

CHEMICAL ENGINEERS IN THE BIOMEDICAL FIELD: FROM DISCOVERIES TO SOLUTIONS

*“So long as men can breathe or eyes can see,
So long lives this, and this gives life to thee.” William Shakespeare, Sonnet 18*

The human body is a complex and responsive chemical factory. Muscles shiver to warm the body when the temperature falls. The pancreas produces insulin to control blood sugar levels. The kidneys remove urea, minerals, and water from the blood. White blood cells organize themselves to defend the body against infection.

Efforts to understand and view humans as a collection of interrelated “chemical” systems began in the mid-1800s, when Claude Bernard, a French physician and physiologist, helped introduce the rigors of the scientific method to medicine such as

- establishing the role of the pancreas in controlling digestion,
- determining the glycogenic function of the liver (which later helped understand the critical roles played by glucose and insulin in regulating vital bodily processes), and
- demonstrating that nerves could either expand or constrict blood vessels, a breakthrough that helped understand the vasomotor system (*vaso* refers to blood vessels).

Bernard’s investigations of the role of the nervous system in the control of metabolism, circulation, and respiration also led him to the concept of feedback control loops, which was the forerunner of modern physiological systems theory.

Over the last half century, chemical engineers have contributed to various biomedical endeavors. They have helped modernize disease diagnosis and treatment options, improve the safety and efficacy of drug delivery mechanisms, and achieve better therapeutic outcomes, resulting in longer, healthier, more productive lives for patients.

In the 1950s, a chemical engineering professor, Edward Merrill of the Massachusetts Institute of Technology (MIT), was asked to help local doctors measure the viscosity of lung mucus (for the treatment of cystic fibrosis) and human blood (a fluid’s viscosity is a measure of its thickness, or resistance to flow, when exposed to stress). Despite his

extensive industrial experience devising ingenious instruments for measuring the viscosity of complex fluids, both of these biomedical problems had revealed some technical challenges that continued to defy the engineering community for years to come.

In the 1960s and 1970s, chemical engineers were involved in the analysis of rheologic issues and mass transport phenomena (to establish, for example, diffusion rates through biomembranes) related to such artificial organs as kidney dialysis machines and lung oxygenation units. A growing number of chemical engineers were engaged in solving complex flow problems—related to, among other things, heart valves—by using Newtonian fluid-mechanics analysis. (Newtonian fluids flow like water, while non-Newtonian fluids are those whose viscosity, or ability to flow, changes as the applied rate of strain changes.)

During the 1980s, chemical engineers began applying sophisticated mathematical models to help researchers better understand complex biomedical phenomena, such as cancer and arteriosclerosis, and develop advanced options for detection, analysis, and treatment.

Exploiting synergies

Chemical engineers have been developing not only systems that can deliver precise amounts of reactants to chemical reactors and other chemical process operations, but also analytical techniques, monitoring devices, mathematical models, and process control technologies to maximize chemical conversion rates and reaction yields and to manage the reaction kinetics and mass and heat balances.

Over the last several decades, these increasingly sophisticated techniques in the chemical engineers' toolbox have been ingeniously applied to a broad array of biomedical challenges. For example, chemical engineering has been invaluable in scaling up promising biomedical discoveries, and its principles are widely applied to the design and construction of commercial-scale facilities producing antibiotics, vaccines, and other therapeutic drug compounds.

By the 1950s, chemical engineers had become directly involved with the burgeoning biochemical and pharmaceutical industries, and their expertise was routinely used to design world-class facilities that could produce the target compounds. Engineering challenges during the scale-up for these compounds included

- producing products with all the desired properties, at required volumes,
- achieving desired yields and purity levels,
- managing all waste streams to minimize the operation's impact on the environment, and

- controlling costs.

Medical and biomedical researchers continue to decipher the complex phenomena occurring within the human body and to devise therapeutic approaches that help patients manage diseases and medical conditions. And chemical engineers play a key role in the design of complex, innovative medical devices to treat human ailments and highly engineered medical systems that can function as “artificial organs.” They work closely with biomedical researchers in the pursuit of novel drug delivery techniques to ensure the accurate, targeted delivery of drug compounds within the human body and to maximize the safety, efficacy, and therapeutic outcome for the patient, while controlling the dosing and minimizing potential side effects associated with potent or toxic drug therapies. Chemical engineers have improved both unit operations, such as extraction, distillation, filtration, and crystallization, and guideline principles related to thermodynamics, mass and heat transfer, and reaction kinetics, among other things. These efforts have fostered countless promising ideas and lifesaving strategies For the biomedical community.

Biocompatible materials

Many biomedical breakthroughs have been made possible by the discovery of novel materials that provide a certain desired functionality while being both biocompatible with and biodegradable within the human body. In the early days, biocompatible materials were often selected by chance and proven efficacious by trial and error. Recently, more biocompatible materials are designed “from scratch” and then systematically evaluated to meet some functional needs. Ongoing collaboration between chemical engineering and biomedical communities has helped discover and develop many promising materials, and design facilities to produce them at desired purities and commercial-scale quantities.

By 1965, a variety of biocompatible plastics and composites were available for use in prosthetic devices and replacement valves, arteries, and veins. By 1989, the first biodegradable plastic “scaffolds” were developed for producing various types of human tissue.

The discovery of polyacrylamide gels also helped usher in a new era in biomedical-materials research. When subjected to small changes in solvent concentration, acidity, light, magnetic fields, or temperature, these gels swell to hundreds of times their original size—or shrink in volume by as much as 90%. Chemical engineers devised potential uses for such gels in both industrial and biomedical applications. Today the gels are used in gel-based actuators, valves, sensors, optical shutters, molecular separation systems, controlled-release systems for drugs and other substances. Other potential applications of responsive gels in bioreactors containing immobilized enzymes and in improved bioassay systems are also being investigated.

Two chemical engineers in particular have contributed significantly in this area: Edward Merrill of MIT who started working with these responsive gels in the 1960s and Allan Hoffman, also of MIT (and later the University of Washington) who prepared the first pure, radiation-crosslinked gels for use in medical applications in 1964.

Kidney dialysis machines: a classic chemical engineering invention

The development of the widely used kidney dialysis machine provides a good example of the lifesaving synergies that can result when biomedical researchers and chemical engineers work together. Kidney dialysis machines—often called artificial kidneys—are used to treat patients who have lost kidney function owing to disease or injury. The machine is essentially a mass transfer device that cleanses the patient’s blood to remove elevated levels of salts, excess fluids, and metabolic waste products (to control blood pressure and maintain the proper balance of potassium and sodium in the body).

The dialyzer is essentially a large canister that contains thousands of small membrane fibers. During use the patient’s blood is passed a few ounces at a time through these membrane fibers, where it encounters a cleansing fluid (a chemical formulation called dialysate, whose composition is tailored for each patient) that helps to separate unwanted constituents from the blood. Once this highly specialized filtration process is complete, the clean blood is returned to the body.

The first practical “artificial kidney” was developed during World War II by the Dutch physician, Willem Kolff. The original device was a 20-m-long tube that relied on cellophane sausage casing as a dialyzing membrane. While it effectively removed toxins from the blood, it could not extract excess fluid from the bloodstream.

Capillary artificial kidneys (hollow-fiber dialyzers): 1964-1967

Richard Stewart, a physician and researcher, and his group determined that the use of cellulose acetate capillary fibers would have a practical application as an artificial kidney. The original “capillary kidney” demonstrated that substances could be selectively removed from the blood along with excess water. They eventually developed larger versions for clinical use by setting as their criteria that the device must be as efficient as the “twin-coil dialyzer,” but that it must also have a lower priming volume and be more reliable. The capillary artificial kidney has become the standard for hemodialysis today.

Another improvement was the Skeggs Leonards plate dialyzer, which was first developed in 1948 by using membrane sheets sandwiched between rubber pads and relied on

negative pressure to remove excess water from blood by ultrafiltration. It was later used as the SMA 12-60 autoanalyzer for analyzing blood.

In 1964, in an effort to make kidney dialysis more affordable, Charles Bernard Willock had designed and built a prototype using available materials and \$250 for new parts, 500 of which were sold during the first year of operation. Sales increased to 300 machines per month in 1977, but they were suitable only for use in a hospital setting and required refinements to make the treatment more accessible. Meanwhile, also in 1964, Albert Babb, a chemical and biomedical engineer, and his colleagues at the University of Washington designed and developed a portable, fail-safe, single-patient dialysis machine. Within five years this stand-alone single-patient machine would become the dialysis system of choice throughout the world. In 1990, it was named one of the “Ten Wonders of Biomedical Engineering” by the Biomedical Engineering Society.

In the early years operating conditions related to ultrafiltration, blood flow, and fresh dialysate addition rates were set empirically (by direct observation or experimentation). A mathematical model was needed to allow for the most rapid dialysis that do not cause adverse effects, such as brain swelling and related neurological symptoms that can occur when solutes are removed too quickly.

In the late 1960s, Peter Abbrecht, who holds both a Ph.D. in chemical engineering and an M.D. from the University of Michigan and the U.S. Dept. of Health and Human Services, Dept. of Health and Human Services, and Nicholas Prodan, a National Institutes of Health Special Fellow in Bioengineering at the University of Michigan, developed a mathematical model of the artificial kidney system. The model considered the movement of water and solutes across the dialyzer membrane and between extracellular, intracellular, and brain-body fluid compartments, as well as the effects of changing dialyzer operating variables, such as dialysate addition rate, blood flow rate, and ultrafiltration rate. The modeled predictions agreed excellently with data from dialysis patients and thus proved useful for optimizing dialyzer operating variables, reducing dialysis costs, and improving patient’s health and safety under various operating conditions.

Chemical engineers have pioneered breakthroughs in kidney dialysis, which have led to similar advances in heart-lung machines, diagnostic tools and treatment options for cancer, and systems to help keep people alive. In many cases, these systems required, among other things, the development of novel materials not reacting with blood, advanced membranes for biomedical separations, and complex algorithms and related process-control systems to model, optimize, and automate these processes.

Managing diabetes

Currently, about 16 million Americans have diabetes, and the number of people with this chronic disease continues to increase worldwide putting an enormous medical and economic burden on society. Today roughly 16 million Americans have diabetes. It is the leading cause of new cases of blindness in adults between 20- and 74-year-old, and, as a result of the circulatory problems it can cause, diabetes is also responsible for more than half of all lower-limb amputations in the U.S.

Glucose is the main fuel that powers all cells of the body through its energy-releasing reaction with oxygen. The ability to maintain a reasonably constant concentration of glucose in the various body tissues is essential to maintaining one's health. The hormone that regulates glucose metabolism in cells is insulin. It is a critical compound for maintaining normal blood glucose (sugar) levels.

People with type-1 diabetes are unable to produce sufficient levels of insulin in their pancreas. People with type-2 diabetes are unable to use insulin properly within their cells. Both type-1 and type-2 diabetics must regularly monitor their blood glucose concentration. Type-1 diabetics must adjust their blood glucose levels by carefully managing the nature and timing of their food intake and by administering insulin—historically by needle injection. Type-2 diabetics must also adjust their blood glucose concentration by managing the nature and timing of their meals, exercising, and using a variety of prescription medications, including injected insulin.

For diabetics the need to monitor and maintain proper glucose levels in the body on an ongoing basis is challenging, and if levels are not properly maintained, there can be life-threatening implications. For example, excessive insulin levels after injection can result in hypoglycemic (low blood sugar) coma and even death. Conversely, when insulin levels in the blood are not sufficient, the patient will experience rising blood glucose levels and may suffer from hyperglycemia and ketoacidotic coma. Coma may occur with either too little or too much insulin. Low insulin levels can also lead to such long-term complications as blindness, kidney failure, and amputations.

The need to take blood samples and administer insulin injections several times each day is often both uncomfortable and disruptive for the patient. In recent years the chemical-engineering and biomedical communities have worked together to develop improved techniques for both monitoring blood-sugar levels and administering insulin.

To reduce the pain and inconvenience of regular blood sampling, a team led by chemical engineer, Adam Heller, who at the time worked at California-based TheraSense (now Abbott Diabetes Care), developed a rapid, microanalytical technique requiring a much smaller sample of blood than previous sampling techniques—just 300 nL, which is about

one-eighth of what a mosquito draws when it bites a human being. It then uses a miniature electrochemical sensor to analyze and monitor blood glucose levels. First introduced in 2000 and now widely used worldwide, this “thin-strip” device enables most diabetics to sample and monitor blood-sugar levels easily with little or no pain.

A further advance in glucose monitoring is being pursued by Heller and his colleagues at the University of Texas. These researchers have built a miniature continuous glucose monitor by electrically wiring a glucose-reacting protein (enzyme) through an electron-conducting hydrogel. In the early prototype design, a continuous glucose monitor was implanted beneath the skin and connected to a small transmitter on the skin. It transmits instantaneous data related to glucose on a miniature electronic receiver. And also is being developed to analyze the data trend and alarm for actual or impending high or low glucose concentrations. At the heart of this “smart” device are sophisticated, patient-specific medical algorithms (jointly developed by medical researchers and chemical engineers) that gather and analyze the information to provide the most meaningful insight into the dynamic condition of glucose levels in the body. This monitor is also being developed and tested in diabetic patients by Abbott Diabetes Care..

Another advance in treating diabetes is automatic insulin-injection pumps. These precise, computerized device, which draw on well-established micropumping techniques developed by chemical and mechanical engineers, are typically the size of a pager (2 x 3 in.) and can be carried on a belt or shirt pocket. The insulin-pump reservoir is connected by plastic tubing to a catheter or needle under the skin and can be programmed to deliver a continuous infusion of insulin 24 hours a day. This instrument helps patients achieve better blood glucose control.

Meanwhile, to simplify the apparatus required for insulin injections, in 1987 Novo Nordisk introduced the first insulin pen device. This compact device combines the insulin container and the syringe in a single modular unit, which provides patients with precise, convenient insulin delivery “on the go.” Recently, biomedical and chemical engineers have been perfecting promising “jet injector” insulin-delivery systems. These “needleless” devices rely on the use of a compressed gas (such as CO₂) to blast ultrafine particles of insulin through the surface of the skin. Similarly, an inhaler device to deliver insulin is also under development.

Many chemical engineering technologies have been developed to improve the monitoring of glucose level and allow insulin to be delivered without needle injections. For instance, engineers working on these devices had to determine the complex fluid dynamics of particle suspensions and devise ways to deliver insulin as a mist.

Tissue engineering

Tissue engineering involves the use of living cells as engineering materials. Promising research and development activities related to tissue engineering occur at the crossroads of the chemical engineering, materials science and life sciences professions. All three must contribute to developing biological substitutes that can restore, maintain, or improve tissue functions, and even perform as functional substitutes for entire human organs.

A key breakthrough discovery occurred in 1998 that mammalian cells could be divided without limit by extending the length of a cell's telomeres (highly repeated DNA sequences on the ends of the chromosomes, which function as a disposable buffer and protect the cells from degradation). Before this discovery, laboratory cultures of healthy, noncancerous mammalian cells would only divide a fixed number of times.

Engineered tissue and organ substitutes and other ingenious devices are being developed to repair or replace damaged or diseased organs and tissues and to replicate, augment, or extend the functions performed by the human body. Examples include

- the transplantation of cells that can perform specific biochemical functions, such as improving liver or bladder function;
- the repair or replacement of structural tissues, such as artificial skin, bones, cartilage, blood vessels, tendons, and ligaments; and
- activities related to regenerative medicine, such as the use of stem cells to produce various types of functional human tissues.

The advent of a process known as scaffold-guided tissue generation has been a key enabling technology for tissue engineering. Scaffolds, or supports, made from biodegradable, biocompatible polymers are used to encourage the growth and differentiation of the new tissue so that it exhibits the functions of the target tissue.

First, specialized separation techniques—clearly the domain of chemical engineering—are used to separate and collect the specific cells of interest. For example, specific types of blood cells are typically extracted and separated from whole blood using centrifugation. Meanwhile, solid tissues are usually minced, digested with enzymes, and then separated using centrifugation to isolate the targeted cells.

The separated cells are implanted or “seeded” onto highly porous scaffolds made from biodegradable polymers (along with growth factors) and designed to support three-dimensional tissue growth. When isolated cells are injected into the body at random, they cannot form tissue structures, but when they are allowed to grow close together on these

scaffolds, the cells can form desired structures allowing them to function, for example, as capillaries or skin. These scaffolds must be appropriately designed to permit cell attachment, retain the desired biochemical characteristics, provide the cells with nutrients, and remove product wastes.

Cell growth on the scaffolds can be done outside the human body to create usable tissues or within the human body as implants. In either case the scaffolds must be biodegradable so that they can break down and be absorbed by the surrounding tissues to eliminate the need for surgical removal after implantation. Moreover, the degradation rate of the biodegradable polymer scaffolds must roughly match the tissue formation rate so that the new tissue assimilate into normal, healthy tissue as the scaffold biodegrades over time.

The development of suitable replacement human tissues is still in its infancy, but numerous breakthroughs demonstrate the enormous potential of this endeavor. One early example—replacement skin for the treatment of burn victims—has been shown to grow over engineered polymer scaffolds in just weeks to months. Researchers are also pursuing viable techniques to enhance and maintain the functions of mammalian stem cells and neurons.

Biodegradable microbraided polymeric fibers are also being designed as nerve guide conduits to help use tissue engineering during nerve regeneration. All these imaginative endeavors call on the expertise and technical contributions of chemical engineers working in concert with biomedical researchers.

Improved drug delivery methods

Medications have been delivered to patients conventionally by ingestion (orally) or by needle injection (intravenously), both of which have drawbacks. To enhance both the safety and efficacy of drug delivery within the body and the comfort and convenience for the patient, the chemical engineering and biomedical communities have devised a variety of improved drug delivery techniques. Early breakthroughs include nasal sprays delivering a precise amount of a finely atomized version of the drug via inhalation and transdermal patches delivering the medications at precisely controlled rates through the skin. In both cases, the challenge for chemical engineers has been to design methods that can guarantee the delivery of precise, repeatable dosages to minimize the risk for overdose (which could be fatal) or insufficient dosing (which could fail to achieve the therapeutic objective).

A number of controlled-release systems have been developed based on the 1970 work by Robert Langer, a chemical engineer at MIT, and his colleagues. They discovered that when very hydrophobic polymers (ethylene vinyl acetate or lactic glycolic acid

copolymers) are mixed with macromolecules, such as peptides or proteins, under appropriate conditions, highly porous structures can be created through which specific molecules can then be released for 100 of days.

Another innovative application of biodegradable, biocompatible polymers is in a controlled-release wafer that can be impregnated with drugs. This novel drug delivery mechanism has also been pioneered by Langer and his colleagues at MIT. The first such application was a wafer devised from a water-soluble polymer and impregnated with a potent chemotherapy drug called BCNU (carmustine) to treat patients with glioblastoma (an aggressive type of brain tumor). When implanted, the slow-release wafer delivers precise amounts of chemotherapy near the afflicted area. If administered intravenously (the traditional approach), this aggressive drug would damage many healthy cells in the body and create unwanted side effects for the patient. By contrast, the new approach has produces fewer side effects for the patient.

The polymers used to produce the delivery can be engineered to degrade at a constant rate so that the drug becomes available for transdermal adsorption at the correct dosage over the desired period. Nondegradable materials have also been used for controlled-release drug delivery.

Targeted drug-delivery vehicles

In recent years targeted drug delivery has become a Holy Grail of sorts for the biomedical and chemical engineering communities, and an imaginative array of drug delivery vehicles are being developed to design novel drug delivery vehicles that can

- achieve more desirable biodistribution of the therapeutic drug or chemotherapy compound within the body,
- deliver the drug payload precisely to the diseased (inflamed or infected) organs, tissues, or cancerous tumors, and
- release their drug cargo on demand, in response to some internal or external trigger (triggering mechanisms being investigated today include changes in specific environmental conditions, such as temperature, pH, and the presence of certain enzymes, and the use of external stimulants, such as magnetic, ultrasonic, and laser-beam activation).

While such futuristic drug delivery methods were once the stuff of science fiction, today a growing number of viable technologies have been demonstrated and are moving through human clinical trials. Such “Trojan horse” drug delivery mechanisms are of particular importance for prescription medications and chemotherapy drugs that degrade

within the human body, which have dose-limiting toxicity and create unwanted side effects for the patient at high exposure.

Historically, injectable, sustained-release, advanced drug delivery strategies have relied on either the encapsulation of a pharmaceutical product (using, for instance, tiny biodegradable polymeric microspheres, spherical liposomes made from layered lipids, or nanoscaled C_{60} fullerenes as the carrier) or the entrapment of a drug within a hydrogel polymer matrix or polymeric dendrimers (nanoscaled, tree-like macromolecules with branching tendrils) to

- reduce or delay the premature degradation of injected or ingested drugs once in the body,
- improve the drug's ability to both travel through the blood or digestive system and be preferentially absorbed by the diseased areas or cancerous tumors, while bypassing healthy tissue and organs,
- minimize the total amount of the drug to be administered, and
- reduce the potential side effects and collateral damage that often result when healthy tissues and organs are exposed to excessive amounts of potent prescription medications or toxic chemotherapy drugs.

Microencapsulation techniques and nanoscaled carriers are also being developed to refine the delivery of anesthesia and allow for the more targeted delivery of such contrast imaging agents as radioactive dyes, which are used in conjunction with computerized axial tomography (CAT) scanning and magnetic resonance imaging (MRI) techniques. Such efforts are aimed at helping these diagnostic tools pinpoint tumors and other types of cancer earlier.

Considerable work is also under way to “functionalize” the drug-carrying particles to increase circulation time in the body by helping them appear “invisible” to macrophages, which are responsible for removing foreign substances from the blood to navigate more effectively within the body to improve their preferential uptake by diseased cells; and reduce the toxic effects that often occur with less targeted delivery. Such work involves attaching a variety of targeting such ligands as peptides, proteins, and antibodies to the surface of nanoscaled dendrimers, fullerenes, and other drug-encapsulating microparticles.

Chemical engineering principles related to polymer processing, diffusion, and other mass transfer phenomena (to name just a few) have played an integral part in the design,

development, manufacture and use of novel drug delivery vehicles based on biocompatible, biodegradable polymers.

Hydrogels for drug and protein delivery

Hydrogels are crosslinked, highly permeable, hydrophilic polymers that form three-dimensional networks. These gel networks swell—but do not dissolve—in biological fluids under different environmental conditions, and they are stable in acidic environments. The hydrogel's three-dimensional, weblike matrix allows drugs to be entrapped and then released “on demand.” Drug release occurs as a function of changing environmental conditions (such as a change in pH, the presence of enzymes, or a variation in temperature) or the imposition of some other external triggering mechanism (such as the application of a magnetic or electric field or ultrasound irradiation).

Although hydrogels have been used for industrial purposes since the 1930s, they have become the subject of intense medical studies after some promising work in this arena during the 1960s. Researchers discovered that hydrogels offered a valuable potential drug delivery mechanism because such materials allow potent medications to pass intact through the stomach (a highly acidic environment where they would become degraded) into the intestines (where acidity levels are lower). Once there they stick to the mucosal linings within the gastrointestinal tract and then release their encapsulated medications slowly over extended periods.

In the last two decades, research into hydrogel drug delivery systems has focused primarily on systems based on a polyacrylic acid backbone. These hydrogels are known for both their superabsorbency and ability to form extended polymer networks through hydrogen bonding.

In 1997, Nicholas Peppas and his chemical engineering colleagues at Purdue University developed a glucose-sensitive hydrogel that could be used to deliver insulin to diabetic patients using an internal pH trigger. This novel design features an insulin-containing “reservoir” formed by a poly[methacrylic acid-g-poly(ethylene glycol)] hydrogel membrane, in which glucose has been immobilized. The membrane itself is housed between porous, non-swelling “molecular fences.”

Unlike conventional hydrogel systems, which release their entrapped drug cargo as they swell, this system works by shrinking the membrane “gates.” For instance, when an acidic environment is created around the hydrogel, higher acidity triggers the opening of the gates. Within the human body this response occurs when the body produces high sugar levels, the resulting glucose produced reacts with the immobilized glucose oxidase in the membrane gates, yielding gluconic acid. Higher levels of gluconic acid lower the

body's pH, in turn triggering the opening of the gate, which releases the entrapped glucose oxidase. Using this innovative design, the patient's own glucose levels help regulate insulin levels.

Fullerenes and dendrimers for drug delivery

Recently, two nanoscaled structures have generated a lot of excitement for both chemical and biomedical engineers and today are being developed as targeted drug delivery vehicles: polymeric dendrimers (highly branched synthetic macromolecules) and C_{60} fullerenes (also called buckyballs, hollow, soccer-ball-shaped molecules composed of 60 carbon atoms, whose dimensions are measured in terms of nanometers). Today, drug-delivery systems based on so-called dendritic polymers are also being pursued. These tiny, highly branched (treelike) polymer structures are intriguing to biomedical researchers, because their size and structures can be easily controlled during manufacture, they can easily encapsulate small drug molecules, and they are biodegradable.

Fullerenes, or buckyballs, were first discovered in the 1990s by nanotechnology pioneer Richard Smalley (a chemist) and his colleagues at Rice University. The discovery of these novel nanoscaled carbon structures was so significant that Smalley and two other chemists (Robert Curl, Jr. of Rice University and Sir Harold Kroto of the University of Sussex) shared the 1996 Nobel Prize in Chemistry.

Since the initial discovery of fullerenes, a variety of industrial-scale manufacturing techniques have been perfected to enable their large-scale production, purification and use. Here again chemical-engineering principles have been invaluable in moving these novel "chemical oddities" from the test tube to full-scale production and to explore the full breadth and depth of their potential uses in a growing list of industrial and biomedical applications.

In the biomedical area, fullerenes and metallofullerene materials (fullerene cages that enclose metal ions) are being studied to treat cancerous tumors. Fullerenes are ideally suited as a drug delivery vehicle because of their size and resistance to biochemical attack from within the body. Similarly, researchers are exploring the use of fullerenes to carry radioactive atoms within the body to assist in the *in situ* destruction of tumors, while reducing unrelated cell damage and other side effects.

Another use of novel nanoscaled materials for biomedical purposes, for which chemical engineers have been contributing, is quantum dots. These fluorescent semiconductor nanocrystals have novel electroluminescent properties and MRI contrast agents used to image cancer cells. Carbon nanotubes (seamless single- or multiwalled cylinders

composed of carbon atoms in a regular hexagonal arrangement) are also being studied for various therapeutic and diagnostic applications.

Microfluidic devices

Work on microfluidic devices has provided fertile ground for innovative collaboration between the chemical engineering and biomedical communities. These extremely small analytical devices (often called “lab-on-a-chip” assemblies) are used to carry out various chemical, biomedical and thermal reactions, measurements, and analyses with greater specificity, speed, and reliability than conventional macroscaled approaches.

Microfluidic devices allow multiple, extremely complex biomedical analyses to be carried out simultaneously, using just a few microliters or picoliters of fluids (i.e., analytes and reagents) per experiment. For example, such devices are being used to assess the impact of large numbers of potential anticancer drugs on multiple types of tumor cells simultaneously rather than sequentially. This approach gives researchers numerous advantages in terms of screening candidate drugs quickly and cost-effectively.

Microfluidic devices typically have outer dimensions that are measured in millimeters or centimeters—the size of a button, fingernail, or credit card. Inside they are configured with an array of active and passive microstructures, which include smooth or textured microchannels or capillaries, interconnected reaction chambers, and macroscaled mixers, pumps, and valves, whose dimensions are measured in micrometers (1 micrometer equals 10^{-6} , or 1-millionth, of 1 meter). At these tiny dimensions microfluidic devices have an enormous surface-area-to-volume ratio and orders-of-magnitude improvements in both heat and mass transfer compared with conventional macroscaled approaches.

The scientific community has witnessed enormous strides in the design and fabrication of sophisticated microfluidic devices for biomedical, industrial and other applications. Today novel lab-on-a-chip assemblies are being developed for a wide array of applications related to biomedical research, clinical diagnostics, and comparative and functional genomic studies.

Early-stage microfluidic devices are already showing promise for such applications as DNA genotyping, gene sequencing (to identify genetic mutations), analysis of single-nucleotide polymorphism, rapid screening for and diagnosis of various diseases and disorders, genetic predisposition testing, drug-efficacy monitoring, and drug-discovery and development efforts. Such analytical devices are also being developed for the fast and accurate identification of microbes and pathogens in water, soil, and food, and as field-ready devices for various types of forensic criminal and environmental investigations.

Researchers also hope to commercialize portable, handheld devices equipped with these inexpensive, self-contained biochips to rapidly and cost-effectively analyze complex biological fluid samples related to disease diagnosis, genetic analysis, forensic criminal and environmental investigations, the detection of biological warfare agents, and more. Such devices are expected to provide significant time and cost advantages compared with conventional laboratory-based analyses.

A rich past, a promising future

For more than a half century, chemical engineers have helped revolutionize the field of biomedical engineering and bridge the gap between promising ideas and actual, life-changing therapeutic compounds, medical devices, and engineered systems for diagnosing and treating human ailments and improving quality of life. Although until the 1960s no academic institutions in the world offered courses that linked chemical engineering to biomedical engineering and medicine (except MIT that established this academic link in 1963 with the help from Edward Merrill), the useful synergy between these two disciplines has been firmly established and continues to grow in importance.

The exciting biomedical advances described here are only the tip of the iceberg. Based on achievements of the last four-five decades, biomedical and chemical engineering principles and practices will continue to be applied to an ever-expanding array of such new areas as gene-therapy delivery, biosensor design, and the development of improved therapeutic compounds, imaging agents, and drug delivery vehicles. And the close working relationships between biomedical researchers and chemical engineers will continue to strengthen in their depth and diversity.