BEYOND DISCOVERY

THE PATH FROM RESEARCH TO HUMAN BENEFIT

POLYMERS AND PEOPLE

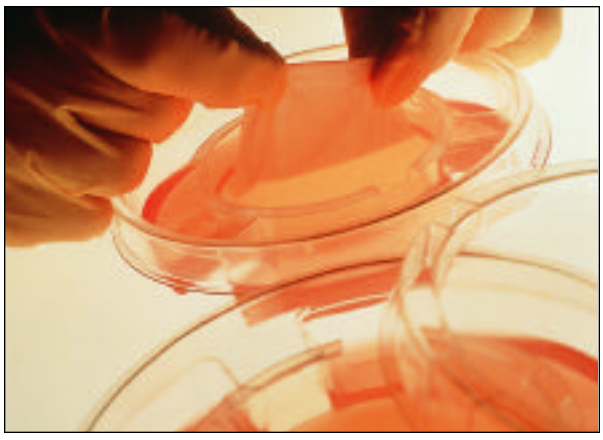
In April 1997 Dr. Frank Baker, an emergency medicine specialist from the Chicago area, took part in a clinical trial to test a form of artificial skin for treating insulin-dependent diabetics whose tissue had been degraded by the secondary effects of chronic high blood sugar. Baker, who has had diabetes for more than four decades, was in danger of losing a foot because of hard-to-heal skin ulcers. For him the trial results were close to miraculous: the laboratory-grown skin didn't just cover and protect his wound, it released chemicals that caused his own tissue to grow back much faster. As Baker put it, the artificial skin "saved my foot."

The material that worked this medical wonder was synthesized from polymers, long molecular chains formed by the chemical bonding of many small molecules of one or more types. Most people are probably more familiar with polymers in the form of the plastics that make up such everyday products as plastic food containers, bubble wrap packing, and videotape. But polymers also are found everywhere in nature. Wood, animal and vegetable fibers, bone, and horn are polymers, for example, as is the deoxyribonucleic acid (DNA) inside the cell nucleus and the membrane that separates one cell from another. Indeed, when the polymer industry began in the nineteenth century, it made materials that were derived from natural polymers—artificial celluloid from plant cellulose, for instance. Eventually the industry began synthesizing new materials, such as nylon, that replaced natural materials and were made without natural precursors. Today products that straddle the boundary between living and nonliving—like Frank Baker's artificial skin—are beginning to suggest exciting possibilities for improving human health.

Behind these developments lies more than 150 years of progress in polymer research by hundreds of scientists as well as more than a century of research in cell biology and organ transplants. As described in the following article, which highlights the work of only a few of many researchers, the path to recent advances in modern medical treatment began with the investigations of scientists interested in a better basic understanding of chemistry and biology.

Sorting Out Nature

Humanity has a long history of trying to understand the substance and structure of the physical world around us, whether by simple observation or experimental manipulation. In ancient Greece, for example, Aristotle concluded that all materials were made up of combinations of only four elements: air, earth, fire, and water. During the Middle Ages, alchemists tried in vain to convert common metals into gold. By the late eighteenth century, chemists had begun

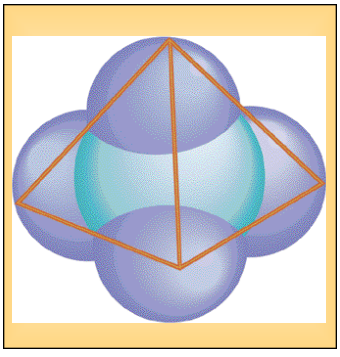


Artificial skin grown in the laboratory on scaffolding made of long chain molecules called polymers can help heal the wounds of patients with ulcers caused by poor blood circulation. (Photo courtesy of Organogenesis Inc.)

synthesizing and breaking down chemicals in an effort to determine their fundamental components. Early in the nineteenth century, English chemist John Dalton, observing that chemicals would combine only in specific ratios, concluded that matter was made of indivisible "atoms" (a concept first proposed by the Greek philosopher Democritus in about 400 BC). Nineteenth-century chemists also determined that it was possible to synthesize so-called organic compounds, once believed to be made only in living organisms, from inorganic chemicals.

Even as chemists pursued their investigations into the nature of nature, inventors were creating new materials by treating natural substances with various chemicals at elevated temperatures and pressures. In 1839, American inventor Charles Goodyear discovered a technique, which he called vulcanization, for manipulating the properties of the sap from rubber trees by treating it with heat and sulfur. The process converted a gummy, springy material used mainly to erase ("rub out") into a dry, tough, elastic material that would make automobile tires possible—and eventually a transportation revolution.

Investigators working at the theoretical level were equally productive, arriving at a series of independent realizations that would eventually lay the foundation for the polymer industry. In 1858, German chemist Friedrich Kekulé developed the framework for understanding the structure of organic molecules when he showed that a carbon atom can form chemical bonds with up to four other atoms and that multiple carbon atoms can join together to create long chains—a discovery also made at about the same time by Scottish chemist Archibald S. Couper. Then, in 1874, Jacobus van't Hoff of the Netherlands and Joseph Le Bel of France independently suggested that the carbon atom's four bonds are arranged so that they point at the corners of a tetrahedron, or pyramid. Since carbon atoms are the framework for natural and artificial polymers, the two discoveries would in time furnish a three-dimensional picture of the molecular structure of polymers.



A key discovery in the late 19th century was that the carbon atom can form bonds with up to four other atoms, each marking one corner of a tetrahedron, or pyramid. Many carbon atoms can bond, forming long molecular chains, or polymers, in possible combinations that number in the billions.

Launching the Polymer Industry

In 1870, four years before the structure of the carbon atom was elucidated, American inventor John Wesley Hyatt won a contest to find a material for billiard balls to replace ivory—then as now in short supply. Hyatt's prize-winning contribution was celluloid, based on cellulose, a polymer that is the basic structural material of plant cell walls. It was the start of the polymer industry. Hyatt treated cellulose nitrate, or guncotton—an explosive material made by exposing cotton plant fibers to nitric and sulfuric acids—with alcohol and camphor. What he got was a hard, shiny material that could be molded when hot. Cheap and uniform in consistency, this new material did indeed replace ivory in billiard balls. Occasionally though, when the celluloid billiard balls collided, they created a small detonation like a firecracker because of the explosive nature of cellulose nitrate, which is related to trinitrotoluene (TNT) in composition. Celluloid also replaced horn in combs, found wide use in housewares, and was made into the first flexible photographic film. In 1887, Count Hilaire de Chardonnet created a related product when he learned to spin cellulose nitrate into Chardonnet silk, the first synthetic fiber to enter production and a forerunner of rayon, nylon, and Dacron.

Both celluloid and Chardonnet silk were polymers created by altering natural polymers. The first truly synthetic polymer did not come along until 1909, when American inventor Leo Baekeland treated phenol, or carbolic acid, another derivative of coal tar, with the preservative formaldehyde under heat and pressure. His product, Bakelite, was hard, immune to harsh chemicals, electrically insulating, and heat resistant—characteristics that made it useful for a myriad of household goods and electrical parts. Soon Bakelite was being used to make tools, machines, and cookingware.

Science Explains Polymers

The rapid success of Bakelite sparked a flurry of synthesis investigations and innovations in both America and Europe. As the financial stakes rose, the hit-or-miss garage inventor's approach that had dominated the industry gave way to more systematic

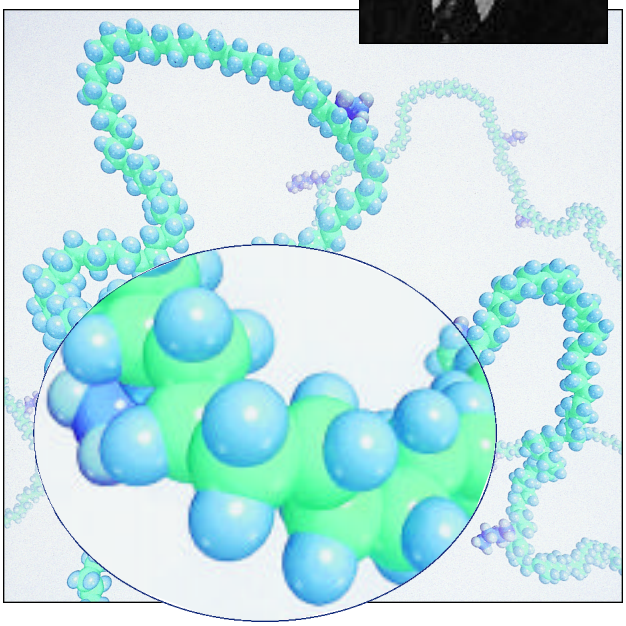
efforts. No longer content simply to tinker with raw materials and various processing conditions, scientists began basic research designed to understand the molecular structure of polymers.

In 1920, the German chemist Hermann Staudinger, fascinated by the seemingly unique properties of polymers, began investigating their behavior and chemical characteristics. Staudinger's research suggested that polymers are composed of long chain molecules of many identical or closely related chemical units. Moreover, he suggested that their unusual tensile strength and elasticity are a result of that great length or, in chemical terms, of their high molecular weight. Staudinger's ideas may not sound especially radical today, but at the time he was ridiculed by his colleagues in organic chemistry, and his theories had little impact on the scientific community. Indeed, the existence of polymeric chain molecules was not accepted until 1928, when Kurt Meyer and Herman Mark, working for the German chemical trust I. G. Farben Industrie in Ludwigshafen, demonstrated their existence by examining the crystalline structure of polymers with x-rays. Many years later Staudinger was recognized for his efforts and persistence, when in 1953 he became the first polymer chemist to receive a Nobel Prize.

Staudinger's key insights—that polymers are long chains of many small chemical units and that chain length plays a crucial role in determining physical properties and behavior—pointed up the need for tools to assess molecular weight and thus chain length. One of the first tools was the ultracentrifuge, invented by the Swedish chemist Theodor Svedberg. The ultracentrifuge spins samples at very high speeds and can separate molecules according to their size. It can be used to estimate both the size of the molecules and the distribution of sizes in a given polymer sample.

By the end of the 1920s, armed with better tools and better theories, polymer scientists were making dramatic breakthroughs. In 1928, the DuPont Corporation hired chemist Wallace Hume Carothers to build new kinds of polymers in a new laboratory dedicated to basic research. To test Staudinger's still-controversial theory, Carothers carefully joined small organic compounds into long chains and examined the properties of his products. He found that collections of very long chain molecules produced stiffer, stronger, and denser materials. By 1930, Carothers's systematic synthetic approach was bearing fruit as he came up with a new class of polymers called polyamides, or "nylons." These polymers could be melted and drawn into a remarkably strong fiber.

In 1920, German organic chemist Hermann Staudinger proposed that the unusual strength and elasticity of polymers was due to their great length and high molecular weight. (Photo of Hermann Staudinger courtesy of Institute for Macromolecular Chemistry, Freiburg, Germany); (Diagram of a polymer, in this case, polyethylene strands, courtesy of Biografx)



The Glory Years

When nylon was introduced as a substitute for silk in stockings in 1937, the new material—strong, cheap, and easy to work with—became an unqualified commercial hit. The instant success of nylon fibers and neoprene, the first synthetic rubber, taught the polymer industry an important lesson—that basic research can lead to products that can replace natural materials. It can also eventually lead to Nobel prizes. Paul Flory of Stanford University received one for his career contributions to polymer science while working in both academic and industrial laboratories. Flory was instrumental in developing the theory of how polymer molecules behave, especially through mathematical and statistical analysis of the shape and properties of polymer chains.

The 1930s were the glory years for the development of new synthetic polymers, producing polyvinyl chloride (PVC), polyurethane, polytetrafluoroethylene (Teflon), and polystyrene, which together would

revolutionize the fabric, coating, houseware, packaging, and insulation industries. These new materials bore no resemblance to their raw materials (which were commonly oil or natural gas) and were celebrated for their very artificiality. Because many of these polymers became malleable when heated, they came to be called "plastics" from the Greek word meaning "able to be molded."

Another important development beginning in the late 1930s and 1940s was the large-scale production of artificial rubber, spurred by the booming automobile industry and the military demands of World War II. By 1930, two new forms of artificial rubber had been developed in Germany, both based on the petroleum byproduct butadiene. As tensions grew in Europe, the U.S. government recognized the vulnerability of the nation's rubber supply and in 1941 established the Rubber Reserve Company to produce 10,000 tons of rubber annually. By the middle of 1942 the production goal had soared to 850,000 tons annually in response to the Japanese occupation of the East Indies, whose vast rubber tree plantations had supplied the world with the raw material for rubber. Polymer scientists and engineers worked together to develop a variety of new processes to meet wartime demands. One of the most important was a light-scattering technique developed by Peter Debye of Cornell University, who used it to determine the molecular weight and sizes of very long polymers. Polymer scientists used this knowledge to analyze the artificial rubber. Modern versions of his technique are invaluable to researchers characterizing complex molecules.

Polymers from Petroleum

Although both the science and technology of polymers had advanced remarkably by the early 1950s, formidable challenges remained to be surmounted. Because of the abundant supply and low cost of their component petroleum-derived building blocks or "monomers," hydrocarbon polymers containing only carbon (C) and hydrogen (H) atoms represented a potentially highly useful class of substances. Particularly attractive targets were polymers of the smallest and most abundant such monomers, ethylene and propylene (containing two and three carbon atoms, respectively). The general ability of such molecules, containing pairs of carbon atoms connected by "double bonds," to join together to form long chains (see figure opposite) had long been recognized (a familiar example being polystyrene). However, in the case of ethylene and propylene this presented a formidable challenge. The "polymerization" of ethylene had been accomplished, but only at undesirably

Timeline

This timeline shows the chain of research that led to an understanding of polymers and the development of some of their medical uses.

1839
Charles Goodyear invents the process of vulcanization, which makes rubber into a dry, tough, springy material.

1858
Chemists Friedrich Kekulé and Archibald Couper show that organic molecules are made up of carbon atoms combined chemically into different shapes.

1870
John Wesley Hyatt markets celluloid, a plastic made of chemically modified cellulose, also called cellulose nitrate.

1887
Count Hilaire de Chardonnet introduces a way to spin solutions of cellulose nitrate into Chardonnet silk, the first synthetic fiber.

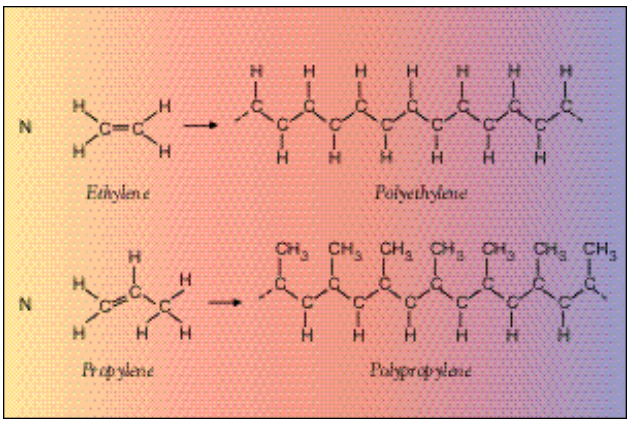
1909
Leo Baekeland creates Bakelite, the first completely synthetic plastic.

1920
Hermann Staudinger proposes that polymers are long chains of smaller units that repeat themselves hundreds or thousands of times. He later receives a Nobel Prize for his research on the synthesis and properties of polymers.

1920s
Kurt Meyer and Herman Mark use x-rays to examine the internal structure of cellulose and other polymers, providing convincing evidence of the multiunit structure of some molecules.

Late 1920s
Wallace Hume Carothers and his research group at DuPont synthesize and develop applications for synthetic polyesters, neoprenes, and nylons.

1930
Germans develop two types of synthetic rubber (Buna-S and Buna-N) from butadiene, a petroleum byproduct.



Polymerization of ethylene and propylene to polyethylene and polypropylene.

high temperatures and pressures, yielding polymers whose properties left much to be desired. The polymerization of propylene remained to be achieved.

In 1953, while engaged in basic research on the reactions of compounds containing aluminum-carbon bonds, the German chemist Karl Ziegler, working at the Max Planck Institute for Coal Research in Mulheim, discovered that adding salts of certain other metals such as titanium or zirconium to these compounds resulted in highly active "catalysts" (substances that speed up chemical reactions) for the polymerization of ethylene under relatively mild conditions. Furthermore, the polymers formed in this way, because the chains were longer and more linear, had greatly superior properties such as strength, hardness, and chemical inertness, making them very useful for many applications.

Building on Ziegler's discovery, Italian chemist Giulio Natta, working at the Milan Polytechnic Institute, demonstrated that similar catalysts were effective for the polymerization of propylene. Furthermore, with such "Ziegler-Natta catalysts" it was possible to achieve exquisite control of the chain length and structures of the resulting polypropylene polymers and, thereby, of their properties. Among other remarkable achievements of this class of catalysts was the synthesis of a polymer that is identical to natural rubber.

Industrial applications of "Ziegler-Natta catalysts" were realized almost immediately and with various subsequent refinements continue to expand. Today, polyethylene produced with such catalysts is the largest volume plastic material and, together with polypropylene, accounts for about half of the U.S.'s current annual 80 billion pound production of plastics and resins. The uses of polyethylene and polypropylene extend to virtually every facet of industry and daily life, including building and construction materials, containers, toys, sporting goods, electronic appliances, textiles, carpets and medical products. In many of these applications polymers replace other substances, such as glass and metals, but their distinctive properties

1930s
Paul Flory develops a mathematical theory to explain the creation of polymer networks "in which polymer fluids form cross-links and become, like rubber, elastic." Flory would receive a Nobel Prize for his lifetime contributions to polymer chemistry in 1974.

1940s
Peter Debye develops a light-scattering technique for measuring the molecular weight of large polymers.

1953
Karl Ziegler discovers catalysts for polymerization of ethylene. Giulio Natta synthesizes polypropylene. Their discoveries were recognized by a Nobel Prize.

1963
Edward Schmitt and Rocco Polistina file a patent for the first absorbable synthetic sutures, made of polyglycolic acid, a key plastic in tissue engineering.

1975
Robert Langer and M. Judah Folkman use polymers to isolate chemicals that stop the formation of blood vessels, suggesting a new way to attack cancer. These studies also establish the feasibility of controlled release of macromolecules.

1986
Langer and Joseph Vacanti demonstrate that liver cells grown on a plastic framework can function after being transplanted into animals, opening the door to the new field of tissue engineering.

1996
The U.S. Food and Drug Administration approves polymer wafer implants for treating brain cancer.

1997
Clinical trials show that artificial skin can heal diabetic skin ulcers, establishing the potential clinical feasibility of tissue engineering.

also have given rise to entirely new applications, including medical uses.

In 1963, the Nobel Prize in chemistry was awarded to Ziegler and Natta "for their discoveries in the field of the chemistry and technology of high polymers." In his acceptance speech, recalling the circumstances of his pioneering discovery and the scientific obstacles that had to be overcome, Ziegler went on to say:

"But a much more formidable impediment might have presented itself. In order to illustrate this, I must elaborate on the paradox that the critical concluding stages of the investigations I have reported took place in an institute for 'coal research.' When I was called to the Institute for Coal Research in 1943, I was disturbed by the objectives implied in its name. I was afraid I would have to switch over to the consideration of assigned problems in applied chemistry. Since ethylene was available in the Ruhr for coke manufacture, the search for a new polyethylene process, for example, could certainly have represented such a problem. Today I know for certain, however, and I suspected at the time, that any attempt to strive for a set goal at the very beginning would have completely dried up the springs of my creative activity."

Working with Nature

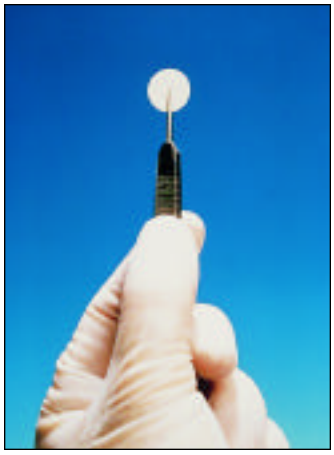
As new applications for polymers were being found, some researchers wondered whether they could also play a role in the human body, perhaps in repairing or replacing body tissues and cartilage. The idea was not entirely new. The natural polymer collagen, found in animal connective tissue, had been used as surgeon's thread for more than 2,500 years. And as early as the 1860s, an artificial polymer called collodion, invented a decade earlier by the French chemist Louis Ménard, was used as a liquid dressing for minor wounds. Collodion, made from a solution of cellulose nitrate in alcohol and ether, formed a solid film that could be peeled off after the wound healed. The excellent barrier properties of polymers were also central to an experiment in 1933 by Italian biologist Vincenzo Bisceglie, who implanted tumor cells encased in a nitrocellulose membrane in a guinea pig. The cells survived, protected by the membrane against attack by the host animal's immune cells.

Meanwhile, the question of contending with the body's immune system was becoming a critical one in medicine. Scientists were beginning to recognize that many diseases of the heart, liver, and kidney actually involved failures of these organs, and they were initiating efforts to replace damaged organs with healthy ones. However, the body's immune cells—which are designed to seek out and destroy any foreign tissue—are unable, for example, to distinguish between an unwanted bacterial infection and a much-desired transplanted kidney. Although some early drugs, such as corticosteroids, azothropine, and 6-mercaptopurine, helped in combating rejection, the problem began to fade only after 1969, when Swiss microbiologist Jean Borel discovered that a soil fungus, cyclosporin A, would selectively interfere with the specific immune cells that drive the rejection reaction. The 1983 approval of cyclosporin A by the U.S. Food and Drug Administration (FDA) gave transplant surgeons a tool that has since saved the lives of thousands of patients with heart, liver, or kidney failure.

Designer Polymers

Cyclosporin A encouraged a wave of transplants and also helped set the stage for the current rise in "tissue engineering," as scientists call the construction of whole artificial organs. Transplant surgeons, who no longer lost patients because of the rejection of their transplants, now were faced with a new frustration—losing patients for lack of donor organs. One of those frustrated doctors was Joseph Vacanti at Boston's Children's Hospital, home of the first

Physician Joseph Vacanti (left) and chemical engineer Robert Langer joined forces in the early 1980s in an effort to create artificial tissues. Within a few years they had grown liver cells on a polymer framework, giving rise to the field of tissue engineering. (Photo of Vacanti courtesy of Charles Vacanti, of Langer courtesy of Robert Langer).



Roughly the size of a dime, biodegradable polymer wafers (left) can be implanted in specific places in the brain after cancer surgery to deliver cancer-killing drugs at a controlled rate. The implanted wafers deliver drugs only to the brain (far right) rather than to the whole body. (Photos courtesy of Guilford Pharmaceuticals)

successful human organ transplant. In 1983, Vacanti began talking with his friend Robert Langer, a chemical engineer at the Massachusetts Institute of Technology, about the feasibility of making an artificial liver and possible other artificial tissues to save the lives of his young patients.

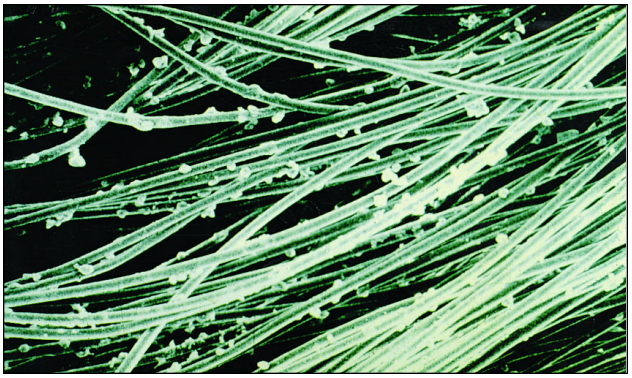
It was a tall order. Nobody had built any kind of working organ, let alone one as complex as the liver. In addressing this task, Langer called considerable experience to bear on attacking the problem in a rational way. In the mid-1970s, he had developed some polymer systems for M. Judah Folkman of Harvard University, who was then investigating the role of new blood vessels in promoting the growth of cancerous tumors, and was looking for a slow-release mechanism to release compounds that block the chemical messengers that control angiogenesis, the formation of new blood vessels. Langer discovered that polymers such as ethylene-vinyl acetate, which absorb very little water, could slowly deliver these chemical messages.

One polymer that Langer eventually focused on was polyglycolic acid, or PGA, which was also used in synthetic degradable sutures and had reached the market in 1970. PGA itself had been known since at least 1950, when Norton Higgins of DuPont patented a three-step process for making it from glycolic acid by carefully manipulating temperature and pressure. The patent Higgins filed did not mention medical applications, but in 1963 Edward Schmitt and Rocco Polistina of American Cyanamid Company filed a patent for the formation of sutures from PGA. When the sutures reached the market seven years later, they were rapidly adopted as a strong, reliable, and workable replacement for the traditional collagen-based absorbable sutures that surgeons had used until then.

Using PGA and similar polymers, Langer crafted degradable and nondegradable polymer pellets into an intricate porous structure that allowed the slow diffusion of large molecules. (This finding is the foundation of much of today's controlled drug delivery technology.) Loaded with chemical messengers, the pellets played a key role in Langer and Folkman's 1975 discovery in cartilage of the first compound that blocks the formation of new blood vessels, thereby halting tumor growth.

In 1984, at about the same time he was approached by Joseph Vacanti, Langer teamed up with Henry Brem, a brain cancer surgeon at Johns Hopkins Medical Institutions, to test his new techniques using polymers against brain cancer. Although there were new tools for finding tumors, including computed tomography and magnetic resonance imaging scanners, the most malignant brain cancers remained largely untreatable. Cancer cells remaining after the tumor's removal were protected from chemotherapy drugs by the so called blood-brain barrier, which prevents a variety of blood-borne chemicals from penetrating the brain. Brem wondered if polymers could slowly release cancer-killing drugs right where they were needed—in the brain itself.

Langer responded by designing surface-degrading polymers that released medicines at a controlled rate. In 1992, Brem and Michael Colvin, now director of the Duke Cancer Center, implanted drug-bearing polymer wafers after brain surgery. The wafers prolonged the lives of both experimental animals and human patients. Since the chemicals were released locally, they did not result in the systemic toxicity typical of anticancer drugs. With FDA approval in 1996, the wafers represent the first new treatment for brain cancer in 25 years. Similar slow-delivery systems are



A scanning electron micrograph reveals cells growing on long polymer fibers, the first step in creating artificial tissues. (Photo courtesy of Robert Langer)

now being used to treat prostate cancer, endometriosis, and severe bone infections.

All these efforts laid the groundwork for researchers' continuing search for a framework for growing replacement body parts and organs, such as livers. By now scientists had learned that human cells grown on flat plates did not produce the normal array of proteins, while cells grown on three-dimensional scaffolds had relatively normal biochemistry. At first the best results were obtained from PGA, but since the best source of fibrous PGA in 1984 was degradable sutures, hours were spent unwinding sutures to transform the fibers into meshlike plastic scaffolds to support liver cells. Still, by 1986, liver cells on plastic frameworks were surviving and functioning after transplantation into animals, laying the groundwork for using polymer scaffolds to create a variety of tissues, from bone to cartilage to skin.

The polymer scaffolds, made with nonwoven fabric techniques borrowed from the textile industry, have now been used to grow at least 25 types of cells in animals or people and have thus become a kind of generic framework for artificial organs. Biotechnology firms are using the scaffolds to make artificial skin for treating diabetic ulcers and severe burns. They multiply living cells in culture (from tissue that is normally discarded during surgery), and then "seed" the cells on the polymer scaffold. Applied to the patient's wound, the material protects against deadly infection and fluid loss. More important, the cells it carries release chemical growth factors, signals that stimulate normal cellular growth at the wound site. These chemicals account for the roughly 60 percent improvement in healing that diabetics like Frank Baker experience with artificial skin. As tissue engineers look to the future, they are talking about using polymer scaffolds to grow nerve cells for use in spinal cord repairs, bone or cartilage cells for joint repairs, pancreatic cells to make insulin for diabetics, and liver cells to make livers for transplantation.

Through all of these efforts by many kinds of scientists, several facts stand out. The path from need to benefit travels through many areas of science and technology and depends crucially on the insights provided by basic research. The first polymer inventors made progress by transforming natural materials in hit-or-miss fashion, but their work greatly accelerated after basic researchers clarified the fundamental characteristics, such as the relation between size or molecular weight and physical properties, that govern the behavior of polymers. Similarly, the progress in medicine and biology that gave birth to organ transplantation still relies on basic research into the role of chemical messengers, genetic codes, and cellular function. As polymer science and materials engineering join forces with biology and medicine to produce these modern miracles, we again see how interdisciplinary collaboration and essential basic and applied research remain the true source of benefits as simple—and profound—as a living tissue that can be created in the laboratory.

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