The Future of Medicine: Biomaterials

Henry R. Piehler

> The abdomen, the chest, and the brain will forever be shut from the intrusion of the wise and humane surgeon.
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> —Sir John Eric Ericksen, British surgeon, appointed Surgeon-Extraordinary to Queen Victoria 1873.

> Those who forget the past are condemned to relive it.
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> —Santayana

Introduction

One commonly used definition of biomaterials is any material that is used to replace or restore function to a body tissue and is continuously or intermittently in contact with body fluids.[1] It is widely perceived that there will be significant advances in the development and use of biomaterials in the near future. In fact, many believe that biomaterials will soon become the dominant focus of materials research and that significant economic expansion will flow from this research. The very breadth of this field precludes a comprehensive, in-depth projection in all areas of biomaterials, which currently include orthopedic, cardiovascular, neurological, drug delivery, and other applications.[2] Projected future applications include the use of microrobotic devices for disease detection, drug delivery, and neurological applications, for example. Gene therapy is also identified as an alternative approach to many of these same clinical problems. Some unanticipated biomaterials-related events and changes will continue to occur; two such events which occurred during the preparation of this article will be described in the case studies to follow.

In order to provide an overview of possible future directions in biomaterials, it is useful to focus on three time frames[3]:

- The past: removal of tissues
- The present: replacement of tissues
- The future: regeneration of tissues.

Tissues are currently replaced by transplants or implants. Transplants include autografts (as in vertebral fusion), homografts (human organ transplants), and heterografts or xenografts (tissues from other species). Implants are stabilized in the human body by either cement, biological, or bioactive fixation techniques. Transplants have problems such as their availability, the need for immunosuppressant drugs, and possible viral contamination. Today's implants have a variety of shortcomings related to their fixation, and, unlike living tissues, cannot self-repair or adapt to changing physiological conditions. Tissue regeneration has the potential for avoiding these problems associated with transplants and implants through the use of engineered tissues, regenerative bioactive materials, and gene therapy. While the tendency toward regeneration rather than replacement of tissues is clearly the ultimate long-term objective, I do not believe that we have exhausted the incremental improvements possible to improve the processing and properties of our existing tissue-replacement materials, which should not be totally neglected in our pursuit of tissue replacement.

Another issue not typically addressed when considering the performance of biomaterials is the general area of information, which again can be usefully divided into three separate categories:

- information regarding the *in vivo* performance and performance limitations of biomaterials, including areas of current uncertainty and significant disagreement within and among the scientific, engineering, and medical communities;
- increased usage of information-storage and data-processing capabilities in implantable medical devices; and
- the potential utility, if any, of information technology (IT) processes such as data mining to improve the safety and efficacy of biomaterials.

Finally, no assessment of the future of biomaterials would be complete without examining the societal context in which new biomaterials or biomaterials fabrication processes are introduced. In essence this focuses on the kinetics of change as well as the thermodynamics of change, which is largely engineering and biological in origin. The Medical Device Amendments of 1976 require that all new biomaterials used in applications (or existing biomaterials used in new applications) which are life-sustaining or involve significant risks to patients must undergo premarket approval to establish their safety and effectiveness. The basic requirements are that the material be biocompatible within the bodily environment in which it is used and that it perform its intended function safely and effectively in that environment. Clinical trials involving both animals and humans are typically part of the premarket approval process. Biocompatibility testing of a new material is an extensive and expensive procedure which is undertaken only when significant performance increases in biocompatibility and/or functionality are anticipated. The tort liability litigation system also influences innovations in the use of biomaterials in that lawsuits involving not only biomaterial production defects but also materials selection or design defects are still possible even though the material has successfully undergone premarket approval. These regulatory and legal processes are traditionally described as stifling to innovation in biomaterials and medical devices; however, innovations have occurred in response to information concerning device and biomaterial deficiencies which was generated by the regulatory and/or legal processes. A final influence on the continued use or substitution of biomaterials or fabrication processes is marketplace information. Manufacturers' sales representatives are constantly seeking information about deficiencies in their competitors' products and are not reticent about conveying this information to their current and potential customers.

A number of years ago I posed several questions to address the processes of innovation and change in medical technology[4] which I believe are equally applicable to innovation and change in biomaterials:

- When and how does it become prudent to substitute a new, potentially safer and/or more effective biomaterial or biomaterial fabrication process for an older, perhaps less safe one?
- How should physicians and engineers divide their efforts between new device development and surveillance of existing devices, particularly over the long term?
- How should the normal information flow and decision making between physicians and engineers be influenced, if at all, by legal, regulatory, and risk management concerns, particularly in the case of new biomaterials or biomaterial fabrication processes?
- What roles should physicians and engineers play in formulating and communicating biomaterial risk information to patients, particularly risks associated with new biomaterials and biomaterial fabrication processes?

Materials Challenges For The Next Century presents a series of articles speculating on the role of materials in society in the coming century and beyond.

In this article, I will use case studies involving orthopedic and cardiovascular biomaterials and fabrication processes and the information issues just identified to address these questions for the near, intermediate, and long term as we move from the era of tissue replacement to the era of tissue regeneration.

Orthopedic Implants

By weight or volume orthopedic implants far exceed any other biomaterial application, both in total weight currently implanted and current implantation rate. Orthopedic implants are used both as fracture fixation devices (which may or may not be removed after fracture healing) and as joint replacement devices or prostheses. Early fracture fixation efforts involved using noble metals, probably responding to perceived biocompatibility concerns. Vanadium steels, aluminum, cobalt-chromium alloys, stainless steels, and titanium alloys have been subsequently used for both fracture fixation and prosthetic applications. Nonmetallic materials used in prosthetic applications include Teflon, silastic, and polyethylene. Data published by the American Academy of Orthopedic Surgeons[5] indicate that 138,000 hip prostheses and 245,000 knee prostheses were implanted in the United States in 1996. For 2030, these figures are projected to be 248,000 and 454,000, respectively.

While difficulties have and undoubtedly will continue to be encountered with the use of existing orthopedic biomaterials, their overall efficacy in increasing mobility and decreasing pain is unquestioned. The short- and intermediate-term questions then focus on the steps by which improved materials and processes (and designs) should be substituted to ameliorate the remaining present difficulties. The very introduction of hip prostheses by Sir John Charnley is a classic case study of adaptation to problems not anticipated at the time devices were first introduced. Charnley originally used Teflon acetabular cups in an effort to reduce friction between the acetabular and femoral components; subsequent experience revealed that Teflon flaked in this application. Sir John, in what has to be the world's largest individual recall program, removed hundreds of Teflon acetabular cups and replaced them with polyethylene cups in response to this information.

Polyethylene wear is currently considered to be the most important problem associated with orthopedic implants. Wear debris when digested leads to the production of enzymes which can cause bone loss. Near-term efforts to address the polyethylene wear problem include cross linking the polyethylene plus switching to entirely new materials systems such as metal on metal, ceramic on ceramic, and metal on ceramic. These new systems are currently being pursued primarily in Europe.

Intermediate-term solutions to the polyethylene wear problem center on the use of tissue engineering to create scaffolds on which to grow articular cartilage either outside or within the body, thus obviating the need for polyethylene. C.M. Agrawal has summarized the requirements for a scaffold as needing to be biocompatible, bioabsorbable, highly porous, extremely permeable, while at the same time providing sufficient mechanical strength and a surface that promotes cell attachment and growth.[6]

Long-term solutions are now focused on the use of gene therapy to regenerate tissues without the need of a scaffold. However, the recent death of an 18-year-old patient in a gene therapy study[7] has curtailed many U.S. studies involving human subjects, which are currently outlawed in countries like France, for example.

In some instances involving orthopedic biomaterials, new approaches have been abandoned and older practices readopted. Such is the case with polymethyl methacrylate, a bone cement (really a grout) which was used initially to secure all components of both hip and knee replacements. Some of these cemented prostheses, especially those first introduced into the marketplace, experienced bone cement failures which led to loosening and eventual revision surgery. About a decade ago this problem was addressed by the introduction of porous surfaces for bone or tissue ingrowth or ongrowth, thus eliminating the need for cement entirely. The desired response was never achieved, and cement use once again increased. A common current practice for total hip replacements is to use cobalt chromium heads and stems which are cemented into the femur in conjunction with uncemented titanium or cobalt chromium cups with a polyethylene liner. For total knee replacements the femoral, tibial, and patellar components are typically cemented, although the femoral component is sometimes uncemented.

A leading organization in the development of standards and related information is Committee F-4 on Medical and Surgical Materials and Devices of the American Society for Testing and Materials (ASTM). Beginning in 1960, ASTM has been an active participant in the voluntary consensus effort related to the generation of standards and related knowledge for biomaterials and medical devices. This consensus requires representation from manufacturers, users, and general interest constituencies. None of these three constituencies can represent a majority of the voting interests of the committee. However, to be effective, all constituencies must have equal access to credible biomaterial and medical device performance information. The shift in sponsorship of biomaterials research from government to industry, while shortening the time for innovations to reach the market, may also create an informational asymmetry which can be detrimental to managing and monitoring the risks associated with biomaterials and medical devices.

Prosthetic Heart Valves

Prosthetic heart valves were first introduced around 1960 and have continued to evolve in both their configuration and their materials and fabrication processes. Two basic categories of prosthetic heart valves are mechanical and tissue valves. Mechanical valves have evolved through several geometries starting with the first caged ball devices, followed by the caged disk, tilting disk, and bileaflet configurations. Initially metals were used for the primary structural components and polymers were used for the balls and disks. The Björk-Shiley radio opaque spherical tilting disk heart valve introduced in 1969 originally had a Delrin disk; problems with disk wear prompted the introduction of pyrolyltic carbon disks in the early 1970s. This was followed by the introduction of the all pyrolytic carbon St. Jude valve in 1983. Mechanical valves require the use of a blood thinner to prevent clotting. Tissue valves, which require the use of little or no blood thinner, are typically fabricated from porcine aortic valves or bovine pericardial tissue. All tissues are treated or fixed prior to implantation, and these treatments have evolved over the years to increase the lifetime of tissue valves, which now is estimated to be in the range of 8–12 years. The net result is the valve replacement market, which was initially dominated by mechanical valves, is more or less equally divided between mechanical and tissue valves. Current estimates for developed markets are 182,000 valves annually, of which 55% are mechanical and 45% tissue, with the tissue valves closing so that the mix may actually be 50% of each type. In the emerging world 78,000 valves are implanted annually, of which 80% are mechanical and 20% tissue valves, a mix which is not expected to change in the near future.

Two case studies will next be examined to illustrate potential pitfalls in the evolution of mechanical heart valves. The first of these involves the Björk-Shiley 60° convex-concave tilting disk heart valve, the sec-

ond the St. Jude pyrolytic carbon bileaflet valve. Each example points to the need for caution in the kinetics of innovation involving biomaterials and biomaterials processing and the need for postmarket surveillance to ensure that the anticipated benefits are actually realized and that no unanticipated adverse effects occur.

The Björk-Shiley 60° convex-concave tilting disk heart valve was introduced in 1979 ostensibly to reduce the thromboembolic complications associated with its predecessor valve, the Björk-Shiley radio opaque spherical (rs) tilting disk valve, of which about 120,000 were implanted. The rs valve contained the tilting disk between two struts, an inlet strut upon which the disk came to rest on valve closure and an outlet strut which stopped the disk in the open position. Each of these wire-fabricated struts was welded in two places to the annulus or ring of the heart valve. All components were made of the cobalt, chromium, tungsten alloy, Haynes 25. There were reports of some failures of the inlet strut welds, but the number was small compared to the total number of rs valves implanted (the number 11 has been mentioned). One change introduced in the cc valve was to make the inlet strut integral with the annulus and increase its cross sectional area at the junction with the annulus.

Three other changes were made to the rs valve to create the cc valve. The first of these was to change the geometry of the previously symmetric disk to an airfoil-like convex-concave geometry. The second involved moving the position of the outlet strut welds downstream in an effort to wash away any thrombus that might form at the still welded junctions of the outlet strut and the annulus or ring. The third was that angle which the outlet strut made with the annulus was increased, again ostensibly to reduce thrombus formation. One outlet strut failure occurred during premarket approval; this was apparently dismissed as surgical error.

A total of 86,000 cc valves were implanted worldwide until the final valves were recalled in the fall of 1986. Present estimates are that there have been 1,450 outlet strut fractures in the cc valves, leading to approximately 1,000 deaths. Several recalls and attempts to eliminate or reduce the outlet strut fracture rate were instituted. These included attempts to induce a residual compressive stress at the potential fracture site by altering the disk insertion process by bending upward as the final step. Another was to increase the opening angle from 60° to 70° to reduce the stress on the base of the outlet strut on valve opening. None of these efforts were successful; as a matter of fact, the 70° valves, which were sold only outside the United States, had fracture rates several times higher than the 60° valves. Finally the observation of wear flats on the tips of the outlet struts led to the conclusion that abnormally high loads were being applied during closure, loads which were not initially anticipated in the design of the valve. These loads on valve closure came about because the changes in the outlet strut weld position and angle allowed the disk the freedom to over rotate on closure and sometimes make contact with the tip of the outlet strut, leading to very high bending loads. Documents indicate that this abnormal loading on closure was known or suspected in 1981. It was not until April of 1984 that changes in weld position and strut angle and additional quality control procedures were instituted to eliminate over rotation. By that time Shiley had lost significant market share to the St. Jude pyrolytic carbon bileaflet valve, which is currently often used to replace cc valves which are voluntarily explanted. The time involved in solving this problem also attracted Congressional attention.[8] Valve fractures have led to a substantial number of lawsuits, including a class action lawsuit, almost all of which were settled prior to trial. Many investigators are of the opinion that weld quality contributes to strut fracture, although some consultants for the defendants vigorously deny this. A scanning electron micrograph of a single leg fatigue fracture is shown in Figure 1. Weld involvement is supported by the fact that currently used statistically based guidelines for explantation are based on valve type, valve orientation, weld date, and welder identity.

The St. Jude valve introduced in 1983 has been implanted in an estimated 600,000 people with very few reports of valve fracture (the number 28 has been mentioned). Many of these fractures have been attributed by St. Jude to mechanical damage during implantation or explantation. In any event the fracture rate is miniscule compared to the Björk-Shiley cc valve. However, St. Jude recently recalled all of their mechanical valves and other products with their Silzone® coating.[9] This silver coating to the sewing ring was introduced in an effort to reduce infection or endocarditis. However, it was subsequently found that there is a statistically higher rate of paravalvular leaks requiring explantation in patients with Silzone® coated sewing rings than in uncoated rings. Although statistically significant, this difference is based on relatively small numbers. Of 398 patients with Silzone® coated sewing rings, 11 experienced paravalvular leaks, eight of which required explantation; this compares to four incidents of paravalvular leaks in 394 patients with conventional sewing rings,

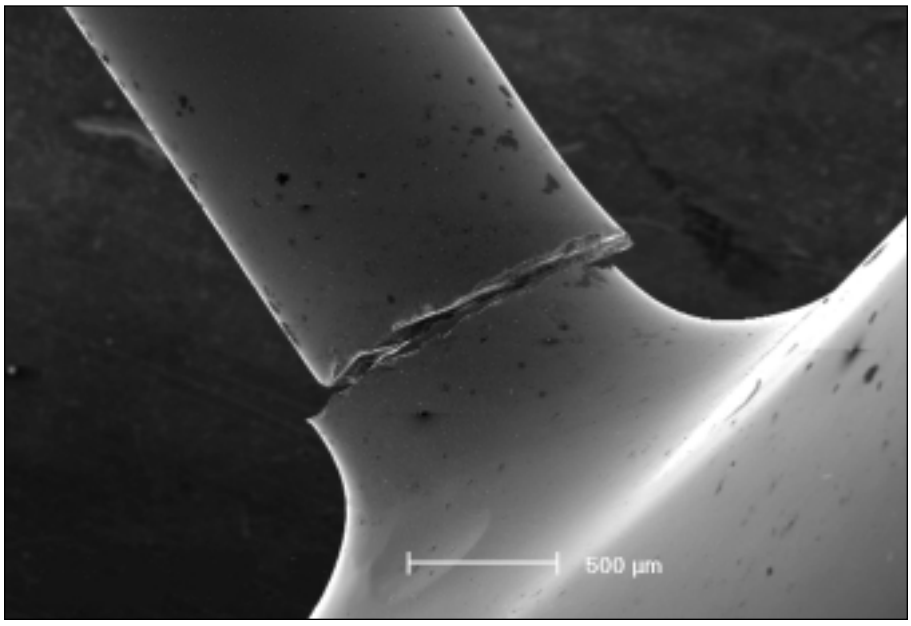

Figure 1. Single leg strut bending fatigue fracture in an explanted Björk-Shiley 60° convex-concave prosthetic heart valve. The pyrolytic carbon disk typically embolizes after the second strut leg fractures. Note that fracture did not occur in the area of maximum bending stress, suggesting that weld quality in addition to abnormal loading caused the strut to fracture.

only one of which required explantation. It is interesting to note that, like the Björk-Shiley cc valve, changes designed to improve the performance of the market dominant St. Jude mechanical valve resulted in unforeseen undesirable consequences. However, St. Jude's time frame for action was shorter than Shiley's. Yet, despite this recall action, 36,000 Silzone® coated heart valves and annuloplasty rings have been implanted since 1997.

Cardiac Pacemakers

Cardiac pacemakers, which have had a remarkable clinical history, have not to date been able to make use of modern data storage and computing capabilities, which could extend their range of functionality and performance. A typical pacemaker has 32k of memory and 4k of RAM. Because of battery lifetime requirements, pacemakers typically operate at currents between 200 and 300 μA. Hence improvements in the performance of batteries, which currently occupy 1/3 to 1/2 of the volume of a pacemaker, must occur to take advantage of modern data storage and computing capabilities.

Cardiovascular Stents

One of the most rapidly growing cardiovascular products is the cardiovascular stent,[10] which is used to provide support to blocked vessels which have been opened by a balloon catheter. This product was developed in response to the limitations of balloon angioplasty, which resulted in a substantial number of repeated blockages in the same area. Early stent designs, however, were unable to produce results demonstrably better than those achieved using balloon angioplasty alone. The Palmaz-Schatz tubular slotted stent was the first stent to achieve these improved results and at one time had about 90% of the stent market share. Several newer stent configurations introduced subsequently have reduced this share to under 10% within several years, which reflects the dynamic nature of the stent industry.

A cardiovascular stent must be flexible or trackable in order to be able to be deployed to small and possibly curved vessels. Flexibility is primarily dependent on the mechanical configuration of the stent, although the yield stress of the material should be high enough to avoid or minimize plastic deformation. On the other hand the yield stress of the stent material should be low enough to allow balloon expansion of the stent to occur at pressures which are low enough to avoid vessel damage. Finally, the yield stress and fatigue resistance of the expanded stent must be high to withstand the stresses imposed by the expansion and contraction of the blood vessel. It is interesting to note that 316L stainless steel, whose use has diminished in orthopedic applications, is currently widely used in cardiovascular stents. In the annealed condition its yield stress meets the flexibility and expandability requirements and its high work hardening rate provides the necessary resistance to yielding and fatigue after expansion.

Areas of performance improvement to stents include the use of surface treatments to improve biocompatability and the addition of drug delivery capabilities. Surface treatments have not always been successful, as evidenced by the Silzone® experience and similar situations over the years with orthopedic implants. Careful postmarket surveillance will still be necessary to detect and respond in a timely fashion to unexpected adverse consequences.

Bioactive Gel-Glasses: A Regenerative Material?

Natural tissues are regenerated by the processes of restoration of structure, restoration of function, restoration of metabolic and biochemical behavior, and restoration of biomechanical performance to achieve tissue regeneration. Evidence exists that tissue regeneration in bone is possible using bioactive gel-glasses based on the system CaO-P_2O_5-SiO_2 using a rabbit femoral defect model.[2] The challenge remaining is to extend these results to larger animals and then humans to design engineered regenerative materials, probably first in bone and then in soft connective and cardiovascular tissues.

Microrobots and Nanotechnology in Medicine: Visionary or Quixotic?

The long-term alternatives to the more traditional use of biomaterials and biomaterials fabrication processes include the proposed use of microrobots and nanotechnology. For example, Robert Freitas, Jr., of the Foresight Institute has predicted that, within the lifespan of baby boomers, medical nanorobots will be used to clear obstructions in the circulatory system, poison cancer cells, treat bacterial and viral infections, deliver oxygen to damaged tissues, and monitor and diagnose diseases.[11] Others are not as optimistic about these developments, especially on the time scale predicted.

A real question society must face is how we should divide our efforts between the development of new tissue regeneration technologies and the surveillance and incremental improvement of existing biomaterials and biomaterials processing operations?

Conclusions

It appears that it is appropriate to approach the future of biomaterials and biomaterials processing with great optimism tempered with prudent caution as we move from replacing to regenerating tissues. The lessons of the past should caution us that our knowledge concerning the performance of biomaterials is incomplete, even in the more traditional areas. Given the complex, materials-specific causal patterns involved in the cases examined, it is hard to imagine that IT techniques such as data mining could have any utility at all in biomaterials and medical device risk reduction. The relevant data are simply not there to be mined. However, individual patients or patient groups are increasingly getting information concerning the risks and performance of their implants via the Internet, and their risk information is now often comparable to that of their physicians.

Appropriate postmarket surveillance, while perhaps lacking visionary appeal, appears to be a valuable risk management tool as well as a source of insights for continued improvement in the performance of biomaterials and future tissue regeneration procedures. Caution should especially be exercised in introducing change in areas where the current performance of biomaterials and devices has had an excellent track record. On the other hand, taking no risks is not in the long-term best interests of the patient population. Therein lies the balance and the challenging future of biomaterials as we move in the direction of regeneration rather than replacement of tissues.

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