (R&D) programs focusing on these materials.

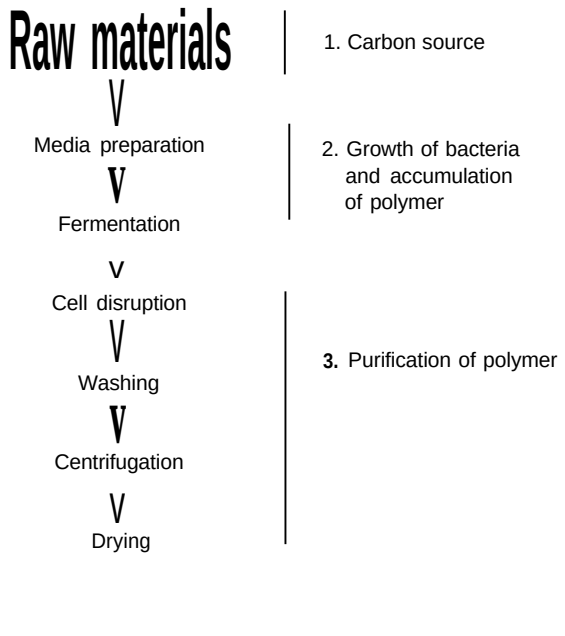
2 Thermoplastics are polymers that will repeatedly soften when heated and harden when cooled.

3 y. Doi, ''~crobiat synthesis and Properties of Polyhydroxyalkanoates, *Materials Research Bulletin,* vol. 17, No. 11, November 1992, pp. 39-42.

Production of PHAs is carried out through fermentation. The general process is illustrated in figure 2-1. In their final stages of preparation, they can be processed by standard extrusion and molding techniques. Careful control of the carbon sources (starting materials) and the choice of production organism enables the production of an entire family of PHA copolymers with different properties. The PHB homopolymer is produced by a variety of bacteria that use it as a source of carbon and energy. The homopolymer is a brittle material that is difficult to use and is thermally unstable. However, by combining polyhydroxyvalerate (PHV) with PHB, a nonbrittle copolymer—polyhydroxybutyrate-polyhydroxyvalerate (PHBV)--can be created.[4] Other PHA copolymers have also been produced.[5] Currently, Zeneca's production of PHBV (BIOPOL) uses the bacterium *Alcaligenes eutrophus,* which occurs widely in soil and water. PHBV is formed when the bacterium is fed a precise combination of glucose and propionic acid.[6] It has properties similar to polypropylene and polyethylene, including excellent flexibility and toughness. The discovery and development of PHBV and other PHA copolymers have proven to be a major step forward in expanding the potential industrial utility of the PHAs.

PHAs biodegrade in rnicrobially active environments. Since PHAs function as an intracellular energy and carbon source, bacteria can degrade PHAs and use them as reserve materials. Microorganisms attack PHBV by secreting enzymes (depolymerases) that break down the polymer into its basic hydroxybutyrate (HB) and hy - droxyvalerate (HV) constituents. The HB and HV fragments are then consumed by the cells to sustain growth. Under aerobic conditions, the final biodegradation products are water and carbon dioxide; under anaerobic conditions, methane is produced as well. The degradation of PHBV can be quite rapid in biologically active systems (see figure 2-2).[7] A range of soil microor-

Figure 2-I—PHA Polymer Production Process



SOURCE: BioInformation Associates, Boston, MA.

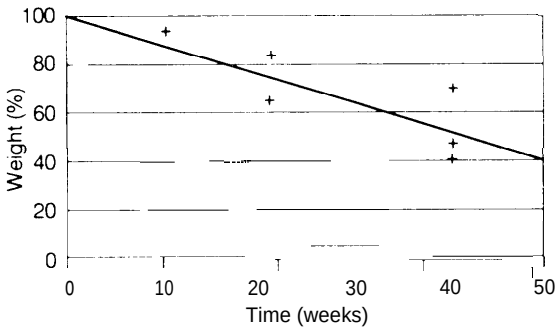
4 William D. Luzier, ' 'Materials Derived from Biomass/Biodegradable Materials,' National Academy of Sciences, vol. 89, February 1992, pp. 839-842.

[5] For example, researchers at the Tokyo Institute of Technology have produced a versatile PHA copolymer of 3-hydroxybutyrate and 4-hydroxybutyrate. This material has been extracted and fermented from the bacterium *Alcaligenes eutrophus* under starvation conditions. By altering the ratio of the copolymers, the elasticity and strength of the material can be varied (Doi, op. cit., footnote 3).

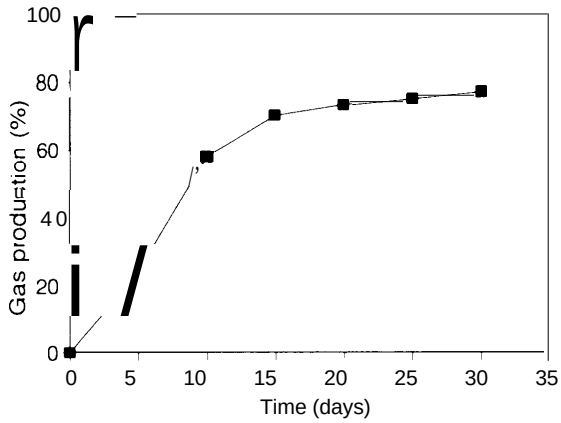
6 Glucose is derived from agricultural feedstocks such as sugar beets and cereal crops, whereas propionic acid can be produced from petroleum derivatives or by fermentation of wood pulp waste.

[7] When 50 bottles made of PHBV material were inserted into a compost heap (6 cubic meters of organic waste) for a period of 15 weeks, at temperatures between 60 and 70"C, only about 20 percent (by weight) of the PHBV material remained. It is important to note, however, that PHBV and other biopolymers will not degrade in sanitary landfills, because they are essentially biologically inactive systems. See Petra Püchner and Wolf-Rüdiger Müller, "Aspects on Biodegradation of PHA," H.G. Schlegel and A. Steinbüchl (eds.), *Proceedings International Symposium on Bacterial Polyhydroxyalkanoates 1992* (Göttingen: Goltze-Druck, 1993).

Figure 2-2—Biodegradation of PHBV Polymers



Degradation of PHBV landfill simulation



Anaerobic degradation of PHBV 27% **copolymer**

PHBV **can degrade relatively** quickly **in biologically active systems. in a simulated landfill environment with an elevated moisture content, PHBV showed a 40-percent weight loss In 40 weeks (left). Under anaerobic sewage conditions, where biodegradability is measured by gas production, the PHBV polymer decomposed nearly 80 percent in 30 days (right). Other data indicates that PHBV readily degrades under aerobic conditions.**

SOURCES: Petra Pochner and Wolf-Rudiger Muller, "Aspects on Biodegradation of PHA," H.G. Schlegel **and** A. Steinbüchl (eds.), *Proceedings International Symposium on Bacterial Polyhydroxyalkanoates 7992* (Göttingen, Goltze-Druck: 1993); William D. Luzier, "Materials Derived from Biomass/Biodegradable Materials," *Proceedings National Academy of Sciences, vol. 89,* February 1992, pp. 839-842.

ganisms, both bacterial and fungal, can utilize PHAs as a source of carbon and energy.

CURRENT AND POTENTIAL APPLICATIONS

PHAs have many possible uses. The inherent biocompatibility[8] of these bacterial materials suggests several medical applications: controlled drug release, surgical sutures, bone plates, and wound care. PHAs could also be used as structural materials in personal hygiene products and packaging applications. At present, higher-volume commodity plastic applications are limited because of economic constraints. PHBV, for example, costs $8 to 9 per pound. However, costs have fallen from about $800 per pound in 1980, and it is believed that the price of PHBV can be brought to around $4 per pound by 1995. (Petroleum-based polyethylene and polypropylene polymers cost about 50 cents per pound.) PHBV is now being used in a variety of molding applications in the personal care sector (e.g., biodegradable cosmetic containers-a market where the cost of the container is almost negligible in relation to the cost of the contents). In addition, Zeneca is in the process of commercializing films and paper coatings from BIOPOL resin. Mitsubishi Kasei (Japan) is actively involved in the development of PHAs for use as a biodegradable replacement of monofilament fishing nets. Because of the desirable environmental characteristics of PHAs, the number of such niche markets is likely to multiply.

Over the past 5 years, there has been a substantial increase in the number of publications dealing with the biosynthesis, fermentation, and characterization of the PHA family of biopoly - mers. It soon may be possible for these polymers to compete as specialty plastic products. The ability to genetically engineer the different spe-

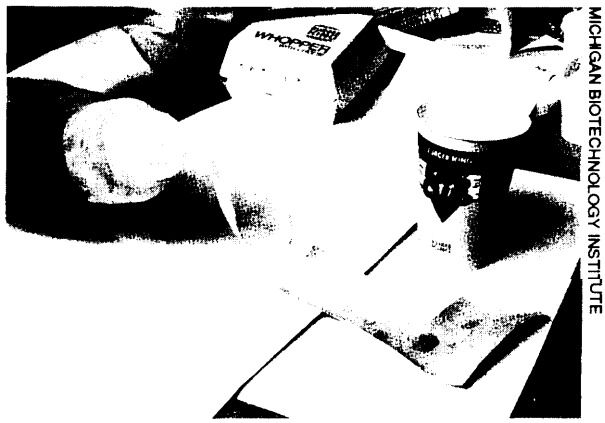
[8]The final degradation product of one type of PHB is a normal constituent of human blood.

cies of bacteria used to produce PHAs (e.g., by modifying the enzymes inside the bacteria) could result in the creation of highly customized polymers. Researchers have made significant progress in unraveling the biosynthetic pathways involved in the production of PHAs. The genes encoding the enzymes involved in PHA production have been isolated and cloned, and thus scientists can now tailor the biosynthesis process to produce polymers with different properties. Over the long term, there is the possibility that these materials can be made economically in plant species.[9]

Recently, PHB was successfully synthesized by using a genetically engineered experimental plant *(Arabidopsis thaliana).*[10] Researchers are now exploring how to produce PHAs by modifying the enzyme machinery of corn or potatoes.[11] Although significant technical challenges remain, the PHA family could potentially become a major agricultural commodity, either as a fermentation product using raw materials (e.g., glucose) from the starch industry or, in the longer term, as a new crop.

Recombinant Protein Polymers

Proteins are polymers composed of amino acids. The specific amino acids used and the sequence of amino acids in a protein polymer chain are determined by the corresponding DNA template. Many proteins are of commercial interest because of their catalytic (enzymatic) or pharmaceutical properties. However, nature has also provided a vast array of proteins whose principal function is to form structural materials in living organisms. Some of the more familiar protein materials include wool, leather, silk, and gelatin (jello is a simple, modified form of the protein collagen[12]). Although many of these structural proteins have been used throughout history, the advances in recombinant DNA technology have presented new approaches and opportunities for the design and synthesis of protein materials. In addition, many traditional proteins prepared by the extraction of animal (e.g., collagen) or plant (e.g., soy or zein from corn) tissue are being chemically or physically modified for



Coatings based on corn protein (zein) have good moisture and grease barrier properties and are being used to replace polyethylene and wax-coated paper and paperboard.

9 The genetic manipulation of bacteria could also alter the economics of PHA production. However, the manufacturing costs for PHAs are determined primarily by the purification steps rather than the bacterial production steps (see figure 2-l).

10 Although early work in this area is encouraging, achieving controlled gene expression of PHB in plants is a formidable undertaking. Inserting the genes that encode the PHB-producing enzymes is relatively straightforward. However, regulating the PHB enzymes and the existing plant enzymes is a more difficult challenge. See Yves Poirier, Douglas Dennis, Karen Klomparens, and Chris Somerville, ' 'Polyhydroxybutyrate, a Biodegradable Thermoplastic, Produced in Transgenic Plants," *Science,* vol. 256, Apr. 24, 1992, pp. 520-523.

11 Robert Pool, ''In Search of the Plastic Potato, " *Science,* vol. 245, Sept. 15, 1989, pp. 1187-1189.

12 Collagen is a fibrous protein that is the principal component of animal connective tissue. It is the most abundant of all proteins found in mammals, typically accounting for more than 30 percent of body protein. The arrangement of collagen fibers depends on the nature of the tissue. For example, in tendons, fibers are arranged parallel to one another to give a structure with the tensile strength of a light steel wire. In skin, where strength and flexibility are required, collagen fibers are randomly oriented and woven together like felt.

Table 2-2—Repeat Units Found in Protein Materials

Protein	Source	Amino acid repeat unit[a]
Silk	Silk worm	GAGAGS
Collagen	Mammals	GPP[b]
Adhesin	Mussel	AKPSYPPTYK
Elastin	Pig	VPGVG
Synthetic	Chemically synthesized genes	Various

[a]There are 20 different amino acids, designated here in short form: A = alanine; G = glycine; K = lysine; P = proline; S = Serine; T = threonine; V = valine; and Y = tyrosine. For a full list of amino acid symbols, see Albert Lehninger, *Biochemistry* (New York, NY: Worth Publishers, 1975), p. 72.
[b]Often one of the prolines in collagen is hydroxyproline.

SOURCES: BioInformation Associates, Boston, MA; Office of Technology Assessment.

new applications in the biotechnology and food industries.[13] The discussion here focuses on protein polymers that are being developed by using the methods of recombinant biotechnology.

PRODUCTION OF RECOMBINANT PROTEIN POLYMERS

The extraordinary functional diversity of natural proteins underscores the potential advantages associated with harnessing the genetic code. In theory, proteins can be designed to have virtually any structure, and thus specific physical and chemical properties. The fact that one-dimensional genetic sequences can specify proteins having complex three-dimensional structures over distances of hundreds of nanometers reveals the power of nature's material synthesis processes. Current chemical synthesis techniques are essentially limited to creating polymers in one dimension only,[14] with lengths of less than 10 nanometers .15

A number of proteins that form important structural materials in various organisms have been studied extensively. The fibrous proteins such as collagen and silk have been the subject of considerable attention. More specialized proteins, such as the adhesive material that bonds the sea mussel to the ocean bed and proteins that contribute to the formation of 'ceramic-like' materials (e.g., oyster shells and teeth), are also being actively studied. A common feature of many of these proteins is the presence of repeated amino acid sequences in the polymer product (see table 2-2). These proteins, or specific regions of these proteins, have structural features similar to block copolymers (see figure l-l).

Some of the structural proteins have been chemically synthesized. In this approach, specific peptides (sequences of amino acids) are created and then linked together to form a polypeptide (the protein polymer). However, chemical synthesis of proteins can be quite expensive[y] and

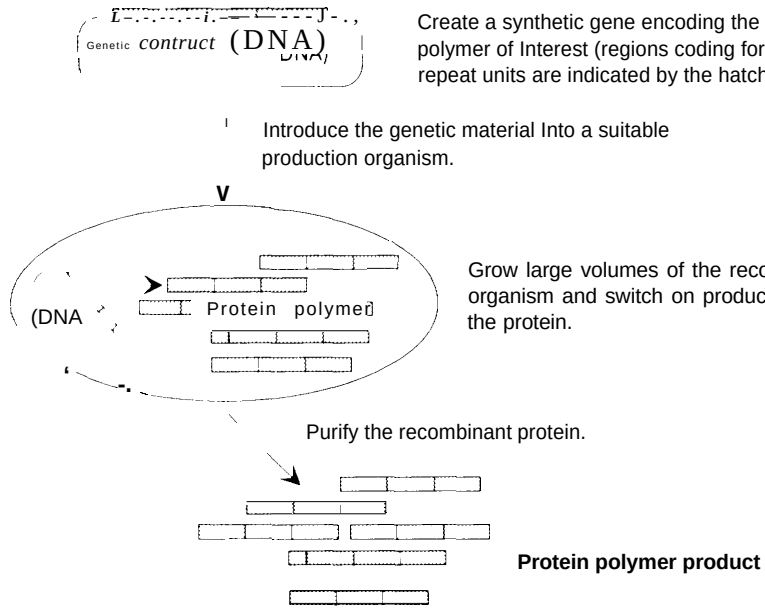
13 Soy and corn proteins are used primarily as coatings for paper and paperboard. Soy paper coatings impart a smoother surface and improve surface appearance. Zein has excellent grease and moisture barrier properties. Soy proteins are also being used as structuring agents in water-based inks, because they are regarded as environmentally preferable to solvent-based inks. See Thomas L. Krinski, "Emerging Polymeric Materials Based on Soy Protein," Rowell et al. (eds.), op. cit., footnote 1.

14 There have been some advances recently in the synthesis of two-dimensional synthetic polymers. However, this work is still somewhat preliminary. See *Scientific American,* "Flat Chemistry," April 1993, p, 26.

15 See Joseph Cappello, "Genetic Production of Synthetic Protein Polymers," Materials *Research Bulletin,* October 1992, pp. 4S-53.

16 In a few cases, though, some firms have been able to develop relatively inexpensive approaches for synthesizing complex polypeptides. For example, Monsanto developed commercial chemical methods for making somatotropin, a complicated polypeptide, for about $15 per pound.

Figure 2-3—Production of Recombinant Protein Polymers



SOURCE: BioInformation Associates, Boston, MA.

typically does not yield products with sufficient physical and chemical uniformity.

In contrast, the recombinant DNA approach allows for the production of protein polymers that have high purity, specific molecular weights, and excellent lot-to-lot uniformity. This is possible because the exact sequence of amino acids in the polymer and the desired molecular weight are specified by the DNA sequence of the gene. In the long term, recombinant DNA technology could become an important strategy for producing high-value, ‘‘knowledge-intensive’ materials that are custom-designed for specific applications. The steps involved in producing recombinant proteins are illustrated in figure 2-3, Currently, all of the proteins shown in table 2-2 are being produced or investigated by using recombinant DNA techniques. The fact that it is now possible to chemically synthesize genes encoding any repeat unit suggests almost limitless possibilities for creating novel protein polymers with unique physical and functional properties. Although researchers are addressing major technical problems such as genetic instability, toxicity in foreign hosts, and metabolic incompatibility, considerable progress in genetically engineered protein synthesis has occurred in recent years.[17] Initial work in the synthesis of artificial genes has led to the creation of proteins that could be used as coatings and adhesives, membrane separators, and medical and optical materials.[18]

17Because foreign DNA imposes a metabolic burden on host cells, in some cases these DNA segments can be destroyed. In particular, the highly repetitive gene sequences that are necessary to create artificial protein polymers are frequently unstable in microorganisms. In addition, novel proteins that are encoded by synthetic genes maybe toxic to the host cells, thus causing cell death before the polymer can be accumulated in useful quantities. See David A. Tirrell et al., ‘ ‘Genetic Engineering of Polymeric Materials, ’ *Materials Research Bulletin,* July 1991, pp. 23-28; see also Joseph Cappello, op. cit., footnote 15.

18See *R&D Magazine,* ‘‘Bioderived Materials, ” June 1990, pp. 58-64.



The marine mussel, Mytilus edulis, is shown suspended in water by threads attached with adhesive to a glass plate. Biotechnology research on adhesives produced by rnarine organisms is leading to new adhesives that can be used for many applications such as surgery and undersea structures.

CURRENT AND POTENTIAL APPLICATIONS

More than 25 genetically tailored proteins have been synthesized in microorganisms. Many of these materials are being transformed into films, gels, and fibers. One of the first genetically engineered protein polymers to be introduced commercially, ProNectin F[TM,19] was designed to serve as an adhesive coating in cell culture vessels. The polymer was customized to have two distinct peptide blocks: one block possesses the strong structural attributes of silk; the other has the cell-binding properties of the human protein fibronectin.[20] The peptide blocks were chosen after analyzing which particular structures could provide the desired physical, chemical, and biological properties. ProNectin F has demonstrated excellent adhesion to plastic surfaces such as polystyrene and thus can be used to attach mammalian cells to synthetic substrates.[21]

A similar application of recombinant DNA technology has led to the development of a bioadhesive based on a protein from the sea mussel Mytilus *edulus.*[22] *Researchers* **have genet-***ically* modified yeast cells to produce the basic mussel protein. An enzyme-catalyzed process (the enzyme-a tyrosinase-modifies the tyrosine amino acids in the protein) was also developed to convert this recombinant protein into a true adhesive.[23] This polymer could be used as a marine coating, as a wetting agent for fibers in composite materials, or as a dental or surgical adhesive.[24] For example, it might be employed as a sealant during eye surgery .25

A number of other protein polymers are being investigated by using biotechnology methods. One intriguing new material is a polypeptide based on the natural protein elastin found in cows

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19 The protein is produced by Protein Polymer Technologies, Inc., San Diego, CA.

20 Cappello, op. cit., footnote 15.

21 With certain types of cells, ProNectin F displayed adhesive characteristics superior to that of natural attachment proteins including fibronectin. Ibid.

22 Enzon Corp. (formerly Genex Corp.) developed the genetically designed adhesive under the name AdheraCell. See *Chemical and Engineering News,* "Biotechnology Providing Springboard to New Functional Materials," July 16, 1990, pp. 26-32.

23 This enzyme-catalyzed procedure is known as "post-translational" modification. The sea mussel performs this modification after protein biosynthesis.

24 *Chemical and Engineering* News, op. Cit., footnote 22.

25 *R&D* Magazine, op. cit., footnote 18.

and pigs.[26] This rubberlike material responds to changes in temperature and is able to convert chemical energy into mechanical energy .27 As a consequence, the material could be used as a replacement for ligament tissue, blood vessels, or any other tissues requiring the contractile properties of elastin.[28] Because the peptide is similar in composition to natural elastin, the polymer is not expected to elicit an allergic reaction or unfavorable immune system response.

Another interesting material is the light-sensitive protein bacteriorhodopsin (BR). BR is a retinal protein consisting of 248 amino acids. When subjected to photons (light) of varying energy intensity, BR undergoes reversible color changes. Through substitution of specific amino acids by genetic engineering, the photochemical properties of BR can be precisely modified, which means color changes can be carefully controlled. The unique properties of BR could lead to applications in optical data storage, image processing, light switching (computational processing), and holography. Some initial work indicates that the optical performance of BR is comparable to conventional materials such as liquid crystals.[29]

Recombinant biotechnology is also being used to modify materials that have been utilized for thousands of years. Silk has always been a material of great fascination. Spiders can process silk protein into a material that has a tensile strength 16 times greater than that of nylon[30] and a very high degree of elasticity .31 Researchers have manipulated the genetic code to create silklike materials with a variety of elasticities.[32] Because of their exceptional tensile strength and elastic properties, these polymers could be used as fibers for reinforced plastics and other advanced composite materials. In the medical area, the polymers could potentially be used as wound dressings, artificial ligaments, and skin or as a biocompatible coating for prosthetic devices. However, the yields of genetically modified silk polymers from microorganisms have thus far been fairly 1ow.[33]

Most protein polymer research is focused on high-technology applications, such as elastomers, adhesives, bioceramics, and electro-optical materials. To date, commercial applications have been limited to the use of genetically engineered adhesives for fixing mammalian cells to culture vessels. Because of extremely high production costs, these products will probably have limited

24 Elastin fibers are elastic, load-bearing protein polymers found in connective tissue such as ligaments. Another protein similar to elastin is resilin, a rubberlike polymer found in insects.

27 See *Science*, "Heeding the Call of the Wild," vol. 253, Aug. 30, 1991, pp. %5-%8.

28 *R&D* Magazine, op. cit., footnote 18.

29 See N. Hampp, C. Brauchle, and D. Oesterhelt, "Mutated Bacteriorhodopsins: Competitive Materials for Optical Information Processing?" *Materials Research Bulletin*, vol. 17, No. 11, November 1992, pp. 56-60.

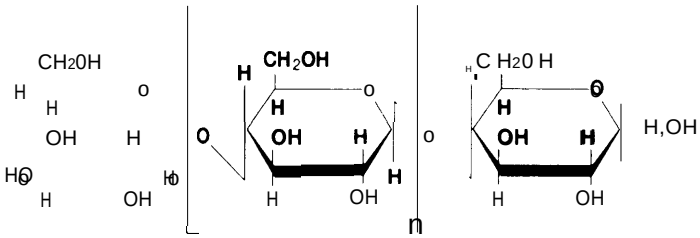
30 Silkworm silk is about two to three times stronger than nylon.

31 Spider dragline silk not only possesses great strength, but also has the ability to "supercontract." Silk fiber will contract to less than 60 percent of its original length when wet, This results in a nearly thousandfold decrease in the elastic modulus and an enhanced ability to extend when necessary. This property allows the spider web to tighten each day when wetted with dew, while still maintaining its shape and tension. Although some human-made materials can sup-contract in organic solvents, no synthetic materials can supercontract-as spider silk does-in water alone. The web is constructed of several different silks, each of which is produced in a different spider gland. Some of the silk fibers contain a number of water-soluble compounds that keep the fibers wetted, allowing them to stretch and entangle prey that hit the web. See Randolf V. Lewis, "Spider Silk: The Unraveling of a Mystery," *Accounts of Chemical Research*, vol. 25, No. 9, 1992, pp. 392-398.

32 Protein Polymer Technologies, Inc. has produced recombinant polymers based on silkworm silk. The company has developed an artificial silk gene that appears to be stable in host *Escherichia coli* cells. However, the stability of cloned silk genes in host systems still remains a significant problem *(R&D Magazine*, op. cit., footnote 18; *Chemical and Engineering News*, op. cit., footnote 22. Also see David L. Kaplan et al., "Biosynthesis and Processing of Silk Proteins," *Materials Research Bulletin*, October 1992, pp. 41-47.

33 Lewis, op. cit., footnote 31.

Figure 2-&The Structure of Cellulose



The cellulose molecule is composed of glucose units connected by B(1-4) bonds (see Figure 1 -3). Starch has an identical chemical composition to cellulose except for its connecting bonds-a(l -4). The different linkages in starch molecules endow them with a greater water volubility than cellulose. In humans, starch can be digested while cellulose cannot be digested.

SOURCE: Office of Technology Assessment, 1993.

success (e.g., experimental quantities of the genetically derived sea mussel adhesive were at one time selling for about $45 per milligram, or $20 million per pound). However, over the long term, genetic techniques may allow production to be scaled up significantly at reasonable cost. Once programmed with the proper genetic instructions, bacterial cells can work in parallel by the billions to produce polymer materials.[34] Although some biotechnology companies have been involved in protein polymer research for 10 years, most recombinant protein materials are still in early stages of development.

Nevertheless, this area of research is one of the most active and better funded in the biopolymer field. In addition to providing new materials, genetic engineering is now enabling scientists to study how biological systems transform proteins into final products. It is remarkable that living organisms are able to produce sophisticated materials under mild processing conditions (i.e., low temperature and pressure in water-based environments), without creating toxic byproducts. This is certainly not the case for a variety of human-made materials.[35] Spiders and silkworms, for example, can transform water-soluble protein droplets into globally aligned insoluble fibers.[36] The fibers are spun with very little energy consumption. Thus, protein polymer research could also lead to the development of radically new industrial processing methods that pose little threat to the environment.

The Microbial Polysaccharides

BACTERIAL CELLULOSE

Cellulose is the most abundant component of biomass and the basic feedstock of the paper and pulp industries. Traditionally extracted from plant tissue (trees, cotton, etc.), cellulose can also be produced by certain bacterial species by fermentation, yielding a very pure cellulose product with unique properties.

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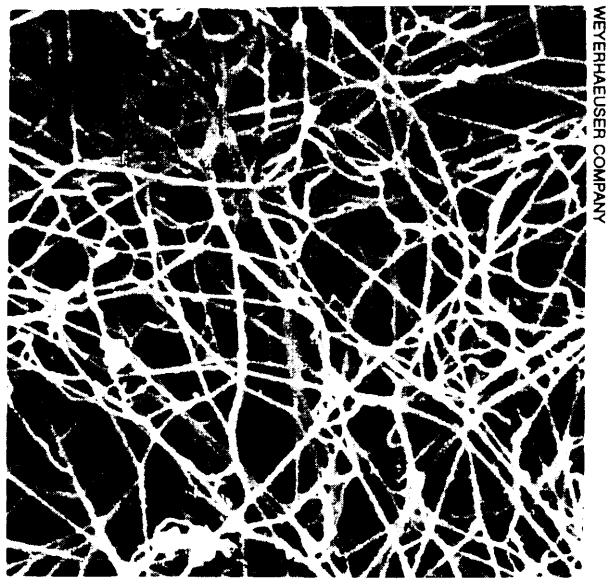
34 *Science*, op. cit., footnote 27.

35 Many advanced materials are synthesized at extremely high temperature and pressure, and require toxic substances at various stages of processing. See U.S. Congress, Office of Technology Assessment, *Advanced Materials by* Design, OTA-E-351 (Washington, DC: U.S. Government Printing Office, June 1988).

36 Silk fibers are pulled from spiders, not forced out by pressure. The fibers are formed as they travel down a tubular duct kid@ from the gland to the exit valve. The key chemical and physical events that change the soluble proteins into solid fibers occur during this journey. As the protein molecules travel down the duct, they align themselves into regular arrays. It appears that the mechanical and frictional forces at work in the duct facilitate the transformation of the soluble protein droplets into solid fibers. See Lewis, op. cit., footnote31; Kaplan, op. cit., footnote 32.

Cellulose is a polysaccharide consisting of linear glucose chains (see figure 2-4). Bacterial cellulose is synthesized in a process whereby the polymer material is extruded from the bacterial cells. Most cellulose-producing bacteria (e.g., *Acefobacter)* extrude cellulose as a ribbonlike product from a single fixed site on the cell surface. This results in the formation of a network of interlocking fibers.

Bacterial cellulose is produced under conditions of agitated fermentation. High polymer production rates occur when the growth medium contains glucose, salts, corn steep liquor, iron chelators, and various productivity enhancers. Current yields are more than 0.2 gram of cellulose per gram of glucose, and production has been demonstrated in commercial 50,000-gallon fermenters. After fermentation, the bacterial cells are destroyed during a hot caustic treatment. Bacterial cellulose is a water-insoluble material that has a very large surface area because of its large network of fibers, Bacterial fibers have roughly 200 times the surface area of fibers from wood pulp.[37] This, coupled with their ability to form hydrogen bonds, accounts for their unique interactions with water. Bacterially derived cellulose materials can absorb up to six times their weight of water, and when used as suspensions, they have pseudoplastic thickening properties. Sheets prepared from bacterial cellulose have excellent mechanical properties.



Cellulon® engineered bacterial cellulose fiber is a product under development at Weyerhaeuser Company. The unique reticulated network of fine fibers gives the biopolymer its thickening, binding, and coating properties. The fibers have a typical diameter of 0.1 microns (0.1 millionth of a meter), while some wood pulp fibers have a diameter of 25 to 35 microns.

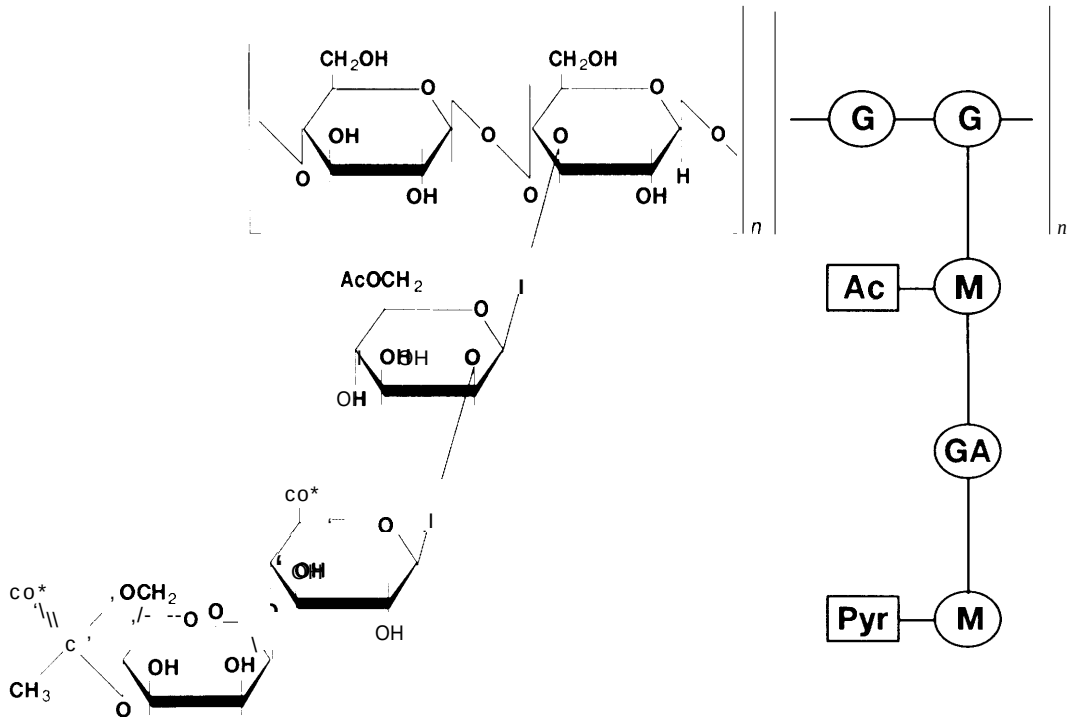
CURRENT AND POTENTIAL APPLICATIONS

Considerable progress has been made in the field of bacterial cellulose synthesis in the past few years. Bacterial cellulose is now available in limited quantities from Weyerhaeuser in the United States and Ajinomoto in Japan. The most prevalent applications of bacterial cellulose exploit its very large surface area and its ability to absorb liquids. Consequently, very low concentrations of bacterial cellulose can be used to create excellent binding, thickening, and coating agents. Because of its thickening properties, many applications in the food industry are possible. Paper that is coated with bacterial cellulose is extremely smooth and protects the underlying fibers from moisture. End uses in oil and gas recovery, mining, paints, adhesives, and cosmetics are also envisioned. This material is currently used by Sony Corporation in the production of high-end audio speaker systems because of its excellent acoustic properties.[38] In the last 10 years, at least

37 Weyerhaeuser's bacterial cellulose fibers (the product is called Cellulon) have a typical diameter of 0.1 microns as opposed to some wood pulp fibers that are 25 to 35 microns across. The small fiber diameter results in an extraordinarily high surface area and is responsible for much of the fiber's functionality as a thickener and binder. A. Robert Winslow, Cellulon Fiber Business Marketing Manager, Weyerhaeuser Company, personal communication, Aug. 31, 1993.

38 The high-fidelity headphones employ bacterial cellulose as diaphragms. The headphones retail fOr about $4,000 a set.

Figure 2-&The Structure of Xanthan Gum



The Xanthan gum repeat unit is made of 5 sugar groups: two glucose (G) groups, two mannose (M) groups, and one gluouronic acid (GA) unit. Pyruvate (Pyr) and acetyl (Ac) units are also present in the mannose structures. The degree of pyruvate and acetate substitution varies with the specific fermentation conditions. The charged pyruvate molecule alters xanthan's electrical properties, while the acetate serves to stabilize the conformation or spatial arrangement of xanthan.

SOURCE: BioInformation Associates, Inc.., Boston, **MA.**

50 patents on the production and applications of bacterial cellulose have been filed. Currently, bacterial cellulose sells from $35 to $50 per pound. If the material is to be used in commodity as opposed to niche applications, production costs will have to drop. A Japanese consortium was recently formed to reduce the manufacturing costs of bacterial cellulose.[39]

XANTHAN

Xanthan gum, a complex copolymer produced by a bacterium, was one of the first commercially successful bacterial polysaccharides to be produced by fermentation. The xanthan polymer building blocks or "repeat units" contain five different sugar groups (see figure 2-5). The xanthan-producing bacterium, *Xanthomonas campestris,* is one of the frost bacterial polysaccharide

[39] The commercial venture in bacterial cellulose technology is supported financially by the Japan Key Technology Center, a joint organization under the Ministry of International Trade and Industry and the Ministry of Post and Telecommunications, along with 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).

production systems targeted for genetic engineering. Under certain conditions, genetic modification of *Xanthomonas* by using recombinant DNA technology has increased the rate of xanthan production by more than 50 percent.[40] In the future, recombinant DNA technology may enable entirely new xanthan biosynthetic pathways to be created in host organisms.

Xanthan gum is produced by large-scale fermentation of X. *campestris* using a number of different feedstocks including molasses and corn syrup. The gum is extruded from the bacteria during the polymerization process and can be recovered by alcohol precipitation following removal of the bacterial cells. For some applications such as enhanced oil recovery, the crude culture broth can be used directly following sterilization. Probably the most significant technical problem in the production of xanthan is the fact that as the polymer is produced, the fermentation medium becomes increasingly viscous. This increases the energy required for the mixing process that feeds oxygen to the bacterial cells.

CURRENT AND POTENTIAL APPLICATIONS

The unusual physical and mechanical properties of xanthan gum make it an attractive polymer for industrial and biological use. It is used extensively in both the food and the nonfood industries. Examples of industrial applications include oil recovery (provides viscosity control in drilling mud fluids), mineral ore processing (used as a biocide), paper manufacturing (used as a modifier), agriculture (acts as plant growth stimulator), pharmaceuticals (being evaluated for sustained drug release), and cosmetics (controls dust release). Food applications include gelling agents for cheese spreads, ice creams, puddings, and other deserts. More recently, xanthan has been used in the new clear-gel toothpastes. Reading the labels on many of the processed foods in the supermarket should give one a clear picture of the wide use of this material. Good examples are packet soups and many of the fat-free foods that have recently become available.

In terms of production volume, xanthan gum is the most widely used microbial polysaccharide. Worldwide production is currently in the range of 10,000 to 20,000 tons. Companies such as ADM and Merck have recently announced the expansion of their xanthan production facilities. About 60 percent of the xanthan produced is used in foods, with the remaining 40 percent used in industrial applications. Food-grade xanthan costs about $8 to $10 per pound, while non-food grades sell for about $5 per pound. Thus far, only experimental samples of genetically modified xanthan have been produced.[41]

DEXTRANS

Dextran is the generic name of a large family of microbial polysaccharides that are assembled or polymerized outside the cell by enzymes called dextran sucrases. This class of polysaccharides is composed of building blocks (monomers) of the simple sugar glucose and is stored as fuel in yeasts and bacteria. Dextrans are produced by fermentation or enzymatic conversion of the feedstock sucrose, a product of the sugar beet and sugarcane industries. Most commercial dextran

40 See T.J. Pollack and J. Thorne, Syntro Corp., "Enhanced Manufacture of Xanthan Gum with Genetically Modified *Xanthomonas*," European Patent Application EP 287,367. CA: 9358z; and M. Yalpani, *Polysaccharide Synthesis, Modification, and Structure/Property Relations, Studies in Organic Chemistry 36* (Amsterdam: Elsevier, 1988).

41 Two small biotechnology companies, Syntro (San Diego, CA) and Synergen (Boulder, CO), worked on genetically engineered xanthan gums in the 1980s. Neither fii was successful in marketing these xanthan products because their manufacturing costs were much higher than conventional xanthan production methods. The relatively high production costs of genetically modified polymers is a major problem that could seriously constrain biopolymer commercialization efforts. "Conventioml wisdom' holds that biopolymer production costs must fall below $20 per pound for most niche market applications, and below $5 per pound for more general applications. Because of these manufacturing hurdles, some producers of genetically derived biopolymer compounds are focusing on low-volume, high value-added applications such as medical materials or specialized industrial adhesives. David Manyak, President, Adheron Corporation personal communication Aug. 24, 1993.

production uses the microorganism *Leuconstoc mesenteroides.* Dextran can be synthesized by using either large-scale industrial fermentors or enzymatic filtration methods. The latter approach is generally favored since it results in an enhanced dextran yield and a uniform product quality, which allows the product to be readily purified. Both of these production methods permit system conditions to be adjusted so as to control the molecular weight range of the products. This feature is an integral requirement for polysaccharide biosynthesis.

CURRENT AND POTENTIAL APPLICATIONS

Dextran polymers have a number of medical applications. Dextrans have been used for wound coverings, in surgical sutures, as blood volume expanders, to improve blood flow in capillaries in the treatment of vascular occlusion, and in the treatment of iron deficiency anemia in both humans and animals. Dextran-hemoglobin compounds may be used as blood substitutes that have oxygen delivery potential and can also function as plasma expanders. Chemically modified dextrans such as dextran sulfate have both antiulcer and anticoagulant properties. Other modified dextrans such as Sephadex@ are used extensively in the separation of biological compounds.

In the industrial area, dextrans are being incorporated into x-ray and other photographic emulsions. This results in the more economical usage of silver compounds and at the same time reduces surface gloss on photographic positives. Dextrans are used extensively in oil drilling muds to improve the ease and efficiency of oil recovery. They also have potential use in agriculture as seed dressings and soil conditioners. The protective polysaccharide coatings are found to improve germination efficiencies under suboptimal conditions.

Although many applications have been proposed for dextrans, only a small number of these have been realized and developed on a large scale. There is considerable potential for using low-molecular-weight dextrans in the biomedical industry in surgery and drug delivery systems. However, low-molecular-weight dextrans sell for about $80 per pound. As new and higher-volume applications for these materials are developed, large-scale production of dextrans may represent a major new market for the sugarcane and sugar beet industries.

PULLULAN

Pullulan is a water-soluble polysaccharide produced outside the cell by several species of yeast, most notably *Aureobasidium pullulans. Pullulan* is a linear polymer made up of monomers that contain three glucose sugars linked together (see figure 2-6).

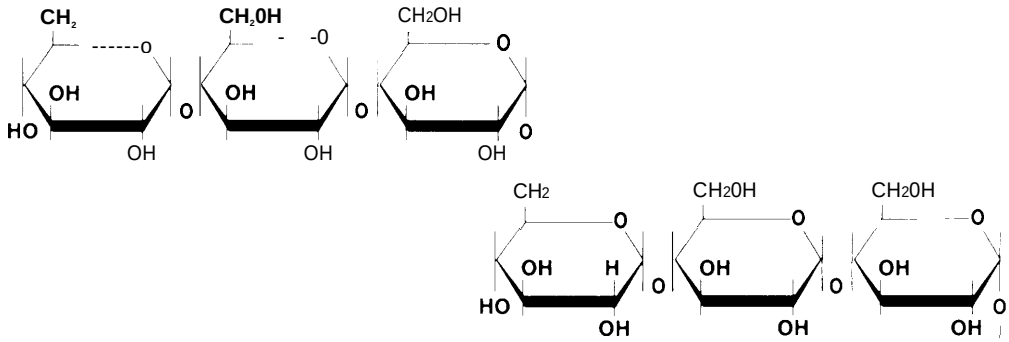
For more than a decade, a Japanese firm, Hayashibara Biochemical Laboratories, has used a simple fermentation process to produce pullulan. A number of feedstocks are used for this process, including waste streams containing simple sugars. Pullulan can be chemically modified to produce a polymer that is either less soluble or completely insoluble in water. The thermal and ionic (electrical) properties of pullulans can also be altered.

CURRENT AND POTENTIAL APPLICATIONS

Pullulan and its derivatives have a number of useful properties and consequently have many possible applications. Hayashibara Biochemical Laboratories currently sells three different pullulan grades: industrial grade ($6.50 per pound), food grade ($11 per pound), and medical grade ($15 per pound). Current efforts to increase the yields of pullulan from the fermentation of various strains of *A. pullulans* suggest lower production costs are likely in the future. Pullulan compounds are biodegradable in biologically active environments, have high heat resistance, and display a wide range of elasticities and solubilities. This versatility allows them to be utilized in many different ways.

Pullulan has many uses as an industrial plastic. It can be formed into compression moldings that resemble polystyrene or polyvinyl chloride in

Figure 2-6-The Structure of Pullulan



Pullulan is **made up of glucose sugars linked together in groups of three. The three member repeat units are connected together in a branched fashion.**

SOURCE: Office of Technology Assessment, 1993.

transparency, gloss, hardness, strength, and toughness, but is far more elastic. It decomposes above 200'C, apparently without the formation of toxic gases.[42]

A completely different application of pullulan can be found in the food industry. It can be used as a food additive, providing bulk and texture. It is tasteless, odorless, and nontoxic. It does not break down in the presence of naturally occurring digestive enzymes and therefore has no caloric content. Consequently, it can be used as a food additive in low-calorie foods and drinks, in place of starch or other fillers. In addition, pullulan inhibits fungal growth and has good moisture retention, and thus can be used as a preservative.

Pullulan can also be used as a water-soluble, edible film for the packaging of food products. It is transparent, impermeable to oxygen, and oil- and grease-resistant. Foods can be either immersed in a solution of pullulan or coated by a polymer spray. After the pullulan coating is dried, an airtight membrane is formed. The membrane can be used in the packaging of drugs and supplements, as well as oil-rich food products that are vulnerable to oxidation, such as nuts and fried foods. It is not necessary to remove the pullulan coating before eating or cooking. In the packaging of tobacco, pullulan enhances product longevity and retention of aroma. It also protects against oxidative degradation as well as attack by mold. Water insoluble coatings may be made by using the esterified or etherified forms of pullulan.

Ester and ether derivatives of pullulan have adhesive qualities similar to those of gum arabic. Viscosity and adhesive properties depend on the degree of polymerization. Modified pullulan can be used as a stationary paste that gelatinizes upon moistening. Fibers can be made from concentrated solutions of pullulan having high viscosity. The fibers have a gloss resembling rayon and a tensile strength similar to that of nylon fibers. Pullulan and its ester or ether derivatives can also be used as binders, in conjunction with other materials, for the production of nonwoven fabrics. With or without the addition of other vegetable pulps, it can be used to make paper that is suitable for printing and writing. Because it is

42 However, it should be noted that partial combustion of carbohydrates can produce carbon monoxide.

an antioxidant, pullulan can substitute for gum arabic in lithographic printing.

There are a plethora of other applications. Pullulan can be used as a binding agent for solid fertilizers, allowing time-released fertilization and thereby avoiding the burning of crops by controlling the release of nitrogen in the fertilizer. As a binding agent in sand molds used for metal casting, pullulan prevents the generation of dust or toxic fumes. The biopolymer can be used as a flocculating or aggregating agent for the precipitation of potash clays, uranium clays, and ferric hydroxide from slurries used in the beneficiation of mineral ores. (Currently, synthetic chemicals are primarily employed in mineral processing.) Pullulan can be used as an additive to resins and paints, where its preservative and antioxidation properties help retain color and gloss. Also, pictures or illustrations printed on pullulan film with edible ink can be transferred onto food products. In the medical area, pullulan acts as a plasma extender without undesired side effects. After metabolic turnover, it is completely excreted. Pullulan compounds can also serve as drug carriers, and can be used as medical adhesives.

Although markets for many of the applications listed here are still relatively small, with some applications only in the exploratory stage, pullulan appears to have long-term commercial potential. In sum, pullulan's many disparate uses may entitle it to become known as a biopolymer ''wonder material.

GLUCANS

Glucans are, by definition, any homopolymer of the simple sugar glucose. This large group includes cellulose, pullulan, and yeast glucan. However, the term ''glucan' is commonly used to describe the glucan component of the yeast cell wall. A common source for this glucan is baker's yeast, *Saccharomyces cerevisiae*, although it is also found in a number of other sources (bacteria, fungi, lichen, and higher plants, e.g., barley).

Large supplies of inexpensive yeast are available from both the baking and the brewing (brewer's yeast) industries. Glucans are the most abundant polymers in yeast, making up approximately 12 to 14 percent of the total dry cell weight. Glucan is readily purified from yeast cells by using hot alkali treatment to remove all other cellular materials, thereby allowing recovery of the insoluble glucan material. Yeast glucan particles purified by this method contain both high molecular weight and lower molecular weight polymers.

CURRENT AND POTENTIAL APPLICATIONS

Glucans have a number of potential medical uses.[43] Glucans that are extracted from yeast cell walls are found to markedly increase the ability of some organisms (e.g., mice) to resist invading foreign bodies. Because of its action as an immunomodulator, or enhancer of the immune system, a number of studies have been performed exploring the use of glucan as an anti-infectious agent. Glucan is also effective as an antiviral agent in plants. For example, one form of glucan is very effective in protecting many species of tobacco plant against invasion by the tobacco mosaic virus and tomato black ring virus. Plants can be either injected or sprayed with the glucan polymer.

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[43] Since polysaccharides play an important role in cell adhesion and as molecular recognition elements (glycoproteins), they potentially have a number of medical applications. Recent developments in the cloning and expression of enzymes known as oligosaccharyl transferases could facilitate the creation of new carbohydrate-based pharmaceuticals. See *Chemical and Engineering News*, "*Race* Is on To Develop Sugar-Based Anti-inflammatory, Antitumor Drugs, " Dec. 7, 1992, pp. 25-28. Apart from genetic engineering methods, some of these enzymes can also be chemically isolated. A new enzyme isolation method is being used to simplify the synthesis of novel polysaccharide compounds. Some of the new compounds have been found to prevent bacterial pneumonia in animals and are also being evaluated as anti-infective drugs. The enzymes could also be used to create polysaccharides that act as industrial coatings (e.g., as coatings on ship hulls to improve fuel efficiency and prevent marine corrosion). Stephen Roth, Neose Pharmaceuticals, personal communication, Sept. 3, 1993. Also see *Chemical and Engineering News,* "Patent Grants Broad Protection to Enzymatic Carbohydrate Synthesis," Mar. 29, 1993, pp. 24-27.

Several studies using different tumor models in mice and rats have revealed that glucans can inhibit tumor growth. The less toxic, soluble form of glucan is effective as an antitumor agent, although it is slightly less effective than the particulate form. Many antitumor glucans are currently being used in Japan on human subjects. In the United States, one company (Alpha Beta Technology of Worcester, Massachusetts) has yeast glucans that are undergoing clinical trials as immune-stimulating agents. Another interesting property of glucans is that they are radioprotective (i.e., they appear to enhance survival by preventing death due to postirradiation infection). This enhances the survival of test animals after otherwise lethal doses of radiation.

Although glucans are being exploited principally for their antitumor, anti-infectious, and radioprotective properties, they also have nonmedical applications. Glucans resist breakdown when attacked by digestive enzymes, and thus can be used as noncaloric food thickeners. Other possible applications include use in sustained-release tablets, encapsulation of oxygen for mass transfer in fermentation reactions, and as a solid support material for chromatographic separations.

GELLAN

In addition to xanthan, pullulan, and glucan, a number of other microbial polysaccharides are being investigated for applications as thickening agents. These include succinoglycan, scleroglucan, and the three structurally related polymers rharnsan, welan, and gellan. Among these, gellan gum is the most recent microbial polysaccharide to be given Food and Drug Administration (FDA) approval for applications in food products (September 1990). Gellan is a complex polysaccharide having a four sugar repeat unit (glucose-glucuronic acid-glucose-rhamnose). It is produced by the bacterium *Pseudomonas elodea,* which is derived from plant tissue.

The production of gellan follows essentially the same fermentation process described for xanthan. The properties of gellan can be easily modified. A hot caustic treatment of gellan yields a polymer that has the desirable characteristic of low viscosity at high temperature. Cooling gellan in the presence of various cations (e.g., calcium) results in the formation of strong gels.

CURRENT AND POTENTIAL APPLICATIONS

Gellan gum represents the newest member of the microbial polysaccharides to be developed commercially. Developed and produced by the Kelco Division of Merck under the trade names Kelcogel and Gelrite, this polymer has applications in the food industry as a gelling agent in frostings, glazes, icings, jams, and jellies. GelIan currently sells for about $5 per pound.

SELECTED POLYMERS OF PLANTS AND HIGHER ORGANISMS"

Starch

Starch is the principal carbohydrate storage product of higher plants. The term starch actually refers to a class of materials with a wide range of structures and properties. Starch polymers can be extracted from corn, potatoes, rice, barley, sorghum, and wheat. The principal source of starch for industrial and food purposes is corn. In the United States, about 4.5 billion pounds of cornstarch is used annually for industrial applications.[45] Starches are mixtures of two glucan polymers, amylose and amylopectin.[46] These polymers are accumulated in plants as insoluble energy storage granules, with each granule containing a mixture of the two polymers. Plant

44 Higher organisms (i.e., eukaryotes) refer to all organisms except viruses, bacteria, and blue-green algae.

45 See 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).

46 Amylose is a *linear* polymer of glucose units, while amylopectin is a branched polymer of glucose units (see figure 1-3).

breeding techniques have been used to produce new strains with altered ratios of amylose to amylopectin (e.g., waxy corn contains only 0.8 percent amylose compared with natural corn, which contains 28 percent amylose, and amylomaize can contain up to 80 percent amylose). The ability to manipulate the ratio of amylose to amylopectin by strain development has drastically reduced the economic costs associated with physical separation of the two polymers. This is important because amylose and amylopectin have different properties and applications.

CURRENT AND POTENTIAL APPLICATIONS

Because of its low cost and widespread availability, starch has been incorporated into a variety of products. Chemical modification of starch polymers can lead to a number of useful derivatives. Current U.S. production of ethanol requires about 400 million bushels of corn. An additional several billion pounds of cornstarch is used for nonfuel purposes. Approximately 75 percent of the industrial cornstarch produced is transformed into adhesives for use in the paper, paperboard, and related industries. Because cornstarch can absorb up to 1,000 times its weight in moisture, it is used in disposable diapers (about 200 million pounds annually), as a treatment for burns, and in fuel filters to remove water. Cornstarch polymers are also used as thickeners, stabilizers, soil conditioners, and even road deicers.[47]

In recent years, starch has attracted considerable attention as a biodegradable additive or replacement material in traditional oil-based commodity plastics. Although a number of starch-plastic material blends have been used in different products, particularly packaging and garbage bags, there has been considerable controversy as to whether these starch-polymer composites can biodegrade.[48] Starch itself degrades readily, and is in fact one of main components of the biological food chain. When added to petroleum-derived polymers such as polyethylene, starch can in theory accelerate the disintegration or fragmentation of the synthetic polymer chains. Microbial action consumes the starch, thereby creating pores in the material, which weakens it and enables it to break apart. Many have incorrectly characterized this process as a form of biodegradation. Independent tests of polyethylene-starch blends show that starch may biodegrade, but that the overall polymer formulation will not biodegrade at any significant rate. Distintegration of polyethylene-starch blends is not the same as biodegradation. Moreover, studies indicate that degradation rates vary considerably under different temperature, oxygen, and moisture conditions. In landfills, for example, degradation rates, even for readily degradable materials, are extremely s1ow.[49] Under optimal conditions, breakdown of starch-plastic blends that contain less than 30 percent starch is quite slow. Some research indicates that the starch composition needs to exceed about 60 percent before significant material breakdown occurs.[50]

These problems have led to the development of a new generation of biodegradable materials that contain very high percentages of starch. Under certain conditions, starch can be combined with water and other compounds to create a resin that is somewhat similar to crystalline polystyrene. Warner-Lambert has recently introduced the NOVON@ family of polymers that contain from 40 to 98 percent starch and readily dissolve in water. The NOVON resins combine starch with other biodegradable materials, and when dis-

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47 U.S. Congress, op. cit., footnote 45, pp. 90-99.

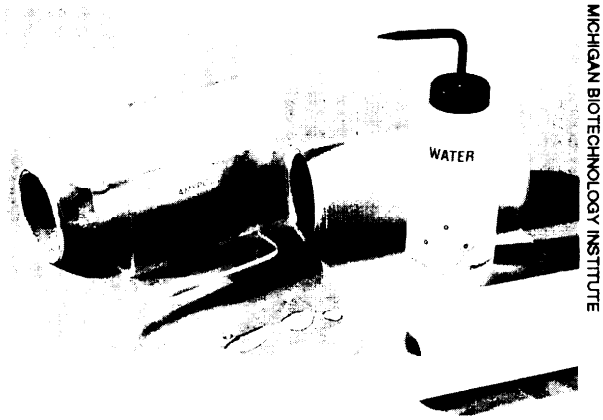
48 See "Degradable Plastics Generate Controversy in Solid Waste Issues," *Chemical & Engineering News*, June 25, 1990, pp. 7-14; and "Degradable Plastics," *R&D Magazine*, March 1990, pp. 51-56.

49 Sanitary landfills are essentially biologically inactive environments. See the testimony of Joan Harn on "Degradable Plastics and Municipal Solid Waste Management" before the Senate Committee on Governmental Affairs, July 18, 1989.

50 U.S. Congress, Office of Technology Assessment, op. cit., footnote 45, p. 96.

posed in biologically active environments such as compost facilities and wastewater treatment systems, display degradation characteristics similar to lignocellulosic materials (e.g., leaves, woodchips, and paper) .51

Properties of these new materials can be varied as the composition of starch and other material components change. They can replace traditional plastics used in food service, food packaging, personal health care, agricultural, and outdoor markets. Early applications of NOVON polymers include compost bags, degradable golf tees, loose-fill packaging, cutlery, pharmaceutical capsules, and agricultural mulch films. The company opened a 100-million-pound NOVON manufacturing facility in 1992. The materials are being targeted for markets where the benefits of their biodegradability can be clearly demonstrated. To fully take advantage of their environmental characteristics, however, a coordinated compost infrastructure will have to be established.[52] Although these starch-based resins cost two to four times more than commodity resins ($1.50 to $3 per pound), their novel properties might lead to the creation of new specialty markets.



New starch-based thermoplastic biopolymers such as the AMYPOL™ family of resins are water resistant and can be extruded, pelletized, and injection-molded into industrial and consumer products and films.

Plant Cellulose

As mentioned previously, cellulose is one of the most abundant constituents of biological matter.[53] It is the principal component of plant cell walls. Among the plant cellulose, cotton fiber is the most pure, containing around 90 percent cellulose. Wood, on the other hand, consists of about 50 percent cellulose. Cellulose serves as an important material feedstock for many industries. U.S. production of cellulose fibers amounted to 485 million pounds in 1991. By adding various functional groups to the basic glucose building blocks of cellulose (see figure 2-4), a range of useful derivatives (cellulosics) can be created.

CURRENT AND POTENTIAL APPLICATIONS

Chemically modified plant cellulose are used in a remarkably diverse set of applications. Cellulose derivatives are used to forma variety of fibers, thickening solutions, and gels. For example, carboxymethylcellulose (CMC) is used as a thickener, binder, stabilizer, suspending agent, or flow control agent. The major markets for CMC are detergents, food, toothpaste, shampoo, skin lotions, textiles, paper, adhesives, ceramics, and latex paints. In the biotechnology area, CMC gels are used for separating molecules. Hydroxyethylcellulose (HEC) is a water-soluble compound that has major applications in the oil industry. HEC is used as a thickener in drilling fluids and as a fluid-loss agent in cementing. Hydroxypropylcellulose (HPC) has excellent surface proper-

51 The company reports that the end products of these new materials are carbon dioxide, water, and biomass, with no persistent synthetic residues. See the testimony of Ken Tracy, Vice-President of Environmental Technology, Warner Lambert Company, before the Senate Committee on Environment and Public Works, June 5, 1991.

52 For more on this subject, 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).

53 Because of cellulose's abundance it sells for about 30 to 40 cents per pound.

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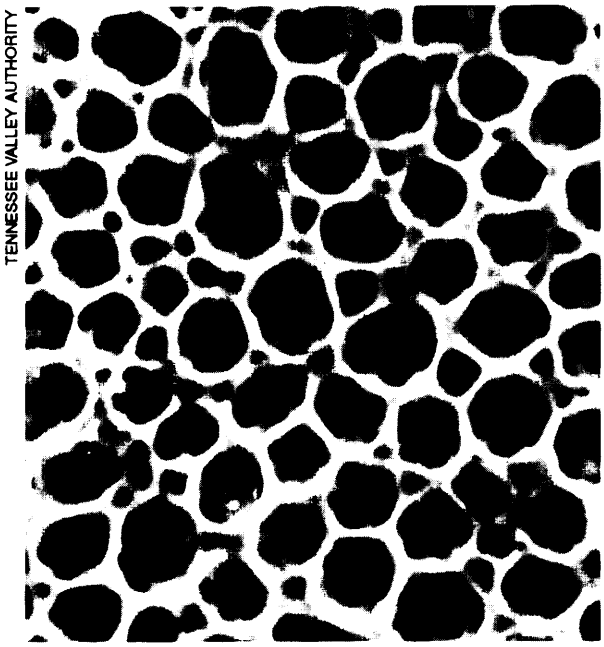

A photomicrograph shows modified ethyl cellulose films magnified by a factor of 2,000. The materials are being evaluated as carriers for the controlled-release of nitrogen fertilizers.

ties and forms highly flexible films. It is used in coating pharmaceutical tablets, in molding operations, in paper coatings, and as a suspending agent in inks, cleaners, and polishes. In the medical area, hydroxypropylmethylcellulose (HPMC) has shown considerable promise as an agent for lowering blood cholesterol levels.[54]

There are many other useful derivatives. Cellulose acetate is a plastic-grade material that is widely used in packaging, particularly for blisters, skins, transparent rigid containers, and windows in folding or setup boxes.[55] In addition, cellulose acetate is used in some fabrics and as a write-on pressure-sensitive tape (e.g., for credit card receipts). Methylcellulose, created by treating cellulose fibers with methyl chloride, has excellent absorption properties and is a good thickener. It has been used in a variety of food products, including salad dressings, pie fillings, and baked goods. Nonfood applications include adhesives, agricultural chemicals, tile cements, plywood glues, printing inks, and cosmetics.

Cellulose is also receiving considerable attention as a potential feedstock for liquid fuels, particularly ethanol. By either acid or enzymatic treatment (biological enzymes break down the cellulose into its basic sugars), cellulose can be converted to fermentable glucose and then distilled to remove ethanol. Although not currently competitive with ethanol derived from corn or sugarcane, the economic attractiveness of cellulose-derived fuel could very well change with advances in biotechnology .56

Cellulose will no doubt continue to be a major material feedstock for a wide spectrum of industries. Future research is likely to focus on the development of new chemical derivatives and the creation of composites that combine cellulose with other biodegradable materials.

Lignin

Lignin is a polymer found in woody and herbaceous plants. Its principal function is to provide structural support in plant cell walls. Lignin consists of phenylpropane building blocks and belongs to the polyphenol family of polymers. Along with cellulose and hemicellulose, lignin is one of the three chemically distinct components occurring in plant tissue. Typically, woody and herbaceous biomass consists of *50* percent cellulose, 25 percent hemicellulose, and

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54 See *Genetic Engineering News*, "High Molecular Weight Cellulose Derivative Shown to Lower Cholesterol," July 1993, p. 26.

55 However, cellulose esters such as cellulose acetate are not degradable.

56 U.S. Congress, Office of Technology Assessment, *Fueling Development: Energy Technologies for Developing Countries*, OTA-E-516 (Washington DC: U.S. Government Printing Office, April 1992), pp. 226-227.

57 In addition to these three principal biomass components, small amounts of other compounds can be present depending on the plant species. Common examples include fatty acids, waxes, tannins, and more specialized compounds such as terpene (used as a substitute for chlorofluorocarbons in electronics manufacturing) and taxol (a compound being explored as an anticancer dreg).

25 percent lignin.[57] Wood is a complex lingocelluolosic composite,[58] Lignin polymers are highly amorphous, three-dimensional structures that are associated with hemicellulose and play a key role in preventing decay of the lignocellulosic material. Lignin is generated in great quantities as a byproduct of wood pulping processes and consequently is relatively inexpensive. The most common commercial form of lignin is lignosulfonate, a compound derived from sulfite pulping. Higher-purity lignin can be obtained from "kraft" pulping, but this process is more costly .59

CURRENT AND POTENTIAL APPLICATIONS

At present, most of the lignin that is isolated from pulping processes is burned as an on-site fuel source. However, the material is increasingly being used in nonenergy applications.[60] Because lignin acts as a natural adhesive holding cellulose fibers together in plant cell walls, many of its commercial applications take advantage of this property. Millions of pounds of lignosulfonates are used annually for road dust control, Lignosulfonates are also employed as binding agents in molding applications and in animal feed. Lignin derivatives are beginning to be used as phenolic adhesives that can replace formaldehyde-based compounds in applications such as industrial packaging and tape.

The ionic properties of lignosulfonates and kraft lignins allow them to act as dispersants. They are being used to prevent mineral buildup in boilers and cooling towers, as thinning agents in oil drilling muds and concrete admixtures, and as dispersing agents in pesticide powders. Some major chemicals are also produced from lignin precursors. For example, vanillin, the principal ingredient in artificial vanilla, is derived from the aromatic components of lignin. In addition, chemically modified lignins are being explored for possible pharmaceutical applications. The development of specialized lignin compounds, such as electrically conducting polymers and engineering plastics, is an area of considerable research.

Chitin

Chitin, a polysaccharide, is one of the most ubiquitous polymers found in nature. It is almost as common as cellulose, and possesses many of the structural and chemical characteristics of cellulose (see figure 2-7). Chitin is an important structural component of the exoskeleton of a great number of organisms such as insects and shellfish. It also serves as a cell wall component of fungi and of numerous plankton and other small organisms in the ocean (see box 2-A for examples of other marine polysaccharides). Because of the different biological requirements of these various species, chitin is an extremely versatile natural polymer. Chitin and its most important derivative, chitosan, have a number of useful physical and chemical properties, including high strength, biodegradability, and nontoxicity.[61] Currently, the principal source of chitin is shellfish waste, but given the seasonal fluctuation of shellfish harvests, genetically engineered microbial sys-

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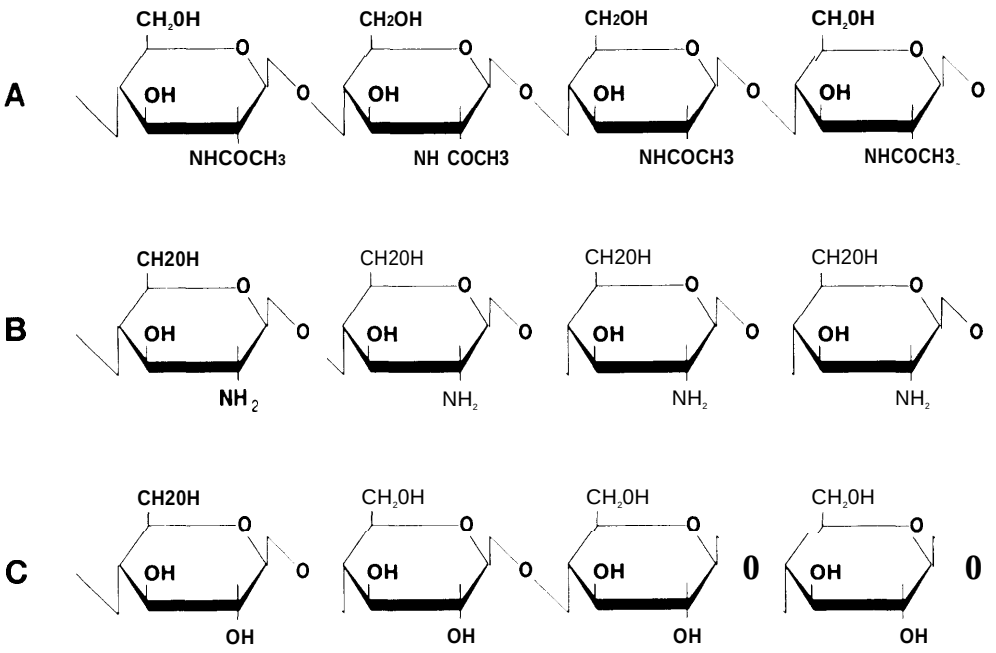
58 Apart from their traditional use as wood products, lignocellulosic fibers are being used to create high-performance structural materials (see Roger Rowell, "Opportunities for Lignocellulosic Materials and Composites," Rowell, et al. (eds.), op. cit., footnote 1).

59 In the kraft pulping process, lignin is isolated from the rest of the woody tissue by sodium hydroxide treatment. Lignin can also be broken down by enzymatic means-a process that is cleaner than kraft or sulfite pulping, but considerably more expensive.

60 See Robert Northey, "Low-Cost Uses of Lignin," R. Rowell, T. Schultz, and R. Narayan (eds.), *Emerging Technologies for Materials and Chemicals from Biomass* (Washington DC: American Chemical Society, 1992).

61 When chitin acetyl groups (CH_3CO) are replaced by hydrogen to form amino groups (NH_2), chitosan is created (figure 2-7). When exposed to acids, these NH_2 groups attract hydrogen ions, forming $(NH_3)+$, imparting a net positive charge to the chitosan polymer. This enables chitosan to remove negatively charged compounds and contaminants from wastewater. The positively charged chitosan forms solid precipitates with these negatively charged compounds. Chitosan is one of few natural polysaccharides that has this "ionic" property (i.e., a positive charge).

Figure 2-7-Chitin and Its Polysaccharide Relatives



Although polysaccharides are made up of simple sugars, slight medications can lead to dramatically different chemical and physical properties. Shown here are the structures of: A) **chitin,** B) **chitosan, and C) cellulose. The** only difference between cellulose and chitosan is that cellulose has hydroxide (OH) groups instead of amino (NH_2) groups. Chitin is identical in composition except for the acetylated amine groups ($NHCH_3OH$).

SOURCE: Office of Technology Assessment, 1993.

terns might be used to provide a stable supply of high-grade chitin compounds.[62]

CURRENT AND POTENTIAL APPLICATIONS

The chitin family of polymers is being widely used in medicine, manufacturing, agriculture, and waste treatment. In the biomedical area, chitosan is incorporated into bandages and sutures in wound-healing treatment, because it forms a tough, water-absorbent, oxygen permeable, biocompatible film. It can be used to accelerate tissue repair and can be applied directly as an aqueous solution to treat burns. Because of its high oxygen permeability, chitosan is used as a material for contact and intraocular lenses. Chitosan has also been found to expedite blood clotting. The fact that chitin compounds are biodegradable (the human body breaks chitin down into simple carbohydrates, carbon dioxide, and water) makes them particularly appropriate for use in drug delivery systems. Chitosan carriers can release drugs slowly. This property is extremely valuable in cancer chemotherapy since the agents are often highly toxic and require long periods of time for administration. A chitosan compound is also

62 Certain algae, for example, produce a relatively pure form of chitin fiber that can be readily extracted and processed. However, these algae grow quite slowly. The application of biotechnology may lead to the development of fast-growing strains of algae that produce large quantities of chitin. In addition, some fungi produce chitosan directly. By modifying these strains, greater amounts of chitosan could be produced, eliminating the need for chemical treatment of chitin. See New *Scientist*, "*Life* after Death for Empty Shells," Feb. 9, 1991, pp. 46-48.

Box 2-A–Polymers oft he Sea

As **major repositories of the earth's genetic diversity, the oceans are a rich source of proteins, polysaccharides, and other polymeric compounds. Because marine organisms live in a variety of different environments-some of them extremely harsh-they have developed polymers with a wide range of properties. For example, the hard calcium carbonate shell of the abalone is held together by a** glue composed of proteins and sugars, and ocean species in polar climates are able to survive extremely cold temperatures by producing antifreeze proteins. Other proteins regulate the mineralization processes involved in the creation of shells and crystals (e.g., the calcite crystals of sea urchin spines). Polysaccharides serve as structural components in **crustaceans (e.g., chitin), and in a number of algal species** such as kelp.

Chitin and some algal polysaccharides such as **agar, alginate, and carrageenan are widely** used in industry and medicine. The market for these marine polymers is several hundred million dollars annually. Agar, a major component of the cell walls of certain red algae, is used as a photographic emulsifier; a gel for cosmetics, toothpaste, and medical ointments; an inert drug carrier, a corrosion inhibitor, an adhesive, and a thickening agent in confectioneries and dairy products. Alginate is a principal structural constituent of brown algae (rockweeds and kelps), and carrageenan is extracted from red seaweed. Like agar, these two natural sugars have excellent gelling and colloidal (suspending) properties. They are used extensively in the production of ice cream and other dairy items, as well as in the textile, paper, printing, and biomedical (e.g., wound dressing and dental impression) industries.

Other marine-derived compounds are being used to formulate new drug agents, such as the anti-inflammatory compound Fucoside B. Marine organisms provide a vast range of biological processes and substances that could be genetically modified for novel medical and manufacturing purposes. The Federal investment in marine biotechnology research was about $44 m ill ion in f iscal year 1992.

SOURCES: Federal Coordinating Council for Science, Engineering, and Technology, Committee on Life Sciences and Health, Biotechnology *for the* 27st Century (Washington, DC: U.S. Government Printing Office, February 1992); Office of Technology Assessment, 1993.

being investigated as an inhibitor of the AIDS virus.[63]

The high moisture retention and film-forming characteristics of chitosan have resulted in a number of applications in the cosmetics and personal care areas. Chitosan is being utilized in hair spray, skin cream, shampoo, soap, nail polish, toothpaste, and personal hygiene products.[64] In paper manufacturing, the addition Of 1 percent chitin by weight greatly increases the strength of paper fibers, particularly when wet. Thus, chitin has been incorporated into diapers, shopping bags, and paper towels.[65] In addition to paper-chitin composites, some researchers have developed complexes of chitin and cellulose that have excellent water-resistant properties.[66] The material can be molded or made into biodegradable plastic films. Eventually, high-strength chitin polymers could be used in food packaging. One company, Technics of Japan, in trying to replicate

63 This research is being led by Ruth Ruprecht at Harvard University, See "Chitin Craze," Science News, vol. 144, July 31, 1993, pp. 72-74.

64 *New* Scientist, op. cit., footnote 62.

65 Ibid.

66 J, Hosokawa et al., " 'Biodegradable Film Derived from Chitosan and Homogenized Cellulose,' *Industrial Engineering Chemical Research, vol. 29, 1990,* pp. 800-805.

the acoustic properties of crickets' wings, has even constructed audio speaker vibrators from chitosan materials.[67]

In terms of actual sales, agricultural end uses constitute the largest and most successful market for chitin and chitosan polymers. The fungi-resistant properties of chitosan have resulted in its application as a fertilizer, soil stabilizer, and seed protector. It is a yield-enhancing agent for wheat, barley, oats, peas, beans, and soybeans.[68] Thus, chitosan is used both as a seed coating and as a plant growth regulator. Chitosan is also used to recover protein wastes, particularly dairy products such as cheese whey, that are subsequently added to animal feed.

Because of its binding and ionic properties (i.e., in solution, the chitosan polymer carries a positive charge), chitosan can be used as a flocculating agent to remove heavy metals and other contaminants from wastewater.[69] Current applications in this area include treatment of sewage effluents, paper mill wastes, metal finishing residues, and radioactive wastes. In several countries, particularly Japan, chitosan is used to purify drinking water. Chitosan is also being evaluated for use in the bioremediation of toxic phenolic compounds.[70] This could greatly improve the efficiency of pharmaceutical and plastic manufacturing, by eliminating phenolic contaminates.

Chitin and its various derivatives have become important constituents in a number of diverse products and industrial processes. Pharmaceutical-grade chitin sells for about $32 per pound, while industrial grade chitin/chitosan compounds range from about $7 to $27 per pound (specific cost depends on the application). The unique chemical properties and biodegradability of this family of biopolymers presage an even wider range of applications in the future.

Hyaluronic Acid

Hyaluronic acid (HA) is a natural product that is found throughout vertebrate tissue. It also occurs as an extracellular polysaccharide in a variety of bacteria. HA plays an important physiological role in many organisms. Research indicates that HA aids tissue formation and repair, provides a protective matrix for reproductive cells, serves as a regulator in the lymphatic system, and acts as a lubricating fluid in joints. Currently, most of the HA used for research and commercial purposes is extracted from rooster combs. In the future, it is likely that this biopolymer will be produced from fermentation broths of *Streptococcus* and other bacteria.

Hyduronic acid, discovered in 1934, is a long, unbranched polysaccharide chain, composed of repeating twin sugar units. Because of the high density of negative charges along the polymer chain, HA is very hydrophilic (has a strong affinity for water) and adopts highly extended, random-coil conformations. This structure occupies a large volume relative to its mass and forms gels even at very low concentrations. It is extremely flexible and has a high viscosity.

CURRENT AND POTENTIAL APPLICATIONS

Since hyaluronic acid plays an important role in many developmental and regulatory processes of the body, it has been used principally in biomedical applications. It is an extremely attractive polymer material because it is a natural

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67 *New Scientist*, op. cit., footnote 62.

68 This particular chitosan product is marketed under the tradename YEA by Bentech Laboratories. An estimate of the potential market for YEA is about $160 million annually (BioInformation Associates, Inc., "Technology and Commercial Opportunities in Biodegradable Polymers, " Boston, MA).

69 See *Chemical and Engineering News,* "Chitin Removes Textile Dyes from Wastewater, " July 12, 1993.

TO This application is being developed by Marizyme Corp. (Hanover, MD) in collaboration with researchers at the University Of Maryland. *Science News*, op. cit., footnote 63.

Table 2-3—Biomedical Uses of Hyaluronic Acid

Area	Application
Disease indicator	Identifies presence of liver cirrhosis, arthritis, scleroderma (tissue disease), and tumors.
Ear surgery	Scaffold material for ear surgery, healing of tympanic membrane perforations
Eye surgery	Protects corneal tissue; used In retinal reattachment, and in glaucoma surgery
Wound healing	Stimulates tissue repair.
Tendon surgery	Repair of flexor tendon lacerations, degenerative joint disease in animals
Antiadhesion	General surgery.
Scar control	General surgery

SOURCE BloInformatIon Associates, Boston, MA

product that degrades into simple sugars. Presently, its major uses are in eye surgery, treatment of arthritis, and wound-healing preparations; it is also being used in some cosmetic products. Various biomedical applications for HA are listed in table 2-3.

The unique physiochemical and structural characteristics of hyaluronic acid make it an excellent candidate for applications that require biocompatibility. However, the prices of HA are extremely high, more than $100,000 per kilogram. A recent survey estimates a total market for HA of $425 million by 1996.[71] The largest segment of this market is for surgery. The smallest segment is for cosmetics. Because of its utility in surgical treatment, the demand for hyaluronic acid is likely to expand. Some firms are now investigating genetically engineered HA produced by microbes. While the application of genetic techniques may produce HA that has greater polymer uniformity, switching to bacterial production (from rooster comb extraction) probably will not lower total production costs because of the need for expensive purification steps .72

POLYMERS PRODUCED BY CHEMICAL POLYMERIZATION OF BIOLOGICAL STARTING MATERIALS

Polymers that are created by the chemical polymerization of naturally occurring monomers are attracting considerable commercial interest. Although these polymers are not produced by biological systems, the fact that they are derived from basic biological building blocks confers on them many of the same properties as microbially or plant-derived biopolymers. These may include nontoxicity, biodegradability, and biocompatibility. In addition, these polymers are by definition drawing on feedstocks that are renewable. While there are several different classes of chemically synthesized biopolymers, two particular groups stand out. One is the family of polymers produced from lactic acid, a molecule used extensively in the food industry. The other is the growing ensemble of polyamino acid polymers.

Polymers Synthesized from Lactic Acid

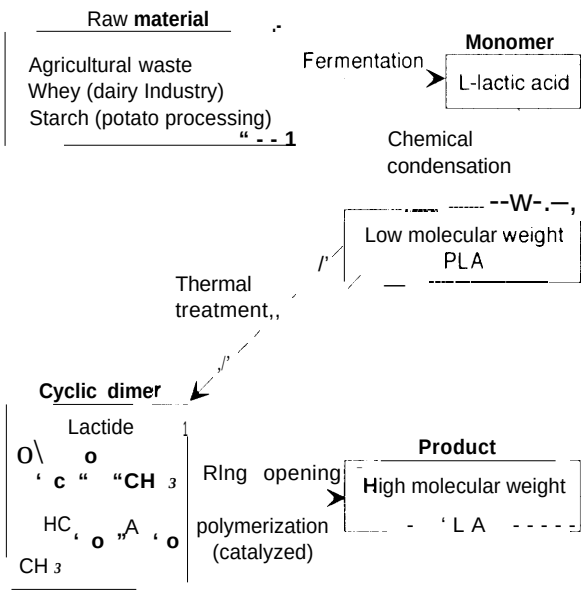
Lactic acid (lactate) is a natural molecule that is widely employed in foods as a preservative and a flavoring agent.[73] It is also used in biomedical

71 See *Genetic Engineering News,* ‘‘*Complex* Carbohydrate Therapeutic Products: Tomorrow’s Billion $ Market, ” January 1993, pp. 6-7.

72 James Brown, Division Director, Molecular and Cellular Biosciences, National Science Foundation personal communication, July 28, 1993.

73 Lactic acid can exist in two different forms: l-lactic acid and d-lactic acid. These two compounds are chemically identical except that they are mirror images of each other. Such mirror image structures are called stereoisomers. Because the stereoisomers have different spatial configurations, they have different reactive properties. Only the l-lactide is found in animals, whereas both the d and 1 forms of lactic acid are found in lower organisms, such as the *Lactobacilli*, a class of bacteria used for centuries in the dairy industry.

Figure 2-8-Commodity-Scale Production of Polylactide



SOURCE: BioInformation Associates, Boston, MA.

applications in intravenous and dialysis solutions. It is the main building block in the chemical synthesis of the polylactide family of polymers. This family includes polylactide homopolymers (PLA) and copolymers with glycolic acid (PLA-PGA). (Glycolic acid occurs naturally in sugarcane syrup and in the leaves of certain plants, but is generally synthesized chemically).

Lactic acid is found in blood and muscle tissue, where it is a product of the metabolic processing of glucose. Although it can be synthesized chemically, lactic acid is produced principally by the microbial fermentation of sugars such as glucose or hexose. These sugar feedstocks are drawn from agricultural (potato skins and corn) and dairy wastes. The lactic acid monomers produced by fermentation can be used to create either low or high molecular weight polylactide polymers (figure 2-8). Variation of the reaction conditions, such as temperature and choice of catalyst, provides control over the molecular weight of the polymer. In this way, the physical and chemical properties of polylactide can be adapted for different applications.

CURRENT AND POTENTIAL APPLICATIONS

Polylactide polymers are the most widely used biodegradable polyester materials. Although their principal area of application has been in the health care field, agricultural and manufacturing uses have been found as well. Polylactides are frequently used in combination with polyglycolic acid. PLA-PGA copolymers are employed as medical materials and as platforms for the sustained release of agricultural chemicals. In the industrial sector, PLA commodity polymers are being developed for use as pulping additives in paper manufacturing and as degradable packaging materials.[74] Commodity-grade polylactide sells for about $5 per pound, but manufacturers expect to bring the price down to the $2 to $3 range. Medical grade polylactide prices range from $100 to $1,000 per pound. The properties of these materials are being tailored to meet a variety of different needs.

Most applications of PLA-PGA materials have been for therapeutic purposes. Devices made of PLA-PGA copolymers have been used for the controlled release of antibiotics, anticancer and antimalarial agents, contraceptives, hormones, insulin, narcotic antagonists, and proteins.[75] The copolymers have been molded into microsphere or microcapsules, pellets, implants, and hollow fibers.

There are several other important medical applications. Polylactide sutures are widely used

74 Cargill, Inc. is building a manufacturing facility that will be capable of producing 10 million pounds of polylactide annually. The materials will be used as biodegradable plastics. See *Wall* Street *Journal*, "Concern Will Expand Move into Biodegradable Plastic," May 20, 1993, p. A7. Also, Dupont Chemical and ConAgra have formed a joint venture, EcoChem, that is developing polylactide polymers.

75 PLA-PGA copolymers are used as drug delivery vehicles. Since protein-based drugs are quickly degraded in the body, timed-release delivery by PLA-PGA devices can decrease the rate of drug degradation.

in surgery because they degrade within the body after the incision has healed. Commercial absorbable sutures such as Vicryl® are made of copolymers containing 90 percent PLA and 10 percent PGA. This ratio creates fibers that have excellent durability, absorbency, and tensile strength. Sutures made from PLA-PGA copolymers are stronger and absorb faster than sutures, such as Dexon®, made only of PGA. A considerable amount of ongoing research is focused on the application of PLA-PGA copolymers as sutures, clips, staples, and reinforcement materials.

PLA-PGA copolymers have also been successfully applied in experimental orthopedic surgery. Compression-molded copolymers have been used as plates or screws for the treatment of fractures and to fill in bone defects. The materials have also been used as scaffolding to facilitate the formation of new cartilage material in the body.[76] Copolymers of PLA and PGA are more useful than homopolymers of PLA and PGA because their rate of degradation can be adjusted. An advantage of using prostheses made of PLA-PGA copolymers is their biocompatibility and nontoxicity. The breadth of current research efforts suggests that the range of biomedical applications for PLA-PGA materials will expand considerably in coming years.

Polyamino Acids

Polyamino acids are an important class of synthetic polymers produced by chemical polymerization of the same amino-acid building blocks found in naturally occurring proteins.[77] Polyamino acid chains are sometimes referred to as polypeptides. Approximately 20 amino acids can be found in proteins, and from these basic building blocks a variety of homopolymers and complex copolymers have been synthesized. Because of the great chemical diversity of amino-acid monomers—anionic, cationic, hydrophobic, polar, nonpolar, thermally stable-polyamino acids can be envisioned for virtually all types of polymer applications.[78]

Currently, two principal chemical procedures are used to produce polyamino acids. One approach specifically links amino-acid monomer units together by amide bonds. These are the same type of bonds that exist in natural proteins. This particular type of chemical synthesis is a fairly complex process and is used primarily to create the high-purity materials needed for biomedical applications. In the future, this method of synthesis may be supplanted by bacterial fermentation[79] or recombinant DNA techniques. One type of bacterial species, for example, can produce poly-glutamic acid, a polypeptide that has many therapeutic uses. As highlighted earlier, recombinant DNA technology is being used to develop a new class of polymers based on spider silk (silk is a natural polyamino acid).

Polymer chains consisting of glutamic acid, aspartic acid (a component of Nutrasweet™), leucine, and valine are the polypeptides most frequently used for biomedical purposes. Lysine and methionine are also important amino-acid building blocks in polypeptide polymers.[80] Glutamic acid is the sodium salt form of monosodium

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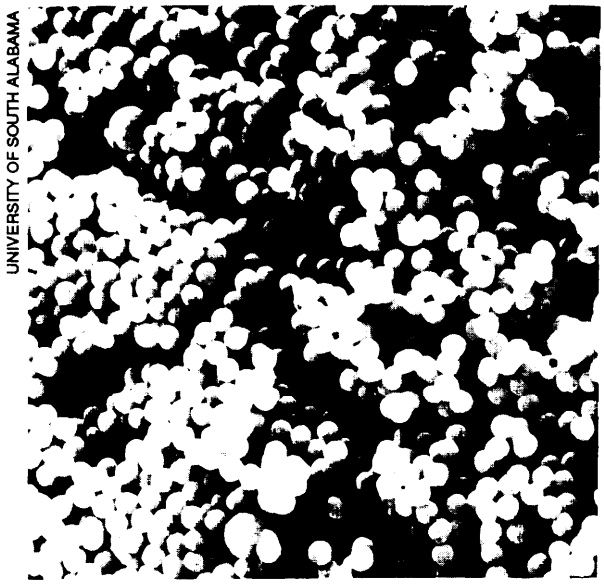
76 See Robert Langer and Joseph Vacanti, "Tissue Engineering," *Science*, vol. 260, May 14, 1993, pp. 920-925.

77 As with lactic acid (footnote 73), amino acids also occur as stereoisomers; that is, as righthanded (d) or lefthanded (l) mirror image structures. One of the distinguishing features of proteins is that they are constructed only from left-handed amino acids. The synthetic polyamino acids discussed here are for the most part derived from l-amino acids. Polymers that contain only l-isomers or only d-isomers are known as homochiral structures. Like the phenomenon of DNA self-replication homochirality is a unique property of living systems. See V. Avetisov et al., "Handedness, Origin of Life, and Evolution," *Physics Today*, July 1991, p. 33.

78 "Anionic" monomers are negatively *charged;* "cationic" monomers are positively charged.

79 New bacterial fermentation processes that involve immobilized enzymatic reactions could potentially lower the cost of polyamino acid production.

80 Lysine and methionine are widely used as food and animal feed additives. Methionine is produced chemically, whereas lysine is bacterially produced.



Polyamino acid microsphere can be used to encapsulate bugs and agricultural chemicals, thereby ensuring that such active agents can be released in a controlled fashion. The microsphere shown here have a diameter of about 1.5 microns (1.5 millionth of a meter). Microsphere occur naturally and figure prominently in a theory of the origin of living cells over 3 billion years ago.

glutamate (MSG) and is a major product of the fermentation industry, with an annual production level of around 600 million pounds. A major advantage of using glutamic acid is its low cost and relative abundance. Glutarnic acid and aspartic acid are hydrophilic (they have high water affinity), whereas leucine and valine are hydrophobic (low water affinity). When these hydrophilic and hydrophobic building blocks are combined, copolymers with vastly different rates of biodegradation can be created. This allows the copolymers to be used as delivery systems for a variety of different drugs. The fact that homopolymers and copolymers of these simple amino acids are nonimmunogenic (i.e., they do not produce an immune response when injected into animals) makes them particularly attractive for medical applications. Polyamino acid microspheres—spheres ranging in size from 50 nanometers (billionth of a meter) to 20 microns (millionth of a meter)--are currently being developed for oral drug administration.[81] (Polyamin o acid microsphere can also be used for the controlled release of fertilizers.) In addition to drug delivery systems, polyamino acids are being investigated for use as biodegradable sutures, artificial skin, and orthopedic support materials.

A less complex chemical procedure is used to produce polyamino acids for commodity-scale industrial applications. Polypeptides are made by thermal polymerization of amino-acid building blocks at moderately high temperature (160 to 240°C), followed by a mild alkaline treatment at 60 to 80°C to open ring structures that may form. This process is not very specific and yields a polymer product in which the monomers are linked by two different types of bonds. However, the advantage of this method is that large quantities of polypeptides can be synthesized at low cost.

This approach has been used to create polyaspartate polymers from aspartic acid.[82] The polyaspartate polymers are analogues of natural proteins, particularly the aspartate-rich proteins from oyster shells that play a key role in

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81 Protein-based drugs are extremely difficult to insert into the human body. Because proteins are easily broken down by digestive enzymes and cannot readily pass through the skin, they are currently administered by injection. By encasing protein drugs in polyamino acid materials, researchers are trying to protect the proteins long enough so that they can slip past digestive enzymes in the stomach and be absorbed into the bloodstream. This would allow oral administration of genetically administered proteins. However, in animal studies conducted thus far, only about 10 percent of an orally administered drug dose makes it to the bloodstream. One company involved in this area is Emisphere Technologies of Hawthorne, NY. See "Stand and Deliver: Getting Peptide Drugs into the Body," Science, vol. 260, May 14, 1993, pp. 912-913.

82 Aspartic acid is fairly inexpensive as it can be produced from ammonia and maleic anhydride.

Table 2-4-Possible Applications of Industrial Polyaspartates

Water treatment	Antiscaling, anticorrosion, flocculation. Cooling towers, evaporators (for example in pulp processing), desalinators, boilers
Dlspersants	Detergents, paint pigments, drilling mud, portland cement, etc
Air pollution control	Remove sulfur dioxide by preventing deposition of Insoluble sulfates
Ceramics	Promotion of crystallization of specific minerals (e g insulators)
Oilfield applications	Prevent mlneralization and corrosion in well holes
Fertilizer preparation	Prevent calcification of phosphate slurrles
Mineral pocesslng	Antiscalants used to keep ores at an optimum size after grlnding.
Textile Industry	Addition of crystallization regulators results in better fibers
Antifouling	Prevent growth of calcified organisms on marine/freshwater surfaces
Superabsorbents	Diapers
Bioplastics	At high molecular weights, polyaspartates become solid materials that may have a number of uses,
Dental treatment	Tartar control agents (toothpaste)
Biomedical devices	Prosthetic devices (heart valves), prevention of pathological calcification, microencapsulation for drug delivery, surface coatings for Implants to promote crystallization

SOURCE Steven Sikes, Department of Biological Sciences, University of South Alabama, personal communication, Aug. 11, 1993

regulating mineralization,[83] Consequently, these polymers have intrinsic antiscalant and anticorrosive properties that can prevent the buildup of mineral deposits on the surfaces of ships, cooling towers, heat exchangers, and other industrial equipment. Since the polyaspartate compounds are derived from natural precursors, they are biodegradable[84] and can be used to replace petroleum-derived polymers such as polyacrylate and polyacrylamide.[85] Because of their unique mineralization and ionic properties, there exists an enormous range of possible applications for the polyaspartate materials (see table 2-4).

At present, markets for these synthetic biopolymers are only now being identified. Nevertheless, there exist opportunities to use polyaspartates for a variety of specialized biomedical purposes, as well as a number of high-volume applications such as flocculants, dispersants, and superabsorbents. Industrial polypeptides, particularly water treatment chemicals, are likely to become commercially available in the near future.[86] It is expected that these compounds will cost from one-third to twice the price of existing synthetic chemicals such as the polyacrylamides (about $1.30 to $2 per pound).

83 Matrix proteins from oyster shells are powerful regulators of mineral formation. These polypeptides can inhibit mineral deposition where it is not wanted and, under certain conditions, can promote crystallization where it is needed. The formation of minerals in solution (e.g., the calcium carbonate structure of oyster shells) is a fundamental process of living and nonliving systems, It is apparent that nature has produced some extraordinary polymers to regulate the mineralization process. By investigating the properties of these natural polymers, researchers are trying to develop new biopolymers that can be tailored for a variety of industrial applications. See C. S. Sikes and A. P. Wheeler, ' 'Regulators of Biomineralization,'' *Chemtech*, October 1988, pp. 620-626.

84 Preliminary tests of polyaspartate degradability are promising. See A.P. Wheeler and L.P. Koskan, "Large Scale Thermally Synthesized Polyaspartate as a Substitute in Polymer Applications, " *Materials Research Society Symposium Proceedings,* vol. *292,* pp. 277-283.

85 Synthetic polymers having multiple positive or negative charges, such as polyacrylate and polyacrylamide, are widely used as water treatment additives, components in paper manufacturing, active ingredients in detergents, and tartar control agents in toothpaste, Their worldwide use amounts to billion of pounds annually, They are excellent materials in terms of their chemical activity and cost. However, they are not biodegradable.

86 Several chemical and biotechnology companies have ongoing R&D programs involving polyaminoacids. Steve Sikes, Department Of Biological Sciences, University of South Alabama, personal communication, July 9, 1993.

SUGGESTED FURTHER READING

Microbial Polyesters: Polyhydroxyalkanoates

Sumner A. Barenberg, John L. Brash, Ramani Narayan, and Anthony E. Radpath, Degradable *Materials: Perspectives, Issues and Opportunities* (Boca Raton, LA: CRC Press, 1990).

James H. Brown, ''Research Opportunities for Biologists in Bimolecular Materials," National Science Foundation, Division Director, Molecular and Cellular Biosciences, internal report, June 1992.

Yoshiharu Doi, *Microbial Polyesters (New* York, NY: VCH Publishers, 1990).

Oliver P. Peoples and Anthony J. Sinskey, "Polyhydroxybutyrate (PHB): A Model System for Biopolymer Engineering II," E.A. Dawes (cd.), *Novel Biodegradable Microbial Polymers,* NATO Advanced Science Institute Series (Holland: Kluwer Academic Publishers, 1990), vol. 186, pp. 191-202.

Recombinant Protein Polymers

James H. Brown, ''Research Opportunities for Biologists in Bimolecular Materials," National Science Foundation, Division Director, Molecular and Cellular Biosciences, internal report, June 1992.

D.R. Filpula, S.-M. Lee, R.L. Link, S.L. Strausberg, and R.L. Strausberg, "Structure and Functional Repetition in a Marine Mussel Adhesive Protein, " *Biotechnology Progress, vol. 6, 1990,* pp. 171-177.

S.D. Gorham, "Collagen," D. Byrom (cd.), *Biomaterials: Novel Materials from Biological Sources (New* York, NY: Stockton Press, 1991), pp. 55-122.

D.L. Kaplan, S.J. Lombardi,, W.S. Muller, and S.A. Fossey, 'Silks, ' D. Byrom (cd.), *Biomaterials: Novel Materials from Biological Sources (New* York, NY: Stockton Press, 1991), pp. 1-53.

D. McPherson, C. Morrow, D.S. Minehan, J. Wu, E. Hunter, and D.W, Urry, "Production and Purification of a Recombinant Elastomeric Polypeptide, G-(VPGVG)19-VPGV from E.. *coli," Biotechnology Progress, vol. 8, 1992,* pp. 347-352.

Bacterial Cellulose

P. Ross, R. Mayer, and M. Benziman, "Cellulose Biosynthesis and Function in Bacteria," *Microbiological Revues, vol. 55,1991, pp. 35-58.*

D.C. Johnson, R.S. Stevens, and J.A. Westland, "Properties and Uses of Bacterial Cellulose Produced in Fermenters,' presented at the American Chemical Society Meeting, Boston, MA, Apr. 24, 1990.

D.C. Johnson, H.G. Folster, and A. Ben-Bassat, "Bacterial Cellulose from Agitated Culture: Process Development, Scale-up and Applications, ' presented at the Cellulose '91 Conference, New Orleans, December 1991.

Xanthan

R.A. Hassler and D.H. Doherty, "Genetic Engineering of Polysaccharide Structure: Production of Variants of Xanthan Gum, *Xanthomonas campestris, Biotechnology Progress, vol. 6, 1990, pp. 182-187.*

J.F. Kennedy and I.J. Bradshaw, "Production and Applications of Xanthan, " M.E. Bushell (cd.), *Progress in Indutrial Microbiology, vol. 19, 1984, pp. 319-371*

Dextrans

R.M. Alsop, "Industrial Production of Dextrans,' M.E. Bushell (cd.), *Progress in Industrial Microbiology* (Amsterdam: Elsevier, 1983), pp. 1-44.

C. Larsen, "Dextran Prodrugs-Structure and Stability in Relation to Therapeutic Activity," *Adv.Drug Delivery Review,* vol. **3, No.** 1, pp. 103-154.

Pullulan

Chemical and Engineering News, "Japanese Develop Starch-Derived Plastic, " vol. 24, December 1973, p. 40.

A. Jeanes, "Dextrans and Pullulans: Industrially Significant Alpha-D-Glucans," P.A. Sandford and A. Laskin (eds.), *Extracellular Microbial Polysaccharides,* ACS Symposium Series, vol. 45, 1977, pp. 284-298.

Y.C. Shin, Y.H. Kim, H.S. Lee, S.J. Cho, and S.M. Byun, "Production of Exopolysaccharide Pullulan from Inulin by a Mixed Culture of *Aureobasidium Pullulans* and *Kluyveromyces Fragilis,' Biotechnology & Bioengineering, vol. 33, 1989, pp. 129-133.*

Glucans

E. Cabib, R. Roberts, and B. Bowers, 'Synthesis of the Yeast Cell Wall and Its Regulation, ' *Annual Review of Biochemistry, vol. 5, No. 17, 1982, pp. 63-793.*

N.R. Di Luzio, D.L. Williams, R.B. McNamee, B.F. Ewards, and A. Kitahama, "Comparative Tumor-Inhibitory and Anti-Bacterial Activity of Soluble and Particulate Glucan," *International Journal of Cancer, vol. 24, 1978,* pp. *773-779.*

P.W.A. Mansell, G. Rowden, and C. Hammer, "Clinical Experiences with the Use of Glucan," M.A. Chirigos (cd.), *Immune Modulation and Control of Neoplasia by Adjuvant Therapy (New* York, NY: Raven Press, 1978), pp. 255-280.

D.L. Williams, E,R. Sherwood, LW. Browder, R.B. McNamee, E.L. Jones, and N.R. Di Luzio, "The Role of Complement in Glucan-Induced Protection Against Septic Shock," *Circulatory Shock,* vol. 25, 1988, pp. 53-60.

Gellan

V.J. Morris, ' 'Science, Structure and Applications of Microbial Polysaccharides, " G.O. Phillips, D.J. Wedlock, and P.A. Williams (eds.), *Gums and Stabilizers for the Food Industry, vol. 5, 1990, pp. 315-328.*

Starch

R.L. Whistler, J.N. BeMiller, and E.F. Paschall, *Starch Chemistry and Technology,* 2nd Ed. (New York, NY: Academic Press, 1984).

R.P. Wool and S.M. Goheen, ''Degradation Mechanisms in Polymer-Starch Composites," *International Symposium on Biodegradable Po[ymers, Biodegradable Plastic Society,* October 1990, pp. 137-143.

Lignin

W. Glasser and S. Sarkanen (eds.), *Lignin: Properties and Materials* (Washington, DC: American Chemical Society, 1989).

Fred Boye, *Utilization of Lignins and Lignin Derivatives* (Appleton, WI: Institute of Paper Chemistry, 1985).

Robert Northey, "Low-Cost Uses of Lignin," R. Rowell, T. Schultz, and R. Narayan (eds.), *Emerging Technologies for Materials and Chemicals from Biomass* (Washington, DC: American Chemical Society, 1992).

Chitin

G.G. Allan, L.C. Alturan, R.E. Bensinger, D.K. Ghost, Y. Hirabayashi, A.N. Neogi, and S. Neogi, "Biomedical Applications of Chitin and Chitosari, ' J.P. Zikakis (cd.), *Chitin, Chitosan and Related Enzymes (New* York, NY: Academic Press, 1984), pp. 119-135.

A. Naude, "Drug and Cosmetic Uses Targeted for Chitin Products,' *Chemical Marketing Reporter,* Dec. 11, 1989, pp. 24-25.

E.R. Pariser and D.P. Lombardi, *Chitin Sourcebook: A Guide to the Chitin Research Literature (New* York, NY: John Wiley & Sons, 1989).

Hyaluronic Acid

A. Scheidegger, "Biocosmetics in Japan: New Wrinkles Beneath the Make-Up, " *Trends in Biotechnology,* vol. *7, 1989,* pp. 138-144.

J. van Brunt, "More to Hyaluronic Acid than Meets the Eye, ' *Biotechnology,* vol. 4, 1986, pp. 780-782.

Polymers Synthesized from Lactic Acid

S.J. Holland, B.J. Tighe, and P.L. Gould, ''Polymers for Biodegradable Medical Devices,

the Potential of Polyesters as Controlled Macromolecular Release Systems, ' *Journal of Controlled Release,* vol. 4, 1986, pp. 155-180.

M. Vert, P. Christel, M. Audion, M. Chanavaz, and F. Chabot, "Totally Bioresorbable Composites Systems for Internal Fixation of Bone Fractures, ' E. Chiellini et al. (eds.), *Polymers in Medicine II (New* York, NY: Plenum Press, 1985, pp. 263-275.

R.H. Wehrenberg, "Lactic Acid Polymers: Strong, Degradable Thermoplastics," *Mechanical Engineering ,* September 1981, pp. 63-66.

Polyamino Acids

J.M. Anderson, K.L. Spilizewski, A. and Hiltner, "Poly Alpha-Amino Acids as Biomedical Polymers, ' D. F. Williams (cd.), *Biompatibility of Tissue Analogs,* vol. 1 (Boca Raton, FL: CRC Press, 1985), pp. 67-88.

C.S. Sikes and A.P. Wheeler, "Regulators of Biomineralization,' *Chemtech,* October 1988, pp. 620-626.

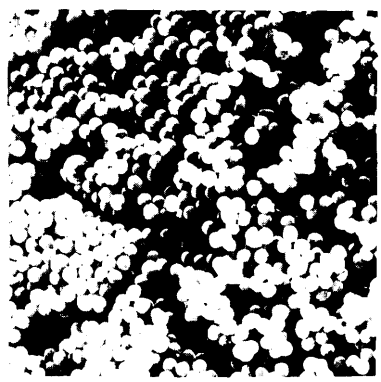
Biopolymer Research and Development in Europe and Japan

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, *lndustrial 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

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[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

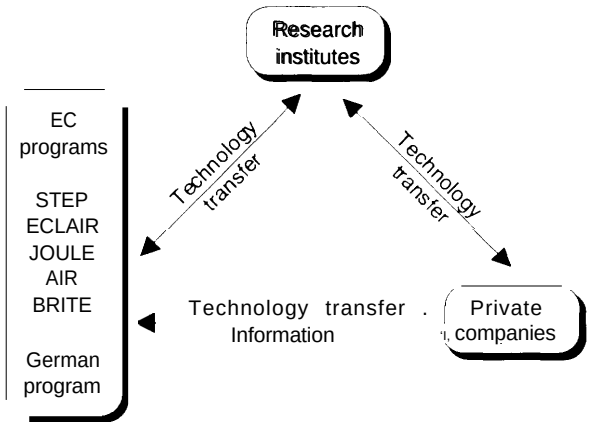
The European Community is currently funding several R&D programs that directly and indirectly involve biopolymer technology. These programs are attempting to develop new nonfood applications for agricultural commodities, alternative energy sources, and materials with superior environmental properties, 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

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-

Figure 3-I—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.

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).

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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-l—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 sugarbeets 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]

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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-

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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.

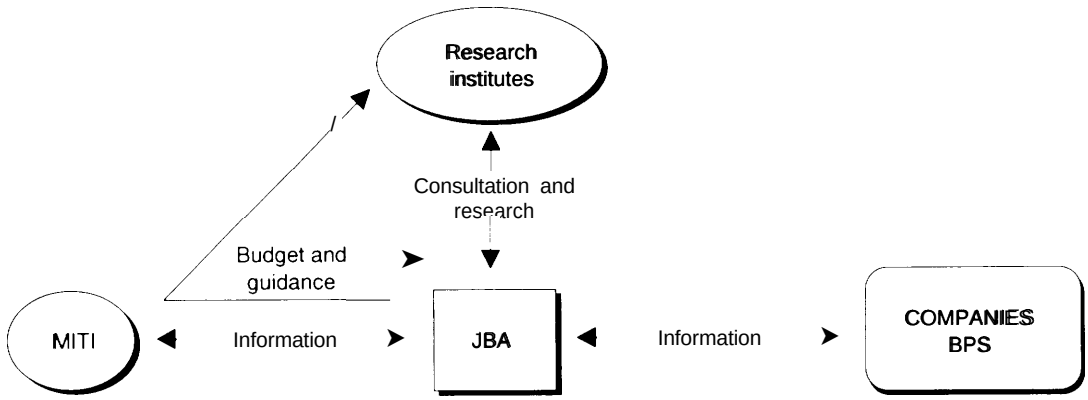
34 For ~-pie, scientists at the Tokyo Institute of Technology are working on genetic modification of PHA materials, and researchers at Keio University are investigating water-soluble polymers based on starch oxidation products and vinyl monomers.

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 biode-

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., .ootnote31.

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 lnk	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 BioInformation 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, Japanese 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: BioInformation 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”	Will 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 BioInformation 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.

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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.

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).

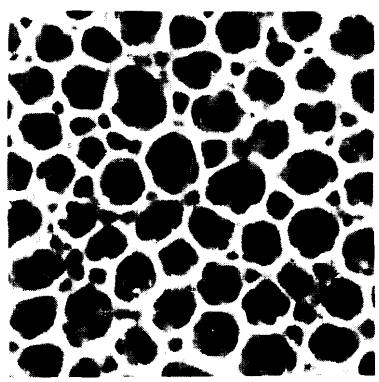

Table 4-1—Federal investment in Manufacturing/Bioprocessing Biotechnology[a] ($million)

	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]Th, 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-

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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 utilitization, 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

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-polyg lycolic 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 Ramanl Narayan, Mlchigan 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

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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 BioInformation 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 biopoly - mers 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.

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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).