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Origins and Development of Biomedical Engineering within Chemical Engineering

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Over the past 45 years, the field of biomedical engineering has found a welcome home in academic chemical engineering departments and in companies working with artificial organs, medical devices, and pharmaceutical formulations. The contributions of chemical engineers to the definition and the growth of the field have been important and at times seminal. The development and early contributions in the biomedical field with special emphasis on the contributions of chemical engineers is examined. © 2004 American Institute of Chemical Engineers AIChE J, 50: 536–546, 2004

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Origins of Chemical (and Biomedical) Engineering

In the changing industrial world of the late 19th century, the chemical industry took a central position. At the end of the 19th century, the competition of England, Germany, and the United States for industrial chemicals had become rather fierce. It was not surprising then that in 1888, Lewis M. Norton (1855–1893) of the Chemistry Department of MIT offered a new course in chemical engineering. As Weber (1980) notes, the material was taken predominantly from Norton's notes on industrial practice in Germany, which at that time had probably the most advanced chemical process industry in the world.

When Norton died in 1893, Frank H. Thorpe (1864–1932), who had received a BS degree from MIT only four years earlier and a doctorate from the University of Heidelberg in 1893, took responsibility for Norton's course. In 1898, he published what may be considered to be the first textbook on chemical engineering, entitled *Outlines of Industrial Chemistry*. This first chemical engineering textbook made mention of the chem-

ical treatment of biological bioproducts, a very faint indication of very early biotechnology processes!

In the next 50 years, the term *Industrial Chemistry* first appearing in Norton's book to broadly describe industrial processes applied in the production of chemicals became associated with chemical engineering. Not until the radical approach to analysis of chemical engineering problems introduced by, among others, R. Neal Amundson and Rutherford Aris in the mid-1950s at the University of Minnesota, and R. Byron Bird, Warren E. Stewart, and Edwin N. Lightfoot at the University of Wisconsin, would "industrial chemistry" be clearly separated from the main goals of "chemical engineering".

Although Norton and Thorpe were the pioneers of chemical engineering at MIT, it was Arthur A. Noyes and later William H. Walker (1869–1934) who introduced fundamental principles to the chemical curriculum (Peppas, 1989). After an MS in Chemistry at MIT (1887) and a doctorate at the University of Leipzig with Ostwald (1890), Noyes established the Research Laboratory of Physical Chemistry in 1903. Meanwhile, William Walker, who had received his doctorate in 1892 at the University of Göttingen with Otto Wallach (Nobel Prize 1910), established in 1908 the Research Laboratory of Applied Chemistry.

During the same period in England, Davis proceeded with the publication of his *Handbook of Chemical Engineering*,

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Table 1. Examples of Important Biomedical Research Contributions by Chemical Engineers

Subject	Researcher	Ref.
Blood Rheology	E. W. Merrill, MIT	(1959)
Artificial Kidney Design	E. Leonard, Columbia	(1959)
Analysis of Hemodialysis	C. K. Colton, MIT	(1966)
Biomembranes	A. Michaels, MIT	(1966)
Heparinized non-Thrombogenic Biomaterials	E. W. Merrill, MIT	(1967)
Radiation Produced Biomaterials	A. Hoffman, MIT, U. Washington	(1969)
Contact and Intraocular Lenses	N. A. Peppas, Purdue Univ.	(1976)
Protein Delivery from Polymer Matrices	R. Langer, MIT	(1976)
Intelligent Hydrogels in Drug Delivery	N. A. Peppas, Purdue Univ.	(1979)

which was revised and published in a second edition of over 1,000 pages in 1904. Davis was the originator of the idea of “unit operations” (especially in the second edition of his book, although the term was coined by Arthur D. Little at MIT in 1915). Unit operations called for analysis of chemical processes by dividing them in distinct operations (distillation, extraction, filtration, crystallization, and so on) that are governed by distinct principles.

The training of chemical engineers was a subject of much debate in the first years of the 20th century. Milton C. Whitaker, a professor of Chemical Engineering at Columbia University, and an important contributor to the ChE literature and societal causes, expressed his views on the training of chemical engineers (Whitaker, 1911) as follows: “The chemical engineer works in the organization, operation, and management of existing or proposed processes with a view to building up a successful manufacturing industry. . . His fundamental training in chemistry, physics, mathematics, and so on, must be thorough and must be combined with a natural engineering inclination and an acquired knowledge of engineering methods and appliances”. He continued by giving a description of the types of courses that should be taught, which he classified as courses for “fundamental training” (chemistry, physics, and mathematics), “associated training” (electrical, mechanical, civil and general engineering, and business economics) and “supplementary training” (laboratory and administration courses). The terms physiology or biology were not in a chemical engineer’s vocabulary yet; it would take until the beginning of World War II before the first efforts in the biomedical field would be recorded.

Whitaker was a most influential educator and researcher, one of the earliest members of AIChE and its President in 1914. Whitaker, who had studied Chemistry (PhD 1902) with Franz Sachs, and received the Perkins medal in 1923, was a chemical engineer who believed in the rapid separation of “industrial chemistry” from “chemical engineering.”

The establishment of the American Institute of Chemical Engineers (AIChE) in 1908 gave shape to the dreams of the converted chemists who were calling themselves chemical engineers, albeit with major obstacles. For example, Hugo Schweitzer (Peppas, 1989) declared in a 1904 ACS meeting: “I am absolutely against the introduction of chemical engineering in the education of chemists.” In the same meeting, M. T. Bogert (Herreshoff, 1904), who joined Columbia in 1907, agreed with Schweitzer saying that progress in “technical chemistry” was achieved in research laboratories by researchers *without* engineering training. On the other side, Whitaker became the apologist of chemical engineers stating that a chemist was “generally not the man who is capable of trans-

mitting from a laboratory to a factory the ideas which he has developed” because he was not educated “in the engineering branches.” With such debates, AIChE had only 40 members (out of about 500 chemical engineers) when it was formed in 1908. The number rose to 214 in 1914 when Whitaker was President; it was not until 1926 that AIChE truly became a representative society of chemical engineers.

Olaf A. Hougen (1979) of the University of Wisconsin notes that it was only “from 1888 to 1923 that industrial chemistry was the chief offering of all chemical engineering departments . . .,” and he continues “in these courses, the sequences of steps in chemical manufacture were described. The approach did not allow much time for discussion in depth of the scientific principles involved.” Hougen remarks also that the introduction of unit operations by Walker, Lewis and McAdams of MIT during the 1920s “marked the beginning of the distinctive American system of chemical engineering education.” Hougen concludes that the next three decades (1920–1950) in the development of the science of chemical engineering “came with the application of physical chemistry to material and energy balances, to thermodynamics, and to rates of chemical reactions in industrial processes.”

It was during that period that the seeds of biotechnology were started, especially with the first studies on biochemical processes, biomass, and engineering devices in biomedicine. The early seeds of bioengineering were set in Europe and the U S in the 1920s and early 1930s. Early chemical engineers involved in chemical processes started applying simple operations on agricultural products as early as 1926 (Peppas, 1989).

It was in a hospital in Amsterdam in the summer of 1941 that Wilhelm Kolff, a practicing physician, designed the first primitive artificial kidney unit for blood purification. This event is marked by many as the historical beginning of the biomedical engineering field, although several other early events are also identified as important events in the history of BME. Kolff’s developments would continue through improvements in the 1950s and 1960s, and would become the field of hemodialysis, a field that benefited by the major contributions of chemical engineers such as Clark Colton and Ed Merrill of MIT, Ed Leonard of Columbia, Ben Lipps of the Dow Cordis Company, Alan Michaels, and many others. Table 1 summarizes some major biomedical research contributions made by chemical engineers in the first 20 years of the field.

Engineering Science and Biomedical Activities

The development of the field of unit operations, and the subsequent introduction of thermodynamics and chemical kinetics led to further developments of the chemical engineering

field, and the emergence of biomedical engineering activities within chemical engineering.

The year 1955 marked an important change in engineering education throughout the United States. In May 1952 S.C. Hollister, President of the American Society for Engineering Education (ASEE), appointed a *Committee on Evaluation of Engineering Education* with the goal to evaluate engineering education and suggest new approaches to teaching engineering. When the report of this committee was published on June 15, 1955 a long chapter in the history of engineering education had ended. The report was only 36 pages long. It was polite to the older tradition, but firm in its recommendations to the new generation (ASEE, 1955). "The objective in engineering curricula will not be achieved. . . by repair of patchwork curricula. It requires complete reconstruction of curricula.

Some attention to engineering art and practice is necessary, but its high purpose is to illuminate the engineering science, analysis or design, rather than to teach the art as engineering methodology.

It is the responsibility of the engineer to recognize those new developments in science and technology that have significant potentialities in engineering. Moreover, the rate at which new scientific knowledge will be translated into engineering practice depends, in a large measure, upon the engineer's capacity to understand the new science as it develops.

Fortunately, some things do not change. Reactions, stresses, and deflections will still occur, and they will have to be calculated. Electrical currents and fields will follow unchanging laws. Energy transformation, thermodynamics, and heat flow will be as important to the next generation of engineers as to the present one. Solids, fluids, and gases will continue to be handled, and their dynamics and chemical behavior will have to be understood. The special properties of materials as dependent on their internal structure will be even more important to engineers a generation hence than they are today. *These studies encompass the solid, unshifting foundation of engineering science upon which the engineering curriculum can be built with assurance and conviction* (authors' italics)."

Gradually the framework of a scientifically oriented curriculum was built. The recommendations of the Hollister report led to the development of *engineering science*. The impact of this committee's views on chemical engineering was monumental. In the early days of *chemical engineering*, the teaching of and research in industrial chemistry was the central theme.

Around 1920, unit operations became the main focus of chemical engineering research and education, and were so until World War II. In the 1930s applied thermodynamics also became an important component of academic chemical engineering.

Two developments that occurred at the University of Minnesota and the University of Wisconsin in the 1950s changed the course of chemical engineering. Five academic researchers would become the leading forces of major changes in chemical engineering education and research. These five researchers were Neal R. Amundson, Rutherford Aris, R. Byron Bird, Edwin N. Lightfoot, Jr. and Warren E. Stewart. Their "message" was controversial and much questioned, but it was gradually accepted by both industry and academia.

Amundson was an educator and researcher with far-reaching insight. He realized that further insight into chemical engineering problems lay in an analysis of chemical processes and

phenomena based on a fundamental understanding of these problems. Applied mathematics, and later the computer, would become excellent tools for generalization and solution of various transport and reaction engineering problems.

At about the same time, a second major educational revolution was occurring at the University of Wisconsin. Professors Bird, Stewart, and Lightfoot, collectively known to future generations of students as BSL, prepared a set of notes (in 1957), and eventually a book (in 1960) entitled *Transport Phenomena*, which offered a new approach to the analysis of chemical engineering unit problems. The main lesson of BSL is that there is a strong unifying backbone to apparently different unit operations in the framework of the continuum equations of transport. The necessity for analysis of individual operations or processes does not disappear, but the differential volume and the balance equations become the central theme of this approach.

Thus, in the mid-1960s the major chemical engineering departments in the U.S., with a handful of exceptions, were adjusting to the new ideas of our profession. Unit operations had definitely declined, and unit processes were almost obsolete as unifying themes for education and research.

In the midst of this major transition, biomedical engineering principles entered the field almost by chance. In fact, biomedical engineering appeared in ChE because some enterprising physicians in Boston and New York had important medical problems that they were willing to discuss with chemical engineers. What is particularly noteworthy is that the origins of biomedical engineering activities in chemical engineering are closely related with the development of transport phenomena in ChE. Several early pioneers of the late 1950s and 1960s indicated to the authors that their first association with biomedical problems was in response to medical needs by practicing physicians in local hospitals. Some of these problems were related to blood separation and purification, blood flow, measurement of viscosity or shear stresses (Merrill, 1967; Merrill et al., 1965), or improvement with simple medical devices (Merrill, 1984).

Early Interdisciplinary Work in Chemical Engineering

The birth of BME within chemical engineering was part of a broader revolution, the implications of which would not be felt until the mid 1970s, but which had started in chemical engineering in the early 1960s. This new trend was initiated by a group of gifted educators and researchers in various universities and industrial government laboratories. These researchers recognized that chemical engineers could contribute to areas outside of the main attention of classical chemical engineering, interdisciplinary areas such as biochemical and biomedical sciences, and polymers. They included Elmer L. Gaden of Columbia and Arthur E. Humphrey of the University of Pennsylvania in biochemical engineering, Arthur B. Metzner of the University of Delaware and R. Byron Bird in polymer rheology, and Edward W. Merrill of MIT and Edward Leonard of Columbia in biomedical engineering.

The changes in ChE research directions were affected by major changes in research funding. The National Science Foundation, National Institutes of Health, and other federal

agencies became important sources for funding of the new work of chemical engineers.

Important new developments in research in bioengineering were initiated in the mid 1950s. Columbia University was in the middle of these changes as young engineers in its faculty became pioneering of the two main branches of bioengineering. Formal instruction in biochemical engineering at Columbia first began in 1950 through the efforts of Elmer Gaden. In the area of biomedical engineering, Ed Leonard initiated his earliest biomedical studies in 1958, and went on to publish two important ChE articles in the biomedical field on analysis of solute transport in hemodialyzers (Leonard and Bluemle, 1959, 1960). Leonard went on to win the Allan P Colburn Award from AIChE in 1969 “for fundamental contributions to the engineering and design of artificial organs”. This was the first recognition of the impact of bioengineering and specifically biomedical engineering to the field.

Another pioneer of the field was Edward W Merrill, an MIT professor. Merrill was educated at Harvard and MIT, and received his ScD in 1947 while working with Herman Meissner on adhesion of polymers. Similar to Leonard, Merrill’s earliest excursion in biomedical engineering was because he was asked by Boston physicians to help solve an important problem of measurement of blood viscosity. Thus, around 1956 he became one of the very early investigators of the non-Newtonian behavior of blood under low and moderate shear rates (Merrill, 2003). He investigated the effect of the hematocrit, various plasma proteins, and white blood cells on blood viscosity and flow behavior, and he developed appropriate experimental tools for rheological investigations of blood (including the patented Gilson–Dauwalter–Merrill (GDM) viscometer) under realistic in vitro conditions. AIChE has recognized Merrill with three awards, including the 2002 Founders Award. It is interesting that Ed Leonard and another pioneer of the biomedical field, Allan Hoffman of the University of Washington, were undergraduate students in the first “Unit Operations” class that Merrill taught at MIT in 1951 (Leonard, 2003). Twelve years later Merrill introduced the first BME graduate course in chemical engineering, the course 10.56 “Engineering in Biology and Medicine.” Merrill and Leonard remain active in biomedical engineering research at MIT and Columbia today, addressing among other issues, biomaterials improvement, and the interaction of cells with surfaces.

The development of biomedical interests in chemical engineering happened at about the same time as in other fields. In electrical engineering, this occurred in 1952. On the occasion of the fiftieth anniversary of the Engineering in Medicine and Biology Division of IEEE, a valuable history of the field was published, that includes numerous oral histories by chemical engineers (Nebeker and Geselowitz, 2002).

The early years of chemical bioengineering focused on bio-rheology and analysis of transport phenomena in artificial organs, especially in hemodialyzers and lung oxygenators. The earliest *AIChE Journal* contribution of biomedical interest was by Powers and associates on mass transfer in blood oxygenators (Landino et al., 1966). Two more articles on the same problem were published in 1968 by Lightfoot (Lightfoot, 1968)) and Dan Hershey (Hershey and Karhan, 1968).

Other chemical engineers conducted important studies examining mass transfer in various blood filtration devices. An important period in Merrill’s research deals with his attention

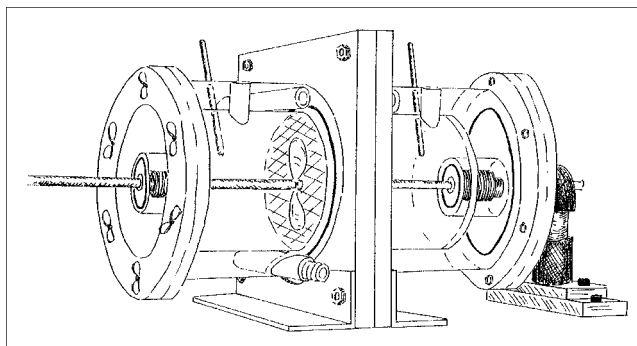


Figure 1. Diffusion cell from the mid 1960s used in detailed studies of solute permeation in biocompatible membranes with possible use in hemodialyzers

to problems related to solute diffusion in biomembranes, and to applications of membranes to artificial kidney devices. With the expert assistance of his graduate student Clark Colton (now at MIT), the foundations were set for what is now the accepted methodology for evaluation of membranes in hemodialyzers. Of numerous outstanding publications in this area, Colton et al. (1969) is particularly significant. This article refers to a free-volume analysis of high-molecular-weight solute diffusion in polymers, and today it is the most acceptable theory for analyzing experimental data of solute diffusion and/or predicting related diffusion coefficients.

Colton (Colton et al., 1971a,b) and Leonard (Leonard and Bluemle, 1959, 1960) were early pioneers in these areas. The work by these two individuals helped define a number of the mass-transport properties of different hemodialysis membranes (Colton, 1987). An early diffusion cell was used in some of the pioneering studies of Colton at MIT in the mid-1960s to analyze solute permeation in candidate membranes for hemodialysis and is shown in Figure 1. In addition, such studies led to a rigorous and consistent set of protocols for characterizing the transport characteristics of hemodialysis membranes (Gotch et al., 1972; Leonard et al., 1974; Klein et al., 1977). Colton provided a better understanding of how different solutes can be removed by hemodialysis (Colton, 1987). Important contributions to the performance of hemodialyzers were also presented by Cooney et al. (1978).

From an educational point of view, the early days of BME within chemical engineering were characterized by the authorship of a wide range of textbooks; both undergraduate and graduate, written by major leaders of the field (see also Table 2). Of these, Cooney’s book became the best-seller of the field in the 1980s, whereas Lightfoot’s monograph was and continues to be a standard graduate textbook. Peppas and Mallinson (1980) conducted the earliest survey of BME in the field of chemical engineering, and reported on trends of that physiology-based, pre-biology BME period. In 1980, 79 U.S. and Canadian ChE departments were offering at least one BME course.

Although significant contributions to biomedical transfer problems were made during that period, chemical engineers contributed also to biomedical fluid mechanics. Lightfoot (1973) summarized a number of flow problems solved through Newtonian fluid mechanics analysis in elastic conduits. Impor-

Table 2. Early Textbooks or Monographs in Biomedical Engineering Contributions by Chemical Engineering

Daniel Hershey, ed. Richard C. Seagrave	Chemical Engineering in Medicine and Biology, Plenum Press, New York (1967) Biomedical Applications of Heat and Mass Transfer, Iowa State University Press, Ames (1971)
Stanley Middleman Kenneth H. Keller Edwin N. Lightfoot Jr. David O. Cooney	Transport Phenomena in the Cardiovascular System, Wiley, New York (1972) Fluid Mechanics and Mass Transfer in Artificial Organs, ASAIO, Washington, DC (1973) Transport Phenomena and Living Systems, Wiley, New York (1973) Biomedical Engineering Principles, Dekker, New York (1976)

tant contributions towards understanding the complex flow in heart valves were initiated in the PhD thesis of Ajit Yoganathan at the California Institute of Technology (for example, Yoganathan et al., 1978) and led, over the next 25 years, to major contributions by Yoganathan's group to our understanding of the flow behavior of blood in artificial hearts.

As mathematical modeling of biomedical phenomena became more advanced in the early 1980s, chemical engineers made seminal contributions to other fields, such as cancer research and arteriosclerosis. With a careful analysis of the heat-transfer characteristics of tumors, Rakesh Jain and his associates at Columbia, Carnegie-Mellon and Harvard (see, for example, Gullino et al., 1982) developed a most successful mathematical analysis of temperature gradients in tumors, and, thus, contributed to our understanding and detection of cancer. Meanwhile, Clark Colton and his associates at MIT (Feig et al., 1982; Truskey et al., 1981) were among several engineers who contributed to our understanding of the development of arteriosclerotic plaques using aortic transport studies with radioactively labeled low-density lipoproteins and cholesterol. Associated modeling analyzed this transport with diffusional, convective, carrier-mediated transport and vesicular transport mechanisms.

Biomaterials

In the early days of biomedical engineering, chemical engineers became pioneers in the development of biomaterials science and engineering. This is probably associated with significant ChE contributions to the broader field of polymer science whose chemical engineers were early pioneers. From 1965 to the early 1980s, contributions by Allan Hoffman, Edward Merrill, Buddy Ratner, Stuart Cooper, Nicholas Peppas, Robert Langer, Larry McIntire, Michael Sefton, David Tirrell and others opened up the field of biomaterials science. Table 3 summarizes some groups of biomaterials to which chemical engineers made contributions in the early days of the biomedical engineering field.

Some of the early contributions in biomaterials involve the

research of Merrill and his coworkers who did some of the first studies, understanding what would cause compatibility of biomaterials in contact with blood. Merrill's initial studies examined whether heparin might allow a surface to be anti-thrombogenic (Merrill et al., 1966; Britton et al., 1968). He and others conducted studies to test whether it was the high water content of hydrogels that could be useful in preventing thrombogenicity, but recognized that this was not sufficient (Merrill et al., 1970). Merrill and colleagues followed these studies by examining hydrophobic polymers such as poly(dimethyl siloxane), but they recognized that these too were thrombogenic (Gifford et al., 1976).

As early as 1974, Merrill and coworkers then turned to poly(ethylene oxide) (PEO), and showed that it could be useful as a biomaterial (Merrill and Salzman, 1982). They found that when PEO was absorbed onto glass vessel walls, subsequent absorption of proteins, or viruses from solution was prevented. Other water-soluble polymers that they studied were not nearly as effective. Building on these studies, Merrill then went on to produce materials in which PEO chains were crosslinked by phase separation of segmented polyurethane ureas (Sa da Costa et al., 1980). He and his colleagues studied PEO and poly(ethylene glycol) monomethyl ether in crosslinked polyfunctional siloxane networks (Pekala et al., 1986), and synthesized PEO networks crosslinked by polyfunctional siloxanes (Sung et al., 1990; Chaikof and Merrill, 1990). They then synthesized PEO networks formed by radio crosslinking (Merrill, 1992), and along with Rempp and colleagues developed PEO star molecules for biomedical applications (Rempp et al., 1990).

Meanwhile, Hoffman studied the use of radiation polymerization techniques to prepare biocompatible hydrogels. Hydrogels are crosslinked hydrophilic polymers that form networks that can swell but not dissolve in biological fluids. Although available for chemical applications as early as 1935, they became the subject of intense medical studies after the pioneering work of Wichterle and Lim (1960), who prepared the earliest poly(hydroxyethyl methacrylate) (HEMA) hydrogels. These materials became the contact lenses of choice (known

Table 3. Some Significant Contributions to Biomaterials Science and Engineering by Chemical Engineers

Biomaterials	Contributors	Ref.
Cellulose Acetate as Hemodialyzer Material	C. Colton, MIT	(1966)
Hydrogels	A. Hoffman, MIT	(1966)
	E. Merrill, MIT	(1966)
Poly(vinyl alcohol)	E. Merrill, MIT	(1969)
	N. Peppas, Purdue	(1975)
	M. Sefton, U. Toronto	(1976)
Polyurethanes	S. Cooper, U. Wisconsin	(1972)
Poly(hydroxyethyl methacrylate)	B. Ratner, U. Washington	(1973)
Poly(ethylene oxide)	E. Merrill, MIT	(1974)
Polyanhydrides	R. Langer, MIT	(1982)

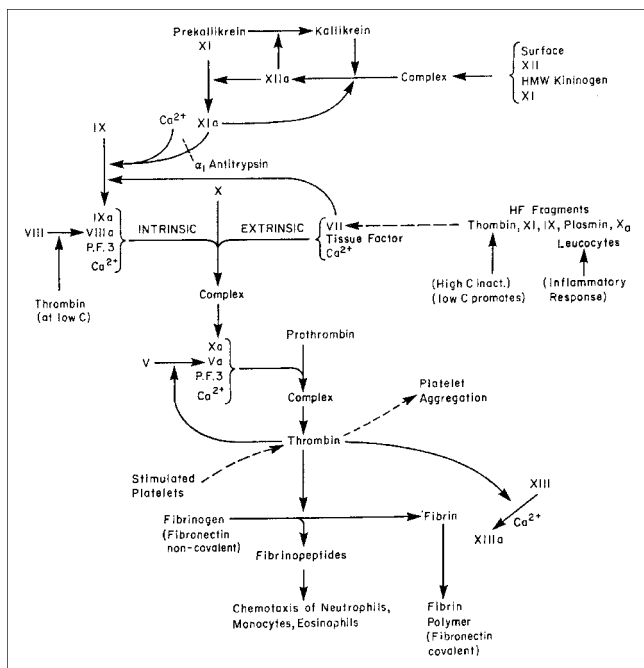


Figure 2. Blood coagulation cascade mechanism as it was known in 1975 when chemical engineers were working on the importance of fibronectin, kallikrein, prothrombin and thrombin in blood coagulation.

also as soft contact lenses) in the 1970s. Hoffman and associates became major contributors to this field.

Ratner, who joined the University of Washington first as a postdoctoral fellow and then as a ChE professor in the 1970s, made numerous contributions to the field of surface characterization of biomaterials (for example, see Ratner et al., 1990). Cooper and associates were early pioneers of the structure and analysis of polyurethanes as biomaterials (Cooper et al., 1997).

Applied thermodynamics and molecular theories were beginning to be applied to the design and understanding of the dynamic behavior of a wide range of biomaterials, and notably hydrogels. Early contributions to the development of heparinized poly(vinyl alcohol) hydrogels (Peppas and Merrill, 1977) and ultrapure polymers led to inert hydrogels for long term potential applications in articular cartilage, contact lenses and linings for artificial hearts (Hassan and Peppas, 2000). McIntire also made a number of important early contributions to biomaterials. For example, he developed new models for studying viscoelastic materials (Yen and McIntire, 1972).

Studies of the mechanisms of blood coagulation were contributed by several chemical engineering researchers including Channing Robertson of Stanford University (Watkins and Robertson, 1977), who developed the earliest internal total reflection technique for examination of protein adsorption on polymer/biomaterial surfaces. The coagulation cascade mechanism as understood in 1975, is shown in Figure 2. The work of Robertson, Merrill, Michael Sefton of the University of Toronto, Stuart Cooper at the University of Wisconsin, and other chemical engineers led to a better understanding of the function of various components in this cascade mechanism, notably kallikrein, fibronectin, and the prothrombin/thrombin mecha-

nism. Robertson along with William Deen, now at MIT, were also major originators of a detailed analysis of the renal microcirculation (Robertson et al., 1977).

Chemical Engineering Contributions to Drug Delivery

One of the medical areas of perhaps the greatest importance in terms of chemical engineering contributions has been controlled drug delivery systems. These systems now have sales on the order of 25 billion dollars a year, and have saved countless lives. Of several chemical engineers, Alan Michaels of MIT and Stanford was perhaps the earliest to conduct important studies showing how membranes could control the release of drugs. He was also a pioneer in the delivery of molecules through the skin (transdermal drug delivery). Michaels and his colleagues (including Kumar Chandrasekaran, a chemical engineer from the University of California at Berkeley and ChE-MIT-trained polymer chemist, Patrick Wong) developed the first methods of predicting what types of drug could pass through the skin (Michaels, 1976, 1985). ALZA Corporation, where Michaels served as its first executive vice-president, went on to develop a number of transdermal systems for drugs, such as estradiol, scopolamine, and nitroglycerin.

However, up until the early 1970s, it was not thought possible to deliver molecules of greater than a few hundred in molecular weight through polymers. In the early 1970s, Langer's research group began examining this issue. They discovered that when very hydrophobic polymers, such as ethylene vinyl acetate, or lactic glycolic acid copolymers were mixed with macromolecules, such as peptides or proteins under appropriate conditions, highly porous structures could be created through which molecules could be released for hundreds of days (Langer and Folkman, 1976) (Figure 3). Building on this work, various companies were able to then create controlled release systems for a variety of peptides, proteins, and other macromolecules. One important example was the development of controlled release systems for luteinizing hormone releasing hormone (LHRH) analogs, such as Zoladex, Lupron Depot, and Decapeptyl. These systems originally released the drug for one month and now do so for three or four months.

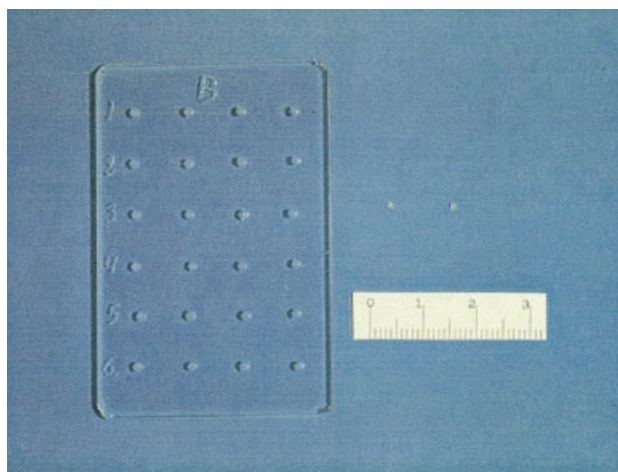


Figure 3. Glass mold and controlled release pellets for macromolecules. This scale is in mm.

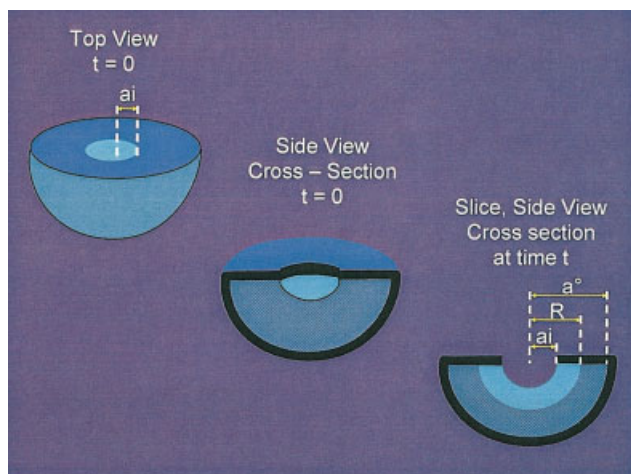


Figure 4. Hemispheric controlled release system.
(Adapted from Hsieh et al., 1983)

These systems provide the most widely used method of treating patients for prostate cancer, endometriosis or precocious puberty. More recently, controlled release systems comprised of injectable microspheres for releasing the human growth hormone (Nutropin Depot) were developed, and can be used to treat patients with pituitary dwarfism for either two weeks or four weeks from a single injection. In addition, drug eluting stents where rapamycin ($MW \sim 1,000$), or other drugs are incorporated into polymers, thus beginning a revolution in the treatment of coronary artery disease and restenosis (Morice et al., 2002; Park et al., 2003).

Chemical engineers have also contributed in creating mathematical models to predict these controlled release phenomena (Langer and Peppas, 1983). Peppas and collaborators (Gurny et al., 1982) and Chandrasekaran and Paul (1982) developed models to describe drug transport from dissolution controlled systems whereas Peppas and coworkers showed how models can predict diffusion rates from various polymer systems (Peppas and Ritger, 1987). Specifically, Peppas et al. showed that a simple exponential relationship describes drug release from most nonswellable and swellable devices. This equation has been used by numerous investigators to analyze the release behavior of various control release systems.

Another major issue is developing drug release delivery systems. If the drug is uniformly distributed in the polymer and released solely by diffusion, the release rate will decrease with time. To address this problem, mathematical models were developed based on Ficks law and material balances (Rhine et al., 1980), enabling prediction of release rates as a function of time. These equations suggested ways to obtain constant release from a matrix type system. One such system is in the shape of a hemisphere coated with an impermeable coating everywhere except for a cavity in the center face. The mathematical model predicts that such a system can release drugs at a constant rate because at early times a drug will diffuse out from near the matrix surface where little drug is available, even though the distance the drug must travel is short (Figure 4). However, at a later time, the drug will travel at a greater distance, which slows it down. The increased area of drug that becomes available as the distance from the surface increases enables the release rate to be essentially constant (Hsieh et al.,

1983). Variations of this system have been used to release drugs for human and animal health, such as antihelmintics to cattle.

Another chemical contribution to the field were the early studies on hydrophilic polymers and hydrogels for the controlled delivery of drugs, peptides, and proteins (Langer and Peppas, 1983). New "swelling-controlled release systems," exhibited an unexpected time-dependent (zero-order) release because of coupling of diffusional and relaxational mechanisms (Peppas and Lustig, 1985). Mathematical analysis with complex transport equations incorporating the viscoelastic behavior of the polymer, and its relaxational behavior led to an analysis during water swelling and drug release. Peppas and Ritger (1987) proposed the now well-known exponential time dependence of the quantity of drug released, which has become a useful equation for the analysis of non-Fickian drug delivery.

Other important contributions to oral drug delivery were in the form of novel mucoadhesive systems for targeted delivery, for example, buccal, nasal, and vaginal release (Gurny et al., 1984). For example, dose-dependent, oral drug-delivery systems that administer insulin through a gel composed of poly(methacrylic acid) (PMAA) and poly(ethylene glycol) (PEG) have been developed in the last few years (Lowman and Peppas, 1999). This is one of the first of such systems that has been shown to work via the oral route. Thus, diabetic patients can potentially avoid the cumbersome continuous injections of insulin and, instead, use dose-dependent capsules. The new system, so far tested in diabetic rats and dogs, can overcome these barriers. In tests on over 150 rats and dogs that were given capsules containing microspheres of this PMAA/PEG graft copolymer carrier, a bioavailability of up to 16% was determined.

New types of pulsatile controlled release systems are being developed. Examples include systems that can be triggered by pH, enzymes, magnetism, temperature, and ultrasound (Kost and Langer, 1991; Brazel and Peppas, 1994; Khare and Peppas, 1993). Most recently, microfabrication has been used to create novel microchips that can be used to create a "pharmacy on a chip" and provide a novel control of drug delivery systems (Santini et al., 1999).

New methods of the preparation of gels with unique molecular recognition characteristics with molecular imprinting methods have also been reported (Peppas and Huang, 2002). For example, biological sensors for glucose are being developed in research that ultimately may help to design "intelligent drug delivery" devices that could be implanted in the body to administer medications, such as insulin. Mesh-like "biomimetic" gels containing glucose molecules are being created, and use a slightly acidic chemical to remove the glucose, leaving behind spaces where the glucose used to be. The approach attempts to mimic how some molecules attach to "binding sites" on other molecules. Such binding is critical to various biological processes. Each binding site possesses the proper shape and other characteristics for it to bind to a specific molecule. An important aspect of the research is that the gels are prepared with benign manufacturing processes.

Another important focus has been on trying to create new materials for drug delivery and other medical areas. In many cases, scientists used "off the shelf" materials that somehow resembled the organ or tissue they were trying to fix. An example was the artificial heart where a polyether urethane was

used, even though it was originally derived from a ladies girdle because it had good flexural properties (Peppas and Langer, 1994). In contrast, chemical engineering design may provide an extremely useful way of creating biomaterials with nearly ideal properties. One example of this can again be found in drug delivery where initially most polymers are degraded by bulk erosion, which could possibly lead to dose dumping. From an engineering standpoint it would be far better if one could achieve surface erosion. A variety of issues must be addressed from an engineering standpoint to do this. The first is whether the materials should dissolve enzymatically or hydrolytically. Enzymatic degradation could lead to a variation from patient to patient, because enzyme levels could vary between individuals. In addition, the cellular response could change over time. However, all individuals have excess water; thus hydrolysis as a mechanism should lead to a very high degree of reproducibility.

Thus, the first design criterion would be that the polymer should be hydrolytically as opposed to enzymatically degraded. The next criterion involves the nature of the monomers. If one were to achieve surface erosion it would be important to use hydrophobic monomers that make it difficult for water to permeate the matrix. The next issue is to enable the polymer to degrade at desired rates. Here, it is important to create bonds that are very hydrolytically reactive. By examining various bond chemistries, the anhydride bond was selected. The next issue is to determine the correct monomers. Working with toxicologists one can select monomers that are able to be synthesized appropriately but will also degrade to safe degradation products. With these criteria, monomers, such as carboxyphenoxypyrone (CPP) and sebacic acid (SA) were chosen (Leong et al., 1986). These polymers were then synthesized (Leong et al., 1987; Domb and Langer, 1987; Domb et al., 1988). Interestingly, by changing the copolymer ratios of CPP to SA, the polymer can be made to last from a few days to many years (Leong et al., 1985). These polymers are now being used in combination with chemotherapy drugs to treat brain cancer patients, and became the first system approved by the US Food and Drug Administration (FDA) for treating brain cancer in over 20 years. Furthermore, this system was the first chemotherapy drug delivery system to be approved by the FDA. The concept of local chemotherapy is now being used to treat different types of cancer as well in cardiovascular disease.

A critical area in guiding drug safety and performance is pharmacokinetics. Here, Bischoff and Dedrick have pioneered the use of simulations in modeling drug disposition and kinetics from *in vitro* to *in vivo* systems, and across species. They were the first to provide simple yet accurate compartmental models for the pharmacokinetic analysis of drug distribution. Their work has been fundamental to explaining the pharmacokinetics of methotrexate and other drugs (Bischoff and Brown, 1966; Bischoff et al., 1972; Dedrick et al., 1972). Rakesh Jain's research has provided a crucial guidance in the delivery of drugs to solid tumors. He and his colleagues have shown that high-pressure is a characteristic of all solid tumors and can compromise the delivery of macromolecules to the tumor site (Helmlinger et al., 1997). He also discovered that the anomalous assembly of the collagen network is a key barrier to the delivery of macromolecules in tumors, and proposed that this barrier can be circumvented by drugs that interfere with collagen synthesis. Another important area involves biosensors to

detect glucose or other molecules. Ongoing work in electrically based biosensors by Heller provides promising research avenues where chemical engineers are developing novel materials based approaches to creating new sensors (Heller et al., 1991)

Tissue Engineering

Chemical engineers have also played a central role in creating novel approaches for forming new tissues. In one approach, cells are placed on highly porous polymer matrices. The concept is that when isolated cells are injected in the body at random, they are not able to form tissue structures. However, when they are placed close enough to each other they actually do form such structures, presumably because of signals that they would be in close contact with each other. This has been shown, for example, by placing endothelial cells close together *in vitro* where they can form capillaries (Folkman and Haudenchild, 1980), and when mammary epithelial cells are placed close together, they form acini and make milk (Bissell and Bacellos-Hoff, 1987).

Langer and Vacanti (Vacanti et al., 1988) hypothesized that by creating the appropriate polymer structures, and with the correct tissue culture medium, an environment could be created where there would be a very large surface area per unit volume, enabling a large number of cells to be grown in such a way that they would be in close contact with each other. The polymers were also designed to be degradable so that possible long-term biologic reactions to them many years later would not be able to occur. The concept was to initially design a tissue outside the body, which could then be transplanted into the body where it could function. The first polymers that were studied were lactic and glycolic acid, which have biodegradability, biocompatibility, and good physical processing properties. A variety of other polymers have been synthesized, such as poly(lactic acid) lysine copolymers that have the ability through the lysine's amino terminus to attach various informational molecules, such as peptide sequences, which could be helpful for specific cells.

Bioreactors also play an important role in growing these cells. An example has been the work of Niklason et al. (1999) who found in trying to create blood vessels, that it was very difficult to create such vessels simply with the conventional approach of growing cells on a polymer under normal tissue culture conditions. However, by connecting the cells on a polymer tube in a bioreactor to a pulsatile pump that could beat at a 165 beats per m simulating a heart, Niklason and coworkers were able to make a fully functional blood vessel that could be implanted in pigs, and stay patent for months. Tissue engineering has already led to the point where new skin can be created for burn victims, and where cartilage is being placed in patients. Various other tissues such as tendons, ligaments, livers, ureters, bones, and others are in animal trials and, in some cases, clinical trials (Langer et al., 1995; Vacanti and Langer, 1999).

A different type of approach in which chemical engineers have played a major role has been to encapsulate cells in polymers, which serve as immunoisolation membranes. Here, the concept is to create membranes that allow small molecules, such as glucose or other nutrients to diffuse through, but can prevent large molecules, such as immunoglobulins or immune cells from entering the membrane. Pioneering work by Chick and Solomon (Sullivan et al., 1991) has shown that hollow-

fiber ultrafiltration membranes could be used to treat diabetic dogs. They used an acrylonitrile vinyl chloride copolymer which is impermeable to antibodies that have molecular weights (MW) greater than 150,000. However, insulin (MW 6,000) and glucose (MW 180) were able to diffuse through it. They were able to use a relatively wide diameter fiber that could be connected to blood vessels, thus able to treat diabetic dogs in the same manner (Sullivan et al., 1991).

Other groups have used microcapsules as immunoisolation membranes. For example, Sefton and coworkers have used polyacrylates, which they were able to dissolve in low toxicity organic solvents and encapsulate islets, liver or other cells (Uludag and Sefton, 1993). They were able to make these membranes by phase inversion (Hwang and Sefton, 2000). Other scientists encapsulated cells in alginate, which can be ionically crosslinked, have synthesized novel polyphosphazenes (Cohen et al., 1990), which also can be ionically crosslinked, created new polymers that could be photopolymerized directly onto the islets (Sawhney et al., 1994).

Modeling studies may also prove useful in designing the right number of ligands on a particular material. Lauffenburger and coworkers have measured rates of migration of smooth muscle cells on surfaces coated with different amounts of either fibronectin or collagen, both of which are adhesive proteins. They discovered that very slow migration could result from low traction at very low surface concentration of the adhesive protein, or from high traction at high concentration. They also found that the rate of migration depends on both the affinity of a cell receptor for a particular adhesion ligand, and the distribution of receptors on the cell surface. When the affinity of the receptor for the ligand is strong, the cells migrate fastest at low ligand concentrations. When the distribution of receptors of the leading and trailing edges of the cell is quite asymmetric, cells migrate fast at a wide range of ligand concentration (Lauffenberger, 1991). Such findings may be useful in creating biomaterials for tissue engineering because they show that the incorporation of too many or too few ligands into this material may be counterproductive.

Future Directions

We believe that biomedical engineering is taking on a continually increased role within the field of chemical engineering. This is reflected by increased student demand, new job opportunities in the newly emerging biotechnology industry, faculty hiring, and even departmental name changes in a number of cases. This increased role reflects the challenges ahead in training and research. From a training standpoint, new courses are being designed to teach fundamentals combining engineering and biology to instruct students on critical aspects of this rapidly changing field (Saltzman, 2001). From a research standpoint, molecular design and engineering principles will be applied in a range of new areas including gene therapy delivery, biosensor design, new imaging agents, novel biomaterials, and other areas where chemistry and engineering will undoubtedly impact medicine. We believe that chemical engineering has played a major role in biomedical engineering in the past, but that its importance in the future will be even more profound.

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