

# 21st Century Challenges for Biomaterials

# CHAPTER 1

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## 1.1. Introduction

During the 20th century a revolution in public health took place. Clean drinking water, disposal of sewerage, and immunization resulted in a greatly increased life expectancy. The large increase in average lifetime has led to a new challenge for the 21st century: how to maintain a high quality of life in an aging population. Now, fewer children die in birth or during their early years. Antibiotics prevent death by many infections. As a consequence, in the 21st century tens of millions of people aged between 60 and 100 are alive. Life expectancy increases every year in the developed world. All people, regardless of age, desire a high quality of life. However, achieving this desire is difficult and expensive.

The problem facing an aging population is that all tissues and organs begin a progressive path of deterioration from the age of 30 onwards. Replacement of aged, diseased or damaged tissues has become routine. This is a result of the development of reliable and affordable biomaterials, and the perfection of surgical procedures for implantation of prostheses along with subsequent reliable methods for rehabilitation of patients. Nevertheless the biomaterials in use today are a compromise compared with the healthy normal tissues they replace. All biomaterials have limitations: mismatches in elastic moduli (stiffness), deterioration of the tissue–material interface, fatigue, wear, loss of blood supply, and other factors lead to 15–50% failure of many medical devices over a 10–30 year lifetime. The data, compiled from a large number of published

peer-reviewed papers,<sup>1</sup> show that few prostheses need to be replaced in the first ten years. During the next ten years many factors lead to a progressive loss of devices.<sup>1</sup> Today, more and more patients outlive their replacement parts. Thirty years of research and development of new biomaterials, new device designs, rigorous quality control, and governmental regulations has had only limited success in extending the lifetime of most prostheses. In general, the extension of patient lifetimes has increased faster than improvement in the lifetime of many medical devices.

Thus, an alternative approach to the replacement of tissues is needed. One new approach to this challenge is regeneration of tissues instead of replacement of tissues, a concept called regenerative medicine. This attempts to stimulate use of the body's own repair mechanisms to regenerate new tissues, and is a great challenge for cross-disciplinary research. Tissue engineering of replacement parts that are composed of living cells grown in temporary man-made templates (scaffolds) is one aspect of regenerative medicine.<sup>2</sup> Numerous chapters in this book address the progress made in using tissue engineering to repair or replace parts of the body. Stem cell technology is also a key component in regenerative medicine. Several chapters address the potential advantages of stem cell therapy, together with the barriers and difficulties in making the technology clinically viable. Chapter 2 discusses some of the controversial aspects of stem cell technology.

There are many factors to address in meeting the challenge towards achieving an affordable long-term quality of life in an aging population, and the 34 chapters in this book discuss many of these. The primary objective of this introductory chapter is to present some of the broad issues involved in modern healthcare technology. Details are presented in subsequent chapters.

## **1.2. Impact of the Media**

In a previous book, *Science, Faith and Ethics*,<sup>3</sup> I point out that a major issue in present-day technology-driven healthcare is a growing perception that modern materials and devices provide "miracle cures." All

too often patients crave replacement parts but do not understand the risks or long-term compromises in life-style that are involved after they receive the implants. Economics and the drive for increased market share and profits by health-care companies frequently lead to so-called “advances” with little long-term evidence to support the claims. This causes uncertainty for the surgeon and the patient who both desire the best outcome. Litigation often results when failure occurs, leading to even greater costs to patient and society.

Articles in the popular press that emphasize these uncertainties have become commonplace but offer few, if any, solutions. I cite a few examples to illustrate the issue of media impact on public perception of health-care technology. The 27 November 2006 issue of *Forbes* magazine, a leading business journal, featured on its cover a surgeon (or actor?) in full operating theatre scrubs and mask, holding up a heart stent implant in his gloved hand.<sup>4</sup> The text on the cover was: “STENTS, DEFIBRILLATORS, SPINAL DISCS, ARTIFICIAL KNEES: ARE THESE AS SAFE AS YOU THINK?”

A headline that is even more frightening to the reader — and to past or potential patients — appears with the article on page 94, written by Matthew Herper and Robert Langreth. In 36-point type, it reads: “DANGEROUS DEVICES. *Twenty million Americans walk around with high tech medical gear grinding away inside them. Are they safe?*”

The article opens with data on the wide-spread use of drug-coated stents that are engineered to prevent reclogging (restenosis) of arteries. The authors report that since 2003, drug-coated stents have been inserted into more than 4 million patients, generating US\$5 billion/year in sales for Johnson & Johnson and Boston Scientific, the companies that manufacture and sell the devices to the hospitals. The controversy highlighted by the article is that some critics claim there is increased risk of heart attacks from drug-coated stents compared with bare metal stents. Also, the article suggests that there is growing concern that the lucrative stent implant business leads to many more people receiving such implants than actually benefit from the devices. These issues are discussed in Chapter 18.

The *Forbes* article cites a similar concern of alleged overuse for the quarter of a million patients implanted with defibrillators. This device is designed to prevent sudden cardiac death by sensing abnormal heart rhythms and shocking the heart back into action with a jolt of electricity. The article presents alarming stories of several patients, and describes other medical devices that are claimed to have been rushed into overuse.

A major point emphasized in the article is the fact that 79 devices have been removed from the medical device market by the Food and Drug Administration (FDA) in the past five years because of potentially fatal side effects. Lesser complications have also led to the recall of 2,300 devices. The FDA (510K) route to gaining regulatory status for a new medical device is to show that the device to be marketed is substantially equivalent to a device marketed prior to enactment of the 1976 Medical Device Amendment. A device approved in this manner is often referred to as a “grandfathered device.” The authors also maintain that device approval is less complicated and the length of trials is shorter than that required for drugs. Consequently, the reader is led to believe that thousands of devices are in the US\$85 billion/year medical device market-place with minimal long-term data guaranteeing safety or efficacy. What is the reality? Regulatory procedures are continually becoming more and more rigorous, which has the effect of reducing the number of new devices entering the clinical arena, as companies are less willing to risk the investment of putting new devices through the expensive regulatory pathways. Chapter 32 explores these issues.

Tracking detailed survivability of the myriad medical devices in use today is a near-impossibility, especially since there are few common criteria for evaluation and comparison of performance. A previous book edited by Hench and Wilson, *Clinical Performance of Skeletal Prostheses*, compared published survivability data for some of the most commonly used devices, such as total hip and knee joints, dental implants, and middle ear prostheses.<sup>1</sup> The published results showed large variability in performance even of similar prostheses, depending upon the source of reporting. Surgical teams

supported by implant manufacturers often reported superior results. The article in *Forbes* discusses the complicated issue of surgeon–manufacturer relationships and the potential effect on survivability and risk/reward for the patient. One purpose of this book is to present published evidence for the successful use of many of these new medical materials and technologies; the authors of the chapters have no economic ties to the manufacturer or the clinician.

Most medical device manufacturers recognize the importance of long-term follow-up despite the implications in the *Forbes* article. For example, Medtronic, a leading medical device manufacturer, has recently introduced stainless steel prostheses for damaged discs in the neck. The implant is designed to mitigate one of the most common human ailments, pain in the neck and other parts of the spine. More than 12 million Americans suffer from chronic or acute problems related to deterioration or damage to the spine, and aging increases the incidence of vertebral deterioration and pain. More than 200,000 cervical procedures are performed annually in the USA, according to the American Association of Neurological Surgeons. Spinal fusion by use of bone grafts is the common method of repair but this procedure can lead to enhanced stress on neighboring discs and also often results in restricted range of motion. Chapter 16 discusses these topics.

The new Medtronic device is a two-piece ball and trough design, anchored by screws, that preserves much of the normal range of motion between the vertebrae. According to the manufacturer, overall success rates are 80% after 24 months, compared to 68% by spinal fusion. Neurological success for the implant *versus* fusion is purported to be even better. Important in the context of this introductory chapter is that Medtronic reports it will continue to conduct a seven-year study to evaluate the long-term safety and effectiveness of the implant, as well as a five-year enhanced surveillance study. This is essential because there have been numerous alternative vertebral replacement devices put into the market, with high rates of failure.

It is always necessary to ask, “What percentage of success is sufficient for a new device? Is 80% success good enough?” For

eight of ten patients the answer is obviously “Yes!” However, two of ten patients will continue to suffer. Unfortunately the same situation exists for most medical devices. Lack of success — that is, failures — is a natural consequence of the use of unnatural means to repair or replace diseased or damaged living tissues. Surgeons, patients, and families must accept that risk and should not expect “miracle cures” and zero rates of failure.

### **1.3. Organ Replacement**

Failure of organs is, as yet, unresolved by the use of man-made replacement parts. Modest progress has been made to augment or supplant the function of the heart, lungs, liver or kidney, but for the present the only viable alternative for the terminal patient is a transplant, a living replacement from a donor. This book does not cover the current status of organ transplants. For the interested reader, a previous book by the author, *Science, Faith and Ethics*,<sup>3</sup> discusses the socio-economics, ethics, supply, personal costs, and risk/reward issues involved in organ transplants.<sup>3</sup> Books cited in the reference list of that book provide insight into the technical and socio-economic issues of transplants. Availability of viable, healthy organs suitable for transplant is the dominant issue that restricts this approach to saving life. A new name is added to the organ transplant waiting list every 18 minutes, and tens of thousands of patients die every year worldwide while on an organ transplant waiting list.

There is a growing interest in addressing the organ supply problem. Some governments have already acted to require organ donation without patient or family consent. Others, such as that of the UK, are considering enacting such regulations. This is, in part, because “Four out of ten organs that are perfectly suitable for use are not donated because the family does not consent,” as reported in a *Telegraph Magazine* article, 26 January 2008, titled “The Donor Dilemma.”<sup>5</sup> This continues the debate launched earlier when a headline in the *Sunday Times* of 15 July 2007 proclaimed “Doctors: We Must All Donate Organs.”<sup>6</sup> The article was based

upon a report that the chief medical officer of the UK, Sir Liam Donaldson, is supporting a change in the British law to create an organ donation system that will presume patients have given consent for their body parts to be available for transplantation. Such a system would require that individuals who want to opt out would have to register in a similar way to those who now carry organ donor cards.

This is a controversial and fundamental change in the bio-ethical position of the UK government because it essentially gives the state new powers over people's bodies. Critics maintain such a law violates the first principle of ethics, the right of autonomy. Proponents of the change, including the British Medical Association (BMA), maintain:

Each year many people die waiting for an organ transplant. At the same time bodies are buried or cremated complete with organs that could have been used to save lives, not because the deceased objected to organ donation but simply because they never got around to signing up to the NHS (National Health Service) Organ Donor Register or informing their relatives of their wishes.<sup>6</sup>

Other countries in the European Union (EU) have already introduced "presumed consent" laws that have led to a large increase in donor organs. Belgium passed such a law in 1986 and Spain in 1989. However, following Sir Liam Donaldson's report to the British Parliament recommending a "presumed consent" law, an editorial appeared in *The Times* on 18 July 2007 arguing against the change.<sup>7</sup> *The Times* maintains that a change to presumed consent will not solve the problem. An important limitation, the editorial asserts, is the safeguards needed to ensure that organs are removed only from patients who have absolutely no hope of life. Two doctors are required to certify that the patient is brain dead. The doctors must also ask permission of next of kin, an essential provision of the so-called "soft opt-out" system. This is a big barrier because families often refuse donation. There is a short time of

viability of donor organs, depending on which organ is to be transplanted. Thus, a rapid decision by a family is required for the organ to be useful. A decision at an emotionally distressed time can lead to additional trauma for the family. Refusal is the easier choice. The UK's present system of registered donation avoids much of the uncertainty, whereas a presumed consent system does not.

Another issue in the organ transplant debate is illegal trafficking of organs — organs for sale. Sales of organs in developed countries are illegal. However, sales of organs in so-called third world or developing countries have all too frequently become commonplace on the black or blood market. Kidneys are available for approximately US\$2,000, more than a year's income for many donors in such countries. Corneas are sold for equivalent sums. The recipient, however, runs great risk due to potential infection, uncertain disease transmission, and lack of tissue matching. Transplant failure rates are high in the best of circumstances, even in transplant centers in the US and Europe, and highly dangerous to the patient if illegal organs are used.

Recently a major criminal case of theft of body parts came to light in the USA, with the head of the business, Biomedical Tissue Services, found guilty and convicted with a long prison sentence. The cadaver bodies came from funeral homes in New York, Pennsylvania, and New Jersey. The company had harvested bone, skin and tendons from the bodies and shipped them to three publicly traded firms, as well as to two non-profit agencies, for tissue processing. The illegal parts were used in vertebral disc replacements, knee operations, dental implants, bone grafts, and various other surgical procedures performed by unsuspecting surgeons in the USA and Canada. Court records indicate that about 10,000 people received tissues illegally procured by Biomedical Tissue Services. The extent of this type of illegal trade in human tissue is unknown. The consequences to the families of the stolen body parts and the patients receiving the parts are also unknown.

If a safe, ethically sound, affordable alternative source of viable tissues and organs can be created, as is the goal of regenerative medicine, there will be no need for illicit trade in body parts. The next chapter addresses one of the newest approaches to achieving

this goal and meeting the challenges of the 21st century, stem cell technology and tissue engineering. A guide to the various experimental approaches to developing engineered tissues and organs is the book *Future Strategies for Tissue and Organ Replacement* edited by Julia M. Polak, Larry L. Hench, and Paul Kemp.<sup>8</sup> This book addresses the following topics:

1. the clinical need for organ replacement;
2. future advances in organ transplantation;
3. revolutionary therapies being developed; and
4. regulatory issues of such living products.

Progress continues to be made in meeting the challenge of new approaches to organ replacement, but routine clinical use is still to be achieved. The references in Chapter 2 are a guide to the potential and the problems of creating a new approach to repair and replacement of human body parts. The remaining chapters in this book provide a starting point for achieving such an understanding.

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