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# HANDBOOK OF POLYMER APPLICATIONS IN MEDICINE AND MEDICAL DEVICES

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# Preface

The applications of polymer chemistry and plastics engineering to the design and manufacture of medical equipment are evolving at a rapid pace not seen before in the medical device industry. These modern advances, however, reflect decades of incremental progress in biomaterial science. Initially guided by the principles of physiology and chemistry, medical plastics are now influenced by an array of emerging scientific disciplines that include nanochemistry, toxicology, and informatics. The current volume reflects this new interdisciplinary paradigm as it reviews modern innovations in the use of traditional polymers, introduces leading-edge technologies in medical diagnostics and therapeutics, and covers the logistical and regulatory challenges that confront the complex market of medical devices. It is intended as a primer for a broad audience of both medical and engineering professionals who share an interest in this quickly changing, but ever-expanding field.

The book begins (Chapters 2−4) with an overview of the varied applications of synthetic polymers in medical devices. The primary considerations in the design of new biomaterials are reviewed, including biocompatibility, durability, and sterility. The book then shifts (Chapters 5−10) to a specific focus on the medical applications of plastics in the fields of orthopedics, infectious diseases, dentistry, cardiology, pulmonology, critical care, anesthesiology, and neurosurgery. The next section (Chapters 11−13) examines novel applications for medical polymers on a nanoscale and in the contexts of diagnostic ultrasound and tissue engineering. The book concludes (Chapter 14) with a summary of the regulatory policies that influence medical device design and development.

# Author Biographies

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**Sina Ebnesajjad, PhD**

# 1 Introduction

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OUTLINE

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*Science and technology do not develop seamlessly but rather by major and painful changes in accepted wisdom. Such changes are preceded by a period of profound uncertainty as the accepted solutions become plainly unsatisfactory at solving the problem.*

**—Thomas S. Kuhn, *The Structure of Scientific Revolutions* [1]**

The history of plastics and medical devices traces a complex course of slowly evolving ideas punctuated by moments of intellectual revolution. When viewed from the vantage of retrospect, it becomes apparent that milestones in the progress of biomaterial science represent culminations of gradual shifts in theory and iterative experimentation. This has been as true for methodological developments in polymer chemistry as it has for technological breakthroughs in medical equipment design. The two disciplines, now inextricable from one another, initially advanced along largely separate and occasionally redundant paths. Until the latter decades of the twentieth century, physicians and surgeons modified existing materials to create and refine devices according to their clinical needs while chemists and engineers synthesized materials *de novo* without specific attention to their potential medical applications. In the modern era, however, the lines between the chemical and biological sciences have blurred, paving the way for an interdisciplinary approach toward the design and application of medical plastics.

The current anthology reflects this new paradigm, examining issues surrounding the use of medical plastics through the mutifaceted lens of chemical and biomedical engineering, microbiology, toxicology, nanochemistry, physics, and informatics. Historically, plastics as biomaterials have been reviewed almost entirely in the context of surgical implants. The collection of chapters that follows surveys a broader, newer array of applications for medical plastics that includes diagnostic equipment, product packaging, drug delivery devices, and tissue regeneration. These novel uses for plastics have translated into a surge in the volume of medical devices and equipment being employed around the world. Newer technologies, such as medical molding and packaging, have been responsible for much of the growth in the past several years. However, traditional applications of medical plastics continue to drive the industry forward as well. For example, 300,000 people around the world undergo cardiac valve replacement every year [2]. And in 2011, more than 150 million people wore silicone or hydrogel-based contact lenses, a 25% rise from a decade earlier [3]. The increasing demand for these products has led to an economic resurgence for the field as a whole. Although medical products still only account for 1% of the plastics market share, the consumption of medical devices has tripled in the past decade to become a $300 billion global industry [4]. Over the next several years, the business of biological implants is expected to grow by 7% annually [5]. These trends are in large part a consequence of an aging population, a rising prevalence of chronic diseases, and a shift from invasive surgeries toward minimally invasive implantation procedures.

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## 1.1 History

The emergence of synthetic polymers as a dominant force in medicine, though a recent phenomenon, is rooted in a long history of biomaterials that extends back several millennia. Historical evidence demonstrates that humans have been repurposing natural substances for medical use since the beginnings of civilization. Several thousand years ago, ancient Babylonians and Egyptians were fashioning surgical sutures from flax, hemp, and catgut. The archeological record is relatively quiet on surgical implants, though, until the seventh century AD when Mayans began grafting seashells to their mandibles. Another thousand years would pass before any additional progress was made in biomaterials. In the sixteenth and seventeenth centuries, Renaissance men Leonardo Da Vinci and Rene Descartes proposed their own designs for contact lenses [6]. But theory did not become practice for another two hundred years when the first glass lenses were manufactured for human use. Around this time, in the mid-1800s, the Industrial Age was in full force giving birth to a rapidly rising number of inventions. Even more importantly, scientists and engineers were making their discoveries through repeated experimentation. A new adherence to the scientific method was quickening the pace of biomaterials research, as the seeds of scientific thought grew into practical therapies within the course of several years instead of centuries.

The story of plastics begins here in the mid-nineteenth century (Figure 1.1) when, in 1862, a metallurgist named Alexander Parkes unveiled his eponymous invention, Parkesine, at the London International Exhibition (Figure 1.2). It was a chemically treated celluloid he had patented several years earlier to waterproof clothing fabrics. By adding solvents to a natural product, Parkes was able to create the first artificially modified thermoplastic. Parkes' invention is often heralded as the birth of plastics. However, he owed much to the vulcanization process developed by Charles Goodyear and Thomas Hancock several decades earlier. Parkes, in fact, began his career by improving upon Hancock's methods. And John Wesley Hyatt, a few years after Parkes, invented celluloid by applying the chemical principles of the same predecessors [6]. The work of these pioneers demonstrated proofs of concept that naturally occurring polymers

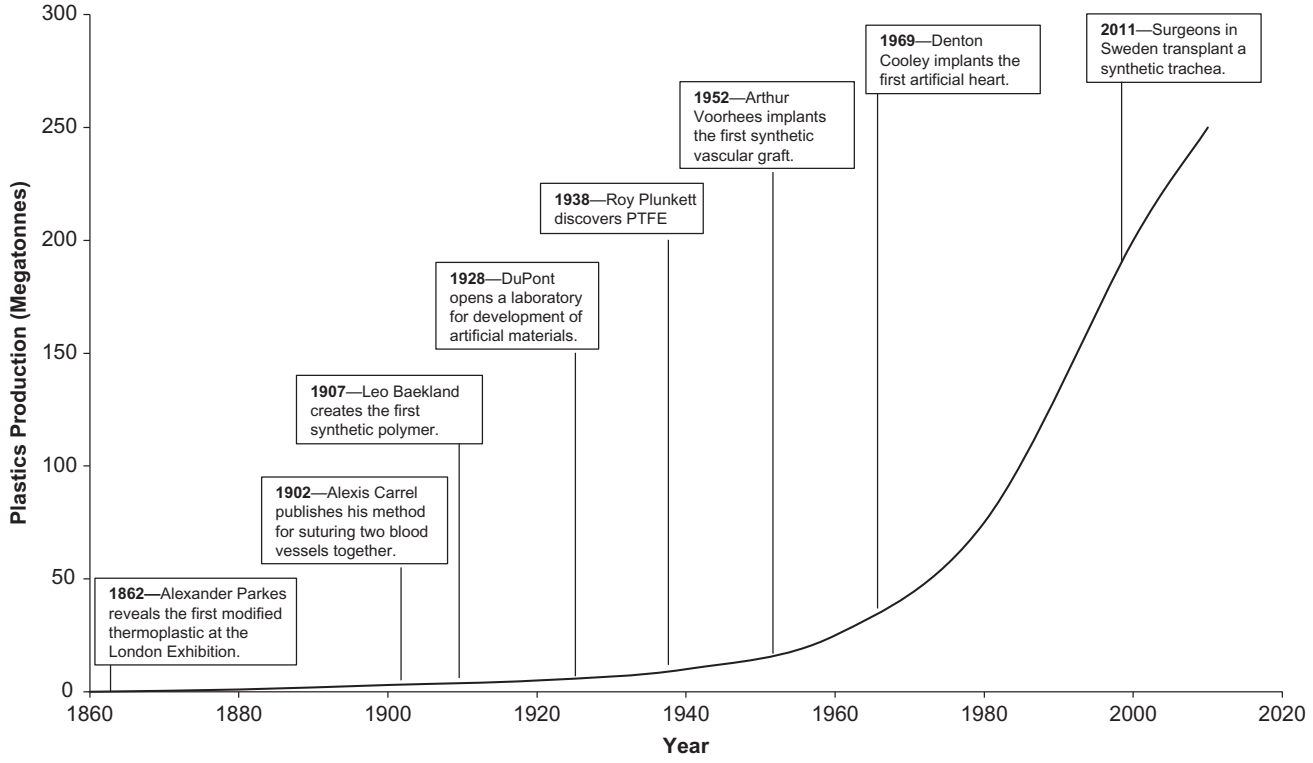



**Figure 1.1** A timeline of medical plastic development and production.



**Figure 1.2** Alexander Parkes, inventor of the first modified thermoplastic. (*Science Museum/Science & Society Picture Library*)

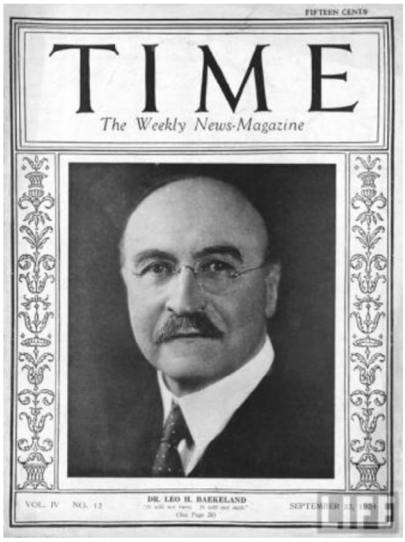



**Figure 1.3** Leo Baekeland, inventor of the first entirely synthetic polymer.

could be molded for human use. And though these inventions were innovative in their own right, they still relied on the availability of compounds in the environment.

It wasn't until the turn of the twentieth century that a polymer was synthesized *de novo*. In 1909, Leo Hendrik Baekeland combined formaldehyde and phenol to create a thermostable material that he, like Parkes, named after himself. Bakelite significantly accelerated the growth of the plastics industry by eliminating the need to procure natural products for alteration (Figure 1.3) [7]. By the 1930s, dozens of synthetic polymers were being produced for mass consumption. Textiles, toothbrushes, and furniture were in much larger supply and at a cheaper cost than they had ever been. Within the span of several decades, plastics had moved from a scientific oddity to a household staple. The demand for plastics, however, was far from reaching its peak. Consider the 1941 text, *Plastics*, that opens with a forecast of how humans will live in a world made entirely of plastic.

> *This plastic man will come into a world of colour and bright shining surfaces where childish hands find nothing to break. . .The walls of his nursery, his bath. . .all his toys, his cot, the moulded light perambulator in which he takes the air, the teething ring he bites, the unbreakable bottle he feeds from. . .all will be plastic.... As he grows, he cleans his teeth and brushes his hair with plastic brushes, clothes himself with in plastic clothes, writes his first lesson with a plastic pen and does his lessons in a book bound with plastic. . .[In the end] His own teeth are gone and wears a denture with silent plastic teeth and spectacles with plastic lenses. . .until at last he sinks into his grave in a hygienically enclosed plastic coffin.*
>
> **—Yarsley and Couzens, *Plastics* [8]**

Written at the dawn of World War II, their prediction may have seemed hyperbolic at the time. However, during the war years that followed, plastics production quadrupled from 1 to 4 kilotonnes (now plastics use exceeds 250 megatonnes annually) [9,10]. World War II also drove the expansion of plastics from the home to the battlefield. Parachutes and aircraft parts, gun barrels, and helmets were all taking advantage of the malleable and durable properties of synthetic polymers. Even the Manhattan Project relied on polytetrafluoroethylene (PTFE), or Teflon®, to contain the corrosive byproduct of uranium hexafluoride used to make the atomic bomb [11].

But it wasn't until the post-war period that the plastics industry targeted medicine as its new

**Table 1.1** Medical Plastics in Common Use

| Polymer | Discovered | Medical Applications |
|---|---|---|
| Polytetrafluoroethylene (PTFE, Teflon, Gore-Tex®) | 1938 | Vascular grafts, catheters, introducers |
| Poly(ethylene terephthalate) (polyester, Ethibond, Dacron®) | 1941 | Vascular graft, drug delivery, non-resorbable sutures |
| Poly(methyl methacrylate) (PMMA) | 1877 | Bone cement, intraocular lens |
| Polyurethane | 1937 | Catheters, tubing, wound dressing, heart valves, artificial hearts |
| Silicone rubber (polydimethylsiloxane, PDMS) | 1943 | Catheters, feeding tubes, drainage tubes, introducer tips, flexible sheaths, gas exchange membranes |
| Polycarbonate | 1953 | Renal dialysis cartridge, heart–lung machine, trocars, tubing interconnectors |
| Hydrogels (poly(ethylene oxide), poly(ethylene glycol), poly(vinyl alcohol) | | Drug delivery, wound healing, hemostasis, adhesion prevention, contact lenses, extracellular matricies, reconstruction |
| Polyamides (nylon) | 1935 | Non-resorbable sutures |
| Polypropylene (i.e., prolene) | 1954 | Non-resorbable sutures, hernia mesh |

frontier. Other materials, such as metals, had been regularly used as bone and dental implants for decades. However, the union of polymers and medicine could not have occurred any earlier than it did, as neither had yet achieved a level of maturity that would enable fruitful application. Fortunately, mid-twentieth century advances in plastics engineering were matched by concurrent progress in the areas of immunology, microbiology, toxicology, and radiology. Advances in each of these disciplines overcame problems with implanting foreign materials into the human host. With a better understanding of immunology came improvements in the design of biocompatible materials. A deeper appreciation of chemical toxicity translated into definitions for what and how much substance could leach from its site of implantation. And the primary importance of sterility in all clinical products helped to both prescribe safety parameters for plastics and propel the field forward. Since the first use of nylon sutures in the early 1940s through to the present day, medical plastics have evolved considerably to become the broadest class of biomaterials. A catalog of plastics in current clinical use would exceed the scope of this chapter; however, a selected list of the most important examples is provided in Table 1.1. Thus, instead of broadly surveying each development in the history of medical plastics over the last half-century, I will focus on one historically significant case that illustrates the benefits and challenges that follow from the application of plastic solutions to clinical problems.

## 1.2 A Historical Example

In 1902, a young French surgeon by the name of Alexis Carrel published a manuscript in the *Lyons Medical* journal on his ability to successfully anastamose small caliber blood vessels [12]. Several years earlier, the French President, Sadi Carnot, had been stabbed by an assassin and died by exsanguination. Carrel, a medical student at the time, was convinced that the President would have survived had he been able to restore the integrity of his vasculature. Carrel responded to the tragedy by taking embroidery lessons to develop a technique that would enable two vessels to be sewn together. Sutures had been used for thousands of years to sew wounds, but until the turn of the century, arterial and venous injuries had little remedy. Six years before Carel published his seminal paper, his mentors Jaboulay and Briau demonstrated perfect union of two ends of the carotid artery. Carel improved

upon their methods and was awarded the Nobel Prize for this work in 1912 [13]. Other pioneering surgeons quickly moved forward to apply Carel's techniques to arterial bypasses and aneurysms. As the field moved from biologic to synthetic sutures, approximation of blood vessels became more facile. Situations would arise, however, when vessels could not be attached end-to-end. In these instances, patients needed grafts that could replace parts of their vasculature.

Fifty years after Carel began developing and refining his methods in vascular repair, another young surgeon, Arthur Voorhees, made a seminal observation while an intern at Columbia University in New York. From a postmortem examination of an experimental animal, Voorhees noticed that a silk suture left in the animal's heart had become overgrown with endocardial tissue. The observation prompted Voorhees to hypothesize that a cylinder of silk cloth might elicit the same reaction and serve as an arterial prosthesis. He initially experimented on dogs with a silk handkerchief (donated by his wife) but soon moved to Vinyon, the synthetic polyvinyl chloride (PVC) used to make parachutes in World War II. After several years of animal experimentation, Voorhees had the chance, in 1952, to test his device on a human who had suffered an aortic aneurysm rupture [14]. With his tube made of PVC, Voorhees was able to save the patient from an almost certain fatal outcome.

Grafts from human and animal donors had been used previously, but they were in limited supply and ran the risk of host rejection. PVC, on the other hand, was relatively abundant and immunologically inert. But within five years of Voorhees' groundbreaking surgery, PVC was already outdated and replaced by polyethylene terephthalate (PETE) or Dacron®. By the 1960s, this new synthetic polymer had made prosthetic vascular grafts the standard of care for the repair and reconstruction of large diameter (>10 mm) vessels (Figure 1.4) [15]. Compared to its predecessors, PETE was more pliable, durable, and impermeable. Synthetic grafts, in general, were found to be well suited for large vessels (*i.e.* aortic and carotid arteries) with high flow rates and low resistance. When synthetic grafts were used for smaller vessels, however, they had inferior long-term patency as compared to autologous vessels. This limitation is largely due to thrombi that form at the site of anastomosis as a result of endothelial hyperplasia [16]. Expanded PTFE (ePTFE) emerged on the market as an alternative to PETE in 1976 to lower the thrombogenicity and permeability of vascular grafts. They demonstrated little-to-no difference from PETE grafts in patency [17]. Consequently, PETE still constitutes the majority of synthetic vascular grafts (80%). ePTFE has carved a niche, however, in the area of hemodialysis access because of its lower rate of forming aneurysms and greater facility for thrombolysis. Both synthetic graft types have a finite life span depending on the purpose and anatomical location of the graft. Five-year patency is generally 50% for dialysis access and femoro-popliteal grafts but rises to 90% for both PETE and PTFE aortiobifemoral grafts [18]. Arguably, an even greater challenge to the longevity of artificial grafts is their risk of infection; synthetic grafts carry a 2% annual incidence of infection. Although relatively low, this rate is four times that of autologous grafts and has remained unchanged for decades despite advances in sterilization procedures and surgical techniques [19]. Research in antibiotic impregnation of grafts has failed to yield clinically viable products. Despite these limitations, vascular grafts continue to be used with increasing frequency and success [20]. One million vascular grafts are implanted around the world every year, making it a $200 million market in 2012 alone. The storyline of synthetic vasculature, from simple observations in a laboratory to a global industry, recapitulates that of many other medical plastics.



**Figure 1.4** A Dacron® vascular graft. *(www.clevelandclinic.org, Lars Svensson, MD, PhD)*

## 1.3 Anthology Architecture

This book is a hybrid of previously published and newly written chapters, unified by a theme of plastics applications in medical devices and equipment. The content has been chosen to accommodate the background and interests of both medical and engineering professionals. The book's organization loosely reflects the two eras in medical plastics development. The first period, lasting until the 1990s, was characterized by the appropriation of available synthetic polymers for medical purposes. More recently, medical plastics have become more sophisticated as polymers are synthesized for specific use in the clinical arena [21]. Thus, traditional as well as leading-edge clinical applications of synthetic polymers are reviewed. The first half of the book covers medical plastics that have been in use for several decades, while the latter chapters introduce novel applications for synthetic polymers.

This book begins (Chapters 2–4) with an overview of the varied applications of synthetic polymers in medical devices. The primary considerations in the design of new biomaterials are reviewed, including biocompatibility, durability, and sterility. These properties are evaluated for the most widely used polymers in medicine. The book then shifts to a more narrowed focus (Chapters 5–10), discussing specific medical applications in the fields of orthopedics, infectious diseases, dentistry, cardiology, pulmonology, critical care, anesthesiology, and neurosurgery. The next section (Chapters 11–13) examines novel applications for medical polymers on a nanoscale and in the context of diagnostic ultrasound as well as in the burgeoning field of tissue engineering. This book concludes (Chapter 14) with a summary of the economics and regulatory policies that influence medical device design and development.

## 1.4 Summary

Materials and biologic sciences have been co-evolving over millennia. Plastic, a relatively new class of synthetic substance, has been in use for only 150 years. However, in the last century, the volume and distribution of synthetic polymers in the medical industry has outpaced those of any other biomaterial. Given the complexities of human physiology and immunology, future medical devices—both external and implantable—will rely on synthetic materials that are both versatile and enduring in function. The collection of chapters included in this anthology provides a unique perspective on how far the field of medical plastics has advanced and the directions where it is headed. The journey toward modern biomaterial science is marked by modest observations followed by bold intellectual leaps. The way forward in the field of medical plastics is likely to recapitulate that voyage with increasing speed and reward.

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# 2 Application of Plastics in Medical Devices and Equipment

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This chapter will present a look at the medical device market with a particular focus on the materials of construction of devices and what we can expect in new products looking ahead. A deeper look at some other trends that have an effect on the direction of the medical device industry will be done. Finally, consideration will be given to a number of global factors that can have dramatic effect on our industry.

## 2.1 Device Industry Overview

The medical device industry has roots in the foundation materials of glass intravenous (IV) bottles, rubber tubing, and metal operating room instruments. The development of plastics in the 1930s, 1940s, and 1950s enabled the development of medical devices that overtook and eventually replaced the foundation materials with newer and better materials such as polyvinyl chloride (PVC) for IV bags and tubing, silicone tubing for catheters and balloons, polyolefins for trays and bottles, and fluoropolymers for IV catheters. New polymeric material developments continued to allow a virtual explosion of devices and implements which were able to rely on the excellent properties that were offered by engineering polymers, newer commodity plastics, and improved processing technologies.

As the availability of new products continued to grow, the health-care industry grew as well and by offering life-giving procedures, led to improved health of the population in general. New drugs such as sulfa drugs, penicillin, the Salk polio-vaccine, and insulin all led to the health-care industry being

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able to provide treatments to a great segment of the overall population, not just the elite, privileged classes or the wealthy. The wide availability of good quality, clean, sterile products at prices that were not absurdly high allowed the widespread growth of smaller hospitals and clinics where the sick and injured could receive medical treatment.

The device industry has grown together with the population expansion following World War II and with the globally expanding baby boomer generation. New technology in materials science, processing, and assembly, and in the health-care community combined to make the global medical device market a $200 billion market in 2008. With a growth rate of 8%, by 2012, the size grew to over $250 billion. The United States is reported to consume between 45% and 47% of the world market for medical devices, while US exports account for an estimated $37 billion, with these products going primarily to Europe (46%) and Japan (12%). The 42% which goes to the rest of the world accounts for approximately 57% of US exports and this segment is growing more rapidly than both the European Union (EU) and Japan as so-called third world or emerging economies begin to consume the basic health-care products for their demanding needs of their populations.

Analysis has shown that the "BRIC" countries of Brazil, Russia, India, and China will be those markets that have the most rapidly growing demand for medical devices. Growth of health care in other parts of the world such as Eastern Europe, the Middle East, and Africa will follow. However, as in any economy, before the general population can be served with a comprehensive health-care system in a country, there needs to be a stable political environment and where basic needs of food, clean water, sanitation, and shelter are available.

Another requirement is the establishment of a health-care delivery infrastructure. It does no good to ship sophisticated or even basic medical devices to parts of the world that have a need for these products if there is no one available to monitor, distribute, and administer the products and to provide for their proper use. Surgical suites cannot effectively operate for more than just the short term in temporary shelters or make-shift buildings. It will take a commitment on the part of the local governments to begin to provide facilities and utilities to the health-care professionals that would then begin dispensing care to the local population.

Evidence of this process is the rebuilding of the war ravaged country of Viet Nam in the late 1970s and 1980s. By no means has this part of Southeast Asia emerged into a sophisticated health-care provider but once stability had been restored, the infrastructure was slowly developed in the population centers, and hospitals and clinics were then able to provide care to their citizens.

## 2.2 Health-care Trends

Any review of the medical device industry will quickly reveal that several trends are emerging that are shaping the device industry. Three that I will note are:

1. The trend toward minimally invasive surgeries (MIS)
2. The growing popularity of alternate site treatment
3. A strong movement toward prevention vs. treatment of disease.

### *2.2.1 Minimally Invasive Surgeries*

Not many years ago, when a heart patient presented with blocked or restricted arteries, the only course of treatment was to do open heart surgery or coronary artery bypass graft (CABG) surgery. This complicated, expensive, and traumatic surgery required the blood to be circulated by way of blood pumps and tubing through oxygenator devices, while the heart was taken "off-line" allowing the surgeon to replace the occluded blood vessels with harvested vessels usually from the patient's leg. These new vessels were grafted to the heart muscle and bloodstream to "bypass" the occluded vessels effectively restoring normal flow of blood to the heart muscle. The "bypass" surgery required cutting and spreading open the chest of the patient allowing the surgeon access to the heart. Often the recovery from all the steps taken to gain access to the heart muscle took longer than the recovery of the heart surgery itself! Recovery times were counted in weeks in the intensive care unit and hospital rooms and months

more at home before normal activity could be resumed.

The development of the heart catheter that was able to deliver a vascular stent or scaffold changed the landscape for treatment of blocked arteries. Cardiovascular surgeons were suddenly able to access the occluded artery using these balloon catheters which were inserted through the femoral artery in the area of the groin. Newly developed imaging technologies gave the cardiovascular surgeon a way to accurately position and deploy a stent in the occluded artery immediately restoring the normal flow of blood through the once occluded artery.

Other products such as multiple instrument access ports allowed for minimally invasive surgeries to be performed within the peritoneal cavity through a single incision in the abdomen. The port would be positioned through the incision and by inflating the cavity using a process called "insufflations," and the surgeon could view inside the body using an endoscope or viewing instrument. The surgeon could then perform procedures such as biopsies, appendectomies, gallbladder procedures, hernia repair, and hysterectomies without the need to open the abdomen beyond the one small incision. Recovery times are greatly reduced, there is far less blood loss, the risk of infections and other complications from the open procedures have been drastically reduced, and the added benefit is that the cost of health care has also dropped.

These new minimally invasive surgical techniques, however, have also led to the development of many new products designed to improve how the procedures are performed. It seems that every medical device company has introduced its own version of the access port and the procedures carry unique names such as Natural Orifice Transluminal Endoscopic Surgery (NOTES). The benefits of MIS are obvious and the amount of new development being done to extend the procedures that are possible with MIS continues to grow.

Orthopedic procedures are possible using MIS with arthroscopy for joint exam and repair being the most commonly used joint repair procedure. Total joint replacement of the hip is now possible with products that rely on endoscopy. And linking this technology with computer-driven robotics has enabled the development of the DaVinci remote surgical system. This takes the possibility of alternate site health care to a new level with the surgeon being able to be remotely located from the patient on whom the procedure is being performed.

### 2.2.2 Alternate Site Treatment

The norm had for many years been that anyone sick or requiring medical assistance would go to the doctor and likely end up in the hospital for care and treatment. With the emergence of chronic illnesses such as renal or kidney dialysis, it became clear that quality care could be offered to special segments of the population in specially designed outpatient facilities. Doctors' offices became locations where X-rays could be taken, broken bones treated, and minor surgical procedures would be performed. Emergency clinics became satellite locations for the general hospital in the area, and these clinics were staffed with doctors and nurses that in many cases enabled patient care that eliminated the need to even go to the hospital.

Hospitals continue to be the place for major surgeries, intensive care units (ICU), trauma care, and specialty care such as in burns units. Patients that were mobile and otherwise active, however, could get their chronic care by way of the outpatient clinics in conveniently located sites near their homes and communities. Oncology patients could receive the twice or thrice weekly IV infusions at the alternate site, and rehab services, which only had been available at the hospital, were now offered at locations other than the hospital.

The trend to seek health care at locations other than the hospital brings other opportunities for the medical device industry. Products used at the alternate site must be the same good quality as offered by the hospital, but in some cases since the healthcare providers may not have the same level of experience as the hospital staff, the medical devices and equipment need to be made so that new or inexperienced users can reliably and effectively use the product as intended. Products for use in the non-hospital settings should have ease-of-use built into them and the instructions for use must be easy to read and understand.

One final alternate site trend is the tendency to take health care to the home. The cost of health care and the increased restrictions by insurance providers is leading to shorter hospital stays, earlier discharges, and a greater reluctance to admit patients, instead often opting for outpatient treatments. This trend places a greater burden on the

family of the patient or requires a mobile healthcare provider to visit and look in on the condition of the patient and sometimes administer medications, therapy, or treat recovering wounds.

When the burden of responsibility falls on the family, medical products and devices must be designed and made so that the non-professional care giver can understand clearly how to use them easily. Often an elderly spouse is the only person available to care for a loved one and if medication containers are difficult to open, if devices are hard to hold and operate, or if the instructions are not clear, it becomes a challenge for the provider to comply as they should.

So to summarize, medical device companies need to consider how their products will be used and by whom. As alternate site delivered medical care becomes more commonplace, products must be made so that even complicated care procedures can be done without a chance of compromising the health of the patient or the care provider.

### 2.2.3 Prevention vs. Treatment

One final trend that is worth considering in this review is the trend toward prevention of disease or health problems by early diagnosis of a problem and early treatment. Current improvements in diagnosis of a patients' condition can enable the physician to detect the early onset of a problem condition whether that condition is high blood sugar levels pointing toward diabetes, chronic high blood pressure pointing toward heart disease, or the early onset of prostate cancer as indicated by increased prostate specific antigen (PSA) levels.

Effective diagnosis can be done using small samples of blood or urine or other body fluids. These tests are becoming less expensive and therefore are more likely to be done and reimbursed by insurance programs thereby leading to better monitoring of patients' health over the course of their life.

Other more sophisticated diagnostic procedures involve more intensive testing and analysis such as genetic screening. In the case of inherited genetic mutations, genetic testing can detect a patients' likelihood of developing breast cancer. Genetic testing can also determine if a patient has the inherited precursor to breast cancer leading to early and continuous monitoring of their health or leading to those patients seeking preventive surgical intervention such as mastectomies.

Earlier detection of health problems allows earlier treatment of the condition and in many cases the treatment will prevent the full onset of the diseased condition. The patient can avoid the effects of a fully engaged condition and with early treatment the disease may be completely avoided.

This trend toward disease prevention rather than treatment points to the ever-increasing demand for diagnostic products. From instruments that perform the analysis to the containers and reagents that are consumed during the testing to the devices that are used to collect the blood, fluid, and tissue samples, all these require carefully designed and manufactured medical devices. This is a very rapidly growing segment of the industry.

## 2.3 From Legacy Materials to Advanced Specialty Polymers for Devices

The need for high-quality medical devices has been explained in this chapter, but the construction of these devices has not been addressed. The emergence of PVC, polyolefin polymers, and other traditional commodity plastics was briefly touched upon in Section 2.1. But with the assessment of the trends described in Section 2.2, the full range of medical devices from single use disposables (SUDs) to reusable devices to hardware (e.g., pumps, ultrasonic instruments, heart monitors, and even MRI equipment) all require materials of construction designed to meet the needs of the product and survive the rigors of use, either single use or long-term use. The majority of products made for the device industry are made from commodity polymers or readily available, inexpensive polymeric materials. As the requirements for components or new medical device requirements push the limits of the most generally used materials, new materials are selected that meet the more rigorous requirements.

Examples are higher temperature polymers designed to survive continuous use at elevated temperatures or a polymer that can withstand exposure to aggressive cleaners or solvents now being used to reduce the frequency of hospital acquired infections (HAIs) or materials that can be precisely molded into micro-sized parts with very high tolerance requirements while also surviving the rigors of use.

The primary materials in use continue to be the four mainstay polymers: of polyvinyl chloride (PVC), polypropylene (PP), polyethylene (PE), and polystyrene (PS)—with styrene copolymers of ABS and SAN. But more devices are being made from additional materials which provide improved performance. Some of these materials are PC (polycarbonate), polyethylene terephthalate (PET), or any of the many available polyesters, TPU (thermoplastic urethane), TPE (thermoplastic elastomers), and polyamides (PA, both traditional nylons and amorphous nylons).

With newer devices constantly being developed, the need for new components and new specialty materials continues to increase. At the same time, new polymers and polymer formulations available for use continue to grow. Suppliers are continuing to develop new options that better meet the need for improved performance, allow the use of new technology, and extend the reach of the latest therapies.

An example of a relatively recent new material entering the device industry was the family of materials called liquid silicone rubber (LSR). LSRs allowed component products made from this silicone elastomer formulation to replace the more expensive and more difficult to process gum rubber silicones or different two-part silicone compounds that also were not as easy to process as the LSRs. These new formulations have the superior properties that make silicone so desirable for the medical device industry while also having the ability to be easily injection molded into quality parts. These materials rival the best TPEs as well as the traditional silicone rubber formulations.

There have been new polyolefins developed that can be used as tubing materials for applications which make PVC or silicone unacceptable. These softened olefins have even been considered as PVC replacement materials for such applications as steam sterilized fluid containers. Instruments that must be repeatedly cleaned and sterilized, sometimes multiple times in a day such as dental instruments, can now be made from high-performance polymers such as polyether imide (PEI) or polyether ether ketone (PEEK) polymers. Even some of the commodity polymers are being improved, for example, linear low density polyethylene (LLDPE) is new offered with better clarity, improved heat seal temperature range, and superior seal strength. All these improvements result in better medical devices often at lower manufacturing cost.

## 2.4 Driving Trends Leading to New Material Requirements

The earlier assessment of trends in health care led to a review of why certain areas of the industry are growing and showed why specific types of medical devices are being developed to meet the needs of the most recent industry trends. This section focuses on the factors that directly affect the devices that are being designed and made to serve the needs of industry. There are four trends listed below that cover how the industry from the suppliers to the convertors to the final device manufacturer are all responding to the needs of the ever-evolving industry.

### *2.4.1 Functionality*

Components of devices must be made in a way that the resultant device or instrument can be used without an operational problem. Newer polymers allow the design of multiple features into one molded component that, for example, may be able to replace metal components or multiple smaller parts. Product redesign and design for manufacturing with the latest materials can bring improved performance to the medical device while reducing the cost of the device.

An example of this is the ability to preprint labeling or bar code information on a film that is then fabricated into a laminate for final manufacture into a fluid container. The critical information contained on the film is printed on an inner layer of the laminate and then sandwiched between outer layers of the laminate. The printing is protected from abrasion or exposure that might damage the printing as it would a label that is printed or affixed to the outside of the container after fabrication. Only with the ability to make dimensionally controlled films, and with the availability of polyurethane adhesives suitable for medical devices, is this technology possible.

Other new adhesives developed to improve the bonding of plastic components can offer better joints while also eliminating the use of volatile solvents. Ultraviolet light-cured adhesives can be used to bond a tubing to a connector while giving

superior bonds and a controlled method of application and cure as compared to other methods of bonding. This type of adhesive also enables the use of automation for certain products and with the cost of manufacturing such a critical part of making any medical device, the possibility of eliminating labor by using automation is a meaningful benefit.

Medical devices continue to get smaller and the complications related to making these ever smaller devices and their components present a challenge for both the material and the processes used to make small or micro-components. Multifunctional devices such as the Pill Cam rely on extremely tiny components but together they offer a product that gives remarkable results improving the diagnosis of the condition of a patient's colon.

The Pill Cam is designed to be swallowed by a patient needing a colon exam. Once swallowed, the Pill Cam will track through the body, eventually passing through the entire length of the large intestine, and is then eliminated from the body. During the transit, which is reported to average about 17 hours, it takes two pictures or images of the walls of the large intestine every second. These images are transmitted wirelessly to a receiver outside the body for later analysis. Any irregularity or polyp or lesion can be detected and diagnosed by the surgeon who previously relied on the examination of the colon using a colonoscope. The older procedures called colonoscopies are done on mildly sedated patients in a hospital examination room. This invasive procedure often requires two or three health care professionals and may take up to an hour to complete. The Pill Cam provides this problem by viewing of the entire length of the colon. The resultant set of information available to the surgeon is so large that it often requires retraining to enable the health-care professional to read and understand the dataset obtained from the Pill Cam. This new technology improves the diagnosis accuracy, helps eliminate false positives, or the need for investigatory biopsies, but also is more cost effective and from a patient perspective, a far more comfortable option to the colonoscopy.

One final example of a polymer allowing the improvement of patient care by the use of improved materials and manufacturing technology is the move toward individual specific product labeling that the US FDA (Food and Drug Administration) is implementing. Only with the availability of materials, techniques and equipment can there be a system of UID (unique identification) for devices in the market. Low cost but reliable options will make possible improved device tracking for patients having long-term implantable products or devices.

### 2.4.2 Compatibility

The term compatibility can be defined in a couple of different ways. The first way is the compatibility of one material with another material which would allow, for example, reliable overmolding of one material onto another material and expecting good adhesion between the two. One example is a housing that needs to be watertight. It incorporates an overmolded sealing gasket directly onto the housing where it would be joined and sealed to the other half of the housing. Unless the materials can be selected each having compatibility with the other, the seal might not perform as expected.

In another example, overmolding was used by an orthopedic instrument company not only to reduce the weight of the tools such as bone hammers and chisels, but also to enhance the performance by giving the user a better gripping surface. These tools are most often used by the surgeon who is gloved and the gloves are not always dry. By using a material that provides improved wet grip characteristics, the reduced weight of the tool, the ergonomic design for finger gripping, and better wet grip made these tools award-winning products. And it was the use of properly selected TPEs that allowed these products to be made effectively. The instruments are repeatedly cleaned and sterilized. The proper selection of the material for compatibility with the process is one of the biggest challenges with this product.

The other use of the term compatibility which is being covered in this review is perhaps more properly termed biocompatibility. But specifically what is meant in this context is the compatibility of the plastic medical device with the health-care need. There are medical devices now available that can be used as joint replacement materials. These materials have been found to provide better long-term outcomes for patients instead of the stainless steel (SS) materials of construction. The implant is made from PEEK polymer that is selected to better match the normal flexibility of the bone into which the implant is secured. When an SS implant is used, the adhesion between the implant and the bone over an extended period of time tends to loosen

because the bone has a small amount of flexibility, whereas the SS implant does not flex. This lack of flexibility is called "stress shielding". But using the PEEK polymer as the implant stem, the polymer has close to the same flexibility as the bone and there is a reduced tendency for the implant to loosen over time. This compatibility between bone and polymer makes a more effective medical device and one that will allow better long-term outcomes especially as the average length of implant gets longer with an increase in life span of the general population.

One other similar trend that is dictating the selection of a new medical device material is the concept of resorbability. Resorbable polymers are the newest family of polymers getting serious attention as new products made from them enter the scene. Resorbable polymers have long been used for internal sutures to eliminate the need for a second surgery to retrieve the sutures positioned somewhere under skin. There is an ever-increasing list of new uses for these polymers which include polylactic acid (PLA), poly glycolic acid (PGA), polycaprolactone (PCL) polymers, and all the various copolymers in between. Devices made from these resorbables, when the material is properly selected, provide the mechanical integrity and strength to allow recovery of the patient. But after the bone or tissue heals, the natural process of the body will begin to digest and dissolve the implant. Examples of this family of polymers being used are for bone screws, plates and pins, tissue anchors, sutures, and one of the most recent developments for cardiovascular stents. In theory, any foreign material positioned in the body for an extended length of time has the potential to cause some unexpected complication. But if the long-term implant is made from a material that will gently be digested and metabolized and excreted, there is no foreign body left behind to cause a problem. For this reason, there is a great deal of attention being given to this new class of polymeric materials and the list of new products which are based on these bioresorbables will continue to grow.

## *2.4.3 Cost*

### 2.4.3.1 Material Costs or Process Improvements

There are few products in the medical device industry that have the luxury of freedom from the cost of material and final product cost in order to be a viable product. The large majority of products are very price sensitive and any way that costs for the final product can be reduced is continually being considered. If for example by using a material with higher temperature properties the time it takes to sterilize the product can be reduced by using a higher sterilization temperature and not affect any other aspect of the product, this would be a very favorable option. The length of time to sterilize and ultimately manufacture the product would be reduced leading to significant cost savings. Large volume products such as IV bags would benefit from such a material improvement.

Any material that can be offered to a device manufacturer that has the potential to reduce the cost of manufacturing can bring an advantage to that product. It could be as simple as easier injection moldability or faster cycle times or something that would help reduce the reject rate or reduce scrap; all these would be considered worthwhile investments to qualify a new material for use in a long-term, high-volume product.

### 2.4.3.2 Light Weighting

Some products could be made for lower costs and result in savings based on light weighting of the product from both a materials consumed standpoint and reduced transportation costs. The example of the orthopedic instruments mentioned above shows that light weighting or reducing the overall weight of the product gives a functional advantage to those products allowing greater ease of use and resulting in less fatigue in the hands and arms of the surgeons who use these tools often on several patients in a row during their day of surgery.

Light weighting can bring down the ultimate cost of disposal of the used medical devices, not an insignificant cost of doing business in this industry. Smaller product footprint reduced size of packaging and improved shipping and handling costs all result from light weighting or downsizing the medical device as long as there is no commensurate loss in quality or functional performance.

### 2.4.3.3 Commoditizing Materials of Construction

This last subcategory of trends that helps drive material costs down is a trend to expand the products that a company manufactures but making the

components and devices using a common polymer or raw material. As the consumption of a particular polymer grows, the purchase pricing is improved. Additional advantages are that instead of using multiple types of plastics, if one plastic can effectively satisfy the requirements across multiple product lines, then the qualification of new materials is eliminated, there is no need to stock multiple grades or different types of plastics, and the need for incoming testing all those various materials goes away.

All this points to the need for material suppliers to offer materials that have the properties needed for products. If one material can survive exposure to all three of the most common sterilization methods, steam, ethylene oxide gas, and irradiation, then this material would have an advantage over a polymer that is suited to only one or the other or two of the three methods, all else being equal.

One additional consideration for this recommendation is to try if possible to build products on the one material that works. This is that a company becomes familiar with how a material is processed, how it needs to be assembled, and how the product works with that material. This collective knowledge will result in better product, more efficient manufacturing operation, and a reduced product cost.

#### 2.4.3.4 Technology Innovations

New device design and processing technologies can improve products and result in better market share and reduced product costs. Companies that stay current with the latest technology will have the advantage over others that don't. Take for example the move from gated molds with sprue and runner systems to hot runner systems. The cold runner systems generated scrap with every shot that needed to be either discarded or reground and used. Hot runner systems eliminated that loss of material.

Vision systems can be installed on manufacturing cells that provide 100% checking of product to eliminate the concern that one of the products may get into the marketplace that is out of tolerance or otherwise unacceptable. Robotics are now available to move product from one place to another thereby eliminating the need for human handling or other random conveyance systems. This helps keep the component or assembly or device cleaner, free from contamination, and allows for the exact location of that product. Knowing the location of a part allows subsequent steps to be taken in the manufacturing of that product from placing it into a tray, putting a critical label on the product assembling it into a product or packaging it.

By using the latest technology available for manufacturing the medical device, the best possible product will be offered to the customer. Micromolding, two shot molding, and metal injection molding are all new process technologies that can affect a product and drive that product to the front of the line. Each new development in technology will put new requirements on materials but in the end, these innovations will enable the development and introduction of game-changing new devices.

### 2.4.4 Ecological and Environmental Concerns and Influence of the Consumer

The final trend that drives new material requirements to be addressed here is the influence of the consumer especially in the current climate of eco-consciousness and environmental awareness. Gone are the days of medical devices being bought based on the personal relationship of the doctor and the company sales representative. No longer are products used because of their appealing color or because of the reputation of the supplier. Buying decisions are being influenced by patients, families of patients, hospital committees that evaluate the products, stockholders or investors of the buying groups, and these days, even politicians are involved. Most medical device manufacturing companies are aware of the need to be environmentally responsible in design of their products, how the products are being manufactured, how these products are used and even how they are discarded after use.

Technologists responsible for the design and manufacturing of medical devices must continue to use the latest materials and process technologies to offer the best products possible. The recent evolution of antimicrobial materials shows a materials technology that at least on first glance seems to have potential to benefit the medical device industry; especially if it actually does reduce the spread of infectious pathogens. The idea of antimicrobial sounds good and is quickly adopted by the general public as an improvement (be it real or just

perceived) and it will be up to the device manufacturers to decide on the best way to incorporate such new technology into their products.

To summarize this subcategory of the influence of the consumer on medical device materials, it is important to recognize that there are other players in the scheme of health-care business. Those that will have a significant influence on products that will be a success in the marketplace and those that will not. The consumer of today has information at their fingertips that allows them to be a better informed health-care consumer and empowers them to request and at times even demand the type of product they feel is best. It will benefit the device industry if this influence on products is carefully considered.

## 2.5 Market Factors Affecting the Industry

Behind the scenes of the medical device industry and health care are the continuing investigations to ensure safety of the general population. Sometimes the investigations are done at universities, sometimes they are done by companies or their competitors and sometimes independent researchers conduct the investigations. Often there are governmental-funded investigations or studies done by activist groups. But no matter who does the investigation and sometimes it does not even matter if the study is done well or not, the results usually will affect the industry, and products in the health-care market will be affected.

### *2.5.1 Concerns Over DEHP and Sometimes Even PVC*

If it were not for the improved ability for blood storage in diethyl hexyl phthalate (DEHP) plasticized PVC coupled with the low-cost superior performance of PVC medical devices, it is not likely that this industry would continue to rely so heavily on this controversial polymer. But flexible PVC is quite a remarkable material meeting so many important needs of the industry from providing safe high-quality inexpensive IV fluid products for patient care, to tubing for conveying the IV fluids, drug therapies and blood, and finally blood collection and storage. There continues to be a drum beat throughout industry alleging that phthalate plasticizers and specifically DEHP poses a danger to those exposed to it from these PVC medical devices. Thousands of studies conducted over more than 40 years of its use have not found reason to stop using f-PVC (flexible polyvinyl chloride). To be precise in this explanation, the studies have not found a problem; but as in any investigation, it is virtually impossible to prove that PVC is safe under all conditions and at every exposure level for every possible population segment. Proving a negative is virtually impossible. At best, industry experts can point to the lack of data showing harmful effects, can further indicate that for billions of uses and in millions of patient infusions, there has not been shown to be any harmful effects in patients exposed to DEHP plasticized PVC, even those listed under the special concerns listing by the FDA. Chemotherapy patients, chronic hemodialysis patients, patients receiving lipid emulsions, and premature infants were all categories of patients that may be more susceptible to adverse effects of high-dose exposure to DEHP. Nevertheless, if alternative materials are available, and if the practitioner were to have concern related to DEHP exposure, it would be a simple matter to use the other materials. But if the choice is between using DEHP plasticized PVC and not giving the patient infusion therapy because alternative materials are unavailable, it would be irresponsible to withhold treatment.

There are strong feelings about this issue and the influence by those holding these opinions has been successful in causing major companies and buying groups to choose to avoid using products that are based on f-PVC. As yet the feedback has not been available regarding the compromise of properties and the effect on patients when using newer materials or the effect of the additional costs of the newer products. It was originally reported that there would be significant savings to the users by switching to the newer materials. This assertion has not yet been verified.

### *2.5.2 Bisphenol A*

Another external factor affecting the medical device community are concerns raised by researchers and voiced in the last five years related to bisphenol A (BPA) coming from plastics. This chemical, a building block for making polycarbonate (PC) plastic, is extracted in minute amounts from containers under certain conditions and

potentially finds its way into humans from either certain beverage containers or medical devices which use PC in their construction. The level of BPA found in the bloodstream of mothers and newborn infants was reported to be detectable and higher than expected and the inference was that the chemical came from medical devices. The reason for the concern is that BPA is reported to have hormone-mimicking properties and is therefore said to be a chemical to which humans should not be exposed. The reality of the hazard is not confirmed but in a move toward caution, baby bottle and sport drink container manufacturers have changed the material from PC to alternative materials.

A review of the use of PC in medical devices shows that it is used primarily in connectors and fluid directing components such as manifolds and catheter hubs. The potential exposure of the IV fluids or blood to the PC surfaces is very short duration and the surface area of contact is extremely small leading most device engineers and toxicologists studying the situation to have little concern. The mood of the general public however has caused enough of an uproar that some companies are seeking PC alternative materials. As yet, this situation has not been fully played out.

## 2.5.3 The Need for "Green"

The consumer is much more aware of the effects of products, including medical devices on the planet, and would like to see products made with renewable resources that reduce the dependence on non-renewable materials. With this in mind, many companies are looking for ways to include renewable materials in their product-line and slowly reduce the amount of non-renewable plastics on which they rely.

It would serve the medical device community well to understand the materials available from companies such as NatureWorks, Metabolix, and Braskem as new products are developed. And every effort to follow the 3Rs—Reduce, Reuse and Recycle—would be to the advantage of every product manufacturing company.

## 2.5.4 Globalization of Markets

Populations across the face of the earth are becoming more aware of and seeking basic levels of medical care that have become the norm in developed nations. The availability of relatively inexpensive transportation costs makes it possible to expand health-care services to places unreachable only 20 years earlier. With a willing and invested government, basic health care needs can be met with commodity medical devices. As the need becomes apparent, local efforts by local companies in these emerging areas are working to establish manufacturing for medical devices primarily for in-country use.

## 2.5.5 Globalization of Manufacturing

Multinational companies have been very successful in manufacturing product in parts of the world where low cost labor is available. That product is then shipped to where the market demand exists. Several factors are changing this situation including the rising cost of labor, even in the most remote parts of the world, increasing energy costs affecting transportation of product, and the growing demand for product in every corner of the world. As local manufacturing is established, distant transport is reduced or eliminated. However, the level of quality is expected to be the same as products made in the primary manufacturing plants and if it is, market growth will match the increase in evolving economies.

### 2.5.5.1 Energy Costs

A major factor affecting globalization of manufacturing is the cost of energy. Transportation costs have already been mentioned as having an influence on where medical devices are made, but another factor is the cost of both raw materials and energy to produce the final product. Further considerations are the requirements for support of the remote operation from corporate headquarters.

## 2.5.6 Global Influences

### 2.5.6.1 Infectious Diseases (MRSA, SARS, H1N1)

Several other factors to consider in the global assessment of health care and the medical device industry are the effects of contagious diseases such as avian bird flu, SARS (severe acute respiratory syndrome) and MRSA (methicillin-resistant *Staphylococcus aureus*). These contagious diseases

and others can rapidly spread around the world affecting countless numbers of the global population. Products are needed that can help stop the spread of any outbreak and treat patients that contract the disease. Part of the problem is that rarely is any attention given to this problem until there is actually an outbreak. Preventive measures are difficult to justify but unless done, the after-the-fact response is usually too little, too late.

#### 2.5.6.2 Economic Pressures

A final market factor that is worth mentioning is the global economic situation. No longer can one country's economy be considered independent of other countries since there has developed in most parts of the world a global interdependence. When the EU falters, it affects the economy in the Middle East and Asia as well as in the United States. Governmental elections often cause market swings across the world and when conflict or war breaks out, the ripple effect can be seen throughout the world. It is with this in mind that medical device companies now are encouraged to keep a global perspective even if their primary markets are not spread across multiple continents. Companies are advised to be aware of what is happening around the world in order to stay current and relevant in meeting current and future demands of the health-care needs of people everywhere.

## 2.6 Conclusion

It is essential that any review of the medical device market includes not only the materials of construction of existing medical devices but also takes into account new materials, new processing technologies, and the ever-changing needs of the marketplace. We exist in a global economy that is constantly changing and only by staying aware of and up to date on influences that affect our industry can a company keep their product mix at the forefront of health-care delivery.

# 3 Plastics Used in Medical Devices

*Laurence W. McKeen, PhD*

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Medical devices range from simple devices, to test equipment, to implants. Plastics are used more and more in these devices, for weight, cost, and performance purposes. Examples of medical devices include surgical instruments, catheters, coronary stents, pacemakers, magnetic resonance imaging (MRI) machines, X-ray machines, prosthetic limbs, artificial hips/knees, surgical gloves, and bandages.

This chapter will discuss plastics used in the construction of medical devices in three sections. The first section will review the general composition of plastic materials which will include the materials added to the basic polymers. The second section will discuss many factors that contribute to the plastic selection. The final section will review the chemistry, the response to sterilization

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processes, and the application of most common plastic materials in medical products.

## 3.1 Plastic Compositions

The basic components of plastic and elastomer materials are polymers. The word polymer is derived from the Greek term for "many parts." Polymers are large molecules comprised of many repeat units, called monomers, that have been chemically bonded into long chains. There are thousands of commercially available polymers that are the basis of plastics. While some plastics are neat polymers, more often than not they are formulated products containing a blend of ingredients each added for a purpose.

### *3.1.1 Polymer Properties*

For any given polymer type, there can be hundreds of grades manufactured by multiple resin manufacturers with distinctly different properties. Some of these grades include variations of the basic polymer: its size or its structure. Other variations are the added ingredients (or additives) which may be incorporated to modify performance, appearance, or other purposes. Variations in the polymer structure are discussed in the next section.

#### 3.1.1.1 Linear, Branched, and Cross-linked Polymers

Some polymers are linear, a long chain of connected monomers. Polyethylene, polyvinyl chloride (PVC), Nylon 66, and polymethyl methacrylate (PMMA) are some linear commercial examples found in this chapter. Branched polymers can be visualized as a linear polymer with side chains of the same polymer attached to the main chain. While the branches may themselves be further branched, the secondary branches do not connect to another polymer chain. The ends of the branches are not connected to any other chemical structure. Special types of branched polymers include star polymers, comb polymers, brush polymers, dendronized polymers [1], ladders, and dendrimers. Cross-linked polymers, sometimes called network polymers, are characterized by connection of different chains. The branches are essentially connected to different polymer chains on the ends. These three polymer structures are shown in Figure 3.1.

#### 3.1.1.2 Isomers

Isomers (from Greek isomerès, isos = "equal," méros = "part") are compounds with the same molecular formula but a different arrangement of atoms. There are many kinds of isomers and the properties can differ widely or almost not at all.

*Structural Isomers*

Structural isomers have the atoms arranged in a completely different order as shown in Figure 3.2. Here both polymer repeating groups have the same formula, $-C_4H_8-$, but the atoms are arranged differently. The properties of structural isomers may be very different from each other.

Often the repeating group in a polymer has exactly the same formula, but the repeating group is flipped over as shown in Figure 3.3. If one views the repeating group as having a head and a tail, then the different ways to connect neighboring repeating units is head−tail, head−head, and tail−tail.

*Geometric Isomers*

When there is a carbon−carbon double bond in a molecule, there may also be two ways to arrange the groups attached to the double bonds. This is

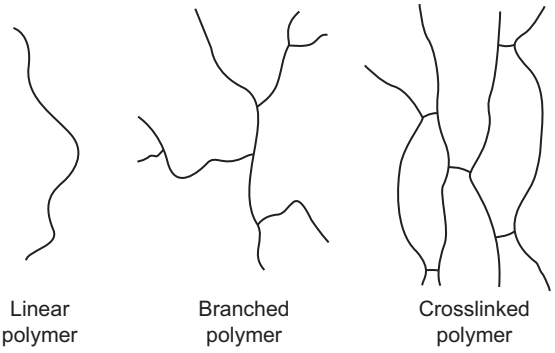



**Figure 3.1** Linear, branched, and cross-linked polymers.

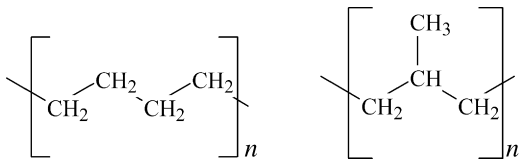



**Figure 3.2** Structural isomers.

best seen in side-by-side structures as shown in Figure 3.4.

These structures are called *geometric isomers* which owe their existence to hindered rotation about double bonds. If the substituents are on the same side of the double bond, then the isomer is referred to as *cis-* (Latin: on this side). If the substituents are on the opposite side of the double bond, these are referred to as *trans-* (Latin: across).

### *Stereoisomers—Syndiotactic, Isotactic, Atactic*

Stereoisomerism occurs when two or more molecules have identical molecular formula and the same structural formula (i.e., the atoms are arranged in the same order). However, they differ in their two or three dimensional (spatial) arrangements of their bonds. This means distinct spatial arrangements of the atoms—even though they are bonded in the same order. The concept would best be understood by an example.

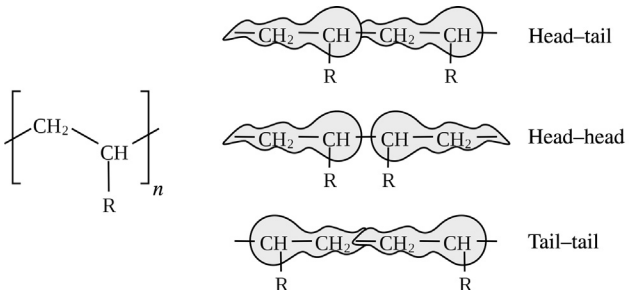



**Figure 3.3** Head to tail isomers [2].

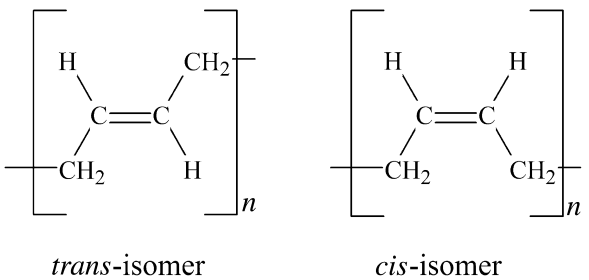



**Figure 3.4** *cis-* and *trans*-isomers.

Polypropylenes (PPs) all have the same simplified structural polymer formula of polypropene as shown in Figure 3.5.

There are, however, subtle differences in the ways the polypropene structure can be arranged. Figure 3.6 shows a longer structure of polypropene, one that also shows some three-dimensional structure. This structure shows how some bonds (the dotted lines) are behind the plane of the paper while others stick out of the paper (the ones on the ends of the little triangular wedges). In this structure, some of the $-CH_3$ groups are presented above the paper plane and others are behind the paper plane. This is called *atactic* polypropene.

Atactic polypropene has at random about 50% of hydrogen/methyl groups in the front and the back of the C—C—C chain viewing plane. This form of polypropene is amorphous (noncrystalline) and has an irregular structure due to the random arrangement of the methyl groups attached to the main carbon—carbon chain. It tends to be softer and more flexible than the other forms of this polymer which are described next.

In *isotactic* polypropene, all the methyl groups are positioned in front of the C—C—C chain viewing plane and all of the hydrogen atoms are at back, as shown in Figure 3.7. This stereoregular structure maximizes the intermolecular contacts and thus increases the intermolecular forces as compared to the atactic form. This regular structure is much stronger (than the atactic form) and is used in sheet and film form for packaging and carpet fibers.

*Syndiotactic* polypropene has a regular alternation of 50% of hydrogen/methyl groups in front/

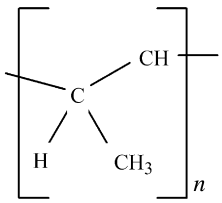


**Figure 3.5** The structure of polypropene.

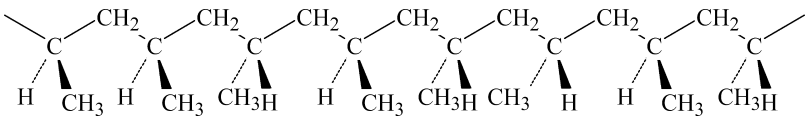


**Figure 3.6** The structure of atactic polypropene.

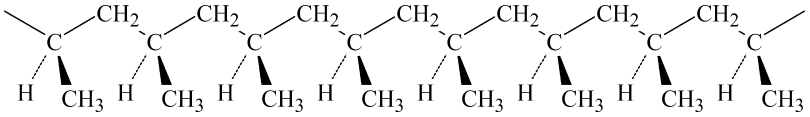


**Figure 3.7** The structure of isotactic polypropene.

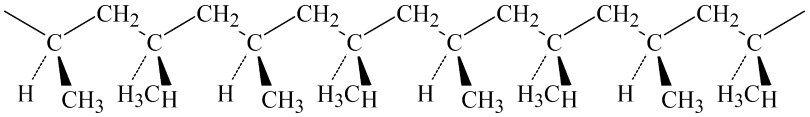


**Figure 3.8** The structure of syndiotactic polypropene.

back of the C—C—C chain viewing plane as shown in Figure 3.8. Its properties are similar to isotactic polypropene rather than the atactic form, i.e., the regular polymer structure produces stronger intermolecular forces and a more crystalline form than the atactic polypropene.

#### 3.1.1.3 Molecular Weight

A polymer's molecular weight is the sum of the atomic weights of individual atoms that comprise a molecule. It indicates the *average* length of the bulk resin's polymer chains. All polymer molecules of a particular grade do not have the exact same molecular weight. There is a range or distribution of molecular weights. Another common means of expressing the length of a polymer chain is the *degree of polymerization*; this quantifies the average number of monomers incorporated into the polymer chain. The average molecular weight can be determined by several means, but this subject is beyond the scope of this book. Low molecular weight polyethylene chains have backbones as small as 1000 carbon atoms long. Ultrahigh molecular weight polyethylene (UHMWPE) chains can have 500,000 carbon atoms along their length.

Many plastics are available in a variety of chain lengths or different molecular weight grades. These resins can also be classified indirectly by a viscosity value or by a proxy parameter called *melt flow rate*, rather than molecular weight. Within a resin family, such as polycarbonate (PC), higher molecular weight grades have higher melt viscosities. For example, in the viscosity test for PC, the melt flow rate ranges from approximately 4 g/10 min for the highest molecular weight, standard grades to more than 60 g/10 min for lowest molecular weight, high-flow, specialty grades.

Molecular weight of the polymers that are used in medical plastics affects a number of their properties. While it is not always possible to quantify the molecular weights of plastics, as mentioned previously, higher flowing plastics of a given series of products generally have lower molecular weights.

### 3.1.2 Polymer Blends

Polymers can often be blended. Occasionally, blended polymers have properties that exceed those of either of the constituents. For instance, blends of PC resin and PET polyester originally created to improve the chemical resistance of the PC actually have fatigue resistance and low-temperature impact resistance superior to either of the individual polymers.

Sometimes a material is needed that has some of the properties of one polymer and some of the properties of another. Instead of going back into the lab and trying to synthesize a brand-new polymer with all the desired properties, two polymers can be melted together to form a blend that possesses some of the properties of each constituent.

Two polymers that do actually mix well are polystyrene and polyphenylene oxide. Other examples of polymer pairs that form blends include:

- Polyethylene terephthalate (PET) with polybutylene terephthalate (PBT)
- PMMA with polyvinylidene fluoride.

Phase-separated mixtures are obtained when one tries to mix most polymers. But strangely enough, the phase-separated materials also turn out to be sometimes useful. They are called immiscible blends.

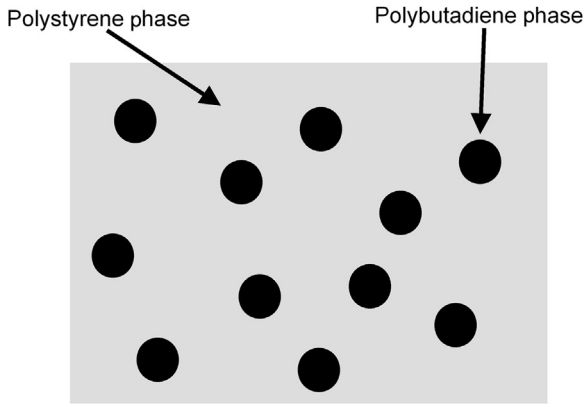



**Figure 3.9** An immiscible blend of polystyrene and polybutadiene.

Polystyrene and polybutadiene are immiscible. When polystyrene is mixed with a small amount of polybutadiene, the two polymers do not blend. Polybutadiene separates from the polystyrene into little spherical blobs. If this mixture is viewed under a high-power microscope, it resembles the picture shown in Figure 3.9.

Multiphase polymer blends are of major economic importance in the polymer industry. The most common examples involve the impact modification of a thermoplastic by the microdispersion of a rubber into a brittle polymer matrix. Most commercial blends consist of two polymers combined with small amounts of a third compatibilizing polymer which typically consists of a block or graft copolymer. Multiphase polymer blends are often easier to process than a single polymer with similar properties.

Blending two or more polymers offers yet another method of tailoring resins to a specific application. Because blends are only physical mixtures, the resulting polymer usually has physical and mechanical properties that lie somewhere between the values of its constituent materials. Additional information on the subject of polymer blends is available in the literature [3–5].

## 3.1.3 Additives

The properties of neat polymers are often ideal neither for production nor for the end use. When this is the case, additives are added to the polymer to improve the performance shortfall. The additives can also improve the processing of polymers in addition to modifying its properties.

Additives encompass a wide range of substances that aid processing or add value to the final product [6,7]. Found in virtually all plastics, most additives are incorporated into a resin family by the supplier as part of a proprietary package. For example, you can choose standard PC resin grades with additives for improved internal mold release, ultraviolet (UV) stabilization, and flame retardance; or nylon grades with additives to improve impact performance.

Additives often determine the success or failure of a resin or system in a particular application. Many common additives are discussed in the following sections. Except for reinforcement fillers, most additives are added in very small amounts.

### 3.1.3.1 Fillers, Reinforcement, Composites

Reinforcing fillers can be added in large amounts. Some plastics may contain as much as 60% reinforcing fillers. Often, fibrous materials, such as glass or carbon, are added to resins to create reinforced grades with enhanced physical or mechanical properties. For example, adding 30% short glass fibers by weight to Nylon 6 improves creep resistance and increases stiffness by 300%. These glass-reinforced plastics usually suffer some loss of impact strength and ultimate elongation, and are more prone to warping because of the relatively large difference in mold shrinkage between the flow and cross flow directions.

Plastics with non-fibrous fillers such as glass spheres or mineral powders generally exhibit higher stiffness characteristics than unfilled resins, but not as high as fiber-reinforced grades. Resins with particulate fillers are less likely to warp and show a decrease in mold shrinkage. Particulate fillers typically reduce shrinkage by a percentage value roughly equal to the volume percentage of filler in the polymer, an advantage in tight tolerance molding.

Often reinforced plastics are called *composites*. The plastic/polymer material containing the reinforcement is referred to as the matrix. One can envision a number of ways different reinforcing materials might be arranged in a composite. Many of these arrangements are shown in Figure 3.10.

Particulates, in the form of pigments, may be added to impart color. Occasionally particulates, called *extenders*, are added to reduce the amount of

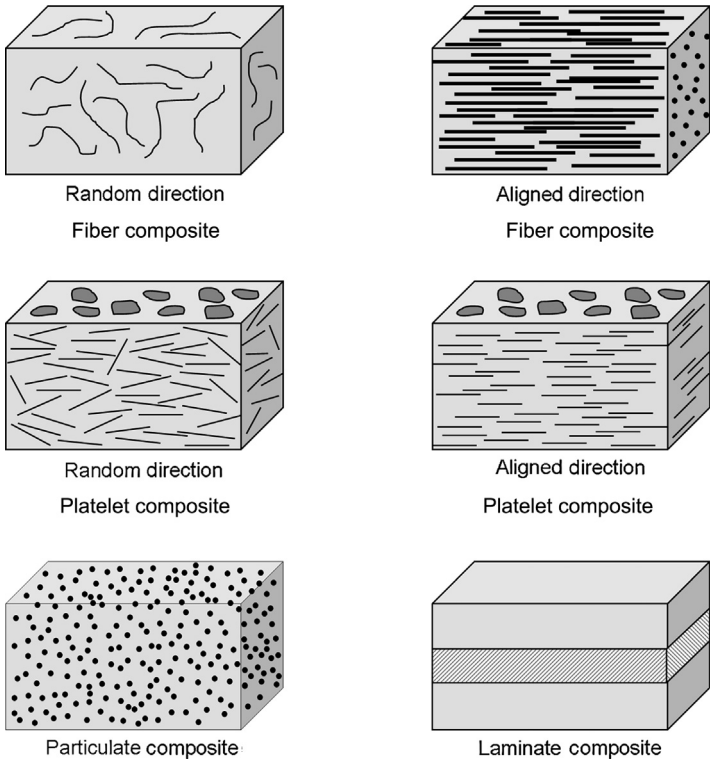



**Figure 3.10** Several types of composite materials.

relatively expensive polymer used which reduces the overall cost.

Platelet additives may impart color and luster, metallic appearance, or a pearlescent effect, but they also can strongly affect permeation properties. Most of these additives have little or no permeation through themselves, so when a film contains particulate additives, the permeating molecule must follow a path around the particulate additive as shown in Figure 3.11. This is called a *tortuous path effect*.

### 3.1.3.2 Release Agents

External release agents are lubricants, liquids, or powders, which coat a mold cavity to facilitate part removal. Internal release agents, which are part of the plastic formulation, can accomplish the same purpose. The identities of the release agents are rarely disclosed, but frequently they are fine fluoropolymer powders (called micropowders), silicone resins, or waxes.

### 3.1.3.3 Slip Additives/Internal Lubricants

When polymeric films slide over each other, they encounter a resistance that is quantified in terms of the coefficient of friction (COF). Plastic films with high COF tend to stick together instead of sliding over one another. Sticking makes the handling, use, and conversion of films difficult. To overcome sticking, slip agents are added.

Slip additives are divided into two migrating and non-migrating types. Migrating slip additives are the most common class and they are used above their solubility limit in the polymer. These types of additives are molecules comprised of two distinct parts, typically pictured as a head and tail as shown in Figure 3.12. One part of the molecule, usually the head, is designed to be soluble in the polymer (particularly when it is molten during processing) making up the plastic. The other part, the tail, is insoluble. As the plastic cools and solidifies from its molten state, these molecules migrate to the surface, where the insoluble end "sticks out" reducing the COF. This process is shown in Figure 3.12. These additives are typically fatty acid amides.

Some common non-migrating slip additives are *dusted* on plastic surfaces. These include:

- PTFE (polytetrafluoroethylene) in micropowder form imparts the lowest COF of any internal

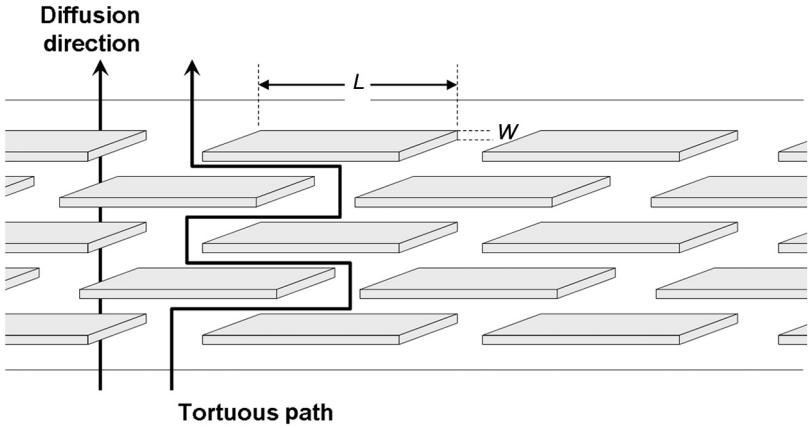



**Figure 3.11** Tortuous path of permeant molecule through a particulate containing film.

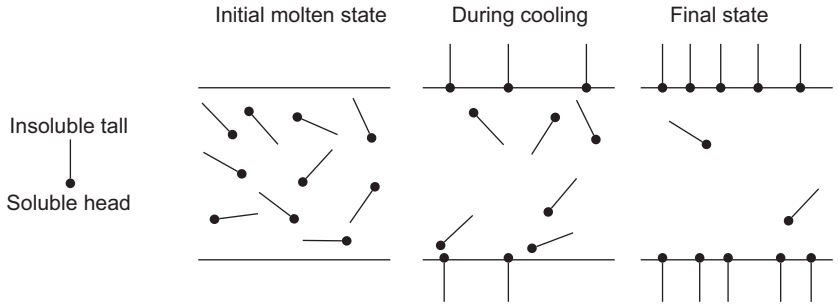



**Figure 3.12** Mode of action of a typical migrating slip additive.

lubricant. Manufacturers and suppliers are many, including DuPont™, Zonyl®, and 3 M Dyneon™.

- Molybdenum disulfide, commonly called "*moly*," is a solid lubricant often used in bearing applications.
- Graphite is a solid lubricant used like molybdenum disulfide.

### 3.1.3.4 Catalysts

Catalysts, substances that initiate or change the rate of a chemical reaction, do not undergo a permanent change in composition or become part of the molecular structure of the final product. Occasionally they are used to describe a setting agent, hardener, curing agent, promoter, etc., and they are added in minute quantities, typically less than 1% usually to thermosetting plastics.

### 3.1.3.5 Impact Modifiers and Tougheners

Many plastics do not have sufficient impact resistance for the use for which they are intended. Rather than changing to a different type of plastic, they can be impact-modified in order to fulfill the performance in use requirements. Addition of modifiers called *impact modifiers* or *tougheners* significantly improves impact resistance. This is one of the most important additives. There are many suppliers and chemical types of these modifiers.

General-purpose impact modification is considered a low level of impact modification. It improves room temperature impact strength but does not take into account any requirements for low-temperature ($<0°C$) impact strength. For most of these types of applications, only low levels of impact modifier is required ($<10\%$).

Low-temperature impact strength is required for applications that require a certain level of low-temperature flexibility and resistance to breakage. For example, this is the case for many applications in the appliances. For this purpose, modifier levels between 5% and 15% of mostly reactive modifiers are required. Reactive modifiers can bond chemically to the base polymer.

Super tough impact strength may be required for applications in which a part must not fail even if it is struck at low temperatures ($-30°C$ to $-40°C$) under high speed. This requirement can only be fulfilled with high levels (20−25%) of reactive impact modifier with low glass transition temperature.

### 3.1.3.6 Radiation Stabilizers

*Radiation stabilizers*, also referred to in the art as "antirads," may be used to mitigate the detrimental effects of the gamma ray dose on plastics generally. Stabilizers like antioxidants and free radical scavengers can prevent degradation and cross-linking. In general, polymers that contain aromatic ring structures are more resistant to radiation effects compared to aliphatic polymers.

*UV stabilizers*: Another way plastics may degrade is by exposure to UV light. UV radiation can initiate oxidation in air. Plastics which are used outdoors or exposed to lamps emitting UV radiation are subject to photooxidative degradation. UV stabilizers are used to prevent and retard photooxidation. Pigments and dyes may also be used in applications not requiring transparency. Photooxidative degradation starts at the exposed surface and propagates throughout the material. Many UV stabilizers, like phenolics, hindered amine light stabilizers, and phosphates, may offer some protection against gamma and electron beam radiation.

### 3.1.3.7 Optical Brighteners

Many polymers have a slight yellowish color. They can be modified to appear whiter and brighter by increasing reflected bluish light (in the range of 400−600 nm). One way to accomplish this is by incorporating an additive that absorbs in the UV range but reemits the energy at higher wavelength in the visible range. This effect is called *fluorescence* and these types of additives are called optical brighteners or fluorescent whitening agents.

### 3.1.3.8 Plasticizers

Plasticizers are added to enhance and maintain flexibility in a plastic. Various phthalates are commonly used for this purpose. Since they are small molecules, they may extract or leach out of the plastic causing a loss of flexibility with time. Just as deliberately added, small molecules may leach out, and small molecules from the environment may be absorbed by the plastic and act like a plasticizer. The absorption of water by nylons (polyamides) is an example of this phenomenon.

### 3.1.3.9 Pigments, Extenders, Dyes, Mica

Pigments are added to impart color to a plastic, but they may also affect the physical properties. Extenders are usually cheap materials added to reduce the cost of a plastic resins. Dyes are colorants that are chemically different to pigments. Mica is a special pigment added to impact sparkle or metallic appearance.

### 3.1.3.10 Coupling Agents

The purpose of adding fillers is either to lower the cost of the polymer, make it tougher or stiffer, or make it flame retardant so that it does not burn when it is ignited. Often the addition of the filler will reduce the elongation at break, the flexibility, and in many cases the toughness of the polymer because the fillers are added at very high levels. One reason for the degradation of properties is that the fillers are not compatible with the polymers, thus form stress rises centers. The addition of coupling agents can improve the compatibility of the filler with the polymer. As a result, the polymer will like the filler more, the filler will adhere better to the polymer matrix, and the properties of the final mixture (e.g., elongation, flexibility) will be enhanced.

### 3.1.3.11 Thermal Stabilizers

One of the limiting factors in the use of plastics at high temperatures is their tendency not only to become softer but also to thermally degrade. Thermal degradation can present an upper limit to the service temperature of plastics. Thermal degradation can occur at temperatures much lower than those at which mechanical failure is likely to occur. Plastics can be protected from thermal degradation by incorporating stabilizers into them.

#### 3.1.3.12 Antistats

Antistatic additives are capable of modifying properties of plastics in such a way that they become antistatic, conductive, and/or improve electromagnetic interference shielding (EMI). Carbon fibers, conductive carbon powders, and other electrically conductive materials are used for this purpose.

When two (organic) substrates rub against one other, electrostatic charges can build up. This is known as tribocharging. Electrostatic charges can impact plastic parts in several ways; one of the most annoying being the attraction of dust particles. One way to counter this effect is to use antistats (or antistatic additives). This effect is principally a surface effect, although one potential counter measure (conductive fillers) converts it into a bulk effect.

Tools that decrease electrostatic charges and hence increase the conductivity of an organic substrate can be classified as:

- external antistat (surface effect);
- conductive filler (bulk and surface effect);
- internal antistat (surface effect).

An external antistat is applied via a carrier medium to the surface of the plastic part. The same considerations and limitations apply as with non-migrating slip additives. Conductive filler is incorporated into the organic substrates and builds up a conductive network on a molecular level. While both approaches are used in organic substrates, they are not the most common.

An internal antistat is compounded into the organic substrate and migrates to the plastic part surface. The same principle considerations apply as for migrating slip additives (see Figure 3.12).

The need to protect sensitive electronic components and computer boards from electrostatic discharge during handling, shipping, and assembly has provided the driving force for development of a different class of antistatic packaging materials. These are sophisticated laminates with very thin metalized films.

There are other additives used in plastics, but the ones discussed above are the most common.

## 3.2 Medical Devices—Material Selection Process

In the United States, medical devices, whether they contain plastics or not, are regulated by the Food and Drug Administration (FDA). Devices are classified into three classes: Class I, Class II, and Class III depending upon their risk and criticality. Table 3.1 provides a few examples of devices of each FDA class.

**Table 3.1** Examples of Medical Devices Associated with FDA Device Class

| | |
|---|---|
| **Class I devices** | Tongue depressors |
| | Bandages |
| | Gloves |
| | Bedpans |
| | Simple surgical devices |
| **Class II devices** | Wheelchairs |
| | X-ray machines |
| | MRI machines |
| | Surgical needles |
| | Catheters |
| | Diagnostic equipment |
| **Class III devices** | Heart valves |
| | Stents |
| | Implanted pacemakers |
| | Silicone implants |
| | Hip and bone implants |

The United States Pharmacopoeia (USP) further classifies medical devices as given in Table 3.2.

Each device class requires a different level of regulation and compliance. Certifying compliance can be a complex and expensive process.

When choosing a plastic for a medical device, design considerations are important. Materials selection, production process selection, and part geometry are interdependent. Usage conditions such as temperature, chemical contact and resistance, and applied stresses during use, are considered. Also, very important for medical devices is sterilization method compatibility including consideration of single vs. repeat sterilization. A summary of many of these considerations follows.

### *3.2.1 Physical and Mechanical Properties*

Physical properties are important; one must know the dimensions, size, and weight requirements for the part or product. If used by a surgeon,

**Table 3.2** USP Classification of Medical Devices

| Device Category | Contact | Exposure Time | USP Class |
|---|---|---|---|
| Surface device | Skin | Limited | USP Class I |
| | | Prolonged | USP Class I |
| | | Permanent | USP Class I |
| Mucosal surfaces | Limited | USP Class I | |
| | | Prolonged | USP Class III |
| | | Permanent | USP Class V |
| | Breached or compromised surfaces | Limited | USP Class III |
| | | Prolonged | USP Class V |
| | | Permanent | USP Class VI |
| External communicating devices | Blood path indirect | Limited | USP Class IV |
| | | Prolonged | USP Class V |
| | | Permanent | USP Class VI |
| | Tissue/bone/dentin communicating | Limited | USP Class IV |
| | | Prolonged | USP Class VI |
| | | Permanent | USP Class VI |
| | Circulating blood | Limited | USP Class IV |
| | | Prolonged | USP Class VI |
| | | Permanent | USP Class VI |
| Implant devices | Implant devices | Permanent | Class VI |

it must be light enough to handle precisely. The design engineer must consider the loads, stresses, and impact that the product might see during its use. Other physical properties can be important including transparency/opacity, color (some items might use color to aid in identification), aesthetics, water absorption, lubricity, and wear resistance. Important mechanical properties are tensile strength, tensile elongation, tensile modulus, impact resistance (all for toughness), and flexural modulus. Details on the importance of these properties and their measurement are available in the literature [8].

### 3.2.2 Thermal Properties

Thermal effects must be evaluated both during the production and use of the part or product. Molding temperatures seen during part production are typically much higher than end-use temperatures. Plastic material properties at melting temperatures, sterilization temperatures, and environmental conditions that include both temperature and humidity need to be characterized. Thermal properties of interest include melting point, processing temperatures, heat deflection (or distortion) temperature under load, glass transition temperature, continuous use temperature, and thermal conductivity.

### 3.2.3 Electrical Properties

Electrical and computer technology is an important part of modern medical treatments, so electrical properties such as conductivity and insulation properties must be considered. Some materials may need to dissipate accumulated static charge, whereas other materials might need electrical insulation properties. Electrical properties to consider are surface and volume conductivity or resistivity, dielectric strength, and comparative tracking index (CTI).

### 3.2.4 Chemical Resistance

Many medical devices may require chemical resistance to various types of oils, greases, processing aids, disinfectant, bleaches, and other hospital chemicals. Chemical resistance must be considered for the product during production, use and cleaning, sterilizing or disinfecting.

### 3.2.5 Sterilization Capability

Many reusable, disposable, implant, and packaging materials will need to be sterilized by various methods like steam, dry heat, ethylene oxide (EtO), electron beam, and gamma radiation. They must be able to withstand these conditions and still maintain their properties for the intended use. Of particular importance is hydrolytic stability for steam sterilization, thermal resistance to steam and autoclave conditions, chemical resistance to EtO, and resistance to high-energy radiation including electron beam, gamma, and UV. This is the subject of a reference work by this author [9].

Examples of the effect of sterilization processes on plastics properties are found in Figures 3.13–3.15.

### 3.2.6 Long-Term Durability

Devices may need to perform for a long period of time under various environmental and thermal conditions. Materials must be selected to meet these long-term aging needs. Instruments must have good ergonomics and functionality. Identification methods like the use of color are also gaining importance. Drug-delivery products comprise needles, tubing, bags, manifolds, Y-sites, clips, and connectors. These are mainly disposable products. Apart from cost, these parts must have excellent chemical and/or lipid

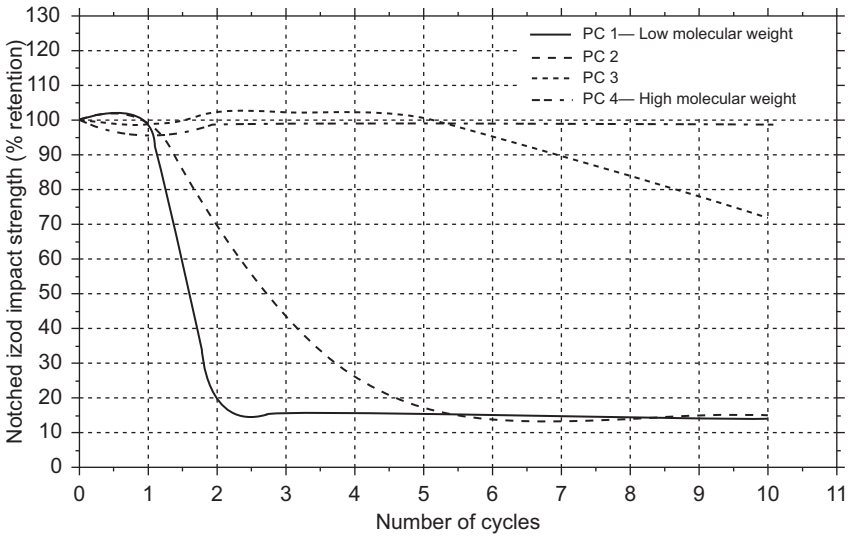



**Figure 3.13** The effect of steam sterilization on the impact strength of PCs [10].

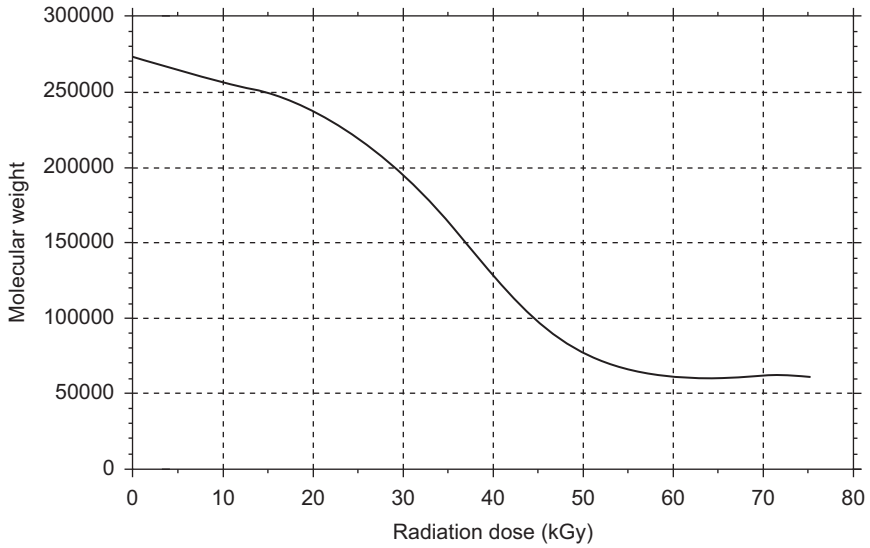



**Figure 3.14** The effect of electron beam sterilization on the molecular weight of polylactic acid (PLA).

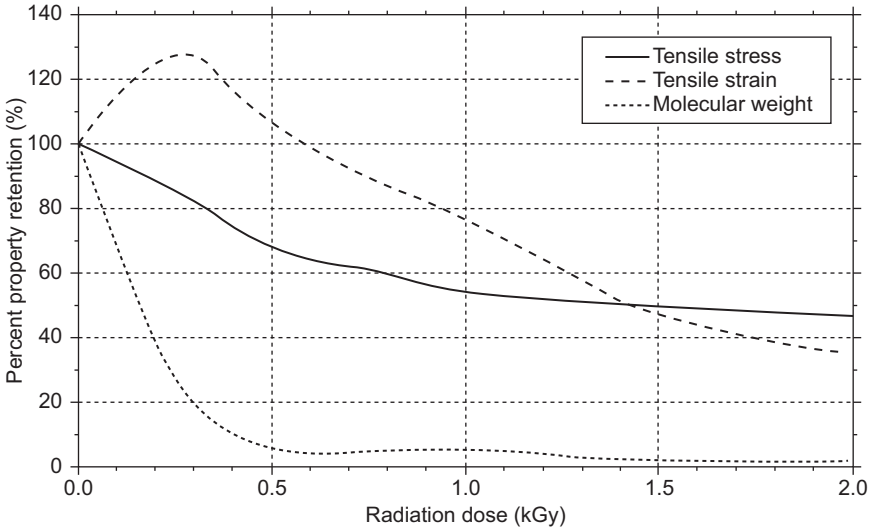



**Figure 3.15** Effect of gamma sterilization on some retention of properties of PTFE.

resistance, flexibility, transparency and clarity, sterilization resistance, toughness, tear and burst strength, softness, and no leachables and extractables (discussed in the next section). End-of-life and disposal requirements are also important. Endoscopy is one area that uses a lot of electronics and ancillary products like cameras, light sources, monitors, and recording equipment. Electric, power, and thermal management is very important, including material durability and toughness. Infection control products and devices include gloves, masks, drapes, and gowns. Apart from fit and comfort, materials for these products must be nonirritating, chemically resistant, and stain resistant.

### 3.2.7 Leachables and Extractables

An important criterion for the use of plastics in medical device applications is quantifying the type and amount and identifying the material that is leached out or extracted from the plastic when in contact with chemicals, reagents, or bodily fluids during the end use. *Extractables* and *leachables* are

compounds that can be extracted from the elastomeric or plastic components, or coatings. This is commonly considered for containers and medical devices that come into contact with solvents such as alcohol at various temperatures of use and storage. The difference between extractables and leachables is slight; leachables is generally a more aggressive exposure that is meant to indicate a worst-case scenario.

Both extractables and leachables are affected by the type and amount of additives in the formulation of the plastic. They include plasticizers, antioxidants, stabilizers, pigments, lubricants, vulcanizers, catalysts, residual monomers and oligomers, residual solvents, and contaminants.

The extracts or leachants are often used for the further biological tests. *Cytotoxicity* is the assessment of the (toxic) effect of chemicals on cells. *Sensitization* tests determine the allergic or hypersensitivity reactions of skin and tissues when exposed to materials or their extracts for prolonged periods of time. *Irritation* tests determine whether the part, material, or extract causes local irritation on skin or mucous membranes via exposure through skin, eye, or mucosa. *Acute system toxicity* testing evaluates whether the extracts cause toxicity effects on various systems of the body when injected into the animal. *Subchronic toxicity* testing is used for all implants. The extract is injected intraperitoneally (in the abdomen walls) or intravenously (in the veins) and evaluated for system toxicity effects. *Genotoxicity* testing evaluates the genetic damage caused by the extracts. *Hemocompatibility* evaluates the compatibility of materials and their extracts with blood and blood components.

### 3.2.8 Supplemental Tests

Additional tests are occasionally required that may include:

- Carcinogenesis—Long-term tests for implants to test for formation of cancerous cells.
- Reproductive—Long-term test on the effects of the materials and extracts on the reproductive system.
- Biodegradation—Long-term evaluation of material degradation in the body.

### 3.2.9 Shelf Life and Aging

Accurate prediction of medical product shelf-life performance is critical. Fortunately, the majority of medical products are constructed from a limited number of polymers that have been well characterized in terms of change in their properties over extended-use periods. A procedure known as the simplified protocol for accelerated aging (also called the "10-degree rule") is used. When applied to well-characterized polymer systems over moderate temperature ranges, the test results obtained can be within the required degree of accuracy [11].

### 3.2.10 Joining and Welding

Medical devices may have complex shapes that cannot be molded directly. In these cases, the plastic parts made need to be separately made and joined together with adhesives or by welding. A number of techniques are used for welding, including:

- Hot gas welding
- Speed tip welding
- Extrusion welding
- Contact welding
- Hot plate welding
- High-frequency welding
- Injection welding
- Ultrasonic welding
- Friction welding
- Spin welding
- Laser welding
- Solvent welding.

Changes in the plastics from welding processes must be considered as well as introduction of adhesives and the chemicals used in them.

### 3.2.11 Medical Grade Plastics

The effort to evaluate many of these factors can be reduced by using medical grades of the plastics of interest. The manufacturers of these plastics may have already had a significant number of the studies done thereby reducing the time and cost of commercialization.

## 3.3 Common Medical Device Polymers

This section covers many of the common plastics that are used in various medical devices. It is primarily focused on the polymers and has a chemistry focus. Included for each polymer are chemical structures, some sterilization guidance, and some example uses.

### 3.3.1 Polyethylene

Polyethylene can be made in a number of ways. The way it is produced can affect its physical properties. It can also have very small amounts of comonomers, which will alter its structure and properties.

The basic types or classifications of polyethylene, according the ASTM D1248, are:

- Ultra-low-density polyethylene (ULDPE), polymers with densities ranging from 0.890 to 0.905 g/cm$^3$, contains comonomer.
- Very-low-density polyethylene (VLDPE), polymers with densities ranging from 0.905 to 0.915 g/cm$^3$, contains comonomer.
- Linear low-density polyethylene (LLDPE), polymers with densities ranging from 0.915 to 0.935 g/cm$^3$, contains comonomer.
- Low-density polyethylene (LDPE), polymers with densities ranging from about 0.915 to 0.935 g/m$^3$.
- Medium density polyethylene (MDPE), polymers with densities ranging from 0.926 to 0.940 g/cm$^3$, may or may not contain comonomer.
- High-density polyethylene (HDPE), polymers with densities ranging from 0.940 to 0.970 g/cm$^3$, may or may not contain comonomer.

Figure 3.16 shows the differences graphically. The differences in the branches in terms of number and length affect the density and melting points of some of the types.

Branching affects the crystallinity. A diagram of a representation of the crystal structure of polyethylene is shown in Figure 3.17. One can imagine how branching in the polymer chain can disrupt the crystalline regions. The crystalline regions are the highly ordered areas in the shaded rectangles of Figure 3.17. A high degree of branching would reduce the size of the crystalline regions, which leads to lower crystallinity.

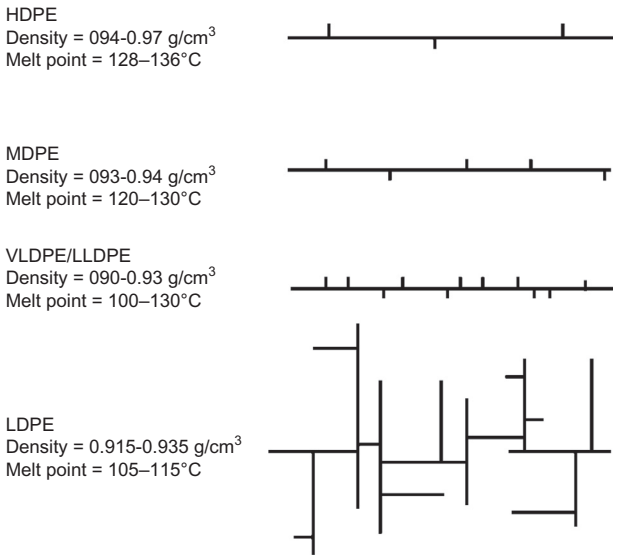



**Figure 3.16** Graphical depictions of polyethylene types.

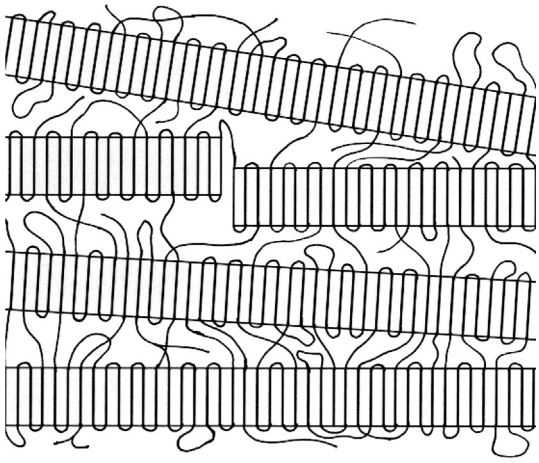


**Figure 3.17** Graphical diagram of polyethylene crystal structure.

*Sterilization:*

The low heat deflection temperatures of polyethylene plastics (30−50°C) make them unsuitable for steam and autoclave sterilization. The plastics would bend, warp, and deform under the temperatures (100−130°C) used in these sterilization methods. EtO, gamma radiation, and e-beam sterilization methods are suitable.

EtO has no effect on the properties of HDPE. Polyethylene will oxidize or cross-link under high-energy radiation and needs to be stabilized to reduce it. In some cases, UHMWPE is deliberately cross-linked with high-energy radiation to improve the wear behavior in the knee and hip implants. Radiation doses of 50−100 kGy are used for cross-linking and standard doses of 25−40 kGy (in an inert atmosphere) are used to sterilize the UHMWPE parts.

*Applications and uses*: Containers, packaging films, pouches, lidstock, breather patches, and headers for bags. UHMWPE is used as the wear-bearing surface of hip and knee arthroplasty and total joint replacement.

### 3.3.2 Polypropylene

The three main types of PP are generally available:

1. *Homopolymers* are made in a single reactor with propylene and catalyst. It is the stiffest of the three propylene types and has the highest tensile strength at yield. In the natural state (no colorant added), it is translucent and has excellent see-through or contact clarity with liquids. In comparison to the other two types, it has less impact resistance, especially below 0°C.
2. *Random copolymers* (homophasic copolymer) are made in a single reactor with a small amount of ethylene (<5%) added which disrupts the crystallinity of the polymer allowing this type to be the clearest. It is also the most flexible with the lowest tensile strength of the three. It has better room temperature impact than homopolymer but shares the same relatively poor impact resistance at low temperatures.
3. *Impact copolymers* (heterophasic copolymer), also known as block copolymers, are made in a two reactor system where the homopolymer matrix is made in the first reactor and then transferred to the second reactor where ethylene and propylene are polymerized to create ethylene propylene rubber (EPR) in the form of microscopic nodules dispersed in the homopolymer matrix phase. These nodules impart impact resistance both at ambient and cold temperatures to the compound. This type has intermediate stiffness and tensile strength and is quite cloudy. In general, the more ethylene monomer added, the greater the impact resistance with correspondingly lower stiffness and tensile strength.

Oriented and multilayered films of PP are also common.

*Sterilization resistance*: The use of PP films in radiation-sterilized applications is somewhat limited. The high ratio of film surface area to mass, combined with the sensitivity of irradiated PP to oxygen-promoted degradation, causes them to be severely embrittled after normal sterilizing doses of radiation. Even resin formulations which yield highly radiation-resistant injection molded devices are badly degraded after irradiation in thin film form. Special formulations of medical PP are coming to market specifically to overcome this disadvantage. Blends of PP and metallocene-catalyzed, ethylene-based plastomers are particularly suited to the construction of highly radiation-resistant, thin-gauge medical device packages.

*Gamma radiation resistance*: Basell offers several grades which are specially formulated to minimize the effects after typical radiation sterilization dosages of up to 5 megarads, as tested by Basell protocol. Catastrophic failures have been reported in gamma-sterilized PP materials that experienced shelf-life storage. This was a result of long-term degradation. "Long-lived free radicals trapped in the crystalline domains migrated toward the crystalline/amorphous interface combining with available oxygen to form peroxy and hydroperoxy radicals that initiated degradation near the interface. As enough tie molecules between crystallites were cut through the chain scission process, significant reduction of PP's elongation could occur which would lead to catastrophic failures" [12].

PP materials that are adequately stabilized can survive the radiation stabilization process with enough antioxidant remaining to protect the sterilized product from further degradation. The stability of sterilized PP depends on the supplier stabilizer system, and the stability of a radiation-sterilized PP can be simply and rapidly determined by oxygen induction testing (OIT) [13].

*Autoclave sterilization*: PP has a melting temperature high enough for autoclave application.

*Applications and uses:*

- Homopolymer: Thermoforming, slit film and oriented fibers, high clarity, syringes, and closures, sutures, drapes, and gowns.
- Random copolymer: Food, household chemicals, beauty aid products, clear containers, and hot fill applications.
- Impact copolymers: Film, sheet, profiles, high-pressure resistance, medical trays, and thin-wall parts.

### 3.3.3 Polystyrene

Polystyrene is the simplest plastic based on styrene. Its structure is shown in Figure 3.18. Pure solid polystyrene is a colorless, hard plastic with limited flexibility. Polystyrene can be transparent or can be made in various colors. It is economical and is used for producing plastic model assembly kits, plastic cutlery, CD "jewel" cases, and many other common objects where a fairly rigid, economical plastic is desired. There are numerous medical applications.

Three general polystyrene types are:

1. General purpose or crystal (PS or GPPS)
2. High impact (HIPS)
3. Syndiotactic (SPS).

*Sterilization:*

Polystyrene is not recommended for steam and autoclave sterilization. Its low heat distortion temperature will cause the parts to warp and disfigure. Polystyrene can be sterilized with EtO.

*EtO resistance*: Polystyrene resins retain their properties after exposure to one normal EtO sterilization cycle. Excessive or multiple exposures to EtO sterilization are not recommended because EtO can cause embrittlement and stress cracking of the polymer [13].

*Gamma and electron beam resistance*: Polystyrene is very stable to gamma radiation and electron beam due to its high aromatic content. Color changes are seen after e-beam sterilization [14].

*UV light sterilization resistance*: Styron is resistant to sterilization by UV light. This technology is based on a short wavelength of 254 nm during which the part-to-lamp distance is controlled [15].

*Applications and uses:*

- *General purpose*: Diagnostic instruments and disposable laboratory ware, Petri dishes, tissue culture components, flasks, and pipettes.
- *Oriented*: Oriented polystyrene films can be printed and laminated to foams for food service plates and trays offering improved esthetics. The films can also be used as a laminate to polystyrene sheet for a high-gloss shine.
- *High impact*: Laboratory ware and other medical devices.

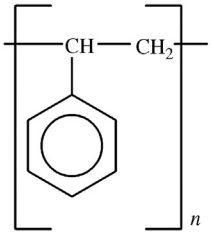



**Figure 3.18** Chemical structure of polystyrene.

### 3.3.4 Polyester

Polyesters are formed by a condensation reaction that is very similar to the reaction used to make polyamide or nylons. A diacid and dialcohol are reacted to form the polyester with the elimination of water as shown in Figure 3.19.

While the actual commercial route to making the polyesters may be more involved, the end result is the same polymeric structure. The diacid is usually aromatic. Polyester resins can be formulated to be brittle and hard, tough and resilient, or soft and

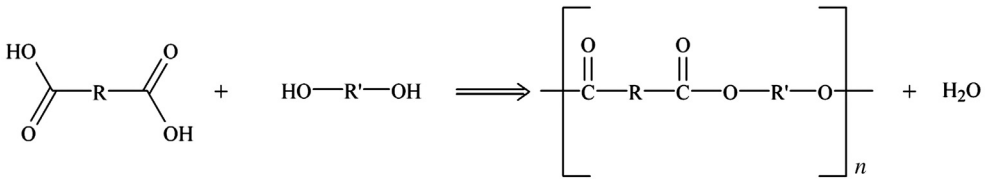



**Figure 3.19** Chemical structure of polyester.

flexible. In combination with reinforcements such as glass fibers, they offer outstanding strength, a high strength-to-weight ratio, chemical resistance, and other excellent mechanical properties. The three dominant materials in this plastics family are PC, PET, and PBT. Liquid crystal polymers are also considered to be polyesters. Thermoplastic polyesters are similar in properties to Nylon 6 and Nylon 66, but have lower water absorption and higher dimensional stability than the nylons.

*Sterilization:*

*EtO Sterilization:*

Polyesters generally can be sterilized with EtO. Due to their low hydrolytic stability (i.e., the polymer chains can be cleaved by hydrolysis) and low glass transition temperatures, steam and higher heat autoclave sterilizations are not recommended. All polyesters based on terephthalic acid contain aromatic groups and hence can be sterilized with gamma and e-beam radiation.

*Gamma radiation resistance*: Ticona Vectra® liquid crystalline polymers (LCPs) have excellent resistance to gamma radiation.

*Steam sterilization resistance*: Ticona Vectra® LCP has good resistance to hydrolysis. Prolonged exposure to hot water and steam at high temperatures (121°C, 2 bar up to 1000 h) leads to hydrolytic degradation however. The glass-fiber-reinforced grades exhibit a more severe decline in mechanical properties, as do many other glass-fiber-reinforced polymers, owing to capillary action at the glass-fiber/polymer interface (wick effect). Ticona Vectra® A625 has particularly good resistance to hydrolysis. Under selected test conditions, virtually no change in tensile strength or elastic modulus occurred after 1000 h.

*PBT* can be sterilized by gamma ray or dry heat, up to about 180°C.

*Applications and uses:*

*Liquid crystalline polymer*: Sterilizable trays, dental tools, and surgical instruments, surgical device control cables, surgical tubing, cannulae, films.

*PBT*: Packaging, syringe pump component, dental instruments, miniature scalpel blade holders, melt blown for liquid filtration applications, high-temperature caps.

## 3.3.5 Polyester (PLA and Other Biosorbable Plastics)

Bioresorbable polymer implants are rapidly growing alternatives to traditional implants in many applications. These implants are only required to serve for a certain time period ranging from weeks to months. PLA is derived from renewable resources, such as corn starch or sugarcanes. PLA polymers are considered biodegradable and compostable. PLA is a thermoplastic, high-strength, high-modulus polymer that can be made from annually renewable sources to yield articles for use in either the industrial packaging field or the biocompatible/bioabsorbable medical device market. Bacterial fermentation is used to make lactic acid, which is then converted to the lactide dimer to remove the water molecule which would otherwise limit the ability to make high molecular weight polymer. The lactide dimer, after the water is removed, can be polymerized without the production of the water. This process is shown in Figure 3.20.

The dimer can be isolated into three forms: the optically active L-lactide, the optically active D-lactide, and the optically inactive DL mixture DL-lactide. These stereoisomer structures are shown in Figure 3.21. The enantiomeric ratio of the dimer can be controlled. Fermentation-derived lactic acid is 95% L-isomer.

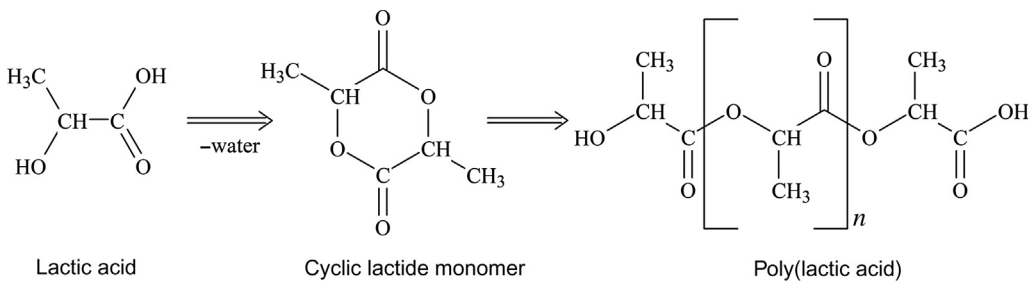



**Figure 3.20** Conversion of lactic acid to PLA.

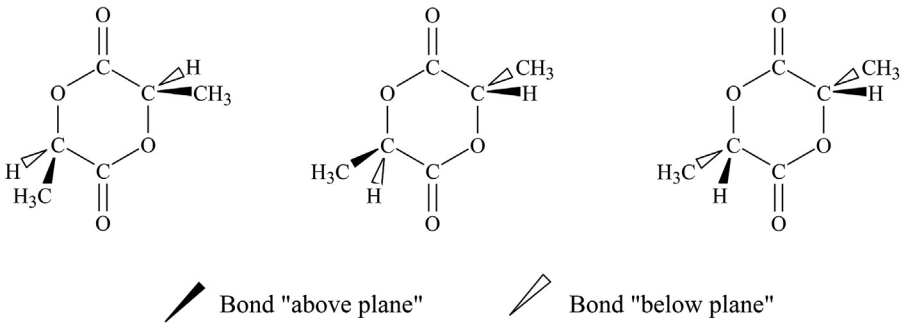



**Figure 3.21** Stereoisomeric structures of the lactide dimer.

Polyhydroxyalkanoates (PHAs) are naturally produced and include poly-3-hydroxybutyrate (PHB or PH3B), polyhydroxyvalerate (PHV), and polyhydroxyhexanoate (PHH). A PHA copolymer called PHBV (poly(3-hydroxybutyrate-co-3-hydroxyvalerate)) is less stiff and tougher, and it may be used as packaging material. Chemical structures of some of these polymers are shown in Figure 3.22.

*Sterilization:*

*Autoclave* and *dry heat* is usually performed at temperatures equal to or higher than 121°C. PLA, PGA, and PLGA implants are susceptible to hydrolysis and their deformation at higher temperatures therefore precludes the use of these sterilization methods.

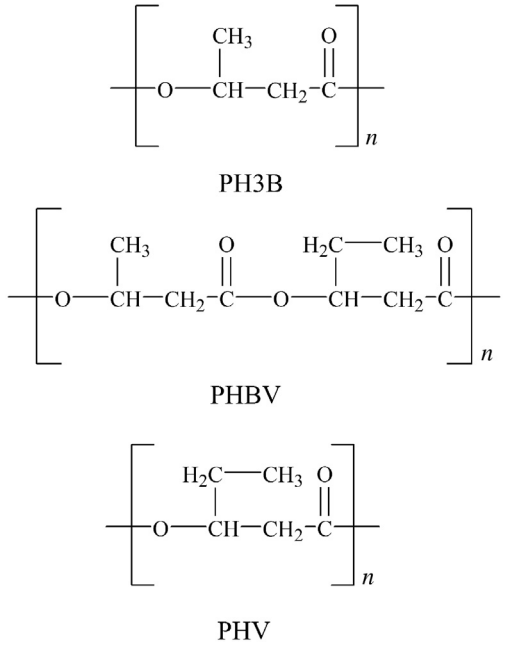



**Figure 3.22** Structures of several PHAs.

*EtO sterilization*: EtO is chemically highly reactive and acts as a plasticizer for PLA, PGA, and PLGA, which can lead to changes in the polymer structure. EtO sterilization is performed at temperatures of 50−60°C, which can lead to molecular weight loss. Therefore, EtO sterilization is not suggested.

*Radiation sterilization*: For the radiation sterilization of bioresorbable polymers, temperature and dose conditions need to be closely controlled to avoid significant degradation. Gamma sterilization at dry ice temperatures is preferred.

*Applications and uses*: Commercially available biodegradable devices are employed in sutures, orthopedic fixation devices, dental implants, ligature clips, tissue staples, and skin covering devices; stents, dialysis media, and drug-delivery devices. It is also being evaluated as a material for tissue engineering.

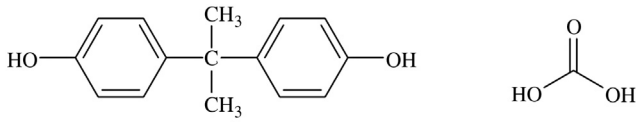
## 3.3.6 Polycarbonate

PC is a type of polyester but is being discussed separately. Theoretically, PC is formed from the reaction of bis-phenol A and carbonic acid. The structures of these two monomers are shown in Figure 3.23.

Commercially, different routes are used (different monomers), but the PC polymer of the structure shown in Figure 3.24 is the result.

PC performance properties include:

- Very impact resistant, is virtually unbreakable and remains tough at low temperatures
- "Clear as glass" clarity
- High heat resistance
- Dimensional stability
- Resistant to UV light, allowing exterior use
- Flame retardant properties.




Dialcohol
bis-phenol A
2,2-bis(4-hydroxy(henyl) propane)

Diacid
carbonic acid

**Figure 3.23** Chemical structures of monomers used to make PC polyester.

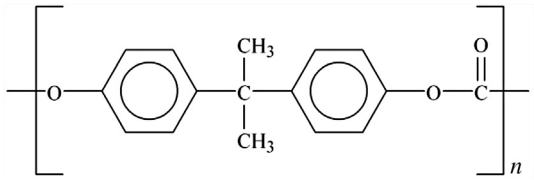



**Figure 3.24** Chemical structure of PC polyester.

Typical application requirements include:

- Optical clarity: transparent and colorable
- Durability/impact resistance
- Ductility to withstand impact of rigorous use
- Biocompatible tested grades
- Sterilizable: gamma, EtO; limited autoclave
- Dimensional stability
- Ultrasonic weldable; bondable

*Sterilization:*

PCs can be sterilized by high-energy gamma and e-beam radiation but must be stabilized to prevent polymer degradation and discoloration.

*Gamma radiation resistance*: PC is much more resistant to gamma irradiation than most polymers. The primary effect of gamma irradiation on PC is chain scission (chain breakage). Fortunately, the high chain stiffness of PC makes it very difficult for the two ends of the chain to move apart. Therefore, many of the broken chains will recombine. In addition, the aromatic nature of the PC gives it other opportunities to absorb the energy from the gamma photon, rather than just breaking the polymer chain. From a retention of mechanical properties point of view, PC has always been considered one of the most resistant materials for gamma irradiation [16]. Assuming that 28 kGy (2.8 megarads) of energy is required to sterilize PC, the resin can be sterilized 10–20 times before any appreciable reduction in mechanical strength occurs. PC does, however, become progressively more yellow with each sterilization. Special stabilizers can make them less susceptible to color changes.

*EtO resistance*: The properties of polystyrene resins are unchanged to 50 EtO sterilization cycles [17]. The temperature during sterilization should not exceed 65°C. Tests have shown that repeated sterilization can cause slight brittleness combined with crack formation. The impact strength of test specimens treated with pure EtO at 55°C for 50 cycles of 6 h each is unchanged in comparison with the starting level despite slight crack formation.

*Steam resistance*: After one to three autoclave cycles (Hi-Vac at 132°C), PC resins have limited utility [18]. Makrolon® DP 1-1262 and Makrolon® Rx-1805 can be sterilized by employing superheated steam (121°C) [18,19]. To prevent deformation of the molded parts, the sterilization temperature should not exceed 125°C. Care must also be taken to ensure that Makrolon parts are not damaged by substances added to the boiler feed water, such as alkaline corrosion inhibitors, and that the article is positioned in such a way that no condensation can accumulate inside it. As a rule, it is possible to sterilize molded parts made of Makrolon many times before gradual chemical decomposition reduces the mechanical strength to a level where it is no longer adequate for certain applications. Sterilization tests on test specimens have shown that even after 100 cycles of 30 min each at 120–125°C, the part still retains comparatively good impact strength. This also generally applies even if the material exhibits hairline cracks and the molded part appears slightly milky as a result of the high stresses imposed on the material by repeated sterilization.

*Sterilization with peracetic acid*: Makrolon can be sterilized with 2% concentration peracetic acid without suffering damage.

*Sterilization with hot air*: Sterilization with hot air plays only a minor role for molded parts in Makrolon, since temperatures of 180–200°C are generally used to save time. No problems are to be expected with molded parts of Makrolon up to a hot air temperature of 135°C.

*Applications and uses*: Medical apparatus (sterilizable), reservoirs, high-pressure syringes, artery cannulas, stopcocks, luers, centrifugal force separators, blood filter housings, dialyzer housings; glucose meters, pumps, insulin pens; surgical device handles and housings.

### 3.3.7 Polyvinyl Chloride

PVC is a flexible or rigid material that is chemically nonreactive. Rigid PVC is easily machined, heat formed, welded, and even solvent cemented. PVC can also be machined using standard metal working tools and finished to close tolerances and finishes without great difficulty. PVC resins are normally mixed with other additives such as impact modifiers and stabilizers, providing hundreds of PVC-based materials with a variety of engineering properties.

There are three broad classifications for rigid PVC compounds: Type I, Type II, and CPVC. Type II differs from Type I due to greater impact values, but lower chemical resistance. CPVC has greater high temperature resistance. These materials are considered "unplasticized," because they are less flexible than the plasticized formulations. PVC has a broad range of applications, from high-volume construction-related products to simple electric wire insulation and coatings.

PVC is the most widely used plastic resin in medical devices. Approximately 25% of all plastic medical products are made of PVC, according to most market estimates. The main reason is the resin's low cost, ease of processing, and the ability to tailor its properties to a wide range of applications. The following is a more thorough list of reasons for the popularity of PVC in medical devices:

- Used successfully for over 50 years in various medical devices with no known adverse or toxic effects.
- Plasticized PVC has good clarity and transparency retention so that tubes and other products allow for continual monitoring of fluid flow.
- PVC can be manufactured in a range of flexibilities and its resistance to kinking in tubing reduces the risk of fluid flow being interrupted.
- PVC can be used in a wide range of temperatures, and it retains its flexibility, strength, and durability at low temperatures.
- PVC formulations exhibit excellent strength and toughness.
- PVC exhibits very good chemical resistance and stability and is also biocompatible for applications in blood bags and drug delivery.
- Plasticized PVC maintains its product integrity under various sterilization environments like steam, radiation, and EtO.
- PVC can be easily welded to various other plastics by a wide range of methods.
- Its relatively lower cost and high-performance value maintains its position as the number one plastic used in medical devices.
- PVC has safety and cost advantages for a wide variety of medical applications, especially for single-use disposable devices.

A large number of plasticizers have been used with PVC to reduce rigidity, the most common family being the phthalates, especially, di(2-ethylhexyl) phthalate (DEHP). It is sometimes called dioctyl phthalate and abbreviated DOP. These plasticizers are incorporated in amounts ranging from 40% to 65%. There are many other plasticizers used in medical applications.

Heat stabilizers are typically used in medical grade PVC, to protect it against not only the high temperatures the resin might see during processing, but also the high heat it may encounter in storage or autoclaving. Barium−zinc additives are very effective heat stabilizers for PVC but are restricted for medical applications in some countries. Alternatives like calcium−zinc formulations are often used to stabilize medical-grade PVC. Heat stabilizers trap the hydrogen chloride that is generated when PVC decomposes at high temperatures. This prevents discoloration and degradation. Rigid PVC may contain up to 15% by weight of thermal stabilizers. Another additive, Tinuvin®−P, 2-(2H-benzotriazol-2-yl)-*p*-cresol, is used to provide stability from exposure to UV light.

*Sterilization:*

*Gamma radiation resistance*: Gamma-ray sterilization generally uses an energy dose of about 2.5 megarads. Sterilization at excessive dosage rates or with excessive sterilization times can result in discoloration or odor. Rigid PVC suffers more severe adverse effects than flexible PVC when inappropriate procedures of this type are used. Specific

gamma radiation-resistant PVC blends are commercially available [20]. PVC degrades by chain scission when exposed to high-energy radiation causing degradation or the radicals can react with oxygen to form oxidized products leading to discoloration.

*EtO resistance*: EtO sterilization is recommended for PVC. When choosing EtO gas sterilization, a 7- to 14-day quarantine period is necessary to assure that there is no EtO residue [10]. Sterilization using EtO gas is a method which has proven particularly useful for PVC products having a large number of cavities or capillaries [10].

*Autoclave sterilization*: Steam sterilization in autoclaves is conducted at temperatures from 121°C to 134°C. The temperature used is above the glass transition temperature of PVC. Rigid unplasticized PVC is unsuitable for use in steam and autoclave sterilizations as the material and parts will warp and distort when exposed to that temperature range. The temperature range poses no problem for flexible PVC, which is a rubbery material. Plasticized, flexible PVC can be sterilized using steam or autoclave. Low-temperature steam sterilization (conducted at 60−80°C) can be used for both rigid and flexible PVC.

*Low-temperature plasma sterilization*: PVC products can also be sterilized using newly developed low-temperature plasma technology (Sterrad® plasma sterilization) [10].

*Applications and uses:*

- Rigid PVC: luer connectors and Y-sites.
- Flexible PVC: secondary packaging, blister packs, solution containers, fluid transport tubes, drip chambers, diaphragms, pull rings, oxygen facemasks, and gloves.

## 3.3.8 Polyethersulfone

Polyethersulfone (PES) is an amorphous polymer and a high-temperature engineering thermoplastic. Even though PES has high-temperature performance, it can be processed on conventional plastics processing equipment. Its chemical structure is shown in Figure 3.25. PES has an outstanding ability to withstand exposure to elevated temperatures in air and water for prolonged periods.

Because PES is amorphous, mold shrinkage is low and is suitable for applications requiring close tolerances and little dimensional change over a wide temperature range. Its properties include:

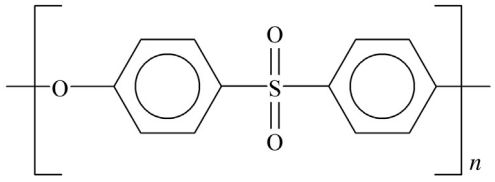



**Figure 3.25** Structure of PES.

- Excellent thermal resistance—$T_g$ 224°C
- Outstanding mechanical, electrical, flame, and chemical resistance
- Very good hydrolytic and sterilization resistance
- Good optical clarity

*Sterilization:*

*General sterilization resistance*: PES withstands cold sterilants, disinfectants, and germicides.

*Gamma and electron beam radiation resistance*: PES offers very high resistance to gamma radiation over the entire range of service temperatures. PES products exposed to high-energy radiation suffer a noticeable decrease in tensile strength at yield and a significant decrease in ultimate elongation. Gassing is very slight; transmittance for gamma rays is very high.

*Autoclave or steam sterilization resistance*: PES parts can be repeatedly sterilized in superheated steam. After more than 100 sterilization cycles, samples remain transparent and largely retain their high level of mechanical properties. PES absorbs more water and is thus suitable only for steam sterilization without a vacuum phase. In order to avoid environmental stress cracking, the level of molded in stress in parts should be as low as possible.

*Applications*: Medical equipment that requires repeated sterilization; fluid handling couplings/fittings.

## 3.3.9 Polyacrylate (Acrylic, PMMA)

While a large number of acrylic polymers are manufactured, PMMA is by far the most common. The structure of PMMA is shown in Figure 3.26. Nearly everyone has heard of Plexiglas®. PMMA has two very distinct properties that set the products apart from others. First, it is optically clear and colorless. It has a light transmission of 92%. The 4%

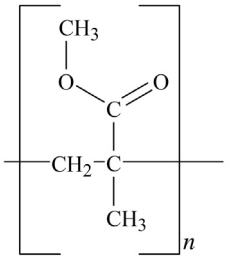



**Figure 3.26** Structure of PMMA.

reflection loss at each surface is unavoidable. Second, its surface is extremely hard. They are also highly weather resistant.

PMMA films show very good abrasion resistance, weather resistance (with a UV absorber), and are absolutely colorless.

Acrylic resins are available as homopolymer (primarily PMMA), copolymer, and terpolymer. Each of these is discussed separately in the following sections.

*Sterilization resistance*: Wet EtO and steam sterilization methods are not recommended for acrylic [21].

*Gamma radiation resistance*: Plexiglas SG-7 exposed to 5.0 megarads of gamma radiation experiences virtually no yellowing or discoloration. Properties such as impact, tensile, and flexural strength, modulus of elasticity, and percent elongation are constant [22]. Gamma sterilization has a tendency to yellow most acrylics. This yellowing is often temporary and recovery can be complete, with the parts retaining their original integrity. The higher the radiation dosage, the greater the yellowing, and the longer the required recovery time. Current techniques have cut recovery time to a week for some grades [22].

*E-beam radiation resistance*: Plexiglas maintains constant impact, tensile, and flexural strength, modulus of elasticity, and percent elongation properties [23].

*EtO resistance*: Acrylics and impact-modified acrylics are compatible with EtO gas and can be EtO sterilized without adversely affecting the medical device.

*Applications and uses*: Clear, disposable plastics—only glass transmits light as well; chest drainage units, medical spikes, breathing apparatus accessories, urological accessories, Y-sites, check valves, filter housings, IV adaptors, IV pump housings, medical cassettes, blood handling components, and catheter accessories.

### 3.3.10 Hydrogel (Acrylate)

Hydrogel is a special acrylic polymer or blend of acrylic and silicone polymers that is used in contact lenses. The acrylic is made from monomers that have hydroxyl (—OH) groups on them that "like" water. One such hydrophilic polymer is poly (hydroxyl ethyl acrylate) (or PHEA) or poly (hydroxyl ethyl methacrylate) (or PHEMA). Blends of a hydrophobic silicone with a hydrophilic PHEMA produce a lens material that has improved oxygen transmissibility.

The oxygen transmission is the difference between silicone hydrogel lenses and conventional hydrogel lenses.

Hydrogels used in dressings are also an important component in many different types of wound care. The hydrogel dressing is designed to hold moisture in the surface of the wound, providing the improved environment for both cleaning the wound, and allowing the body to rid itself of necrotic tissue. The moisture in the wound is also essential in pain management for the patient, and these dressings are very soothing and cooling.

*Sterilization*: Hydrogel contact lenses are generally chemically sterilized by soaking in solutions designed for that purpose.

*Applications and uses*: Soft contact lenses, wound dressings, drug delivery.

### 3.3.11 Polysulfone

Polysulfone (PSU) is a rigid, strong, tough, high-temperature amorphous thermoplastic. The structure of PSU is shown in Figure 3.27.

Its properties are:

- High thermal stability
- High toughness and strength
- Good environmental stress crack resistance
- Inherent fire resistance
- Transparency.

*General sterilization resistance*: PSU maintains a high enough glass transition temperature to withstand different sterilization techniques including steam, EtO, and gamma and electron beam radiation.

*Gamma and electron beam radiation resistance*: PSUs are highly resistant to degradation by gamma

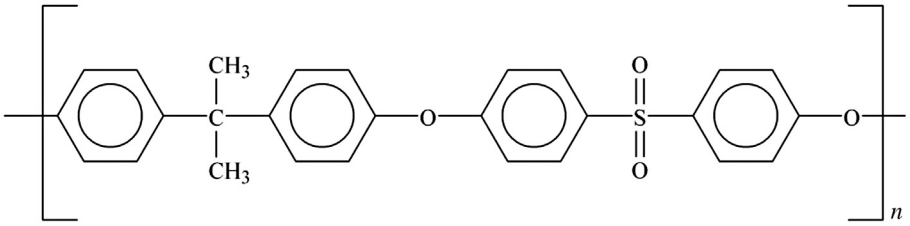


**Figure 3.27** Structure of PSU.

or electron beam radiation. There is no evidence of change in mechanical properties after irradiation at 2.5, 4, or 6 megarads. Tensile strength, elongation, modulus, and notched Izod impact values remain essentially unchanged. There is no significant change in chemical resistance following irradiation. PSU discolors during irradiation; the level of discoloration increases with the radiation dosage.

*EtO resistance*: MPU couplings can be EtO sterilized up to five cycles.

*Autoclave or steam sterilization resistance*: PSU can withstand greater than 1000 autoclave cycles at 140°C with no significant change in mechanical properties. Transparent PSU will retain its clarity during extended service life. PSU parts can be repeatedly sterilized in superheated steam. After more than 100 sterilization cycles, samples remain transparent and largely retain their high level of mechanical properties. MPU couplings can be autoclave sterilized at 121°C (270°F) for 60 min. The maximum number of cycles recommended is 25.

*Dry heat sterilization*: Products made from PSU can be dry heat sterilized at 140°C; recommended exposure is 6 h in dry 125°C heat.

*Chemical sterilants*: PSU performs well, retaining its strength in a wide variety of aqueous disinfectants including buffered glutaraldehyde, phenol, quaternary ammonium, iodophor and formaldehyde types, and detergent germicide.

*Applications*: Membranes and fluid handling applications and MPU couplings.

## 3.3.12 Polyetheretherketone

Polyetheretherketones (PEEK) are also referred to as polyarylketones. The most common structure is given in Figure 3.28.

PEEK is a thermoplastic with extraordinary mechanical properties. The Young's modulus of elasticity is 3.6 GPa and its tensile strength is 170 MPa. PEEK is partially crystalline, melts at around 350°C,

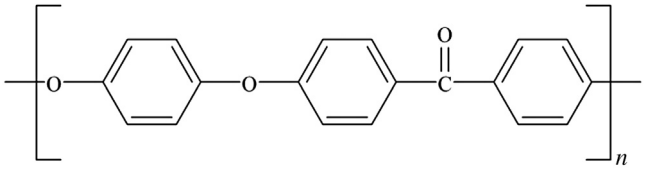


**Figure 3.28** Structure of PEEK.

and is highly resistant to thermal degradation. The material is also resistant to both organic and aqueous environments, and is used in bearings, piston parts, pumps, compressor plate valves, and cable insulation applications. It is one of the few plastics compatible with ultrahigh vacuum applications. In summary, the properties of PEEK include:

- Outstanding chemical resistance
- Outstanding wear resistance
- Outstanding resistance to hydrolysis
- Excellent mechanical properties
- Outstanding thermal properties
- Very good dielectric strength, volume resistivity, tracking resistance
- Excellent radiation resistance

*Gamma radiation resistance*: Victrex® PEEK shows excellent resistance to hard (gamma) irradiation, absorbing over 1000 megarads of radiation without suffering significant damage and showing no embrittlement of the polymer. It is believed that PEEK will resist dose levels of well over 10,000 megarads of particle (alpha or beta) irradiation without significant degradation of properties. Fiber-reinforced grades are expected to show even better performance than this.

*EtO resistance*: PEEK polymers can be sterilized by EtO methods.

*Steam sterilization resistance*: PEEK maintains high mechanical strength, stress cracking resistance, and hydrolytic stability in the presence of

pressurized steam (200°C, 14 bar), dry heat (170−180°C), hot water, solvents, and chemicals. PEEK can withstand high temperatures and pressures for extended periods of time.

*Applications and uses*: Reusable medical components including dental syringes and keyhole surgery devices, catheters, disposable surgical instruments.

### 3.3.13 Thermoplastic Elastomers (TPE, TPU)

An elastomer is a polymer with the property of "elasticity," generally having notably low Young's modulus and high yield strain compared with other materials [23]. The term is often used interchangeably with the term rubber. Elastomers are amorphous polymers existing above their glass transition temperature, so that considerable segmental motion is possible, so it is expected that they would also be very permeable. At ambient temperatures, rubbers are thus relatively soft and deformable. Their primary uses are for seals, adhesives, and molded flexible parts. Elastomers may be thermosets (requiring vulcanization, a form of cross-linking) or thermoplastic, called thermoplastic elastomer or TPE.

TPEs have two big advantages over the conventional thermoset (vulcanized) elastomers. Those are ease and speed of processing. Other advantages of TPEs are the ability to recycle scrap, lower energy costs for processing, and the availability of standard, uniform grades (not generally available in thermosets).

TPEs are molded or extruded on standard plastics-processing equipment in considerably shorter cycle times than those required for compression or transfer molding of conventional rubbers. They are made by copolymerizing two or more monomers, using either the block or graft polymerization techniques. One of the monomers provides the hard, or crystalline, polymer segment that functions as a thermally stable component; the other monomer develops the soft or amorphous segment, which contributes the elastomeric or rubbery characteristic. This is shown in Figure 3.29 in which the hard crystalline parts of the molecule are the thick lined segments of the polymer chain. As shown, the hard segments can be aligned together forming crystalline regions.

Physical and chemical properties can be controlled by varying the ratio of the monomers and the length of the hard and soft segments. Block techniques create long-chain molecules that have various or alternating hard and soft segments. Graft polymerization methods involve attaching one polymer chain to another as a branch. The properties that are affected by each phase can be generalized.

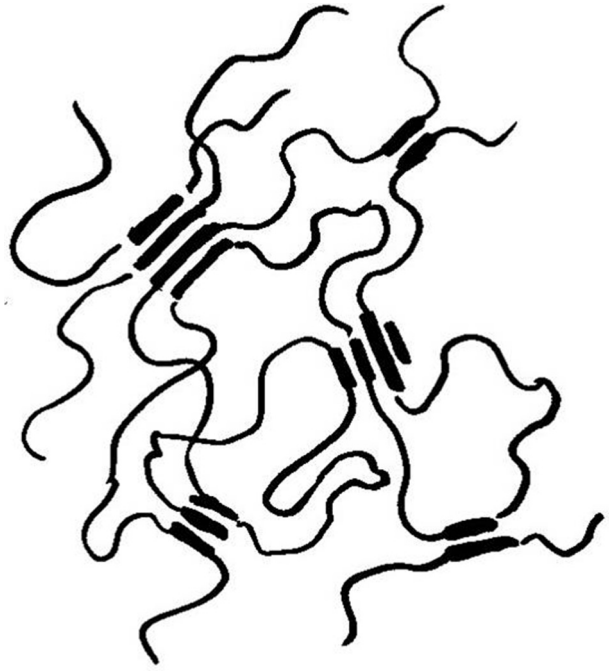


**Figure 3.29** Schematic of the structure of a TPE.

"Hard phase"—plastic properties:

1. Processing temperatures
2. Continuous use temperature
3. Tensile strength
4. Tear strength
5. Chemical and fluid resistance
6. Adhesion to inks, adhesives, and overmolding substrates.

"Soft phase"—elastomeric properties:

1. Lower service temperature limits
2. Hardness
3. Flexibility
4. Compression set and tensile set.

ISO 18064 [8] sets a standard nomenclature system for TPEs. Those having a prefix TP shall be followed by a letter representing each category of TPEs.

The categories are outlined below:

1. TPA—polyamide TPE, comprising a block copolymer of alternating hard and soft segments with amide chemical linkages in the hard blocks and ether and/or ester linkages in the soft blocks.
2. TPC—copolyester TPE, consisting of a block copolymer of alternating hard segments and soft segments, the chemical linkages in the main chain being ester and/or ether.
3. TPO—olefinic TPE, consisting of a blend of a polyolefin and a conventional rubber, the rubber phase in the blend having little or no cross-linking.
4. TPS—styrenic TPE, consisting of at least a triblock copolymer of styrene and a specific diene, where the two end blocks (hard blocks) are polystyrene and the internal block (soft block or blocks) is a polydiene or hydrogenated polydiene.
5. TPU—urethane TPE, consisting of a block copolymer of alternating hard and soft segments with urethane chemical linkages in the hard blocks and ether, ester or carbonate linkages or mixtures of them in the soft blocks.
6. TPV—thermoplastic rubber vulcanizate consisting of a blend of a thermoplastic material and a conventional rubber in which the rubber has been cross-linked by the process of dynamic vulcanization during the blending and mixing step.
7. TPZ—unclassified TPE comprising any composition or structure other than those grouped in TPA, TPC, TPO, TPS, TPU, and TPV.

Urethanes are a reaction product of a diisocyanate and long and short chain polyether, polyester, or caprolactone glycols. The polyols and the short chain diols react with the diisocyanates to form linear polyurethane molecules. This combination of diisocyanate and short chain diol produces the rigid or hard segment. The polyols form the flexible or soft segment of the final molecule. Figure 3.30 shows the molecular structure in schematic form.

The properties of the resin depend on the nature of the raw materials, the reaction conditions, and the ratio of the starting raw materials. The polyols used have a significant influence on certain properties of the thermoplastic polyurethane. Polyether and polyester polyols are both used to produce many products.

The polyester-based TPUs have the following characteristic features:

- Good oil/solvent resistance
- Good UV resistance
- Abrasion resistance
- Good heat resistance
- Mechanical properties.

The polyether-based TPUs have the following characteristic features:

- Fungus resistance
- Low-temperature flexibility
- Excellent hydrolytic stability
- Acid/base resistance.

In addition to the basic components described above, most resin formulations contain additives to facilitate production and processability.

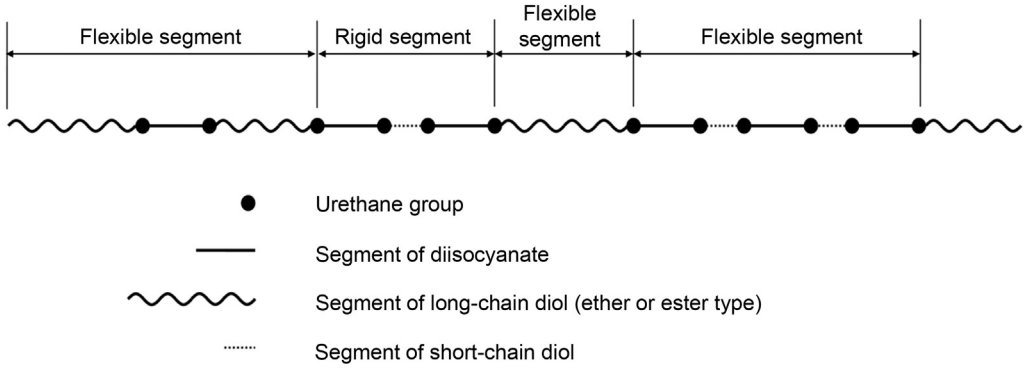



**Figure 3.30** Molecular structure of a thermoplastic polyurethane elastomer.

The polyether types are slightly more expensive and have better hydrolytic stability and low-temperature flexibility than the polyester types.

*Gamma radiation resistance*: The physical properties of transparent rigid thermoplastic polyurethanes are not significantly affected by exposure to a maximum of 10 megarads of gamma radiation. Discoloration is dramatic upon exposure to gamma radiation. Yellowness index increases from 6.3 before exposure to 77.6 after exposure. The discoloration is permanent with minimal bleach-back.

*EtO resistance*: Transparent and opaque rigid thermoplastic polyurethanes are compatible with multiple cycles of EtO sterilization. They generally retain tensile strength and Izod impact properties after exposure to five cycles of EtO gas. Less than 300 ppm residual EtO was present on the first day following exposure with continued degassing over time.

*Applications and uses*: Catheters, valves, needleless syringes, surgical instruments, wound dressing and tape, shunts, drug patches, medical bags, and tubing.

### 3.3.14 Thermoset Elastomers—Silicone

One of the most important thermoset elastomers is silicone, also known as siloxane, polyorganosiloxane, or polysiloxane. Silicone rubber is a semi-organic synthetic. Its polymer backbone structure consists of a chain of silicon and oxygen atoms rather than carbon and hydrogen atoms, as in the case with other types of rubber. The molecular structure of silicone rubber results in a very flexible—but weak—chain. Silicones are very stable at low and high temperatures. Although fillers may improve properties somewhat, tear and tensile strengths remain relatively low. Figure 3.31 shows four of the primary groups that make up a typical polysiloxane. To simplify the discussion of polysiloxane composition, the monomers are identified by letters:

"M" stands for $Me_3SiO$
"D" for $Me_2SiO_2$
"T" for $MeSiO_3$
"Q" for $SiO_4$
"P" for replace Me with phenyl side groups
"V" for replace Me with vinyl side groups (typically $<1\%$)
"F" for replace Me with fluorine.

Some common abbreviations for the polymers include MQ, VMQ, PMQ, PVMQ, PDMS poly(1-trimethylsilyl-1-propyne) or PTMSP.

Because silicones, in general, are temperature and moisture resistant, they are typically not affected by most sterilization methods. The most common sterilization methods used for medical devices that contain silicone include dry heat, steam autoclaving, EtO, gamma radiation, and electron beam (e-beam) radiation.

*Dry heat or steam autoclaving* will most likely have little effect on silicone's physical properties because of its moisture and heat resistance. The drawback to heat sterilization of silicone materials is that the high heat may cause the silicone to expand which must be taken into consideration how the device is configured and packaged.

*EtO sterilization*: Silicones generally have a high permeability to EtO molecules allowing the EtO to diffuse through the polymer network, inducing sterilization throughout the polymer matrix. The only precaution is to ensure that all of the EtO has been removed from the silicone device before it is used, which usually takes 24 h.

*Gamma and electron beam sterilization*: Radiation is known to induce changes in the molecular architecture of silicone rubber, increasing its molecular weight and decreasing elasticity.

*Applications and uses*: prostheses, artificial organs, facial reconstruction, catheters, artificial skin, contact lenses, drug-delivery systems, contact lenses.

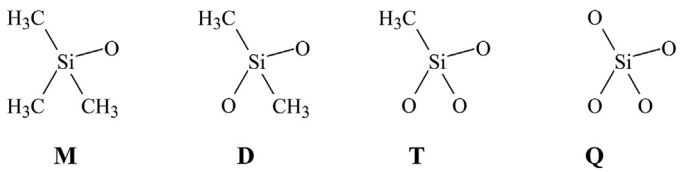



**Figure 3.31** Structure of groups that make up polysiloxanes.

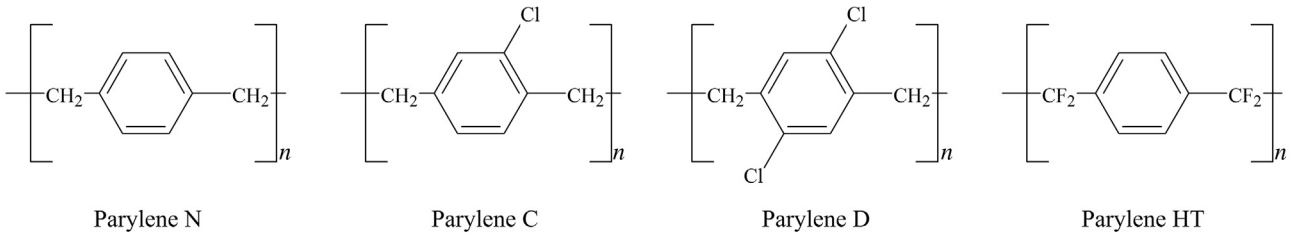



**Figure 3.32** Structures of the Parylene polymer molecules.

### 3.3.15 Poly-p-xylylene (Parylene)

Parylene is the generic name for members of a series of polymers. The basic member of the series, called Parylene N, is poly-para-xylylene, a completely linear, highly crystalline material. The structures of four Parylene types are shown in Figure 3.32.

Parylene polymers are not manufactured and sold directly. They are deposited from the vapor phase by a process which in some respects resembles vacuum metalizing. The Parylenes are formed at a pressure of about 0.1 torr from a reactive dimer in the gaseous or vapor state. Unlike vacuum metalizing, the deposition is not line of sight, and all sides of an object to be encapsulated are uniformly impinged by the gaseous monomer. Due to the uniqueness of the vapor phase deposition, the Parylene polymers can be formed as structurally continuous films from as thin as a fraction of a micrometer to as thick as several millimeters.

The first step is the vaporization of the solid dimer at approximately 150°C. The second step is the quantitative cleavage (pyrolysis) of the dimer vapor at the two methylene−methylene bonds at about 680°C to yield the stable monomeric diradical, para-xylylene. Finally, the monomeric vapor enters the room temperature deposition chamber where it spontaneously polymerizes on the substrate. The substrate temperature never rises more than a few degrees above ambient.

Parylene is used as a coating on medical devices ranging from silicone tubes to advanced coronary stents, synthetic rubber products ranging from medical grade silicone rubber to EPDM (ethylene propylene diene monomer rubber).

The manufacturer of coating equipment and starting materials is Para Tech Coating, Inc. They also offer coating services.

*Sterilization:*

Parylene coatings respond to these sterilization methods in a variety of ways (see summary of responses in Table 3.3). With regard to tensile properties, Parylene N and C were largely unaffected by any of these sterilization techniques. Only steam appears to have had any effect, causing an annealing impact on samples coated with Parylene C, seen as an increase in film crystallinity with a slight change in the tensile properties. Similarly, the tensile modulus property of Parylene N exhibited a minor change.

*$H_2O_2$ plasma sterilization* treatment appeared to alter dielectric strength, with a minimal change in Parylene C, and no change in Parylene N.

*Applications and uses*: Needles, prosthetic devices, implantable components, catheter, electrodes, stents, epidural probes, cannulae assemblies.

### 3.3.16 Fluoropolymers

PTFE polymer is an example of a linear fluoropolymer. Its structure in simplistic form is shown in Figure 3.33.

Formed by the polymerization of tetrafluoroethylene (TFE), the (−$CF_2$−$CF_2$−) groups repeat many thousands of times. The fundamental properties of fluoropolymers evolve from the atomic structure of fluorine and carbon and their covalent bonding in specific chemical structures. The backbone is formed of carbon−carbon bonds and the pendant groups are carbon−fluorine bonds. Both are extremely strong bonds. The basic properties of PTFE stem from these two very strong chemical bonds. The size of the fluorine atom allows the formation of a uniform and continuous covering around the carbon−carbon bonds and protects them from chemical attack, thus imparting chemical resistance and stability to the molecule. PTFE is rated for use up to (260°C). PTFE does not dissolve in any known solvent. The fluorine sheath is also responsible for the low surface energy (18 dynes/cm) and low COF (0.05−0.8, static) of PTFE. Another attribute of the uniform fluorine sheath is the electrical inertness (or non-polarity) of the PTFE molecule. Electrical fields impart only slight polarization in

**Table 3.3** Effects of Various Sterilization Methods on Parylene [24]

| Sterilization Method | Parylene N | | | | | Parylene C | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Dielectric Strength | WVT | Tensile Strength | Tensile Modulus | COF | Dielectric Strength | WVT | Tensile Strength | Tensile Modulus | COF |
| **Steam** | None | Δ43% | None | Δ12% | Δ38% | None | Δ5* | Δ17% | Δ9% | None |
| **EtO** | None | Δ21% | None | None | Δ33% | None | 8% | None | None | None |
| **E-beam** | NA | None | None | None | None | NA | None | None | None | None |
| **$H_2O_2$ plasma** | None | None | None | None | Δ48% | Δ9% | None | None | None | Δ188% |
| **Gamma** | None | None | None | None | None | None | Δ5% | None | None | None |

**5% values are not likely to be statistically significant. NA = not applicable; COF = coefficient of friction; WVT = water vapor transmission.*

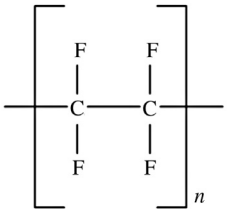



**Figure 3.33** Chemical structure of PTFE.

this molecule, so volume and surface resistivities are high.

The PTFE molecule is simple and is quite ordered. PTFE can align itself with other molecules or other portions of the same molecule. Disordered regions are called *amorphous* regions. This is important because polymers with high crystallinity require more energy to melt. In other words, they have higher melting points. When this happens it forms what is called a crystalline region. Crystalline polymers have a substantial fraction of their mass in the form of parallel, closely packed molecules. High molecular weight PTFE resins have high crystallinity and therefore high melting points, typically as high as 320−342°C (608−648° F). The crystallinity of as-polymerized PTFE is typically 92−98%. Further, the viscosity in the molten state (called melt creep viscosity) is so high that high molecular weight PTFE particles do not flow even at temperatures above its melting point. They sinter much like powdered metals; they stick to each other at the contact points and combine into larger particles.

PTFE is called a *homopolymer*, a polymer made from a single monomer. Recently many PTFE manufacturers have added minute amounts of other monomers to their PTFE polymerizations to produce alternate grades of PTFE designed for specific applications. Fluoropolymer manufacturers continue to call these grades modified homopolymer at below 1% by weight of comonomer. These modified granular PTFE materials retain the exceptional chemical, thermal, antistick, and low-friction properties of conventional PTFE resin, but offer some improvements:

- Weldability
- Improved permeation resistance
- Less creep
- Smoother, less porous surfaces
- Better high-voltage insulation

The copolymers described in the next sections contain significantly more of the non-TFE monomers.

*Sterilization:*

Exposure to high-energy (ionizing) radiation, regardless of the source, degrades PTFE by breaking down the molecules and reducing its molecular weight, resulting in a marked decrease in melt viscosity. As in thermal degradation, radiation stability of PTFE is much better under vacuum compared to air.

*Applications and uses*: fittings, valves, pumps, tubing.

*Expanded PTFE*[25]:

One of the most unique and remarkable developments in the processing of homofluoropolymers is the expansion of the polymeric matrix without the use of soluble fillers, foaming agents, or chemical additives. This invention constitutes the physical inducement of billions of small pores in the structure of an article of PTFE resulting in new properties and significant savings in material consumption. W.L. Gore and Associates invented this technology in the early 1970s. The trademark Gore-Tex® is well known in lightweight waterproof and breathable fabrics, microfiltration membranes, medical implants, microwave carriers, industrial sealants, and high tensile fabrics.

*Applications and uses*: microfiltration membranes, medical implants.

*Fluorocoatings:*

Fluorocoatings are used in medical devices. They often provide dry lubrication, insulation, and nonstick properties. Coatings are used on catheter guide wires and on metered dose inhaler canisters and valves.

## 3.4 Summary

There are many more polymers used in medical device applications than those listed in this chapter and more are being developed and used all the time. There are also dozens of other ways to sterilize than the ones mentioned. Table 3.4 provides a basic summary of the performance of a wide range of polymers used in plastics when sterilized by the most common methods.

**Table 3.4** Sterilization Matrix of Plastics [26]

| Polymer | Polymer Abbreviation | Steam | Dry Heat | Ethylene Oxide | Gamma Radiation | Electron Beam |
|---|---|---|---|---|---|---|
| **Polyolefins** | | | | | | |
| High-density polyethylene | HDPE | Poor | Poor | Good | Good | Good |
| Low-density polyethylene | LDPE | Poor | Poor | Good | Good | Good |
| Ultrahigh molecular weight polyethylene | UHMWPE | Poor | Poor | Good | Good | Good |
| Polypropylene[a] | PP | Good | Fair | Good | Fair | Fair |
| Polypropylene copolymers | | Good | Fair | Good | Fair | Fair |
| Cyclo olefin copolymer | COC | Fair | Fair | Good | Good | Good |
| Polyvinyl chloride plasticized[a,b] | PVC | Fair | Fair | Good | Good | Good |
| Polyvinyl chloride unplasticized[a,b] | PVC | Poor | Poor | Good | Fair | Fair |
| **Polystyrene/styrenics** | | | | | | |
| Polystyrene | PS | Poor | Poor | Good | Good | Good |
| Acrylonitrile butadiene styrene copolymer (Abs) | ABS | Poor | Poor | Good | Good | Good |
| Styrene–acrylonitrile copolymer (San) | SAN | Poor | Poor | Good | Good | Good |
| Acrylonitrile styrene acrylate | ASA | Poor | Poor | Good | Good | Good |
| Methacrylate acrylonitrile butadiene styrene copolymer | MABS | Poor | Poor | Good | Good | Good |
| Styrene–butadiene copolymer | SBC | Poor | Poor | Good | Good | Good |
| Acrylics[a,b] | | Poor | Poor | Good | Good | Good |
| Polycarbonates[a,b] | | Fair | Fair | Good | Good | Good |
| High heat polycarbonates | | Good | Good | Good | Good | Good |
| Polyurethanes | | Poor | Poor | Good | Good | Good |
| Acetals | POM | Good | Good | Good | Poor | Poor |
| **Polyamides** | | | | | | |
| Nylon 6, Nylon 66 | PA6, PA66 | Fair | Fair | Good | Fair | Fair |
| Aromatic | | Good | Good | Good | Good | Good |
| Nylon 12, 6/12 | PA12 | Poor | Poor | Good | Fair | Fair |

(*Continued*)

**Table 3.4** Sterilization Matrix of Plastics [26]—*Cont'd*

| Polymer | Polymer Abbreviation | Steam | Dry Heat | Ethylene Oxide | Gamma Radiation | Electron Beam |
|---|---|---|---|---|---|---|
| **Polyesters** | | | | | | |
| Poly butylene terephthalate | PBT | Fair | Fair | Good | Good | Good |
| Poly ethylene terephthalate | PET | Poor | Poor | Good | Good | Good |
| Copolyesters | | Poor | Poor | Good | Good | Good |
| **High-temperature thermoplastics** | | | | | | |
| Polysulfones | PSU | Good | Good | Good | Good | Good |
| Polyphenylene sulfide | PPS | Good | Good | Good | Good | Good |
| Liquid crystalline polymer | LCP | Good | Good | Good | Good | Good |
| Polyetherimide | PEI | Fair | Fair | Good | Good | Good |
| Polyamide–imide | PAI | Fair | Fair | Good | Good | Good |
| Polyetheretherketone | PEEK | Good | Good | Good | Good | Good |
| **Fluoropolymers** | | | | | | |
| Polytetrafluoroethylene[a] | PTFE | Fair | Fair | Good | Poor | Poor |
| Fluorinated ethylene propylene | FEP | Good | Good | Good | Fair | Fair |
| Perfluoro alkoxy | PFA | Good | Good | Good | Good | Good |
| Ethylene chlorotrifluoroethylene | ECTFE | Good | Good | Good | Good | Good |
| Ethylene tetrafluoroethylene | ETFE | Good | Good | Good | Good | Good |
| Polyvinyl fluoride | PVF | Good | Good | Good | Good | Good |
| Polyvinylidene difluoride | PVF2 | Good | Good | Good | Good | Good |
| **Elastomers** | | | | | | |
| Silicones | | Good | Good | Good | Good | Good |
| Urethane thermoplastic elastomer | TPU | Poor | Fair | Good | Good | Good |
| Copolyester thermoplastic elastomer | TPC | Poor | Good | Good | Good | Good |
| Polyamide thermoplastic elastomer | TPA | Poor | Poor | Good | Good | Good |
| Styrenic thermoplastic elastomer | TPS | Poor | Poor | Good | Good | Good |
| Olefinic thermoplastic elastomer | TPO | Poor | Fair | Good | Good | Good |

(*Continued*)

**Table 3.4** Sterilization Matrix of Plastics [26]—*Cont'd*

| Polymer | Polymer Abbreviation | Steam | Dry Heat | Ethylene Oxide | Gamma Radiation | Electron Beam |
|---|---|---|---|---|---|---|
| **Biopolymers** | | | | | | |
| PLLA | PLLA | Fair | Good | Good | Good | Good |
| Polylactic acid | PLA | Poor | Fair | Good | Good | Good |
| Polyhydroxybutyrate | PHB | Poor | Poor | Good | Fair | Fair |
| Polyglycolic acid | PGA | Good | Good | Good | Good | Good |
| Poly(lactic-co-glycolic acid) | PLGA | Poor | Poor | Good | Fair | Fair |
| Polycaprolactone | PCL | Fair | Good | Good | Good | Good |

[a]*Radiation stable grades should be considered for gamma and e-beam radiation sterilization.*
[b]*PVC, acrylics, PC—require corrective tint to compensate for discoloration.*

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# 4 Polymeric Biomaterials

*Wei He and Roberto Benson*

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Biomaterials are an indispensable element in improving human health and quality of life. Applications of biomaterials include diagnostics (gene arrays and biosensors), medical supplies (blood bags and surgical tools), therapeutic treatments (medical implants and devices), and emerging regenerative medicine (tissue-engineered skin and cartilage). Polymers, being organic, offer a versatility that is unmatched by metals and ceramics. The wide spectrum of physical, mechanical, and chemical properties provided by polymers has fueled the extensive research, development, and applications of polymeric biomaterials. The significance of polymers as biomaterials is reflected in the market size of medical polymers, estimated to be approximately $1 billion. Many of these polymers were initially developed as plastics, elastomers, and fibers for nonmedical industrial applications, but were later developed as biomedical-specific materials. With rapid growth in modern biology and interdisciplinary collaborative efforts, polymeric biomaterials are being fashioned into bioactive and biomimetic materials, with excellent biocompatibility.

## 4.1 Introduction

Biomaterials is an exciting and highly multidisciplinary field. These materials have matured into an indispensable element in improving human health and quality of life in the modern era. Applications of biomaterials range from diagnostics such as gene arrays and biosensors, to medical supplies such as blood bags and surgical tools, to therapeutic treatments such as medical implants and devices, to emerging regenerative medicine involving tissue-engineered skin and cartilage, etc. A general classification divides biomaterials into three main categories: metals, ceramics, and polymers. Polymers, being organic in nature, offer a versatility that is unmatched by metals and ceramics. The wide spectrum of physical, mechanical, and chemical properties that polymers can provide has fueled the extensive research, development, and applications of polymeric biomaterials. Furthermore, the significance of polymers in the field of biomaterials is clearly reflected in the staggering market size of medical polymers, estimated to be roughly $1 billion with yearly growth of 10–20% [1].

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This chapter provides a brief overview of several medical applications that polymers have made seminal contributions to over the years. Many of the polymers discussed here are initially developed as plastics, elastomers, and fibers for nonmedical industrial applications. They were "borrowed" by the surgeons post-World War II to address medical problems. Since then, they have led to the development of biomedical-specific materials. Currently, with the rapid growth in modern biology and collaborative effort, cross-discipline work involving materials science, engineering, chemistry, biology, and medicine, is resulting in polymeric biomaterials that are bioactive, biomimetic, and, most importantly, have excellent biocompatibility. Examples of this newer generation of polymeric biomaterials are also included in this chapter.

## 4.2 Polymeric Biomaterials in Ophthalmology

Ophthalmology focuses on the diseases of the eye, which is a complex and vital organ for daily life. Application of biomaterials in ophthalmology can be dated back to the mid-nineteenth century, when Adolf Fick successfully invented the glass contact lens. Since then, a wide variety of ophthalmological biomaterials have been developed and some are finding overwhelming success in clinical applications. Applications of biomaterials in ophthalmology include contact lenses [2], intraocular lenses (IOLs) [3], artificial orbital walls [4], artificial corneas [5], artificial lacrimal ducts [6], glaucoma filtration implants [7], viscoelastic replacements [8], drug delivery systems [9], scleral buckles [10], retinal tacks and adhesives [11], and ocular endotamponades [12]. Although ceramics and metals have also been used in ophthalmology, modern ophthalmic implants are mainly made of polymers. The focus of this section will be on polymers used for contact lens, IOL, and artificial corneas.

### 4.2.1 Polymeric Contact Lens

A contact lens is an optical device placed on the cornea of the eye for corrective, therapeutic, or cosmetic effects. It is estimated that there are approximately 125 million contact lens wearers worldwide. A myriad of principle properties have been sought in high performance contact lens materials, including (1) good transmission of visible light; (2) high oxygen permeability; (3) tear-film wettability; (4) resistance to deposition of components from tear-film, such as lipid, protein, and mucus; (5) ion permeability; (6) chemical stability; (7) good thermal conductivity; and (8) amenability to manufacture [13]. A wide variety of polymers have been used in contact lenses, and their modulus of elasticity defines contact lenses to be either hard or soft. Structures of the various monomers commonly used in contact lenses are shown in Figure 4.1. The first generation of polymeric contact lenses was made of poly(methyl methacrylate) (PMMA), a polymer commercially known as Plexiglas® and a classical example of hard or rigid lens material. PMMA can be prepared using bulk free radical polymerization and lathed into lens shape. It has excellent optical properties such as index of refraction with greater clarity than glass, remarkable durability, and good resistance against deposition of components from the tear-film due to its hydrophobicity. However, major drawbacks such as lack of oxygen permeability and tendency to change the shape of the eye have limited the usage of PMMA contact lenses. In order to improve the permeability of oxygen, rigid gas-permeable (RGP) contact lenses were developed in the late 1970s. Materials used for RGP contact lenses are typically copolymers of methyl methacrylate (MMA) with a monomer that imparts high oxygen permeability, e.g., methacryloxypropyl tris(trimethylsiloxy silane) (TRIS), hexafluoroisopropyl methacrylate (HFIM), and 2,2,2-trifluoroethyl methacrylate (TFEMA). The incorporation of highly hydrophobic siloxane into the copolymer reduces the lens wettability, which leads to undesired increase of lipid deposition. Therefore, hydrophilic monomers, such as methacrylic acid (MAA), 2-hydroxyethyl methacrylate (HEMA), or *N*-vinyl-2-pyrrolidone (NVP), are commonly used as wetting agents in RGP lens formulation to compensate for reduction in wettability.

Soft contact lenses emerged in the 1960s when Otto Wichterle developed poly(2-hydroxyethyl methacrylate) (PHEMA) [14] and forever changed the contact lens industry. Generally, soft contact lenses are made from hydrogel, a cross-linked network capable of retaining a significant amount of water. The first PHEMA soft lens contained 40% water of hydration. Despite its improvement in wearer comfort over rigid lens, the low oxygen

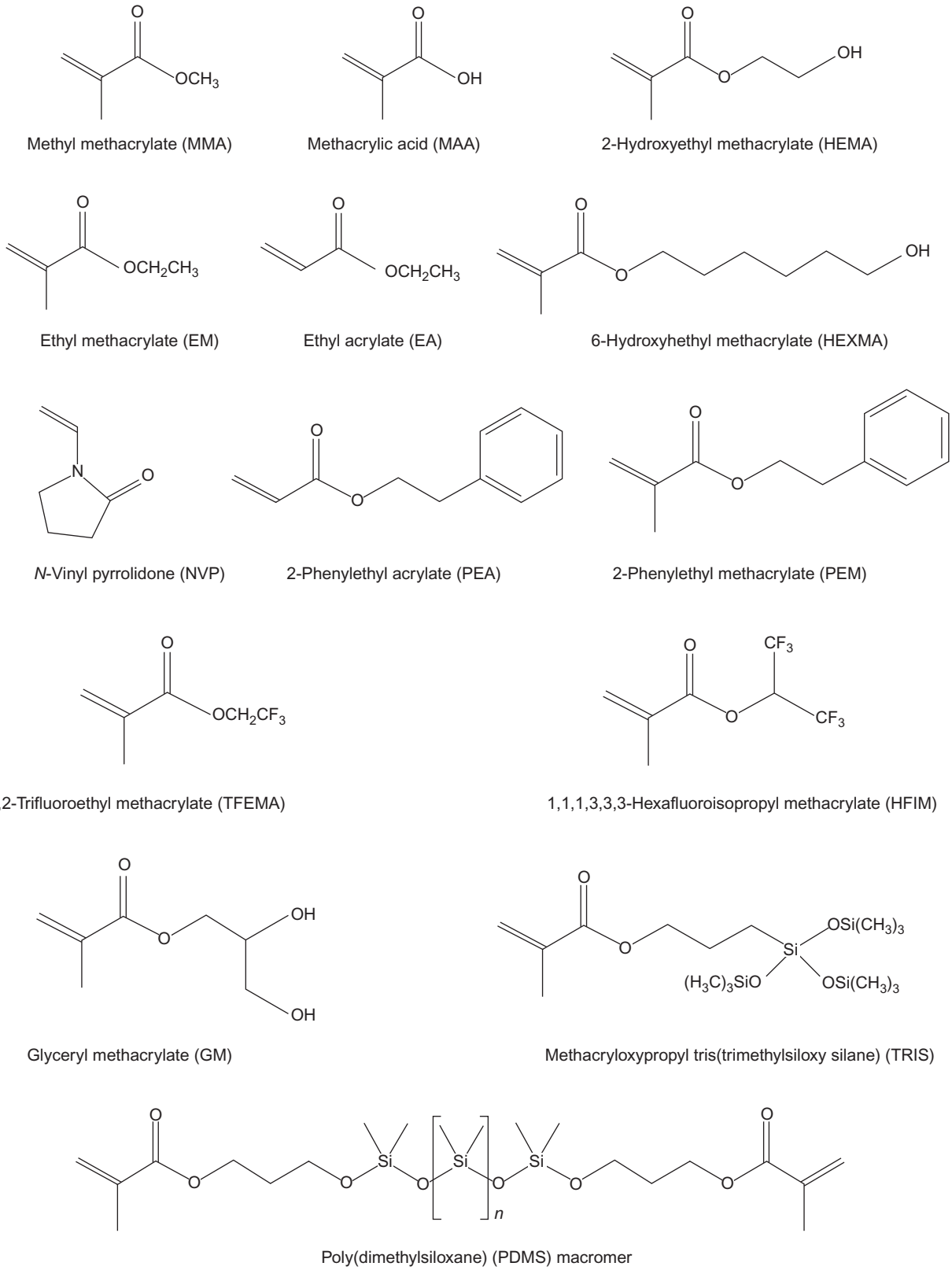



**Figure 4.1** Chemical structures of common monomers used in contact lenses and intraocular lenses.

permeability of PHEMA was interfering with the normal corneal metabolism. Since the extent of hydration directly affects the permeability of oxygen, hydrogels with high water content ($>50\%$) have been developed by copolymerizing HEMA with highly hydrophilic monomers such as NVP, MAA, and glyceryl methacrylate (GMA). A drawback associated with increased hydrophilicity is the higher protein binding to the lens, which could cause discomfort and complications such as increased bacterial adhesion [15]. High water content hydrogels also tend to cause corneal desiccation. In the quest for high oxygen permeability, researchers have developed a new type of siloxane-containing hydrogels for soft contact lenses. It is well known that due to the bulkiness of the siloxane groups ($-Si(CH_3)_2-O-$) and the chain mobility, siloxane-containing materials typically have high diffusivity of oxygen. On the other hand, siloxane materials are highly hydrophobic and, therefore, prone to lipid deposition and are less comfortable with rubbery-like behavior. To offset these shortcomings, functionalized siloxane macromer (shown in Figure 4.1) was copolymerized with hydrophilic monomers (e.g., NVP and HEMA) into hydrogels that offer sufficiently high oxygen transmission required by the cornea as well as the softness for comfortable extended wear. Currently, commercialized siloxane hydrogel contact lenses include Focus® Night & Day™ (lotrafilcon A by CIBA Vision Corp.) and PureVision™ (balafilcon A by Bausch and Lomb). It is worth noting that the presence of siloxane moieties on the surface of these hydrogels demands further treatments in order for the lens to be tolerated on the eye. Examples of surface treatment for siloxane hydrogels include radiofrequency glow discharge (RFGD) [16] and graft polymerization of hydrophilic monomers (e.g., acrylamide [17]) on the lens surface to improve surface hydrophilicity.

### 4.2.2 Polymeric Intraocular Lens

IOLs are commonly used to replace natural lenses and provide clear optical imaging for patients undergoing cataract surgery. IOL is a major area in ocular biomaterials research for its critical role in treating cataract-induced blindness, which was predicted to reach 40 million cases by the year 2020 [18]. IOL also holds a special place in the biomaterials history, where its invention was originated from Sir Harold Ridley's accurate observations of the biological reaction to accidentally implanted pieces of canopy in a World War II pilot's eyes. Since the canopy material, PMMA, was well tolerated by the eye, Ridley was inspired to use the material to invent the first biocompatible IOL, and it is well recognized as a pioneering breakthrough in biomaterial science. The key material requirements for IOLs include the optical property, i.e., able to maintain a clear path for optical imaging and the long-term biocompatibility as the implant is intended to reside in the eye permanently. PMMA dominated the IOL market for 40 years before other materials emerged. Despite its excellent optical properties and relative tolerance by the eye, PMMA still induces damage to the tissues around the IOL implant. Of primary concern are the injury of the corneal endothelium associated with the lens rigidity, and the accumulation of inflammatory cells to the IOL surface, which can lead to complications such as iris adhesion to the IOL, uveitis, and loss of vision [19]. Such issues have led to newer IOL designs and materials selection. In contrast to the original hard and bulky PMMA IOL, common IOLs nowadays are featured as soft and foldable.

The most widely used foldable IOL, AcrySof®, is fabricated from a copolymer of phenylethyl acrylate and phenylethyl methacrylate with a cross-linking reagent and a UV-absorbing chromophore. Its improved optical property, i.e., higher refractive index ($n = 1.55$) compared to PMMA ($n = 1.49$), allows a thinner IOL configuration. The mechanical characteristic of the copolymer results in a slow and better controlled unfolding of the IOL, which contributes to the significant reduction in posterior capsular opacification (PCO). Other materials used in foldable IOL fabrication include silicone elastomers, hydrophilic acrylics (with water content higher than 18%), and collagen copolymers (Table 4.1). Although hydrophilic acrylic IOLs have shown good uveal biocompatibility due to the reduction in protein adsorption and macrophage adhesion, they tend to present higher rate of PCO and cause anterior capsular opacification, which has reduced their application in the market [22–25].

### 4.2.3 Polymeric Artificial Cornea

The cornea is a transparent tissue situated at the front of the eye. It is the main element in the ocular

**Table 4.1** Examples of Biomaterials for IOLs

| Manufacturer | Lens Type | Material | Refractive Index |
|---|---|---|---|
| Advanced Medical Optics | Rigid | PMMA | 1.49 |
| ALCON | ACRYSOF® foldable | PEA/PEMA | 1.55 |
| Bausch & Lomb | Hydroview® foldable | HEMA/HEXMA | 1.47 |
| Calhoun Vision | Multifocal foldable | PDMS | 1.41 |
| STAAR Surgical | Collamer® foldable | Collagen/HEMA | 1.45 |

*(Modified from Lloyd and Patel [20,21])*

optical system, and plays various roles from refracting light onto the retina to form an image, to acting as a protective barrier for the delicate internal eye tissue. Damage to the cornea can result in loss of vision, which accounts for the second most common cause of blindness worldwide after cataract [26]. The most widely accepted treatment of corneal blindness is transplantation of human donor corneas. However, limitations in the availability of donor cornea tissues have called for design and development of artificial cornea substitutes. Artificial corneas, also known as keratoprostheses, come in a variety of forms, from fully synthetic to tissue-engineered. The focus of this discussion will be on polymer-based synthetic keratoprostheses. Several excellent comprehensive reviews on artificial corneas are available for further reading [27–29].

The cornea tissue is complex, avascular, highly innervated, and immune privileged. It is arranged in three major cellular layers: an outer stratified epithelium, an inner single-layered endothelium, and sandwiched in between a stromal compartment, which is responsible for the optical properties of the cornea. Although it is challenging to duplicate the complex structure of the natural cornea, it is possible to construct an artificial cornea that can simulate the physical features of the natural cornea and restore some functional level of vision. An ideal artificial cornea should meet the following specific requirements: (1) transparent with a smooth anterior surface of appropriate curvature, (2) suitable refractive index, (3) flexible and sufficient tensile strength for surgical handling, (4) ability to heal with the host cornea, (5) ability to promote and sustain the growth of epithelium over the anterior surface of the artificial cornea, (6) ability to avoid the formation of a retrocorneal fibroblastic membrane, and (7) biocompatibility [30]. Early generations of artificial corneas were made from a number of different hydrophobic polymers, such as PMMA, nylon, poly(tetrafluoroethylene) (PTFE), polyurethane (PU), and poly(ethylene terephthalate) (Dacron®) [20,31–33]. The design evolved from one material button-like full piece to the more widely used "core-and-skirt" configuration, where the core is made from transparent material with good optical properties and the skirt is made either from the same or different material to ensure host integration. Among these polymers, PMMA is arguably the most extensively used due to its remarkable optical properties, as discussed in the above IOL section. Even though the application of PMMA in artificial cornea continues, the associated complications such as retroprosthetic membrane formation, glaucoma, extrusion, endophthalmitis, and rejection [34–36] have led to the development of soft, hydrogel-based artificial corneas. Most of the research has been directed toward HEMA-based hydrogel. An interesting observation with HEMA is that when the monomer is polymerized with the presence of 40% or less of water, it forms a homogeneous transparent hydrogel; when the water content is higher, phase separation occurs during polymerization, and the resulting hydrogel is heterogeneous and opaque. Taking advantage of such characteristics, the first "core-and-skirt" hydrogel-based artificial cornea was created using HEMA, and the device is commercially known as AlphaCor [37]. The core is the transparent, lower water content PHEMA, and the skirt is the phase-separated, macroporous opaque PHEMA. Even though PHEMA is considered a hydrophilic polymer, its water content remains far below the water level found in the natural cornea (78%). Such high water content is essential for the stability and survival of

the epithelium as it facilitates nutrient diffusion. In order to increase the water content of the artificial cornea, various strategies have been explored. Examples include copolymerization of HEMA with an ionic acrylate MAA [38], and hydrogels made from homopolymer of poly(vinyl alcohol) (PVA), which can contain over 80% water at equilibrium [39,40]. Several groups have also reported making biomimetic hydrogels for artificial corneas. As the extracellular matrix of the cornea is dominated by type I collagen, it has been used in the preparation of a copolymeric hydrogel based on *N*-isopropylacrylamide (NIPAAm), acrylic acid, *N*-acryloxysuccinimide, and collagen [41]. The engineered hydrogel is essentially a network comprising of collagen cross-linked to the copolymers of acrylic acid and NIPAAm using the succinimide pendant groups. This material has demonstrated the biomechanical properties and the required optical clarity to be used for corneal transplantation. *In vivo* animal studies have shown successful regeneration of host corneal epithelium, stroma, and nerves [41]. Clinical trials are currently underway to evaluate this material for therapeutic use in humans.

Interpenetrating polymer networks (IPNs) have also been used for artificial cornea applications. IPN represents a mixture of polymer networks where one polymer is cross-linked in the presence of another polymer network to form a mesh of two different polymers. The major advantage with IPN is that it combines the beneficial properties of both polymers into the final material. Early application of IPNs in artificial corneas was at the connection between the optical core and the peripheral skirt, where an interdiffusion zone of IPN provides a permanent and reliable union of the PHEMA sponge skirt with the PHEMA core [42]. More recent efforts focus on incorporating IPNs in the entire artificial cornea construct. One design is based on IPNs of poly(dimethylsiloxane) (PDMS) and PNIPAAm [43], where the mechanical strength, transparency, and oxygen permeability of PDMS is combined with the hydrophilicity and nutrient permeability of PNIPAAm to form a functional artificial cornea. Another example is IPN of a neutral cross-linked poly(ethylene glycol) (PEG) and a charged, loosely cross-linked polyacrylic acid (PAA) [44,45]. Such IPN has displayed optical transparency with good mechanical properties and glucose diffusion coefficients comparable to that of the natural cornea [46]. Although most of the artificial corneas have shown satisfying biocompatibility in animal models, it is critical to ensure that the materials are nontoxic, nonimmunogenic, and nonmutagenic, and do not result in corneal opacification.

## 4.3 Polymeric Biomaterials in Orthopedics

Traditionally, orthopedic biomaterials are mainly metallic, largely due to the close property resemblance to that of bone tissue such as high strength, hardness, and fracture toughness. Polymers have also been used in orthopedics over the years, and they are receiving increasing interest for bone tissue engineering. Historically, the use of polymers in orthopedics for the most part is reserved for those capable of performing well for fixation of structural devices and under cyclic load-bearing conditions such as in knee and hip arthroplasty. Despite hundreds of orthopedics applications available in the market, they are dominated by only a few types of polymers, including ultrahigh-molecular-weight polyethylene (UHMWPE) and PMMA.

### 4.3.1 Polyethylene

UHMWPE is a linear polyethylene with molecular weight usually between 2 and 6 million. The fracture toughness, low friction coefficient, high impact strength, and low density of UHMWPE have made it a popular choice as the articulating surfaces of joint replacements, such as hip, knee, ankle, and shoulder. Although UHMWPE possesses numerous attractive bulk and surface properties, these properties can be compromised by the presence of long-term radicals in the bulk resulting from the ionizing radiation employed in the sterilization process [47]. These radicals can interact with oxygen, leading to the generation of oxygen containing functional groups and deterioration of the surface and bulk properties, particularly the rate of production of particles during the wear process. An overproduction of wear debris has been linked to the inflammatory reaction in the tissues adjacent to the implant. This adverse tissue response will lead to granulomatous lesions, osteolysis, bone resorption, and implant failure [48]. In an effort to overcome the oxidation, a number of additives, such as

antioxidant α-tocoferol and vitamin C, are currently used to retard oxidation and enhance surface properties [49]. UHMWPE has been considered the weak link in any total joint replacement because of the wear issue. To improve wear resistance, highly cross-linked UHMWPE has been produced and used in joint replacement. Cross-linking is achieved by irradiating UHMWPE with electron beam or gamma irradiation, followed by a melting step to eliminate the free radicals produced during irradiation. Currently, there is a debate on cross-linking and the clinical performance of UHMWPE. Those in favor have shown evidence of the efficacy of highly cross-linked UHMWPE in reducing the wear in total joint arthroplasties and the associated periprosthetic osteolysis [50]. The opposition states that improvement of wear resistance by cross-linking is at the expense of reduction in the static mechanical properties, such as tensile and yield strength as well as fatigue crack propagation resistance, which could affect the implant longevity, especially in total knee arthroplasty [51]. Complete data regarding the ultimate long-term performance of highly cross-linked UHMWPE will help settle the scientific debate.

### 4.3.2 Polyacrylates

Application of PMMA as fixative for bone was first demonstrated by Charnley [52]. The PMMA bone cement is composed of the liquid monomer MMA, a partially polymerized PMMA powder, an initiator (commonly used dibenzoyl peroxide), an activator (*N*,*N*-dimethyl-*p*-toluidine), a radiopacifier (visible to X-rays) such as barium sulfate or zirconium oxide, and a copolymer to influence the mixing and handling of the cement [53]. In some cases, an antibiotic (e.g., gentamicin) is included in the formulation to minimize infection during implantation. The polymerization is initiated by the interaction between the activator and the initiator, yielding a free radical that reacts with the monomer. The solidified polymer is able to secure a firm fixation of the prosthesis in the bones. Although acrylic bone cements are widely used in orthopedics, several drawbacks are related with their use. The residual monomer could leak into the body and cause fat embolism [54]. The exothermic nature of the polymerization process can be a potential cause for necrosis of the surrounding tissue. The most critical drawback is aseptic loosening, i.e., loosening of the implant within the cement. The cause of aseptic loosening could be mechanical and/or biochemical. Mechanically, cyclic loading of the implant could lead to fatigue fracture of the cement [55]. Biochemically, wear debris of the polyethylene component could migrate to the bone−cement interface and trigger inflammatory response, leading to osteolysis and weakening the implant interface [56]. In order to improve upon PMMA fixation, a possible strategy is to avoid cement fracture by increasing the mechanical strength of the cement. Researchers have developed bone cement with higher bonding strength and compressive modulus than conventional PMMA, using a bisphenol-A-glycidyl dimethacrylate (Bis-GMA)-based resin impregnated with bioactive glass ceramics [57,58]. Another approach takes advantage of composites by reinforcing PMMA with hydroxyapatite (HA) [59] and bioactive glass [60], which combines strength and elasticity with bioactivity.

The other acrylate bone cement is based on polyethylmethacrylate (PEMA) and *n*-butylmethacrylate (*n*-BMA) monomer [61]. Comparing to PMMA cement, less heat is produced during polymerization of the PEMA-*n*-BMA cement, and the polymer has a relatively low modulus and high ductility to reduce the issue of fracture. The biocompatibility of the PEMA-*n*-BMA cement has been excellent [62]. But these bone cements have been found to be susceptible to creep. To improve creep resistance, bioactive HA particles were incorporated [63]. Although HA improved bioactivity and creep behavior of the cement, the cement failed at lower number of cycles.

### 4.3.3 Natural Polymers

Natural polymers are finding increasing applications in the area of bone replacement and hard tissue augmentation. Ideally, materials used for such purpose should be biocompatible; able to mimic the three-dimensional characteristics, physical, and mechanical nature of the bone and hard tissue; able to support appropriate cellular functions; and able to be replaced gradually by the regenerating new tissue. A variety of natural polymers have been used, including extracellular matrix proteins such as collagen [64]; polysaccharides such as chitosan [65], alginate [66], starch [67], and cellulose [68]; as well as glycosaminoglycans such as hyaluronic acid [69]. Some of the natural polymers can

provide a template for biomimetic apatite formation, which is highly desirable to induce rapid bone colonization. Recent studies by Hutchens *et al.* [70] revealed the formation and characterization of bacterial cellulose/hydroxyapatite composites with the potential for bone replacement. Both degradable and nondegradable bacterial cellulose were used to form the composite. The hydroxyapatite present in the composite has ordered nanometer needle-like particles with nonstoichiometric composition similar to that observed in human bone. The combined bioactivity and biocompatibility substantiates the potential of this composite for orthopedic application.

## 4.4 Polymeric Biomaterials in Cardiovascular Diseases

Biomaterials have played a vital role in the treatment of cardiovascular diseases; examples of applications include heart valve prostheses, vascular grafts, stents, indwelling catheters, ventricular assist devices, total implantable artificial hearts, pacemakers, automatic internal cardioverter defibrillators, intra-aortic balloon pumps, etc. A key requirement for materials in cardiovascular applications, particularly blood-contacting devices, is blood compatibility, i.e., nonthrombogenic. Additional requirements include mechanical and surface properties that are application-specific. Surveying the field of polymers used in cardiovascular applications reveals that PUs, polyethylene terephthalate (PET), and expanded PTFE (ePTFE) are the most commonly used. This section will review each of the three polymers followed by a brief introduction of other emerging polymers for use in the cardiovascular area.

### *4.4.1 Polyurethanes*

PUs are among the most commonly selected biomedical polymers for blood-contacting medical devices. They can be found in hemodialysis bloodlines, catheters, stents, insulation for pacemaker leads, heart valves, vascular grafts and patches, left ventricular assist devices (LVADs), etc. PUs are characterized as segmented block copolymers with a wide range of mechanical and blood contact properties, simply by varying the type and/or molecular weight of the soft segment and coupling agents. The urethane linkage, $-NH-C(=O)-O-$, in biomedical PUs can be formed through a two-step process. The initial step is a reaction involving the end-capping of the macrodiol soft segments (e.g., polyether, polyester, polycarbonate, and polysiloxane) with diisocyanate to form a prepolymer. The second reaction is the coupling of the prepolymer with a low-molecular-weight chain extender—generally a diol or a diamine [71]. The hard segment usually refers to the combination of the chain extender and the diisocyanate components.

Due to the chemical incompatibility between the soft and hard segments, the morphology of PUs consists of hard segments aggregation to form domains that are dispersed in a matrix formed by the soft segments [72,73]. Such unique morphology is responsible for the exceptional mechanical properties and biocompatibility of the biomedical PUs. For example, depending on the relative molecular weights and amounts of the hard and soft segments, the obtained PU can be elastomeric or rigid. The mechanical properties of PU can also be tailored by changing the chemical nature of the chain extender. Generally, PUs prepared with aliphatic chain extender are softer than those with aromatic chain extender. Biocompatibility of PU is also closely related to the chemical nature of the chain extender and the soft segment. Early studies by Lyman *et al.* [74] showed that changes in the molecular weight of the polypropylene soft segments affected protein adsorption. Lysine diisocyanate and hexamethylene diisocyanate are preferred over aromatic diisocyanates in the synthesis of biodegradable PUs, partly because of the putative carcinogenic nature of aromatic diisocyanates [75]. Recent studies have reported using natural polymers, such as chitin [76] and chitosan [77] as chain extender to improve the biocompatibility of PUs.

Biostability has been and continues to be a main research focus of PUs. Depending on the intended medical applications, the desired biostability of PUs varies. For example, PUs used as a pacemaker lead covering should have superior long-term stability, whereas PUs used as a scaffold to build engineered tissue construct for the replacement of diseased cardiovascular tissues should be biodegradable. The challenge to maintain long-term *in vivo* biostability of PUs lies in the fact that biodegradation of PUs is a complicated and multifactor-mediated process. Mechanisms responsible for PU biodegradation include (1) hydrolysis,

(2) oxidative degradation, metal or cell catalyzed, (3) enzymatic degradation, (4) surface cracking, (5) environmental stress cracking, and (6) calcification [75]. It is well known that PUs containing polyester soft segments have poor hydrolytic stability, and PUs with polyether soft segments are prone to oxidative degradation. Guided with valuable information collected from extensive investigation of molecular pathways leading to the biodegradation of PUs, more bioresistant PUs have been designed over the years. These strategies include using polycarbonate macrodiols [78,79], polyether macrodiols with larger hydrocarbon segments between ether groups [80], and siloxane-based macrodiols [81–83]. On the other end of the spectrum, bioresorbable PUs are attracting increasing attention as elastomeric tissue engineering scaffolds. For this class of PUs, soft segments such as polylactide or polyglycolide, polycaprolactone, and polyethylene oxide are most commonly used [84]. Furthermore, degradation is engineered into the hard segments. Enzyme-sensitive linkages have been incorporated into the hard segment, leading to specific enzymatic degradation in contrast to nonspecific hydrolytic degradation [85–87]. Another interesting addition to the hard segments is bioactive molecule such as antimicrobial drug [88]. Polymer degradation will thus lead to free drug release, making this class of PUs very attractive for biomedical applications.

### 4.4.2 Polyethylene Terephthalate

PET is a member of the engineering polyester family. It is a semicrystalline polymer with industrial applications as synthetic fibers and beverage and food containers. In the medical field, PET is widely used as prosthetic vascular grafts, sutures, and wound dressings in either fiber or fabric form (commercially known as Dacron®). Despite the presence of hydrolytically cleavable ester linkage, PET is relatively stable *in vivo* largely due to the high crystallinity and hydrophobicity. It is one of the two standard biomaterials of prosthetic vascular grafts used clinically. It is widely used for larger vessel (diameter $>6$ mm) applications. PET for vascular applications can be prepared either woven or knitted, which will determine the porosity and mechanical property of the graft. Generally, a woven finish has less porosity than a knitted graft, therefore, reducing the chance of transmural blood extravasation. Dacron® vascular graft is strong and stiff, much less compliant than natural arteries [89]. Such compliance mismatch has been considered the cause of patency loss of the graft over a long time frame ($>6$ months) [90]. The other major complication related to the PET graft is its thrombogenicity. When the graft comes in contact with blood, plasma protein is adsorbed to the luminal and capsular surfaces, leading to thrombus formation and inflammatory response. Various strategies have been explored to make the graft surface thrombo-resistant, including passivating the surface with albumin [91], coating with fluoropolymer [92], coating with hydrophilic polymer [93], covalent or ionic binding of the anticoagulant heparin–albumin [94–96], covalent linkage of antithrombotic agent thrombomodulin [97], etc. Although some improvement has been reported in terms of acute thrombosis, there is still a long way to go to achieve satisfying long-term functionality of PET-based vascular grafts.

### 4.4.3 Expanded PTFE

ePTFE, commercially also known as Gore-Tex®, is one of the two standard biomaterials of prosthetic vascular grafts used clinically. Besides vascular uses, ePTFE is also used as patches for soft tissue regeneration, such as hernia repair, and surgical sutures. It is produced by a series of extrusion, stretching, and heating processes to create a microporous material with pore size ranging from 30 to about 100 μm. Similar to PET, ePTFE is highly crystalline, hydrophobic, and highly stable. It has an extremely low coefficient of friction, making it easy for handling. Its tensile strength and tensile modulus are lower than those of PET. Even though the compliance of ePTFE grafts is relatively lower than that of PET grafts, it is still too high compared to natural arteries. Generally, ePTFE is the choice over PET to bypass smaller vessels. However, it still faces a patency issue. Femoropopliteal reconstruction using ePTFE has a 5-year patency rate of 40–50%, compared to the 70–80% achieved by using autogenous vein grafts [98]. Similar to PET, the cause of low patency is the thrombogenicity of the material. It has been reported that the graft fails to develop a full coverage of endothelial cells on the lumen side of the graft [99,100]. To address this issue, one approach is to increase the porosity to promote tissue ingrowth. But it requires a careful balance to prevent leakage of blood elements as

mentioned earlier. Other approaches focus on reducing surface thrombogenicity, including carbon coating to increase surface electronegativity [101], attachment of anticoagulant or antithrombotic agents [102,103], and impregnation with fibrin glue to deliver growth factors that can promote endothelialization [104,105]. The actual benefits of these treatments are yet to be determined through longer-term *in vivo* investigations.

The challenge posed by small diameter vascular repair has spurred research for alternative biomaterials that would match or surpass the autograft. A notable effort is to build a tissue-engineered graft *ex vivo* using a synthetic biodegradable scaffold. Conceptually, such graft will have mechanical properties closely mimicking those of the native tissues without the concern of chronic inflammatory responses commonly induced by the presence of synthetic materials. Till date, a wide variety of biodegradable polymers have been used to build such constructs, including poly(α-hydroxyesters); poly(glycolic acid) (PGA); poly(lactic acid) (PLA); and their copolymers poly(lactic-*co*-glycolic acid) (PLGA), polycaprolactone, polyanhydride, polyhydroxyalkanoate, and polypeptide. Several excellent reviews are available discussing the current status of materials as scaffolding for vascular tissue engineering [106–108].

The other cardiovascular application in which polymers are poised to make a significant impact is biodegradable stents. Current stents are mainly made of metallic materials, such as stainless steel, cobalt–chromium, or Nitinol. However, long-term complications associated with metal stents have prompted research of fully degradable replacement. Several key requirements have to be satisfied by the polymeric stent, with the top two being mechanical properties and degradation characteristics. In terms of degradation, the products of degradation should be biocompatible, and the degradation process should not compromise the structural integrity of the device up to 6 months [90]. As for mechanical properties, the polymer should withstand the deployment and the blood vessel contractions. Both requirements are challenging, but with a good appreciation of the underlying biology and the versatility of polymer structure–property relationship, newer materials are likely to emerge in the near future. For example, researchers are imparting degradation and shape memory capabilities into polymers that can self-expand and degrade over time [109,110].

## 4.5 Polymeric Biomaterials for Wound Closure

Surgical wounds can be closed by various means, including sutures [111], adhesives [111], tapes [111], staples [111], and laser tissue welding [112]. Among these methods, sutures are the most frequently used. The sutures are sterile filaments used to approximate and maintain tissue until the healing has provided the wound with appropriate strength to withstand mechanical stresses. Sutures can be classified based on the origin of the materials as natural or synthetic; performance of the materials as absorbable or nonabsorbable; and physical configurations as monofilament, multifilament, braided, or twisted. In general, polymers selected for sutures should elicit minimal adverse biological response in addition to having fiber-forming rheological properties. The sutures must have minimum tissue drag, good strength retention, and knot security. To improve the lubricity and reduce tissue drag, coatings such as tetrafluoroethylene and silicones are normally applied to the suture. The following sections will discuss some of the common nonabsorbable and absorbable polymeric sutures currently commercially available.

In general, nonabsorbable sutures can retain their tensile strength longer than 2 months [113]. The synthetic polymers used to make nondegradable sutures include polypropylene (PP), polyamides, polyesters such as PET and polybutylene terephthalate (PBT), and polyether–ester based on poly(tetramethylene glycol), 1,4-butanediol, and dimethyl terephthalic acid [114]. The base polymer and filament configurations for common nonabsorbable sutures are summarized in Table 4.2.

The PP monofilament sutures are made from isotactic polypropylene [115]. During preparation, the PP monofilament is subjected to a series of post-spinning operations including annealing, designed to increase crystallinity [116]. Although PP sutures are highly resistant to hydrolytic degradation, it can undergo thermo-oxidative degradation [117]. PP sutures are usually sterilized by ethylene oxide or autoclave due to their susceptibility to ionizing radiation such as γ-radiation from cobalt-60 source

**Table 4.2** A List of Commercially Available Nonabsorbable Suture Materials

| Generic Name | Polymer | Configuration | Trade Name |
|---|---|---|---|
| Polyamide | Nylon-6, nylon-6,6 | Monofilament | Dermalon |
| | | Multifilament, braided | Nurolon |
| | | Multifilament, braided and silicone coating | |
| Polypropylene | PP | Monofilament | Prolene |
| | | Monofilament | Surgipro |
| Polyethylene | Polyethylene | Monofilament | Dermalene |
| Polyester | PET | Braided | Dacron |
| | | Braided with silicone coating | Ti-Cron |
| | | Braided with polybutylate coating | Ethibond |
| | | Braided with PTFE coating | Polydek |

that is normally used for radiation sterilization. In terms of performance, PP sutures cause one of the lowest tissue responses.

Polyamide sutures are commonly made out of nylon-6 and nylon-6,6. Nylon-6 is synthesized by ring-opening polymerization of caprolactam, while nylon-6,6 is prepared by condensation polymerization of adipic acid and hexamethylene diamine. These polyamide sutures are processed into monofilament, braided multifilament, and core−sheath configurations. The braided multifilament nylon sutures are often coated (e.g., silicone coating) to reduce tissue drag. The observed decrease in strength retention over time is associated with the susceptibility of the amide bond to hydrolytic degradation in the nylon structure. The tensile strength of nylon sutures decreases at a yearly rate of approximately 15−25% [118]. The tissue reaction to nylon sutures appears to be independent of configuration, with both braided and monofilament eliciting low reactivity.

The need to suture very delicate and complicated tissues have led to the development and use of sutures based on fluoropolymers such as PTFE and polyvinylidene fluoride (PVDF), and copolymers of PVDF and hexafluoropropylene (HFP) [119]. PTFE is a stable ($T_m = 327°C$) semicrystalline linear polymer. ePTFE sutures are highly crystalline microporous fibers prepared by wet spinning an aqueous mixture of PTFE powder and cellulose xanthate. The morphology of ePTFE fibers consists of nodules connected by thin crystalline fibers that control tensile strength. The mechanical properties, biological response, and handling can be directly correlated with the porosity of the PTFE fibers [120]. The bending stiffness of ePTFE sutures is low due to the microporous structure [121], but the porous structure also contributes to the decrease in strength. PVDF is also highly crystalline ($T_m = 175°C$). Sutures prepared from PVDF exhibit good creep resistance and tensile strength retention. Morphological studies have demonstrated high surface stability, i.e., no visible signs of bulk or surface fracture [122]. PVDF sutures are susceptible to thermo-oxidative degradation, but can be readily sterilized with $\gamma$-radiation. PVDF elicits moderate tissue and cell response—a behavior similar to PP sutures. Sutures derived from copolymers of PVDF and HFP were originally designed to combine the beneficial handling properties and biological response of PVDF and PP into one material. In addition, PVDF/HFP sutures were also designed to emulate the durability of polyester sutures. The tensile strength, size, biological response, and handling of the PVDF/HFP sutures can be tailored by manipulating the copolymer compositions. The major target areas for usage of PVDF/HFP sutures are wound closure during cardiovascular, neurological, and ophthalmic surgeries [119]. These PVDF/HFP sutures are normally used as uncoated monofilaments.

Among the most commonly used polyester-based nonabsorbable sutures are PET and PBT. In addition, there are polyester-based sutures made from copolymers of poly(tetramethylene ether terephthalate) and poly(tetramethylene terephthalate) called polyetheresters. PET is synthesized by condensation

polymerization of ethylene glycol and terephthalic acid. PET is a polymer with a melting temperature of approximately 265°C. The thermal stability of PET enables melt spinning to form monofilament fibers with variable profiles. During processing, the fibers are subjected to hot drawing that enhances molecular orientation, crystallinity, and tensile strength. The PET sutures are commercially available as coated or uncoated monofilament or braided multifilament configurations. The surface treatments of PET sutures include coatings of PTFE and silicone. PET sutures are very stable in the biological environment with no evidence of hydrolytic degradation. The strength retention of PET sutures remains for an extended period of time. The tissue response to PET sutures is dependent on the configuration with braided multifilament and monofilament having moderate and low tissue reactivity, respectively. Compared to PET, PBT sutures are generally less brittle and stiff, due to the longer aliphatic segment in the polymer structure. Polybutester sutures are obtained from block copolymers of PBT and poly(tetramethylene ether) glycol terephthalate (PTMG). In the copolymer, the PBT is the hard segment and PTMG is the flexible segment. Chemical incompatibility between the hard PBT and soft PTMG blocks renders these copolymers elastomeric. Such unique mechanical behavior makes the polybutester sutures ideal for wounds prone to edema formation.

The synthetic absorbable sutures are made from polymers capable of degradation in the biological environment without adverse effects. One overall advantage of absorbable sutures is the elimination of clinical visits for their removal. These sutures are either homopolymers or copolymers based on degradable polymeric units such as polyglycolic acid, polylactic acid, or poly-*p*-dioxanone.

Polyglycolic acid (PGA) can be synthesized by condensation or ring-opening polymerization. Sutures based on PGA were the first absorbable sutures made [123]. PGA sutures are commercially available coated or uncoated in a braided configuration. Glycolide has been copolymerized with lactic acid, trimethylene carbonate, and ε-caprolactone [119]. Glycolic acid was copolymerized with L- or DL-lactic acid to form random copolymer. The performance of the glycolide-L-lactide sutures is dependent on composition. The initial tensile strength and retention through the healing process of the glycolide-L-lactide sutured wound is directly dependent on the concentration of the crystallizable glycolide monomers [124]. Copolymers based on the DL-lactide do not exhibit the same composition dependence as observed for the L-lactide copolymers [119]. Glycolide has been copolymerized with trimethylene carbonate to form a triblock copolymer where the middle block is a random copolymer of glycolide and trimethylene carbonate and the terminal blocks based on glycolide. These sutures are available as uncoated monofilaments. The copolymerization of glycolide and ε-caprolactone leads to formation of segmented copolymers. In these copolymers, the glycolide and ε-caprolactone form the soft and hard segments, respectively.

Poly-*p*-dioxanone (PDS) is synthesized by ring-opening polymerization of 1,4-dioxanone-2,5-dione. The monofilament sutures are produced by melt spinning. The fibers are subjected to a drawing process to improve tensile strength and performance. Recently, attempts have been made to copolymerize PDS with PGA and PLLA to produce sutures with different properties [125].

Current research focus in wound closure suture is to incorporate extra functionality to the suture besides closing the wound. These efforts include to control wound infection by developing antimicrobial sutures, and to accelerate the wound healing process by using bioactive material such as chitin, or to deliver therapeutics that can impact the wound healing response.

## 4.6 Polymeric Biomaterials in Extracorporeal Artificial Organs

Extracorporeal artificial organs provide mass-transfer operations to support failing or impaired organ systems [126]. Common examples include kidney substitute, hemodialysis, cardiopulmonary bypass (CPB), apheresis therapy, peritoneal dialysis, lung substitute and assist, and plasma separation. A critical component involved in the extracorporeal artificial organ is the membrane that serves to separate the undesired substance from the blood or plasma. Ideally, materials used as the membrane in these particular applications should have appropriate cellular and molecular permeability, as well as blood compatibility (i.e., hemocompatibility). Over the years, both natural and synthetic polymers have been used as membrane materials.

The most widely used natural membrane is cellulosic. Taking hemodialysis as an example, early applications of cellulose membrane in the dialyzer used regenerated cellulose, i.e., unsubstituted with rich hydroxyl groups along the repeating saccharide units. Studies have found that regenerated cellulose has poor hemocompatibility. It activates the complement system, which leads to inflammation and other serious immune responses. The complement activation has been attributed to the high concentration of hydroxyl groups on the membrane rendering it nucleophilic and susceptible to protein deposition, particularly C3b. Such observation spurred later research of using substituted cellulose for dialysis membrane, examples include cellulose acetate and cellulose triacetate, where in both cases a fraction of the hydroxyl groups are replaced with acetate functionality. These modified cellulose materials greatly limit complement activation by eliminating the active surface sites for complement protein interaction. Besides chemically blocking complement interaction, approaches using steric hindrance effect have also been explored. A bulky chemical group such as benzyl substitution group or tertiary amine group has been used to replace the hydroxyl group to sterically minimize the complement protein interaction with the membrane [127,128].

Current dialysis membranes are mostly made from synthetic polymers, including polysulfone, polyethersulfone, polyacrylonitrile, PMMA, polyamide, and polypropylene hollow fibers. Compared with natural cellulosic membrane, synthetic membranes are less prone to complement activation. The reason behind the improved complement compatibility is the diminished level of surface nucleophiles for C3b deposition. Furthermore, some of the synthetic membranes are rich in negative charges on the surface, which can absorb the activated cationic complement peptide (e.g., C5a) and minimize the subsequent cascade of inflammation. Synthetic membranes generally have significantly larger pore sizes and higher hydraulic permeability than cellulosic membranes [129]. Therefore, synthetic membranes are the choice for high-flux applications. The larger pore size also allows for removal of middle molecules with molecular weight between 500 and 2000 Da, which have been deemed bioactive and may have a potential biological impact [130]. The hydrophobic nature of most synthetic membranes contributes to the adsorptive capacity toward noxious compounds such as interleukin-1, tumor necrosis factor, interleukin-6, and $\beta_2$-microglobulin [131]. PMMA and polyacrylonitrile usually exhibit the most pronounced adsorption capacity. Regardless of their origin, the membranes have been used either in hollow-fiber design, which is most common, or as sheet films in parallel-plate design.

## 4.7 Polymeric Biomaterials for Nerve Regeneration

Repair of the damaged nerves presents enormous challenge due to the physiology complexity of the nervous system. Even though progress has been made over the past decades, it is still not possible to fully repair the damage so that lost functions of the nervous systems can be restored. The nervous system is generally classified into the central nervous system (CNS) and the peripheral nervous system (PNS). Various strategies have been explored for nerve repair in both the CNS and the PNS, including guidance conduits, scaffolds with cell transplantation, and delivery of therapeutics. This section will mainly focus on polymers used in the nerve guidance conduit approach.

It has been widely accepted that physical guidance of axons, the long processes extending from the neuron cell body and conducting electrical signals, plays a critical role in nerve repair. The nerve guidance conduit is designed to (1) direct the outgrowth of axons from the proximal nerve end bridging across the lesion, (2) provide a channel for the diffusion of biomolecules secreted by the injured nerve ends, and (3) reduce the scar tissue invasion to the regeneration zone [132]. To fulfill these functions, an ideal nerve guidance conduit should be semipermeable with oriented topographical features inside the conduit, supportive of electrical activity, able to deliver bioactive factors, and able to support cell adhesion and migration. The versatility of polymers makes them the top choice in engineering of nerve guidance conduits. Early research has used nondegradable synthetic polymers including silicone [133] and ePTFE [134]. Although silicone nerve guidance conduits have shown success in bridging gaps up to 10 mm, they have failed to support regeneration across larger defects. Therefore, effort has been shifted to develop biodegradable

guidance conduits. The advantage of using a degradable material lies in the fact that long-term complications such as fibrotic reaction and nerve compression can be minimized. The degradation characteristics of the material should meet the following requirements: (1) the degradation profile should match with the axonal outgrowth profile, so that the guidance conduit will maintain sufficient mechanical support during the regeneration process and (2) the degradation product(s) should induce minimum to zero tissue reaction. A series of degradable polymers have been used, including biodegradable poly(esters) such as PGA [135], PLA [136], PLGA [137], and poly(caprolactones) [138]; polyphosphazenes [139]; polyurethanes [140]; and poly (3-hydroxybutyrate) [141].

Since the emergence of studies showing that electrical charge affects neurite extension *in vitro* [142,143] and improves nerve regeneration *in vivo* [144], polymers that can provide electrical stimulus have been included in guidance conduit development. These polymers include piezoelectric polymers such as PVDF and its copolymer [144], and conducting polymers like polypyrrole and its biologically modified derivatives [143,145]. Other electroactive polymers, such as polyaniline, may also provide support for nerve growth, as studies have shown encouraging results with cardiac myoblast cells [146].

Nerve guidance conduits can be hollow or filled with matrix to support axonal elongation. A popular filler choice is natural polymeric gel. Ideally, the gel should be soft with mechanical properties matching those of the nervous tissue, porous to allow axonal ingrowth, biodegradable, and biocompatible. A number of natural polymers have been investigated, including agarose [147], chitosan [148], methylcellulose [149], hyaluronic acid [150], alginate [151], fibrin gels [152], collagen [153], keratin [154], and self-assembling peptide scaffolds [155]. Agarose is a thermally reversible polysaccharide hydrogel. Its gelling temperature can be modified by changing the functional groups attached to the sugar residues. It can also be functionalized with various biological motifs, such as laminin-derived peptide sequences RGD, YIGSR, and IKVAV, to enhance neurite extension [156]. Fibrin is a natural wound-healing matrix that can be found in the early stages of regeneration. It is formed from the blood coagulation cascade to restore hemostasis and initiate tissue repair. Using fibrin gels as the filler can closely mimic the natural matrix formed in the guidance conduit bridging short nerve gaps, where a fibrin cable is usually formed from the exuding serum by the damaged blood vessels in the nerve ends [157]. Peptide sequences have also been cross-linked into the filling fibrin matrix to further induce neurite extension [158]. In addition to gel filler, longitudinal filaments, either synthetic or natural, have been used in the conduit to align the growing axons in the direction of regeneration. Materials used in filament preparation include polyamide, catgut, polydioxanone, polyglactin, poly(acrylonitrile-*co*-methylacrylate), collagen, PLA, PGA, etc. [159–162].

Recently, materials research on nerve guidance conduits has been taken to a new level, where the old paradigm of passive material has shifted to new bioactive material design. Chemical messengers such as neurotransmitters have been polymerized into the polymer backbone to impart neuroactivity for the resulting biomaterial [163]. The first example of this new class of polymer is dopamine polymerized with a diglycidyl ester to form a biodegradable material that has shown vigorous neurite outgrowth *in vitro* and good tissue compatibility *in vivo*. Another example of new bioactive polymer is polysialic acid and its hydrogel. Polysialic acid is a dynamically regulated posttranslational modification of the neural cell adhesion molecule [164]. It has been shown to significantly improve cell adhesion and viability *in vitro*. With the increasing understanding of the biology behind nerve regeneration, it is expected that more bioactive materials will be developed in the future to achieve timely functional recovery from nerve damage.

## 4.8 Conclusions and Future Outlook

Polymers have made significant impact on biomedical research and medical practice, and will continue to be the major workforce for biomaterials in the twenty-first century. The polymeric biomaterials and their applications presented here are only the tip of an iceberg. With the growing understanding of the biological response to existing biomaterials and a better grasp of human organ composition, function, biomechanics, and disease etiology, chemists and polymer scientists should

continue working collaboratively with biologists, physicians, and engineers to develop tailor-made polymers for biomedical applications. In contrast to the old inert synthetic polymers, bioactive, biomimetic, and smart polymers will be at center stage. Furthermore, as the interactions of the biological system with polymers occur at the interface, surface-related research will continue to thrive, especially surface characterization and surface modification. One can be hopeful to foresee a better management of diseases with the help of a new generation of biomaterials, and a seamless integration of the biomaterials into the body.

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# 5 Biofilms, Biomaterials, and Device-Related Infections

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## 5.1 Introduction

The initial design criteria in the choice of indwelling materials for medical and dental purposes may be pragmatic, and based on the necessary mechanical properties required to fashion a functional device. Orthopedic implants require strong materials for weight-bearing, and articulating surfaces such as joints require durability and resistance to wear. Stents and shunts require flexibility and patency, and sutures require a high tensile strength yet also must be flexible enough for intricate manipulation. As the devices became more sophisticated and developments in materials science provided more options for manufacture, implants are being used more frequently and with longer anticipated lifetimes. Concurrently, the design process increasingly incorporated biocompatibility and comfort into the design criteria. However, with longer lifetimes, the more frequent use of invasive surgical procedures involving indwelling devices and biologically-friendly materials, there has been a rise in the number of incidences of device-related infection. Urinary catheters have been estimated to account for 30% of all nosocomial infections [1]. Between 66 and 88% of these occur after urinary catheterization [2]. It is also reported that almost 100% of catheterized patients develop an infection in an openly draining indwelling catheter which has been in place for four days or more [2]. For some

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procedures, such as orthopedic joint arthroplasties, the diagnosed surgical site infection rates are relatively low (between 1% and 2%; [3]); however, the increasing number of patients undergoing joint-replacement surgery translates to large numbers of patients afflicted with the consequences of complicating infections per year. Furthermore, infection of artificial joints can be devastating, since oral or IV antibiotic therapy frequently fails to resolve the infection, with the only remaining course of action being surgical debridement or partial or total revision. These two examples, the first with very high numbers of patients but of lesser severity in terms of impact to the individual, and the second, low numbers but severe patient impact, reflect the incentive to pursue a third design criteria—that of infection resistance—into materials and devices [4]. In the following sections we will discuss the role of bacterial biofilms in infection, and the growing literature highlighting biofilms as an important cause of device-related infection.

## 5.2 Bacterial Biofilms

### 5.2.1 What Are Biofilms, Where Are They Found, and Why Are They Problematic?

Bacterial biofilms are communities of bacteria which attach and subsequently grow on surfaces of abiotic materials, as well as host tissues [5,6] (Figure 5.1). The bacteria embed themselves in a highly hydrated protective matrix termed "extracellular polymeric substance" (or sometimes slime) (EPS) [7]. Biofilm development is an ancient adaptation of prokaryotes which is believed to have facilitated survival in hostile environments, and allowing colonization of new niches by active dispersal mechanisms [8–12].

Bacteria in biofilms also demonstrate coordinated behavior that culminates in the development of complex three-dimensional structures comprised of functionally heterogeneous bacterial communities on virtually all surfaces. Phenotypic heterogeneity and localized specialization in biofilms can be seen by differential expression of pili, fimbriae, flagella [13], carbohydrate [14], adhesins [15,16], and genes associated with dormancy [17,18] and antibiotic resistance [19]. Biofilm bacteria coordinate their behavior by cell–cell communication using

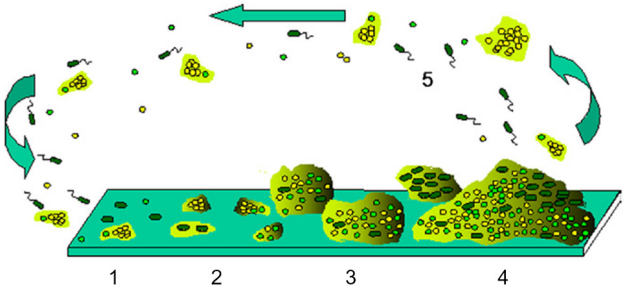



**Figure 5.1** Key processes in biofilm development based on the conceptual model described by Stoodley *et al.* [5]. For illustrative purposes this schematic shows a mixed biofilm consisting of rods capable of swimming motility (i.e., *P. aeruginosa* shown in red) and two types of non-motile cocci (i.e., *S. aureus* and *S. epidermidis* shown in green and yellow). The EPS slime matrix surrounding the cells is shown in green. (1) Initial attachment of single cells and clumps of detached biofilm bacteria. (2) Production of EPS to more firmly adhere cells to the surface. (3) Early development of biofilm clusters by clonal expansion (can be mixed or single species colonies). (4) Mature biofilm when the biofilm is in (pseudo) steady-state. (5) Dispersion of single cells by motility-driven swarming dispersion (*P. aeruginosa*) and the sloughing of biofilms clusters containing cells and EPS.

secreted chemical signals which allow the bacteria to sense and respond to their environment by assessing cell density or environmental cues, resulting in modification of gene expression. This ability to adapt to and modify micro-niches at a surface interface allows bacteria in biofilms to facilitate survival at a population level.

### 5.2.2 Adaptation of Biofilm Structure for Survival in Changing Environments

Biofilms growing in highly varied environments from hot springs to urinary catheters appear to utilize similar strategies to attach and grow on surfaces, and can also show remarkable structural similarity suggesting a selective advantage that surface association offers. This suggests that structural specialization in different environments reflects an important survival strategy. For example, biofilm growth under high fluid shear often exhibits

filamentous streamers, while biofilms grown in low shear environments form towers or mound-like structures which vary according to different nutrient conditions or mass transfer-determined localized growth patterns. These observations suggest that bacteria in biofilms can rapidly adapt to their local environment, to an extent not possible with multicellular eukaryotic organisms [7,20].

### 5.2.3 Resistance of Bacteria in Biofilms

Numerous studies document that bacteria in biofilms are more resistant to environmental stresses, such as dehydration, metals toxicity, and UV light exposure, than free floating or planktonic, bacteria. These strategies which have evolved for survival in the natural environment appear to be readily adapted to facilitate survival against human attempts to eradicate them with modern materials, antibiotics, and antimicrobials. The exact nature of the resistance is not fully understood, but the most commonly considered mechanisms are: (1) bacteria in the interior of the biofilm enter a dormant-like state [21], possibly induced by nutrient depletion caused by consumption by bacteria on the periphery of the biofilm cell clusters [22]; (2) reaction of the antimicrobial agent with the extracellular polymeric slime (EPS) matrix (binding and/or degradation) [23]; and (3) the development of resistant populations, such as slow growing small colony variants or "persister" cells which occur at greater frequency and in higher numbers in biofilm populations than in planktonic populations [24].

The first and second mechanisms have been referred to as "tolerance" rather than "resistance," the latter of which is usually associated with a genetic basis [25]. In addition to providing a nidus for bacterial biofilm formation, foreign materials also suppress the efficacy of phagocytic clearance. The EPS matrix of carbohydrates, proteins, and extracellular bacterial DNA (eDNA) provides structural integrity, as well as protecting the bacterial cells within from phagocytic attack [26–28]; although *in vitro* experiments suggest that the degree of protection also depends on the species and age of the biofilm [29]. The EPS also reduces the ability of IgG human antibodies to penetrate the biofilm [30,31]. Therefore, biofilm formation also appears to be a mechanism which helps bacteria to evade host immunity. Indeed, many diseases associated with biofilms (infection of the cystic fibrosis (CF) lung, otitis media, gingivitis) are also associated with chronic inflammation. Mounting evidence suggests that the "inappropriate" inflammatory response to biofilms often fails to eradicate the biofilm, and may in fact contribute to the pathology pathogenesis by degrading host tissue, which in turn provides nutrients to the bacteria.

## 5.3 Biofilm Microbiology and Infectious Disease

Many of the concepts and techniques that have served microbiologists well in the understanding, diagnosis, and treatment of many acute epidemic bacterial diseases, are being re-evaluated with respect to device-related and other biofilm-associated infections. This section on biofilm microbiology will focus on how biofilm bacteria differ from their planktonic counterparts, and the importance of using appropriate biofilm *in vitro* assays to assess the potential bacterial colonization of biomaterials *in vivo*.

### 5.3.1 Bacterial Adhesion to Surfaces

Derjaguin, Landau, Verwey, and Overbeek (DLVO) theory is often applied to the study of bacterial adhesion to surfaces [32]. This classic concept of colloid behavior characterizes a planktonic bacterial cell as a smooth particle that interacts with a surface in a manner based on the charges on both surfaces, which overcome the basic repulsion of individual particles. However, direct observations of the surfaces of planktonic bacteria using electron microscopy have demonstrated that these surfaces are not smooth [33]. In addition to protein appendages (i.e., flagella and pili) projecting as much as 2–6 μm from the cell, the entire surface of bacterial planktonic cells is covered by a structured matrix of hydrophobic exopolysaccharide (EPS) fibers and protein. The external glycocalyx of planktonic cells is anchored to the polysaccharide O antigen fibers that project from the lipopolysaccharide (LPS) of the outer membrane of gram-negative cells, and to the polysaccharide teichoic acid fibers that project from the cell wall of gram-positive cells. Elegant freeze-substitution microscopy preparations have shown that the actual surface of planktonic bacterial cells capable of interacting with a surface

to be colonized consists of a 0.2−0.4 μm thick layer of protein and polysaccharide fibers. Thus, the planktonic bacterial cell is not a smooth-surfaced colloid particle, and the actual interaction of these cells with surfaces is based on the bridging of bacterial fibers with fibers adsorbed to the surface being colonized. Therefore, DLVO theory has a limited application in the study of bacterial adhesion.

Moreover, the reliance on bacteria isolated from the system of interest, but subcultured repeatedly in rich media, also does not serve us well in biofilm studies relevant to medical devices. This method, which dates from the 19th century, may select for strains of bacteria that exhibit rapid planktonic growth on rich media, since slow-growing strains might not be cultured or overgrown, and strongly adherent bacteria may not be readily transferred. Such strains may lack many surface structures that would be necessary for their survival in the real world on a surface where they are challenged by antibacterial agents, nutrient limitation, competing bacteria or host defenses. However, these laboratory-adapted strains used in studies of bacterial adhesion to biomaterials may be physically closer to the smooth-surfaced colloidal particles suggested in DLVO theory, potentially confounding data designed to further the understanding of device-related infections [33]. This may help to explain why many novel biomaterials perform less successfully *in vitro* when tested with clinical isolates, and further highlights the necessity of using clinical strains in biomaterials testing. However, there are also challenges with using clinical isolates. Techniques such as rapid genomic sequencing [34] and multi-locus strain typing (MLST) [35] have revealed an enormous amount of genomic and phenotypic diversity between strains of the same species, and indeed biofilms appear to accelerate the generation of variants [36,37]. Thus, data generated from any one clinical isolate might, like reference strains, also not be generalizable. Thus, ideally, anti-biofilm assays should be conducted with reference strains to allow benchmark comparisons between studies in different laboratories, as well as at least two or three low-passage clinical isolates.

Many researchers in the biomaterials field have intuitively speculated that a few key surface characteristics can inhibit (or favor) bacterial adhesion, and surfaces engineered with various combinations of these characteristics have been tried in the search for colonization-resistant biomaterials. Bacteria adhere equally well to very hydrophobic (e.g., Teflon™) and to very hydrophilic (e.g., PVC) surfaces, can colonize smooth surfaces as well as rough surfaces [38,39], and can colonize surfaces in relatively high physiologically-relevant shear flows [26]. Indeed, Bos et al. have reported that hydrophobicity had little correlation with initial attachment of various bacterial strains to surfaces, but was correlated with attachment strength [40]. Thus, currently, while there is no perfect biocompatible biomaterial surface which also inherently resists bacterial colonization, more sophisticated nonfouling surfaces which incorporate designer antimicrobial peptides to target and kill bacteria [41] or zwitterionic surfaces which are generally resistant to protein adhesion [42] show potential for this application.

### 5.3.2 Processes of Biofilm Formation

When planktonic cells adhere to a surface, they exhibit behaviors that have been divided into "reversible" and "irreversible" patterns [43]. Motile organisms (e.g., *P. aeruginosa*) may use their flagella for initial attachment, followed by type IV pili for twitching motility that allow them to form elaborate structures [13]. However, surface appendages and motility are not required for biofilm formation, staphylococci and streptococci are both capable of forming biofilms *in vitro* and *in vivo*, although in these cases it is assumed that biofilm structures develop from clonal growth. Movies showing the attachment of various biofilm bacteria are available on the Center for Biofilm Engineering (CBE) web site (www.erc.montana.edu). Such movies show that many cells that adhere to surfaces may also quickly detach, before they make the phenotypic switch to initiate irreversible attachment and subsequent biofilm formation.

When a bacterial cell colonizes a surface, the pattern of gene expression is profoundly different from the previous planktonic phenotype, resulting in a distinct biofilm phenotype that may differ by as much as 70% in the proteins expressed [44]. Among the first genes that are upregulated in adherent cells are those involved in the production of molecules associated with the EPS that forms the biofilm matrix and anchors the cell irreversibly to the surface. In mucoid *P. aeruginosa*, the

upregulation of *algC*, which is a part of the alginate synthesis pathway, occurs within 18 minutes of initial cell adhesion [45], and there is a secretion of bacterial biofilm matrix material by these cells within 30 minutes. Once attached, cells which have triggered the conversion to the biofilm phenotype and the formation of a multicellular community on the colonized surface begin to accrete larger numbers of cells through growth. As they increase in numbers and produce more EPS matrix material, the attached cells form microcolonies which constitute approximately 10% of the volume, with the EPS matrix occupying approximately 90% of the biofilm. Recent data suggest that the structure of the EPS is much more sophisticated than previously thought, with confocal and SEM (scanning electron microscope) images showing features such as "honeycombs" and 3D networks in *P. aeruginosa* and staphylococcal biofilms grown *in vitro* [46]. Borlee et al. [47] have found evidence for secreted proteins which specifically cross-link extracellular polysaccharides, suggesting a possible mechanism for extracellular remodeling of the EPS.

The microcolonies can assume tower-like, frond, and mushroom-like structures in many natural and cultured biofilms, but other morphologies may be dictated by individual species characteristics, and by nutrient availability. As the biofilm matures and undergoes more phenotypic changes, the processes of growth and recruitment are balanced by detachment of planktonic cells from the sessile community and sloughing of larger pieces of biofilm. *In vitro* studies suggest that biofilms reach a mature thickness and a stable community structure within a week or two of their initiation of colonization [5]. Numerous *in vitro* studies show that both gram-negative and gram-positive pathogens are clearly capable of forming extensive biofilms on commonly used medical materials, including devices themselves, such as surgical sutures and meshes [48], and orthopedic implants and catheters [49,50].

## 5.4 Device-Related Infection

Although biofilm formation may be an ancient adaptation of prokaryotic life, the full impact of biofilms on human health is only now being realized, through one of the fastest technologically advancing fields—the development of medical devices, which are all susceptible to colonization with microorganisms growing in biofilms.

Medical and surgical practices rely on an increasing array of biomedical implants, and tens of millions are implanted each year. Intravenous catheters, prosthetic heart valves, joint prostheses, peritoneal dialysis catheters, cardiac pacemakers, cerebrospinal fluid shunts, and endotracheal tubes certainly save millions of lives, but all carry the risk of surface-associated infections. Device-related infections were among the first clinical problems to be identified as having a bacterial biofilm etiology. Biofilms associated with medical devices were first noted in the literature in the early 1980s, although Bayston and Penny published a report in 1972 that correlated *Staphylococcus mucoidy* as a possible factor in the colonization of Holter shunts [51]. Electron microscopy revealed bacteria deposited on the surface of indwelling devices such as intravenous catheters and a cardiac pacemaker lead [38]. However, the relationship between medical devices and infection is arguably best established for catheters [52]. Many types of catheters and fluid management devices, such as central venous catheters, dialysis catheters, ventilators, neurosurgical shunts, and drains are also commonly associated with infection [53].

Implant infections are common occurrences, with rates estimated between 4–5% for orthopedic implants and 7% for cardiovascular implants [54,55]. Due to the increasing use of these interventions, infections affect millions of patients per year, making device related infections a serious clinical problem that is being addressed from many perspectives.

There is a clear correlation between implanted devices and risk of infection, which may not be surprising since any time the protective skin barrier is breached, the possibility for introduction of bacteria to normally sterile sites exists. A 1979 study by Fitzgerald [56], and discussed in Subbiahdoss et al. [57], reported that during surgery a wound was exposed to approximately 270 bacterial-carrying particles per $cm^2$ per hour. No doubt with improved operating room (OR) facilities, such as laminar flow air handling and the implementation of more rigorous practices aimed at reducing the rates of nosocomial infections, this rate will have decreased. Nevertheless, the study illustrates that possible airborne contamination can occur within the "sterile field." Possibly of greater concern is the introduction of skin pathogens during the procedure. Higher

rates of infection associated with more heavily microbially-colonized anatomical sites (such as the groin or armpit), suggest that transmission from the skin, despite disinfection of the skin, is an important route of transmission. Even devices which are not transdermal or surgically implanted, such as urinary catheters, are associated with a high risk for infection, in part due to the fact that these devices are placed in patients who are already immunocompromized, and it is likely that many catheters are being placed in an already infected site.

In the controlled condition of a hospital the device be implanted is sterile immediately out of the packaging. However, once it is exposed there is potential for the implant to be contaminated with bacteria that might also have inadvertently enter the wound during surgery. The probability of infection has been related to the relative time taken to colonize the artificial surface by host cells or infectious microorganisms. This was termed "The race to the surface" by Gristina et al. [58], who hypothesized that if a surface was colonized with host cells before a biofilm could become established, the probability of subsequent infection was low, even if bacteria were introduced during the procedure. Subbiahdoss et al. [57] experimentally demonstrated the importance of the "race to the surface" by showing that the successful colonization of a glass substratum by osteosarcoma cells was negatively influenced by preseeded *S. epidermidis* cells on the surface. Whether this observation is generalizable to the *in vivo* situation remains to be verified.

Although device-related infections are initially localized to the site where the device is inserted, these infections are often chronic in nature and can be a source of periodic acute sepsis. The direct link between the presence of a foreign body and bacterial sepsis in hemodialysis catheters is illustrated in a study by Feely [59]. In a group of hemodialysis patients with a history of recurrent bacteremia, the rate of catheter-related bacteremia went down from 9.13 per 1000 catheter days to 1.04 after catheter-lock solutions (CLS) were instigated. When CLS was discontinued, the rate rose back up to 7.94 per 1000. Catheter lock is a technique whereby a controlled volume of antibiotic solution is introduced into a catheter so as to fill the catheter, but is not allowed to enter the bloodstream. Thus, much higher concentrations of antibiotics can be applied directly to the catheter than would otherwise be tolerated systemically. This study clearly implicates the foreign body as harboring the source of infection.

The organisms most frequently observed with medical devices are the staphylococci, both the coagulase negative staphylococci (particularly *Staphylococcus epidermidis*) and *S. aureus* followed by *P. aeruginosa* and other opportunistic bacteria that survive in the environment. Biofilm formation on medical implants, most notably by *S. epidermidis*, has led to the characterization of a new infectious disease: "chronic polymer-associated infection" [60,61]. *S. epidermidis*, a common colonizer of the skin, is therefore frequently found in wounds and implants. It was not considered even an opportunistic pathogen until device-related infections became problematic [62]. Biofilm formation therefore can be considered a virulence factor in the context of device-related infections—a bacterial strategy that contributes to its ability to cause and maintain an infection.

### 5.4.1 Biofilm Formation by Staphylococci

Staphylococci are particularly problematic in biofilm-associated infections with surgical site infection of deep tissue implants. This is partly due to the propensity of these organisms to form biofilms, and the increasing spread of multi drug-resistant methicillin-resistant *S. aureus* (MRSA) and *S. epidermidis* (MRSE). Biofilm formation is characterized by two stages with staphylococci: (1) adhesion to a solid surface; and (2) growth-dependent cell accumulation resulting in multiple cell layers in microcolonies. In *S. epidermidis*, the cell−cell layer aggregation is specifically linked with a β-1,6-linked glycosaminoglycan polysaccharide complex know as polysaccharide intercellular adhesin (PIA) [63]. Proteins involved in the synthesis of this matrix polysaccharide are regulated by the *ica* gene locus in *S. epidermidis* [64,65] which is conserved among phyologenetically related staphylococci. However, PIA and *ica* are not absolutely required for biofilm formation, since mutants lacking the *ica* locus have been isolated which can still form biofilms, suggesting complex, redundant mechanisms for biofilm development. For example, an *S. epidermidis* transposon mutant, unable to form biofilms on polystyrene, formed biofilms on glass, suggesting that bacterial adhesion mechanisms vary according to the substratum [64].

A further level of complexity comes from the numerous environmental factors that can affect biofilm formation. For example, biofilm formation in *S. epidermidis* is strongly influenced by sugar substrate, oleic acid, antibiotic treatment, oxygen levels, iron, osmolarity, temperature, and ethanol stress [61]. Also, the initial adhesion stage alone is multifactorial, depending on the physio-chemical properties of the biomedical polymer material, and the nature of the bacterial cell surface. Bacterial surface proteins contribute significantly to adhesion, and several key proteins have been identified that play a role in staphylococcal biofilm formation. In *S. aureus*, teichoic acid lacking D-alanine (dltA) resulted in a change in surface charge that affected several characteristics, including biofilm formation [66]. Interestingly, dltA mutants were defective in the ability to attach to polystyrene and glass. While consistent with charge equilibrium of surface interactions, the biofilm defect was re-established by the addition of magnesium ions. Other researchers found that *S. epidermidis* biofilm formation was enhanced by $Mg^{2+}$ and inhibited by EDTA [67]. Another surface protein in *S. aureus*, the biofilm-associated protein or bap, was shown to contribute to biofilm formation on microtiter plates, but more importantly showed increased pathogenesis in a mouse foreign-body infection model [68].

### 5.4.2 Detecting Device-Related Infections

Biofilm-associated infections are often difficult to detect using conventional culturing methods [69], and many of the clinical studies which conclude that biofilms were present on a medical device rely on indirect evidence such as the recovery of bacteria removed using sonication [70–72] or the culture of strains positive for slime production or biofilm formation [73]. Arguably, at the present time microscopic examination of the devices and associated tissue themselves, are still the only way to definitively demonstrate the presence of biofilm [6,38]. Confocal microscopy has an advantage over electron microscopy, in that it can be performed on fully hydrated specimens using water immersion objectives, which, in itself, demonstrates firm attachment of the bacteria to the surface, and is also compatible with a wide range of specific fluorescent staining techniques, including antibody labeling and fluorescent *in situ* hybridization (FISH), to identify bacterial species, or membrane integrity-based nucleic acid viability staining methods to detect live and dead bacteria. Figure 5.2 shows an example of predominantly staphylococcal biofilm growing on a surgical screw.

Bacteria can also be identified through the detection of their DNA. First, a specimen or swab is digested to release any bacterial DNA. Next the polymerase chain reaction (PCR) is used to amplify specifically targeted fragments of DNA. In some cases the targets are specifically designed for a certain species, genus or strain. In other cases sections of universal genes, such as 16s ribosomal DNA (rDNA), are amplified using primers to highly conserved regions while the sequencing of the variable region between the primers can identify the bacteria.

While PCR-based 16S rDNA detection methods appear to be much more accurate than conventional clinical culture, which has increasingly been shown to produce high levels of false negatives in chronic biofilm-associated infections, PCR for targeted genes does not differentiate between biofilm and planktonic infections. PCR has also been criticized for being too sensitive, and producing false positives from contaminants which are not clinically relevant. However, the visual demonstration of clusters of bacteria firmly attached to devices demonstrates a "growth-in-place" process, which is unlikely to have resulted from contamination during the relatively short period of the surgery. Therefore, confocal microscopy, PCR, and reverse transcriptase PCR (RT-PCR) have been used in combination to provide strong evidence for the presence of active bacterial biofilms on various implant materials [74–77] as well as host tissue [78–81]. However, a drawback of confocal microscopy-based diagnosis of biofilm is that it requires highly specialized equipment and training, along with laborious searching for clusters of bacteria with dimensions as low as 10s to 100s of microns on implants that might have large areas with convoluted surfaces.

While confocal microscopy might be useful to validate more rapid methods which are conducive to standardization in the setting of a clinical laboratory, it will require refinement of the existing technology before it can be used as a routine diagnostic tool. Ideally, the diagnosis of a biofilm infection would be made prior to surgery. One approach is to devise enzyme-linked immunosorbent array (ELISA) type assays to detect biofilm specific proteins through a simple blood test [82]. Another approach is to

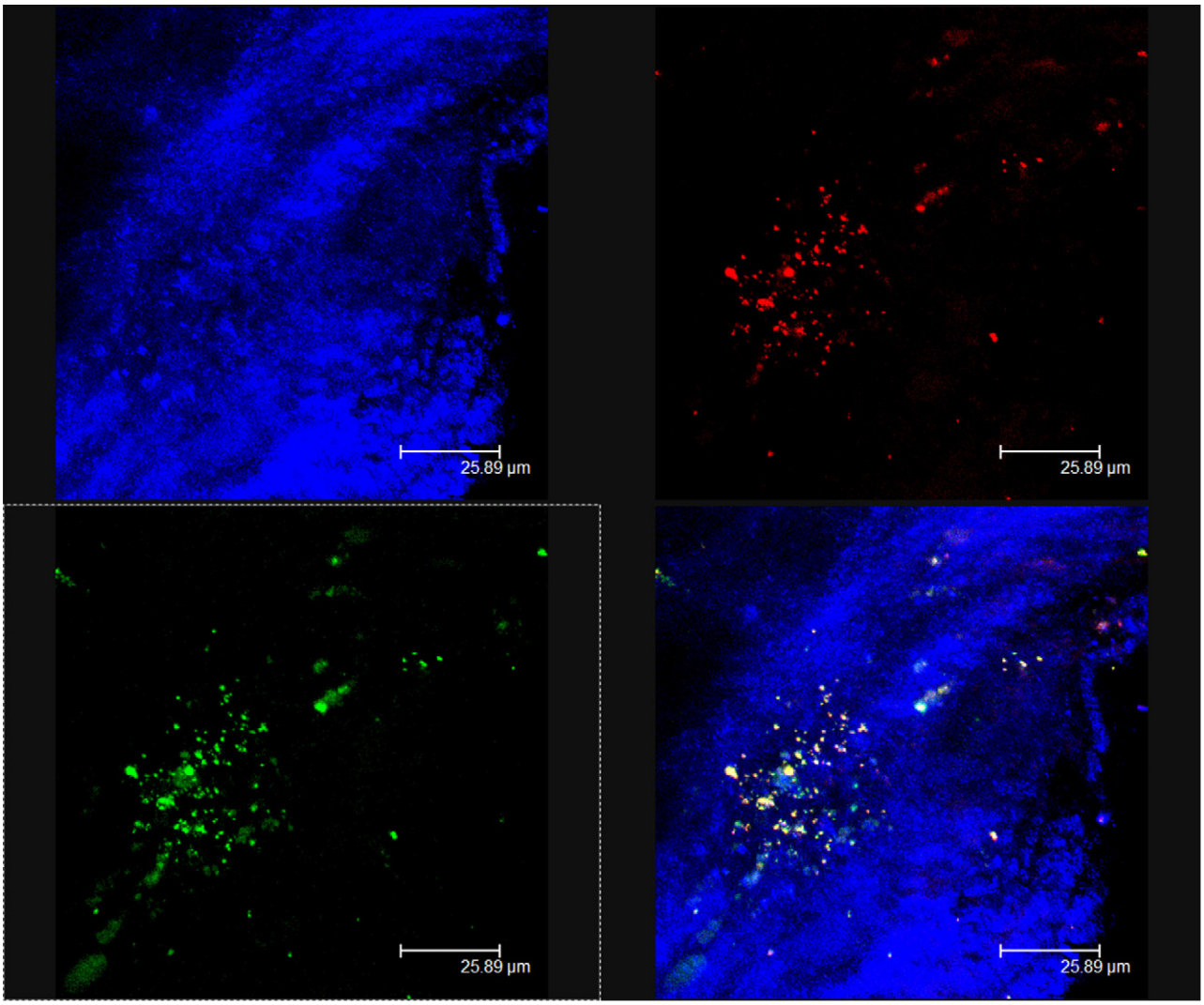



**Figure 5.2** Biofilm attached to orthopedic screws from a non-union fracture case. The surface of the screw and associated invested tissue are blue and imaged by reflected confocal microscopy. Staphylococci were stained red by fluorescence *in situ* hybridization (FISH) using the Sau probe. General bacteria were stained green with the Eub338 probe. The overlay (bottom left) shows that the biofilm consisted primarily of staphylococci with occasional other types of cocci. Scale bar = 25 μm.

develop medical imaging techniques, such as X-ray computed tomography (CT) scan or magnetic resonance imaging (MRI) scans, so that biofilms can be visualized in place. However, the small size of the biofilm, and the lack of contrast between biofilm and host tissue, makes imaging a challenge. In diagnostic imaging for cancer detection contrast agents are used which help distinguish the malignant cells from the healthy tissue. The importance of more effectively treating cancer through early detection has led to much research and development in the imaging of ever smaller tumors, and it is possible that techniques developed in oncology could be utilized for detection of biofilms. Imaging is not only useful for diagnostics, but also has the added advantage in that it can be invaluable in monitoring and planning surgical intervention.

### 5.4.3 Nucleic Acid-Based Detection Methods

PCR-based detection techniques generally fall into one of two categories. One approach is targeted PCR in which genus, species or strain-specific primers or combinations of primers are used to detect pathogens of interest. However, this

approach does not provide any information regarding the presence or absence of non-targeted bacteria. A second approach is a "finger-printing method," by which primers are used to amplify universal DNA sequences (16S rDNA is commonly used). The amplicon is separated out as bands on a gel by techniques such as denaturing gel gradient electrophoresis (DGGE) [83] or, after digestion using restriction enzymes, by restriction fragment length polymorphism (RFLP) [84]. The separation patterns can be used to identify specific species. However, in polymicrobial infections the many overlapping and complex patterns of bands can be difficult to resolve. A more specific approach is to sequence the various 16S amplimers from individual bacterial colonies in a clone library or directly by high-throughput sequencing techniques, such as 454 pyrosequencing [85,86]. Individual species can be identified by comparing the cloned sequences with database sequences, using tools such as the Basic Local Alignment Search Tool (BLAST). The drawback of these approaches is that they are relatively time consuming, either in the preparation of the library or the data analysis, and are not yet conducive for utility where a rapid diagnosis is needed. An alternative approach is the combination of PCR with ion spray mass spectroscopy to precisely weigh each complementary strand of the amplimer. Bacterial species can be identified by mass due to differences in the nucleotide ratios. Multiple sets of primers are used to amplify sequences from genes which are universal to bacteria (i.e., 16S and 23s rDNA), and genes or alleles specific to certain species or strain [87]. More targeted primer sets can be designed to identify site-specific pathogens or the presence of the bacterial virulence genes, such as *mecA* which is responsible for methicillin resistance in *S. aureus* (MRSA) [77,88]. primer sets could be designed to detect genes associated with biofilm formation, such as the *ica* operon which regulates EPS production in staphylococci.

## 5.5 Clinical Examples of Biofilm Infections

### 5.5.1 Infection Related to Surgical Repair Materials

Surgical repair materials, such as staples, sutures, and meshes, have also been identified as possible foci of infection in such diverse anatomic sites and procedures as abdominal wall repair and ocular and dental procedures [48,74,89,90]. The implication of the foreign body as a causative factor of infection is supported in a study by Wissing et al. [91], who reported that the late post-operative incidence of suture sinus development associated with fascia repair after midline laparotomy was significantly greater with nonabsorbable sutures (nylon) than with absorbable sutures (polyglactin or polydioxanone). There was a direct relationship between material absorption time and incidence of sinus formation, which was 3−4% for polyglactin, which is fully absorbed after 70 days, 11% for polydioxanone, which is fully absorbed after 180 days, and 23% for nylon, which is permanent. This study nicely illustrates the compromise that has to be made between functionality of the material and the risk of infection, since there was an inverse relationship between the incident rate of incisional herniation and suture absorption time caused by the loss of tensile strength during the absorption process.

### 5.5.2 Bacterial Biofilms on Sutures

Bacterial adherence to, and colonization of, suture material has been of interest to the surgical community for decades. Thirty years ago Osterberg and Blomstedt observed that multifilament "capillary" suture material recovered from *S. aureus*-inoculated tissues in a rat model harbored substantially greater quantities of bacteria than "non-capillary" suture [92]. Their conclusion was that: "in the case of the capillary suture material, the bacteria would tend to be protected through their enclosure in the interstices of the material." In a subsequent study, Osterberg further commented that "bacteria which are enclosed in the interstices of multifilament suture material, and protected from the phagocytic activity of leukocytes, can sustain and prolong an infection" [93]. These prescient early observations concur well with our present understanding of bacterial biofilm formation and persistence, but suture material as a host for pathogenic biofilm in patients has thus far been only occasionally examined (principally in the ophthalmologic literature). We have reported several cases where biofilm was documented on clinical specimens of explanted permanent suture material, with resolution of the infection on

removal of the offending suture substratum [94,95] (Figure 5.3). Multiple studies have noted that "suture sinuses" are associated with nonabsorbable suture materials, presumably due to resident biofilm, although direct evidence was lacking [96,97].

Prevention of infectious complications by modifying the suture material itself has recently become an area of intense interest. A number of studies have focused on suture materials coated with the antimicrobial agent triclosan. *In vitro* and *in vivo* animal experiments have shown that coated polyglactin 910 suture (braided) can significantly decrease the number of viable bacteria recovered from inoculated suture material versus a non-coated control [90,98]. Similar antimicrobial activity has also been reported with the addition of triclosan to poliglecaprone 25 [99] and polidioxanone [100] suture. Early clinical experience has also been promising: use of triclosan-coated polyglactin 910 suture versus uncoated polidioxanone suture in

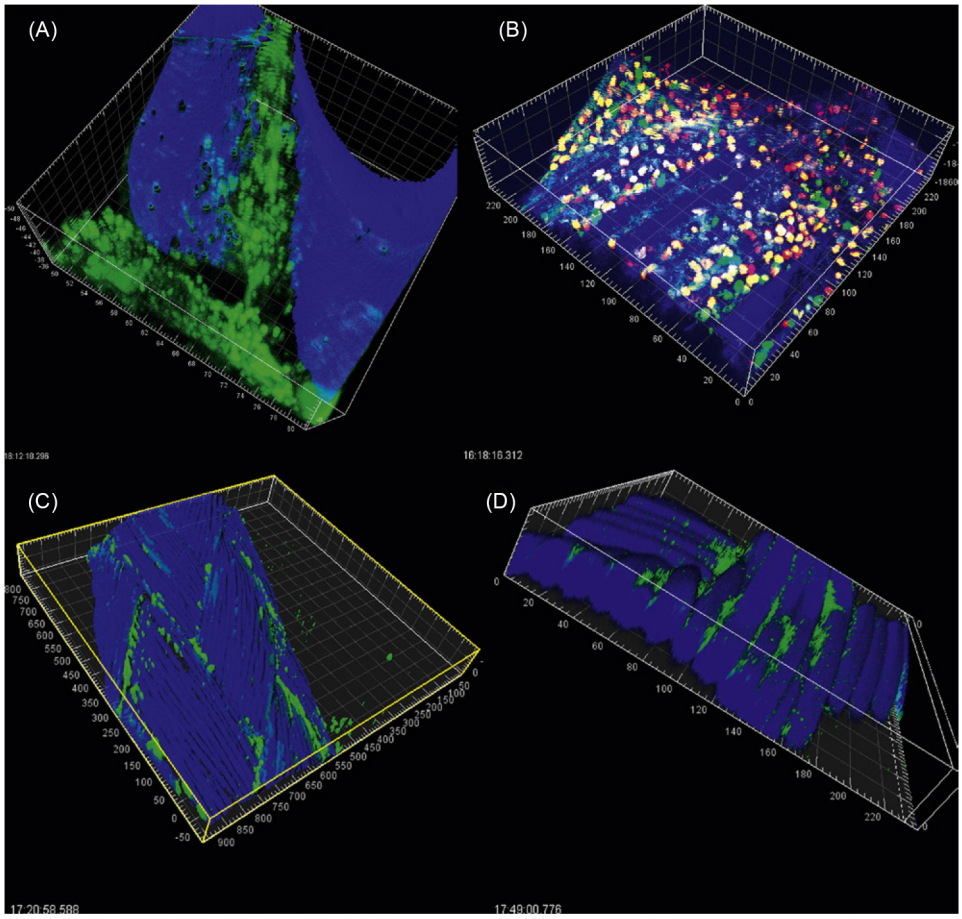



**Figure 5.3** Biofilm infected sutures. (A) Ti-cron braided polyester suture used for hernia repair following open gastric bypass surgery removed from a chronic draining wound was found to have a biofilm formed from live cocci (stained green with the BacLight™ Live/Dead® kit). Diffuse green staining (arrow) is suggestive of eDNA in the biofilm slime matrix. The individual filaments of the suture are shown by autofluorescence (blue). Biofilm was particularly noted in the crevices formed from the braiding. Scale bar = 4 μm. (B) The same suture as in "A" but at a location a few mm away. In this location there were many inflammatory cells indicated by nuclear morphology (nuclei stained yellow and red). Scale bar = 20 μm. (C) *In vitro* biofilm grown on braided sutures from a clinical MRSA (stained green with the Live/Dead® kit) isolated from a patient with an infected surgical repair mesh. Similar to the *ex vivo* image the biofilm preferentially grew in the protected crevices between individual filaments in the braid. Scale bar = 50 μm. (D) Higher magnification confocal image of the suture at a different location. Scale bar = 20 μm.

2088 patients undergoing midline laparotomy resulted in a significantly reduced reported incidence of wound infection [101].

### 5.5.3 Bacterial Biofilms on Surgical Mesh

Surgical mesh implants are routinely used to address the clinical problem of hernia. These implants typically restore structural domain to the abdominal/pelvic wall and prevent extrusion of visceral contents. Multiple complications have been associated with the use of surgical mesh, including infection, extrusion, and erosion into subjacent structures (i.e., development of enterocutaneous fistula). Not infrequently, surgical mesh implants must be removed, often due to infectious complications, and recently an entirely new "current procedural terminology" code (11008) describing the explantation of abdominal wall mesh due to chronic and necrotizing infection has been recognized.

Multiple studies have examined the morphological and surface characteristics of various available meshes, and have documented the ability of both gram-negative and gram-positive organisms to form biofilms on these materials [102,103]. The hydrophobicity of the mesh surface, as well as the presence of numerous niches (or pockets) in multifilament mesh configurations, appear to correlate with the extent of biofilm formation *in vitro* [102]. We have been able to demonstrate biofilms present on clinical specimens of explanted mesh from patients with a variety of clinical presentations (Stoodley et al., manuscript in preparation).

A similar approach to modifying mesh materials (as has been done with suture) may prove beneficial to reducing the infectious complications noted with surgical mesh, but these studies are in their infancy. Monofilament polypropylene mesh modified with a coating to release nitric oxide in bactericidal quantities was found to significantly inhibit biofilm from multiple organisms *in vitro*, but had little effect in an *in vivo* animal model [104]. Clinically, acellular dermal grafts composed entirely of organic materials and therefore presumably less susceptible to the establishment of persistent biofilms, have recently gained popularity as alternatives to mesh reconstruction in abdominal wall surgery.

### 5.5.4 Bacterial Biofilms in Orthopedic Prosthetic Joint Infection

Orthopedic implant infections differ clinically from the previous infections described, for several reasons. First, although they are chronic and persistent like all biofilm infections, they often develop months or years after the implant. Second, these infections are often difficult to detect in orthopedic implants via routine examination or culturing, thereby delaying diagnosis and treatment. Third, unlike the catheter lock solution treatment, there is no easy way to deliver high doses of antibiotics to the site. Therefore, orthopedic infections often require repeated antibiotic applications to resolve the infection, which increases the risk of the development of antibiotic resistance. Finally, treatment of chronic infections that fail to resolve with conventional antibiotic treatment may require sustained high dose antibiotic therapy, removal of the implant, and replacement of the orthopedic implant, resulting in pain and discomfort, immobility, and excessive costs to the patient and healthcare facility. The failure of antibiotics to effectively and fully treat these infections suggests that other strategies are necessary; approaches to resolve these problems range from enhancing hospital sterility protocols to the investigation of active release [54], non-adhesive or bactericidal coatings [105–107]. Despite researchers' best efforts, often the only treatment for intractable implant infections is revision surgery, requiring removal of the infected implant and placement of a new one. However, secondary (revisional) total hip replacements have a higher infection rate (3.2%), and secondary total knee replacements exhibit a remarkable 5.6% re-infection rate. To compound the problem, in revision surgery a larger implant must be used, since bone is destroyed during the original implantation and subsequent explantation. This process may require splintering the surrounding bone, along with substantial soft tissue resection and debridement. The patient is then confined to absolute bed rest and continuous intravenous antibiotic therapy for several weeks. If the revisional surgery fails, limb amputation may occur. The number of total hip and knee replacements within the United States surpassed 1,000,000 in 2009 (http://www.cdc.gov/nchs/fastats/insurg.htm), and is expected to increase

dramatically over the next several decades due to specific risk factors within the US population that include obesity, sports injuries, and longer lifespan. In addition to the physical and emotional costs, the financial cost of revisions is high, with explant surgery, post-procedural medical treatment, and re-implantational surgery exceeding $500,000 per patient. Conservative estimates put the current costs of revisional therapy in excess of two billion dollars annually.

Addressing this objective, the 2004 Association of Bone and Joint Surgeons Musculoskeletal Infection Workshop [108] suggested that orthopedic materials designed to prevent bacterial biofilm formation would be a relevant clinical strategy for reducing orthopedic device infections. Therefore, the investigation of antimicrobial surfaces that inhibit or retard biofilm development represents a significant new direction in the antimicrobial arsenal against bacterial biofilm formation and implant infections. These antimicrobial surfaces fall into two broad categories: (1) those surfaces that are made of materials that resist bacterial attachment; and (2) those materials that are impregnated or coated with antimicrobial compounds, which upon diffusion from the surface inhibit or abrogate bacterial growth at the implant site. This direction of research is at an early stage, and represents an important part of the unmet need of the pharmaceutical therapeutic market, but most saliently, the proven effectiveness of orthopedic materials specifically designed to resist bacterial colonization and biofilm formation would result in a significant advance in patient care.

Total joint replacement (TJR) is one of the most common and successful surgical procedures in orthopedics. The majority of patients undergoing TJR benefit from marked improvements in their pain, functional status, and overall quality of life [109]. Infection following primary TJR is uncommon, occurring with a prevalence of $\sim 1-3\%$, but it can be a debilitating complication of TJR surgery. Infection following revision arthroplasty is significantly higher, approaching 10% [110]. In the US, revisions are usually in two stages with a period of time between removal of the old hardware and replacement of the new which allows resolution of the infection. However, the fact that infection rates in revised cases are higher than for primary surgeries suggests that, although the symptoms might have resolved, the bacterial source of the underlying infection might not have been fully eradicated. The treatment of an infected joint prosthesis is both complicated and expensive. Diagnosis can itself be problematic, and the necessary intervention may vary depending on the clinical picture; e.g., acute post-operative infections may be initially managed with operative debridement, intravenous antibiotics, and retention of the implant, whereas late chronic infections will likely ultimately require more extensive surgery, typically in multiple stages. Even with aggressive measures there is a $\sim 10\%$ rate of failure to eradicate the infection, and the patient may proceed to resection of the arthroplasty, arthrodesis, or even amputation, in each case with significantly greater morbidity [110].

Although the concept of biofilm as a relevant physiological factor in prosthetic joint infections has gained some currency, there are actually few examples of experimentally imaged bacteria in biofilm configuration from any orthopedic implanted material. Gristina and Costerton first found bacteria in biofilms on orthopedic explants by scanning electron micrography [111]. Confocal microscopy has visualized biofilm on the surface of an explanted hip prosthesis, and the microscopic identification of clusters of bacteria consistent with biofilms were present in sonicate from infected explanted prostheses, where the sonication was used to dislodge any extant attached biofilm [112]. We have documented bacterial biofilm in the aspirate, on tissue, and on bone cement originally impregnated with gentamicin in a patient with a chronic infection after total elbow arthroplasty [75]. The majority of reports imputing biofilms on orthopedic prostheses and surfaces, however, have been in *in vitro* systems, and a major argument for biofilm involvement in chronic orthopedic prosthetic joint infections remains the highly suggestive clinical features demonstrated by such infections, supported by our general understanding of the bacterial propensity to occupy available abiotic surfaces.

Nethertheless, surgeons and investigators have become increasingly interested in adjuvant techniques and technologies that minimize the risk of prosthetic joint infection, possibly by preventing adherence to and colonization of the implant in the first place. Orthopedic surgeons already routinely use antibiotic-loaded bone cement in surgery, and the use of other antibiotic-supplemented materials is under active investigation. Direct covalent attachment of an antibiotic moiety (vancomycin) to a

titanium surface has been shown to inhibit both *S. aureus* and *S. epidermidis* colonization of the modified implant material *in vitro*, despite repeated challenges and over prolonged incubation times [113]. The use of vancomycin-modified titanium implants in a rat model similarly showed evidence of reduced bacterial adherence [114]. An alternative approach to direct modification that would still provide high local concentrations of antibiosis to an implant surface is the deployment of antibiotic-loaded conforming films or sheaths for orthopedic prostheses [115].

## 5.6 Prevention and Treatment

### 5.6.1 Biofilm-Resistant Biomaterials

In previous sections we have discussed biofilm-related complications associated with considerable morbidity and mortality. Here we will discuss some of the new agents and strategies that may give more effective control over the colonization of biomaterials, and the incidence of device-related infections. Finally, we will discuss new methods for the release/delivery of these agents at the surfaces of biomaterials. But first we discuss the evaluation of novel surfaces for resistance to bacterial adhesion, and the formation of bacterial biofilms.

### 5.6.2 Testing for Antibacterial and Antibiofilm Properties of Biomaterials

There are serious concerns with the utility and information content of some of the methods used to assess the biofilm resistance of biomaterials; namely, if a biomaterial gives a positive zone of inhibition test, what does this mean? Fundamentally, this widely-used test indicates that the biomaterial contained an antibacterial agent, which was released in the moist environment of the surface of an agar plate, was still active, and the agent could prevent the planktonic bacteria deposited on the agar from growing. The major parameter operative in the test is the diffusion of the antibacterial agent through the agar or in the fluid on the agar surface, as well as the effectiveness of the agent. A very potent agent may produce a small or no zone of inhibition, if it is not released or moves slowly through agar, and a less potent agent may produce a large zone if it diffuse rapidly through agar. Shake flask test such as the ASTM E2149-10 tests, in which candidate biomaterials are suspended in a growth medium that is simultaneously inoculated with planktonic bacteria, are equally naïve. If the biomaterials release enough of an antibacterial agent in the first few minutes of the test, all of the planktonic cells in the inoculum will be killed, resulting in a situation where there are no organisms left to colonize the biomaterial. So, an antibiotic-releasing biomaterial that releases all of its antibacterial agents in a few minutes may emerge from this test as a favorable candidate, although this may not reflect a physiologically relevant timescale over which the biomaterial is expected to perform. Generally, tests are conducted over a few hours in rich medium, in an essentially "closed" system, while *in vitro* the biomaterials might be expected to perform over days, or even years, in open systems where leached active agents can diffuse away. Therefore, such conventional tests are largely inappropriate, and may lead to the development of biomaterials that fail in biofilm resistance in animal and clinical trials.

More appropriate tests are ones that mimic the conditions in the systems in which the biomaterial is targeted for use. If the biomaterial will be subjected to flow or fluid exchange, the test should include these parameters. If the biomaterial will be used in a body fluid, such as blood or urine, an accurate simulation of that fluid should be used in the test, and the bacteria supplying the challenge should be adapted to the fluid. One of the pitfalls of laboratory testing is to base a culture medium on the relevant physiological chemistry, but then to add rich components, such as yeast or amino acid extracts, to stimulate growth to allow for rapid testing, typically over a 24-hour period or less. The concept is valid, that is, to accelerate natural processes; however, as discussed earlier, a rich medium and much higher concentrations of bacteria than might be physiologically relevant might also unintentionally interfere with surface chemistry and product efficacy.

Flow cells are useful for quantifying the rates of bacterial attachment and biofilm formation under a defined fluid shear stress, because they allow direct observation of the surface which can be monitored continuously. Confocal microscopy is particularly suited for biofilm assays since it allows the

examination of living hydrated preparations, microbial cells that adhere to the biomaterial surface can be easily visualized (Figure 5.4). If the adherent cells survive, they will initiate biofilm formation, and the adherent cells will gradually form matrix-enclosed structured biofilm cell clusters (Figure 5.4, bottom panel), within which the cells will be separated by EPS. The formation of biofilms requires that the adherent cells must be alive, so the observation of live biofilm on surfaces that make antibacterial and antibiofilm claims could have unfortunate clinical consequences [116].

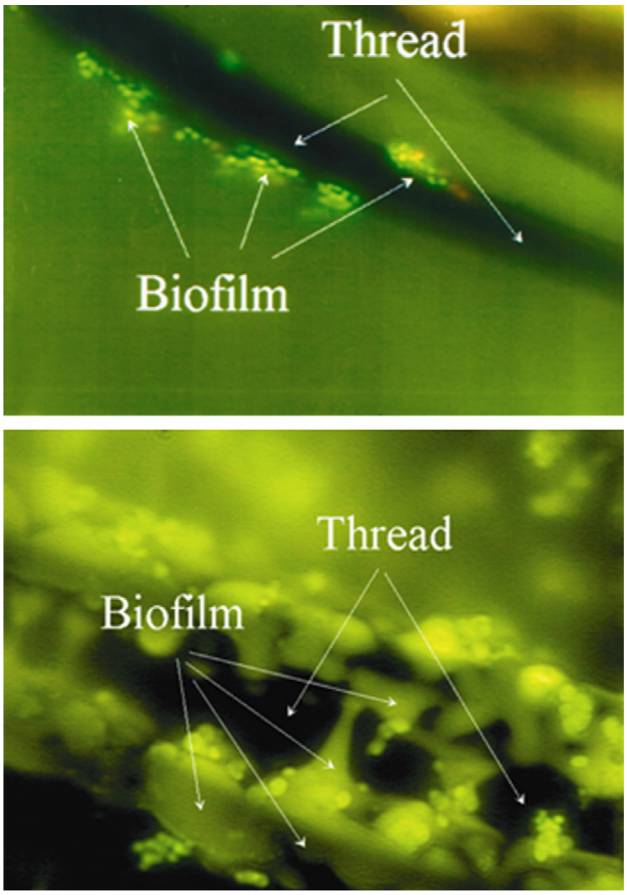



**Figure 5.4** Confocal microscope images of unfixed biofilms formed on individual fibers of the cloth-like material used to form the sewing cuffs of mechanical heart valves. The biofilms formed when fibers of a silver-coated medical device were exposed to planktonic cells of *Staphylococcus epidermidis*, in a flow cell [116] after 24 (top panel) and 48 hours (bottom panel). Staining with the Live/Dead® BacLight™ probe showed that many cells were live (green) in marked contrast to dead cells (red). After 48 hours distinct biofilm cell clusters had formed on the fibers. Diffuse staining between and around the individual cells with the green nucleic acid stain Syto9 is associated with staining of the eDNA in the EPS slime matrix.

Optimally the preference is for biomaterials which inherently resist attachment or kill colonizing bacteria, and do not retain these dead cells on the surface, i.e., prevention rather than treatment. For this reason, one of several available live/dead probes to ascertain the viability of adherent bacterial cells on biomaterials can be used. The Molecular Probes® BacLight™ Live/Dead® kit has become a standard research method for distinguishing live cells on the basis of membrane integrity; live cells stain green while dead cells stain red. In practical terms, biomaterials set up in flow cells can be exposed to realistic fluid shear containing potentially pathogenic bacteria, and the colonization of its surface can be monitored by confocal microscopy.

Although direct observation is still the "gold standard" to test the resistance of biomaterials to bacterial colonization, confocal microscopes are complex and relatively expensive. Alternatively, sessile biofilm bacteria can be removed from colonized surfaces and enumerated by standard microbiological techniques; commonly referred to as "scraping and plating." The theory behind the technique is that it first removes all biofilm from a surface, then completely breaks up the clumps of bacteria into single unassociated cells, and finally spreads various dilutions of the cells on the surface of an agar plate so that each cell gives rise to one colony when the plate is incubated. Although this technique can drastically underestimate the actual surface cell concentration (usually expressed as colony forming units/$cm^2$, CFU/$cm^2$), microscopy can be used to validate the removal and homogenization steps which can be major sources of error. First, some cells may be left on the surface by the removal method, whether it is physical scraping, sonication or another method. Second, the removed biofilm must be completely homogenized to break up clumps of bacteria to ensure that each living bacterium gives rise to one colony on the agar plate. This step is usually achieved by vortexing, sonicating or use of a homogenizer. Sonication may kill some cells, so it is therefore important to calibrate the sonication time for each type of biofilm until microscopy shows that the resultant

suspension is mostly single cells, and most of these cells are alive.

When scraping and plating are used without such validation, this method can yield data that are up to 4 logs lower than the bacterial numbers seen by direct microscopy. However, the scrape and plate method can yield accurate and consistent *in vitro* data when it is properly calibrated by microscopy, and the first biofilm method using this enumeration technique was ASTM Method E 2196-02. Darla Goeres and Marty Hamilton at the Center for Biofilm Engineering were instrumental in developing this method, and have been actively involved in developing other statistically robust experimental methods for biofilm evaluation which undoubtedly will form the basis for standard testing and claims substantiation in the anti-infective biomaterials industry. More rapid approaches include the development of conventional multi-well plates or biofilm-specific devices, used in combination with a plate reader to estimate biofilm biomass by general stains such as crystal violet staining or live/dead ratios.

### 5.6.3 Potential Agents for the Control of Microbial Colonization of Biomaterials

The strategy most commonly used in current antibacterial biomaterials is the incorporation of conventional antibiotics into the material, with the objective of killing incoming planktonic cells before they can adhere and initiate biofilm formation at the implant site [54]. The release strategy has been used for years to infuse bone cements with gentamicin, and is actively pursued with researchers showing that release of NO, antibiotics, antibodies, and silver ion ($Ag^+$) from polymers and hydroxapatite materials reduce bacterial growth on plates in culture [107,117,118]. This approach shows promise, and is being actively pursued. However, one problem is that these coatings are not synthetically flexible or covalently adhered to the surface, leading to bursts of antimicrobial activity and localized toxicity stemming from the introduction of non-resorbable coatings into the body [107].

The quandary of balancing antimicrobial efficacy against the danger of promoting bacterial resistance does not affect the large cohort of bacterial manipulation molecules that is currently moving briskly toward the biomaterials market. Some of these biofilm control molecules are specifically targeted to interfere with the bacteria's own developmental signaling pathways to affect both biofilm formation and detachment. The theory is that by influencing natural signaling processes, bacteria can be manipulated not to form biofilms or to detach by triggering a dispersal event, thus reducing the likelihood of inducing defense responses or the generation of resistant mutants. Natural antibiofilm strategies developed by marine seaweeds, which use furanones to interfere with natural biofilm signaling pathways show promise since these defense strategies have been presumably developed over millions of years of coevolution, yet still remain effective [119]. The pivotal concept is that bacteria in contact with a biomaterial would be prevented from forming a biofilm on its surface, would be "locked" in the planktonic phenotype, and would be subsequently killed by host defenses (antibodies and activated leukocytes) and any antibiotics that might be present. The best described signal pathways are the acetyl homoserine lactone (AHL) systems of some gram-negative species [120], and the autoinducer two (AI2) signaling peptides in both gram-negative and gram-positive species [121]. Of relevance to the design of biomaterials which utilize signal blocking is the finding that the effect of AI2 on biofilm is concentration dependent [122], and while very low, μM concentrations added exogenously inhibited biofilm formation, higher concentrations showed no effect or actually stimulated biofilm formation.

A third class of signaling molecule which controls biofilm formation in staphylococci is RNAIII-inhibiting peptide (RIP) which targets the RNAIII-activating protein (RAP), and has been shown to prevent infection on implant materials in rats [123]. When specific antibiotics were administered to these test animals, while the challenging bacteria were locked in the planktonic phenotype, no live cells could be recovered from the biomaterial surfaces of the surrounding tissues. More recently, attention has been focused on the secondary messenger cyclic-di-GMP, which is not secreted into the surrounding medium but is intracellular [124]. Cyclic di-GMP is influenced by nitric oxide, but as with AI2, concentration is important. At higher concentrations, NO is toxic to the cells, but at nM levels appears to act as a dispersal signal [10], thus highlighting the importance of precisely controlling

the concentration to achieve the desired effect, perhaps a difficult challenge in an *in vivo* setting. Another potential biofilm dispersal signal is the fatty acid signal *cis*-2-decenoic acid, which is produced by *P. aeruginosa* (and possibly other species) and has been shown to be active *in vitro* against a broad range of organisms, over a wide range of concentrations [11]. Such a signal makes a good candidate for antibiofilm biomaterials. However, while existence of a "universal" biofilm prevention or dispersal signal is attractive, the reality might be elusive. From an evolutionary perspective it seems unlikely that a diverse multitude of bacteria would so easily give up control of their biofilm development to a single molecule produced by competing species [125].

### 5.6.4 Delivery of Biofilm Control Agents at Biomaterial Surfaces

Killing the planktonic bacteria before they have time to initiate biofilm formation is the objective of many research programs, and this can be accomplished by three general strategies:

1. Systemic antibiotic therapy that produces bactericidal concentrations in the body fluids in the operative field;
2. Release of antibiotics and other bacterial manipulation molecules from the biomaterials to produce sustained effective concentrations of the agent in the immediate vicinity of the device;
3. Irrigation and other techniques that deliver antibiotics to the biomaterial surface after the device is installed, but before the operative wound is closed.

Many surgeons use systemic antibiotic therapy in the perioperative timeframe, and most also use this strategy in subsequent operations (including dental procedures) if a device has recently been installed and might not be fully epithelialized. The simplest manifestation of the antibiotic-releasing biomaterial strategy is a class of materials that can be "loaded," such as a sponge, by soaking them in a solution of the antibiotic in question immediately before the device is installed. In the case of filler or adhesive materials, such as poly-methylmethacrylate (PMMA), an active agent can be directly mixed prior to polymerization in the OR. Whenever a molecule is loaded into or onto a polymer there will be an immediate initial burst of diffusion in the early timeframe, followed by a tapering off over time as the concentration in this reservoir is depleted. These biomaterials are useful, but the low-level release of the agent for months or years after this effective timeframe cannot be controlled. This produces a prolonged period in which the agent is present at a sublethal concentration, near the device and sometimes in the whole body, and raises the specter of the development of acquired antibiotic resistance in many potentially dangerous bacterial species. Recently, several papers have even shown that subinhibitory concentrations of antibiotic may actually induce biofilm formation [126].

There is a similar problem with antibiotic impregnated coatings, since usually these coatings are not synthetically flexible or covalently adhered to the surface, leading to bursts of antimicrobial activity, and possibly localized toxicity stemming from the introduction of non-resorbable coatings into the body. The controlled release of active agents is one of the most problematic aspects of devices which rely on this technology for infection protection. One solution is to engineer surfaces to release active agents "on demand." Biomaterials can be coated with a molecular "skin," a self-assembled surface layer, that completely contains molecules loaded into an underlying plastic and can be temporarily deranged (by ultrasonic energy) to yield a controlled release [127]. Such a coating has been used to deliver insulin, as well as ciprofloxacin in controlled pulses in the laboratory [128]. High concentrations of these agents could be released at the surfaces of medical devices perioperatively or at any preliminary signs of device-related infection.

### 5.6.5 The Bioelectric Effect as an Adjunct to Antibiotics

Coatings which release antibiotics at the site of potential infection have the advantage over systemically administered antibiotics, in that they can achieve much higher local concentrations and avoid toxicity effects, since the overall amount of antibiotic can be relatively small. However, due to difficulties with the controlled release and surfaces which are challenging to modify, it is desirable to be able to sensitize bacteria to conventional antibiotics. As discussed previously, one approach is to

use signals in an attempt to induce a planktonic phenotype through cell signaling. Another promising area is to achieve planktonic-like antibiotic sensitivity by applying low voltage electrical fields [129]. The so called "bioelectric effect" has recently shown promise at treating *S. epidermidis* chronic foreign-body osteomyelitis in a rabbit model [130]; however, the same group also reports that the efficacy is dependant on the pathogen and the class of antibiotic [131].

#### 5.6.5.1 Biomaterials that Resist Bacterial Attachment and Biofilm Formation

An alternative approach to killing posited by the Association of Bone and Joint Surgeons Musculoskeletal Infection Workshop is to design coatings for implant surfaces that resist bacterial attachment. Most of the work in the literature has focused on the model systems of self-assembled monolayers (SAMs) on gold or polymeric coatings [132,133]. SAMs have many advantages as a flexible platform over macromolecules (Figure 5.5). One major advantage of SAMs is their ease in engineering interfacial structures at the molecular level, due to the fact that they form defined structures on the surface and therefore present functional tail groups in a consistent, active manner [134–136]. They are also synthetically flexible, which allows for the modification of the tail group for prevention of non-specific adsorption of cells. However, the SAM technology developed in model systems is not necessarily directly transferable to metal oxide systems used in biomaterials, and coating the surface with gold is not always practical. Alkanethiols form SAMs on gold and other noble metals, such as silver or copper, but not on oxide surfaces, such as those used in biomaterials [137]. Functional groups can be immobilized through basic organic chemistry at the tail groups of the monolayer or by synthesizing molecules with functional tail groups and forming a mixed SAM that includes multiple functionalities. Delivering multiple, active groups in a single polymeric coating is synthetically challenging [138]. Polymeric coatings that are peptidomimetic have been successful in the laboratory at resisting bacteria adhesion, and could also be used as platforms for further functionalization [106,136,139]. As a result, new chemistry for non-specific bacterial resistance on metal oxide surfaces must be developed that is appropriate for orthopedic implant materials.

The underlying mechanism by which SAMs render surfaces inert is under study. Many tail groups have been employed to render gold surfaces inert to protein and non-specific cellular adhesion. SAMs techniques are also being applied to more relevant metals used in surgery. The technique has been used to tether gentamicin and vancomycin to 316L stainless steel, which retarded biofilm formation for up to 48 hours [140]. While oligo-ethylene glycol has been the standard by which inert surfaces are measured, and is the only SAM system used to mitigate bacterial adhesion, other groups such as mannitol, maltose, taurin [141], and tertiary amine oxides have rendered gold surfaces inert to protein and cellular adhesion. A survey of literature suggests that formation of an inert surface utilizing self-assembled monolayers is a combination of many parameters including substrate wettability, tail functionality, lateral packing density, conformational flexibility of the molecule, structure of water on the surface, and kosmotropicity (the degree to which solutes stabilize water-to-water interactions, and hence affect molecular interactions) [141]. The underlying reason for their inert effect on surfaces

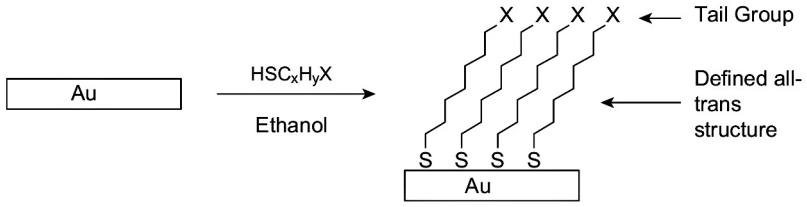



**Figure 5.5** Self-assembled monolayers form spontaneously on a surface placed in a solution. They consist of organic monomers with reactive head groups and exposed tail groups. Tail groups can be designed to accomplish a task, such as cell resistance, or to participate in chemical reaction for further functionalization of the surface. SAMs on gold form defined structures in which all of the carbon–carbon bonds are oriented "trans" to one another (at an angle of 109.5°). These monolayers are considered ordered.

may be due to their ability to order surrounding water molecules, excluding them from the surface and rendering the surface inert to protein adsorption. However, the molecular basis for the resistance of some surfaces continues to be debated, in part due to conflicting data in the literature, with some favoring the hydrophobic effect as the driving force [142], while others disagree. Due to the large interdependent, complex interactions between cells and organically modified surfaces, the understanding and harnessing of the phenomenon of controlling adhesion on oxide surfaces has been difficult.

Biomimicry or bioinspiration is another approach used by engineers in the design of inherently nonfouling surfaces [125]. Nano-textured patterns found on the skins of sharks have been found to resist initial bacterial attachment in laboratory experiments. It is thought that this approach, originally designed as a control for marine biofouling [143], might be utilized for medical devices [144], illustrating the importance of interdisciplinary collaboration and thinking in the area of biomaterials design. A similar approach was used in the development of the natural and synthetic furanone cell signal blockers, which were first discovered to play a role in the resistance of red algae to marine biofouling, and are now being developed for infection protection of medical devices [119].

## 5.7 Conclusions

Undoubtedly, medical devices will be increasingly used in patient management, whether temporarily or intermittently for fluids exchange, as in the case of catheters, or as permanent implants to repair loss of function, as is the case for orthopedic joints and cardiovascular stents. What is also ensured is that as more devices are used bacteria will take advantage of an access site into the body and with the convenience of an abiotic surface to colonize the spread of antibiotic resistant strains may likely increase. For permanent implants, overall rates of infection may drop as data show that there is an inverse correlation with surgical-site infection and numbers of procedures performed per institution and surgeon. However, the overall number of patients with surgical-site infections will inevitably rise, as more and more people undergo such surgeries, whether out of absolute necessity or to improve quality of life. To a certain extent, infection associated with permanent implants can be minimized through the controlled environment of the OR and the ever-increasing experience of the surgeon. Infections associated with catheters might present a greater challenge, since they require frequent manipulations and are usually managed in less controlled environments.

A challenge to biomaterials engineers and surface scientists is to design and develop materials for the manufacture of devices which are functional, biocompatible, resistant to infection, and do not add to the development of resistant strains. While 100% biofilm-proof surfaces may be a long way off, we at least now know our enemy much more intimately than even less than a decade ago. Observational studies of biofilms have begun to reveal the true complexities and coordination that pathogenic bacteria are capable of, and molecular techniques are revealing the mechanisms of biofilm development and dispersal, as well as revealing the full extent of diversity of biofilm populations, including the genetic and phenotypic divergence that develops in biofilms formed from a single strain in only a matter of hours to days. The challenge is formidable, but the rewards are great, with the potential to improve the quality of life of millions of people. To quote from *The Art of War* written by Sun Tzu in the 6th century: "So it is said that if you know your enemies and know yourself, you can win a hundred battles without a single loss. If you only know yourself, but not your opponent, you may win or may lose. If you know neither yourself nor your enemy, you will always endanger yourself." With our current understanding of biofilms we are only just beginning to know the enemy with respect to device-related biofilm infections. Even if the "biofilm-proof" surface proves elusive, the challenge is to effectively utilize what we have learned about biofilm biology to engineer playing fields which tip the balance for the race to the surface in favor of ourselves and away from the bacteria.

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# 6 Adhesives for Medical and Dental Applications

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This chapter focuses on adhesives used in direct physiological contact in dental and medical procedures. Activity in both areas has been quite extensive outside the United States for decades. In contrast, adhesive use in medical devices, patches, and plasters has been ongoing in the United States for a long time. In the case of medical devices, adhesion is concerned with the joining of materials such as plastics, elastomers, textiles, metals, and ceramics, which are examined in other chapters of the present volume and are covered in various references [1–6], The coverage of this chapter is devoted to applications where adhesives are in direct contact with tissues and other live organs.

## 6.1 Introduction

The use of adhesives in medicine and dentistry is often critical and functional and with little visibility to patients. Infant immunization, flu shots, restorative dental fillings, blood transfusions, heart bypass surgery, urological surgery, anesthetic administration, intravenous drug delivery, and numerous other medical procedures would not be possible today if not for advanced adhesives. The modern adhesives are used to assemble thousands of medical devices around the world, or they are used in direct physiological interactive modes [7].

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There are different types of commercially available tissue adhesives, classified into three categories: natural or biological, synthetic and semisynthetic, and biomimetic adhesives. The biological tissue adhesives such as fibrin glues and collagen are quite effective in select applications. Their drawbacks are high cost and limited availability. Biomimetic adhesives are based on adhesion of algae to wet surface and the Gecko's ability "to stick" its paws to surfaces [8].

## 6.2 Natural Adhesives

Surgical adhesives and sealants based on natural polymers, cross-linked via biochemical reactions, offer in general a more biocompatible alternative to synthetic glues. The main biological adhesives are based on fibrin and collagen. Gelatin and polysaccharide-based adhesives are newer adhesive classes which have attracted attention and research. Fibrin sealants are made from a number of components produced from pooled human plasma that enables the adhesive to mimic the final stages of blood clotting. The most basic fibrin sealants consist of combinations of thrombin and fibrinogen. Collagen-based adhesives adsorb blood and coagulation products on their fibers, trapping them in the interstices and adhering well to the wound. This biopolymer also induces platelet adhesion and aggregation, and activates coagulation factors [9].

## 6.3 Synthetic and Semisynthetic Adhesives

Semisynthetic and synthetic surgical adhesives include gelatine–resorcinol–formaldehyde (GRF), urethane prepolymers, and cyanoacrylates. These adhesives have some shortcomings such as low bioabsortion and metabolic rates, cytotoxicity (low biocompatibility), low adherence to wet surfaces and chronic inflammation induced by the release of formaldehyde from GRF, and cyanoacrylate polymers and aromatic diamine from aromatic polyurethanes [10].

## 6.4 Cyanoacrylic Adhesives

These so-called *wonder* adhesives are marginally thermosetting materials and were first introduced commercially by Eastman Chemicals. They form strong thermosetting bonds between many materials without heat or an added catalyst. They are particularly useful in bonding metal to nonmetal. Lap-shear strengths of 13.7 MPa have been reported. However, the resistance capability of these adhesives to moisture is still somewhat low [11]. These materials set very quickly when squeezed out to thin film between many types of adherends.

A cyanoacrylate adhesive is a relatively rapid curing adhesive also from the acrylic family tree, but has a completely different cure system. Cyanoacrylate monomer (Figure 6.1) is made from

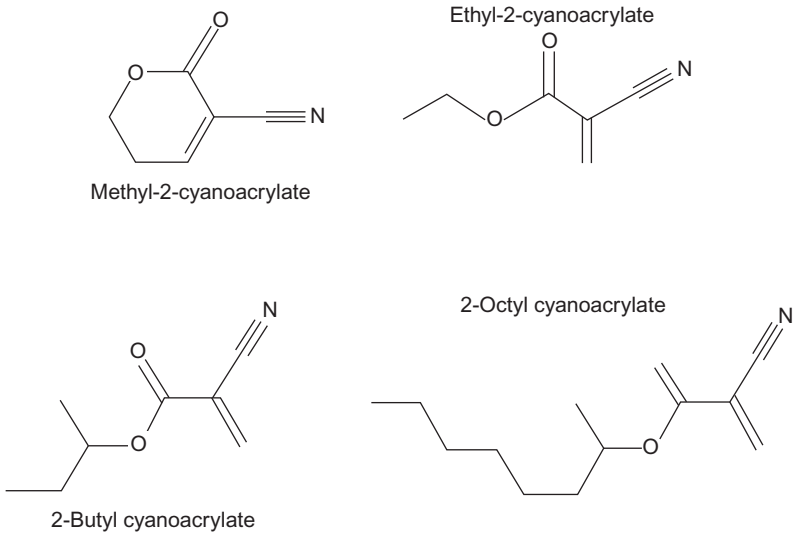



**Figure 6.1** Structures of some cyanoacrylate monomers.

a complex chemical process. The monomer produces a very reactive polymerization. The reaction or polymerization process is stabilized and the monomer is kept in the liquid state by the addition of a small amount of an acid stabilizer material [12].

When a drop of cyanoacrylate adhesive is put on the surface of a part, the acid stabilizer molecules react with the water molecules present on the surface of the part from the relative humidity in the air. The reaction of the water and acid causes the acid stabilizer to be neutralized. The cyanoacrylate molecules then react with each other and form polymer chains without cross-linking [12].

Cyanoacrylate adhesives undergo anionic polymerization in the presence of a weak base, such as water, and are stabilized through the addition of a weak acid. The stabilizer is usually in the form of a weak acidic gas such as $SO_2$, NO, or $BF_3$. An essential function of the stabilizer is to prevent polymerization in the container, which is usually made of polyethylene. When the adhesive contacts a slightly alkaline surface, trace amounts of adsorbed water or hydroxide ions ($OH^-$) that are present on the substrate's surface neutralize the acidic stabilizer in the adhesive, resulting in rapid polymerization as shown in Figure 6.2.

The amount of stabilizer molecules in cyanoacrylate is very small—measured in parts per million—and very little moisture molecules are required to cause rapid polymerization. Cyanoacrylates begin to form polymer chains immediately on contact with the water vapor on the surface of the part. If parts are moved during initial contact, the polymerization process and polymer chains are stopped. The process must start again at a new catalyzed site [12].

Cyanoacrylates are very rapid in curing and provide high bond strengths on plastic and rubber materials. These adhesives are versatile which renders them highly useful in all industries. Some of the larger application areas are in electronics for printed circuit board wires and components, and in medical technology for disposable plastic medical devices. Other applications include toy, small and large appliance, automotive, and cosmetic packaging. Applications exist in all industries for repair of all rubber and plastic parts as well as some metal parts. The consumer market is a large volume user of cyanoacrylate adhesives for repairing everything in the home from wallpaper tears to broken toys to torn and false fingernails.

Cyanoacrylate adhesive can be made from different acrylate monomers, such as methyl, ethyl, butyl, and isopropyl. These molecules differ in size and adhesives made from them exhibit different physical properties. Methyl is the smallest molecule and seems to work best on metal and rubber parts, whereas ethyl works best on plastic parts. Many modifications can be made to the monomers to alter or improve their properties as adhesives. They can be toughened with rubber or formulated to have low odor, resistance to thermal cycling, or less sensitivity to surface conditions, which tend to stabilize the adhesive and slow down the cure [12].

As with other acrylics, the monomers are liquids of low viscosity that polymerize very easily in the presence of a slightly basic surface containing adsorbed water. Polymerization is ionic. The resulting polymers have different properties, depending on the alkyl group. The methyl ester (methyl-2-cyanoacrylate) is the most commonly used compound. This material is formulated with a thickener (to prevent starved joints from being formed) and a plasticizer to make it more resistant to shock loading. The thickener can be a polymer of the same

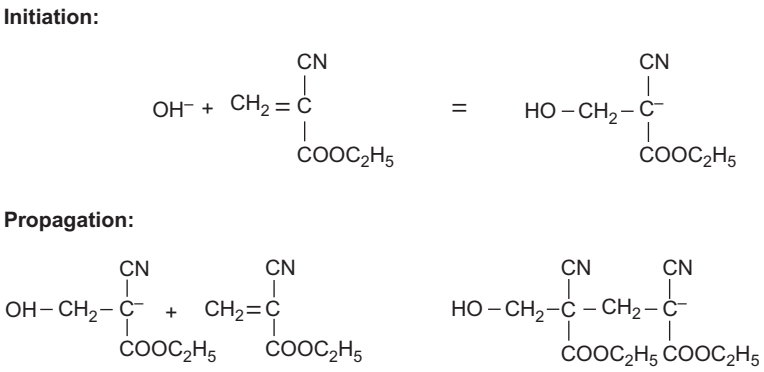



**Figure 6.2** Polymerization reaction of cyanoacrylate adhesives [13].

monomer. An essential feature is a stabilizer to prevent polymerization in the adhesive container, which is usually made of polyethylene [14].

The polymerization of cyanoacrylates is inhibited by low pH (high acidity), thus it does not proceed satisfactorily on acid surfaces such as wood. The suggested incorporation of poly-*N*-vinyl pyridine or polyethyleneamine, or even simple amines, presumably serves the dual purpose of thickening the liquid and increasing the pH.

Adhesives based on higher homologs than the methyl form have been in use for a number of years. These include the ethyl, propyl, and butyl esters of cyanoacrylic acid. Moisture resistance of the methyl-2-cyanoacrylate is only fair. Ethyl cyanoacrylate has been shown to form stronger bonds than the methyl form between several different types of plastic surfaces. The higher homologs, however, generally do not form bonds as strongly as the methyl form. The most important step in the successful application of a cyanoacrylate adhesive is the application of a thin adhesive film between two well-mated surfaces. The thinner the film is, the faster the rate of bond formation, and the higher the bond strength. Bond strength is dependent on proper surface preparation.

In general, aging properties of the cyanoacrylates are good. Rubber-to-rubber and rubber-to-metal bonds typically have endured outdoor weathering for over 7 years. These bonds have also passed stringent water-immersion and salt-spray tests. Plastic-to-plastic and plastic-to-rubber bonds have aged satisfactorily for 3–5 years. Metal-to-metal bonds generally age rather poorly, except under special conditions where the minimal glue line is exposed to moisture. Solvent resistance is also generally satisfactory. Dilute alkaline solutions weaken the bond considerably, while dilute acid solutions weaken it to a lesser degree. Impact resistance is generally poor because of the thin, inflexible bond.

This is especially true with two rigid substrates, such as metals. The methyl cyanoacrylate bond melts at approximately 165°C. Prolonged exposure to temperatures in this range results in a gradual but permanent breakdown of the bond. Generally, the upper temperature limit for continuous exposure is about 77°C. At low temperatures, bonds remain intact at least down to −54°C. Grades of cyanoacrylates with specialized improved properties are available. For example, one grade has improved heat resistance to 246°C, high viscosity, and very fast setting ability [15].

Among the advantages of the cyanoacrylates are the following (see also Table 6.1):

- Very fast bond formation
- High bond strength with thin glue line
- No added catalyst or mixing needed
- No solvent to evaporate during bond formation
- Contact pressure is usually sufficient
- Very low shrinkage
- Economical because of minute quantities needed, although relatively expensive.

**Table 6.1** Benefits and Limitation of Cyanoacrylate Adhesives [13]

| Benefits | Limitations |
|---|---|
| • Excellent adhesion to a wide variety of substrates<br>• Substrate variety<br>• Simple cure mechanism<br>• Rapid strength development<br>• High strength possible on polyolefins and fluorocarbons using primers<br>• Available in USP Class VI compliant formulations<br>• High shear strength<br>• No measuring or mixing required | • Blooming/frosting<br>• Difficult to cure fillet or exposed liquid adhesive without activator<br>• Limited gap cure<br>• Stress cracking could occur to some plastics<br>• Soluble in polar solvents<br>• Thermal and chemical stability not as good as with certain other structural adhesives<br>• Unmodified formulations have low peel **and** impact strengths<br>• Relatively high materials cost<br>• Pungent odor associated with early formulations |

The Loctite Corporation offers a rubber-toughened cyanoacrylate adhesive, such as 380 Black Max®, which is reported to achieve improved strength, resiliency, and fast fixturing at the expense of a rather limited shelf life (about 4 months) [16]. This adhesive cures to fixturing strength in 2 min in the case of most substrates. It reaches to 80% strength in 24 h and to full strength in 72 h (Table 6.2). On aluminum, its average strength is 16.6 MPa after full room temperature cure, vs. 6.2 MPa for a typical epoxy adhesive and 3.8 MPa for "instant" adhesives. After 240 h of tensile-shear thermal-cycling tests, this adhesive improved its strength to 21.3 MPa for "instant" adhesive. Loctite claims that this adhesive is consistently 20 times stronger than epoxies on aluminum, 10 times stronger on neoprene, 4 times stronger on steel, and 2 times stronger on epoxy/glass after the tests. This adhesive is designed for assembly-line cure (Table 6.3) [17].

### 6.4.1 Medical Grade Cyanoacrylate Adhesives

*Butyl cyanoacrylate* is an intermediate-length cyanoacrylate (Figure 6.1) adhesive that was the first product to be broadly used for closing cutaneous wounds. This compound has been approved for use in Europe and Canada as Histoacryl® Blue (trademark of Aesculap, Inc.) and GluStitch® (trademark of GluStitch, Inc.) for nearly 40 years. It had not been approved by the US Food and Drug Administration (FDA) for use in the United States for a long time. In Europe, Canada, and Japan, it

**Table 6.2** Typical Performance of Cured Loctite 380 Cyanoacrylate Adhesive [16]

| *Adhesive properties* | | |
|---|---|---|
| After 24 h at 22°C | | |
| Lap shear strength, ISO 4587 | | |
| Steel (grit-blasted) | $N/mm^2$ (psi) | 26 (3,770) |
| Aluminum (etched) | $N/mm^2$ (psi) | 18 (2,610) |
| ABS | $N/mm^2$ (psi) | >6 (>870) |
| PVC | $N/mm^2$ (psi) | >4 (>580) |
| Polycarbonate | $N/mm^2$ (psi) | >5 (>725) |
| Phenolic | $N/mm^2$ (psi) | 10 (1,450) |
| Neoprene | $N/mm^2$ (psi) | >10 (>1,450) |
| Nitrile | $N/mm^2$ (psi) | >10 (>1,450) |
| Tensile strength, ISO 6922 | | |
| Steel (grit-blasted) | $N/mm^2$ (psi) | 18.5 (2700) |
| After 48 h at 22°C | | |
| Lap shear strength, ISO 4587 | | |
| Steel (grit-blasted) | $N/mm^2$ (psi) | $\geq 17.2^{LMS}$ (≥2,495) |
| Cured for 24 h at 22°C, followed by 24 h at 121°C, tested at 121°C | | |
| Lap shear strength, ISO 4587 | | |
| Steel (grit-blasted) | $N/mm^2$ (psi) | $\geq 6.9^{LMS}$ (≥1,000) |
| Cured for 24 h at 22°C, followed by 24 h at 121°C, tested at 22°C | | |
| Lap shear strength, ISO 4587 | | |
| Steel (grit-blasted) | $N/mm^2$ (psi) | $\geq 19.3^{LMS}$ (≥2,800) |

*LMS, Loctite material specification.*

**Table 6.3** Bond Strength of Methyl or Ethyl Cyanoacrylate Adhesive as a Function of Substrate and Time [13]

| Joint Substrates | Age of Bond | Shear Strength, psi |
|---|---|---|
| Steel–steel | 10 min | 1920 |
| | 48 h | 3300 |
| Aluminum–aluminum | 10 min | 1480 |
| | 48 h | 2270 |
| Butyl rubber–butyl rubber | 10 min | 150[a] |
| SBR rubber–SBR rubber | 10 min | 130 |
| Neoprene–neoprene | 10 min | 100[a] |
| SBR rubber–phenolic | 10 min | 110[a] |
| Phenolic–phenolic | 10 min | 930[a] |
| | 48 h | 940[a] |
| Phenolic–aluminum | 10 min | 650 |
| | 48 h | 920[a] |
| Aluminum–nylon | 10 min | 500 |
| | 48 h | 950 |
| Nylon–nylon | 10 min | 330 |
| | 48 h | 600 |
| Acrylic–acrylic | 10 min | 810[a] |
| | 48 h | 790[a] |
| ABS–ABS | 10 min | 640[a] |
| | 48 h | 710[a] |
| Polystyrene–polystyrene | 10 min | 330[a] |
| Polycarbonate–polycarbonate | 10 min | 790 |
| | 48 h | 950[a] |
| Polyester glass–polyester glass | 10 min | 680 |

[a]*Substrate failure.*

has been used for middle ear procedures, to close cerebrospinal leaks, to repair incisions and lacerations, and to affix skin since the 1970s [18–24].

Short-chain cyanoacrylates (methyl, ethyl) are toxic to tissue; this is not the case with butyl cyanoacrylate when applied topically. In an experimental model of incision wound healing in hamsters, butyl cyanoacrylate resulted in less inflammation than 4.0 silk sutures on histologic assessment [19]. Randomized clinical trials were conducted in a study of just under 100 patients with facial lacerations suitable for tissue adhesive closure. The patients underwent closure using either butyl cyanoacrylate or octyl-2-cyanoacrylate (2-OCA), and results failed to reveal a difference in cosmetic result after 3 months. The ratings were from photographs by a plastic surgeon using a visual analog scale [25]. A toxic reaction was prevented by taking precaution to prevent the adhesive from being trapped in the wound itself might cause [26]. Because of these concerns, *n*-butylcyanoacrylate has been recently approved by FDA for use in the United States. In 2010, B. Braun manufactured Histoacryl that consists of *n*-butyl-2 cyanoacrylate. This sterile, liquid topical skin adhesive is available in two formulations: Histoacryl and Histoacryl Blue [27].

2-OCA has a longer chain than butyl cyanoacrylate. It was approved by the FDA for use in the United States in August 1998 for certain types of laceration. Its applications have been expanded and are now marketed as Dermabond® (a trademark of Ethicon, Inc., a Johnson & Johnson Company) topical skin adhesive for closure of lacerations and incisions in place of sutures or staples. Later on, a 2-OCA formulated for greater flexibility, Liquid Bandage, was approved for use in the over-the-counter market in the United States for the treatment of minor cuts and abrasions [28].

The longer side chain gives 2-OCA several potential advantages over shorter chain cyanoacrylates. 2-OCA, for instance, produces a stronger bond and is more flexible than butyl cyanoacrylate. It has four times higher volumetric break strength than butyl cyanoacrylate [29]. The increased strength and flexibility and reduced risk of tissue toxicity, 2-OCA is now widely used in the United States for closure of wounds. It is currently one of the best selling bandage brands in the United States.

Here is an excerpt of a 2004 but useful review of the tissue adhesives by Singer and Thode [30]: "Octylcyanoacrylate is a medical grade topical tissue adhesive that has been approved for closing surgical incisions and traumatic lacerations. We reviewed animal and human studies that evaluated its use for a variety of surgical indications and

specialties. We also performed a metaanalysis of all clinical trials using octylcyanoacrylate. Data sources: Animal and human studies published in peer-reviewed articles as well as published abstracts. A search of Medline was performed using the MESH terms: tissue adhesives, cyanoacrylates, and octylcyanoacrylate. The current review and metaanalysis demonstrate that octylcyanoacrylate can be used successfully in a wide variety of clinical and surgical settings for multiple types of wounds covering most of the surface of the human body. Prior knowledge of the limitations and technical aspects specific to wound closure with octylcyanoacrylate as well as appropriate wound selection and preparation will help ensure optimal results."

### 6.4.2 Commercial Grades of Cyanoacrylate Tissue Adhesives

Some of the manufacturers of cyanoacrylate tissue adhesives are listed below:

**Company Name**: AESCULAP, Inc.

**Address**: 3773 CORPORATE PKWY

Center Valley, PA 18034

**Product**: TISSUE ADHESIVE

**Proprietary Device Name**: HISTOACRYL® & HISTOACRYL BLUE® TOPICAL SKIN ADHESIVE

**Web site**: www.aesculapusa.com

**Company Name**: CLOSURE MEDICAL CORP.

**Address**: 5250 GREENS DAIRY RD.

Raleigh, NC 27616

**Product**: TOPICAL TISSUE ADHESIVE

**Proprietary Device Name**: DERMABOND® TOPICAL SKIN ADHESIVE

**Website**: www.closuremed.com

**Company Name**: ETHICON, INC.

**Address**: Route 22 West

Somerville, NJ 08876

**Product**: TISSUE ADHESIVE

**Proprietary Device Name**: DERMABOND® TOPICAL SKIN ADHESIVE

**Website**: www.impactfs.com

**Company Name**: GEM S. r. l.

**Address**: Via dei Campi, 2—PO Box 427

Viareggio, LU, 55049, ITALY

**Product**: TISSUE ADHESIVE

**Proprietary Device Name**: Glubran2®

**Website**: www.gemitaly.it/web/en/glubran2.html

**Company Name**: HENKEL IRELAND LIMITED

ELECTRONIC AND BIOMEDICAL FACILITY

**Address**: Whitestown, Dublin, 24 EI

**Product**: TISSUE ADHESIVE

**Proprietary Device Name**: INDERMIL® TISSUE ADHESIVE

**Website**: www.henkel.com/cps/rde/xchg/henkel_com/hs.xsl/indermil-17865.htm?automaticTransfer = 3

**Company Name**: MEDISAV SERVICES, INC.

**Address**: 56 ELSON ST., #B

Markham, Ontario, L3S 1Y7 CA

**Product**: TISSUE ADHESIVE FOR REPAIR OF MINOR CUTS & LACERATIONS

**Proprietary Device Name**: EPIDERMGLU®

**Website**: http://www.ethicon.com

**Company Name**: PRAXIS, LLC.

**Address**: 1110 WASHINGTON ST.

Holliston, MA 01746

**Product**: TISSUE ADHESIVE

**Proprietary Device Name**: PRAXI STAT®

**Website**:

**Company Name**: SKINSTITCH CORP.

**Address**: 89 OLD RIVER RD.

P.O. BOX 179

Massena, NY 13662

**Product**: TISSUE ADHESIVE FOR REPAIR OF MINOR CUTS & LACERATIONS

**Proprietary Device Name**: SKINSTITCH™

**Website**: www.skinstitch.com

Cyanoacrylate tissue adhesives can be used vice sutures in a number of surgical procedures

contributing to make the recovery easier and more comfortable [31]. They include:

1. OB/GYN surgeries, such as C-sections where excellent cosmetic outcomes are desired [32], as well as the ability for new mothers to shower immediately and move about without the discomfort of staples or sutures [33].
2. General surgeries, such as many abdominal surgeries, back surgeries, and routine surgeries of the face, neck, arms, and legs [34].
3. Cardiovascular surgeries that may involve incisions in the arm or leg as well as the chest [34].
4. Cosmetic surgery, particularly facial incisions, on areas such as the eyelid and the nose where suture removal can be painful. No stitches means no "suture marks" [35].
5. Sports surgery, involving lacerations that may need immediate attention, to help players to return to the game [36].

Dermabond (2-octylcyanoacrylate by Ethicon, a Johnson & Johnson Company), the latest in cyanoacrylate technology, has less toxicity and almost four times the strength of *N*-butyl-2-cyanoacrylate. Special plasticizers have been added to the formula to provide flexibility. It is marketed to replace sutures that are 5-0 or smaller in diameter for incision or laceration repair. Patients, especially children, readily accept the idea of being "glued" over traditional methods of repair [37]. This adhesive reaches maximum bonding strength within 2.5 min and is equivalent in strength to healed tissue at 7 days post-repair [38].

Dermabond (2-octylcyanoacrylate) has been found to create [39] a microbial barrier over the wound and protect against the penetration of the following bacteria, commonly associated with surgical site infections:

*Staphylococcus aureus* (*S. aureus*)

*Staphylococcus epidermidis*

*Enterococcus faecium*

*Escherichia coli* (*E. coli*)

*Pseudomonas aeruginosa*.

Dermabond adhesives [39]:

1. Provide the strength of healed tissue at 7 days in less than 3 min.
2. Offer three-dimensional strength that is at least three times stronger than *n*-butyl cyanoacrylate, another leading type of adhesive.
3. Help protect and seal out bacteria that can lead to infection.
4. Promote a moist wound-healing environment that has been shown to speed the rate of epithelialization.
5. Cause less pain and relieve anxiety over sutures, particularly important for pediatric patients; have been found to be as safe and effective as conventional sutures with equivalent cosmetic results.
6. Save valuable clinical time in that they can be applied more quickly than sutures, eliminating the need for the following process:
   a. Injecting a local anesthetic into the wound
   b. Waiting for the anesthetic to numb the area
   c. Closing the wound with sutures
   d. Placing a dressing over the wound.
7. Slough off naturally over time (usually 5–10 days), eliminating the need for a follow-up visit to remove stitches.

## 6.5 Test Methods to Characterize Strength of Tissue Adhesives

The following four test methods are used [40] to provide a means for comparison of the adhesive strengths of tissue adhesives for use as surgical adhesives or sealants on soft tissue. These or equivalent methods may be used in support of the bench testing outlined above:

*ASTM F2255-05* Standard Test Method for Strength Properties of Tissue Adhesives in Lap-Shear by Tension Loading

*ASTM F2256-05* Standard Test Method for Strength Properties of Tissue Adhesives in T-Peel by Tension Loading

*ASTM F2258-05* Standard Test Method for Strength Properties of Tissue Adhesives in Tension

*ASTM F2458-05* Standard Test Method for Wound Closure Strength in Tissue Adhesives and Sealants.

## 6.6 Medical and Dental Applications of Adhesives

The use of adhesives in medical applications has been restricted, for some time, to the manufacture of self-adhesive bandages (plasters, self-adhesive strips of fabric, etc.). The first pressure sensitive adhesives used for this were based on natural rubber, decades ago. This first usage was later partially superseded by synthetic rubbers (e.g., polyisoprene, polyisobutylene). In the mid-twentieth century, pressure sensitive adhesives based on polyacrylic acid esters gained significance in general use and in the composition of bandage materials [41].

Today, adhesives are used in various areas of medicine, replacing traditional methods with "friendlier" processes. Often, stitches can be avoided by applying special cyanoacrylate adhesives to quickly close skin wounds. An advantage of this method is that the whole wound can be covered, thereby largely suppressing secondary bleeding and the risk of infection. Cyanoacrylic acid butyl ester is normally preferred over the methyl and ethyl esters because it cures more slowly and the polymerization produces less heat. Cyanoacrylic also causes less tissue irritation. By and large, this adhesive is only used for relatively small wounds, and it is occasionally used in vascular surgery.

Consider the transdermal patches where the drug delivery mechanism to the bloodstream is through the skin: adhesives enable a more efficient method of drug delivery, rather than prescribing a high-ingestion dosage (which is subsequently flushed out of the body by the liver). Transdermal patch technology is highly effective because the adhesive that sticks the patch to the skin—made of products of chemistry like acrylic, acrylic-rubber hybrid, polyisobutylene, and styrenic rubber solution—actually controls the rate at which the drug enters the body. This mechanism ensures that the drug dosage is continuously and evenly administered throughout the day, without the spikes and falls associated with medicines administered orally [41].

The applications of these patches are numerous, including smoke cessation and hormone replacement, and cardiovascular aid, such as nitroglycerin delivery, is commonplace. New transdermal patches hit the market every day, with more items like pain cessation becoming a reality. Other innovative products, such as foot care and cosmetic patches, and nasal dilator strips, have hit the market in recent years. Their existence is possible because of the unique functional properties of the pressure sensitive adhesives integral to the product [41].

One of the newest bio-adhesives on the market enables drugs to be delivered through the inside of the mouth, nasal passages, and other mucus membranes, rather than only being administered through skin. The newest bio-adhesives adhere extremely well to the soft, wet mucus membranes of the body because the adhesives are made from starch-poly acrylic acid blends, which then completely erode and disappear. Drug makers are able to put their medicine into tablet, film, or powder form, and the patient is able to attach the product directly to a mucus membrane, providing a means for controlled delivery of drugs to specific areas of the body or systemically (throughout the body) [41].

Fibrin, which is made from fibrinogen, a soluble protein recovered from blood, is a key sealing agent in heart surgery. It has a hemostatic effect, meaning that it is an antihemorrhagic agent: a substance that promotes hemostasis, the halting of blood flow. Fibrin is much gentler on the body tissues when compared to cyanoacrylates. The disadvantage of fibrin is that before use it must undergo a special treatment in order to prevent microbial infection.

The use of methacrylate-based adhesives has been a great success in orthopedics for the purpose of anchoring hip socket implants to the bone. There are currently no other types of adhesive used for this application. The adhesive products comprise (a) a powder component (a mixture of polymethyl methacrylate (PMMA) and a polymerization initiator) and (b) a liquid component (whose main components are methyl methacrylate (MMA) and a polymerization accelerator). In spite of considerable stress that these adhesives exert on bone and tissue due to intense heat development, hip and knee implants anchored using this adhesive are in 90% of cases functional for 15 years [41].

In dentistry, restorative fillings based on UV curing acrylates have largely replaced traditional filling materials such as amalgams. The products have a long pot life or *open time* (the period during which they can be used after mixing) and bond in just a minute or so when exposed to UV light.

There are numerous orthodontic appliances or devices that are used to correct dental conditions in

minor and adult patients. Most of these appliances involve use of adhesives. The advent of adhesive dentistry and direct bonding of orthodontic brackets is a dramatic event that has changed the course of clinical orthodontics. Product development and technological advances have occurred quite rapidly. This rapidity has, at times, complicated the decision-making process for practitioners [42].

### 6.6.1 Adhesives for Skin Closure

This section reviews the use of adhesives as an alternative to stitches. The key advantage of supplanting stitches with an adhesive is that the adhesive overlays the entire wound as a continuum. The global coverage prevents secondary bleeding and reduces the risk of infection by creating a temporary barrier while healing takes place. Other advantages of gluing the skin are that it is quick, saves surgery time, is inexpensive, does not have stitch removal, and is waterproof. The disadvantage of gluing is that doing so can be messy if applied incorrectly.

One of the adhesive options is copolymeric hydrogels, comprised [43] of aminated star polyethylene glycol and dextran aldehyde (PEG:dextran). These materials exhibit physicochemical properties that can be modified to achieve organ- and tissue-specific adhesion performance. The investigators reported that resistance to failure under specific loading conditions, as well as tissue response at the adhesive material−tissue interface, can be modulated through regulation of number and density of adhesive aldehyde groups.

There are two common adhesive choices: cyanoacrylic and methyl metacrylic. Cyanoacrylic acid butyl ester is usually preferred over the methyl and ethyl esters because of its slower cure (polymerization) rate. Consequently, the polymerization produces less heat; it also causes less tissue irritation. Cyanoacrylate glue is commonly used for approximation of skin after various surgical procedures [44], and is occasionally used to embolize blood vessels [45,46] and to occlude fistulas [47].

There is no need to apply a dressing to cover the wound after gluing the skin. Apart from eyes and mucous membranes, adhesive may be used to close various clean wounds of the skin, including to cover wounds of the face if there is no contraindication. However, glue application has some disadvantages: some glue applications are messy, may not hold oozing wound edges, and may stick to the instruments and gloves. Meticulous attention to different techniques in various situations may avoid most of the disadvantages. Gluing is common in surgery, but it is not formally taught. This illustrated chapter has been written to educate junior doctors without any practical experience in using tissue glue.

FDA approved cyanoacrylate adhesives are considered comparable to 5-0 sutures but are not recommended to be used alone in high tension areas.

### 6.6.2 Case Studies of Tissue Adhesives

In this section, examples of the use of tissue adhesives, namely cyanoacrylates, in the closure of different types of lacerations and surgical incisions are discussed. *In vitro* and *in vivo* animal and human studies have been conducted to assess the efficacy and outcome of tissue adhesives as compared to traditional stitching.

#### 6.6.2.1 Comparison of Effects of Suture and Tissue Adhesive on Bacterial Counts

In this study [48], the effects of closing lacerations with suture or cyanoacrylate tissue adhesive on staphylococcal counts in inoculated guinea pig lacerations are investigated. Wounds closed with adhesive alone had lower counts than wounds containing suture material ($P < 0.05$). The results of a time-kill study were consistent with a bacteriostatic adhesive effect of the adhesive against *S. aureus*.

Another study used a well diffusion method to conclude that cyanoacrylate adhesive is bacteriostatic for gram-positive organisms [49]. It is also known that suture material increases the risk of wound sepsis by serving as an adherent foreign body [49,50]. In contrast, *Staphylococcus epidermidis* adheres to cyanoacrylate adhesive, which may thus promote wound infection [51]. The authors studied the difference in wound bacterial counts among the following wound closure methods (the terms are given in parentheses): use of a cyanoacrylate adhesive alone (glue), adhesive and subcutaneous suture (glue/SQ), skin suture alone (suture), and skin suture with subcutaneous suture (suture/SQ).

Four lacerations each, with a length of 3 cm, were made parallel to the spine to deep fascia. The lacerations were inoculated with *S. aureus* (ATCC 11632) and adjusted to a spectrophotometric absorbance of 0.138−0.139. Inocula were quantified at approximately 108 CFU/ml by standard microbiological methods. After inoculating the lacerations, the four wounds on each animal were approximated in one of four ways: (1) with Nexaband Liquid (*n*-butyl-2-cyanoacrylate and D and C violet number six dye) (glue), (2) with subcutaneous suture (i.e., intradermal stitches buried beneath the skin) followed by application of Nexaband Liquid (glue/SQ), (3) with simple skin suture (suture), or (4) with intradermal subcutaneous suture followed by simple skin suture (suture/SQ).

Table 6.4 summarizes the wound data. Any lacerations subject to protocol abrogations were excluded. Wound bacterial counts for glue were significantly lower than those for glue/SQ, suture, and suture/SQ. A time-kill study of Nexaband with *S. aureus* was also performed according to National Committee for Clinical Laboratory Standards guidelines [52]. Four drops of Nexaband, the approximate amount used to close each laceration, was suspended in Trypticase soy broth before vortexing. The results of the kill study are summarized in Figure 6.3. Broth containing cyanoacrylate exhibited bacterial growth levels significantly lower than those of the control.

The study concluded that contaminated wounds sealed with cyanoacrylate alone have appreciably lower staphylococcus counts than lacerations containing suture material. The presence of suture material in some wounds may be the reason for this effect. Bacteriostatic behavior of the products containing cyanoacrylate may also be at work. No study has, however, found any adhesive present in the wound after closure.

The microbiological permeability of cyanoacrylate compounds, using Liquiseal (MedLogic Global Ltd, Plymouth, UK) as an example, was studied [53] to verify its reported primary attribute as a compound that remains impervious to microorganisms and water for 1 week following application. The occlusive dressing used was OpSite (Smith & Nephew, London, UK), commonly used in surgical procedures. The methods used in the study are well established in the investigation of bacterial penetration through various materials [54]. The organisms selected were *S. aureus* and *E. coli*, both known to be common pathogens causing surgical site infections.

**Table 6.4** Bacterial Counts for Contaminated Lacerations Treated with Tissue Adhesive and Suture[a][48]

| Treatment Method | Mean Bacterial Count ± SD[b] | 95% Confidence Interval |
|---|---|---|
| Glue | 1.78 ± 1.9 | 0.5−3.06 |
| Glue/SQ | 4.42 ± 1.92 | 3.1−5.7 |
| Suture | 3.72 ± 1.4 | 2.83−4.62 |
| Suture/SQ | 4.58 ± 1.43 | 3.67−5.49 |

[a]*The adhesive used was* n*-butyl-2-cyanoacrylate tissue adhesive; skin sutures were done with monofilament nylon, and subcutaneous sutures were done with braided absorbable suture.*
[b]*Values are log10 conversions of CFU per gram of tissue.*

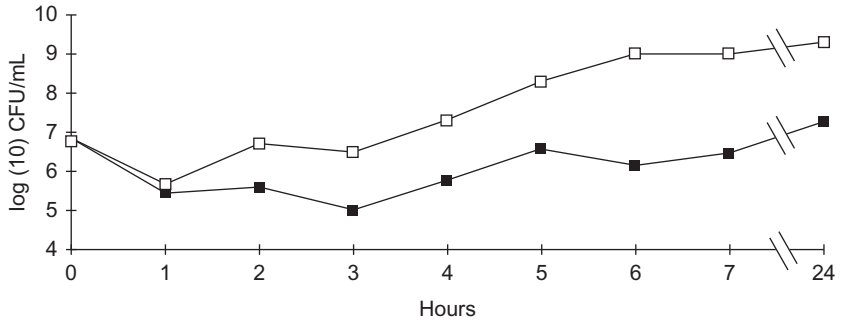



**Figure 6.3** *S. aureus* kill curve [48].

This study [54] demonstrated that, as a barrier to microbiological penetration, cyanoacrylates are as effective as standard occlusive dressings. The limitations of the two types of dressing are similar; both have the potential to allow bacteria to travel around the edges of the dressing and potentially infect the wound. However, as suggested by Bady and Wongworawat, the adhesion that the cyanoacrylate compounds makes to the skin is effective in preventing the translocation of microorganisms across the skin [55].

#### 6.6.2.2 Sutureless Anastomoses of Small and Medium Vessels

In a study in China [56], an animal model was used to assess the efficacy of sutureless anastomoses using tissue adhesives. The two cut ends of the rabbit common carotid artery were sutured by three stitches with a 1208 interval circumferentially. Then two optional threads were pulled horizontally and 0.1 ml cyanoacrylate adhesive was smeared on the attached surfaces of the two ends. The three stitches were removed after completion of anastomosis. The burst pressure of the anastomosis was measured and compared with that of a traditional sutured artery. The glued anastomosis was associated with a shorter completion time ($8.25 \pm 6.34$ min vs. $20.67 \pm 14.24$ min, $P < 0.01$), less bleeding ($3.17 \pm 9.04$ ml vs. $11.04 \pm 16.28$ ml, $P < 0.01$), and equivalent patency (93.8 vs. 87.5%, $P < 0.05$). The sutureless anastomosis was associated with less intimal thickening (decreased by 31.4, 24.5, 23.9, and 31.9%, $P < 0.01$ compared with the traditional suture group at 1, 2, 4, and 12 weeks, respectively). The study concluded that glued anastomoses provide an effective, simple, and feasible way for anastomosing small or medium caliber vessels. This technique can also reduce intimal injury (i.e., to the inner lining of the vessels).

Another paper [57] presents the results of an experimental study of small arterial anastomosis, combining suture with the cyanoacrylate tissue adhesive. At the distal end of the vessel, two parallel incisions were made, 180° apart from each other, and two sutures were placed passing from the proximal end to exit from the most distal part of the longitudinal incisions. The tissue adhesive was then applied to the proximal vessel, and the full-thickness vascular "lid" flap was closed over it on anterior and posterior surfaces. Eighty anastomoses were carried out at the left and the right femoral arteries of 40 Wistar rats. For all of the animals, conventional end-to-end anastomosis was carried out on the left side, and the lid technique was used on the right side. There was no statistically significant difference between the patency rates of the groups (two non-patent in control and two in the study group) ($P > 0.05$), whereas significantly reduced operation time (mean 16.2 and 10.7 min in control and study groups, respectively) ($P < 0.0001$) and bleeding time (median 1.5 and 0.5 min in control and study groups, respectively) ($P < 0.0001$) were documented in the study group. Histopathological evaluation of both the patent and non-patent vessels at day 21 revealed no signs of tissue toxicity or intraluminal adhesive leakage. In view of these data, the investigators concluded that using cyanoacrylate tissue adhesive provides an effective and simple method for end-to-end anastomosis of small-size arteries.

Akhtar [58] has put forth contradictory studies regarding the toxicity and long-term effects of cyanoacrylate. He cites that Barbalinardo et al. [59], who compared relative effectiveness of isobutyl 2-cyanoacrylate, fibrin adhesive, and oxidized regenerated cellulose, were determined by application of these hemostatic agents to sources of point bleeding. They found, in the meantime, that hemostasis was shorter in the cyanoacrylate group, but the reported inflammatory response that it induced, and its possible carcinogenicity, limited its availability for clinical use. Ellman et al. [60], also using oxidized cellulose (Surgicel) as control, assessed two formulations of a new cyanoacrylate compound. Long-term graft patency was assessed angiographically at 4, 6, and 18 months. Tissue reaction at 2 weeks, 1, 6, and 18 months was assessed grossly by vascular surgeons and microscopically by a blinded pathologist. There were no significant differences between groups with regard to graft patency. Histopathology showed mild to moderate tissue reaction at 2 weeks and 1 month in the cyanoacrylate groups compared with controls. Mild tissue reaction was seen at 6 and 18 months. Their conclusion was that the cyanoacrylate compound was an effective suture line sealant.

#### 6.6.2.3 Tissue Adhesive as Dressing after Open Pediatric Urological Procedures [61]

In 2003, an effectiveness study of 2-OCA (Dermabond by Ethicon, Inc.) tissue adhesive as a

sole dressing after open pediatric urological procedures. For a period of 6 months, February to August 2003, the investigators prospectively evaluated patients undergoing extragenital open and laparoscopic pediatric urological procedures at the Children's Hospital, University of Colorado School of Medicine in Denver, Colorado. All open incisions were closed in layers using a final layer of self-absorbing subcuticular stitches for the skin before applying Dermabond cyanoacrylate adhesive at the skin level alone. In laparoscopic cases, Dermabond alone was applied to the port sites (3 mm or less in diameter) and instrument sites without any sutures beneath the skin. No adjuvant occlusive dressings were applied to any of these wounds. All patients were allowed to bathe and return to normal lifestyle activities immediately postoperatively.

A total of 146 patients comprised the study with a total of 200 incisions (open 146, laparoscopy 54). Of these children, 103 who had had 142 incisions returned for follow-up visits during the period of study. Only one complication was identified. The subject, a 6-month old infant, presented with omental prolapse through the umbilical port (3 mm port) requiring urgent closure in the evening of surgery. There were no cases in which appreciable healing problems were identified by surgeon or parent examinations. No wound infection occurred. Dermabond alone provides a simple coverage for a vast range of pediatric urological surgical wounds. Immediate bathing and return to normal lifestyle activities do not seem to affect the wound healing adversely as long as a simple skin barrier is applied to the wound sites [61].

### 6.6.2.4 Tissue Adhesive Applications in Gastrointestinal Endoscopic Procedures [62]

This section is based on a 2006 review paper by Rayou and Thompson. Cyanoacrylates and other tissue adhesives can be applied locally for a variety of indications, including hemostatic, wound closure, and fistula repair. The main classes of tissue adhesives currently used in gastrointestinal (GI) endoscopy include cyanoacrylates, fibrin glues, and thrombin. The focus of this section is on applications of cyanoacrylates.

#### *Gastric Variceal Bleeding*

Injection therapy with cyanoacrylates is now the first line of endoscopic intervention for bleeding gastric varices as well as secondary prevention of gastric variceal bleeds outside of the United States [63].

In a randomized controlled trial of 59 patients, cyanoacrylate injection of bleeding gastric varices was reported to be more effective and safer than band ligation. Both initial hemostatic rate and rebleeding rates were lower in the cyanoacrylate group compared with the band ligation group. Initial hemostatic rates were 87% in the cyanoacrylate group compared with 45% in the band ligation group ($P = 0.03$); rebleeding rates in the cyanoacrylate group were 31% compared with 54% in the band ligation group ($P = 0.0005$). Treatment-induced ulcer bleeding occurred in two patients (7%) in the cyanoacrylate group and eight patients (28%) in the band ligation group ($P = 0.03$). The amount of blood transfusions required were also higher in the band ligation group than in the cyanoacrylate group ($4.2 \pm 1.3$ vs. $2.6 \pm 0.9$ units, respectively) ($P < 0.01$) [64].

#### *Esophageal Variceal Bleeding*

Several randomized controlled studies have demonstrated that injection of cyanoacrylate is comparable to sclerotherapy in the endoscopic hemostasis of acute variceal bleeding and prevention of rebleeding [65–67].

#### *Peptic Ulcer Bleeding*

In a randomized controlled trial comparing injection of cyanoacrylate and hypertonic saline for bleeding gastroduodenal ulcers, initial hemostasis was similar in both groups and the rebleeding rate was lower after cyanoacrylate injection [68]. There are no studies comparing glue injection to a combination of injection and cautery or application of clips, which are considered more effective than saline injection alone for the treatment of bleeding ulcers.

#### *Bleeding from Other Sources*

Cyanoacrylate injection has been used successfully in the management of a few patients with Dieulafoy's lesions and bleeding tumors [69–70].

#### *Closure of Fistula*

Cyanoacrylates have been shown to be successful in the closure of pancreatic fistulas, biliary fistulas [71], and GI fistulas [72] (Seewald and coworkers reported successful closure of pancreatic fistulas in 8 of 12 patients using endoscopic injection of Histoacryl into the fistulous tract and

endoscopic drainage) [73]. Seven of the eight successful patients required only one treatment over a median follow-up period of 21 months. Closure was temporary in two patients, unsuccessful in one patient, and there was one death within 24 h of treatment from pulmonary embolism.

Some complications have been described with the use of cyanoacrylates such as systemic inflammatory reaction to foreign body (pain and fever, local tissue necrosis) and inflammatory reaction to foreign body (mediastinitis, esophageal pleural fistula, duodenal ulcer perforation, pancreaticoduodenal necrosis, inflammatory pseudotumor of pancreatic tail) [74–78]. Other types of complications have also been reported [79–83].

### 6.6.2.5 Tissue Adhesives in Topical Skin Wounds [84]

There are over 7 million traumatic lacerations [85] in addition to tens of millions of surgical incisions. All require closure by surgeons, emergency physicians, and primary care practitioners [86]. These wounds and incisions have been traditionally closed with sutures, staples, or surgical tapes, and more recently tissue adhesives. An ideal wound closure device should be user friendly, quick, pain free and result in excellent cosmetics, without device removal requirement, and of course be cost-effective [87]. None of the current closure devices possess all of these requirements. Topical cyanoacrylate tissue adhesives, however, have a number of the characteristics of an ideal wound closure device.

Cyanoacrylate topical adhesives have some obvious advantages over sutures such as ease of use and pain-free application of the adhesive. Consequently, local anesthetics are unnecessary. In addition, because the cyanoacrylate adhesives slough off spontaneously within 5–10 days, no removal is required which is a procedure that may be painful and threatening, especially to children. Although the cost of the cyanoacrylate adhesives is higher than most sutures, a formal cost-effective analysis conducted several years ago that included the costs of the suture kits, suture removal kits, and dressing materials demonstrated that use of the adhesives actually reduces the costs [88]. The use of the topical cyanoacrylate adhesives also reduces the risks of needle sticks [89] and prevents the formation of suture marks on either side of the wound. Unlike suturing that has a learning curve of up to 2 years [90], proficiency at using the cyanoacrylate adhesives is rapidly attained [91]. They also have the potential to save operative time, especially with longer incisions and lacerations. In surveys, most surgical patients prefer topical adhesives to sutures or staples [92,93]. In contrast, in a study of 724 emergency department patients, of which two-thirds had a prior or current laceration, more patients preferred sutures to adhesives [53]. The surgical tapes offer many of the same advantages that the topical skin adhesives offer and are a reasonable alternative for closure of appropriate wounds [25,32]. The surgical tapes are easy to use, rapid, painless, and comfortable, do not require removal and are less costly than any of the wound closure devices. However, because of their low bursting strength and tendency to fall off, the use of surgical tapes is limited to simple very-low-tension wounds. Furthermore, the surgical tapes do not have microbial barrier properties. A summary of the advantages, disadvantages, and common indications for the various wound closure devices is presented in Table 6.5. A summary of potential pitfalls associated with the cyanoacrylates together with possible solutions is presented in Table 6.6.

### 6.6.2.6 Tissue Adhesive for Closure of Hernia Incisions

This study [94] intended to elucidate that suture-based permanent mesh fixation can be replaced by fixation with *n*-butyl-2-cyanoacrylate glue (Glubran® 2 by GEM S. r. l., Italy) for surgical repair of abdominal wall hernias. The aim of this study was to investigate in a rat animal model the efficacy of the use of a small amount of modified *n*-butyl-2-cyanoacrylate (Glubran 2) in abdominal mesh fixation as a feasible alternative to sutures and staples. Glubran 2 is a class III medical-surgical product (for internal and external surgical use) which has outstanding hemostatic and adhesive properties and, once set, produces an effective antiseptic barrier against infectious agents or pathogens commonly found in surgical settings. At the present, it is used in open and laparoscopic surgery, digestive tract endoscopy, interventional radiology, and vascular neuroradiology.

In 25 Wistar rats, two hernia defects (1.5 cm in diameter) per animal were created bilaterally in the midline of the abdominal wall. The peritoneum was spared. The lesions were left untreated for 10 days

**Table 6.5** Comparison of the Wound Closure Devices [84]

| | **Sutures** | **Staple** | **Tapes** | **Adhesives** |
|---|---|---|---|---|
| Advantages | Most meticulous approximation | Fast | Fast | Fast |
| | Great tensile strength | Good tensile strength | Simple | Simple |
| | Low dehiscence rate | Simple | Inexpensive | No risk of needle stick |
| | Time honored | Lower tissue reactivity | Minimal reactivity | No need for removal |
| | | Lower risk of needle stick | No risk of needle stick | Microbial barrier |
| | | | No need for removal<br>Comfortable | Occlusive dressing<br>Comfortable |
| Disadvantages | Painful | Less meticulous approximation | Lowest tensile strength | Lower tensile strength than sutures |
| | Prolonged learning curve | Painful | Highest risk of dehiscence | Limited moisture resistance |
| | Require removal | Require removal | No moisture resistance | |
| | May leave suture marks | | | |
| | Risk of needle stick | | | |
| | Most reactive | | | |
| Indications | Most incisions and lacerations | Long linear incisions and lacerations | Linear low tension wounds and lacerations | Linear low tension wounds and lacerations |
| | | Scalp wounds | Fragile skin (flaps and skin tears) | Fragile skin |
| | | | Wound support after suture/s taple removal | Under splints/casts |
| | | | Under splints/casts | |
| Contraindications | Infected or heavily contaminated wounds | Inadequate hemostasis | Inadequate hemostasis | Inadequate hemostasis |
| | | Complex irregular wounds | High tension | High tension |
| | | | Hear bearing area<br>Uncooperative patients<br>Circumferential use around digits<br>Proximity to moist areas | Hear bearing area<br>Proximity to moist areas |

**Table 6.6** Potential Cyanoacrylate Pitfalls and Pearls [84]

| Potential Pitfall | Pearl |
|---|---|
| Runoff | Position wound horizontally |
| | Apply small amount of adhesive |
| Spillage into eyes | Cover eyelids with ointment and moist gauze |
| | Place patient in Trendelenburg for wound above eye and reverse |
| | Trendelenburg for wounds below eye |
| | Apply small amount of adhesive |
| Burning sensation | Apply small amount of adhesive |
| | Avoid pooling of adhesive |
| | Spread out evenly |
| Wound dehiscence | Avoid in high tension wounds unless in conjunction with deep tension relieving sutures, surgical tapes, and immobilization |
| Wound infection | Use proper wound preparation |
| | Avoid in wounds with high risk of injection |
| Adherence to wound | Apply small amount of adhesive |
| | Horizontal positioning of wound |
| | Alternate the hand used to appose wound edges before complete polymerization |
| Introduction of adhesive into wound | Ensure meticulous wound apposition |
| | Avoid pressing down on wound with applicator (glide over wound surface) |
| | Remove adhesive by applying ointment |
| | Removal may be facilitated by using substance containing isopropyl merystate (such as silver sulfadiazine) |

to achieve a chronic condition. Then the defects were covered with TiMESH extra light and fixed by 30 μL of Glubran 2 or traditional suture. The time points of sacrifice were 17 and 28 days, 3, 4, and 5 months. At autopsy, histology and immunohistochemistry were performed to evaluate the inflammatory response and the presence of apoptotic cells, respectively. Mesh fixation was excellent in all samples at each time point. At application sites, the inflammatory reaction was mild with a small number of macrophages and vascularized connective tissue presence around glue and mesh threads. Glue residues were observed in histologic sections at each time point. No presence of apoptotic cells was found. This study demonstrated that Glubran 2 can effectively replace traditional sutures in mesh fixation without affecting tissue healing and determining a physiological inflammatory reaction at the abdominal wall site.

In conclusion, on the basis of these experimental results, the use of a right amount of Glubran 2 can effectively replace traditional suture threads in fixing abdominal mesh, guaranteeing a long-term firm adhesion without increasing inflammation.

In another study [95], the investigators compared the skin adhesive 2-octylcyanoacrylate to subcuticular suture for closure of pediatric inguinal hernia incisions to determine if skin adhesive improves wound cosmesis, shortens skin closure time, and lowers operative costs. They prospectively randomized 134 children undergoing inguinal herniorrhaphy at the Children's Hospital of the University of Michigan to have skin closure with either skin adhesive ($n = 64$) or subcuticular closure ($n = 70$). Data collected included age, sex, weight, type of operation, total operative time, and skin closure time. Digital photographs of healing incisions were taken at the 6-week postoperative visit. The

operating surgeon assessed cosmetic outcome of incisions using a previously validated visual analog scale, as well as an ordinate scale. A blinded assessment of cosmetic outcome was then performed by an independent surgeon comparing these photographs to the visual analog scale. Operating room time and resource use (i.e., costs) relative to the skin closure were assessed. Comparisons between groups were done using Student's $t$ tests and $\chi^2$ tests.

Children that enrolled in the study had a mean age of $3.7 \pm 0.3$ years and weighed $16 \pm 0.8$ kg. Patients were predominantly male (82%). Patients underwent one of three types of open hernia repair as follows: unilateral herniorrhaphy without peritoneoscopy ($n = 41$; 31%), unilateral herniorrhaphy with peritoneoscopy ($n = 55$; 41%), and bilateral herniorrhaphy ($n = 38$; 28%). Skin closure time was significantly shorter in the skin adhesive group (adhesive = $1.4 \pm 0.8$ min vs. suture = $2.4 \pm 1.1$ min; $P = 0.001$). Mean wound cosmesis scores based on the visual analog scale were similar between groups (adhesive = $78 \pm 21$; suture = $78 \pm 18$; $P = 0.50$). Material costs related to herniorrhaphy were higher for skin adhesive (adhesive = \$22.63 vs. suture = \$11.70; $P = 0.001$), whereas operating room time costs for adhesive skin closure were lower (adhesive = $\$9.33 \pm 5.33$ vs. suture = $\$16.00 \pm 7.33$; $P = 0.001$). Except for a 7% incidence of erythema in both groups, there were no complications encountered. In the meantime, the data from this trial suggest that skin adhesive wound closure in inguinal hernia repair is associated with a small reduction in operative time without effect upon total cost, complication rate, or cosmesis.

#### 6.6.2.7 Use of Tissue Adhesive for Skin Closure in Plastic Surgery [96]

Abdominoplasty and mammoplasty are cosmetic surgeries that demand relatively more time for skin closure. Methods: Skin closure with 4.0 Mononylon (Ethicon) continuous subcuticular suture and with Dermabond (Ethicon) (octylcyanoacrylate) was compared among 37 patients who had undergone body contouring surgery (23 abdominoplasties and 14 mammoplasties). Each side of the scar, randomly selected, was closed either with adhesive or suture. The time required for skin closure and the aesthetic aspect of these scars were compared. Three observers evaluated the scars at 3, 6, and 12 months postoperatively using a categorical and a modified visual analog scale. Results: The average time for closure using suture was 7 min and 45 s for the abdominoplasty and 4 min and 25 s for the vertical incision of the mammoplasty. This was significantly different statistically, as compared with the 2 min required for polymerization of the skin adhesive. The mammoplasty and abdominoplasty scars showed no statistical difference at 3, 6, and 12 months according to both scales. Conclusions: The aesthetic aspects of the mammoplasty and abdominoplasty scars were similar on both sides at 3, 6, and 12 months. However, the adhesive allowed a shorter surgical time.

## 6.7 Bone Adhesives

One of the unmet clinical needs of orthopedic trauma surgeons is a ''bone glue'' or an adhesive to fix a broken bone instead of the conventional metal plates, nails, pins, and screws. Simplicity, quickness and preservation of joint function, especially when fixing fractures with many small fragments, are the main benefits of a bone adhesive. An additional benefit is elimination of a metal removal from fractures fixed solely with a biodegradable adhesive.

The development of bone adhesives has been under way since 1950s. It is still in relatively early stages and has not resulted in adhesives which meet the many requirements of a successful product (Table 6.7). There are a number of bone cements and bone void fillers on the marker though none claim any adhesive properties. Probably the best known of these products is PMMA bone cement that has long been used for the fixation of implants such as hip and knee replacements into bone. However, this material acts merely as a grout between the implant and bone and any attempts to use it to glue bones have generally been unsuccessful [97].

## 6.8 Dental Applications of Adhesives [98]

Dental adhesives are basically intended to provide retention to composite fillings or composite cements. A good adhesive not only should withstand

**Table 6.7** Characteristics of a Successful Bone Adhesive [97]

| *Preferred* |
|---|
| • High level of adhesion to bone, often in the presence of contaminants such as fats, proteins |
| • Bonds to wet surfaces/bond strength stable in wet environment |
| • Mechanical stability under tension, compression, shear |
| • Easy/quick to prepare and apply in operating room conditions |
| • Adequate working time for the surgeon to apply and form bond |
| • Rapid setting lime (typically 1−10 min) |
| • Low exotherm on setting−no thermal necrosis |
| • Non-toxic and biocompatible (including any leachables, degradation products) |
| • Allows healing of the fracture |
| • Sterilisable |
| • Adequate shelf life |
| • Cost effective to use |
| • Commercially viable to manufacture |
| *Desirable* |
| • Adhesion to surgical alloys (e.g., stainless steel, Ti−6A1−4V, Co−Cr−Mo) |
| • Biodegradable in a controlled manner and timescale |
| • No special storage conditions (stable at room temperature) |
| • Ability to deliver drugs/bioactive agents, e.g., stimulate bone healing, prevent infection |

mechanical forces, particularly shrinkage stress from the lining composite, but should be able to prevent leakage along the restoration's margins. Clinically, failure of restorations occurs more often due to inadequate sealing, with subsequent discoloration of the cavity margins, than due to loss of retention [99,100].

Capability of dental adhesives is dependent on two conditions. First, the adhesive must bond to enamel and dentin, and second, the adhesive adheres to the lining composite. The second condition has been shown to be due to a process of copolymerization of residual double bonds (−C═C−) in the oxygen inhibition layer. Bonding to enamel and dentin is believed to be by micromechanical adhesion as the main adhesion mechanism [101]. This takes place through an exchange process where inorganic tooth material is replaced by resin monomers that become interlocked in the retentions after polymerization [102,103]. Diffusion and capillarity are the primary mechanisms of micro-mechanical retention. Microscopically, this process is called "hybridization" [104]. Comprised of simple interlocking resin in etch-pits in enamel, entanglement of resin within the exposed collagen lattice occurs in dentin. Self-etch adhesives with a mild (relatively high) pH do not, however, completely expose collagen anymore. An additional mechanism of ionic bonding of acidic monomers and calcium in hydroxyapatite was established in 2004 [105] that might explain the successful clinical performance of some of these mild self-etch adhesives [106].

Some of the requirements of adhesive systems can be defined [98] using the knowledge of bonding mechanisms. Micromechanical interlocking occurs after consecutive demineralization, resin infiltration, and polymer setting. Consequently, adequately removing the smear layer together with demineralizing enamel and dentin to a small extent, good wetting, diffusion, penetration, and good polymerization of the resin components are all important. Chemical bonding can be achieved by adding specific monomers with affinity for hydroxyapatite. Finally, sufficient copolymerization between the adhesive and the lining composite will provide good adhesion to the composite.

Chemical composition of adhesives should be (is) selectively defined [98] such that the above mechanistic requirements may successfully be fulfilled. Even though dental adhesives can be classified into two main groups, i.e., etch and rinse (E&Rs) and self-etch adhesives (SEAs) (Figure 6.4), they all contain similar ingredients, irrespective of the number of bottles of which an adhesive consists. Nevertheless, the proportional composition differs between the different classes of adhesives. Traditionally, adhesives contain acrylic resin monomers, organic solvents, initiators and inhibitors, and sometimes filler particles. It is obvious that every component has a specific function. Good insights in the chemical properties of the adhesives' components are paramount to understand or even predict

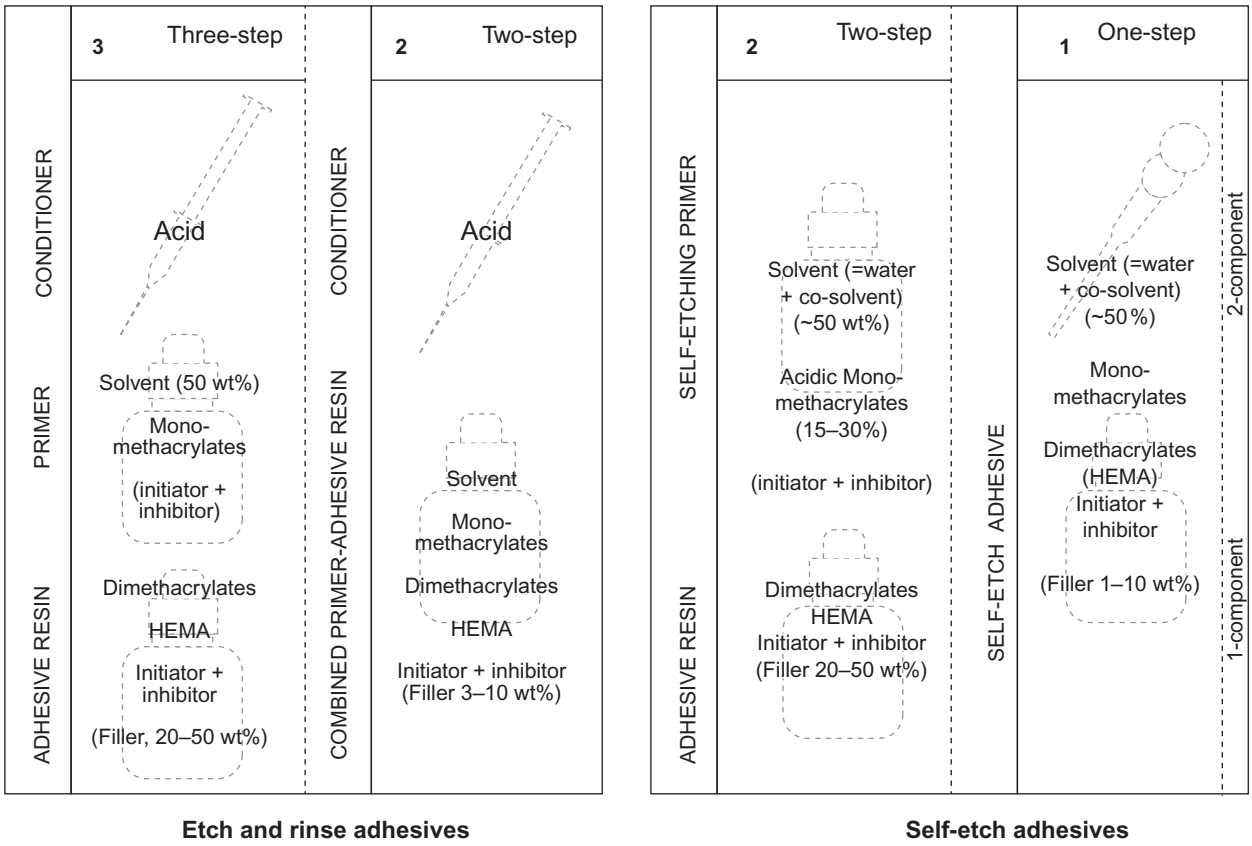



**Figure 6.4** Classification of adhesives by Van Meerbeek et al. [101]. Adhesives' performance may differ significantly when the same components at different proportional amount of ingredients.

their behavior. Table 6.8 gives a list of the various ingredients of dental adhesives.

Resin monomers in dental adhesives play a similar role to those of composites. Just as in the composites, the cured resin in the adhesive forms a matrix which functions as a backbone providing structural continuity and thus physico-mechanical properties such as strength. Monomers are the most essential ingredient of the adhesive because they are the key constituents of adhesives. There are two classes of monomers: cross-linking and functional monomers. Typically, the functional monomers only have one polymerizable group while cross-linking monomers have two or more polymerizable groups such as vinyl linkages (—C═C—) [107]. Functional monomers, in addition to polymerizable group, exhibit a particular chemical group, which the functional species that embodies the monomer-specific functions imparted to the polymer.

Functional monomers form linear polymers upon polymerization contrary to the cross-linkers which supply the linkages for cross-linked polymers. Compared to linear polymers, the latter have proven to exhibit better mechanical strength, and cross-linking monomers are therefore important to the reinforcement of the adhesive resin [108—111]. Important characteristics of more common dental adhesive monomers are briefly covered in the followings sections [98].

## 6.8.1 Methacrylic Acid

Methacrylic acid (MA) is a strong irritant and corrosive because of its strongly acidity. It can also rapidly penetrate gloves and skin causing allergic reactions. This monomer is, therefore, seldom added to adhesives. It is, however, most likely to be present to different extents in the majority of adhesive resins, thanks to the hydrolysis of the ester group in

**Table 6.8** Ingredients of Dental Adhesives [98]

| *Monomers* |
|---|
| MAEPA: 2,4,6 trimethylphenyl 2-[4-(dihydroxyphosphoryl)-2-oxabutyl]acrylate<br>MAC-10: 11-methacryloyloxy-1,10-undecanedicarboxylic acid<br>10-MDP: 10-methacryloyloxydecyl dihydrogen phosphate<br>MDPB: methacryloyloxydodecylpyridinium bromide<br>4-META: 4-methacryloyloxyethyl trimellitate anhydride<br>4-MET: 4-methacryloyloxyethyl trimellitic acid<br>MMA: methyl methacrylate<br>MMEP: mono-2-methacryloyloxyethyl phthalate (sometimes also called PAMA: phthalic acid monomethacrylate)<br>5-NMSA (or MASA): *N*-methacryloyl-5-aminosalicylic acid<br>NPG-GMA: *N*-phenylglycine glycidyl methacrylate<br>NTG-GMA: *N*-tolylglycine glycidyl methacrylate or *N*-(2-hydroxy-3-((2-methyl-1-oxo-2-propenyl)oxy)propyl)-*N*-tolyl glycine<br>PEGDMA: polyethylene glycol dimethacrylate<br>PEM-F: pentamethacryloyloxyethylcyclohexaphosphazene monofluoride<br>PENTA: dipentaerythritol pentaacrylate monophosphate<br>Phenyl-P: 2-(methacryloyloxyethyl)phenyl hydrogen phosphate<br>PMDM: pyromellitic diethylmethacrylate or 2,5-dimethacryloyloxyethyloxycarbonyl-1,4-benzenedicarboxylic acid<br>PMGDM: pyromellitic glycerol dimethacrylate or 2,5-bis(1,3-dimethacryloyloxyprop-2-yloxycarbonyl)benzene-1,4-dicarboxylic acid<br>Pyro-EMA: tetramethacryloyloxyethyl pyrophosphate<br>TCB: butan-1,2,3,4-tetracarboxylic acid di-2-hydroxyethylmethacrylate ester<br>TEGDMA: triethylene glycol dimethacrylate<br>TMPTMA: trimethylolpropane trimethacrylate<br>UDMA: urethane dimethacrylate or 1,6-di(methacryloyloxyethylcarbamoyl)-3,30,5-trimethylhexaan |
| *Initiators and inhibitors* |
| BHT: butylhydroxytoluene or butylated hydroxytoluene or ,2,6-di-(tert-butyl)-4-methylphenol (inhibitor)<br>BPO: benzoylperoxide (redox initiator)<br>BS acid: benzenesulfinic acid sodium salt (redox initiator)<br>CQ: camphorquinone or camphoroquinone or 1.7.7-trimethylbicyclo-[2,2,1]-hepta-2,3-dione (photo-initiator)<br>DHEPT: *N*,*N*-di-(2-hydroxyethyl)-4-toluidine (co-initiator)<br>MEHQ: 4-methoxyphenol or monoethyl ether hydroquinone (inhibitor)<br>ODMAB: 2-(ethylhexyl)-4-(dimethylamino)benzoate (co-initiator)<br>TPO: Lucirin TPO, BASF (photo-initiator)<br>UV-9: 2-hydroxy-4-methoxybenzophenone (photo-initiator) |
| *Fillers and silane coupling factors* |
| Coupling factor A174: g-methacryloxypropyltrimethoxysilane<br>F-PRG: full reaction type pre-reacted glass-ionomer fillers<br>NaF: sodium fluoride<br>Na2SiF6: disodium hexafluorosilicate<br>POSS nano-particulates: polyhedral oligomer silsesquioxanes |

other monomers as seen in Figure 6.5. Hydroxy ethyl methacrylate (HEMA) hydrolyzes and generates MA. Hydrolysis of methacrylate monomers is a problem associated with self-etching adhesives which routinely contain water and have fairly low pH, both of which result in easy hydrolysis [112].

### 6.8.2 Methyl Methacrylate

MMA, similar to MA, is one of the oldest monomers and is rarely sporadically added to adhesives because of the risk of allergic reactions [113]. It is no longer used for cosmetic applications because of

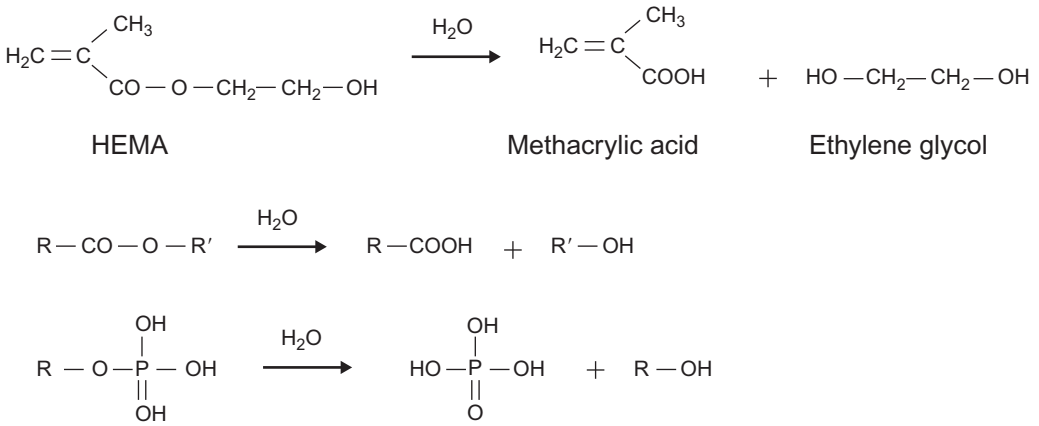



**Figure 6.5** Hydrolysis of hydroxy ethyl methacrylate, an ester, and a phosphate [98].

a ban. Its role in adhesives is limited to dissolution of other monomers.

### 6.8.3 Hydroxy Ethyl Methacrylate

HEMA is a small monomer with widespread use, not only in dentistry but also in medical applications because of its relatively good biocompatibility [114] even though the uncured monomer is notorious for its high allergenic potential [115,116]. Unpolymerized HEMA appears as a fluid that is quite soluble in water, ethanol, and acetone. HEMA is purported to evaporate from the adhesive solutions, although only in small amounts [117]. A key characteristic of HEMA is its hydrophilicity. Even though this monomer cannot be used as a demineralizing agent, its hydrophilicity makes it an excellent adhesion-promoting monomer [118–122]. By enhancing wetting of dentin, HEMA significantly improves bond strengths [123,124]. In monomeric and polymerized states, HEMA will readily absorb water. Water uptake adversely influences the mechanical strength of its HEMA copolymers; high amounts of HEMA will result in flexible copolymers with inferior qualities. Homopolymer of HEMA is a flexible porous polymer [125,126]. As such, high concentrations of HEMA in an adhesive may have deteriorating effects on the mechanical properties of the resulting polymer.

### 6.8.4 4-Methacryloyloxyethyl Trimellitic Acid

4-Methacryloyloxyethyl trimellitic acid (4-MET) is used both as an adhesion promoter and demineralizing monomer [127,128]. 4-MET is known to improve wetting to metals, such as amalgam [129] or gold [130]. Its popularity is partially due to its easy synthesizing method and broad availability. 4-MET is available in anhydride form (4-META) which is a crystalline powder. After addition of water to 4-META powder, hydrolysis reaction occurs rapidly to form 4-MET. The two carboxylic groups bonded to the aromatic ring increase acidity thus demineralizing properties as well as wetting. The aromatic group, however, is hydrophobic and will moderate the acidity and the hydrophilicity of the carboxyl groups [77].

### 6.8.5 4-Acryloyloxyethyl Trimellitate Anhydride

4-Acryloyloxyethyl trimellitate anhydride (4-AETA) differs from the structure of 4-META slightly having an acrylate polymerizable group instead of a methacrylate group. The acrylate group is regarded as an advantage for polymerization because of higher reactivity [131]. Apart from facilitating resin penetration into dentin, the highly reactive acrylate group of 4-AETA is regarded as an advantage for better polymerization.

### 6.8.6 10-Methacryloyloxydecyl Dihydrogen Phosphate

10-Methacryloyloxydecyl dihydrogen phosphate (10-MDP) is a monomer that was originally synthesized by Kuraray (Osaka, Japan). Its main use is as an etching monomer, due to the dihydrogen phosphate group, which can dissociate in water to form

two protons [112]. Structurally, the long carbonyl chain renders this monomer quite hydrophobic. Consequently, ethanol and acetone are most suitable solvents for this monomer. It is clear that 10-MDP is relatively hydrolysis stable. Yoshida et al. [105] demonstrated this monomer is capable of forming strong ionic bonds with calcium because of the low dissolution rate of its Ca-salt in its own solution.

### 6.8.7 Other Monomers

These monomers include 11-methacryloyloxy-1, 10-undecanedicarboxylic acid (MAC-10). This monomer is hydrophobic, which may reflect in limited dissolution in water. Another compound is 2-(methacryloyloxyethyl) phenyl hydrogen phosphate (Phenyl-P) [132,133] which was used as one of the first acidic monomers in self-etching primers. It is seldom used in contemporary. Two other monomers are phosphates: di-2-hydroxyethyl methacryl hydrogen phosphate (Di-HEMA-phosphate) and 2-hydroxyethyl methacryl dihydrogen phosphate (HEMA-phosphate) [134]. Di-methacrylates are cross-linking agents and methacrylamides is an interesting matrix monomer because of its similarity to amino acids of which collagen consists [135] thus promoting the formation of hydrogen bonds between the carboxyl and amide groups of the monomer with the carboxyl groups of collagen.

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# 7 Silicones

*André Colas and Jim Curtis*

OUTLINE


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Silicone materials have been widely used in medicine for over 60 years. Available in a variety of material types, they have unique chemical and physical properties that manifest in excellent biocompatibility and biodurability for many applications. Silicone elastomers have remarkably low glass-transition temperatures and maintain their flexibility over a wide temperature range, enabling them to withstand conditions from cold storage to steam autoclaving. They have high permeability to gases and many drugs, advantageous respectively in wound care or in transdermal drug delivery. They have low surface tension and remarkable chemical stability, enabling biocompatibility and biodurability in many long-term implant applications.

However, versatile as they are, present-day silicone materials still have limitations. The mechanical properties of silicone elastomers, such as tensile strength or tear resistance, are somewhat lower than for other implantable elastomers such as polyurethanes (although generally speaking, polyurethanes are less biodurable). While resistant to a wide array of chemical environments, silicone elastomers are susceptible to degradation in very strongly basic or acidic conditions, such as those found in the stomach. Like all hydrophobic implant materials, silicones are quickly coated with proteins when placed in tissue contact; and a scar tissue capsule forms to surround an implant during wound healing, walling it off from the host. Additionally, silicone elastomers are thermosetting materials, requiring different processing from conventional thermoplastics, which can on occasion be seen as a drawback.

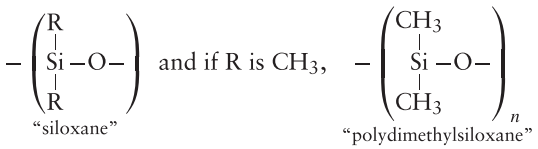
## 7.1 Chemical Structure and Nomenclature

Silicones are a general category of synthetic polymers whose backbone is made of repeating silicon-to-oxygen bonds. In addition to their links to oxygen to form the polymeric chain, the silicon atoms are also bonded to organic groups, typically methyl groups. This is the basis for the name "silicones," which was assigned by Kipping based on their similarity with ketones, because in most cases there is on average one silicone atom for one oxygen and two methyl groups [1]. Later, as these materials and their applications flourished, more specific nomenclature was developed. The basic repeating unit became known as "siloxane," and the most common silicone is polydimethylsiloxane, abbreviated as PDMS.

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**Table 7.1** Key Milestones in the Development of Silicone Chemistry

| | |
|---|---|
| 1824 | Berzelius discovers silicon by the reduction of potassium fluorosilicate with potassium: $4K + K_2SiF_6 \rightarrow Si + 6KF$. Reacting silicon with chlorine gives a volatile compound later identified as tetrachlorosilane, $SiCl_4$: $Si + 2Cl_2 \rightarrow SiCl_4$. |
| 1863 | Friedel and Crafts synthesize the first silicon organic compound, tetraethylsilane: $2Zn(C_2H_5)_2 + SiCl_4 \rightarrow Si(C_2H_5)_4 + 2ZnCl_2$. |
| 1871 | Ladenburg observes that diethyldiethoxysilane $(C_2H_5)_2Si(OC_2H_5)_2$, in the presence of a diluted acid gives an oil that decomposes only at a "very high temperature." |
| 1901–1930s | Kipping lays the foundation of organosilicon chemistry with the preparation of various silanes by means of Grignard reactions and the hydrolysis of chlorosilanes to yield "large molecules." The polymeric nature of the silicones is confirmed by the work of Stock. |
| 1940s | In the 1940s, silicones become commercial materials after Hyde of Dow Corning demonstrates the thermal stability and high electrical resistance of silicone resins, and Rochow of General Electric finds a direct method to prepare silicones from silicon and methylchloride. |



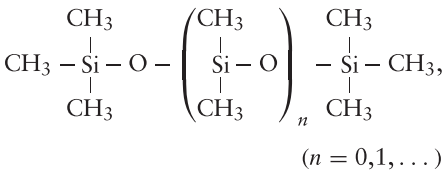

Many other groups (e.g., phenyl, vinyl, and trifluoropropyl) can be substituted for the methyl groups along the chain. The simultaneous presence of organic groups attached to an inorganic backbone give silicones a combination of distinctive properties, making their use possible as fluids, emulsions, compounds, resins, and elastomers in numerous applications and diverse fields. For example, silicones are common in the aerospace industry, due principally to their low and high temperature performance. In the electronics field, silicones are used as electrical insulation, potting compounds, and other applications specific to semiconductor manufacture. Their long-term durability has made silicone sealants, adhesives, and waterproof coatings commonplace in the construction industry. Excellent biocompatibility makes many silicones well suited for use in numerous personal care, pharmaceutical, and medical device applications.

## 7.1.1 Historical Milestones in Silicone Chemistry

Key milestones in the development of silicone chemistry, thoroughly described elsewhere by Lane and Burns [2], Rochow [3], and Noll [4], are summarized in Table 7.1.

## 7.1.2 Nomenclature

The most common silicones are the trimethylsilyloxy end-blocked polydimethylsiloxanes, with the following structure:




These are linear polymers and liquids, even for large values of *n*. The main chain unit, $-(Si(CH_3)_2O)-$, is often represented by the letter D for $(CH_3)_2SiO_{2/2}$, because with the silicon atom connected to two oxygen atoms this unit is capable of expanding within the polymer in two directions. M, T, and Q units are defined in a similar manner, as shown in Table 7.2.

**Table 7.2** Shorthand Notation for Siloxane Polymer Units

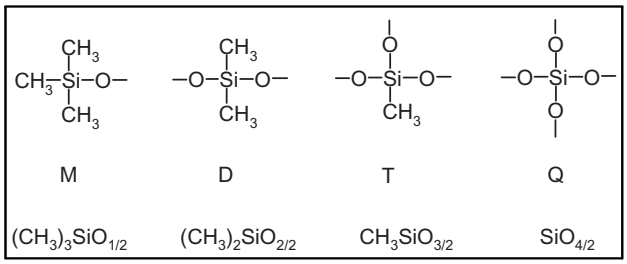
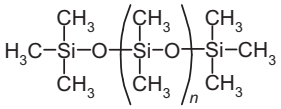
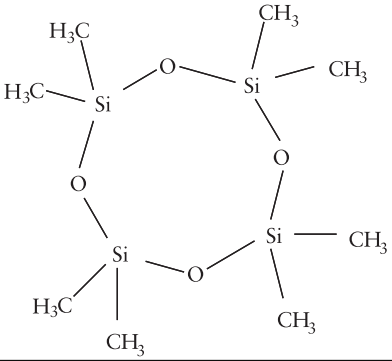
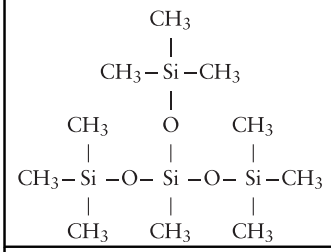
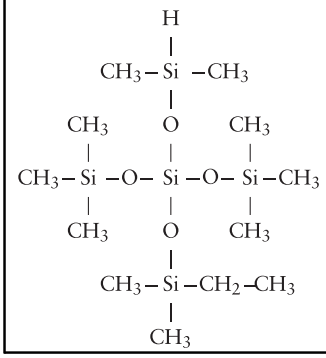


**Table 7.3** Examples of Silicone Shorthand Notation

| | | |
|---|---|---|
|  | $MD_nM$ | $MD_nM$ |
|  | $D_4$ | $D_4$ |
|  | $TM_3$ | $TM_3$ |
|  | $QM_2M^HM^{C_2H_5}$ or $QM_2M^HM^{Et}$ | $QM_2M^HM^{C2H5}$ or $QM_2M^HM^{Et}$ |

The system is sometimes modified by the use of superscript letters designating nonmethyl substituents, for example, $D^H = H(CH_3)SiO_{2/2}$ and $M^\phi$ or $M^{Ph} = (CH_3)_2(C_6H_5)SiO_{1/2}$ [5]. Further examples are shown in Table 7.3.

## *7.1.3 Preparation*

### 7.1.3.1 Silicone Polymers

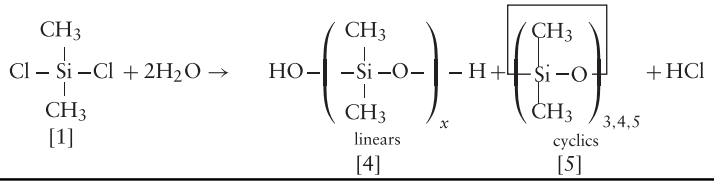
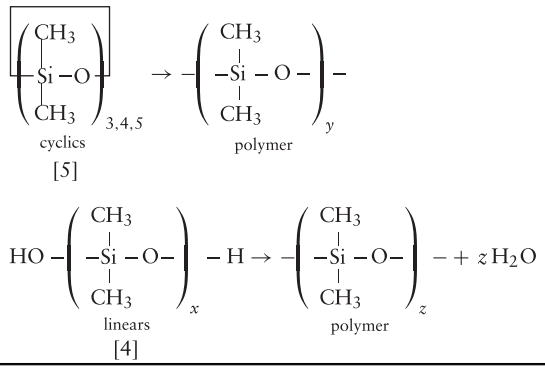
The modern synthesis of silicone polymers is multifaceted. It usually involves the four basic steps described in Table 7.4. Only step 4 in this table will be elaborated upon here.

### 7.1.3.2 Polymerization and Polycondensation

The linear [4] and cyclic [5] oligomers resulting from dimethyldichlorosilane [2] hydrolysis have chain lengths too short for most applications. The cyclics must be polymerized, and the linears condensed, to give macromolecules of sufficient length [4].

Catalyzed by acids or bases, cyclosiloxanes $(R_2SiO)_m$ are ring-opened and polymerized to form long linear chains. At equilibrium, the reaction results in a mixture of cyclic oligomers plus a distribution of linear polymers. The proportion of

**Table 7.4** The Basic Steps in Silicone Polymer Synthesis

| | |
|---|---|
| 1. Silica reduction to silicon | $SiO_2 + 2C \rightarrow Si + 2CO$ |
| 2. Chlorosilanes synthesis | $Si + 2CH_3Cl \rightarrow \underset{[1]}{(CH_3)_2SiCl_2} + \underset{[2]}{CH_3SiCl_3} + \underset{[3]}{(CH_3)_3SiCl} + CH_3HSiCl_2 + \cdots$ |
| 3. Chlorosilanes hydrolysis |  |
| 4. Polymerization and polycondensation |  |

cyclics depends on the substituents along the Si−O chain, the temperature, and the presence of a solvent. Polymer chain length depends on the presence and concentration of substances capable of giving chain ends. For example, in the KOH-catalyzed polymerization of the cyclic tetramer octamethylcyclotetrasiloxane $(Me_2SiO)_4$ ([5] or $D_4$ in shorthand notation), the average length of the polymer chains depends on the KOH concentration:

$$x(Me_2SiO)_4 + KOH \rightarrow (Me_2SiO)_y + KO(Me_2SiO)_zH$$

A stable hydroxy-terminated polymer, HO $(Me_2-SiO)_zH$, can be isolated after neutralization and removal of the remaining cyclics by stripping the mixture under vacuum at elevated temperature. A distribution of chains with different lengths is obtained. The reaction can also be made in the presence of $Me_3SiOSiMe_3$, which acts as a chain end-blocker:

$$\sim\!\!\sim Me_2SiOK + Me_3SiOSiMe_3 \rightarrow \sim\!\!\sim Me_2SiOSiMe_3 + Me_3SiOK$$

where $\sim\!\!\sim$ represents the main chain.

The $Me_3SiOK$ formed attacks another chain to reduce the average molecular weight of the linear polymer formed.

The copolymerization of $(Me_2SiO)_4$ in the presence of $Me_3SiOSiMe_3$ with $Me_4NOH$ as catalyst displays a surprising viscosity change over time [4]. First a peak or viscosity maximum is observed at the beginning of the reaction. The presence of two oxygen atoms on each silicon in the cyclics makes them more susceptible to a nucleophilic attack by the base catalyst than the silicon of the end-blocker, which is substituted by only one oxygen atom. The cyclics are polymerized first into very long, viscous chains that are subsequently reduced in length by the addition of terminal groups provided by the end-blocker, which is slower to react. This reaction can be described as follows:

$$Me_3SiOSiMe_3 + x(Me_2SiO)_4 \xrightarrow{cat} Me_3SiO(Me_2SiO)_nSiMe_3$$

or, in shorthand notation:

$$MM + xD_4 \xrightarrow{cat} MD_nM$$

where $n = 4x$ (theoretically).

The ratio between D and M units defines the average molecular weight of the polymer formed.

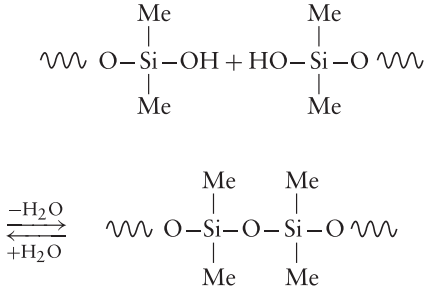
Catalyst removal (or neutralization) is always an important step in silicone preparation. Most catalysts used to prepare silicones can also catalyze the depolymerization (attack along the chain), particularly at elevated temperatures in the presence of traces of water.

$$\sim\!\sim\!\sim(Me_2SiO)_n\sim\!\sim\!\sim + H_2O \xrightarrow{\text{cat}} \sim\!\sim\!\sim(Me_2SiO)_y H + HO(Me_2SiO)_z\sim\!\sim\!\sim$$

It is therefore essential to remove all remaining traces of the catalyst, providing the silicone optimal thermal stability. Labile catalysts have been developed. These decompose or are volatilized above the optimum polymerization temperature, and consequently can be eliminated by a brief overheating. In this way, catalyst neutralization or filtration can be avoided [4].

The cyclic trimer $(Me_2SiO)_3$ has internal ring tension and can be polymerized without re-equilibration of the resulting polymers. With this cyclic, polymers with narrow molecular weight distribution can be prepared, as well as polymers only carrying one terminal reactive function (living polymerization). Starting from a mixture of cyclics with different internal ring tensions also allows preparation of block or sequential polymers [4].

Linears can combine when catalyzed by many acids or bases to give long chains by intermolecular condensation of silanol terminal groups [4,6].



A distribution of chain lengths is obtained. Longer chains are favored when working under vacuum or at elevated temperatures to reduce the residual water concentration. In addition to the polymers described above, reactive polymers can also be prepared. This result can be achieved when re-equilibrating oligomers or existing polymers to obtain a polydimethylmethylhydrogenosiloxane, $MD_zD^H_wM$.

$$\begin{aligned} &Me_3SiOSiMe_3 + x(Me_2SiO)_4 \\ &+ Me_3SiO(MeHSiO)_ySiMe_3 \\ &\xrightarrow{\text{cat}} \text{cyclics} + Me_3SiO(Me_2SiO)_z(MeHSiO)_w \\ &SiMe_3 \end{aligned}$$

[6]

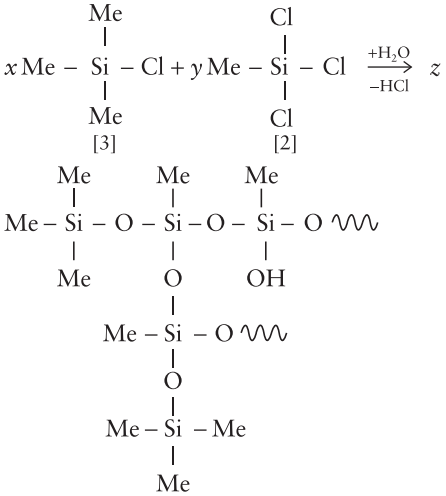
Additional functional groups can be attached to this polymer using an addition reaction.

$$Me_3SiO(Me_2SiO)_z(MeHSiO)_wSiMe_3 + H_2C=CHR$$

[6]

$$\xrightarrow{\text{Pt cat}} Me_3SiO(Me_2SiO)_z\,(Me\underset{\displaystyle CH_2CH_2R}{\overset{|}{Si}}O)_wSiMe_3$$

All the polymers heretofore shown are linear or cyclic, comprising mainly difunctional units, D. In addition, branched polymers or resins can be prepared if, during hydrolysis of the chlorosilanes, a certain amount of T or Q units are included, which allow molecular expansion in three or four directions, as opposed to just two. For example, consider the hydrolysis of methyltrichlorosilane in the presence of trimethylchlorosilane, which leads to a branched polymer:



The resulting polymer can be described as $(Me_3SiO_{1/2})_x\ (MeSiO_{3/2})_y$ or $M_xT_y$, using shorthand notation. The formation of three silanols on the $MeSiCl_3$ by hydrolysis yields a three-dimensional structure or resin after condensation, rather than a

linear polymer. The average molecular weight depends upon the number of M units that come from the trimethylchlorosilane, which limits the growth of the resin molecule. Most of these resins are prepared in a solvent and usually contain some residual hydroxyl groups. These groups could subsequently be used to cross-link the resin and form a continuous network.

### 7.1.3.3 Silicone Elastomers

Silicone polymers can easily be transformed into a three-dimensional network by way of a cross-linking reaction, which allows formation of chemical bonds between adjacent chains. The majority of silicone elastomers are cross-linked according to one of the following three reactions.

*Cross-linking with radicals*

Efficient cross-linking with radicals is achieved only when some vinyl groups are present on the polymer chains. The following mechanism has been proposed for the cross-linking reaction associated with radicals generated from an organic peroxide for the initiation, propagation, and termination steps [6]:

$$R^{\cdot} + CH_2 = CH - Si\equiv \rightarrow R - CH_2 - CH^{\cdot} - Si\equiv$$
$$RCH_2 - CH^{\cdot} - Si\equiv + CH_3 - Si\equiv$$
$$\rightarrow RCH_2 - CH_2 - Si\equiv + \equiv Si - CH_2^{\cdot}$$
$$\equiv Si - CH_2^{\cdot} + CH_2 = CH - Si\equiv$$
$$\rightarrow \equiv Si - CH_2 - CH_2 - CH^{\cdot} - Si\equiv$$
$$\equiv Si - CH_2 - CH_2 - CH^{\cdot} - Si\equiv + \equiv Si - CH_3$$
$$\rightarrow \equiv Si - CH_2 - CH_2 - Si\equiv + \equiv Si - CH_2^{\cdot}$$
$$2\equiv Si - CH_2^{\cdot} \rightarrow \equiv Si - CH_2 - CH_2 - Si\equiv$$

where $\equiv$ represents two methyl groups and the rest of the polymer chain.

This reaction has been used for high-consistency silicone rubbers (HCRs), such as those used in extrusion or compression and injection molding, which are cross-linked at elevated temperatures. The peroxide is added before processing. During cure, some precautions are needed to avoid the formation of voids by the volatile residues of the peroxide. Post-cure may also be necessary to remove these volatiles, which can catalyze depolymerization at high temperatures.

*Cross-linking by condensation*

Although mostly used in construction sealants and caulks, condensation-cure silicone materials have also found utility in medical device manufacturing as silicone adhesives (facilitating the adherence to materials of silicone elastomers), encapsulants, and sealants.

One-part products are ready to apply and require no mixing. Cross-linking starts when the product is squeezed from the tube or cartridge and comes into contact with moisture, typically from humidity in the ambient air. These materials are formulated from a reactive polymer prepared from a hydroxy end-blocked polydimethylsiloxane and a large excess of methyltriacetoxysilane.

$$HO - (Me_2SiO)_x - H + \textit{excess}\ MeSi(OAc)_3 \xrightarrow{-2AcOH} (AcO)_2MeSiO(Me_2SiO)_x OSiMe(OAc)_2$$

[7]

where $Ac = -\overset{\displaystyle CH_3}{\overset{|}{C}} = O$

Because of this excess, the probability of two different chains reacting with the same silane molecule is remote. Consequently, all the chains are end-blocked with two acetoxy functional groups. The resulting product is still liquid and can be packaged in sealed tubes and cartridges. Upon opening and exposing the sealant to room humidity, acetoxy groups are hydrolyzed to give silanols, which allow further condensation to occur.

$$\sim\!O - \overset{\displaystyle Me}{\overset{|}{Si}} - OAc \xrightarrow[-AcOH]{+H_2O} \sim\!O - \overset{\displaystyle Me}{\overset{|}{Si}} - OH$$
$$\qquad\qquad\quad OAc \qquad\qquad\qquad\quad OAc$$

[7] [8]

$$\sim\!O - \overset{\displaystyle Me}{\overset{|}{Si}} - OH + AcO - \overset{\displaystyle Me}{\overset{|}{Si}} - O\sim$$
$$\qquad\quad OAc \qquad\qquad\quad OAc$$

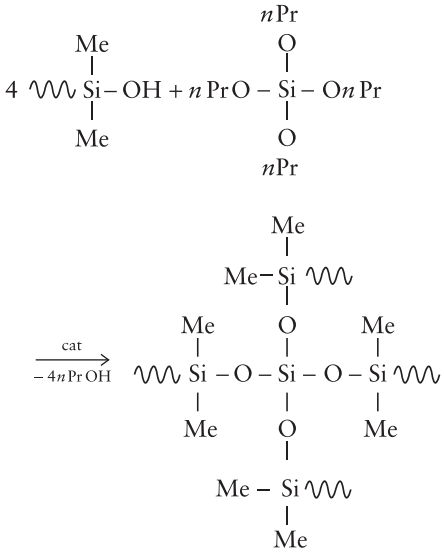
[8] [7]

$$\xrightarrow[-AcOH]{} \sim\!O - \overset{\displaystyle Me}{\overset{|}{Si}} - O - \overset{\displaystyle Me}{\overset{|}{Si}} - O\sim$$
$$\qquad\quad OAc \qquad\quad OAc$$

In this way, two chains have been linked, and the reaction continues from the remaining acetoxy

groups. An organometallic tin catalyst is normally used, and the cross-linking reaction requires moisture to diffuse into the material. Accordingly, cure will proceed from the outside surface inward. These materials are called one-part RTV (room temperature vulcanization) sealants, but actually require moisture as a second component. Acetic acid is released as a by-product of the reaction. Problems resulting from the acid can be overcome by using other cure (cross-linking) reactions developed by replacing the methyltriacetoxysilane $MeSi(OAc)_3$ with oximosilane $RSi(ON{=}CR')_3$ or alkoxysilane $RSi(OR')_3$.

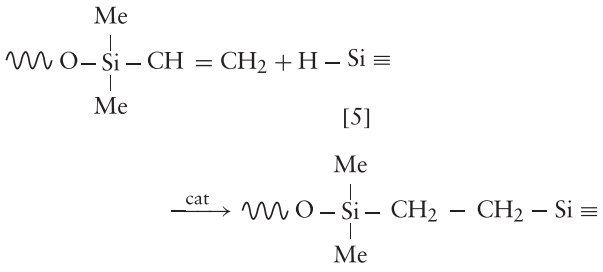
Condensation curing is also used in some two-part products where cross-linking starts upon mixing the two components (e.g., a hydroxy end-blocked polymer and an alkoxysilane such as tetra-*n*-propoxysilane, $Si(OnPr)_4$) [4]:



Here, no atmospheric moisture is needed. Usually an organotin salt is used as a catalyst, but it also limits the stability of the resulting elastomer at high temperatures. Alcohol is released as a by-product of the reaction, leading to some shrinkage after cure at room temperature (0.5–2% linear shrinkage). Silicones with this cure system may not be suitable for the fabrication of parts with precise tolerances.

### *Cross-linking by addition*

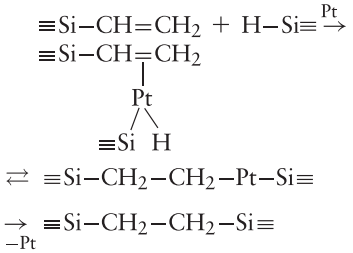
Use of an addition-cure reaction for cross-linking can eliminate the shrinkage problem mentioned above. In addition-cure, cross-linking is achieved by reacting vinyl end-blocked polymers with $\equiv$ Si–H groups carried by a functional oligomer such as described above [6]. A few polymers can be bonded to this functional oligomer [6] [6]:



[5]

where $\equiv$ represents the remaining valences of the Si in [6].

The addition occurs mainly on the terminal carbon and is catalyzed by Pt or Rh metal complexes, preferably as organometallic compounds to enhance their solubility. The following mechanism has been proposed (oxidative addition of the $\equiv$ Si–H to the Pt complex, H transfer to the double bond, and reductive elimination of the product):



where, to simplify, other Pt ligands and other Si substituents are omitted.

There are no by-products with this reaction. Molded silicone elastomer components cured at room temperature by this addition-reaction mechanism are very accurate in terms of dimensional tolerance (i.e., there is no shrinkage). At elevated temperatures, some shrinkage occurs because of the thermal expansion during cure. However, handling these two-part products (i.e., Si–Vi polymer and Pt complex in one component, Si–Vi polymer and SiH oligomer in the other) requires some precautions. The Pt in the complex is easily bonded to electron-donating substances such as amine or organosulfur compounds to form stable complexes with these "poisons," rendering the catalyst complex inactive and inhibiting the cure.

The preferred cure system can vary by application. For example, silicone medical bonding adhesives use acetoxy cure (condensation cross-linking),

while platinum cure (cross-linking by addition) is used for precise silicone parts with no by-products.

*Elastomer filler*

In addition to the silicone polymers described above, most silicone elastomers incorporate "filler." Besides acting as a material extender, as the name implies, filler acts to reinforce the cross-linked matrix. The strength of silicone polymers without filler is unsatisfactory for most applications [4]. Like most other noncrystallized synthetic elastomers, the addition of reinforcing fillers reduces the tackiness of the silicone, increases its hardness, and enhances its mechanical strength. Fillers might also be employed to affect other properties; for example, carbon black is added for electrical conductivity, or barium sulfate to increase radiopacity. These and other materials are used to pigment the otherwise colorless elastomer; however, care must be taken to select only pigments suitable for the processing temperatures and end-use application.

Generally, the most favorable reinforcement is obtained by using fumed silica, such as Cab–O–Sil®, Aerosil®, or Wacker HDK®. Fumed silica is produced by the vapor phase hydrolysis of silicon tetrachloride vapor in a hydrogen/oxygen flame:

$$SiCl_4 + 2H_2 + O_2 \xrightarrow{1800°C} SiO_2 + 4HCl$$

Unlike many naturally occurring forms of crystalline silica, fumed silica is amorphous. The very small spheroid silica particles (in the order of 10 nm in diameter) fuse irreversibly while still semi-molten, creating aggregates. When cool, these aggregates become physically entangled to form agglomerates. Silica produced in this way possesses remarkably high surface area (100–400 $m^2/g$), as measured by the BET method developed by Brunauer, Emmett, and Teller [4,7,8].

The incorporation of silica filler into silicone polymers is accomplished prior to cross-linking, by mixing the silica into the silicone polymers on a two-roll mill, in a twin-screw extruder, or in a Z-blade mixer capable of processing materials with this rheology.

Reinforcement occurs with polymer adsorption encouraged by the large surface area of the silica, and when hydroxyl groups on the filler surface lead to hydrogen bonds between the filler and the silicone polymer. In this way, reinforcing filler contributes to the high tensile strength and elongation capability of silicone rubber [9]. The addition of filler increases the already high viscosity of the polymer. Uncured silicone elastomers can have viscosities from 10,000 to well over 100,000 mPa · s. Chemical treatment of the silica filler with silanes enhances its incorporation in, and reinforcement of, the silicone elastomer, resulting in increased material strength and tear resistance [2] (Figure 7.1).

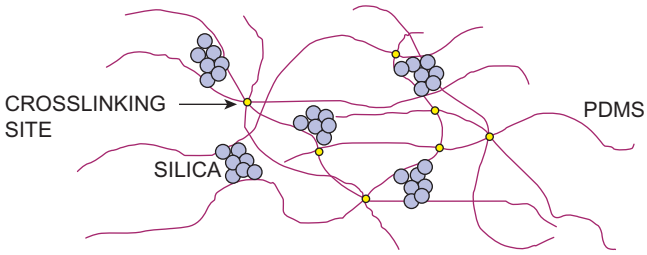



**Figure 7.1** Silicone elastomer/silica network.

Silicone elastomers for medical applications normally use fumed silica as filler, and occasionally appropriate pigments or barium sulfate. Because of their low glass transition temperatures, these compounded and cured silicone materials are elastomeric at room and body temperatures without the use of plasticizers, unlike other medical materials such as PVC, which might contain phthalate additives.

*Processing of silicone elastomers*

In addition to the polymer blend with amorphous silica filler, other ingredients are needed: an initiator or cross-linker plus catalyst. To avoid premature cure during shipment and storage, these ingredients must be separated. Consequently, products for making silicone elastomers are generally supplied as two components or two-part kits, for example, a base and a peroxide paste, or a kit made of Part A containing polymer and catalyst, and Part B containing polymer and cross-linker. These two components are mixed at a fixed ratio at the point of use and formed into the desired shape before cure.

Silicone elastomers are thermosetting materials. They must be formed into the appropriate shape and configuration prior to cross-linking. Unlike a thermoplastic, which can be remelted and formed again, a cured silicone elastomer part cannot be reprocessed. Suitable processing methods for shaping silicone elastomers include casting, extrusion, and molding. The process selected depends on the

viscosity of the feedstock elastomer material, and the shape and configuration of the desired cured elastomer product.

*High Consistency Rubber* (*HCR*). If very high molecular weight silicone polymers are used (silicone "gums" in the trade), the result is high consistency rubbers, which are desirable as they allow for high tear strengths and tensile elongations. Uncured HCRs are putty-like materials that require high shear equipment for processing. These are usually supplied in two parts to be mixed prior to use, either as a silicone base plus a peroxide initiator or as two-part kit using a Pt cure system. These parts are combined using high shear two-roll mills. The mixed material is then shaped into "preforms" before use in compression, transfer or injection molding at elevated temperature. *Compression molding* requires the simplest equipment: a preform is inserted in a mold and cured under high pressure at elevated temperature. The preform must be of an approximate shape that corresponds well to the mold cavity. This allows sufficient material to fill the cavity without producing excessive flash, the overflow material that remains attached to the parts from around the edge of the mold. Removal of flash requires post-processing. *Transfer molding* requires less preparation of the preform: a more precise but simply shaped preform is transferred from a receiving cavity to the mold cavity. *Injection molding* allows for more automation: an extruder system is used to inject a simple ribbon preform directly into the mold cavity. Typical considerations in this case are controlling the exact amount of material sent to the molding cavity to avoid flash, and maximizing speed but avoiding "scorching" (premature cure before the mold cavity is properly filled). HCRs are also used for *extrusion* to produce tubing, as they have enough "green strength" or mechanical integrity when leaving a cooled extruder and prior to enter a curing oven. When peroxides are used, post-cure in a well-ventilated oven is necessary to remove peroxide by-products, which could bloom at the surface and can reduce the stability of the cured elastomer. One part HCR materials, for which all ingredients have been premixed by the supplier, are also available, but have limited shelf-life depending on the cure system.

*Liquid Silicone Rubber* (*LSR*). If lower molecular weight silicone polymers are used, the silicone polymer/silica blend viscosities are lower, leading to liquid silicone rubber. These LSRs are provided as two-part materials that can be used in liquid injection molding—pumped, metered, mixed, and then directly injected in the molding cavity. Processing is eased by the shear-thinning effect that occurs during pumping and injection, reducing the viscosity of the LSR blend and the injection pressures compared to HCR processing. LSRs are particularly well-suited for long automated production runs. Mixing LSR Parts A and B from two 200-liter drums is typically automated using a static mixer prior to direct injection of the precise amount needed. In contrast with the handling of small quantities of HCR on a two-roll mill, preforming, and molding, LSR processing allows more automation. Yet liquid injection molding requires higher investment in the equipment to control the injected amount (to avoid under- or over-filling the mold) precisely. Precise mold cavity temperature control is needed, as cold material is quickly and repeatedly injected into a hot mold. With LSRs, complex molds are needed, preferably with cold runners to avoid premature cure in the feeding lines between injection cycles, with tight specifications still allowing venting (air escape from the mold cavity during injection). The molds may be equipped with complex ejectors to remove parts quickly at the end of the cure, enabling the processing of the next part without loosing thermal control of the mold. The acquisition cost of liquid injection molding machines and sophisticated molds is usually justified for large production runs, as they provide for more efficiency in terms of mold cycle time, overall processing time, and material usage. Cycle time is dependant on operator skills, equipment, and the part to be cured. Typical conditions for LSRs are 0.3−3.0 seconds injection time, 150−200°C cure temperature, and 3−5 sec/mm thickness cure time, depending on formulations [10].

Fabricators of silicone elastomer parts should be aware that these LSRs and other addition-cure products contain an inhibitor, a substance that weakly bonds to the platinum catalyst to moderate its activity, permitting sufficient pot life by avoiding premature cure. If contamination occurs with substances capable of bonding more strongly to the platinum catalyst (e.g., amino or thio compounds), the catalyst (which is present in only minute quantities, typically about 10 ppm) may lose activity, resulting in inhibition of elastomer cure.

*Room Temperature Vulcanizing (RTV) elastomers.* In addition to HCRs and LSRs, which are designed to cure by exposure to heat, other silicone elastomers, known as RTVs, are intended to be cured at room temperature. Typically, RTV elastomers are provided in two-part systems and can be viewed as a variation of the LSRs, but with lower viscosity and less inhibitor. They can be mixed with a spatula and cast after de-airing, and are typically used for laboratory trials and commercially in medical applications for dental impression molding. RTVs are also available as one-part silicone elastomers provided ready to use, usually as adhesives. These materials rely on a condensation reaction and on moisture in the air as the second component to achieve cure.

### 7.1.3.4 Silicone Gels

Silicone gels are typically composed of a very lightly cross-linked silicone elastomer whose polymer network has been swollen with silicone fluids; however, these gels contain no silica or other fillers. Medical applications for silicone gels include breast, testicular, and other soft-tissue implants for tissue augmentation or to help restore one's appearance after cancer surgery. In addition, silicone gel external breast prostheses can be worn in or attached to garments, such as brassieres, for similar purposes. Silicone gel is often supplied in a two-part fluid system and cures via a platinum-catalyzed addition reaction. Parts A and B are mixed at a desired ratio and cured (usually by exposure to elevated temperature) to yield a sticky, cohesive mass of the desired consistency. The consistency of the material can be controlled by the degree of cross-linking, as well as quality and quantity of swelling fluid. After mixing but before curing, the mixture is still liquid and can be pushed through a large gauge needle, enabling the filling of a silicone elastomer implant shell or the thermoformed pouch of an external breast prosthesis made of a thin polyurethane film.

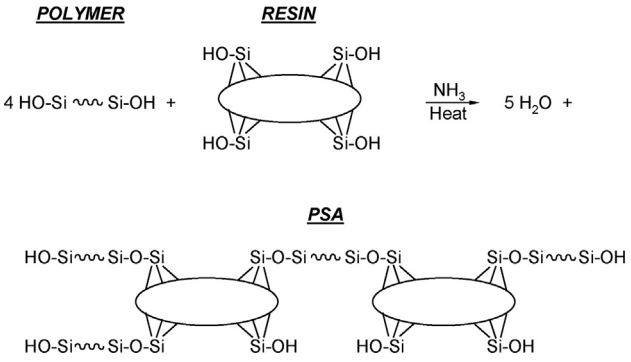
Beyond gel implants and external prostheses, silicone gels find application in skin-contacting sheet goods in wound and scar care.

In addition to gels composed entirely of silicone materials, the gel used in some gel pads for the prevention of pressure sores or for orthotic applications are comprised of a cross-linked silicone polymer network swollen with non-silicone fluids such as mineral oil.

### 7.1.3.5 Silicone Adhesives

Three basic types of silicone adhesives are used in medical applications: bonding, pressure-sensitive, and gel.

1. *Bonding adhesives.* Silicone bonding adhesives are used to attach components together and to seal seams and junctions. Electrical components can also be encapsulated and insulated using silicone bonding adhesive. Silicone bonding adhesives are most commonly formulated as one-part RTV elastomer systems that use a condensation cross-linking reaction, as described earlier in this chapter.
2. *Pressure-sensitive adhesives.* Silicone PSAs are typically formulated in solvent. A silanol end-blocked PDMS undergoes a polycondensation reaction with a silicate resin in the presence of ammonia as catalyst. The ammonia is stripped with heat, and usually the solvent is exchanged.




In some applications, a hot melt silicone PSA is used ostensibly without solvent.

Silicone PSAs have properties that make them well-suited for application in the medical area. Besides their biocompatibility, the materials are highly flexible and permeable to moisture vapor, $CO_2$, and oxygen. Silicone PSAs can provide strong adhesion to the skin, facilitating the attachment of hairpieces, prosthetics, and other devices to the body, and they are widely used in transdermal drug delivery. Due to compatibility concerns with amine-containing drugs, an additional class of silicone PSAs have been generated by the further reaction of the PSA with hexamethyldisilazane to convert the pendant $\equiv$ SiOH groups into $\equiv SiOSi(CH_3)_3$.

3. *Gel adhesives.* Silicone gel adhesives, also known as soft skin adhesives, are used in wound care, and are found to be gentler and less traumatic on removal than the pressure-sensitive types. Unlike PSAs, which are typically formulated in solvent, silicone gel adhesives are supplied in solventless two-part systems. In addition to wound care applications, the materials are also used in the treatment of hypertrophic and keloid scars. Evidence suggests this therapy may reduce scar height and appearance [11].

#### 7.1.3.6 Silicone Film-in-Place, Fast-Cure Elastomers

In addition to the cured silicone elastomers in skin contact applications, *in situ* cure materials have been developed. These materials form films when spread or sprayed on the skin, and then undergo RTV cure. Products such as spray-on wound dressings or drug-loaded lotions have been evaluated. The ability of silicone to spread and form films is related to its low surface tension as described in Section 7.1.4 below [12].

### 7.1.4 Physico-Chemical Properties

The position of silicon just under carbon in the periodic table led to a belief in the existence of analog compounds where silicon would replace carbon. Most of these analog compounds do not exist, or behave very differently from their carbon counterparts. There are few similarities between Si—X bonds in silicones and C—X bonds [2,6,13,14].

Between any given element and Si, bond lengths are longer than for the element and C. The lower electronegativity of silicon ($\chi_{Si} \approx 1.80$, $\chi_C \approx 2.55$) leads to a very polar Si—O bond compared to C—O. This bond polarity also contributes to strong silicon bonding; for example, the Si—O bond is highly ionic and has a high bond energy. To some extent, these values explain the stability of silicones. The Si—O bond is highly resistant to homolytic scission. On the other hand, heterolytic scissions are easy, as demonstrated by the re-equilibration reactions occurring during polymerizations catalyzed by acids or bases.

Silicones exhibit the unusual combination of an inorganic chain similar to silicates and often associated with high surface energy, but with side methyl groups that are very organic and often associated with low surface energy [15]. The Si—O bonds are moderately polar, and without protection would lead to strong intermolecular interactions [6]. Yet, the methyl groups, only weakly interacting with each other, shield the main chain (see Figure 7.2).

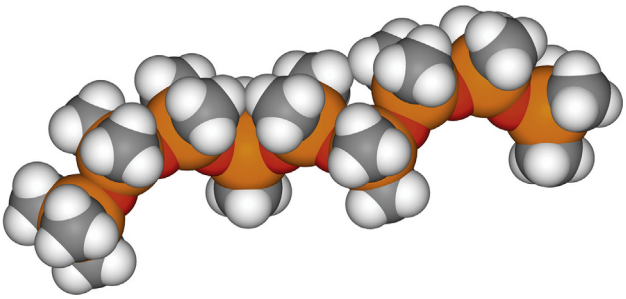


**Figure 7.2** Three-dimensional representation of eicosamethylnonasiloxane, $Me_3SiO(SiMe_2O)_7SiMe_3$ or $MD_7M$. *(Courtesy T. Lane, Dow Corning.)*

The surface activity of silicones is evident in many ways [15]:

- Polydimethylsiloxanes have low surface tension (20.4 mN/m) and are capable of wetting most surfaces. With the methyl groups pointing to the outside, this configuration gives very hydrophobic films and a surface with good release properties, particularly if the film is cured after application. Silicone surface tension is also in the most promising range considered for biocompatible elastomers (20—30 mN/m) [16].
- Silicones have a critical surface tension of wetting (24 mN/m), higher than their own surface tension. This means silicones are capable of wetting themselves, which promotes good film formation and surface coverage.
- Silicone organic copolymers can be prepared with surfactant properties, with the silicone as the hydrophobic part (e.g., in silicone glycol copolymers).

The low intermolecular interactions in silicones have other consequences [15]:

- Glass transition temperatures are very low (e.g., 146°K for a polydimethylsiloxane compared to 200°K for poly-isobutylene, the analog hydrocarbon).

*Continued*

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- The presence of a high free volume compared to hydrocarbons explains the high solubility and high diffusion coefficient of gas into silicones. Silicones have a high permeability to oxygen, nitrogen, or water vapor, even though liquid water is not capable of wetting a silicone surface. As expected, silicone compressibility is also high.
- The viscous movement activation energy is very low for silicones, and their viscosity is less dependent on temperature compared to hydrocarbon polymers. Furthermore, chain entanglements are involved at higher temperature, and contribute to limit viscosity reduction [6].

This shielding is made easier by the high flexibility of the siloxane chain. Barriers to rotation are low, and the siloxane chain can adopt many configurations. Rotation energy around a $H_2C-CH_2$ bond in polyethylene is 13.8 kJ/mol, but is only 3.3 kJ/mol around a $Me_2Si-O$ bond, corresponding to a nearly free rotation. In general, the siloxane chain adopts a configuration so that the chain exposes a maximum number of methyl groups to the outside, whereas in hydrocarbon polymers, the relative rigidity of the polymer backbone does not allow selective exposure of the most organic or hydrophobic methyl groups. Chain-to-chain interactions are low, and the distance between adjacent chains is also greater in silicones. Despite a very polar chain, silicones can be compared to paraffin, with a low critical surface tension of wetting [15].

## 7.2 Conclusion

Polydimethylsiloxanes are often referred to as silicones. They are used in many applications because of their stability, low surface tension, and lack of toxicity. Methyl group substitution or introduction of tri- or tetrafunctional siloxane units leads to a wide range of structures. Polymers are easily cross-linked at room or elevated temperature to form elastomers, without losing their advantageous properties.

## Acknowledgments

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# 8 Review of Research in Cardiovascular Devices

*Zbigniew Nawrat*

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## 8.1 Introduction

Remarkable advances in biomedical engineering create new possibilities of help for people with heart diseases. This chapter provides an overview of research in cardiac surgery devices. An explosion in multidisciplinary research, combining mechanical, chemical, and electrical engineering with physiology and medicine, during the 1960s created huge advances in modern health care. This decade opened new possibilities in aerospace traveling and in human body organ replacement. *Homo sapiens* after World War II trauma became not only the hero of mind and progress but also the creator of the culture of freedom. Computed tomographic (CT) scanning was developed at EMI Research Laboratories (Hayes, Middlesex, England) funded in part by the success of EMI's Beatles records. Modern medical imaging techniques such as CT, nuclear magnetic resonance (NMR), and ultrasonic imaging enable the surgeon to have a very precise representation of internal anatomy as preoperative scans. It creates possibilities of realizing new intervention methods, for instance, the very popular bypass surgery. It was a revolution in disease diagnosis and generally in medicine. In cardiovascular therapy, lifesaving implantable defibrillators, ventricular assist devices (VADs), catheter-based ablation devices, vascular stent technology, and cell and tissue engineering technologies have been introduced.

Currently, the number of people on Earth is more than 6 billion: increasingly lesser number of living organisms and about million increasingly more "intelligent" robots accompany them.

Robotics, a technical discipline, deals with the synthesis of certain functions of the human using some mechanisms, sensors, actuators, and computers. Among many types of robotics is the medical and rehabilitation robotics—the latest but rapidly developing branch at present, which includes the manipulators and robots providing surgery, therapy,

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prosthetics, and rehabilitation. They help fight pareses in humans and can also fulfill the role of a patient's assistant. Rehabilitation manipulators can be steered using ergonomic user interfaces—e.g., the head, the chin, and eye movements. The "nurse" robots for patients and physically challenged persons' service are being developed very quickly. Partially or fully robotic devices help in almost all life actions, such as person moving or consuming meals, simple mechanical devices, science education, and entertainment activities. HelpMate, an already existing robot-nurse, moving on the hospital corridors and rooms delivers meals, helps find the right way, etc.

On the one hand, robots are created that resemble the human body in appearance (humanoids), able to direct care; on the other hand, robotic devices are constructed—telemanipulators—controlled by the human tools allowing to improve the precision of human tasks. Robots such as ISAC (Highbrow Soft Arm Control) or HelpMate can replace several functions of the nurse, who will give information, help find the way, bring the medicines and the meal. In case of lack of qualified staff, to provide care for hospice patients at home, these robots will be of irreplaceable help.

Robotic surgery was born out of microsurgery and endoscopic experience. Minimally invasive interventions require a multitude of technical devices: cameras, light sources, special tools (offering the mechanical efficiency and tissue coagulation for preventing bleeding), and insufflations (thanks to advances in computer engineering, electronics, optics, materials, and miniaturization). The mobility of instruments is decreased [from seven, natural for human arm, to four degrees of freedom (DOFs)] due to the invariant point of insertion through the patient's body wall. Across the world, physicians and engineers are working together toward developing increasingly effective instruments to enable surgery using the latest technology. The leading technology presents robots intended to keep the surgeon in the most comfortable, dexterous, and ergonomic position during the entire procedure. The surgery is complex and requires precise control of position and force. The basic advantages of minimally invasive robot-aided surgery are safe, reliable, and repeatable operative results with less patient pain, trauma, and recovery time. Conventional open-heart surgery requires full median sternotomy, which means cracking of sternum, compromising pulmonary function, and considerable loss of blood.

| Milestones in the Evolution of Cardiac Devices | |
|---|---|
| 1628 | William Harvey, St Bartholomew's Hospital, London, presented his theory of the circulatory system. He described the function of the heart, arteries, and veins. It is considered to be one of the greatest advances in medicine. |
| 1812 | Julien-Jean Cesar LeGallois, a French physician, proposed the idea of artificial circulation. |
| 1882 | German von Schröder introduced the first bubble oxygenator. |
| 1929 | Werner Forssmann, a German surgeon, developed the technique of cardiac catheterization, the first to document right heart catheterization in humans using radiographic techniques (won the Nobel Prize in 1956). |
| 1934 | Dr Michael DeBakey invented the DeBakey pump (peristaltic). |
| 1937 | Artificial heart designed by the Soviet scientist W.P. Demichow was first successfully applied on the dog for 5.5 h. |
| 1949 | IBM developed the Gibbon Model I heart–lung machine, delivered to Jefferson Medical College, Philadelphia, PA, USA. It consisted of DeBakey pumps and film oxygenator. |
| 1952 | Paul Zoll developed the first cardiac pacemaker. |
| 1952 | Charles Hufnagel sewed an artificial valve into a patient's aorta. |
| 1953 | Dr John H. Gibbon, Jr, Jefferson Medical College Hospital, Philadelphia, PA, USA, first successfully applied extracorporeal circulation in an 18-year-old female with an atrial septal defect. |

(*Continued*)

*—Cont'd*

| Milestones in the Evolution of Cardiac Devices | |
|---|---|
| 1953 | Dr Michael DeBakey, Baylor University, Houston, TX, USA, implanted a seamless, knit Dacron tube for surgical repairs and/or replacement of occluded vessels or vascular aneurysms. |
| 1957 | Wild et al. reported the use of ultrasound to visualize the heart noninvasively. |
| 1957 | Dr C. Walton Lillehei and Earl Bakken, an electronic engineer, developed the first portable pacemaker. Bakken later formed the Medtronics Corporation. |
| 1957 | Drs William Kolff and Tetsuzo Akutsu at the Cleveland Clinic implanted the first artificial heart in a dog. The animal survived for 90 min. |
| 1958 | Dr Mason Sones, a cardiologist at the Cleveland Clinic Foundation, developed coronary angiography. |
| 1960s | Semm et al. developed laparoscopic instrumentation. |
| 1960 | Dr Albert Starr, an Oregon surgeon, developed the Starr–Edwards heart valve. One of the most successful heart valves produced until the late 1970s. |
| 1967 | René Favaloro, an Argentine surgeon in the United States, performed the first coronary bypass operation using the patient's native saphenous vein as an autograft. |
| 1967 | Christiaan Barnard performed the first heart transplantation. |
| 1968 | A. Kantrowitz et al. performed the first clinical trial in a man with intra-aortic balloon pumping. |
| 1969 | Dr Denton Cooley, Texas Heart Institute, Houston, TX, USA, implanted a total artificial heart (TAH) designed by Domingo Liotta. The device served as a "bridge" to heart transplantation until a donor heart was found, for 64 h. The heart transplant functioned for an additional 32 h until the patient died of pneumonia. |
| 1971 | White—ECMO on newborn babies using veno-venous bypass for up to 9 days. |
| 1975 | A. Gruentzing developed the first balloon catheter. |
| 1975 | Dr Willem Kolff, University of Utah, designed a nuclear-powered artificial heart (Westinghouse Corporation). |
| 1975 | BioMedicus BioPump (Centrifugal) introduced for clinical applications. |
| 1975 | Computerized axial tomography, the "CAT scanner," was introduced. |
| 1977 | Newer generations of mechanical prostheses included the mono-leaflet (Medtronic-Hall) and the bi-leaflet (St Jude Medical). |
| 1979 | The Jarvik TAH was designed using a flexible four-layer diaphragm and a structural design that fits in the human chest. This design was a larger 100 cc version of today's CardioWest TAH-t, which is 70 cc. |
| 1981 | Dr Denton Cooley implanted another pneumatically driven artificial heart designed by Dr Akutsu. This artificial heart was used for 27 h as a "bridge" to cardiac transplantation. |
| 1982 | Dr William DeVries implanted the Jarvik 7 into Barney Clark, DDS. Dr Clark lived for 112 days. |
| 1984 | Baby girl Faye's native heart, Loma Linda Medical Center, was explanted and replaced with a baboon heart. She survived for 3 weeks. |
| 1984 | First human implant and successful bridge-to-transplant—a Novacor® LVAS. |
| 1985 | The FDA gave approval for Hershey Medical Center to perform six PennState artificial heart implants as bridges to human heart transplantations. This heart is no longer used with human subjects. |

(*Continued*)

*—Cont'd*

| Milestones in the Evolution of Cardiac Devices | |
|---|---|
| 1985 | At the University of Arizona, Dr Jack Copeland implanted a prototype TAH in a patient who had rejected a recently transplanted heart. |
| 1986 | The first atherectomy devices that remove material from the vessel wall were introduced. |
| 1987 | Introduction of the first use of coronary stent (by 1997, more than 1 million angioplasties had been performed worldwide). |
| 1990 | First LVAS patient discharged home with a Novacor LVAS. |
| 1990–1992 | The FDA had withdrawn the Investigational Device Exemption (IDE) from Symbion for the clinical study of the Jarvik TAH. Symbion subsequently donated the TAH technology to University Medical Center (UMC), Tucson, AZ, USA, which reincorporated the company and renamed it CardioWest. |
| 1994 | First FDA-approved robot for assisting surgery [automated endoscopic system for optimal positioning (AESOP) produced by Computer Motion (CM; Goleta, CA, USA)]. |
| 1994 | FDA approved the pneumatically driven HeartMate® LVAD (Thoratec Corporation, Burlington, MA, USA) for bridge to transplantation (the first pump with textured blood-contacting surfaces). |
| 1994 | HeartMate LVAS has been approved as a bridge to cardiac transplantation. |
| 1996 | REMATCH Trial (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart failure, E. Rose principal investigator) initiated with HeartMate® VE (Thoratec Corp.). Results published in 2002 showed mortality reduction of 50% at 1 year as compared to patients receiving optimal medical therapy. |
| 1998 | Simultaneous FDA approval of HeartMate VE (Thoratec Corporation, Burlington, MA, USA) and Novacor LVAS (World Heart Corporation, Ontario, Canada), electrically powered, wearable assist systems for bridge to transplantation, utilized in more than 4000 procedures to 2002. Till now, we can estimate 4500 HeartMate XVE, more than 440 IVAD (Implantable Ventricular Assist Device) and more than 1700 Novacor in this kind of blood pump. |
| 1998 | First clinical application of next-generation continuous-flow assist devices. DeBakey (MicroMed Inc.) axial-flow pump implanted by R. Hetzer, G. Noon, and M. DeBakey. |
| 1998 | Carpentier and Loulmet performed first in the world endoscopic operation of single bypass graft between left internal thoracic artery and left anterior descending (LITA–LAD) and first operation inside the heart–mitral valve plastic and atrial septal defect closure was performed using surgical robot da Vinci (Intuitive Surgical, Sunnyvale, CA, USA). |
| 1998 | Mohr and Falk bypass surgery and mitral valve repairs in near endoscopic technique (da Vinci). |
| 1999 | First clinical application of a totally implantable circulatory support system. LionHeart LVAS implanted in a 67-year-old male recipient by R. Koerfer and W. Pae. |
| 1999 | D. Boyd first totally endoscopic coronary artery bypass graft (E-CABG) using Zeus robot (Computer Motion, CA, USA, currently intuitive surgical, not in the market). |
| 2000 | Physicians in Houston, USA, have realised the implantation and have got the first patient in the clinical investigation of the Jarvik 2000 Heart. Jarvik Heart, Inc. and the Texas Heart Institute began developing the Jarvik 2000 Heart in 1988. |
| 2000 | THI was granted permission by the Food and Drug Administration to evaluate the Jarvik 2000 Heart as a bridge to transplantation in five patients. |
| 2000 | The FDA gave permission to extend the study. Patients have been sustained for more than 400 days with this device. (http://www.texasheartinstitute.org/Research/Devices/j2000.cfm). |

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| Milestones in the Evolution of Cardiac Devices | |
|---|---|
| 2001 | The AbioCor was implanted in Robert Tools by cardiac surgeons Laman Gray and Robert Dowling on July 2, 2001, at Jewish Hospital in Louisville, Kentucky. L. Robert Tools aged 59 years with the artificial heart survived 5 months. He died because of the blood clot. |
| 2001 | Doctors Laman Gray and Robert Dowling in Louisville (KY, USA) implanted the first autonomic artificial heart—AbioCor (Abiomed, Inc., Danvers, MA, USA). The FDA approved the Abiocor for commercial approval under a Humanitarian Device Exemption in September, 2006. ABIOMED is also working on the next generation implantable replacement heart, the AbioCor II. Incorporating technology both from ABIOMED and Penn State, the AbioCor II is smaller and is being designed with a goal of 5-year reliability. The BVS 5000 was the first extracorporeal, or outside the body, ventricular assist device on the market and is still the most widely used bridge to recovery device with systems located in more than 700 institutions throughout the world. Abiomed also offers the Impella 2.5—a minimally invasive, percutaneous ventricular assist device that allows the heart to rest and recover (http://www.abiomed.com/products/faqs.cfm). |
| 2001 | Drs Laman Gray and Robert Dowling in Louisville (KY, USA) implanted the first autonomic artificial heart—AbioCor (Abiomed Inc., Danvers, MA, USA). |
| 2001 | The first transatlantic telesurgery—Lindbergh operation—surgeon from New York operated patients in Strasburg using Zeus system. |
| 2001 | The first full implantable TAH Lion Heart (the Texas Heart Institute in Houston, Abiomed in Danvers, US) was used. The first-ever human implant of the LionHeart™ left ventricular assist system took place October 26, 1999 at the Hearzzentrum NRW in Bad Oeynhausen, Germany. Eight patients have lived with the device for more than 1 year, and four patients have lived with the device for more than 2 years. The Food and Drug Administration approved the first series of US clinical trials for the Arrow LionHeart™ heart assist device in February 2001. Penn State Milton S. Hershey Medical Center implanted the device in the first US patient later that month (http://www.hmc.psu.edu/lionheart/clinical/index.htm). |
| 2001 | The first totally implantable TAH LionHeart (the Texas Heart Institute in Houston, TX, USA; Abiomed in Danvers, MA, USA) was used. |
| 2002 | FDA approved the HeartMate VE LVAD forpermanent use (Thoratec Corp.). |
| 2002 | Novacor LVAS became the first implanted heart assist device to support a single patient for longer than 5 years. |
| 2002 | The first percutaneous aortic valve replacement was performed by Alain Cribier in April of 2002. |
| 2004 | The CardioWest TAH-t becomes the world's first and only FDA-approved temporary total artificial heart (TAH-t). The indication for use is as a bridge to transplant in cardiac transplant patients at risk of imminent death from nonreversible biventricular failure. SynCardia Systems, Inc. (Tucson, AZ, USA) is the manufacturer of the CardioWest™ TAH-t. It is the only FDA- and CE-approved TAH-t in the world. It is designed for severely ill patients with end-stage biventricular failure. The TAH-t serves as a bridge to human heart transplant for transplant eligible patients who are within days or even hours of death. A New England Journal of Medicine paper published on August 26, 2004 (NEJM 2004; 351: 859−867), states that in the pivotal clinical study of the TAH-t, the 1-year survival rate for patients receiving the CardioWest TAH-t was 70% versus 31% for control patients who did not receive the device. One-year and 5-year survival rates after transplantation among patients who had received a TAH-t as a bridge to human heart transplant were 86% and 64%. The highest bridge to human heart transplant rate of any heart device is 79% (New England Journal of Medicine 2004; 351: 859−867). Over 715 implants account for more than 125 patient years on the TAH-t (http://www.syncardia.com). |

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| Milestones in the Evolution of Cardiac Devices | |
|---|---|
| 2005 | A total of about 3000 cardiac procedures were performed worldwide using the da Vinci system. This includes totally endoscopic coronary artery bypass grafting (TECAB), mitral valve repair (MVR) procedures, ASD closure, and cardiac tissue ablation for atrial fibrillation. |
| 2006 | The next-generation pulsatile VAD, the Novacor II, entered a key phase of animal testing with the first chronic animal implant. |
| 2006 | The FDA approved the first totally implantable TAH—developed by AbioCor—for people who are not eligible for heart transplantation and who are unlikely to live more than a month without intervention. |
| 2006 | Have experience with human implantation: Edwards Lifesciences ($>100$ patients) and Core Valve ($>70$ patients). (www.touchbriefings.com/pdf/ 2046/Babaliaros.pdf) |
| 2006 | US FDA approval to start pilot clinical trial for Impella 2.5 (Abiomed, Inc., Danvers, MA, USA). To date the Impella 2.5 has been used to support over 500 patients during high-risk PCI, post PCI, and with AMI with low cardiac output. |
| 2007 | More than 4,500 in 186 centers advanced heart failure patients worldwide have been implanted with the HeartMate XVE. Longest duration of support (ongoing patient on one device): 1,854 days, age range: 8–74 (average 51). The REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) clinical trial demonstrated an 81% improvement in two-year survival among patients receiving HeartMate XVE versus optimal medical management. A Destination Therapy study following the REMATCH trial demonstrated an additional 17% improvement (61% vs. 52%) in one-year survival of patients receiving the HeartMate XVE, with an implication for the appropriate selection of candidates and timing of VAD implantation. |
| 2008 | State of art in 2008, based on the experience almost 20–30 years shows among others:<br>– future of long-term heart support methods will be connected with rotary pumps, the stop of activity in pulsating pump technology is observed (rotary pumps are smaller and comfortable in the implantation especially it is possible introduce mini invasive surgical methods)<br>– the mono-leaflet disk valve are applied more and more seldom (they require during the implantation the definite orientation in the heart) in the comparison with bi-leaflet<br>– the new kind of biological valve prostheses based on tissue engineering method get into the clinical experiment<br>– the multiple companies have engineered percutaneous heart valves (PHV), primarily for aortic stenosis |
| 2008 | There have been 867 unit shipments worldwide—647 in the United States, 148 in Europe and 72 in the rest of the world (http://www.intuitivesurgical.com). Devices for "robotic surgery" are designed to perform entirely autonomous movements after being programmed by a surgeon. The *da Vinci* Surgical System is a computer-enhanced system that interposes a computer between the surgeon's hands and the tips of microinstruments. The system replicates the surgeon's movements in real time. |

## 8.2 The Heart Diseases

The human biological heart has two sets of pumping chambers. The right atrium receives oxygen-depleted blood from the body, which is pumped into the lungs through the right ventricle. The left atrium receives aerated blood from the lungs, which is pumped out to the body through the left ventricle. With each heart beat, the ventricles contract together. The valves control the direction of blood flow through the heart.

Congestive heart failure, a condition in which the heart is unable to pump the blood effectively

throughout the body, is one of the leading causes of death. This disease is caused by sudden damage from heart attacks, deterioration from viral infections, valve malfunctions, high blood pressure, and other problems. Although medication and surgical techniques can help control symptoms, the only cure for heart failure is heart transplantation. Artificial hearts and pump assist devices have thus been developed as potential alternatives.

Ischemic heart disease is caused by progressive atherosclerosis with increasing occlusion of coronary arteries resulting in a reduction in coronary blood flow. Blood flow can be further decreased by superimposed events such as vasospasm, thrombosis, or circulatory changes leading to hypoperfusion. Myocardial infarction (MI) is the rapid development of myocardial necrosis caused by a critical imbalance between the oxygen supply and the oxygen demand of the myocardium. Coronary artery bypass grafts (CABGs) are implanted in patients with stenosed coronary arteries to support myocardial blood flow.

Valvular heart disease is a life-threatening disease that affects millions of people worldwide and leads to valve repairs and/or replacements.

In the USA and Europe alone, with more than 600 million inhabitants and more than 6 million patients with heart failure, the prevalence of advanced heart failure, constituting 1−10% of the heart failure population, is estimated to total between 60,000 and 600,000 patients. More than 700,000 Americans die each year from heart failure, making it the number one cause of death in the USA, as well as worldwide. About half of these are sudden cardiac deaths, which occur so quickly that there is not enough time for intervention with a cardiac assist or replacement device. For the remaining half, heart transplantation is one of the few options available today. Though hundreds of thousands are in need, only about 2,000 people in the USA will be able to receive donor hearts every year. This consistent shortage in the supply of donor hearts in the USA demonstrates the need for an alternative to heart transplantation. The total potential market for the artificial heart is more than 100,000 people in the USA each year (http://www.abiomed.com).

## 8.3 The Cardiovascular Devices in Open-Heart Surgery

Cardiac surgery is surgery on the heart and/or great vessels. This surgery is a complex procedure requiring precise control of position and force. Conventional open-heart surgery requires full median sternotomy, which means cracking of sternum, compromising pulmonary function, and considerable loss of blood.

The repair of intracardiac defects requires a bloodless and motionless environment, which means that the heart should be stopped and drained of blood. Hence, the patient requires the function of the heart and lungs provided by an artificial method.

Modern heart−lung machines can perform a number of other tasks required for a safe open-heart operation. This system preserves the patient's own blood throughout the operation and the patient's body temperature can be controlled by selectively cooling or heating the blood as it flows through the heart−lung machine. Medications and anesthetic drugs can be administered via separate connections. The disadvantages include the formation of small blood clots, which increase the risk of stroke, pulmonary complications, and renal complications. The machine can also trigger an inflammatory process that can damage many of the body's systems and organs. Those risks push today's biomedical engineers to improve the heart−lung machine and oxygenator, while surgeons are developing advances that would eliminate the need for the machine altogether. One such advance is minimally invasive surgery (MIS).

The surgeons have begun to perform "off-pump bypass surgery"—coronary artery bypass surgery without the aforementioned cardiopulmonary bypass. The surgeons operate on the beating heart stabilized to provide an (almost) still work area. One of the greatest challenges in beating-heart surgery is the difficulty of suturing or sewing on a beating heart. A stabilization system makes it possible for the surgeon to work on the patient's beating heart carefully and, in the vast majority of cases, eliminates the need for the heart-lung machine.

### 8.3.1 Blood Pumps

The human heart is a pump that is made of muscle tissue. A special group of cells called the sinus node is located in the right atrium. The sinus node generates electrical stimuli that make the heart contract and pump out blood. The normal human heart beats about 75 times per minute (i.e., about 40 million times a year)—i.e., the heart pumps 5 l of

blood per minute. The normal systemic blood pressure is 120/80 mmHg. The mechanical power (calculated by multiplying the pressure by the flow rate) of the human heart is about 1.3 W. However, to provide this mechanical power, the heart requires 10 times much higher rate of energy turnover, owing to its low mechanical efficiency (less than 10%).

However, the development in biotechnology can open the opportunity for tissue engineering (a branch of biotechnology)—a prospect of saving people with extremely complex or irreversible failure heart will still be realized using mechanical heart support devices.

During the last half-century, various blood pumps were introduced into clinical practice, which can partially support or replace the heart during open-heart surgery or considerably for a longer time period until heart recovers or until transplantation is performed. Several millions of people owe their health and lives to these devices. According to the American Heart Association, an estimated 5 million Americans are living with heart failure and more than 400,000 new cases are diagnosed every year. About 50% of all patients die within 5 years.

The first operation on a beating heart was performed by Gibbon in 1953 using a peristaltic pump. Since then, there has been rapid development in mechanical assist devices, leading to the realization of today's mechanical aid system for blood circulation, based on the requirements using the following:

- intra-aortic balloon pump (IABP)
- continuous blood flow devices—roll and centrifugal rotary pumps
- pulsating flow blood pumps—pneumatic or electro-control membrane pumps

The assumed time of blood pump using in the organism influences the construction and material used in its design. According to this criterion, the pumps can be divided into following categories:

- short-term (during the operation or in sudden rescue operations)
- medium-term—over several weeks or months (as a bridge to heart transplantation or treatment)
- long-term—several years (already at present) and permanently (in the intention) (as the target therapy)

The extracorporeal circulation (*perfusion*) and the controlled stopping of heart action make it possible to perform the open-heart operation. The peristaltic pumps are in common use, where the turning roll locally tightens the silicon drain to move a suitable volume of the blood. The disadvantages of this procedure, such as the damage to blood components, are eliminated or reduced by pump construction and material improvement. The patients with both heart and lung failure are assisted by the system consisting of pump and oxygenator. The method of time oxygenation (supply oxygen to the blood) for extracorporeal blood—extracorporeal membrane oxygenation (ECMO)—was applied the first time in 1972 by Hill. The blood pump, membrane oxygenator, heat exchanger, and a system of cannulas (tubes) for patient's vascular system connection are the elements of the system. Inner surface of all these parts are covered with heparin. The Extracorporeal Life Support Organization Registry has collected (since 1989) data on more than 30,000 patients, most of whom have been neonates with respiratory failure [7]. The currently available centrifugal pump VADs are BioMedicus BioPump (Medtronic, Minneapolis, MN, USA), CentriMag (Levitronix, Zürich, Switzerland), RotaFlow (Jostra, Hirrlingen, Germany), and Capiox (Terumo, Ann Arbor, MI, USA). These pumps have been available since 1989 to support neonates and older children with postoperative cardiac failure but competent lung function.

*Centrifugal pumps* benefit from the physical phenomena (centrifugal, inertia force) of blood acceleration during temporal rotational movement. These pumps consist of a driving unit and an acrylic head driven by a magnetic couple. Input and output blood flow channels are perpendicular to each other. The output velocity of the blood on the conical rotor depends on the input rotary speed, preload, and afterload. Based on vortex technology, these pumps use turbine spins of 10,000−20,000 rpm to create a flow of 5−6 l/min and have generally been applied for temporary assistance of stunned myocardium of the left ventricle. The construction of working pump and its environment conditions influence the blood hemolysis during its use. According to the results of in vitro experiment, with the pump working as VAD and extracorporeal circulation (CPB and ECMO), the use of the pump as VAD caused the least degree of hemolysis, and

the hemolysis of pumps in the time to ECMO strongly depends on the kind of oxygenator used. Pumps with the conical rotor caused a greater degree of hemolysis working with small flows and large pressures (ECMO). On the contrary, a lesser degree of hemolysis was observed for pumps with the flat rotor, regardless of its purpose.

The *intra-aortic balloon* was introduced as a tool for coronary circulation assistance in works of Maulopulos, Topaz, and Kolff in 1960. In 1968, Kantrowitz was the first to prove the clinical effectiveness of intra-aortic counterpulsation. It became the classic method in the 1970s, thanks to Datascope Company for its first device (System 80) for their clinical applications. The balloon (30−40 ml) placed in the aorta, synchronically with the heart, is filled up and emptied by raising the diastolic pressure and the perfusion of coronary arteries. As a result, the myocardial contractibility is improved, and hence, the cardiac output is bigger. This is one of the basic devices in cardiosurgery units. The balloon, rolled up on a catheter, is introduced through the artery. Kantrowitz introduced to cardiosurgery also another type of pump called the *aortic patch*, which has been in clinical use for many years, and uses the natural localization of heart valve. The balloon, which is sewn to cut the descending aorta, is connected through the skin with the pneumatic driver unit. The aortic blood flow is improved by the pulsate balloon filling and the aortic valve blocked the backflow to the ventricle.

New constructions of TAHs and VADs offer new hope for millions of heart patients whose life expectancy is greatly reduced because the number of patients waiting for a transplant far exceeds the donated hearts available. An artificial heart or VAD is made of metal (typically titanium−aluminum−vanadium alloy), plastic, ceramic, and animal parts (valve bioprostheses). A blood-contacting diaphragm within the pump is made from a special type of polyurethane that may also be textured to provide blood cell adherence.

The VAD (Figure 8.1) is an extracorporeal pneumatic blood pump, invented to assist a failure left or right ventricle, or the whole heart until it

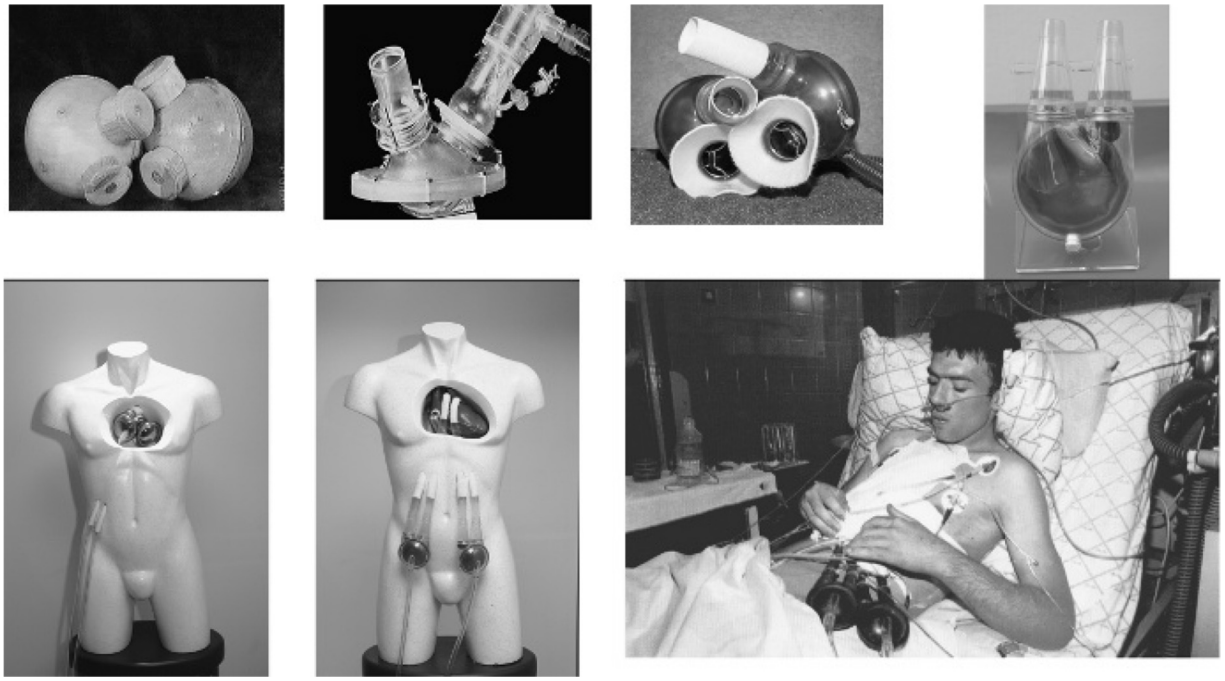


**Figure 8.1** The steps in POLTAH design process (model after cadaver study, transparent model for laser visualization investigation, first polyurethane model for starting animal experiments). Nonsymmetrical shape of POLVAD proposed and designed creates a very good internal flow condition. The first successful POLVAD implantation was performed in 1993 in T. Gruszczyński. Until now, more than 200 POLVAD clinical implantations have been performed, the longest time successful application being over 200 days. Pneumatically driven artificial heart (POLTAH) and ventricular assist device (POLVAD).

recovers or until a replacement by transplantation is performed. A mechanical heart assist is used to support the heart during failure caused by the ischemia of the heart muscle, the small cardiac output, cardiomyopathy, or heart valve diseases. The role of these aid pumps is to support the life function of the brain and other organs and heart treatment (thanks to the devices that partly take over its role) by improving hemodynamic conditions. It is fitted with inflow and outflow cannulas for connecting the VAD with heart and vascular system in parallel with the biological heart ventricle being assisted. The VAD consist one or two ventricles placed outside the body (failing heart is left in place) connected to the control unit.

The TAH (Figure 8.2) is designed for emergency replacement of irreversible damaged natural heart. Because the natural heart is completely removed, the TAH must ensure the hemodynamic, regulatory, and control functions of the circulatory system.

If the total replacement artificial heart is to mimic the function of the natural human heart, it meet the following requirements [1]:

1. Two separate pumps duplicating the left and the right heart
2. Output range of 5−10 l/min from each side
3. Aortic arterial pressure range of 120−180 mmHg
4. Pulmonary arterial pressure range of 20−80 mmHg
5. Physical dimensions permitting easy surgical insertion within the pericardium
6. Low weight to minimize restraints
7. A minimum of noise and vibration
8. A heat output of less than 25 W
9. A low degree of hemolysis
10. Inert to body chemicals

The artificial heart, designed by the Soviet scientist W.P. Demichow, was first successfully applied on a dog for 5.5 h in 1937. Several study groups in the United States in the 1950s performed the first clinical experiments. In 1957T. Akutsu and W. Kolff (Figure 8.3) made the pneumatically driven artificial heart. The artificial heart constructed by D. Liotta with the same drive type successfully replaced the patient heart for 64 h, before heart transplantation in 1969. On 4 April 1969, Dr Denton A. Cooley performed the first human implantation of a TAH when he used a device developed by Dr Domingo Liotta to sustain the life

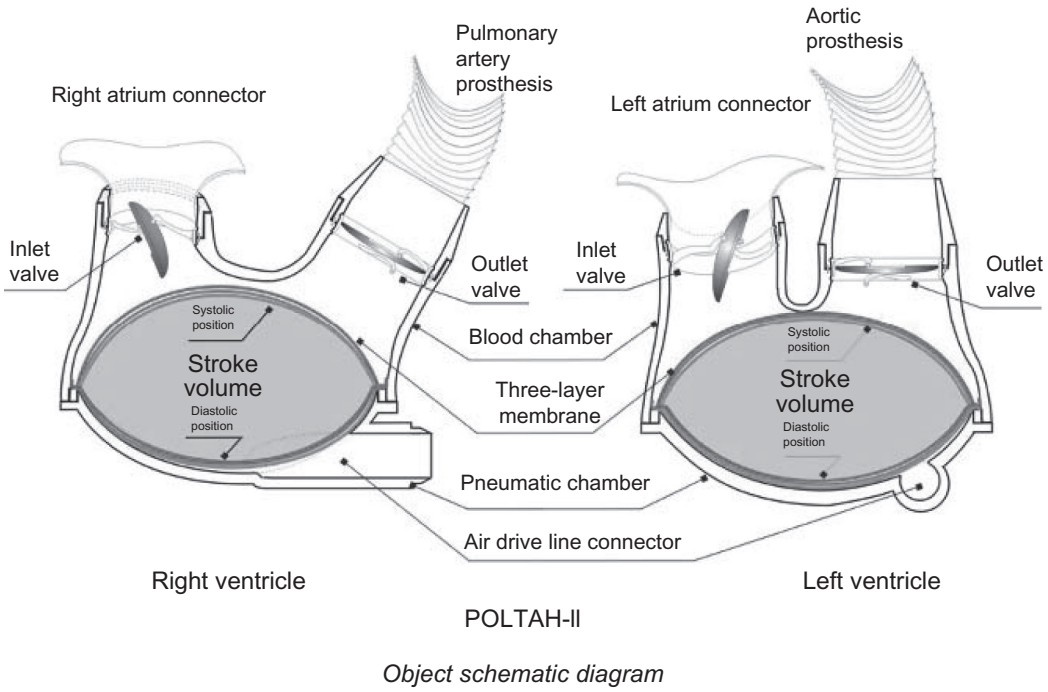



**Figure 8.2** Schematic diagram of an artificial heart.



**Figure 8.3** William Kolff in Kampen and in Gent (*photo taken by the author*).

of Mr Haskell Karp. After having undergone resection of a left ventricular aneurysm, the 47-year-old patient developed cardiac failure. The Liotta heart supported him for nearly 3 days until a suitable donor heart was available and successfully transplanted. This case demonstrated the feasibility of bridging to transplantation with a mechanical circulatory support system.

In 1982 William DeVries (UT, USA) implanted the artificial heart designed by R. Jarvik, cooperating in that time with W. Kolff, *called Jarvik* 7 in a patient for 112 days. The Jarvik heart was pneumatically driven (driver unit called COMDU) through a drain carried out by the skin. Four disk valves from Medtronic-Hall were fixed in the polyurethane body. The inner surface of ventricle was covered with a smooth layer of polyurethane (Biomer, Ethicon Inc.) and a four-layer membrane made from Biomer that separated the pneumatically driven part from the part having contact with the blood. There were two types of these VADs: Jarvik 7−70 and Jarvik 7−100 with 70 and 100 ml of stroke volume, respectively. Since 1993, these types of the artificial heart after a little modification have been clinically used [now under the name CardioWest (the technology transferred from the firm Symbion to CardioWest Technologies Inc., Tuscon, AZ, USA currently Syncardia Systems, Inc. Tucson, AZ, USA) and is marked C-70 and C-100, respectively]. The pump can operate at 30−199 bpm and also has variable systolic duration, delay, and stroke volume. By 1989, such devices had largely become a bridge to human heart transplantations. In a pivotal clinical study [2], these patients were successfully transplanted 79% of the time. The 1-year and 5-year survival rates after heart transplantation among these patients were 86 and 64%, respectively.

In Europe, the hospital La Pitié in Paris has the biggest experiences in implanting the artificial heart in patients. From April 1986 to June 2000, there had been 120 implantations of pneumatically driven Jarvik VADs (with the trade name TAH *Symbion* and at present TAH CardioWest). The total time of the implantation was more 3000 days (with the longest being 607 days implantation). Another type of pneumatically driven TAH named *PennState* was made at the Pennsylvania State University, where ventricles were also made from Biomer, but sacks were used instead of membrane-type construction. PennState VAD with the Björk−Shiley (B−S) disk valves was considerably not as often applied as the Jarvik heart.

As a next stage, the electrically powered PennState artificial heart was constructed. In this device, a DC brushless motor turns over the helical (screw) drive, which causes compression and expansion of segment polyurethane sack resulting in an 8 l/min volume flow with 16−22 W of consumed power. The total animal experimentation time is about 5 years at present, the longest trial being more than 5 months. Searching for the biocompatible and durable biomaterials in 1969, Y. Nose made the steel heart covered with Teflon (so-called *Green Heart*), which he implanted in the ram for 50 h. There were also trials to use properly prepared heart pericardium for the internal structure

of the ventricle. Electrohydraulic artificial heart (Japan) *EHTAH* is equipped with ellipsoidal ventricle membranes made from nonthrombogenic, segmented polyurethane, 21 and 23 mm B−S valves and vascular Dacron grafts (Medox Medical, USA). *Baylor* TAH (Baylor College of Medicine, USA) is the electromechanical pump (the rotation of the screw causes the movement of membrane). The membrane is made from polyolefin rubber, the ventricle body from epoxy Hysol (Dexter Electronic Materials, USA) or at present from coal fibers, which is lighter and stronger. In the laboratory of Kolff, small ventricles with semielastic shell were worked out. They were made from Pellethane 80AE/2363 (Dow Chemical, Japan) by the vacuum forming and glued by dielectric welding. Valves are made from Isoplast, covered with Pellethane, and glued. W. Kolff sent the sets of ventricles to many centers in the world, for realization experiments, to Poland as well. In Zabrze comparative in vitro investigations were carried out with these ventricles to detect the extent of artificially induced thrombogenesis.

*AbioCor* implantable replacement heart (Abiomed, Inc., Danvers, MA, USA) is a fully implantable, electrically driven artificial heart. The rotary pump forces the movement of liquid, which by means of a second motor is directed to the left or right ventricle causing cramp of polyurethane sacks with two polyurethane valves. It does not require a compliance chamber (the internal hydraulic platform was rather applied). The normal flow is 4−8 l/min up to a maximum of 10 l/min. Internal implanted batteries enable 30−60 min of work. The pump regulates automatically its work frequency in the range 60−140 bpm. As a pump biomaterial tested for the last 20 years, the elastomer Angioflex was applied. After successful laboratory investigations on implantation in animals, the clinical experiment begun. On 3 July 2001, Drs Laman Gray and Robert Dowling in Louisville (KY, USA) implanted the first autonomic artificial heart (AbioCor). It consists of two ventricles separated by the pumping mechanism. Four original polyurethane valves are used to direct the flow (identical valves like these had been applied for many years in the Abiomed BVS pump). Energy from the external battery is wirelessly transferred through the skin port. The final goal of AbioCor applications is to reach the 5-year, statistical survival of patients with the replaced natural heart. Unlike the Jarvik 7, the AbioCor is powered by electrical energy that is transmitted from a battery across the skin to an internal coil and a backup battery. Because an opening in the skin is not needed to allow passage for tubes or wires, the risk of infection is greatly reduced. In addition, the external battery pack is designed to be worn on a belt or suspenders, enabling the patient to be mobile. From 2001 to 2004, the patients who had received the heart and survived the operation lived for 5 months, on average, the longest being not more than 17 months. In 2006, the AbioCor was approved for use in patients who do not qualify for a heart transplantation if their life expectancy as a result of heart failure is less than a month; the device is also approved as a temporary measure for patients awaiting a transplant.

The Abiomed Company designed AbioCor based on experience with application blood assist pumps. *Abiomed BVS 500* (Abiomed, Inc., Danvers, MA, USA) is pneumatically driven, two-chamber pump one atrium without any power support and the other pneumatically driven ventricle for pumping freely (means not pneumatically driven, under the natural blood pressure) filled atrium with the freely filled atrium, vertically fixed to the patient's bed. Relatively long cannulas are used for establishing the patient's circulatory system connection. It is relatively easy to adjust, with the full ejection mode (80 ml). As a first, the company introduced the polyurethane valves to the pump (had been in clinical use for more than 10 years). Cannulas are made from Angioflex, which is a nontoxic and durable material (can withstand 100,000 beats/day). Endings of the cannulas sewn to the atrium have a special armature and the shape preserving collapsing the atrium walls or the blocking of the cannula inlet. From the output side, the arterial cannulas have special Dacron collars facilitating their sewing.

In Europe, the most developed construction of implantable artificial heart is located in Aachen and in Berlin. In Poland, apart from pneumatically driven artificial heart POLTAH, in the Artificial Heart Laboratory of Foundation for Cardiac Surgery Development in Zabrze, promising construction of implantable electrohydraulic pump project is being led. According to plan, this project will give as a result a totally implantable VAD with all driven and control units inside the patient's body.

In 1966, the pump designed by M. DeBakey, who was also the constructor of the first roll pump applied to the perfusion of the heart during surgery, was a first successfully implanted membrane VAD for left heart ventricle support. The future of implantable pumps is based on the electric drive. The first VAD of this type was *Novacor* (Novacor Division, World Heart Corporation, Ontario, Canada) with electromagnetic driving system. The blood flows in the rhythmically compressed sack, made from Biomer (polyurethane) having two biological valves (made from pericardium 25 mm or porcine 21 mm from the Edwards Laboratories, Baxter Inc.) working as the one-way flow valves. The controller provides electrical energy, via the percutaneous lead, to actuate the driver during the ejection cycle. The driver's balanced, symmetrical solenoid (electromagnet) converts this electrical energy into mechanical energy, stored in a pair of springs. The spring forces act directly on the blood pump's dual symmetrically opposed pusher plates, pressurizing the blood within the pump, and propelling it into the aorta to support systemic circulation. The ventricle body was made from polyester resin, strengthened by glass fibers. It is located in the left upper square of the stomach. The blood flows into the ventricle from Dacron cannula placed in the apex of the left ventricle and is ejected to the system through the Dacron cannula as well to the side wall of the ascending aorta. It works synchronically with the heart. The pump/drive unit can eject from all-fill volumes (from 25 ml to its maximum capacity of 70 ml), to match the stroke volume received from the left ventricle. A small residual blood volume, proportional to afterload (systemic pressure), remains in the blood pump at the end of ejection. The system can thereby adapt to the natural heart's function without depending on an ECG signal or other physiological measurement. Currently, WorldHeart's Novacor LVAS has been implanted in nearly 100 medical centers worldwide in more than 1700 patients, and is the first mechanical circulatory support device to support a single patient for more than 6 years. Also, 172 primarily bridge-to-transplant patients have been supported by Novacor LVAS for more than 1 year, 45 have been supported for more than 2 years, 24 for more than 3 years, 11 for more than 4 years, and 1 for more than 6 years. Only 1.4% of the pumps have needed replacement. No patient deaths have been attributed to Novacor LVAS failure.

Another type of the implantable VAD used for several years as a pneumatically and electrically driven pump is *HeartMate VAD* (HE HAS; Thermo Corporation, Burlington, MA, USA (http://www.thoratec.com/vad-trials-outcomes)). *HeartMate* is the family of ventricles. First FDA on the mechanical VAD (Pneumatic HeartMate® I) in the United States was designed as the platform to the transplantation. Electrically driven HeartMate received FDA in 1998. All ventricles were made from the especially rough surface facilitating the formation of natural endothelium. This VAD is implanted in abdominal space between the heart apex and the ascending aorta and the power supply is transferred by the wire through the skin. The second pipe (through the same skin port) is used to deaerate the chamber or in emergency states allows an external person to manually drive the pump. The volume flow is up to 11 l/min. Closed in titan body motor through the cam system causes the pulsator to move up and down the synthetic sack filled with the blood, closed at two sides by biological pig valves (25 mm, Medtronic). This company also introduced different solution, assuring biocompatibility of membrane. Instead of focusing on achieving the maximal smoothest of polyurethane bag, they worked out material with built-in network of the fibers that facilitates the creation of natural endothelium. Currently, similarly to R. Jarvik, this company works out the artificial heart with turbine axial pump.

PennState LionHeart, *LionHeart LVD LVAS* (Arrow International, Inc., Reading, PA, USA), is an implantable pulsating pump that has developed since 1994. The stroke volume is automatically controlled, resulting in the 3−7 l/min of flow. A set of external batteries (3.5 kg weight) is adequate for 6 h of work. It was first clinically used in Germany in October 1999.

*Thoratec® VAD* (Thoratec Laboratories, Inc., Pleasanton, CA, USA) is an external pump, applied to the short and long support comparatively often. The new implantable version has streamlined shapes, body made of polished titanium, and rest made from polyurethane and the sack through which the blood will flow from Tharalon. It is supplied pneumatically from the mobile, handy driver, connected through the skin by 9 mm drain. This relatively small VAD is also suitable for the biventricular assistance, weighs 339 g, and has an external volume of 252 ml.

The Thoratec PVAD (Paracorporeal Ventricular Assist Device) provides short-to-intermediate, uni- or biventricular support with the option and benefit of home discharge. With more than 20 years of clinical use, the PVAD has been well established as a Bridge-to-Transplantation or Post-Cardiotomy Recovery option for advanced heart failure patients of any age or size. Around 69% of PVAD patients were successfully supported to cardiac transplantation or device removal for myocardial recovery. More than 4,000 patients implanted at over 240 medical centers in 26 countries, the longest duration of support: 1,204 days (858 days discharged to home), smallest patient: 17 kg (BSA 0.73 $m^2$).

The IVAD (Implantable Ventricular Assist Device) provides intermediate-to-chronic support and is the only biventricular, implantable, and home-dischargeable VAD. It is indicated for Post-Cardiotomy Recovery and Bridge-to-Transplantation. Patients implanted: More than 440 patients at 95 medical centers in 9 countries, longest duration of support: 735 days, smallest patient: BSA 1.31 $m^2$.

As Thoratec's first-line intermediate-to-chronic left ventricular assist device, the HeartMate II has been extensively studied as Bridge-to-Transplantation for advanced heart failure. Over 1,200 worldwide patients implanted, longest duration of support (ongoing patient on one device): 3.6 years, transplanted, recovered, or supported to 180 days: 80%. World Heart registry (http://www.worldheart.com).

In the nearly 100 medical centers worldwide that use Novacor LVAS, it is renowned for its reliability, durability and predictability of wear. Of the more than 1,700 Novacor LVAS recipients to date, 172 primarily Bridge-to-Transplant patients have been supported by Novacor LVAS for more than one year. Among these recipients, 45 have been supported for more than two years, 24 for more than three years, 11 for more than four years and 1 for more than six years. Only 1.4% of the pumps have needed replacement. No patient deaths have been attributed to Novacor LVAS failure. In Germany, the 1,500th patient was implanted with Novacor® LVAS in 2004.

*Medos-HIA VAD* from Aachen is made from biocompatible polyurethane (project led by Helmut Reul). It is similar to natural trileaflet valves also made from polyurethane, but with the valve cusp optimization resulting in a conical shape (natural are spherical). Ventricles are made in the full row of sizes, from 60 to 9 ml (pediatric ventricle). Medos was clinically used in more than 100 cases. The investigations carried out in 1994 allowed to guarantee the minimum time of valve functioning of half-year (18 million of cycles). Since 1990, in Aachen, the HIA TAH has been developed, which is based on electromechanical driving unit. The inclination of the plate on which the membrane is fixed about 2 cm allows to reach the 65 ml stroke volume. Brushless motor rotates in only one direction (similar to the case of HeartMate, but the construction of the cam unit is different). The pump allows to reach above 10 l/min (with the frequency of 140 bpm under physiological conditions).

*HeartSaver VAD* (WorldHeart Corporation, Ottawa, ON, Canada) is the pulsate pump with hydraulic drive (project led by Tofy Mussivand). In 2000, it was almost ready for the starting of clinical experiments. Different types were prepared: the axial pumps for continuous flow and VADs and TAHs for pulsating pumps. All models are driven electrohydraulically (rotor). The external volume of the VAD is approximately 530 ml, the membrane is made from smooth polyurethane, and Medtronic-Hall mechanical valves are used, which according to plan will be replaced with the less thrombogenic biological Carpentier−Edwards valves. The working liquid in this pump is the silicon oil, which is currently not in use.

*Berlin Heart* is a series of external, pneumatically driven, ventricle assist devices, with the 50, 60, or 80 ml ejection, equipped with B−S mechanical valves or the polyurethane valves. Berlin Heart VADs have comfortable silicone cannulas with the wire armature, which renders cannulas a suitable shape. This type of VADs had been successfully in vitro tested for 5 years (more than 210 million cycles), mainly in Berlin. Berlin Heart VAD was used in Poland by Z. Religa's team in first successful mechanical support of heart as a bridge to transplantation.

The pneumatically driven membrane-type Polish ventricle assist devices *POLVAD* (U-shaped) and artificial heart *POLTAH* (spherical) were developed in Zabrze, Poland. Until now, more than 200 VAD implantations have been performed. First successful bridge to transplantation was constructed by Z. Religa's team. The implantation of BVAD produced by Berlin Heart LVAD was performed in May 1991. The patient T. Gruszczyński was

awaiting heart transplantation. After 11 days of support, the heart transplantation was performed and patient returned home. Unfortunately, rejection occurred and the patient needed a second, new heart. In the meantime, author (physicist) designed and B. Stolarzewicz (chemist) performed a new Polish ventricular assist pump named POLVAD. After tests, POLVAD was ready for clinical applications. It happened that the first patient to use POLVAD was the same patient T. Gruszczyński (the heart was rejected after 2 years). Fortunately, the POLVAD worked very well, and after 21 days, the heart transplantation was performed. Unfortunately, the patient died during surgery (second heart transplantation).

In pulsate blood pumps, the part producing mechanical energy is separated from the blood by a biocompatible and durable membrane. Membrane-type VADs have it fixed to the hard or half-elastic body. They divide the artificial chamber in two almost even parts. However, in the ventricle with sack, the membrane is shaped into this bag hung in stiff chamber. The artificial ventricles can be driven pneumatically, hydraulically, or electromechanically. The trials of the nuclear power source introduction failed. The VADs are used for supporting patient's life as a bridge to transplantation or to natural heart recovery. At the end of this procedure, the cannulas connecting VAD to the patient's circulatory system are operationally removed. The TAHs are used in these cases, when heart transplantation is the only rescue for the patient or as a target therapy.

Distinct from above described pulsate pumps, the Jarvik 2000 and MicroMed–DeBakey are the currently used implantable axial pumps with continuous flow. The first axial flow pump to be introduced into clinical practice for intermediate to long-term treatment of end-stage heart failure in adults was the DeBakey VAD®. *MicroMed–DeBakey VAD* is the rotor, axial pump (flow up to 5 l/min), connected by the cable through the skin to the driver unit held on the patient's belt. It is implanted between the heart apex and aorta (ascending or descending). The DeBakey VAD is 30 mm × 76 mm, weighs 93 g, and is approximately 1/10th the size of pulsatile products on the market. In 2000, the first successful usage was performed in Vienna.

*Jarvik 2000* is a small (2.5/5.5 cm) rotor pump (the electromagnetic rotor covered by titanium layer). It fits directly into the left ventricle, which may eliminate problems with clotting. The outflow graft connects to the descending aorta. The device itself is nonpulsatile, but the natural heart continues to beat and provides a pulse. The rotor has ceramic bearings, which are washed by the blood (smearing and the receipt of warmth). The angular velocity of 9000–16,000 rpm ensures 3–6 l/min of output flow with the aortic pressure of 80 mmHg and power consumption of 4–10 W. The system is powered by external batteries remotely through skin using electromagnetic field created by a set of coupled coins or using the wire carried out through the "port" in the skull safety plugged with the pyrolytic carbon. On 25 April 2000, physicians in Houston, TX, USA, have realized the implantation and introduced the first patient in the clinical investigation of the Jarvik 2000. For lifetime use, the Jarvik 2000 has also had proven successful in treating a target population of patients suffering from chronic heart failure due to a prior heart attack or cardiomyopathy. Many have been rehabilitated to a dramatically improved life at home, and in some cases patients have even returned to work. So far, the Jarvik 2000 FlowMaker has been used to treat more than 200 patients in the United States, Europe, and Asia. Of those, roughly 79% received the Jarvik 2000 as a bridge to transplantation and 21% as a permanent implant, with a number of patients in each group being terminally ill, near-death cases. Nearly 70% of those patients were supported successfully. Several surgeons reports have described placement of continuous flow devices without cardiopulmonary bypass. Frazier described a patient in whom he placed this pump while briefly fibrillating the heart and placement of the Jarvik 2000 with an anterior, intraperitoneal approach without bypass. This technique is attractive in reoperative situations.

The University of Pittsburgh–Thermo Cardiosystems *HeartMate® II* is an axial rotary pump with the stone bearing with a volume of 89 ml, weighs 350 g, and the estimated time of use is 5–7 years. As intermediate-to-chronic left ventricular assist device, the HeartMate II (now Thoratec's) has been extensively studied as Bridge-to-Transplantation for advanced heart failure. Over 1,200 worldwide patients implanted, longest duration of support (ongoing patient on one device): 3.6 years, transplanted, recovered, or supported to 180 days: 80%. The third-generation, HeartMate III,

will be the centrifugal pump with the rotor levitating in the magnetic field (without mechanical bearings).

There have been several scientific groups working in the field of artificial heart in Japan, Australia, Austria, Argentina, France, Germany, Poland, Czech Republic, Russia, and so on. But from the market point of view, there is not easy business. Currently, the strongest company offering the wide range of products in the area of blood pumps is Thoratec. Thoratec Corporation is engaged in the research, development, manufacturing, and marketing of medical devices for circulatory support, vascular graft, blood coagulation, and skin incision applications. The Thoratec VAD system is the device that is approved for left, right, or total heart support and that can be used both as a bridge to transplantation and for recovery from open-heart surgery. More than 4300 of these devices have been used in the treatment of over 2800 patients worldwide. With the introduction of the Implantable Ventricular Assist Device (IVAD™), Thoratec delivers the first and only implantable VADs for left, right, and biventricular support for bridge to transplantation and for post-cardiotomy recovery. The HeartMate® XVE Left Ventricular Assist System (LVAS) is now FDA approved as a long-term permanent implant, called destination therapy. In addition, the accompanying Thoratec TLC-II® Portable VAD Driver provides hospitals with the first mobile system that allows these univentricular or biventricular VAD patients to be discharged home to await cardiac transplantation or myocardial recovery. The company is also a leader in implantable LVADs. Its air-driven and electric HeartMate LVAD, which has been implanted in more than 4100 patients worldwide, are implanted alongside the natural heart and take over the pumping function of the left ventricle for patients whose hearts are too damaged or diseased to produce adequate blood flow.

WorldHeart is a developer of mechanical circulatory support systems (e.g., Novacor) with leading next-generation technologies. The Levacor is a next-generation rotary VAD. It is the only bearingless, fully magnetically levitated implantable centrifugal rotary pump with clinical experience. An advanced, continuous-flow pump, the Levacor uses magnetic levitation to fully suspend the spinning rotor, its only moving part, inside a compact housing.

WorldHeart's Novacor II LVAS is a next-generation, pulsatile VAD. It can be fully implanted without a volume displacement chamber, thereby reducing the risk of complications by eliminating the need to perforate the skin. The operation of the pump drive unit is very interesting. When the pusher plate is driven to the right (pumping stroke), the prechamber expands, filling from the left ventricle. Simultaneously, the pumping chamber is compressed, ejecting blood into the body. When the pusher plate returns to the left (transfer stroke), the prechamber is compressed while the pumping chamber expands; blood transfers from the prechamber to the pumping chamber, with no inflow or outflow. Because the total volume of the two chambers remains constant as one fills and the other empties, the system can operate without a volume compensator or venting through the skin. WorldHeart's Novacor II LVAS is not currently available. In 2005, WorldHeart conducted the first animal implant of the Novacor II LVAS—ahead of schedule. WorldHeart Company currently focuses on new products—especially for pediatric patients. The PediaFlow VAD is an implantable, magnetically levitated blood pump based on WorldHeart's proprietary rotary VAD MagLev™ technology. In its pediatric configuration, the device is designed to provide a flow rate from 0.3 to 1.5 l/min. The PediaFlow VAD is being developed to provide medium-term (less than 1 year) implantable circulatory support to patients from birth to 2 years of age with congenital or acquired heart disease.

Pneumatic pulsatile VADs have been available in pediatric sizes since 1992. At Herzzentrum Berlin, VADs are used lasting from several days to 14 months in 70 infants and children with myocarditis and cardiomyopathy, leading to a notable rise in survival in the past 5 years. It is possible to discharge 78% of the infants under 1 year old [3].

Several types of VADs have been used in children and adolescents whose body surface area is greater than 1.2 $m^2$—that is, generally in children older than 5 years. The Thoratec VADs (Thoratec Laboratories, Inc.) have been available since the early 1980s for adult use, but they can also be implanted in older children and adolescents. Several other adult-size VADs, such as the Novacor (Baxter Healthcare Corporation, Irvine, CA, USA), have been applied in adolescents, and a version of the axial flow DeBakey VAD

(MicroMed Technology Inc., The Woodlands, TX, USA) has been developed that is suitable for use in children and has been implanted in several patients. Two miniaturized extracorporeal, pneumatically driven VADs designed specifically for smaller children and infants have been introduced in Europe so far: the Berlin Heart Excor (Berlin Heart AG, Berlin, Germany) in 1992 and the Medos HIA device (Medos Medizintechnik AG, Stolberg, Germany) in 1994. The first reported implantation of a Medos VAD as a bridge to transplantation in a child took place in 1994. Only the extracorporeal, pneumatically driven Berlin Heart Excor and the Medos HIA pulsatile systems have so far proven successful in children of all ages. The pediatric version of the Berlin Heart Excor VAD is mounted with trileaflet polyurethane valves and is available with pump sizes of 10, 25, 30, 50, 60, and 80 ml. The 10-ml pumps are suitable for neonates and infants with body weight of up to 9 kg (body surface area 0.43 m), and the 25 and 30 ml pumps can be used in children up to the age of 7 years (weight 30 kg and body surface area of about 0.95 $m^2$); adult-sized pumps can be implanted in older children. The adult pump has a stroke volume of 80 ml and tilting disk valves. Pediatric-sized pumps are suitable for children with a body weight of 3−9 kg. This pump has a stroke volume of 10 ml and polyurethane trileaflet valves [3].

Several other pulsatile devices developed for the adult population are used in school-aged children: the HeartMate I (Thoratec Laboratories, Inc.), Toyobo (National Cardiovascular Center Tokyo, Japan), Abiomed BVS 5000 (Abiomed Inc., Delaware, MA, USA), and Novacor (World Heart Corporation, Ontario, Canada). Two continuous flow rotary VADs that use axial flow or centrifugal flow—the Incor VAD (Berlin Heart) and the DeBakey VAD—have been introduced into routine clinical care. Some further devices are still being subjected to clinical trials: Jarvik 2000 (Jarvik, New York, NY, USA), HeartMate II, Duraheart® (Terumo Kabushiki Kaisha Corporation, Shibuya-ku, Japan), VentrAssist (Ventracor, Chatswood, NSW, Australia), and CorAid® (Cleveland Clinic, Cleveland, OH, USA) [3].

The Incor device (Berlin Heart AG) is 146 mm long and 30 mm wide and weighs 200 g. MicroMed modified the adult pump to fit children and in 2004 received FDA humanitarian device exemption status, enabling implantation of the DeBakey VAD Child pump for persons, aged 5−16, awaiting heart transplantation.

Berlin Heart AG products are Incor, Excor cannulas, and driving units. In June 2002, the worldwide first implantation of the Incor device took place in the German Heart Center DHZB. By July 2005, no less than 300 Incor devices had been implanted (two patients have been living with the device for 3 years). Excor is an extracorporeal, pulsatile VAD. Various types and sizes of blood pumps and a wide range of cannulas allow us to meet all clinical needs and treat all patients, regardless of their age.

The VentrAssist, which is made by the Australian company Ventracor, has a moving part—a hydrodynamically suspended impeller. It has been designed to have no wearing parts or cause blood damage. It weighs just 298 g and measures 60 mm in diameter, making it suitable for both children and adults. VentrAssist also has an advantage over its one competitor, Incor made by the German company Berlin Heart. The VentrAssist is less likely to damage red blood cells because it moves the blood more slowly with a bigger impeller.

The term VAD has been applied to a wide variety of mechanical circulatory support systems designed to unload the heart and provide adequate perfusion of the organs.

Short-term circulatory support with an LVAD may be indicated for patients with end-stage heart failure (of any etiology) who are awaiting a donor heart for transplantation, and for patients with a severe acute heart failure syndrome from which myocardial recovery is anticipated (such as acute myocarditis). An LVAD is sometimes used if weaning from cardiopulmonary bypass after cardiac surgery fails. In the active arm of a nonrandomized controlled study, 78% (32/41) of patients survived for a mean of 215 days with LVAD support. In another comparative study, 81% (13/16) of patients survived to transplantation (duration of support not stated). One case series showed that at 30 days of bridging to transplantation with an LVAD, survival was 83%, falling to 19% after 24 months' support.

In a nonrandomized controlled trial, posttransplant survival of patients bridged on LVAD support was 66% (21/32) at 41 months, compared with 67% (98/146) of patients at 36 months who had a transplant without circulatory support, although patients in the latter group were significantly older. One case series of 243 patients in whom LVADs

were used to bridge to transplantation reported actuarial post-transplant survival of 91% at 1 year, 70% at 5 years, and 40% at 10 years. Results from case series included in a systematic review showed that between 60% (12/20) and 83% (5/6) of patients survived to transplantation or were still alive awaiting transplantation on LVAD support. Of the total cases of bridge to recovery reported, 58% (7/12) of patients survived to final follow-up; successful explantation of the device or weaning from support was achieved in all these patients [4].

The randomized controlled study showed a reduction of 48% in the risk of death from any cause in the group that received left VADs as compared with the medical therapy group [relative risk 0.52; 95% confidence interval (CI) 0.34−0.78; $P = 0.001$]. Randomly assigned 129 patients with end-stage heart failure were ineligible for cardiac transplantation to receive a left VAD (68 patients) or optimal medical management (class IV heart failure). The rates of survival at 1 year were 52% in the device group and 25% in the medical therapy group ($P = 0.002$), and the rates at 2 years were 23% and 8% ($P = 0.09$), respectively. The frequency of serious adverse events in the device group was 2.35 (95% CI 1.86−2.95) times that in the medical therapy group, with a predominance of infection, bleeding, and malfunctioning of the device. The quality of life was significantly improved at 1 year in the device group. The use of a left VAD in patients with advanced heart failure resulted in a clinically meaningful survival benefit and an improved quality of life. A left VAD is an acceptable alternative therapy in selected patients who are not candidates for cardiac transplantation [5].

All mechanical circulatory support systems are associated with a wide range of possible complications: bleeding, infection, device malfunction, hemolysis, peripheral ischemia, and perforation of a ventricle or the aorta, of which bleeding and thromboembolic complications are the most frequent and most serious. Infections, hemolysis, pulmonary edema, and multiorgan failure have also been reported. It was also noted that implantation of an LVAD could unmask previously subclinical right ventricular dysfunction. Damage to the blood pump equipment rarely causes harm to the patient. As examples, one Jarvik 2000 patient broke a cable connector when he slammed it in a car door; another accidentally cut his cable with scissors while changing his bandage; yet another patient lost connection to his battery and controller when a purse snatcher grabbed his shoulder bag and ran off with it. Fortunately, in all these cases, the patient suffered no harm. Their own natural hearts were able to sustain them until they could connect to their backup equipment. But it can be noticed that the longest-running Jarvik 2000 FlowMaker patient has been supported by the device longer than any patient in the world with any other type of mechanical heart, either TAH or VAD—i.e., more than 4 years.

In September 2006, the FDA approved the first totally implantable TAH (AbioCor) for people who are not eligible for a heart transplant and who are unlikely to live more than a month without intervention. It is a big success, but it also means that many problems are awaiting to be solved in laboratories (Figure 8.4) in the near future.

### 8.3.2 Valve Prostheses

*Valvular heart disease* is a life-threatening disease that affects millions of people worldwide and leads to approximately 250,000 valve repairs and/or replacements every year. Almost 90,000 Americans a year need surgery for valve disease. Malfunctioning of a native valve impairs its efficient fluid mechanical/hemodynamic performance. Human heart valves act as check valves, controlling the direction of blood flow through the heart. The aortic valve is between the left ventricle and the aorta and the mitral valve is between the left atrium and the left ventricle. It opens and closes to control the blood flow into the left side of the heart. The normal aortic valve area is 3.0−4.0 $cm^2$. In general, severe aortic stenosis has been defined as a valve whose area was reduced to 0.75−1.0 $cm^2$. In general, mean transvalvular pressure gradients greater than 50 mmHg represent severe aortic stenosis, while mean gradients less than 25 mmHg suggest mild aortic stenosis. Mitral stenosis causes leaflet/chordal thickening and calcification, commissural fusion or shortening, chordal fusion, or a combination of these processes. The normal mitral valve area (MVA) is 4.0−5.0 $cm^2$. Accordingly, mild mitral stenosis is defined as a condition with an MVA of 1.5−2.5 cm and a mean gradient at rest less than 5 mmHg. Moderate and severe mitral stenoses are defined as conditions with an MVA 1.0−1.5 and less than 1.0 $cm^2$, respectively, with mean gradients greater than 5 mmHg [6].

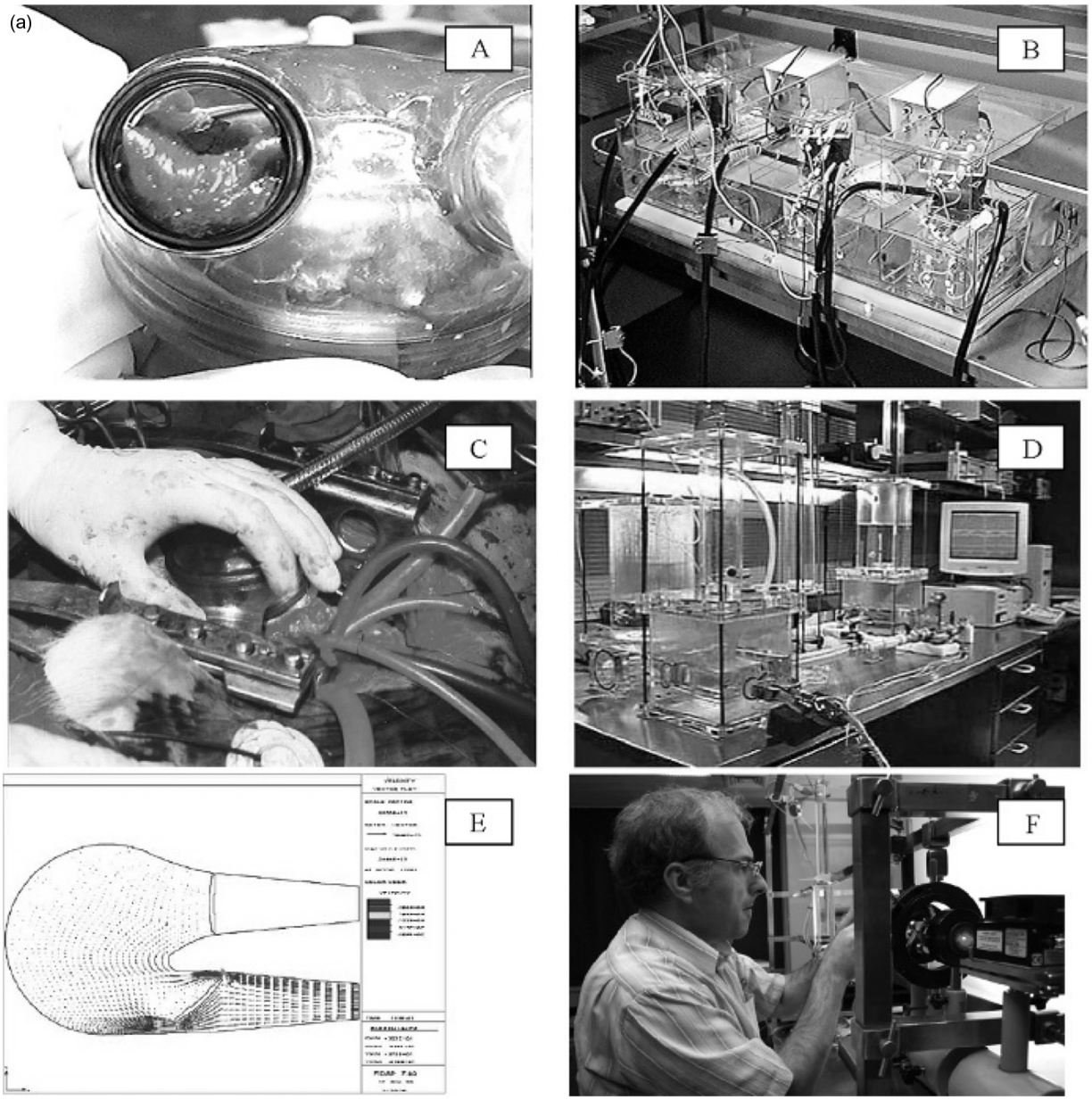



**Figure 8.4** (a) The in vitro cloth formation and hemolysis test [A,B]. The artificial heart POLTAH in vivo (calf) implantation [C] and in vitro blood circulation test stand [D]. Computer flow simulation method (Fidap software) [E] and laser anemometry, flow visualization stand (constructor Z. Małota) [F]. (b) One of the problems that are not satisfactorily solved was the interpretation of laser flow visualization pictures. Proposed by the author in the 1990s, functional analyzing method (FAM) method involves monitoring the quality of a flow system. The artificial heart is a pump that should cause fluid flow from the inlet (atrial) to the outlet channel and provide blood with a determined amount of energy to overcome the load, in order to create clinically desired pressure-flow state in the circulatory system. Both goals must be achieved, while conserving the safe transportation of morphotic blood elements, which is essential for long-term blood pumps. Therefore, it must minimize the undesired phenomena occurring at the blood–artificial surface interface. (c) The chamber was divided into areas where, for a given section, and for every local flow velocity, vectors are assigned with its components in the direction of an outlet $V_o$ and inlet $V_i$ channel as well as the component $V_r$ tangent to the chamber's wall. The results depend on the phase of work cycle. The analysis of time changes of the first two components

(*Continued*)

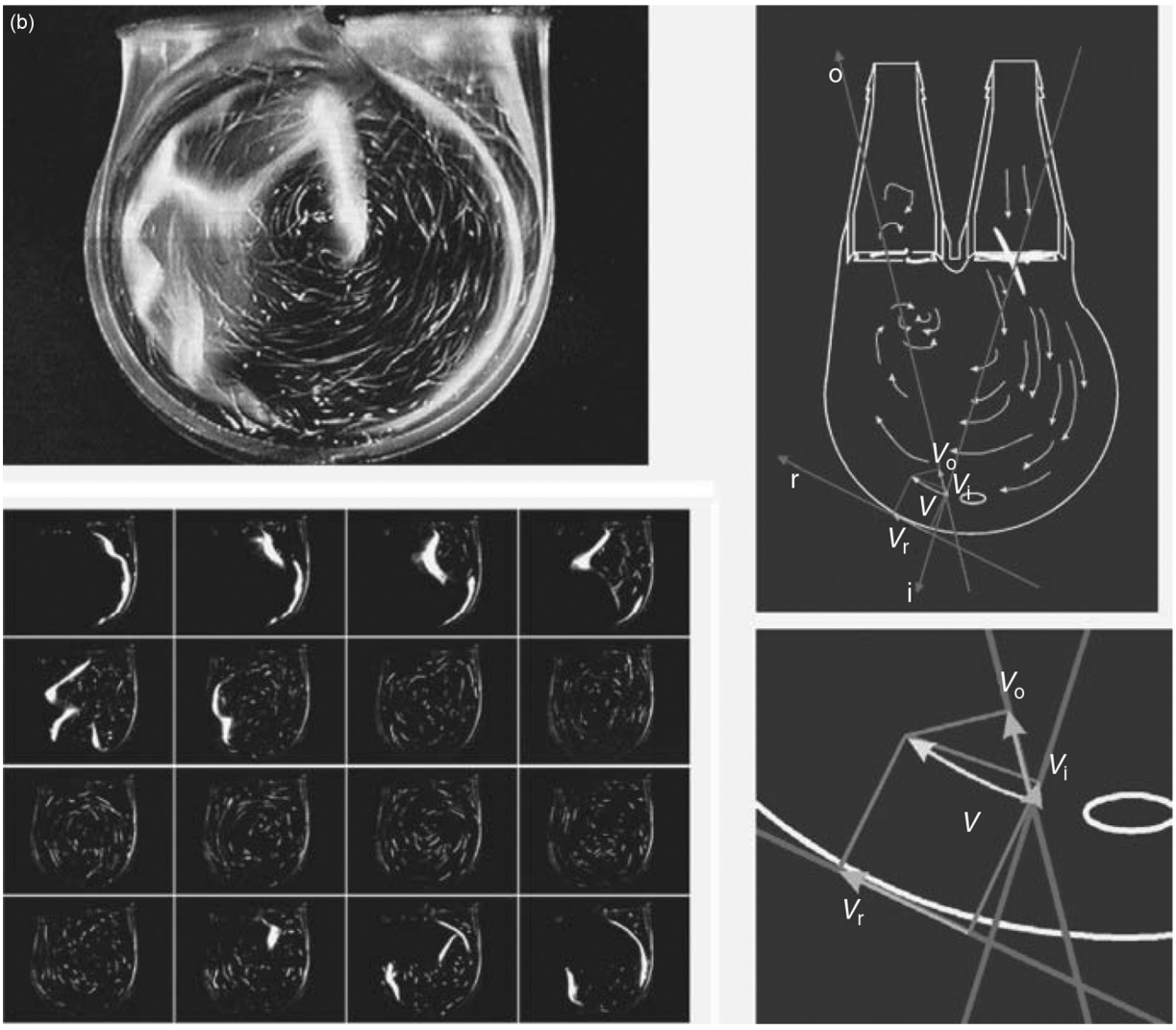



**Figure 8.4** (*Continued*)

*Valve repair* is now the method of choice for surgical treatment of valve disease, thanks to improvements in techniques over the past 40 years. Starr and associates first reported a technique for aortic repair in 1960. In the early 1980s, surgeons who performed percutaneous balloon valvotomy became more involved in aortic valve repair after annular disruptions, and other balloon-induced injuries caused acute insufficiency in young patients requiring immediate repair. Balloon valvotomy may be appropriate for children and adolescents with congenital aortic stenosis, but not for adults with calcific aortic stenosis.

The application of mitral and tricuspid valve repair method allows to maintain the natural anatomy of the heart valve. The surgeon repairs the tissue of the damaged valve and usually implants an *annuloplasty ring* to provide extra support to the valve.

◀ allows to track down the dynamics of flow structure organization during an entire cycle, to detect inertial effects and passage time, while the tangent component is responsible for a good washing of wall vicinity areas. The full analysis makes possible the classification of obtained pictures (since digital picture recording is suitable for computer analysis and gives results that are easy to interpret), so that the conclusions regarding the causes of phenomena and their regulation may be drawn easily.

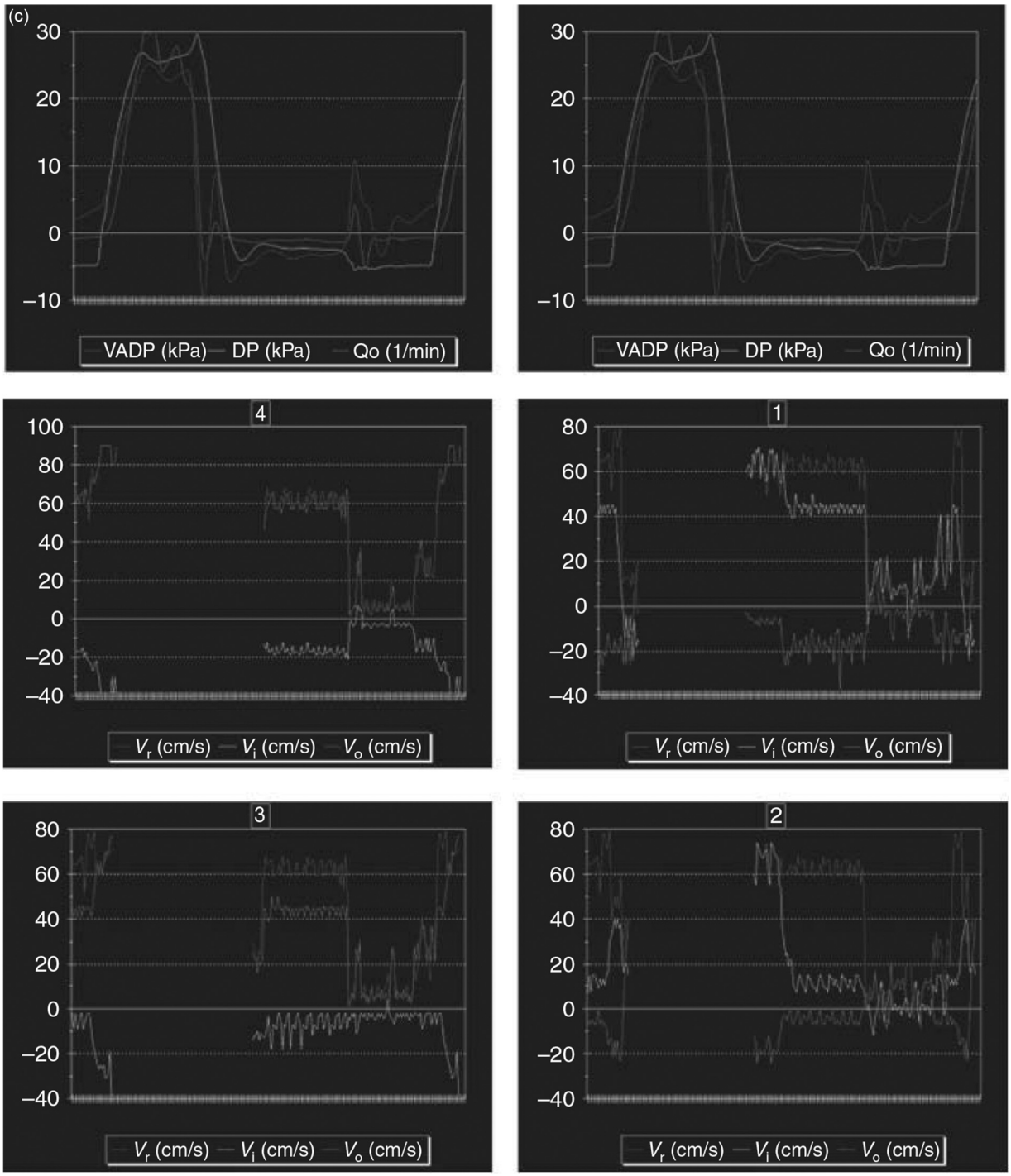



**Figure 8.4** (*Continued*)

Natural valve leaflets are constructed from layers of connective tissue lined with endothelium. The zones of stress concentration are reinforced with bands of collagen fibers. Artificial heart valves should be designed to mimic the natural function and flow dynamics that are optimized in the course of million years of evolution.

The prosthetic valve must be durable and biocompatible, should quickly change phase (close to open, or vice versa), and must allow adequate blood flow with a minimum pressure gradient (energy dissipation), turbulence, and stagnation zones (Figure 8.5). Optimum leaflet valve design creates minimal stress concentration in leaflets, and

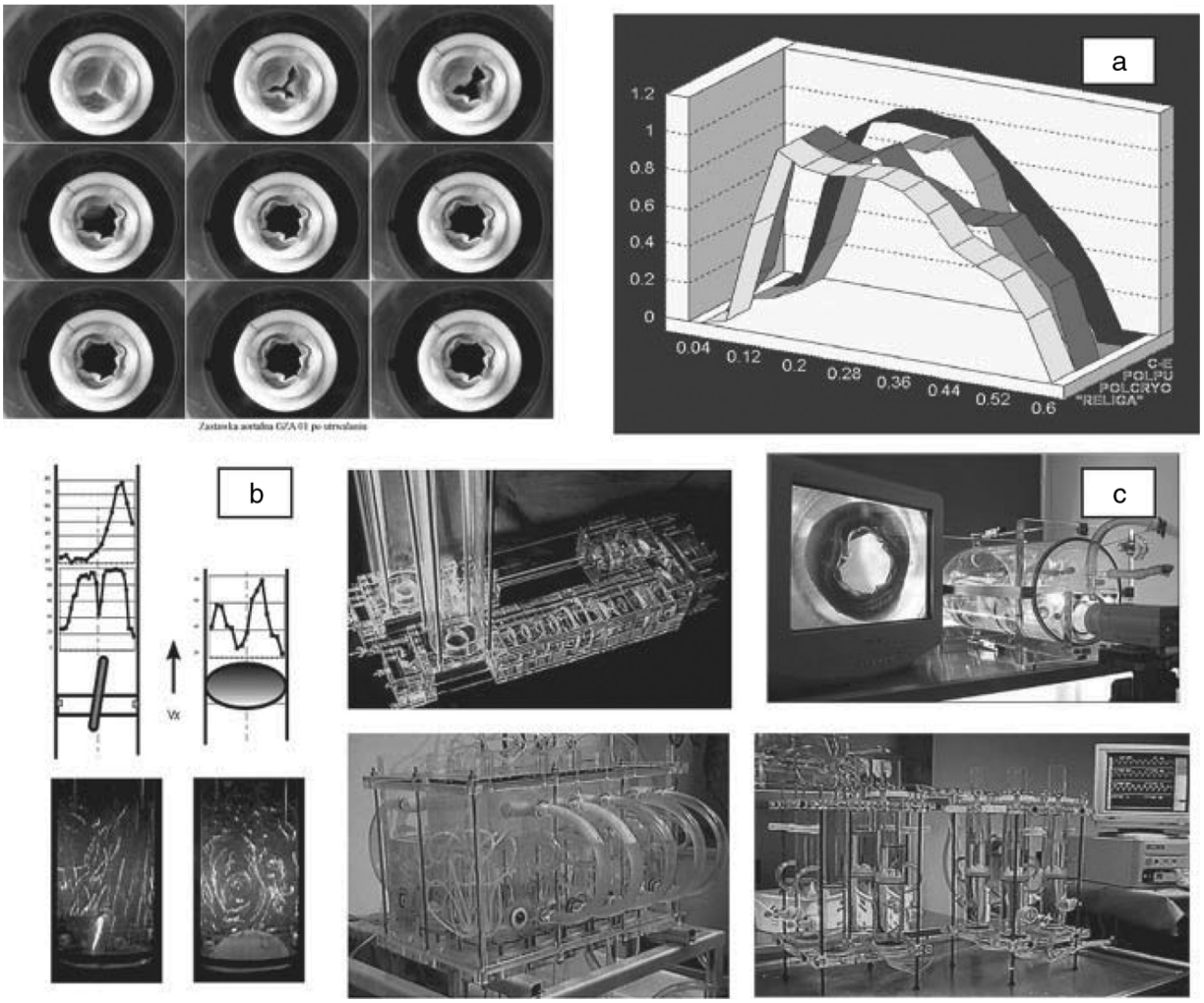



**Figure 8.5** Results of valve test tester designed and introduced in Institute Heart Prostheses, FCSD. The opening area valve test and comparison in one cycle of working biological Religa, Polcryo, and synthetic Polpu prototypes with Carpentier–Edwards bioprotheses (a). The laser visualization and laser anemometer test results of Polish disk valve prototype (b). Several testing apparatus used in our laboratories (c).

optimal cusp shape effects smooth washout, minimal pressure gradient, and adequate longevity. The geometry and the construction of the valve should be surgically convenient to insert in the heart. Most number of valves, including natural ones, are constructed from three leaflets. The simplest configuration (Figure 8.6) shows that it is due to the II number whose value is about 3.

There are two main types of prosthetic valves: mechanical and biological. Mechanical valves can cause various complications, including thrombosis, ischemia, and turbulent flow. Advantages of bioprosthetic valves (porcine and bovine xenografts) include their durability and low incidence of

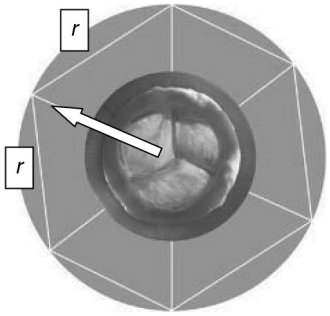



**Figure 8.6** The simplest configurationof avalve:. An open valve ideally constructed using three leaflets lies on the perimeter of the wheel created by the aorta's cross section ($2\pi r$ is equal to about $2r + 2r + 2r$).

thromboembolism. Complications associated with bioprosthetic heart valves include hemorrhage and stiffening of the leaflets.

For over 50 years, materials and construction of cardiovascular prosthesis have been under investigation. Hufnagel was the first to implant a valvular prosthesis in the descending aorta for the treatment of aortic insufficiency (in 1952).

The first artificial heart valve prosthesis for routine prosthetic valve replacement clinical use was the Starr−Edwards mechanical valve, which was introduced in the 1960s. The problem of lifelong anticoagulation therapy in mechanical heart valves was solved with the introduction of biological valves in the 1970s: porcine or pericardial. The most popular tissue valves, the Hancock and the Carpentier−Edwards prostheses, are porcine xenografts. However, their durability was limited and age dependent with faster degeneration at younger age.

In 1977 the new generations of mechanical prostheses were introduced: the mono-leaflet Medtronic-Hall and the bi-leaflet St Jude Medical valves and next CarboMedics valves. Currently, mechanical heart valve prostheses account for 60−70% of the prosthetic heart valves implanted worldwide, with bi-leaflet tilting disk prostheses accounting for the majority.

The development of flexible polymeric heart valves started as early as in 1958 (Roe implanted valves made of silicone rubber). Between 1961 and 1963, 23 patients underwent aortic valve replacement with a tricuspid polytetrafluoroethylene (PTFE) prosthesis by Braunwald et al. Again, mortality was high, and the explanted valves showed severe thickening and rupture of the leaflets. Next aortic prosthesis made of Dacron and silicone was implanted by Roe in 1966, but only four patients survived the operation and lived for 33−61 months. In 1977, Hufnagel implanted a single leaflet aortic prosthesis made of Dacron into the aortic position. Most valves failed, but some patients survived up to 15 years. Embolic complications and fatigue failure were observed frequently in silastic, collagen, and PTFE valves; the latter also exhibited shrinkage. Calcification was also observed frequently, hinting at a destruction of the chemical integrity of the polymer. Polyurethanes have demonstrated the best biocompatibility, durability, and resistance to thromboembolism among all polymers and are, therefore, also used for a variety of medical devices [7].

Currently, some polymeric valves have proven efficacious in assist devices (Abiomed, Medos, and Berlin Heart). However, so far no flexible polymeric heart valve has proven durability for long-term implantation.

All mechanical valves are made up of an orifice ring and occluders, either one or two leaflets through which blood flows through the heart in a forward direction. Because of susceptibility to thromboembolic events, mechanical devices are used in a lifelong anticoagulation therapy (using agents such as Heparin, Warfarin, or Coumadin that delay the clotting of blood, which can cause a heart attack or stroke). The abovementioned drawbacks are minimized or eliminated when bioprostheses are implanted.

Tissue valves (bioprosthetic valves) are made of human or animal tissue. There are three types of tissue valves: pig tissue (porcine), cow tissue (bovine), and human tissue (e.g., aortic or pulmonary valves obtained from human cadavers), or autografts (e.g., the patient's own pulmonary valve, pericardium, or fascia lata). Homograft aortic or pulmonary valves (and associated portions of aortic or pulmonary root) obtained from human cadavers are cryopreserved and implanted directly in place without a synthetic frame.

Heterograft tissue valves for aortic or mitral valve replacement (MVR) are made from natural, animal tissue (porcine aortic valve or bovine pericardium) fixed, usually in dilute glutaraldehyde (GA) and mounted on a synthetic stent—a semi-rigid frame comprising a base ring and struts.

The technically more difficult to implant, similar to the homograft valve, porcine stentless valve is used only for aortic valve replacement.

The mechanical valves are made from Stellite 21, Haynes 25, Titanium (the housing/strut), Delrin, pyrolytic carbon, carbon/Delrin composite, and an ultra-high-molecular polyethylene (UHMPE) (the leaflet).

In bioprostheses, leaflets are made from porcine aortic valve or porcine pericardial tissue fixed by stabilized GA mounted on stents (polypropylene stent covered with Dacron and Elgiloy wire and nylon support band covered with polyester and Teflon cloth).

The sewing ring is made from Dacron and soft silicone rubber insert covered with porous, seamless Teflon cloth or PTFE fabric over silicone rubber filter.

The physical properties of material, valve geometry, stress−strain distribution in leaflets, and the local pressure and flow values near the valve influence the risk of valve failure and can cause damage to the blood components. Dangerous for blood local space are associated with shear velocities and shear stress reaching critical values for morphotic blood elements. For soft (biological) valve durability, the stress on leaflets is the most important factor, which lead to calcifications and, as a result, valve damage.

The global geometry of valve is enforced by the fit criteria and is characteristic of physical nature of work. The biological valve design made from donors (humans or animals) is limited by anatomical valve tissue and heart geometry.

The use of xenograft and allograft biomaterials has typically required chemical or physical pretreatment aimed at preserving and sterilizing the materials and reducing the immunogenicity of the tissue. Multiple chemical and physical cross-linking techniques have been explored to stabilize the collagen-based structure of the tissue, maintaining its mechanical integrity and natural compliance. Bioprotheses are mainly prepared from animal structures, e.g., valves or pericardium, composed primarily of collagen. The main advantage of xenogenic bioprotheses is their structural similarity to human tissues. However, in order to improve prosthesis durability reflected by the enhanced resistance to enzymatic degradation and reduced immunogenicity, animal tissues must be chemically or physically pretreated (fixed). Fixation procedures are connected with crosslinking of tissue proteins. Among chemical methods of crosslinking, the most commonly accepted is treatment with GA. This five-carbon bifunctional aldehyde reacts with free amino groups of proteins—mainly ε-amino groups of collagen lysyl residues—forming inter- or intrachain crosslinks. Prostheses obtained after tissue treatment with GA reveal remarkable reduction in immunogenicity and sensitivity to in vivo degradation.

Patients with mechanical valves require long-term anticoagulant therapy owing to the risk of thromboembolic complications. Reports of strut failure, material erosion, and leaflet escapes as well as pitting (cavitations) and erosion of valve leaflet and housing have resulted in numerous investigations on the closing dynamics of mechanical valves and the pressure distribution on the leaflets and impact forces between the leaflets and guiding struts. This requires the flow through the clearance between the leaflet and the housing in closing position influencing the hemolysis and thrombus initiation.

The valve-related problems are as follows:

- *Mechanical valves:* thromboembolism, structural failure, red blood cell and platelet destruction, tissue overgrowth, damage to endothelial lining, para/perivalvular leakage, tearing of sutures, infection
- *Bioprosthetic valves:* tissue calcification, leaflet rupture, para/perivalvular leakage, infection

The cause of valve failure can be related to the valve components (Figure 8.7).

The probability of survival 5 and 10 years following heart valve replacement is approximately 70 and 50%, respectively. Prosthesis-associated complications often lead to reoperation such that replacements currently account for 15−25% of all valve operations. Thrombotic deposits may form on heart valve prostheses, which is more likely to occur in mechanical heart valves which are more thrombogenic than tissue valves. Hemorrhage rates are higher in patients with mechanical valves in the aortic site than in patients with aortic tissue valves. However, these rates are similar for mechanical and tissue valves in the mitral location. Rates of infection (1−6%) do not differ significantly between tissue and mechanical prostheses. In tissue valves, infection may be localized in the vicinity of the sewing ring. However, the cusps may also be a focus of infection [6].

From the early generation of heart valves, only the Starr−Edwards ball valve design remains in clinical use today. Currently available mechanical valves have been designed with a lower profile and a more effective orifice area, to improve hemodynamics.

The initial design of tilting disk valve consisting of Delrin disk exhibited good wear resistance and mechanical strength. But due to the swelling phenomenon, it was replaced by pyrolytic carbon. Structural dysfunction of the B−S (Shiley Inc., USA) 60° and 70° convexo-concave mechanical heart valve prosthesis occurred at a relatively high frequency (2.2−8.3%). The B−S tilting disk design has been withdrawn from the market, while the Duromedics bi-leaflet prosthesis was reintroduced as the Edwards−Tekna (Edwards Lifesciences,

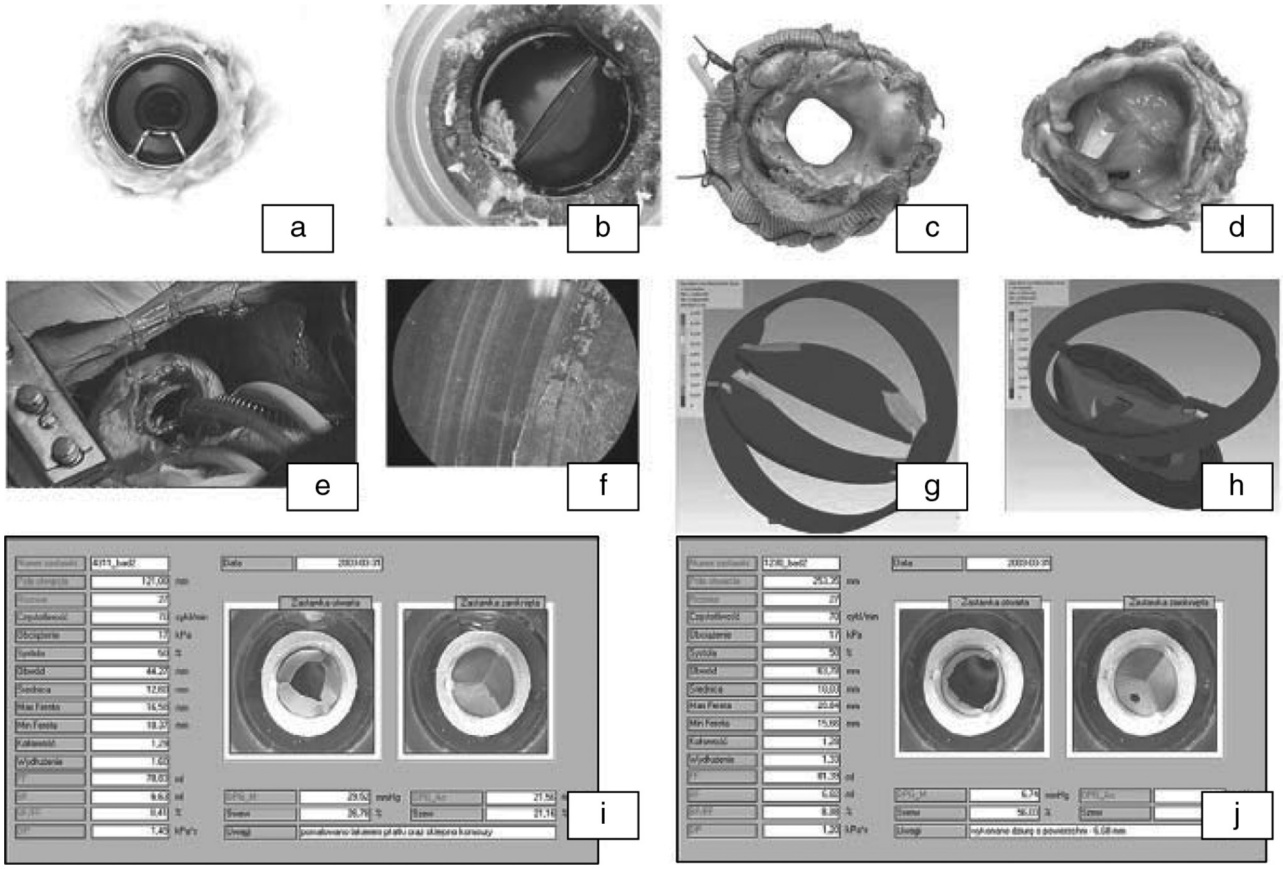



**Figure 8.7** The samples of explanted valves collected in the Institute of Heart Prostheses, FCSD (COST Action 537 project). One-disk (a) and two-disk mechanical valve (b) and two bioprostheses (c,d). The in vivo valve test on ship (e). The microscopic evaluation of valve's disk (f) and modeling of mechanical valves—equivalent elastic strain values (g,h). The effect of biological heart valve prosthesis damage on hemodynamic efficiency has been investigated and analyzed: improper functioning due to leaflet calcification—the opening area of "calcified" (leaflets partially glued (i)) valve decreased by 44%, while the pressure gradient grew up to 22 mmHg. Perforation of a leaflet (j)—significant perforation (hole area 6.68 $mm^2$) of leaflet caused increase in back-leakage of 147% to 8.38 (6.8 ml).

USA) valve following design modifications. The failure mode of the B−S prosthesis is due to failure of the welded outlet strut with resultant embolization of the disk. Fracture of the carbon component in a small number of mechanical valves, including the Edwards−Duromedics (Edwards Lifesciences, USA) and St Jude Medical (St Jude Medical Inc., USA) bi-leaflet tilting disk valves, has also been reported [6].

The most common cause of failure during implantation is leaflet fracture. The most common causes of mechanical valve failure are pannus formation and thrombosis. Structural dysfunction occurs more commonly with tissue valves than with contemporary mechanical valves [6].

The rate of bioprosthetic valve failure increases over time, particularly after the initial 4−5 years after implantation. At 10 years after implantation, 20−40% of porcine aortic valves implanted in either aortic or mitral sites require replacement for primary tissue failure. Up to 50% of such valves fail after 10−15 years. Calcification, cuspal tears, or both are the most common manifestations of tissue failure in bioprosthetic porcine aortic valves.

Stentless bioprosthetic porcine aortic valves have shown minimal cuspal calcification or tissue degeneration for periods up to 8 years following implantation. As with bioprosthetic porcine valves, bioprosthetic heart valves made from bovine pericardium develop both calcific and noncalcific tissue

failure. The second generation of bovine pericardial prostheses, such as the Carpentier−Edwards pericardial valve, have increased durability compared with first-generation pericardial valves [Ionescu−Shiley (Shiley Inc., USA), Mitroflow (CarboMedics, Canada), and Hancock] and excellent hemodynamics. Cryopreserved human homograft (or allograft) aortic valves have equivalent or slightly better durability than contemporary bioprosthetic porcine valves with valve survival rates of approximately 50−90% at 10−15 years [6].

Technology continues to improve the durability of bioprostheses and to reduce the thrombogenic effects of mechanical prostheses.

The most significant changes in mechanical heart valves over the last decade have focused on the sewing ring and the ability to rotate the valve after implantation. The St Jude Medical Regent prosthesis and CarboMedics Top Hat improve valve hemodynamics by introducing modification that allows for the placement of the device in a supra-annular position. The St Jude Medical Silzone (silver nitrate incorporated in the sewing cuff) was withdrawn from the clinical trials due to increased incidence of paravalvular leak in the silzone cohort. The newer generation mechanical prostheses, e.g., the Edwards−MIRA (Edwards Lifesciences, USA) (Sorin Bicarbon mechanical prosthesis with a modified sewing ring), ATS (Advancing the Standard) (ATS Inc., USA), and On-X (Medical Carbon Research Institute, USA), have just completed regulatory clinical trials [6].

The most significant changes in biological heart valves over the last decade have focused on the stent construction and tissue treatment method (changing fixation pressure and chemicals). Stent mounting produces higher transvalvular gradients and also causes premature valve failure. In the brief period in which homografts were stented, the average life expectancy of the valve was less than 10 years (about 90% homografts have a 10-year freedom from valve degeneration). Furthermore, to date, in two large international trials, no Medtronic Freestyle (Medtronic Inc.) and Toronto SPV (St Jude Medical Inc.) stentless valves have been explanted because of primary structural failure [6].

The valves fixed at zero pressure retain a collagen architecture virtually identical to that of native unfixed porcine aortic valve cusps. The 10-year experience with the Medtronic Intact (Medtronic Inc.) (zero pressure fixed) valve reported no cases of primary structural degeneration in patients over 60 years of age and only one case of valve failure in individuals over 40 years of age. The exposed amine residues of the GA molecule promote tissue calcification. Surfactants, particularly sodium dodecyl sulfate (T6) (Hancock II, Medtronic Inc., USA), polysorbate 80 (Carpentier-Edwards standard and supra-annular porcine bioprostheses; Edwards Lifesciences, USA), and toluidine blue (Medtronic Intact, Medtronic Inc.), have been incorporated in the preservation process. No-React detoxification process has been proposed as a method of preventing calcification of GA fixed tissue. Detoxification with homocysteic acid is used in Sorin products (Sorin Group Inc.) [6].

The Carpentier−Edwards PERIMOUNT Pericardial Bioprosthesis, made of bovine pericardial tissue that has been preserved in a buffered GA solution and mounted on fully extensible stents and distensible struts, decreases shearing stresses on valve leaflets and maintains physiologic aortic ring movements to reduce flow turbulence and vibrations. Both the frame and the sewing ring are covered with a knitted PTFE cloth. This material helps facilitate the healing and ingrowth of tissue around the implanted valve.

The Medtronic Company is currently manufacturing two new bioprostheses. One valve is stentless (Freestyle aortic root bioprosthesis) and the other incorporates a stent design (Mosaic bioprosthesis). Both represent new concepts in the manufacture of bioprostheses, specifically, zero-pressure fixation and $\alpha$-amino oleic acid antimineralization treatment. CarboMedics is investigating a Photofix bioprosthetic valve: a patented trileaflet, central-flow prosthesis, with each leaflet mounted on a flexible support frame. The leaflets are prepared from bovine pericardium treated with a unique patented dye-mediated photo-oxidation process. This new fixation process results in collagen crosslinking without the use of GA, a suspected contributor to the calcification failures of other clinically available tissue valves.

The *choice* of prosthesis is again a decision to be made by the surgeon and the patient, with full knowledge of the advantages and disadvantages of the different types available.

From a clinical point of view, the use of bioprosthetic valves is recommended for older patients (over 65−70 years) because of the increased risk of bleeding in the elderly and the low probability of

structural failure of the bioprosthesis in the remaining expected life of these patients. Mechanical prostheses are indicated for patients 70 years of age or younger, even though there is significant valve-related morbidity. The outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve have been reported by the Veterans Affairs randomized trial. All-cause mortality was not different after MVR with mechanical prostheses versus bioprostheses. Structural valve deterioration was greater with bioprostheses for MVR in all age groups but occurred at a much higher rate in those less than 65 years of age. Thromboembolism rates were similar in the two valve prostheses, but bleeding was more common with the mechanical prostheses. In 2003, the Edinburgh randomized trial extrapolated results to 20 years. The prosthesis type did not influence survival, thromboembolism, or endocarditis. Major bleeding was more common with mechanical prosthesis [6].

Thanks to EU grant COST Action 537—"Core Laboratories for the improvement of medical devices in clinical practice from the failure of the explanted prostheses analysis (FEPA)"—organized in Europe. The goal is to improve medical devices in clinical practice from the FEPA—systematic studies of medical evaluation of cardiovascular implants requiring an explantation and assessment of generalized (immunological, inflammatory) and/or remote biological effects in patients with cardiovascular implants and with complications.

Living tissue valve replacements would solve many of the existing problems. In the future, natural biomaterials repopulated with autologous or genetically engineered cells will be used as ideal templates for the design of living tissue grafts. To date, the knowledge about these new materials is not very wide.

Further developments toward the alternative biological valve prostheses based on biological cell-free matrices as ideal valve substitutes using tissue engineering would potentially eliminate the known disadvantages of current valve prostheses. The endothelial cells harvested from the patient may be cultured in laboratory and incorporated into the synthetic scaffolds (polyglycolic acid, polyhydroxyalkanoate, and poly-4-hydroxybutrate) or both heterograft and allograft valvular decellularized tissues.

An ideal heart valve substitute should possess the following characteristics: absolute biocompatibility, long-term durability, nature-like biomechanical properties, no thrombogenic or teratogenic effects, sufficient availability in all common sizes, and moreover, particularly for pediatric patients the growth potential is crucial. Regions of stress concentration on the leaflets during the complex motion of the leaflets have been implicated in the structural failure of the leaflets with bioprosthetic valves. Computational fluid dynamics (CFD) has emerged as a promising tool, which, alongside experimentation, can yield insights of unprecedented detail into the hemodynamics of prosthetic heart valves.

### 8.3.3 Heart Pacemaker

The pacemaker was the first electronic device ever surgically implanted inside a human. In 1950, John Hopps, an electrical engineer, built the first pacemaker. The first successful attempts at designing a totally implantable pacemaker were reported by W. Chardack, A. Gage, and W. Greatbatch (New York). The group's work was recognized by Medtronic, which in 1960 signed a contract with Chardack and Greatbatch to produce an implantable pulse generator. These pacemakers and batteries have improved and saved the lives of millions of people worldwide. The pacemaker was applied for the first time in 1952 (P. Zoll) to stimulate the heart muscle through electrodes placed on the patient's chest. On the next stage, endocavitary electrodes were introduced into the right ventricle through the vein and a new, more effective way of controlling the system was carried out. The size and the weight of pacemakers and their durability had improved after replacing mercury batteries with lithium batteries, which have to be replaced every 10 years. Currently, the average weight of the device is about 15−30 g and 2.5 mm in diameter. In order to reduce the risk of system distortion, the bipolar electrodes should be fixed to endocardium using special methods. The electrode tips are made of special metal alloys and have a porous surface.

## 8.4 The Minimally Invasive Cardiology Tools

Minimally invasive cardiology requires a separate set of tools allowing the surgeon to operate through vessels. For surgical interventions, the

following devices can be used: the guideline (diameter 2−3 mm), catheters (the balloon catheter has a diameter of 0.8 mm), balloons (the balloon has to hold out an inflation up to 20 atm), and broadening vascular stents and devices (about 2 mm in diameter covered with diamond particles) for drilling out and excising the atherosclerotic plaques in coronary vessels, all under X-ray control.

The human circulatory system consists of the heart and the network of vessels transporting blood throughout the body. A pathological state of the aorta, which in more advanced stage blocks the blood flow, can be treated by vascular prosthesis implantation, replacing the damaged fragment of the vessel. Tissue implants (autogenic, allogenic, xenogenic) and synthetic vessels can be used as vascular prostheses in the surgery of vessels and cardiosurgery. If the main aim is to preserve the life of the cells, then depending on the time of tissue treatment, they are stored in antibiotic bath, nutritious liquids, or in hypothermia; or deep-freezed in liquid nitrogen. The blood cannot be used as a preservation solution, because at room temperature, unoxygenated blood becomes toxic. In some cases, vascular stents can also be used, which are constructions for vessel wall supporting to preserve its physiological diameter. They are pipes with diameter up to several centimeters, made of biocompatible materials (Dacron) fixed on a steel frame, assembled in the vessel during operation.

The narrowing or blockage in one or more coronary arteries (those supplying the blood to the heart muscle) can be a direct cause of the coronary artery disease. Currently, several treatment methods are available: e.g., using bypass techniques, vessel stents and minimally invasive, mechanical cloth, or by calcification removing. Pharmacological therapy and tissue engineering are very promising tools for contemporary and future treatment.

The catheter can be brought to the desired location via navigation, propulsion, and steering to perform several functions:

- actuation (ablation of material, balloon angioplasty, deployment of stent)
- sensing (pressure)
- transportation of material or energy (contrast fluid, embolization material, or signal from sensors for diagnostic purposes)

and that it can be retrieved again from the body [8]. The physical contact of the interventionist with the patient's tissue is established by using catheter, and the visual observation is mediated by the X-ray imaging.

Since the origin of the field of interventional cardiology in 1966 with balloon atrial septostomy, a procedure directed at treating congenital heart diseases, pediatric interventional cardiologists have developed percutaneous techniques for treating congenital valvular and great vessel stenoses and transcatheter closure of aberrant vascular channels. Balloon angioplasty [percutaneous transluminal coronary angioplasty (PTCA)] is widely used for treatment of the blockages of coronary artery. Percutaneous coronary intervention (PCI) encompasses a variety of procedures used to treat patients with diseased arteries of the heart. The catheter with balloon is inserted into the vessel (most often the femoral artery) through a small prick in artery. After transferring the balloon to the destination place, it is filled with a physiological saline mixture up to several atmospheric pressure. Due to this pressure, the balloon will expand, thus compressing the plaque, and hence, the narrowed vessel will also expand. The effectiveness of coronary angioplasty can be improved by using vessel prosthesis—a stent that is placed in vessel supports it and prevents it from closing. Typically, PCI is performed by threading a slender balloon-tipped tube—a catheter—from an artery in the groin to a trouble spot in an artery of the heart (this is referred to as the PTCA, coronary artery balloon dilation, or balloon angioplasty). The balloon is then inflated, compressing the plaque and dilating (widening) the narrowed coronary artery so that blood can flow more easily. This is often accompanied by inserting an expandable metal stent. Stents are wire mesh tubes used to prop open arteries after PTCA. The stent is collapsed to a small diameter and put over a balloon catheter. It is then moved into the area of the blockage. When the balloon is inflated, the stent expands, locks in place, and forms a scaffold. This holds the artery open. The stent remains in the artery permanently, holds it open, improves blood flow to the heart muscle, and relieves symptoms (usually chest pain). Within a few weeks of the time the stent was placed, the inner lining of the artery (the endothelium) grows over the metal surface of the stent. More than 70% of coronary

angioplasty procedures also include stenting. Some blockages in the arteries are hard, calcified deposits that do not respond to balloon angioplasty or stent implantation. In this case, the rotablator technique may be introduced. This is a small device used inside of the coronary arteries to "drill" through the calcified blockage. It breaks the calcium into microscopic pieces and disintegrates the blockage.

Percutaneous balloon dilation of isolated congenital semilunar valvular stenoses has proven to be highly effective in providing long-term hemodynamic and symptomatic benefit in neonatal, pediatric, and adult patient populations. Kan and associates described the first clinical application of balloon valvuloplasty in 1982, in which drastic improvement in transvalvular gradient was achieved in five children with pulmonary valve stenosis.

*Percutaneous balloon valvuloplasty* has thus been proposed as a less invasive means of treating mitral stenosis (Figure 8.8). The valve is usually approached in an anterograde direction via an interatrial septal puncture, although a retrograde technique has been reported. One or two tubular balloons or a specialized nylon-rubber (Inoue) balloon is advanced to position across the mitral valve and repetitive inflations are performed until the balloons have fully expanded.

Hemodynamic improvement following mitral valvuloplasty occurs immediately, with valve area increasing on average by 1.0 $cm^2$, with a prompt drop in pulmonary pressures.

A randomized trial comparing mitral balloon valvuloplasty to open surgical commissurotomy among patients with favorable valvular anatomy demonstrated comparable initial hemodynamic results and clinical outcomes among patients treated with either technique, although hemodynamic findings at 3 years were more favorable in the balloon valvuloplasty group.

Pulmonary artery stenosis or hypoplasia may be effectively treated using catheter-based technologies. Success rates following balloon dilation of these vessels have ranged from 50 to 60%, with failures due primarily to elastic recoil. There has also been a limited experience with balloon angioplasty or stent placement for management of aortic coarctation, venous obstruction, or stenoses of Fontan shunts.

Advances in the technology for percutaneous coronary revascularization have been accompanied by a dramatic increase in the number of procedures carried out in the world.

Intravascular stenting of arteries is one of the most frequent operations in cardiovascular surgery. Stents are inserted into a vessel with injured inner wall to avoid its destruction, thrombus formation, or vasoconstriction. Vascular stents should have a shape rendering it relatively elastic and durable with respect to the vessel (Figure 8.9). There have to be (e.g., gold) marker lines, allowing stent observation during procedure (RTG monitoring). Stents are made from metal alloys using various techniques. They can be formed from the wire or through excising from tubes using laser. More recent research uses shape memory alloys (Nitinol). Such stents in cooled stage are transported to the target place, where after warming up to physiological temperature, they reach the final shape. One of the first stents clinically applied (Wiktor-GX stent, Medtronic Interventional Vascular, Holland) is an

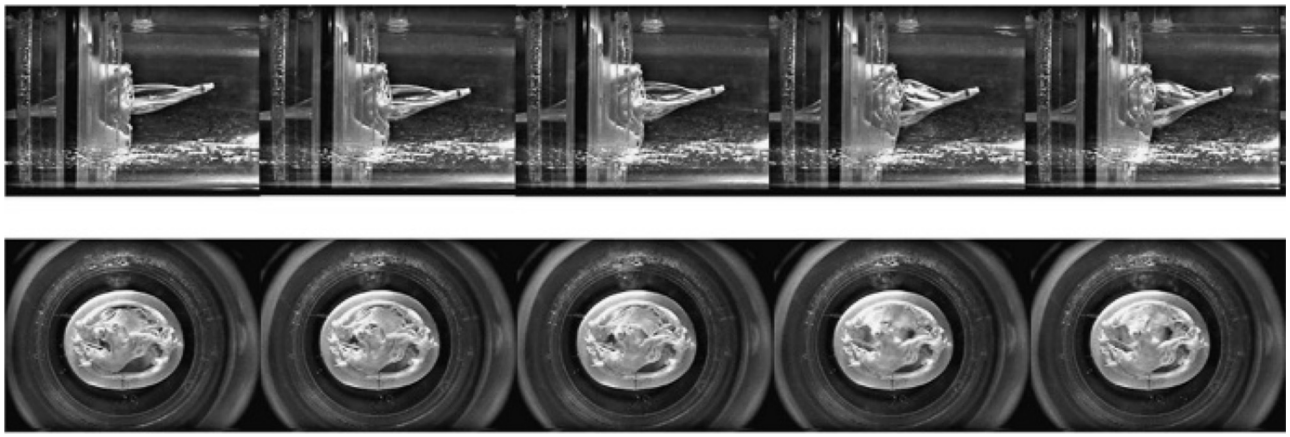


**Figure 8.8** The physical percutaneous balloon valvuloplasty simulation on polyurethane and mitral valve.

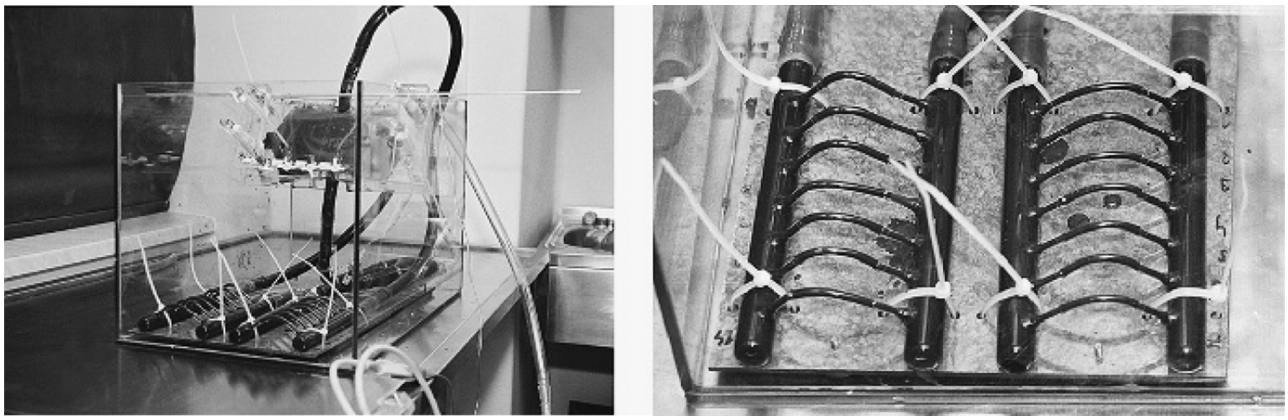


**Figure 8.9** Fatigue tests on the nanocrystalline diamond and steel coronary stents were carried out: Tyrode's physiologic solution; frequency 180 cpm; 3 months. Coronary arteries were simulated using a tube of inner diameter 3 mm and wall thickness 1 mm. After investigations, the corrosion resistance tests of the implants have been additionally performed.

original project of Pole, Dominick Wiktor, in the United States. This stent was created from wire with sinusoidal shape wounded on the cylinder. It is made from tantalum, instead of steel, because of its better contrast in RTG visualization and the electronegative surface improving thromboresistance of the stent. The first clinical implantation of stent was performed in 1989. The materials used for the construction of these stents have changed dramatically over the past 10 years. Unfortunately, metal stents induce thrombus formation. Stent biocompatibility can be enhanced by either modifying the metal surface of the implant or applying biocompatible coatings. To improve its biocompatibility and to prevent the closing of renewed vessel, the surface of stents is covered with heparin. Stenting procedures can also be connected with genetic therapy by covering its surface by a layer of polymer, which when placed into the vessel wall releases the genetic material, which blocks the cell growth. In Poland, the multidisciplinary team works on original vascular stents covered with a layer of nanocrystalline diamond.

Currently, multiple research projects are focused on the design of a stent with better radiopacity, reduced stent-vessel wall contact area, and improved elasticity, and thrombogenic effects are lowered when the stent is coated with the proper antithrombotic substances. The problem that plagues about one-third of patients who receive angioplasty with or without stents is "restenosis"—the recurrence of the narrowing of the blood vessel. The new drug-coated stents release a medication that blocks this scarring process.

Novel technologies will be introduced and developed, directed at the efficient removal or modification of arterial plaques with minimal arterial trauma or at site-specific drug delivery to inhibit thrombosis and restenosis. Concurrently, intravascular ultrasound and angioscopy will be further refined and integrated into revascularization devices, allowing precise guidance and optimization of plaque ablation or remodeling while limiting associated coronary injury. Finally, understanding of the vascular biology of percutaneous revascularization, thrombosis, and restenosis will be improved, leading to pharmacological therapies designed to ameliorate adverse thrombotic, proliferative, and remodeling responses.

## 8.5 The Technology for Atrial Fibrillation

The evolving technologies for ablation of atrial fibrillation include radio frequency, cryotherapy, microwave, laser, and ultrasound. The efforts directed at isolating and ablating percutaneous catheter pulmonary vein have essentially been abandoned because of the extensive length of procedures and the high incidence of pulmonary vein stenosis. The newer technologies have been developed to create transmural lesions during cardiac surgery [6].

*Radiofrequency used in ablation:* Radio frequency corresponds to the frequency of

unmodulated alternating current delivered in the range of 0.5−1.0 MHz between two electrodes, one located on the endocardial surface and the other on the skin. Its heating effect produces homogeneous lesions that measure a few millimeters in diameter and depth. It has been demonstrated that reliable and effective ablation is performed at 70°C for 60 s. The goal temperature should never be set at more than 95°C to avoid potential tissue disruption.

*Cryoablation:* Cryoablation has an excellent clinical safety record, although its use in atrial fibrillation surgery has been limited to creating spot lesions over the tricuspid and mitral valve annuli. The salient features of the procedure are rapid freezing, and slow thawing with repeated freeze−thaw cycles. The coldest temperature (the prime determinant of cell death) may range from −50°C to −150°C and the application time can vary between 0.5 and 5 min, depending on the area of application.

*Laser ablation:* The laser lesion formation is thermal through photon absorption at the surface, with deeper myocardial sites heated through passive conduction. The wavelength chosen for good penetration is 980 nm (using a 980-nm diode laser). This wavelength ablates tissue with absorption of actual laser energy as deep as 4 mm into the tissue and further ablation by conductive heating mechanisms. The lesion times are for 36 s utilizing 5 W/cm, but ablation cannot be longer than 5 cm.

*Microwave ablation:* The electromagnetic microwaves occur at 2.45 GHz to generate frictional heating by induction of dielectric ionic movements. The microwave device can provide a range of 40−45 W of power for 20−30 s, generating a consistent 3−6 mm lesion depth sufficient to produce transmural ablation.

*Ultrasound ablation:* This technology uses an ultrasound transducer to deliver mechanical pressure waves at high frequency. The tissue destruction is thermal and lesion depth corresponds to vibrational frequency. The ultrasound wave emitted from the transducer travels through tissue causing compression, refraction, and particle movement, resulting in kinetic energy and heat [6].

## 8.6 Minimally Invasive Surgery

Minimally invasive surgery, a keyhole surgery, is an operation technique in which access to the inside of the patient's body is achieved via small incisions. The long rigid instruments inserted via trocars can be used to move, retract, and cut tissue in abdomen (laparoscopy), chest (thoracoscopy), blood vessels (angioscopy), gastrointestinal tract (colonoscopy), uterus (hysteroscopy), and joints (artheroscopy). Insufflation of the body cavity may be carded out and maintained by seals on the trocar port, which allow tool manipulation without excessive loss of insufflation gas [8]. The trocars may be sized to provide ports of differing sizes, typically of about 5−11 mm diameter. Currently, tools such as retractors, forceps, graspers, suture needles, scissors, different types of knives, laser incision instruments, and specimen bags are available. A video camera is generally operated through a trocar port for visualization and control of the procedures in the cavity. High-definition video cameras and monitors are then attached to the camera and a surgical team can obtain a clear picture of the affected internal area without resorting to radical, disfiguring surgical incisions to physically open the patient. Another benefit of laparoscopic surgery is the significantly reduced recovery time, when compared to standard surgical procedures, due to the minuscule size of the scalpel incisions and avoidance of the massive internal traumatization known in standard surgical procedures.

Due to fixed entry points of the instruments in the abdominal wall, the DOF is reduced, and the movements are mirrored and scaled. The coupling between observation and manipulation, the hand-eye coordination is disturbed, tactile information about tissue properties partially, due to friction and the poor ergonomic design of instruments, lost. The future is open for semiautomatic tools for MIS. As an example, Medtronic, Inc., has introduced the world's first minimally invasive epicardial lead placement tool. The Medtronic Model 10626 Epicardial Lead Implant Tool allows for perpendicular alignment to the heart from different angle approaches. The tool furthers the trend moving away from invasive sternotomy procedures. Laparoscopy reduces patient trauma, but eliminates the surgeon's ability to directly view and touch the surgical environment. This is reason that the surgeon introduced the small-incision surgery when they have a direct view of the tissue.

The rapid development and growing interest in MIS methods impelled creation of modern, complicated tools: cardiosurgical robots.

### 8.6.1 The Classical Thoracoscopic Tools

Laparoscopic or thoracoscopic surgery requires that surgeons perform complex procedures using a standardized set of tools. For laparoscopic procedures, special sewing devices, ligating instruments, knot pushers, clips, and clip appliers have been developed. The clamp is an essential tool for stopping or controlling blood flow to an organ during surgery. There is a need for a secure and easy method of suturing in laparoscopic surgery. Laparoscopic suturing can be performed with a suture, using automatic sewing devices or clips. When a surgeon wants to suture laparoscopically in the traditional way by using a Roeder knot for instance, the tying of the knot requires some expertise and makes the procedure more complicated and time-consuming. The vascular clips provide a very easy (and secure) method of stopping blood flow while performing procedures on vessels. The locking forceps allows easy, precise, and secure grasping of the surgical clips. The risky point of a clip is the open end of its U-shaped design, which makes it possible for the clip to slip off. Sutures avoid this risk by totally enclosing the structure to be occluded. Knotting instruments require a two-forcep technique, whereas sewing devices require only one working channel.

There has been a tremendous interest in the development of *anastomotic devices* for coronary surgery. Coronary artery disease is a major health problem worldwide, with approximately 850,000 bypass procedures being performed every year. The current methods of coronary bypass surgery can be time-consuming and technically difficult especially when minimally invasive instruments for suturing the blood vessels (the connection is called anastomosis) are used. Alexis Carrel, who many consider the father of anastamoses, received a Nobel Prize for the suturing of blood vessels about 100 years ago. More than 5 million vascular anastomoses are performed annually in the world and more than 70% often are on the CABG market [9].

The requirements of anastomotic devices include reproducibility, ease of use, and a short anastomotic time (less than 1 min). The anastomotic device ideally would work with either vein or artery and so the proximal or distal order of anastomoses should be interchangeable. The device should facilitate a wide range of surgical access points and should have patency comparable to that of hand-sewn techniques [9].

There are manual and automatic anastomotic devices. The manual proximal anastomotic devices Heartstring *Aortic Occluder*™ from Guidant (that acts as an umbrella inside an aortotomy) and the Enclose™ device from Novare Medical (require a separate insertion through the aorta) create a dry area for conventional suturing in aortotomies.

The Symmetry™ Bypass System Aortic Connector is the first in a line of sutureless anastomoses devices for CABG developed by St Jude Medical, Inc., Cardiac Surgery Division—Anastomotic Technology Group (ATG), formerly Vascular Science, Inc. (VSI). There have been more than 50,000 implants performed.

CardioVations™ has released the *Corlink*™ proximal device in Europe. This is a Nitinol-based stent device. The major difference in comparison with Symmetry is that the Corlink device sits outside of the vein graft wall and the Symmetry device lies inside the vein graft wall.

The *Passport*™ automatic proximal device consists of an integrated system that performs the aortotomy, delivers the graft to the aorta, and deploys a stainless-steel connector end-to-side the graft using a delivery device. The stainless-steel stent (more rigid than Nitinol) creates a widely patented anastomosis.

Another proximal anastomotic device is the *Magnaport* from Ventrica. This is also a one-step anastomotic device using rare earth magnets.

*Coalescent Surgical*™ has developed an automatic proximal anastomotic device, called the *Spyder*® based on their proprietary Nitinol (nickel−titanium) clip technology.

The first distal device to market (launched in 2000) was the manual *Coalescent U-CLIP*™. This is a self-closing, penetrating device with bailout. The U-CLIP device is designed to provide an alternative to conventional suture and surgical clips in a variety of applications including anastomosis creation and tissue approximation. The device consists of a self-closing surgical clip attached to a conventional surgical needle by a flexible member. U-CLIP device placement is easy and requires only standard surgical instrumentation. The self-closing clip eliminates the requirement for knot-tying and suture management. A fresh, sharp needle is provided with each clip. The clip is easily removed. The U-CLIP anastomotic device technology

consistently facilitates the interrupted technique in both on-pump (or surgery performed with a cardiopulmonary bypass machine) and off-pump (also known as beating-heart, CABG procedures). Independent core laboratory analysis demonstrated that the left internal mammary artery to the left anterior descending coronary artery (LIMA to LADA) anastomoses created with the U-CLIP anastomotic device were 100% perfectly patented at 6 months [9].

The Spyder device provides fast, automated proximal anastomotic connection by simultaneous delivery of six U-CLIP devices without the use of a side-biting clamp or second manipulation of the aorta. The *JoMed Solem* connector consists of a stented "T"-shaped PTFE graft connected to the internal mammary artery. The *St Jude* distal connector consists of a stent that is deployed with a balloon using a side-to-side technique to create a distal coronary anastomosis. The *Converge Medical* device consists of outer and inner Nitinol couplers that are placed on the vein graft. This device allows for an angled anastomosis and creates elliptical interface. Magnetic Vascular Positioner (MVP), developed by Ventrica (received CE Mark approval in February 2002), uses magnetic attraction to form an instantaneous self-aligning, self-sealing connection between two blood vessels. The elliptical magnets are placed inside the conduit and native vessel. The MVP device connects the "bypass graft" to the coronary artery in seconds, and is designed to be used in the distal, or smallest, portion of the coronary arteries.

Anastomotic devices in OPCAB may play their most important role in the proximal anastomosis. The major meta-analyses reveal the significant benefits of performing OPCAB (off-pump coronary artery bypass) over CCABG (conventional coronary artery bypass) for certain patient populations requiring myocardial revascularization procedures. The technology has potential benefits as a replacement for sutures due to shorter procedure times, uniform and repeatable connections, and the potential to allow for significantly smaller incisions. This would allow proximal anastomoses to be performed with minimal aortic manipulation, which may result in a lower rate of intra- and postoperative embolism. An automated distal device could facilitate lateral wall grafting in OPCAB. In total endoscopic coronary artery bypass (TECAB), a distal automatic device could be critical in evolving the endoscopic procedure. Currently, the Ventrica device is being modified for deployment in a robotic environment. Finally, in multivessel TECAB procedures, distal anastomotic devices are predicted to make a major contribution. Most minimally invasive procedures in the future will be facilitated by an automated anastomotic device. The automated anastomotic device will level the playing field and allow for more surgeons to perform more perfect anastomoses. Wolf concluded that with continued evolution of these devices, it is easy to anticipate that in the near future the majority of anastomoses may be performed with a manual or automatic device as opposed to the current conventional suture technique [9]. The leaders of clinical trials of these new methods are Randall K. Wolf and Volkmar Falk, MD.

Since 1997, Medtronic has been a pioneer in minimally invasive, beating-heart surgery with the introduction of the Octopus tissue stabilizer system and its family of products, and most recently with the release of the Starfish2 heart positioner.

In traditional open-heart surgery, the heart is stopped and an artificial pump is used to maintain blood circulation. This is highly traumatic as the blood flow is rerouted through a machine. Many patients with coronary heart disease undergo open-heart operations, especially bypass surgery. These are traditionally performed with a heart−lung machine. The machine serves as a substitute for the patient's own beating heart and lungs, allowing the organs to function while surgeons operate on a "still" heart.

Endoscopic surgery in a major cavity in the body requires space for manipulation and local cardiac wall immobilization for coronary artery grafting on the working heart. One of the revolutionary instrument used in beating-heart surgery is Octopus. The name comes from its suction device of two arms and a series of "suckers," which allow to position the heart in various places with the chest open.

### 8.6.2 The Surgical Robots

About 4 million MISs are performed in the world every year. The aim is to limit the operative field and spare surrounding tissue, which would be damaged if a traditional surgical technique was used. The number of endoscopic procedures, less invasive than traditional surgery, performed through

natural orifices in the patient's body, or through special openings called ports, is on the rise.

The success of the procedures largely depends on the instruments used. Unfortunately, typical endoscopic (laparoscopic) instruments reduce precision and make the surgery more difficult because they add to hand tremor and almost completely eliminate the natural sense of touch. Additionally, the surgeon does not have a direct view of the operative field—a camera inserted into the body through a third opening transmitting the image to a display. So the surgeon's task is not easy. An ideal noninvasive surgery can be compared to renovating a house through a keyhole without disturbing the household members. Across the world, physicians and engineers are working together toward developing increasingly effective instruments to enable surgery using the latest technology. But how can one enhance instrument precision and maneuverability, which are so important in the case of surgery on the beating heart, for instance? Surgical robots provide such capabilities.

Surgical robots improving precision and facilitating minimally invasive access to the area of the operation make up a great potential instrument for the surgery. Currently, these are mainly telemanipulators, where on the "master" side is the surgeon giving the instructions (movements, tasks), on the "slave" side is the end-effector as a surgery tool tip executing tasks in the definite working space, and in the middle of these "actors" is a control system, which reads, processes the input data, enriches them, and computes the output commands.

Currently, two types of medical robotic systems are used in the surgery:

*Robots replacing the assistant during the operation:* By using systems such as AESOP (Computer Motion – production stopped at present) or EndoAssist (Armstrong Healthcare Ltd, High Wycombe, UK), the surgeon can unaidedly control the position of endoscopic camera, serving as their "eyes" in the closed area of the operation field.

*Surgical robots:* Robots invented for less minimally invasive cardiac surgery are computer-controlled devices, located between surgeon's hands and the tip of a surgical instrument (Figure 8.10). Currently used cardiac surgery robots fulfill the role of telemanipulators, the main task of which is to detect and scale up or down the surgeon's hand movements and precisely translate them to the movements of robot's arm equipped with tools. A cardio-robot was invented in the United States in the 1990s. Two companies, currently merged, Computer Motion (Computer Motion) and Intuitive Surgical (Intuitive Surgical, Mountain View, CA, USA),

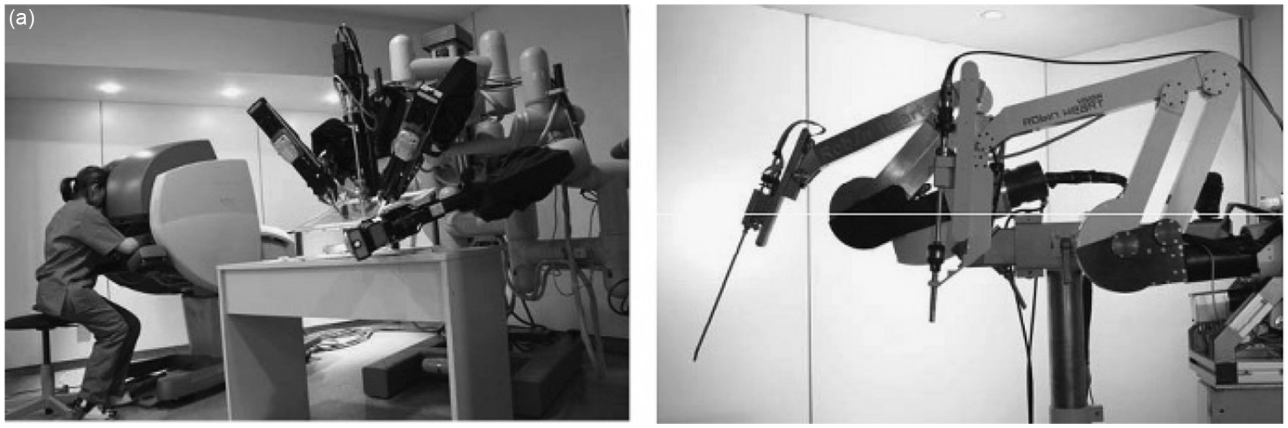



**Figure 8.10** (a) Robot daVinci (*left*) and Robin Heart cardiosurgery robot (*right*). (b) Comparison of different tools: Robin Heart 0,1 and laparoscopic tools; test of Robin Expert advisory system (presented by the author); and the test using animal tissue. (c) Evaluation of Robin Heart robot is carried out using the following measurements: vibration (new accelerometer sensors) [A]; linear movement (using digital micrometer) [B]; system of external trajectory recording (several digital cameras, markers, and image analysis methods) [C]; and physical [D] and computer surgery simulation (*bottom:* general range of robot mobility and workspace equipped with [E] standard laparoscopic tool and [F] Robin Heart I instrument).

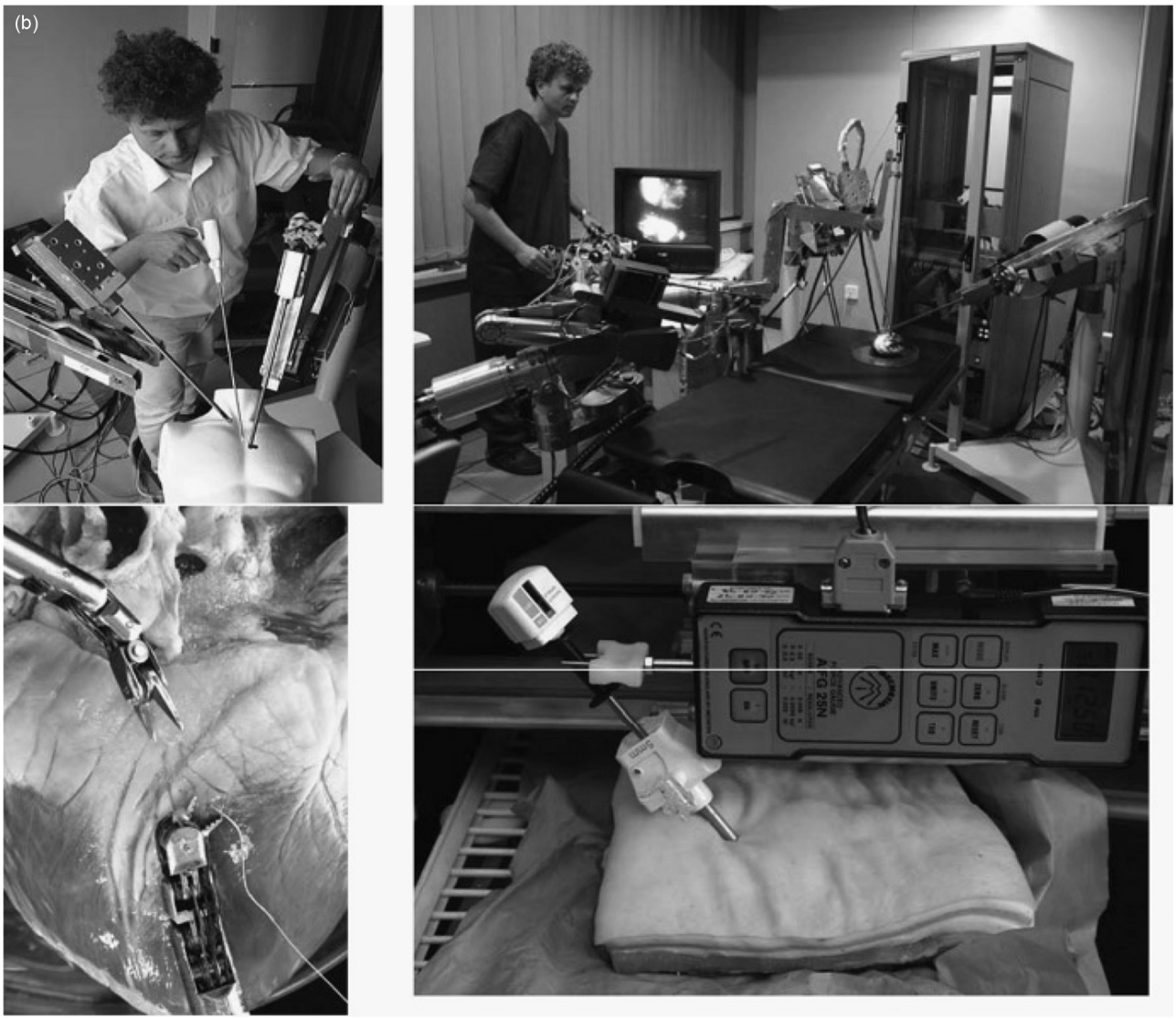



**Figure 8.10** (*Continued*)

were set up based on Star Wars project technologies developed by NASA and Pentagon. In Europe, Poland, the Robin Heart family robots are developed (Figure 8.10). The Foundation of Cardiac Surgery Development (FCSD) in Zabrze in 2000 started issuing the grant for realizing the prototype of a robot useful for cardiac surgery. The multidisciplinary team including specialists in medicine and techniques prepared until now four robot prototypes named Robin Heart [10].

An application of teleoperation allows to remove the tremor and to introduce the scaling of hand movement range via interface of manipulator on exact movements of tool inside the body, thus improving the ergonomics and precision. Supervision is held using visual observation via voice- or manually controlled endocamera (2D or 3D). American cardiosurgical robots have been produced by two, currently merged, companies, Computer Motion and Intuitive Surgical, which was firstly clinically used in Europe.

The first mechanical assistant of surgeon—voice-controlled endoscope positioner AESOP 1000 (automated endoscopic system for optimal positioning)—was introduced by firm CM in 1994. In January–May 1998, a French team in Paris and a German group from Leipzig performed using da Vinci (Figure 8.10a) (IS) telemanipulator the first endoscopic operation of single coronary bypass and

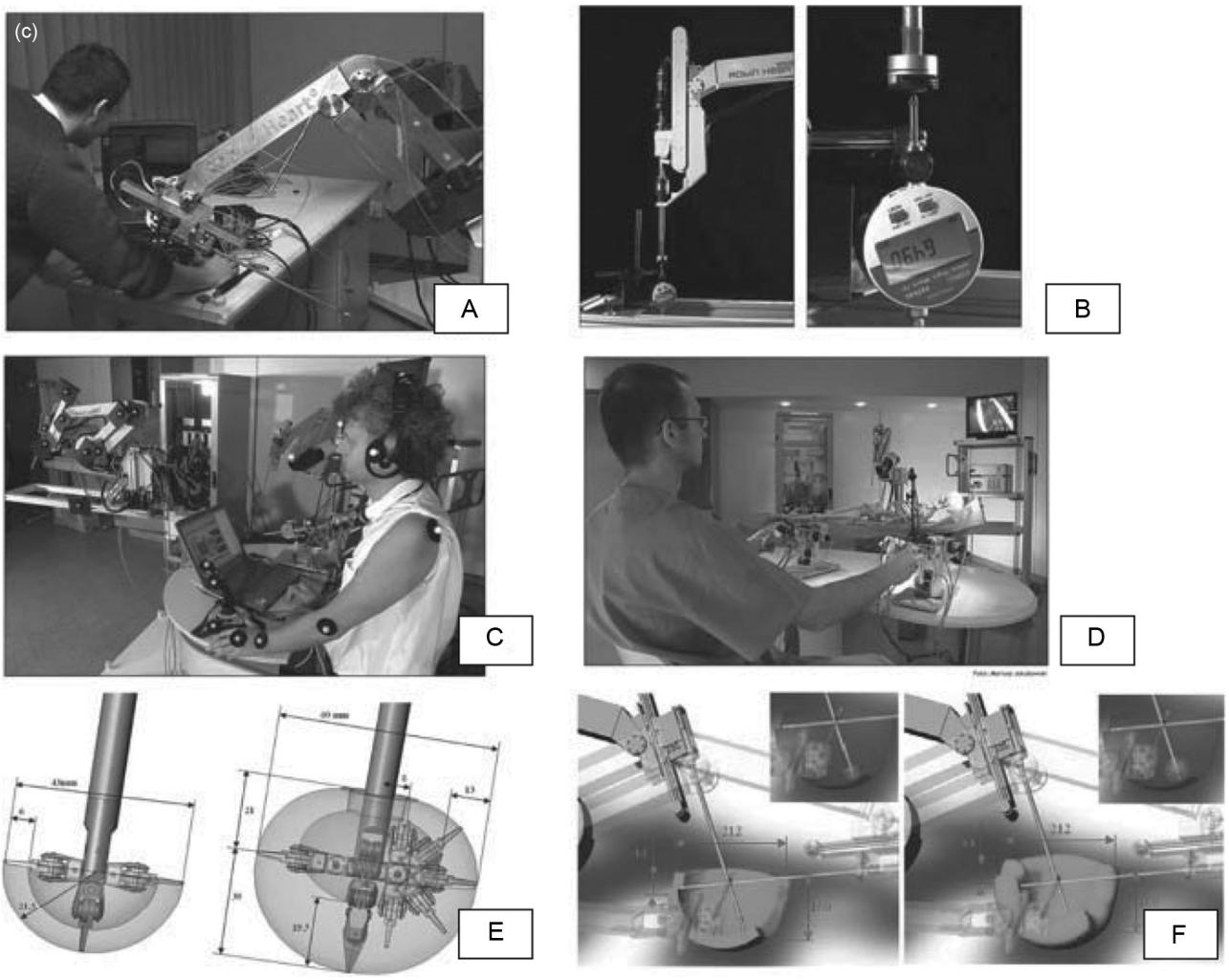



**Figure 8.10** (*Continued*)

mitral valvuloplasty. About 1000 surgical and endocamera robots were installed in clinics; to date, more than 130,000 minimally invasive procedures, across a wide range of surgical applications such as general surgery, gynecology, spinal, urology, and cardiothoracic surgery, have been performed in several counters (also in Poland, Katowice) [11].

In 1999, the Zeus surgical system made history in the world's first robot-assisted beating-heart bypass surgery, by Douglas Boyd, MD. In 2001, the first transatlantic telesurgical procedure was performed using the Zeus system. The doctors in New York removed a gallbladder of a 68-year-old patient in Strasbourg, France, and the procedure was successful with no complications.

In traditional laparoscopic surgery, the operating surgeon does not have direct visual control of the operative field due to manual camera control by an assistant. Ideally, the surgeon should have full control of operative instruments and the operative field. Camera holders should return camera control to the surgeon and stabilize the visual field during minimally invasive procedures. The active and passive camera holders offer the surgeon an alternative and better tool to control the operating surgeon's direct visual field. One of the first, active teleoperated robots introduced into clinical practice was produced by Computer Motion (US) Company. Currently, more than 1500 of Computer Motion's robotic systems (AESOP, Zeus) are in use worldwide in 900 hospitals by more than 3000 surgeons in 32 countries. The Zeus system consists of three robotic arms mounted onto an operating table. Two arms hold surgical instruments, and the third arm holds and positions the endoscope via voice control. All three arms are connected to a master

console where the surgeon telemanipulates the arms. The handles used to control the movement of the surgical instruments are similar to the instruments used in conventional surgery. The surgeon's manual movements are filtered and scaled for the slave instruments to perform precise microsurgery. The Zeus system can be used in combination with an independent 3D visualization system (AESOP). More than 300,000 surgical procedures have been performed with Computer Motion's robotic systems assistance. The AESOP system is both CE marked and FDA approved and has been used in more than 100,000 laparoscopic and endoscopic procedures. The duration of several types of endoscopic surgery was reportedly faster using the AESOP; voice control was considered to be more efficient and faster than either the foot or hand control.

The disadvantages for the AESOP include the constant voice commands, which may be distracting. In addition, the voice control is slower compared to the rapid camera movements achieved by an experienced assistant. The AESOP is intended to facilitate solo-surgeon laparoscopic procedures; however, the surgeon may still need an assistant to control the fourth laparoscopic port. The Intuitive Surgical Inc. (US) da Vinci telemanipulator consists of three or four robotic arms in one set fixed on one common column, placed near the operating table.

In contrast to the AESOP system, da Vinci arm for camera holding is integrated with all robotic arms. Today approximately 400 da Vinci systems have been installed worldwide, and its applications have been described in thousands of scientific publications and presentations. It is CE marked and FDA approved and used in more than 300 hospitals in America and Europe. The da Vinci was used in at least 16,000 procedures in 2004 and sells for about $1.3 million.

In Europe, the Armstrong Healthcare Ltd (UK) produced telemanipulator EndoAssist. A robot system EndoAssist holds a conventional laparoscopic telescope and camera, coordinated by the surgeon's head movements. EndoAssist (CE marked and approved by FDA) has also been used in telesurgical applications with control via a joystick communicating with the robot over a telephone line. About 30 systems installed worldwide now has been used in several thousand clinical procedures.

The future of robotic surgery has significant potential that has been proven in many clinical applications. The procedure completed without the need for an additional assistant is called a "solo surgery." Robotic assistance has enabled a solo surgery approach. The basic principle of manipulator construction is that of a serial architecture of joints and links with a fixed remote center in the corporeal wall. For instance, the da Vinci robot have seven DOFs: three (yaw, pitch, and insertion) have surgical manipulators provide motion coupling to the end-effector, an exchangeable instrument that adds four DOFs (roll, pitch, yaw, and grip) by means of a cable-driven mechanical wrist. The surgeon controls the movements of tools via a human machine. The slave is capable of detecting force feedback (tissue contact, collision of manipulator) greater than 2.2 N. Scaling is useful in the range from 1:1 to 10:1, in combination with tremor filtering greater than 6 Hz [12].

The computer and laboratory tests are required to design a new, smart surgery robot and expanding its applications to the field of medicine. The 3D computer simulation and physical modeling will continue to be supported on Polish grants.

The use of conventional endoscopic instruments allows a limited range of motion by the trocars through which the instruments are introduced and by reduction to only four DOFs for tools. Long and rigid instruments are harder to control and amplify tremor.

Six DOFs are required to perform a free motion. For instance, suturing perpendicular to the four-DOF tool's shape becomes impossible. The study shows that using four-DOF robot (Zeus system, Computer Motion) the 1.5 mm tube anastomosis was performed in 46 min compared to only 12 min performed by six-DOF robots (da Vinci). Endoscopic tissue manipulation and suturing using four-DOF instrumentation requires skill and training.

Cardiac surgery is carried out on soft tissues. Results obtained from surgical action analysis allowed to determine the maximum values of forces needed for typical procedures performed in heart area, using different types of tools. This can be the basis for cardiac surgery robot design assumption, in the field connected with controlling of robot tool movements. The penetration of soft tissue involves actions such as cutting, slicing, inserting a needle, and knotting. The difficulty with soft tissue is that it deforms and changes shape. The map of force resistance during pricking for left and right heart chamber was obtained (i.e., the basic mechanical

properties of typical surgical actions; from the FCSD). For example, the maximal force value for surgical needle Prolene 3/0 during pricking through papillary muscle reached the 150 G, the measured load value equaled 200 G (2 cm depth) during scalpel cutting procedure for the left ventricle (the mitral valve ring), and up to 200 G with 0.1 mm/s test speed for sewing tests—the knot-tying using Prolene needle.

One of the limitations of current surgical robots used in surgery is the lack of haptic feedback. Although current surgical robots improve surgeon dexterity, decrease tremor, and improve visualization, they lack the necessary fidelity to help a surgeon characterize tissue properties for improving diagnostic capabilities. Many research groups focus on the development of tools and software that will allow haptic feedback to be integrated in a robot-assisted surgical procedure.

The surgeon needs assistants of next robot arm during operation mainly for stabilization of the heart (beating-heart bypass grafting) or another tissue. Several trials using two da Vinci consoles delivered good results. In response, the IS prepared the da Vinci S model with four arms.

The devices providing an "inside equipment store" for the surgeon are also needed. A self-sufficient Cargo Module was developed as a transportation and depot device by Dresden group. With the Assist Module, the surgical equipment, tissue, and vessels can be positioned on a desired place in the operating field. This module provides the surgeon an "assistant" inside the closed chest.

Potential applications of robotics in cardiac surgery includes aortic valve replacement (standard or percutaneous technology); tricuspid valve repair; descending thoracic aortic surgery; transmyocardial laser revascularization; ventricular septal defect, patent ductus arteriosus, coarctation; and intramyocardial delivery platform for biological agents such as stem cells, molecular therapeutics, genetic vectors, and AORobAS (Artificial Organs Robotically Assisted Surgery).

In the Institute of Heart Prostheses, FCSD, surgeries related to artificial organ (AO) implantation are performed. Our future plans, AORobAS, include carrying out a robotically assisted less invasive procedures to implant pumps and valves.

The da Vinci system is therefore the only surgical telemanipulator that is currently clinically being used. Due to the actual range of the system acceptance, the number of endoscopic cardiac procedures performed in 2005 worldwide (reported in a company-based registry) was 2984 and it increased steadily. This includes TECAB procedures or small access single- or multivessel coronary artery bypass procedures with endoscopic uni- or bilateral ITA harvest (1784 procedures). The number of MVR increased to about 450 cases in 2004, to more than 600 in 2005, to 850 in the first 10 months of 2006 (reported in a company-based registry) [13].

The number of procedures performed may increase due to development of and improvement in facilitating anastomotic devices (MVP magnetic coupling device) and augmented reality with preoperative planning and intraoperative navigation. Based on the preoperation cardiac surgery simulation results, the optimization of cardiac surgery procedures can be achieved.

The *effectiveness* and *expansion* of robot's application fields requires searching the most effective cardiac robots in the wide application range, building the strategy of its usage, simulating the operation results, and creating the knowledge base supporting the robot's arm navigation and cardiac surgeon decision making, and studying image processing methods for optimal robot's arm navigation [13].

### 8.6.3 Blood Pumps—MIS Application Study

The use of the mechanical circulatory support systems (TAHs and VADs) has evolved significantly over the last 30 years, with more than 10,000 patients being supported by these devices (TAH 2%). The devices have evolved from extracor-poreal devices (such as Jarvik 7, Thoratec, Abiomed systems), driven by large pneumatic consoles, to electrically driven partially implantable devices with portable controllers carried by the patient (such as Novacor, HeartMate).

The future prospects of the mechanical circulatory support clearly lie in three major areas:

1. active left ventricular pump system, which supports and stabilizes the heart in extremely critical situations (e.g., acute heart attack), and can be implanted for a period of up to 5 days (e.g., Impella® Acute)
2. devices as a bridge to recovery (e.g., pulsatile pumps: Novacor, HeartMate; rotary pumps: MicroMed, Jarvik-Heart, Nimbus-HeartMate II)

3. devices as an alternative to the cardiac transplantation and conventional therapy (e.g., destination therapy: LionHeart, AbioCor TAH)

### 8.6.3.1 Minimally Invasive VAD Implantation

Dr J. Donald Hill of the California Pacific Medical Center (San Francisco, CA, USA) has successfully performed the less invasive Thoratec LVAD surgery on several patients.

The patient is placed on the cardiopulmonary bypass using the right or left femoral artery or vein. The VAD cannulation system is placed in the left ventricular apex (VAD inflow) and the ascending aorta (VAD outflow), using two separate incisions. The procedure offers the following advantages: no sternotomy, easier reoperation, less blood use, reduced risk of sensitization, and it is psychologically more acceptable (according to Dr Hill, the Thoratec Laboratories).

General steps in VAD implantation are as follows: anesthesia is administered to the patient; preparing the operating area—cardiopulmonary bypass (if required) and lung deflation; choosing the exit site for LVAD—depending on the need of LVAD alone or of BiVAD, one or two outflow and inflow grafts will be necessary; aortic and pulmonary artery anastomoses performed; left and right ventricular apical or atrial cannulation performed; connecting the VAD to the cannulas, deaerating the VAD; gradually discontinue cardiopulmonary bypass and allow the VAD to run in "fill-to-empty" mode; completing surgery.

Our plans include carrying out robotically assisted less invasive procedures to implant VADs (Figure 8.11), TAHs, valves, and vessel prostheses. The rapid evolution of MIS techniques for heart prostheses will have implications for designing and construction of heart prostheses. Our team works on the designing of heart pumps and valves particularly for robot and MIS applications and special tools of robot are being constructed. I am sure that

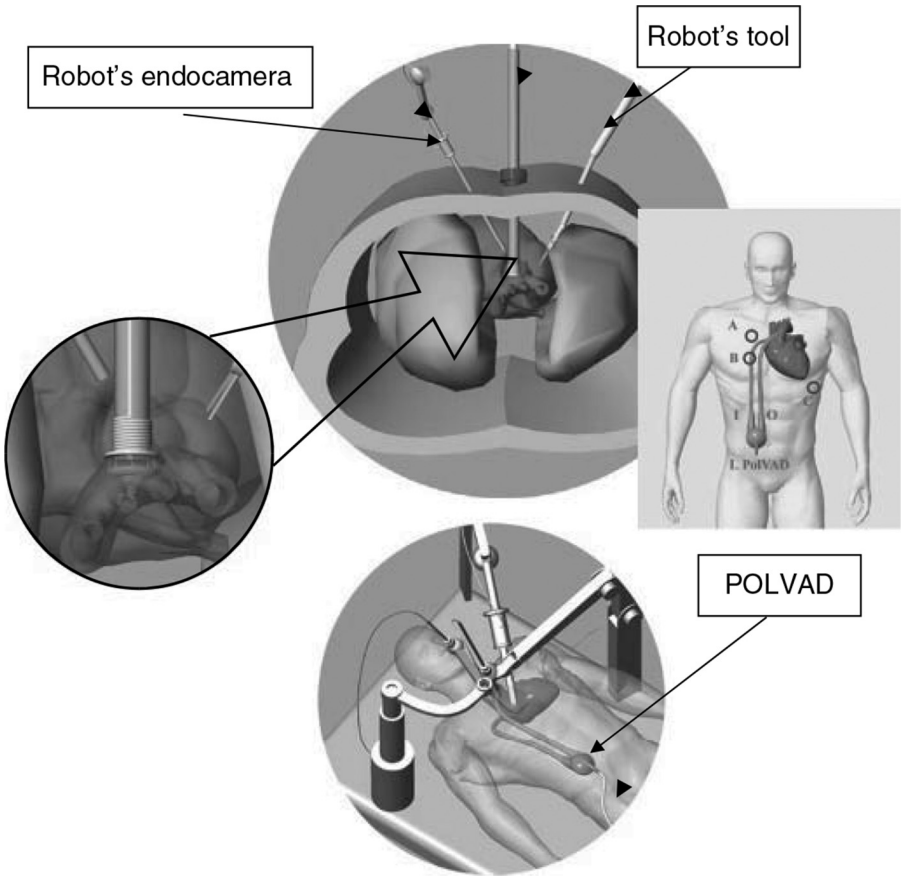



**Figure 8.11** Semiautomatic tools for robotically assisted POLVAD implantation.

this is the future of this domain of biomedical engineering.

### 8.6.3.2 The AORobAS Idea

Currently used VADs, pumps, valves, and pacemakers require to be replaced and repaired throughout the patient's life. A better solution seems to be application of MIS at once by designing AOs with construction ready to easy assembly and disassembly as well as to ensure an access to replace the used parts. For external pumps, an MIS technique of cannula implantation should be performed.

In 2000, a new type of blood pump was introduced into clinical practice. In robot-assisted surgery, the use of the small, axial heart assist pump is very promising. The Jarvik 2000 VAD and the DeBakey VAD, which have been approved for evaluation as a bridge to transplantation, are valveless devices that are electrically powered miniature axial flow pumps. These fit directly into the left ventricle, which may eliminate problems with clotting. The outflow graft connects to the descending aorta. The DeBakey VAD is 30 mm × 76 mm, weighs 93 g, and is approximately 1/10th the size of pulsatile products on the market. The development of this idea causes changes in requirements for blood pump. It should be folding device, with dimension not exceeding the port hole incision diameter. It means that this part must be a cylinder with about 1 cm diameter and the technology for quick mounting of this part on the whole pump inside the chest must be developed. Robots also require special constructions of semiautomatic tools. The surgical procedure requires faster and efficient connection to pulmonary bypass apparatus, because the surgery is performed on a stopped heart. Of course, there are many problems to solve, but this type of surgery has wide perspectives. In our laboratory, the design and simulation study has been conducted. I work on the realization of the following procedure:

- *Stages of AO implantation and assembly:* Parts of the AO, put into capsule through mechanically or pneumatically controlled channel, run into pumped balloon, where they are assembled. The balloon has valves that allows for insertion of additional tools into the workplace. The balloon is supported mechanically or by compressed $CO_2$. In the next stage, the balloon is removed and the AO is implanted. Pumps that fulfill the role of a vessel bypass seem to be most suited to this procedure because their implantation does not require stopping (and hence external circulation) of the heart.
- *Stages of repairing of replacing of the AO:* Laparoscopic tool inserts a tight balloon around the AO, which is removed after repairing. The parts for replace are inserted in special capsules.

Great progress in MIS technique will influence the design and construction of implantable AOs. The goal of this work expresses the evolution of telemanipulator and AOs dedicated to the MIS. The system is named AORobAS (Figure 8.12). The future plans regarding development of Polish robot Robin Heart include carrying out of a robotically assisted MIS to implant AOs,VADs, TAHs, valves, and vessel prostheses. Currently used blood pumps, valves, and pacemakers require to be replaced and repaired throughout the patient's life. This is only a temporary solution. Probably, in the near future, the progress in the subject of biocompatible, long-term durable materials and mechanical construction will not solve this problems. The best for patient will be realization of conception minimally invasive service of AO. Robots may be ideal for this task. The solution seems to be application of robotically assisted MIS at once by designing AOs with



**Figure 8.12** Artificial Organs Robotically Assisted Surgery (AORobAS) system.

construction ready to easy assembly and disassembly and to ensure an access to replace used parts. The development of this idea causes changes in requirements for blood pump. It should be folding device, with dimension not exceeding the port hole incision diameter. It means that this part must be a cylinder about 1 cm diameter and the technology for quick mounting of this part on the whole pump inside the chest must be developed. Robots also require special constructions of semiautomatic tools.

#### 8.6.3.3 The Blood Pump Support in the Palliative (Pediatric) Surgery Study

The aim of the palliative procedure is to increase pulmonary blood flow in children with a congenital heart defect. As a result of a shunt operation [Blalock–Taussig (B–T) shunt or Glenn procedure], the oxygen level in the child's blood is improved. The main problem of such surgery is the small shunt effectiveness and lack of possibility of flow regulation. Our idea is to apply advanced computer simulation methods to give the information to the cardiac surgeon—which procedure will be optimal before realization of the operation. A small axial blood pump can be introduced into B–T shunt or Glenn in order to control the blood flow and prevent the growth of graft stenosis. Based on the results obtained using physical and computer 3D simulation based on finite element method (FEM) (Figure 8.13), it can be concluded that the module graft with axial pump makes possible the exact regulation of blood flow and blood pressures in the pulmonary artery. Its use allowed to decrease the afterload of left heart ventricle. Palliative procedures are only a temporary solution. As a child grows, the graft does not grow, and the size of graft (flow through graft) may be not sufficient. The use of axial pump across regulation blood flow allows to extend the time between necessary operations.

## 8.7 The Minimally Invasive Valve Implantation

Percutaneous (pulmonary and aortic) valve replacement has recently opened new perspectives on transcatheter replacement of cardiac valves. Typically, a bioprosthetic valve is dissected and sutured into an autoexpandable Nitinol stent (which has an initial aortic diameter, for instance, 25 mm) or mounted within a balloon-expandable stent. It has been used in patients who are at high risk for valve replacement surgery. Percutaneous valve repair is also being developed for mitral regurgitation. Direct leaflet repair and percutaneous annuloplasty are being employed in clinical trials. All the percutaneous approaches are based on existing surgical techniques and offer less invasive alternatives. This marked the beginning of the era of percutaneous valve therapy, and ongoing trials will define the clinical role for these new therapeutic modalities. Percutaneous catheter-based systems for the treatment of valvular heart disease have been designed and studied in animal models for several

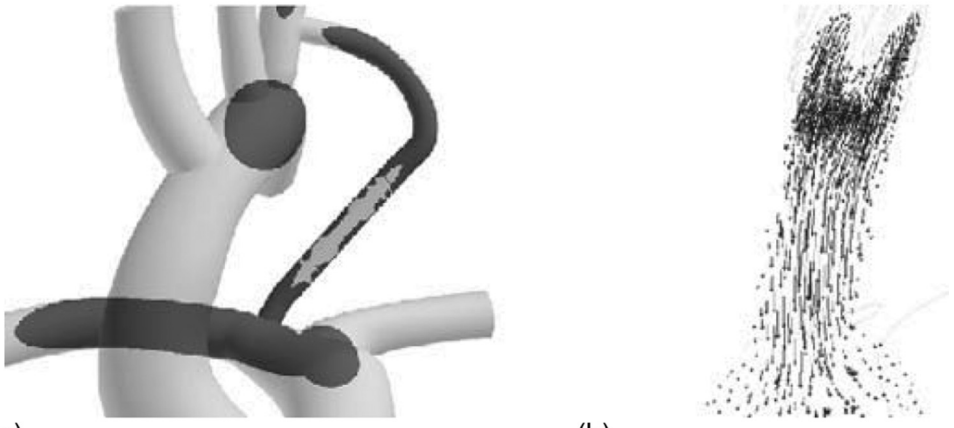



**Figure 8.13** Pulmonary artery axial blood pump used to control blood flow in Blalock–Taussig (B–T): (a) the axial pump in B–T graft and (b) velocity vectors on inlet from pump in B–T graft. The simulations have been performed by Z. Małota.

years. Bonhoeffer et al. were the first to perform percutaneous implantations of artificial valves, using a bovine jugular vein valve mounted within a stent, in children with right ventricle to pulmonary prosthetic conduits. The first human case report of percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis appeared in 2002 [14].

A percutaneously implanted heart valve (PHV) composed of three bovine pericardial leaflets mounted within a balloon-expandable stent was developed (Percutaneous Valve Technologies, Inc.). Using an antegrade transseptal approach, the PHV was successfully implanted within the diseased native aortic valve, with accurate and stable PHV positioning, without impairing the coronary artery blood flow or the mitral valve function, and a with no mild paravalvular aortic regurgitation. Immediately and at 48 h after implantation, valve functioning was excellent, resulting in a marked hemodynamic improvement. Nonsurgical implantation of a prosthetic heart valve can be successfully achieved with immediate and midterm hemodynamic and clinical improvement.

## 8.8 Support Technology for Surgery Planning

Modern medical imaging techniques such as CT, NMR, and ultrasonic imaging enable the surgeon to have a very precise representation of internal anatomy as preoperative scans.

For surgery robots (telemanipulators), the following distinct phases can be realized:

- *Preoperative planning:* The optimal strategy is defined using the 3D computer model.
- *Robot-assisted intervention:* A calibration routine brings robot, patient, and image system to a common frame of reference, for example, using anatomical (or artificial) landmarks.
- *Feedback and replanning:* The robot starts to operate under the supervision of surgeon. Sensor information ensures that the anatomy is as expected and stored by a model in computer. If deviations occur, the surgeon asks for a revised strategy, or for permission to continue.

Computer flow simulation method is important for diagnosing the heart disease development, for optimizing the surgery for a particular patient, and for long-term functioning of graft prognosis. During simulation, the input data (biochemical data, diagnostic data, geometrical data, biophysical data) are transformed into test output data (the hemodynamic pressure and flows or another characterization of biological object modified by surgery).

Remote-control manipulators are proposed for cardiac surgery using a computer-based advisory system. Information in a prepared database (an online expert system) may be of help to a surgeon in decision making. The first step is to simulate the robot-assisted surgery using both computer and physical models of a particular operation type. Based on the preoperation cardiac surgery simulation results, the optimization of the procedures can be achieved.

The main issues of computer simulation support to surgery robots are as follows:

1. *The operation planning:* Based on diagnostic data (images, pressure and flow signals, etc.), computer and physical models can be created. In vitro simulations performed on them may be used to find the optimal way of operation (the joint point localization, the graft selection). A prepared report can be presented to the surgeon as a hint for robot choreography planning. This stage should also include input port localization on patient skin, the type of tools, and the way of removing and preparing the graft branch.
2. *Advisory and control system:* During the operation, diagnostic images or simulation results from various sources can be called by surgeon and superimposed on the real operating image.

The introduction of robots to cardiac surgery created the possibility of direct and practical use of simulation results of surgical procedures in the robot information system.

Surgical planning and augmented reality are likely to enhance robotic surgery in the future. The interesting case of applying preoperatively in robotically assisted cardiac surgery planning, intraoperative registration, and augmented reality was performed by Falk et al. [15]. The regions of interest (i.e., the heart, ribs, coronaries, ITA) were segmented semiautomatically to create a virtual model

of the animal. In this model, the target regions of the total endoscopic bypass procedure along with the ITA and anastomotic area were defined. Algorithms for assessing visibility, dexterity, and *collision avoidance* were developed after defining nonadmissible areas using the virtual model of the manipulator. Intraoperatively, registration of the animal and the telemanipulator was performed using encoder data of the telemanipulator by pointing to the fiducial points. After pericardiotomy, the reconstructed coronary tree was projected onto the videoscopic image using a semiautomatic alignment procedure. In dogs, the total endoscopic bypass procedure was successful on the beating heart.

For medical applications, matching procedures between diagnostic images and off-line intervention planning and real execution are very important. Many problems still remain for soft tissue surgery where deformations may occur. The navigation and guidance of the instruments highly depends on the surgeon's skill who has to combine their intraoperative views with the information extracted from the preoperative images.

Several scientific groups work on *computer method for preparing quasi-stationary view*. The da Vinci robot uses a two-camera endoscope that feeds images to the surgeon's viewer. Images from the left and right cameras are fed to each of the surgeon's eyes separately, providing a 3D view of the tissue being operated on. The Mylonas system exploits this principle by fitting an infrared eye tracker to the viewer. This ensures that each eye detects precisely where the surgeon is looking, and then calculates the distance to the point their gaze is fixed upon using triangulation. The software first constructs a 3D model of the heart by tracking the surgeon's eyes as they move over the organ. Then it creates a real-time moving image by recording the changes in the surgeon's focal point as the heart beats. The endoscope is calibrated to move forward and backward in time with this image, thus making the heart to appear stationary to the surgeon viewing it through the two cameras. The surgical instruments are also calibrated to move in synchrony with the beating heart, removing the need to constantly move them back and forward, and allowing the surgeon to concentrate on performing the operation. The software has so far been tested only on an artificial silicone heart using a robotic arm.

According to surgeons and device executives, surgeon training is the key to the future success of the robotics industry. Because modern surgery is very challenging, the surgeon training will become comparable to fighter pilot training while the robotic systems are having a huge impact on surgical education, and, without doubt, will be integrated into surgeons' future education process. Currently for clinical use of the da Vinci surgical system, the FDA requires a 2-day training course to understand the setup, maintenance, and applications of the surgical system, in addition to animated laboratory training. The device manufacturers have training programs in place to advance the skill sets of both new and experienced surgeons.

Both the *virtual* (Figure 8.14) and the *real* station are used for MIS education. As examples, commercial products include LapTrainer z SimuVision (Simulab Inc., Seattle, WA, USA; www.simulab.com), ProMIS (Haptica Inc., Boston, MA, USA; www.haptica.com), Laparoscopic Surgical Workstation and Virtual Laparoscopic Interface (Immersion Inc., Gaithersburg, MD, USA; www.immersion.com), Phantom devices (SensAble Technologies Inc., Woburn, MA, USA; www.sensable.com), Xitact LS500 Laparoscopy Simulator (Xitact S.A., Lausanne, Switzerland; www.entice.com), Lapmentor (Simbionix Inc., Cleveland, OH, USA; www.simbionix.com); Surgical Education Platform (SEP) (SimSurgery, Oslo, Norway; www.simsurgery.no; www.meti.com), LapSim (Surgical Science Ltd, Gothenburg, Sweden; www.surgicalscience.com), Procedus MIST (Mentice AB, Gothenburg, Sweden; www.mentice.com), EndoTower (Verefi Technologies Inc., Elizabethtown, PA, USA; www.verefi.com), Reachi Laparoscopic Trainer (Reachin Technologies AB, Stockholm, Sweden; www.reachin.se), Vest System (Virtual Endoscopic Surgical Trainer; Select-IT VEST Systems AG, Bremen, Germany; www.select-it.de), and Simendo (Simulator for endoscopy; DeltaTech, Delft, Netherlands; www.simendo.nl).

## 8.9 Conclusions

Notable achievements in cardiovascular research and devices that are currently under investigation and expected in the near future are listed below:

1. New pediatric devices, such as the axial-flow pumps and small-diameter valve prostheses, have been introduced, and some are under

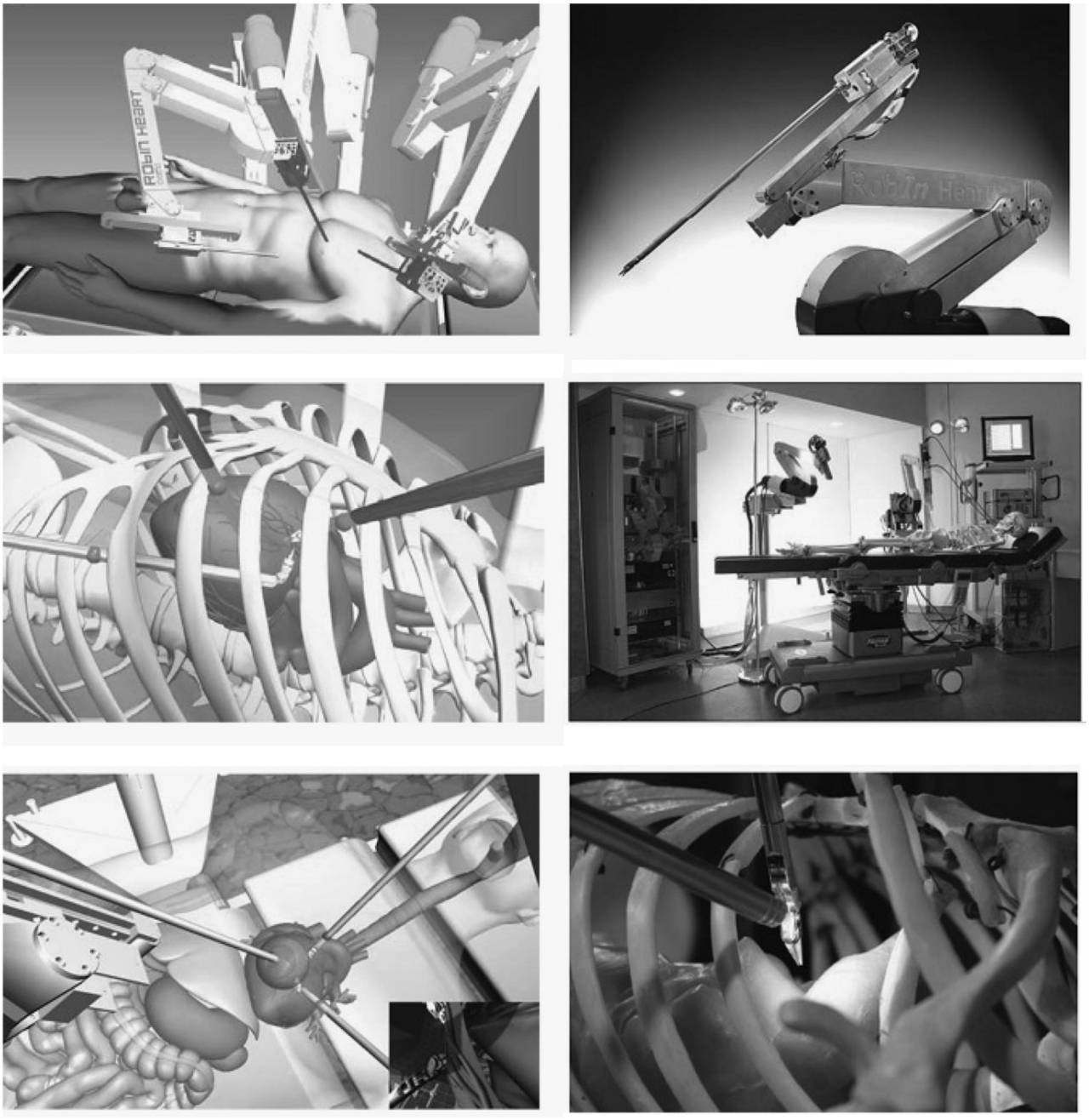



**Figure 8.14** The virtual and the real condition for testing the Robin Heart robot. Using avirtual reality (VR) technology, an interactive model of surgery room equipped with a Robin Heart system was created using EON Professional software. This computer modeling method allows for an advanced procedure training and will be used as a low-cost training station for surgeons in the future. The model allows for a better understanding process of less invasive surgery treatment and a robot behavior. This type of modeling and a computer-aided design (CAD) technique use an accurate CAD robot model in a VR software together with a precise reflection of workspace geometry. This approach gives a surgeon easy and intuitive way to understand the technical details and use it to optimize and plan medical process. The next step in FCSD research work will be establishing the surgery workshops based on the newest technology, and some new projects using affordable semiautomatic robotic tools. Presented model of operating room in VR environment has been successfully used during Surgery Workshop in FCSD (May 2006). This system is intuitive for a user and gives them a very realistic 3D visualization.

construction. As the devices become more and more reliable, mechanical circulatory support will play an increasingly important role, not only for rescue therapy but also for safe treatment of the most complex congenital heart diseases, not only with the aim of bridging to cardiac recovery or transplantation but, eventually, as a permanent solution.

2. The effective miniature blood pumps have been commonly used in minimally invasive cardiology. Transported to the destination place through the arteries, the smart pump mainly for short-term heart support can play an important role in an emergency.
3. New types of devices create possibilities of pump and blood oxygenation introduction into clinical practice. The idea is not new, but thanks to new materials (durable, semiconductive silicon membranes) that are being rapidly developed.
4. New "biomechanical" valves and vessels completely synthetic/artificial, but flexible and durable, will be introduced. The development of small-caliber vascular grafts is very important for bypass and graft surgery.
5. A significant improvement in technical support for preplanning and control surgical interventions, including telemedicine technology, will be observed.
6. Bioartificial myocardial grafts will be introduced in which perfusion by a macroscopic core vessel will be applicable.
7. Improved cell-culture techniques may render human aortic myofibroblasts a native tissue-like structure.
8. Tissue-engineered bioprosthethic valves will be commonly used in clinics.

As the field of surgery robots controlled by surgeons expands, the economical cost is expected to reduce, which will allow surgeons to more commonly use teleoperation in situations that warrants professional staff assistance such as wars, epidemics, and space trips. The situation of "no contact" between the medical personnel and the patient will reduce the risk of loss of health because of the infection(s) from the side of the operating staff.

It is most probable that contemporary telemanipulators will be replaced by adaptive robots in the near future. Currently, the trials of shifting from passive to active systems can be seen. To be clear, let's define the basic concepts: Teleoperators are remotely controlled by operator robot transferring on distance motoric and sensoric functions, whereas adaptive robots have more advanced control system with sensoric and learning abilities. However, creating the next-generation "intelligent" robots is a true challenge. These robots must be able to work unaidedly in various environments, gathering information from their senses. Optimization of their behavior and the effectiveness of given task realization will depend on "self-learning control algorithm," which will more resemble systems based on "instincts" in relation to living creatures and contact with surroundings by means of "senses," zoom, touch sensors (inductive, supersonic, optical, pneumatic, and microwave). I am convinced that they will not be similar to contemporary cardiosurgical robots, but they will be able to replace them considerably. Probably, they will be microrobots that are able to reach, e.g., a given human internal diseased organ (e.g., the heart).

## 8.10 Acknowledgments

This chapter has been illustrated with the experimental data obtained in the Institute of Heart Prostheses, FCSD, Zabrze. The research was supported by the Polish State Committee for Scientific Research and Foundation. The author thanks his numerous collaborators, including R. Kustosz, M. Koźlak, P. Kostka, Z. Małota, L. Podsędkowski, Z. Religa, and M. Jakubowski (special thanks for excellent photography), who prepared the artwork of this chapter.

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# 9 Endotracheal Tube and Respiratory Care

*Thomas C. Mort and Jeffrey P. Keck Jr.*

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## 9.1 Introduction

The earliest recorded use of airway manipulation with an artificial device dates back to early Roman civilization when Asclepiades performed a tracheostomy for laryngeal edema. Today it is clear that the role of the endotracheal tube (ETT) in medicine is as invaluable as that of any other medical device created to date. The establishment of a definitive airway via the ETT in both elective and emergency situations has allowed for the delivery of immediate life-sustaining therapies during resuscitation, the maintenance of oxygenation and ventilation in prolonged illness, and the (temporary) delivery of inhaled anesthesia [1]. This chapter begins with a brief history of the development of the ETT. It describes the various ETTs available along with their indications for use and respective limitations. It reviews basic airway anatomy with regard to ETT placement, proper positioning and stabilization of the ETT, and complications attributed to its use. Finally, it addresses respiratory care of the intubated and mechanically ventilated patient.

## 9.2 Properties of the Endotracheal Tube

### 9.2.1 Anatomy of the Endotracheal Tube

Between the time of Asclepiades and the present, ETTs have been constructed of a variety of materials, including reed, brass, and steel. Eventually, in 1917, Magill and Rowbotham manufactured them from rubber for the purpose of administering anesthesia [2]. In 1928, when Guedel and Waters added a protective cuff to prevent aspiration, the modern ETT was born. Rubber, however, had limitations in this application, such as increased stiffness with rising temperature and limited adhesive properties with different polymers, which required the cuffs to be manufactured from the same polymer as the tube [3]. These shortcomings led to the search for alternative materials. In 1967, polyvinyl chloride (PVC) was popularized by Dr. S. A. Leader, and it has since been the material most commonly used. One property that makes PVC attractive is that it provides stiffness to an ETT at room temperature to assist with intubation yet becomes more malleable with the increased temperature in situ. Other properties include the ability to embed radiopaque lines in the material to assist with positioning and recognition on a radiograph. Because it accepts many materials, the addition of an exteriorized inflation line to connect the pilot balloon to the cuff can allow for varied cuff materials. Finally, it simply is much lower in cost than other available materials [3].

The 15-mm adapter allows for universality between ventilating devices such as a bag-mask ventilation system, anesthesia circuit, or ventilator circuit. The adapter fits ETTs as large as 12 mm internal diameter and as small as 3 mm, thereby providing further commonality among multiple ETTs and ventilating devices. Having one standard size also allows for interchange between devices made for tracheostomies or ETTs. The adapter is removable to allow for passage of intraluminal devices (e.g., bronchoscope, suction catheter) or to allow passage of the ETT via a supraglottic airway device such as a laryngeal mask airway (LMA, LMA North America, San Diego, CA). Adapter removal may facilitate the extraction of extensive biofilm accumulation or mucus plugs. Additionally, some clinicians choose to resize (shorten) the ETT [4].

The Murphy eye, so named for Peter Murphy, an English anesthetist, is designed to provide an extra (secondary) portal for ventilation should the most distal lumen become opacified by bodily fluids, foreign bodies, or soft tissue prolapse. The most typical manifestation of this phenomenon occurs when the distal lumen abuts soft tissue of the tracheal tree, thereby occluding distal flow, or when secretion build-up occludes the distal opening. However, both native and foreign materials are also capable of creating such a dilemma, including mucus, blood, and foreign bodies. Management of such an obstruction is discussed later in this chapter.

The cuffs on the early ETTs were, like the tubes themselves, composed of rubber. The rubber ETT cuffs had limitations such as the need for elevated inflation pressures (high pressure, low volume [HPLV]) to fill the cuff and occlude the airway surrounding the ETT. These high inflation pressures result in the transmission of high lateral pressures to the tracheal wall, albeit in a very minimal contact area, to maintain a seal. The trachea is not circular but rather D-shaped. HPLV cuffs inflate in a circular manner, thereby altering the structure of the trachea; the high pressure exerted on the

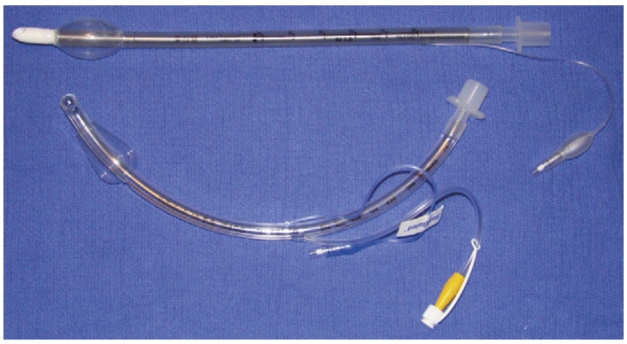


**Figure 9.1** Structural comparison of the intubating laryngeal mask airway (ILMA) high-pressure, low-volume (HPLV) cuff (*top*) and a high-volume, low-pressure (HVLP) cuff (*bottom*). *(Courtesy of LMA North America, San Diego, CA.)*



**Figure 9.2** Taperguard endotracheal tube cuff. *(Courtesy Covidien, Boulder, CO.)*

tracheal wall impairs capillary pressure and possibly results in greater mucosal ischemia [5]. The most commonly used HPLV cuffs in today's practice are the reusable silicone ETTs found with intubating LMAs (ILMAs) (Figure 9.1). Caution should be exercised when using these ETTs for prolonged periods, given their inherent risk of tracheal mucosal damage. The introduction of PVC-based cuffs reduced this problem because the cuff wall was more supple and thinner, allowing the cuff to accommodate high volume and low pressure (HVLP) and thus providing an adequate seal with lower lateral wall pressures [3,5,6]. The main value of the HVLP cuff is its ability to conform to the irregular borders of the trachea [7–9]. Polyurethane is even thinner and more pliable, with increased tensile strength, allowing for higher volumes, larger contact areas, and minimal mucosal pressures [10]. Foam-based cuffs exist and provide maximal conformation to the tracheal walls, but they do little for the prevention of microaspiration [9].

Remodeling of the cuff has been particularly driven by the desire to improve prevention of ventilator-associated pneumonia (VAP), and the shape of the cuff has also been altered. The Mallinckrodt TaperGuard Evac ETT (Covidien, Boulder, CO) is a new option that has been demonstrated in randomized, controlled trials to reduce microaspiration by as much as 83%, compared with traditional HVLP barrel shaped cuffs (Figure 9.2) [8]. It is postulated that a barrel-shaped tube tends to wrinkle and fold in an attempt to conform to the tracheal wall, allowing small channels for potential microaspiration, whereas the bulbous, conical shape of the TaperGuard ETT may reduce wrinkling and thus decrease the incidence of microaspiration. Continued work in this area may lead to improved tracheal wall sealing capabilities at safe levels of pressure while minimizing potential pathways for the translocation of oronasal and gastric secretions, which is thought to be the prime etiologic pathway for VAP [11].

The pilot balloon of an ETT functions as an indirect volume gauge for the ETT cuff, relative to the amount of air located in the cuff (inflated or deflated). The pilot balloon does not provide information about the absolute volume insufflated or the pressure exerted on the tracheal mucosa. When a pilot balloon fails or is an impediment to an intubation, options are generally limited to a tracheal tube exchange [12–14]. Pilot balloon failures have multiple causes. Shearing along the ETT connection (usually due to contact with dentition), cracked inflation valves (from syringe manipulation or trauma), material aging, and pilot tubing laceration due to biting all cause the ETT cuff to lose air over time [15–18]. Simple techniques have been described to replace a pilot balloon in a variety of clinical situations using equipment readily available in the operating room. Needles or intravenous catheters with stopcocks or claves, epidural clamp connectors, and commercially available repair kits (Figure 9.3) provide reliable substitutions for incompetent pilot balloons when they are connected

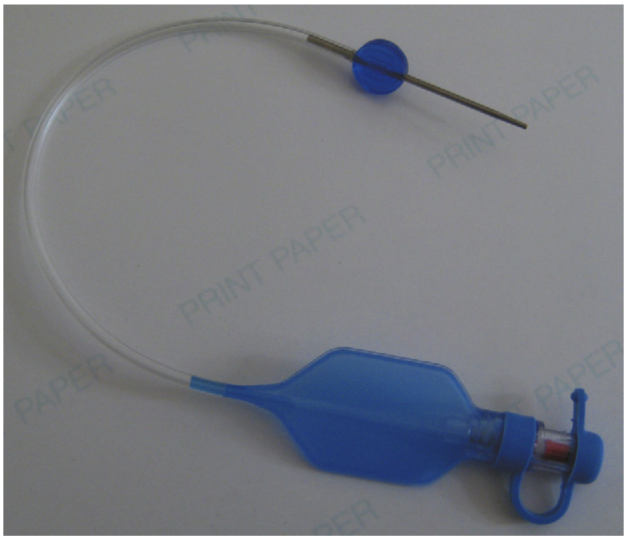


**Figure 9.3** Pilot balloon repair device. *(Courtesy Instrumentation Industries, Bethel Park, PA.)*

to the pilot-cuff inflation line [19,20]. The procedure for replacing an incompetent valve is as follows: cut the inflation tube distal to the pilot balloon; insert a needle or intravenous catheter into the cut end (or affix the hub of an epidural catheter to the cut end); and use a stopcock or clave (an item capable of stemming the entrance of air) on the needle or catheter after insufflation, paying careful attention not to overinflate.

### 9.2.2 Development and Properties of the Endotracheal Tube

The purpose of the ETT has always been the same, and it has always had the same inherent problems. Technology continues to advance the standard ETT for improved function and decreased physiologic insult. Rather than compensate for the resistance produced by a rubber or PVC ETT, a newly designed ETT has been produced of ultrathin polyurethane that is reinforced with wire to resist collapsing and kinking. This wire is unique in that it has an elastic shape memory to prevent deformation. The internal diameter is increased without compromising the rigid shape of the ETT. The result is a tube with a resistance similar to that of the upper airway that is lighter, offers less airflow resistance, and, when compressed, forms an egg shape rather than an oval [21]. Experimentally, this new design has been shown to decrease inspiratory and expiratory resistance by 60% each and the inspiratory, expiratory, and total work of breathing (WOB) by 70%, 47%, and 45%, respectively [22,23].

The use of the ETT continues to expand. No longer is it expected to be simply a conduit for ventilation. As the technology has advanced, the original ETT has steadily been outfitted with a host of successful innovations to improve patient care, whether for convenience or necessity. For example, modifications to the cuff to improve occlusion of the trachea in an effort to prevent microaspiration, coupled with an extra subglottic suctioning port (and other patient care maneuvers), have served to vastly reduce the incidence of VAP [7–9]. Another example is the modification of the surfaces of the ETT to minimize bacterial adhesion and thereby minimize biofilm accumulation [24]. As for bells and whistles, there are ETTs with fiberoptic cameras distally, allowing for ease of placement and the possibility of continued intratracheal surveillance. Another example is the addition of multiple sensors, for so-called bioimpedance cardiography, that are capable of monitoring stroke volume variation, cardiac output, systemic vascular resistance, and arterial pressures (due to the close proximity of the ETT and the aorta) and thereby, at least theoretically, preventing the need for further invasive technologies. Continued study of these modifications may provide justification to adapt these technologies to patient care.

### 9.2.3 Physiologic Effects of Endotracheal Tube Placement

The placement of an ETT, whether oral, nasal, or translaryngeal, is unnatural. Certain physiologic changes occur that must be addressed, including those created by the ETT itself and those modified by its presence. The properties inherent to the ETT are relatively obvious: it causes a partial obstruction, resulting in a decrease in the normal airway circumference and the possibility of turbulent air flow patterns. Additionally, the narrowed conduit leads to higher pressure relationships with lower flows, possibly leading to damaged mucosa distally. The presence of the ETT is a nidus for the inflammatory cascade. Despite its relatively hypoallergenic profile, it is still a recognizable foreign body and as such triggers well-defined host responses. Placement of the device, regardless of the care used

in placing it, still results in mechanical trauma to all of the periglottic mucosalized regions and therefore decreases the ability of the respiratory mucosa to protect itself. Finally, the ETT may cause airway alteration secondary to pressure injury.

The body's response to the ETT is also multifaceted, affecting mechanics, structure, and physiologic function. Loss of humidity and heat is the most obvious effect of replacing the regular mucosa with a foreign conduit. The gas that is delivered is already dry and cool, but bypassing the patient's natural ability to heat and humidify leads to problems more distally, including reduced ciliary function, inspissated secretions, and increased mucus plugging. The normally motile respiratory cilia are essentially paralyzed, leading to impaired secretion management. The body lacks its normal ability to move debris in a proximal direction, and collection sites develop within the tracheobronchial tree, leading to multiple potential areas for infection. Additionally, these partially or completely occluded areas may result in lobar collapse and, consequently, a ventilation-perfusion mismatch. This obstruction can also create an inability to completely exhale, leading to breath stacking and auto-PEEP (positive end-expiratory pressure) and possibly resultant barotrauma.

### 9.2.4 Complications of Endotracheal Tube Placement

Complications associated with ETT placement should be grouped into three major subcategories: those that occur at intubation, those that occur with the ETT in situ, and postextubation sequelae [25]. The problems associated with placement are numerous and can be worsened in emergencies, with multiple attempts, use of a variety of devices, or inexperience of the operator [26]. Problems at placement include dental and oral problems, maxillofacial damage, displacement of the arytenoid cartilages, vocal cord ulceration or dysfunction, airway perforation, autonomic hyperactivity, and, of course, failed intubation. Structural damage is unlikely to be repaired until the patient no longer requires intubation, unless the damage interferes with ventilation and oxygenation. Problems that occur as a result of an in situ ETT include those related to the ETT, such as aspiration, vocal cord paralysis, or transient nerve palsy; ulceration and granuloma formation in the trachea and on the cords; tracheal synechiae; subglottic stenosis; laryngeal webbing; tracheomalacia; tracheoesophageal, tracheoinnominate, or tracheocarotid fistula; and recurrent and superior laryngeal nerve damage [27]. Other complications are related to mechanical ventilation facilitated by the ETT and include aspiration, barotrauma (pneumothorax, pneumomediastinum), VAP, and dislodgement [28]. Finally, postextubation complications can lead to long-term morbidity or the urgent need for reintubation. Many of the postextubation culprits have already been encountered as complications of ETT placement or presence, particularly subglottic stenosis, vocal cord injury, and hoarseness [28,29].

## 9.3 Endotracheal Tubes and Other Airway Adjuncts

### 9.3.1 Choice of Endotracheal Tube Size

In selecting an ETT, consideration must be given to the functional reason for placement as well as patient-specific factors such as body height, gender, airway integrity, airway pathology, and previous airway manipulation or instrumentation. Theoretically, short-term placement for anesthesia should be different than placement for prolonged support with mechanical ventilation or for fiberoptic bronchoscopy to aid therapy. Generally, the trachea of an adult female accepts a tube of 7.5 to 8.0 mm and that of a male accepts one of 8.5 to 9.0 mm, but typically a 7.0-mm ETT is used for females and an 8.0-mm tube for males, at least in the United States. It is also generally accepted that an ETT of at least 8.0 mm is needed for competent use of an adult-based bronchoscopic investigation [30].

#### 9.3.1.1 Small Tubes and Airway Resistance

The physics of laminar gas flow through a conduit are described by the Hagen-Poiseuille equation, which reflects the relationship of resistance varying inversely with the fourth power of tube radius. Despite the fact that gas flow through ETTs is often turbulent rather than laminar, the effect on resistance to gas flow represented by each millimeter decrease in tube size is considerable, ranging from 25% to 100% [31]. Airway resistance is

affected by more than tube diameter: the presence of secretion within the tube, ETT kinking, and positioning of the head and neck can also increase the tendency for turbulent flow [32,33]. The fundamental principle of which to be mindful is that airway resistance induced by an ETT is inversely proportional to the tube size—hence, the mantra that the largest tube is usually the best size [34].

Airway resistance increases with decreasing ETT diameter, whether due to internal occlusion, smaller size, or external compression. As airway resistance increases, WOB also increases [31]. The increase in WOB associated with a 1-mm reduction in ETT diameter varies in accordance with tidal volume and respiratory rate at a given minute ventilation and can range from 34% to 154% [31]. When ventilation is controlled, the increase in WOB related to ETT resistance is seldom of any consequence, because it is overcome by ventilator adjustments. However, small-diameter tubes create greater difficulty for patients in weaning from ventilatory support due to the higher levels of resistance encountered when attempting to breathe spontaneously [35,36]. It has been suggested that an inability to spontaneously ventilate due to the increased WOB imposed by a 7-mm ETT might indicate that extubation will fail regardless of tube size [37,38].

Increased airway resistance associated with a smaller-diameter ETT may also be associated with inadvertent PEEP. Patients with high oxygen consumption, increased carbon dioxide production, or ventilation-perfusion relationships that produce high dead space ventilation often require higher minute ventilations to achieve appropriate ventilation and oxygenation. The gas flows necessary to maintain such a minute ventilation are also quite high, and the resistance imposed by a smaller-diameter ETT further prohibits the completion of expiratory flow before initiation of the subsequent inspiration. This breath stacking results in air trapping and unwanted PEEP, magnifying the risk of mechanical ventilation because barotrauma and subsequent intrathoracic overpressure could result in circulatory compromise [39].

The restriction to gas flow through any ETT increases dramatically when devices such as a suction catheter or bronchoscope are placed in the lumen. The cross-sectional area of the tube is effectively reduced by an amount equal to the cross-sectional area of the device inserted into the tube. The limitation of gas flow has consequences for both the inspiratory and expiratory phases: inspiratory flow may be inadequate to maintain oxygenation and ventilation during the procedure, and retarded expiratory flow may lead to overdistention resulting in barotrauma or circulatory compromise [40].

#### 9.3.1.2 Large Tubes and Trauma

Whereas smaller-diameter ETTs have disadvantages related to gas flow and airway resistance, larger tubes are more frequently associated with traumatic placements and damage to both the laryngeal structures and the tracheal mucosa [37,38,41]. Larger ETTs are associated with a higher incidence of sore throat after general anesthesia, compared with smaller-diameter tubes, but this difference is relatively negligible with long-term intubation [42]. With prolonged intubation, laryngeal trauma is more likely. Women, because of the inherently smaller size of their airway, are more susceptible to injury than men [43,44].

Laryngeal structures at particular risk for trauma are the arytenoid cartilages and the cricoid cartilage. Trauma results not only from the shape discrepancy between the round ETT and the angular, wedge-shaped glottic opening but also from direct contact and pressure on these structures and from repetitive tube movement, which leads to ulceration or erosion of the protective mucosa [44–46]. Tracheal mucosal injury can also occur because of the irregular surfaces created by wrinkling and folding of the ETT cuff or the externalized pilot tube used to fill the ETT cuff. If the tracheal lumen is "overcrowded," airway injury is more likely to occur when large tubes are used and little cuff volume is required to seal the airway [47].

### *9.3.2 Potentially Beneficial Alternatives to the Standard Endotracheal Tube*

#### 9.3.2.1 Preformed and Reinforced Tubes

Modifications to the ETT that are made in the operating room setting to accomplish specific surgeries are often developed in response to interference and access issues. The ability to work without disturbing the ETT has led to several variations of the ETT that can be placed safely and remove the risk of inadvertent advancement, dislodgement, kinking, or obstruction. ETTs used in remote

locations also have airway access issues associated with tube kinking and partial occlusion, which typically are related to positioning problems and associated comorbidities. In part because of less stringent vigilance, unintended consequences of ETT use outside the operating room may result in more drastic outcomes. In response to these dilemmas, a variety of tubes have been developed to maintain their shape and patency in locations where distortion might cause kinking and occlusion.

Rigid, preformed tubes such as those developed for long-term use in tracheostomy were known to maintain their patency despite the need for angulation. Preformed tubes have been developed for specific application in anesthesia practice as well. The Ring-Adair-Elwyn (RAE) tubes (Mallinckrodt Inc., Pleasanton, CA), both oral and nasal (Figure 9.4), maintain a fixed contour similar to the average facial profile, allowing for head and neck surgery while minimizing surgical field interference. Their contour also reduces the risk of pressure injury to the posterior pharynx when repositioning is desired. The intra-airway length is tied to the size of the ETT, with a relatively appropriate depth based on the average size of a patient for whom the tube might be selected [48,49].

An anode or armored tube with an embedded wire coil is designed to minimize kinking even with quite severe position-induced angulation. Armored tubes are popular for use in head and neck surgery where remote airway access and the potential for kinking of the ETT are concerns. Placement of an armored tube through a tracheostomy for procedures such as laryngectomy is a common practice; it allows placement during surgical procedures such that the tube can be mobilized or the circuit draped away from the field without a high risk of tube kinking. The other common use of a wire-reinforced tube is with the ILMA. These tubes are designed to facilitate placement through the device and to be used for short periods of time. The HPLV cuff and the theoretical possibility of kinking and resultant airway obstruction make the long-term use of ILMAs risky.

The embedded wire concept of the armored ETT has also been developed for long-term tracheostomy use. Although the armored tracheostomy tube is not free of risks, one advantage is that its flexibility allows its length and intratracheal depth to be adjusted, which may be beneficial if tracheomalacia at the level of the cuff develops [50]. These

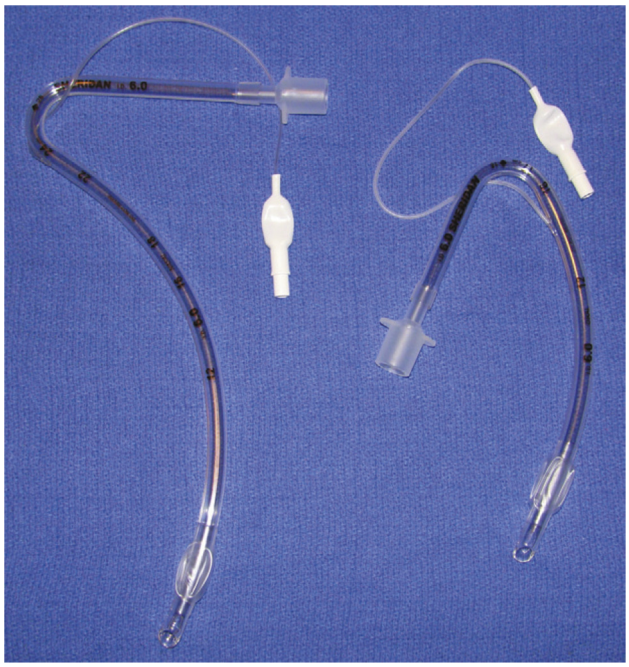


**Figure 9.4** Nasal (*left*) and oral (*right*) Ring-Adair-Elwyn (RAE) preformed endotracheal tubes. *(Courtesy Covidien, Mansfield, MA.)*

tracheostomy tubes are also popular for use in morbidly obese patients, in whom, because of the depth of tissue, preformed tracheostomy tubes may not have the shape required to fit an individual patient. One major consequence of this type of reinforced ETT may occur when external pressure is applied to the wire-reinforced component (i.e., by patient biting). Once a compression threshold is reached, the luminal support provided by the wire may be compromised, and a permanent, irreparable dent remains that can significantly endanger ventilation and suctioning capabilities.

### 9.3.2.2 Laser Tubes

Progress in laser technology has advanced surgical capabilities, particularly for airway surgery. To protect patients and health care providers from laser-induced injury to eyes and airways, special precautions are required. Fire is the most serious danger associated with the use of lasers in the operating room, especially when a laser is used in airway surgery [30,51–53]. A major complication related to the use of lasers for laryngeal surgery is ignition of the ETT [54]. The laser beam may ignite the tube by direct penetration or indirectly if burning tissue is

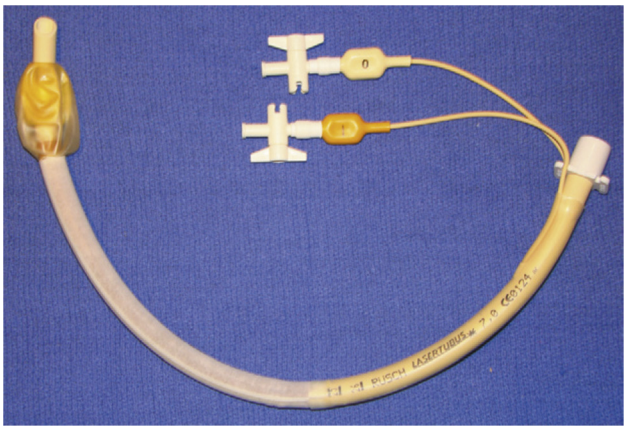


**Figure 9.5** Rusch Lasertubus laser-safe endotracheal tube. *(Courtesy Teleflex Medical, Durham, NC.)*

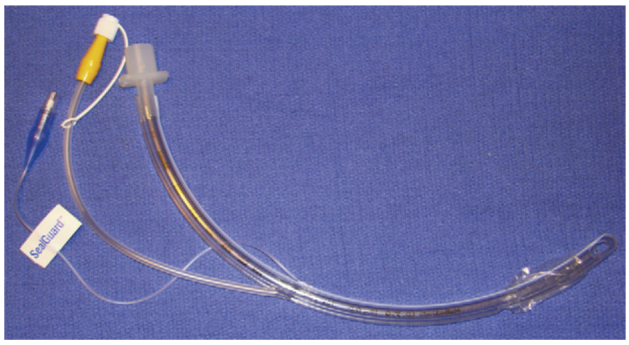


**Figure 9.6** Mallinckrodt Sealguard Evac Endotracheal Tube. *(Courtesy Covidien, Mansfield, MA.)*

inhaled into the tube [30,51,52,55]. The ease of ignition is related to the ETT material, the concentration of oxygen in use, and any other adjunctive materials or gases that could support combustion [30,52,55]. Most ETTs are constructed of PVC, which is highly flammable. Ideally, PVC tubes should not be used for airways when a laser is employed [51,55,56].

ETTs can be laser-proofed or protected from the laser beam by wrapping them with either reflective metal tape or muslin. Ideally, they should be constructed from noncombustible materials. In particular, the ETT cuff is vulnerable to puncture by the laser beam and should be filled with saline or water, which allows more energy to be absorbed before disruption [30,52,55]. One trick to enhance appreciation of a penetrated, defective cuff, is to place a dye indicator, such as methylene blue, into the solution that is instilled into the cuff. Any leakage will clearly mark the airway and alert the provider to the potential dangers [57]. Protecting the tube from the laser beam by wrapping it with a foil tape has proved effective (commercial devices are available) (Figure 9.5) [58]. Tubes made of materials such as metal and silicone and those with special double cuffs also reduce the risk of airway fires and injury during laser airway surgery [51,58].

### 9.3.2.3 Subglottic Suctioning Evac Endotracheal Tubes

Hospitalized patients who require mechanical ventilation are susceptible to the development of aspiration pneumonia. VAP is known to increase hospital length of stay, health care costs, and mortality [59]. Organisms that grow in pooled subglottic secretions above the inflated cuff of the ETT, but beneath the glottis, have previously been unmeasurable with any reliability and are now demonstrated to be a major impetus for VAP. Several nursing care measures may be taken to reduce the incidence of VAP caused by this route, including improved oral care, patient positioning by elevating the head of the bed past 30 degrees, frequent suctioning, and ensuring postpyloric tube feedings, but none of these measures completely stops the production [60].

The presence of these pooled collections has led to the development of specific ETTs that possess a dedicated suction system capable of emptying this area of debris. Drainage of subglottic secretions has been shown to prevent VAP [61–64]. The currently available subglottic drainage ETTs have a suction lumen that opens on the external (posterolateral) surface of the ETT immediately above the cuff (Figure 9.6). The lumen is attached to constant or intermittent suction for active drainage of the space. Although these ETTs are beneficial, their efficacy is not 100%, and therefore all of the aforementioned nursing care actions remain vital to good hygiene and prevention of VAP. The subglottic drainage tubes have been further developed to include variations in cuff construction (materials, shapes, volumes, locations) that help to prevent aspiration of the subglottic debris.

Subglottic secretions are not the only recognized cause for VAP. Biofilm is an accumulation of debris adhered to the internal circumference of the

ETT that is composed of tissue, secretions, mucus, and undetermined bacteria load. Biofilm can be aspirated, leading to a nidus for infection or causing an area of obstruction to airflow. Biofilm removal and reduction by hygiene care are currently better researched than prevention. However, there is a growing interest in the reduction of biofilm through construction of ETTs impregnated with antimicrobial agents [65–67]. The ability of such developments to affect the incidence of VAP has not yet been proved.

### 9.3.2.4 Double-Lumen Endotracheal Tubes

The uses of a double-lumen endotracheal tube (DLT) (Figure 9.7) can be separated into relative and absolute indications. The absolute indications are isolation, to avoid soilage or contamination of the contralateral lung tissue when dealing with infections or frank hemoptysis from a unilateral location, bronchoalveolar lavage, and one-lung ventilation (OLV). The most common reason for placement is OLV for surgical exposure, but OLV can also be important in cases of bronchopleural or bronchocutaneous fistula, unilateral pulmonary hemorrhage, giant unilateral bulla or cyst, and severe unilateral ventilation-perfusion mismatch. The relative indications all deal with surgical exposure. Complementing the DLT as another option for lung isolation, particularly if a DLT cannot be placed, are bronchial blocking devices. However, the DLT has an advantage because of the ability to pass suctioning catheters or fiberoptic devices into the area on collapse without drastically jeopardizing OLV or contaminating the contralateral side.

Relative contraindications to the placement of a DLT are fairly minimal. They include patient refusal (likely due to risk of trauma secondary to the large size), a known difficult airway, and the speed with which an isolated airway must be established. In patients with difficult airways, specially designed airway exchange catheters (Cook Medical, Bloomington, IN) (Figure 9.8) can be used after placement of a conventional ETT to facilitate DLT placement. Additionally, some makers of video laryngoscopic technologies have developed specific DLT devices. The time required for placement is usually the biggest detractor to their use. Situations such as frank hemoptysis may be better served by a rapid-sequence induction and placement of a contralateral, main stem, single-lumen ETT for stabilization.

This technique is not ideal for long-term management. The long-term use of the DLT in the

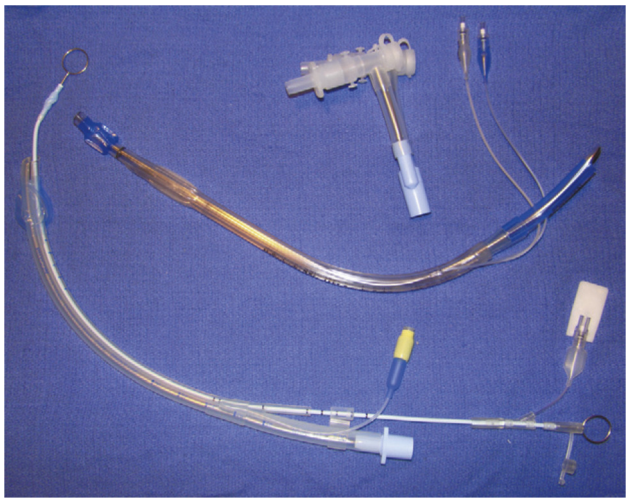


**Figure 9.7** Endobronchial blocking devices for lung isolation. Mallinckrodt Endobronchial Tube (*top*). (Covidien, Mansfield, MA); Fuji TCB Univent Tube (*bottom*). (Phycon Products, Tokyo, Japan).

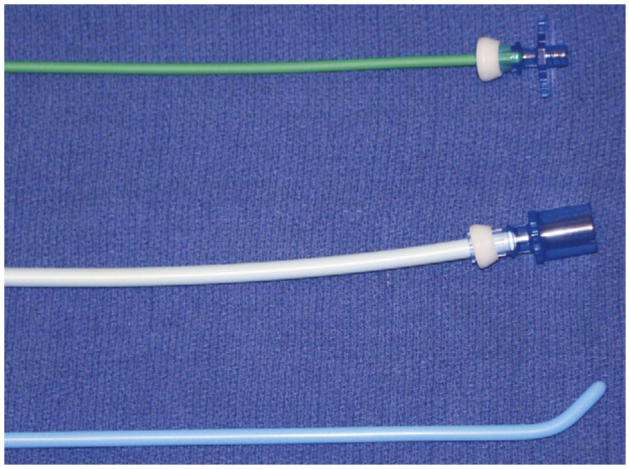


**Figure 9.8** A selection of airway exchange catheters. Double-lumen airway exchange catheter (*top*), Aintree Intubation Catheter (*center*) and Portex Single-Use Bougie (*bottom*). *(Aintree courtesy Cook Medical, Bloomington, IN; Portex courtesy Smiths Medical, Carlsbad, CA.)*

intensive care unit (ICU) setting (>24 to 48 hours) must be approached with caution, because the two smaller-diameter lumens are at significantly increased risk for partial or complete occlusion. Consideration should be given to close monitoring of luminal patency with fiberoptic evaluation on a regular basis and optimization of luminal hygiene to reduce mucus or biofilm accumulation.

#### 9.3.2.5 Supraglottic Airways

Supraglottic devices are continually coming onto the market. Largely designed for shorter surgical procedures to deliver general anesthesia, their use seems to be growing past their original intent. Supraglottic airways (Figure 9.9) such as the LMA, the esophageal-tracheal Combitube (ETC, Tyco Healthcare, Mansfield, MA), the King LT (King Systems, Noblesville, IN), and other variants have provided valuable means of establishing an (unsecured) airway in an emergency. Equally important is their ability to function as a conduit for endotracheal intubation. For example, the ILMA is a blind passage device that is designed to place an ETT through the LMA. Recently, use of the LMA as a conduit for fiberoptic bronchoscopy and subsequent ETT placement has also been demonstrated in emergency situations [68]. Although these devices do not provide classically definitive airways, their utility is unsurpassed in helping to manage the difficult airway.

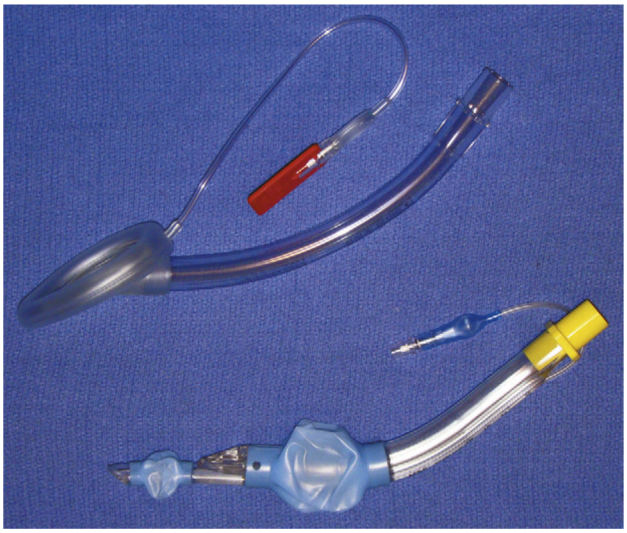


**Figure 9.9** Supraglottic devices. LMA Unique (*top*), (Courtesy USA) King LT Supraglottic Device (*bottom*). *(LMA Unique courtesy LMA North America Inc., San Diego, CA; King LT courtesy King Systems, Noblesville, IN.)*

## 9.4 Proper Safeguarding of the Airway

### *9.4.1 Airway Evaluation: Predicting the Difficult Airway*

The decision to intubate, whether for airway protection, ventilatory failure, inadequate oxygenation, or medication delivery, is often difficult, but equally difficult can be the decision of how to intubate. Each patient and airway is unique, as is the clinical setting and the judgment, skill, and equipment of the airway team that responds. Outside the operating room, time often does not allow a comprehensive evaluation and establishment of a plan complete with contingencies before the decision to intubate must be made. Performance of a proper airway evaluation before intubation is attempted can dramatically improve outcomes.

However, a difficult airway should be assumed when one approaches the patient outside the controlled setting of the operating room. An airway physical examination is paramount to predicting a successful attempt. Criteria such as dental status, mouth opening, thyromental distance, cervical range of motion, Mallampati score, and neck circumference are all standard examination points. However, the emergent intubation presents a host of new, potentially detrimental issues not seen in operating room intubations. For example, hemodynamics may not allow for the controlled process typically seen in the operating room. Trauma patients may have actively unstable facial fractures or cervical vertebral injuries that merit inline stabilization and modified techniques for tube placement. Neurosurgical patients may have external fixators to stabilize injuries or intracranial monitoring devices that make it difficult to position the head. The type of bed a patient is in can also create access issues with intubation. A bariatric bed with an inflatable mattress can be very difficult to properly ramp, thereby making positioning suboptimal. Last, but not least, is the patient with failed extubation who must be reintubated. Issues with anxiety, hypoxemia, decreased functional residual and closing capacities, copious

secretions, residual airway edema, and subglottic stenosis all make a repeat attempt more difficult than the first pass [28].

## 9.4.2 Identifying Proper Position of the Endotracheal Tube

### 9.4.2.1 Detection of Esophageal Intubation

Once the clinician has deemed intubation necessary and has performed the intervention, confirmation of proper ET placement must be provided expeditiously. An incorrectly positioned ETT can produce adverse effects, especially in an already apneic patient. Unrecognized esophageal intubation can have disastrous consequences with a reported incidence as high as 8% in critical patients [69]. Therefore, a brief discussion of verification of ETT placement is warranted.

Once intubation has been accomplished, confirmation of proper placement of the ETT in the trachea needs to be achieved, ideally by the detection of end-tidal carbon dioxide ($Etco_2$) in expired gases using capnography or other capnometric (colorimetric) methods [70]. The detection of $Etco_2$ is not fail-safe and does not guarantee that the ETT is positioned within the tracheal lumen (e.g., the tip may lie above the vocal cords). After three to five breaths, the absence of $Etco_2$ suggests a nontracheal placement. Blockage or soilage of the $Etco_2$ detection device can hamper efforts. $Etco_2$ detection should be complemented with indirect maneuvers such as auscultation, ETT misting or fogging, bag compliance, chest wall excursions, lack of phonation, and improved oxygen saturation. The dependence of any $Etco_2$ detection device on adequate cardiac output has spurred utilization of an esophageal detector device (Figure 9.10). It is essentially an air-filled bulb placed on the end of an in situ ETT. After a vacuum has been created by squeezing the bulb, immediate re-expansion should occur when the bulb is placed on an ETT in the trachea (any column of air). If the ETT is esophageal, the suction created by the bulb will draw the pliable esophageal tissue into the distal lumen of the ETT, preventing full expansion of the bulb on top of the ETT (column of soft tissue) [71–73].

If intubation is to occur in a patient with cardiac arrest, capnometry may be fallible given the amount of down time and the lack of any life-sustaining cardiac output. If cardiopulmonary resuscitation (CPR) is adequate, this technicality is likely to be moot. However, esophageal bulb detectors can be helpful in this situation, although false-positives and false-negatives do occur and confound ETT verification. Still other methods that are independent of carbon dioxide and cardiac output exist, such as a tracheal whistle to verify correct placement (Box 9.1), but not one is without limitations [72–77]. Ideally, two methods are to be considered fail-safe: direct or indirect visualization of the ETT traversing the vocal cords and fiberoptic verification via the ETT lumen. The limitation of direct laryngoscopy is the operator's line of sight to the glottic opening. The key is to identify the ETT positioned in the glottis, not simply to see it go in. An indirect method such as video laryngoscopy does improve the validity of ETT passage. Fiberoptic verification is hampered by equipment availability at the bedside, any airway or ETT soilage, time constraints, and operator skill. Chest rise and condensation from expired gas found in the ETT have also been used, but these signs may occur in esophageal intubations as well [77]. Therefore, the gold standard used today is the presence of $Etco_2$ in expired gases as demonstrated by capnography or other colorimetric techniques [70].

Capnography yields quantifiable measurements of inspired and expired gases in addition to a waveform generated with each tidal volume. Although not without limitations (e.g., lack of portability, need for a power source), capnography reliably identifies initial proper placement of the ETT (non-esophageal) and provides a continuous verification



**Figure 9.10** Esophageal bulb detector and a homemade syringe device. *(Courtesy Wolfe-Tory Medical, Inc.)*

**Box 9.1** Methods used to Verify Endotracheal Tube Placement

- Sustainable, exhaled $CO_2$ by capnography or colorimetric methods
- Fiberoptic visualization of carina
- Videolaryngoscopic visualization of translaryngeal endotracheal tube position
- Direct laryngoscopic visualization of translaryngeal position
- Positive response with esophageal bulb detector device or syringe method
- Auscultation of breath sounds in bilateral lung fields and absence of same in epigastric area
- Visualization of chest wall movement with spontaneous patient efforts
- Reservoir bag synchrony with spontaneous patient efforts
- Palpable ballottement of cuff in suprasternal notch
- Acoustic reflectometry
- Transtracheal illumination
- Chest roentgenogram
- Condensation in endotracheal tube
- Lack of phonation in the nonparalyzed, semiconscious patient
- Bougie passage to distinguish between tracheobronchial tree and esophagus

of ETT security. If esophageal intubation has occurred, a gradual reduction in height of the capnograph waveforms is observed with successive breaths. False-positive results during esophageal intubations may occur in situations of ingested $CO_2$-containing or -liberating substances (e.g., carbonated beverages) before intubation, bag-mask ventilation with inflation of expired air into the stomach, or intubation of the supralaryngeal hypopharynx [78]. Inappropriate extubations may occur due to misinterpretation of a false-negative situation because an $Etco_2$ waveform is lacking despite proper placement. This error may occur with unrecognized circuit disconnections, an obstructed or kinked ETT, a disconnected or contaminated gas sampling line (water, secretions, entrainment of room air), equipment failure, severe bronchospasm, or inadequate cardiac output. Unquestionably, capnography is dependent on pulmonary blood flow. In the absence of perfusion (e.g., cardiac arrest), the utility of capnography can be limited; however, even in very low-flow states (e.g., CPR, separation from cardiopulmonary bypass), it has been shown to provide effective detection. Ornato and colleagues used an animal model to evaluate the relationship between cardiac output (CO) and $Etco_2$. Through manipulation of CO, with inotropes or controlled hemorrhage, a logarithmic relationship between CO and $Etco_2$ was demonstrated [50]. This finding shows that capnography is useful in cardiac resuscitation to assist with evaluation of low-flow states and adequacy of perfusion.

To alleviate the logistic concerns with capnography in emergency situations—mainly the lack of portability and the need for a power source—a portable and reliable means of detecting $Etco_2$ was developed. Colorimetric $Etco_2$ uses a detector impregnated with metacresol purple (Figure 9.11). This indicator is pH sensitive and changes color, from purple to yellow, in the presence of $CO_2$. The devices are disposable, attach between the ETT and the circuit or bag, and provide a rapid and reliable indication of $CO_2$ concentration on a graded scale: A (purple) corresponds to an $Etco_2$ level of 0.5%, B (tan) to a level of 0.5% to 2%, and C (yellow) to a level greater than 2% [70,77]. Limitations of this method are that it is ineffective with exposure to humidified gases, vomitus, or secretions and in cases of prolonged cardiac arrest or low-perfusion states. False-positive results can occur as well, just as in capnography. Delays in recognition of esophageal intubation with colorimetric capnometry have been reported far more often than with capnography, particularly in patients with prolonged bag-mask ventilation or ingestion of $Etco_2$-containing substances before intubation. Therefore, capnography simply is




**Figure 9.11** Example of a colorimetric capnometric device. *(Courtesy Mercury Medical, Clearwater, FL.)*

the best method for detection of esophageal intubation [79].

As mentioned previously, the esophageal bulb detector capitalizes on the physical characteristics of the esophagus, which, unlike the trachea, collapses when negative pressure is applied. Commercial devices exist, but a homemade version can be improvised using a syringe that attaches to the end of the ETT. When the plunger is withdrawn, resistance is appreciated if an esophageal intubation has occurred, because the walls of the esophagus collapse around the ETT. Unencumbered aspiration of the plunger occurs with proper tracheal placement [71]. Bulb detector devices are reported to be reliable and effective, with one study demonstrating a sensitivity of 100% and a specificity of 99% [72]. However, other studies have reported limitations and false-negative results in patients with copious or aspirated secretions, gastric distention, vomitus in the airway, morbid obesity, or reduced functional residual capacity [71,80–83].

A little used but highly effective method of detecting proper ETT location is the passage of a catheter (e.g., bougie) via the ETT to decipher a straight smooth muscle pathway (esophagus without pathology) or a more rigid, angulated tube with reduction in the luminal diameter (tracheobronchial tree). A bougie can be used in this fashion, particularly at the time it is being used as an adjunct to intubation, or later if necessary. Gentle advancement to 28 to 34 cm (in adults) typically results in contact with the carina or a main stem bronchus. Further advancement down a main stem bronchus should be limited by the secondary lobar carina. Gentle unopposed advancement of the bougie beyond 35 cm suggests esophageal placement (assuming no esophageal pathology).

### 9.4.2.2 Confirmation of Appropriate Depth of Insertion

After correct tracheal placement of the ETT has been verified, it is imperative to identify the correct depth of the ETT to ensure adequate ventilation of each lung [49]. Before addressing the various methods that assist in confirmation of appropriate ETT depth, a brief discussion of what is considered to be the correct depth is warranted. Malpositioning of ETTs occurs frequently, with unrecognized right main stem intubation occurring in approximately 4% of chest radiographs [49,69,84]. The generally accepted depth of insertion of the ETT is between 2 and 7 cm above the carina, optimally between 4 and 7 cm above the carina with the head and neck in a neutral position [49,77,85–87]. It is important to realize this, because flexion-extension movements of the neck can displace the ETT upward or downward with resultant extubation or main stem intubation, respectively. Typically the right main stem bronchus is entered, given its straighter trajectory in relation to the trachea. If endobronchial intubation remains undetected, an inadvertent hyperinflation of the ipsilateral lung can occur with subsequent pneumothorax and concomitant atelectasis of the hypoventilated contralateral lung. Indeed, it has been reported that up to 15% of chest radiographs reveal malpositioned ETTs in intubated patients [84,88,89]. This is more frequently seen after difficult airway management.

In the operating room, chest radiographs are not used to confirm proper position; rather, indirect clinical assessment methods are used (i.e., auscultation of bilateral breath sounds, visualization of equal chest expansion, and direct visualization of the ETT tip placed just below the vocal cords). The

ETT is also manufactured with distance measurements to aid with the depth of insertion. In orally intubated patients, a depth of 23 cm at the teeth or corner of the mouth has been advocated for men and 21 to 22 cm for women [90,91]. In nasotracheal intubations, a depth of 26 cm at the nares in women and 28 cm in men should be sufficient for proper tracheal position [92]. Other methods used include direct visualization of the ETT tip in reference to the carina with a fiberoptic scope or catheter [69], transtracheal illumination, and ballottement of the ETT cuff in the suprasternal notch [93–96].

### 9.4.2.3 Cuff Pressure Monitoring

Probably the most often overlooked parameter in daily airway care is cuff pressure [97,98]. Almost universally, this measurement is neglected in operating room intubations. However, it is well documented that excessive forces applied to the tracheal mucosa can cause necrosis and ulceration [9,99,100]. Cuff pressures of 30 cm $H_2O$ for 4 hours have been shown to damage ciliary motility for at least 3 days [100–102]. In addition, animal studies have revealed diminished circulation in the tracheal mucosa with a pressure of just 20 cm $H_2O$, exaggerated greatly in the presence of hypotension [103].

Normal occlusive pressures should be between 20 and 30 cm $H_2O$ to avoid complications while maintaining an adequate seal in the tracheal lumen circumferentially around the cuff to prevent microaspiration and ultimately VAP [100]. Depending on the type of cuff used, the same pressure range seems to be effective at accomplishing this task both in vitro and during in vivo animal studies. For example, standardized HVLP cuffs have been demonstrated to be ineffective at preventing microaspiration with pressures as high as 60 cm $H_2O$ [7], whereas polyurethane tubes seem to be effective down to 15 cm $H_2O$ [7,10,104].

As was previously discussed, ETTs are not without risks. However, it appears that most of the morbidity is related to either inappropriate inflation of an ETT cuff or a defective ETT cuff [98–100]. An often dreaded scenario that leads to increased morbidity is frequent ETT exchanges for suspected cuff leaks. Trended values for cuff pressure could help to alleviate some of these unnecessary procedures. Most importantly, it has been demonstrated that manual palpation of the cuff or instillation of a standard volume of air often underestimates the actual occlusive pressure delivered, leading to unrecognized complications [97,98,100]. Therefore, it is recommended that frequent examination of the cuff pressure be documented and trended using manometry.




**Figure 9.12** Posey Cufflator aneroid manometer (*left*) and the PressureEasy Pressure Controller Device (*right*) for monitoring endotracheal tube cuff pressure. *(Cufflator courtesy Posey Company, Arcadia, CA; PressureEasy courtesy Smiths Medical, Dublin, OH.)*

Reusable aneroid manometers can be onerous to calibrate and are often difficult to locate; in addition, they pose a recurring risk of cross-contamination for each patient. The manometers currently in use in most ICUs provide only a single data point at the time of collection. A commercially available disposable, precalibrated device that constantly measures airway cuff pressures is available. The PressureEasy device (Smiths Medical, St. Paul, MN), among others, attaches to the pilot balloon and exhibits a mark in a fixed window when the measured cuff pressure is in the optimal range of 20 and 30 cm $H_2O$ (Figure 9.12) [97–100].

### 9.4.2.4 Evaluation of an Audible Cuff Leak

Although ETT cuff leaks pertain most often to the ICU or postanesthesia care unit (PACU) setting and longer-duration intubations, short-term tracheal intubation in the operating room may also fall prey to an apparent leak. The most relevant question is, When is a cuff leak really a cuff leak? The audible leak implies that air is escaping from the presumably

**Table 9.1** Causes and Solutions for Apparent ETT Cuff Leaks

| Problem | Solution | Risk Level |
|---|---|---|
| Cuff perforation (pilot balloon deflation) | Exchange ETT (only feasible choice) | High |
| Incompetent pilot valve | Exchange ETT | High |
| | Clamp line (Kelly, hemostat)—short term solution | Low |
| | Place stopcock or cap on valve | Low |
| | Replace pilot balloon−line assembly | Low |
| Broken pilot line | Exchange ETT | High |
| | Clamp line (Kelly, hemostat)—short-term solution | Low |
| | Replace pilot balloon line assembly (homemade vs. commercial) | Low |
| Displaced ETT (intact pilot balloon) | Perform fiberoptic evaluation—diagnostic | Low-moderate |
| | Blindly advance ETT | Very high |
| | Videolaryngoscopy evaluation | Low-moderate |
| | Blindly pass airway exchange catheter | High |
| | Perform direct laryngoscopy (suboptimal line of sight) | Low-moderate |

ETT, *Endotracheal tube.*

closed ETT system. The leak may be caused by a defective ETT cuff that has failed, ripped, or is microperforated (in which case the pilot balloon deflates spontaneously). Equally possible is a defective pilot balloon−line assembly. The valve on the pilot balloon may be faulty and incompetent, the balloon may have a perforation, the line may be cracked or broken or may become disjointed at the tube end or the valve end. Moreover, the intermittent or continuous audible leak may represent an ETT cuff that fails to seal the airway due to malpositioning, deranged shape, or laxity and deformation of the tracheal wall (e.g., tracheomalacia, tracheitis, tracheal erosion). The ETT cuff (intact pilot balloon) may be subglottic, between the vocal cords, or supraglottic, having been displaced during patient movement, transport, repositioning, "tonguing" (dislodging the ETT by moving it with the tongue) of the ETT, excessive coughing, excessive tension on the ETT by the ventilator circuit, or, commonly, positioning for radiography. Once the ETT is partially displaced upward, an audible leak may prompt further ETT cuff insufflation, leading to further displacement. Head and neck movement by the patient may be all that is required to further displace the ETT into the hypopharyngeal region. This must be diagnosed before disaster strikes.

The various sources of a suspected cuff leak require investigation because each necessitates a different solution. Any one solution, incorrectly applied, may lead to morbidity or mortality. For example, a cuff leak resulting from a herniated cuff above the vocal cords may prompt the team to order a chest radiograph. Further displacement may take place during lifting and repositioning of the patient for the examination. Conversely, if an ETT is malpositioned in the hypopharynx (intact pilot balloon) but is assumed to be a properly positioned ETT with a cuff perforation, an exchange catheter passed via the ETT (presumably into the trachea) may exit the supraglottic ETT and enter the esophagus, leading to airway compromise. Table 9.1 highlights the possible causes and potential solutions, with relevant risk assessments for an apparent cuff leak evaluation.

#### 9.4.2.5 Documentation of Placement

Clinicians who care for patients who are intubated for long periods in the ICU may find it onerous to obtain pertinent airway management details.

This can be especially detrimental to future care providers who are faced with a patient with a known or suspected difficult airway. This situation could result for a number of reasons: lack of relevance (routine intubation before the patient's surgery), lack of continuity (the intubator is no longer involved in the patient's care), or an incomplete or total lack of documentation.

As an ICU course progresses, the details surrounding the original ETT placement may prove less relevant because the patient's clinical status and airway are dynamic, not static. A previously easy airway may remain so, but difficulty often increases as edema, trauma, secretion management, and patient status decline to confound an airway intervention. Anatomic abnormalities may be hidden or exaggerated by excessive fluid administration or a capillary leakage phenomenon in the critically ill patient, and examination of the airway may become impossible. Appreciation of the airway adjuncts that have been attempted is imperative for the incoming airway team. Immediate availability of pertinent historical airway management details may prove helpful in delivering better care. Documentation of airway interventions and procedures on a specific sheet (Figure 9.13) may provide the incoming airway team perspective on what to expect in a single concise location.

### 9.4.3 Stabilization of the Endotracheal Tube

After verification and confirmation of proper tracheal placement and position have been achieved, care should be focused on securing the ETT in its proper position, and frequent assessments should be made to recognize malpositioning [105,106].

At the most basic level, recording and confirming the depth of the ETT at the patient's teeth or lips in centimeters should be routine. This measurement should be documented on the respiratory care flow sheet. In patients requiring prolonged mechanical ventilation, the depth should be assessed and documented frequently (e.g., every shift, every 4 hours), along with clinical assessments of ETT patency and hygiene, appropriate chest expansion, and auscultation findings.

Securing and surveillance of the ETT are important not only to ensure proper depth and positioning but also to reduce the incidence of inadvertent extubation [105]. Unplanned extubation is primarily a problem in the ICU. It has a reported incidence of approximately 2% to 16%, with 80% of those extubated requiring reintubation, and contributes to a higher rate of airway-related complications, hemodynamic alterations, patient morbidity, and mortality [48,107–109]. The most frequently identified cause is inadequate sedation of a mechanically ventilated patient, and only a few studies have specifically addressed techniques used to secure ETTs. In a study comparing four such techniques, Levy and Griego concluded that the use of simple adhesive tape split at both ends and secured to both the ETT and patient's face was more effective than proprietary methods and allowed more effective nursing care, improved oral hygiene, and greater comfort for the patient [106]. However, Barnason and colleagues found no statistical difference between two methods studied in preventing unplanned extubation, allowing oral hygiene, or maintaining facial skin integrity [110].

Attention to proper ETT stabilization primarily focuses on the reduction of unplanned extubation, improved comfort for the patient with prolonged ventilatory requirements, minimization of iatrogenic complications related to the method of fixture, and ease of nursing and respiratory care. One study addressed massive air leaks and contributing factors. The authors defined a massive air leak as one that requires extubation. Over a 2-year period, 18 ETTs were removed for massive air leaks, of which 61% were found to be free of mechanical defects (intact cuff). Fourteen of the 18 patients required reintubation; 2 of them aspirated gastric contents on replacement, and 1 suffered severe epistaxis from a blind nasal reintubation, resulting in a 21% complication rate [111]. The authors concluded that malpositioning was the most plausible explanation for the apparent air leaks. This study reinforces the importance of securing the ETT and daily vigilance to ensure that proper depth and positioning are confirmed and maintained.

Despite these studies, no consensus exists concerning the best method of securing the ETT.

#### 9.4.3.1 Taping

The classically described methods are a "barber's pole" technique for operating room intubations, a simple split tape technique (Figure 9.14), and a more secure "four-point" technique for intubations anticipated to last for 24 hours or longer. In each of

**Department of Anesthesiology Airway Management Note**

**Airway Management Procedure:**

[ ] Elective [ ] Urgent [ ] Emergent
[ ] Cardiac or Respiratory Arrest
[ ] Intubation [ ] ETT Exchange [ ] Extubation [ ] Other: _____

**Date:** _____ **Call Time:** _____ **Arrival Time:** _____
**Location:** _____ **Staff:** _____

**Height:** _____ **Weight:** _____ **NPO Status:** _____
**BP:** _____ **HR:** _____ **Oxy Sat:** _____ on… _____ %
[ ] Room Air [ ] Nasal [ ] Facemask [ ] NRB [ ] NIPPV

**Isolation Precautions:** [ ] Contact [ ] Droplet [ ] Airborne
[ ] Vector [ ] Common Vehicle

**Condition Upon Arrival (check all that apply):**

| | | | |
|---|---|---|---|
| [ ] Awake | [ ] Hypoxemic | [ ] Dyspnea | [ ] Secretions |
| [ ] Sedated… | [ ] Hypercarbic | [ ] Tachypnea | [ ] Vomitus |
| [ ] Agitated | [ ] Stridorous | [ ] Bradypnea | [ ] Blood |
| [ ] Unconscious | [ ] Wheezing | [ ] Apnea | [ ] Foreign Matter… |

[ ] Other/Comments: _____

**Underlying Pathologies/Co-Morbidities (if known, mark all that apply):**

**Neurologic:** [ ] CVA [ ] Increased ICP [ ] ICH/SDH [ ] Seizure
[ ] SCI [ ] Δ Mental Status [ ] Drug Overdose

**Pulmonary:** [ ] Asthma [ ] COPD [ ] ARDS [ ] OSA [ ] PE
[ ] PNA… [ ] CAP [ ] VAP [ ] Pulm. Contusion
[ ] Pneumo/Hemothorax [ ] Upper Airway Issue…
[ ] Post-operative Respiratory Failure [ ] NPPE

**Cardiac:** [ ] AMI [ ] CHF [ ] Dysrhythmia… [ ] Tamponade

**Metabolic:** [ ] Acidosis… [ ] Electrolyte… [ ] Alcohol Withdrawal
[ ] UGIB or LGIB [ ] SBO [ ] Mesenteric Ischemia

**Infectious:** [ ] Immune compromised [ ] Sepsis [ ] PTA
[ ] Tonsil/Epiglottitis [ ] Tracheitis/Bronchitis

**Trauma:** [ ] Cranial/Spinal… [ ] Thoracic… [ ] Abdominal…
[ ] Orthopedic…

**Other/Comments:** _____

**Airway Management Procedural Documentation:**

**Preoxygenation:** [ ] Room Air [ ] Facemask/NRB [ ] 100%, Bag-Mask

**Ventilation:** [ ] Assisted [ ] Controlled [ ] Easy [ ] Difficult
[ ] Oral Airway [ ] Nasal Airway [ ] Two-person

**Positioning:** [ ] Supine [ ] Ramped [ ] Elevated HOB
[ ] Sitting [ ] Other: _____

**Induction:** [ ] Awake [ ] Sedated [ ] General Anesthesia [ ] None
[ ] Topical Anesthesia [ ] Airway Block… [ ] Paralysis…
[ ] Rapid Sequence Induction [ ] Cricoid Pressure
[ ] Other: _____

**Medications:** [ ] Etomidate _____ mg [ ] Propofol _____ mg
[ ] Ketamine _____ mg [ ] Other: _____
[ ] Succinylcholine _____ mg [ ] Rocuronium _____ mg

**1st Attempt:** [ ] DL: MAC _____ MILLER _____ [ ] Glidescope/VL [ ] FOB
Other: _____
C-L View: [ ] 1 [ ] 2a [ ] 2b [ ] 3a [ ] 3b [ ] 4
[ ] Secretions [ ] Blood [ ] Edema
AirwayAdjuncts: [ ] Bougie [ ] ILMA [ ] LMA
Other/Comments: _____

**Figure 9.13** Example of a detailed airway record for emergency intubations.

**2nd Attempt:** [ ] DL: MAC _____ MILLER _____ [ ] Glidescope/VL [ ] FOB
Other: _____
C-L View: [ ] 1 [ ] 2a [ ] 2b [ ] 3a [ ] 3b [ ] 4
[ ] Secretions [ ] Blood [ ] Edema
AirwayAdjuncts: [ ] Bougie [ ] ILMA [ ] LMA
Other/Comments: _____

**3rd Attempt:** [ ] DL: MAC _____ MILLER _____ [ ] Glidescope/VL [ ] FOB
Other: _____
C-L View: [ ] 1 [ ] 2a [ ] 2b [ ] 3a [ ] 3b [ ] 4
[ ] Secretions [ ] Blood [ ] Edema
AirwayAdjuncts: [ ] Bougie [ ] ILMA [ ] LMA
Other/Comments: _____

**Airway Device Ultimately Placed:** [ ] ETT… [ ] LMA… [ ] Combitube
Size: _____ Type: [ ] Standard [ ] ORAE [ ] NRAE
[ ] Subglottic EVAC [ ] ECOM
Placement Location: _____ cm @ lip

**Confirmation:** [ ] Esophageal bulb device [ ] $ETCO_2$ [ ] Direct Visual
[ ] Bilateral BS [ ] Bronchoscopy [ ] Chest X-ray

**Post-Procedure Vital Signs:**

BP: _____ HR: _____ Oxy Sat: _____ on… _____ %

**Other/Comments:** _____

**Signature:** _____ **Date/Time:** _____

**Figure 9.13** (*Continued*)



**Figure 9.14** The split-tape method of taping the endotracheal tube.

these methods, tape is used to anchor the ETT to the face. Moisture, in the form of sweat, secretions, or vomitus, can jeopardize the integrity of the bond between adhesive and skin, putting the security of the ETT at risk [105]. Additionally, patient comfort is an issue when tape is used for this purpose. Skin breakdown due to allergic reactions, pressure necrosis, or repetitive trauma has been documented as a potential problem from the use of this method. The four-point method is more secure than the barber's pole technique because the tape encircles the

patient's head and is not as susceptible to moisture because it is anchored to itself as well as to the patient's skin.

#### 9.4.3.2 Commercially Available Devices

Although several options are available, a proprietary device has been developed to help secure the ETT and provide increased patient comfort while facilitating airway care. This device, the AnchorFast (Hollister Inc., Libertyville, IL) (Figure 9.15), incorporates an ergonomically designed frame to minimize well-known pressure points, a latex-free adhesive on a pad, and a padded Velcro-style retaining strap that encircles the head. Preliminary studies comparing this device against classic adhesive tapes showed reduced skin breakdown, fewer lip ulcers, and improved patient comfort [106,112].

Another commercial device used to secure the ETT has been postulated; it mimics the nasal bridling technique used for nasogastric tubes. This product is still in development.

#### 9.4.3.3 Stapling for Facial Burns

The overall incidence of burn patients in most practices is very small, and this creates an unfamiliarity with their care, particularly as it relates to airway management. The focus of this section is to discuss the unique situation presented by the facial burn. Aside from the obvious difficulties of tube placement initially, replacement of an ETT after a burn resuscitation is far more challenging due to a multitude of unique injuries. The two major problems with securing an ETT for the patient with a facial burn are the increased (and increasing) edema due to ongoing inflammatory processes and continued resuscitation, which makes the face ever expanding, and the actual burned skin, which is constantly weeping and often débrided or sloughing. It should be obvious that adhesive devices, both simple tape and proprietary devices, are ineffective in this situation. A well-documented and accepted method in these patients is to secure the ETT with tape and anchor it to the skin by stapling the tape to the burned areas. This is surprisingly well tolerated, but more importantly it is very reliable to maintain the airway and is easy to care for.

One important airway management caveat should be understood regarding proper ETT position at the gum line or lips in all intubated patients: the ETT marking at these locations only assures the location



**Figure 9.15** The AnchorFast system for endotracheal tube stabilization. *(Courtesy of Hollister Inc., Libertyville, IL.)*

of the proximal end; it does not guarantee the depth and location of the distal ETT tip. Although this problem pertains most often to the ventilated PACU or ICU patient, an ETT located at 25 cm at the gum line and seemingly secured by tape or a commercial device does not guarantee tracheal intubation (with or without a cuff leak). Typically, a continuous or intermittent apparent cuff leak leads to further insufflation of the pilot balloon to fix the leak. An intact (inflated) pilot balloon, in this clinical situation, should arouse suspicion that the distal tip is abnormally located outside the glottis. The potential for an airway catastrophe is extreme, especially in the patient with a difficult airway, compounded by significant mechanical ventilatory requirements. Proper assessment of the ETT position, preferably with flexible bronchoscopy for diagnostic and therapeutic maneuvers, is indicated.

### *9.4.4 Rapid Response Cart for Airway Emergencies*

Areas in which care for intubated patients is provided need to have a dedicated set of supplies to establish emergency airways in the event of primary respiratory failure or cardiac arrest to reestablish lost, previously secured airways. The responding airway team must be knowledgeable and competent in advanced management techniques and provided with immediate access to such equipment. Infrequent or casual airway managers should

ask for assistance early in the management process or even immediately, before starting. The American Society of Anesthesiologists difficult airway algorithm (Figure 9.16) should be close at hand to guide less experienced individuals who encounter problems [113]. Supplies on the cart may differ based on personal preference and facility purchase, but there are some items that must be present to help save a life.

Laryngoscopy, ETT exchange, pulmonary toilet, and a "cannot intubate, cannot ventilate" (CICV) scenario must all be covered in the equipment selection. Laryngoscopy includes both conventional (direct) and video laryngoscopy; it is used to assist the team with replacing the ETT after an inadvertent extubation, augmenting the exchange of a damaged ETT over an airway exchange catheter, improving the ability to assess ETT location within the airway, and interrogating the physiologic integrity of an airway slated for extubation [114].

An airway exchange catheter, coupled with video laryngoscopy, greatly reduces the complication rates for necessary airway exchanges in ICU patients, thereby earning its place in an airway response cart within the ICU [114]. A fiberoptic bronchoscope should be available for confirmation purposes, for awake intubation procedures, and for deeper pulmonary toilet needs to improve ventilation and oxygenation [115]. Supraglottic airway devices should be available for situations in which mask ventilation is difficult or as a conduit to facilitate the placement of an endotracheal airway [116]. Lastly, equipment for the placement of a surgical airway must be provided. Despite all of the options available, a scalpel may be the only device capable of establishing the airway. In cases of a known or suspected difficult airway, it is helpful to immediately contact someone with the ability to place a surgical airway should other conventional or advanced noninvasive means fail.

Box 9.2 delineates the contents of a proposed difficult airway cart, which should be readily available in case of any airway catastrophe.

## 9.5 Maintenance of the Endotracheal Tube

There is currently no alternative to the placement of an oral, nasal, or transtracheal ETT, whether to maintain airway patency, perform ventilation, improve oxygenation, remove secretions, or deliver necessary therapies. However, the ETT is only as good as its most pristine state. Despite the unavoidable decision, some still look on the placement of an ETT as a necessary evil. The conundrum arises in preserving or remastering the physiologic function of the host tissues while combating their inherent defenses aimed at reacting to the new artificial airway and protecting the new foreign device to maintain its optimized function as in its original condition.

The presence of the ETT bypasses the host defenses of the upper airway, eliminates the humidification of inspired gases, increases the WOB, limits the administration of medications, and prevents prophylactic oral hygiene. All of these changes promote bacterial colonization, inflammation, and sputum production. Inability to actively clear secretions because of a poor cough or increased difficulty of passive removal by health care personnel can lead to plugging of proximal and distal airways as well as the ETT. These retained secretions may result in the formation of atelectasis, ventilation-perfusion mismatching in the form of a shunt or dead space, hypoxemia, and increased respiratory load, thereby prolonging the duration of mechanical ventilation [117,118]. Therefore, aggressive respiratory care must be provided for the intubated patient to avoid these complications and further morbidity.

### 9.5.1 Heat and Humidity of Inspired Gas

During normal breathing, the air is delivered to the carina at a temperature of 32°C and an absolute humidity of 30.4 mg $H_2O$/L [119]. The insertion of an ETT via the nose, mouth, or trachea bypasses the upper airway and causes the natural ability to heat and humidify inspired gas to be lost. The American Association for Respiratory Care states that devices should provide a minimum of 30 mg of $H_2O$/L of delivered gas at 30°C [120]. If inspired air is not warmed and humidified, the result is a dry, cool gas that is damaging to the respiratory tract and impedes mucociliary function. Secretions may become dry and inspissated, possibly leading to partial or complete occlusion of the ETT lumen. If left unrecognized, this occlusion may lead to barotrauma and death [93]. The most common method to protect against this situation is the use of

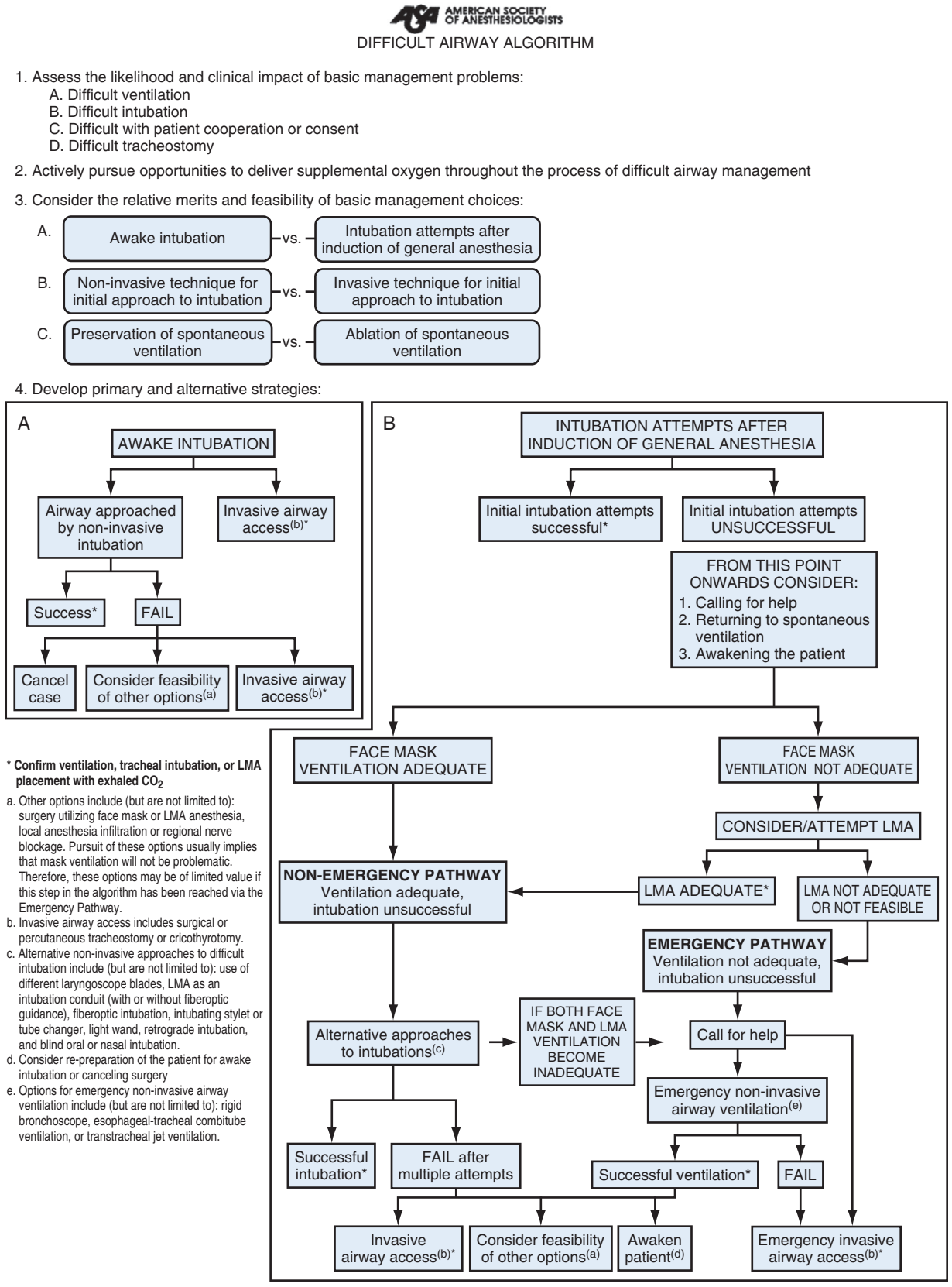



**Figure 9.16** American Society of Anesthesiologists difficult airway algorithm. *LMA*, Laryngeal mask airway. *(Courtesy of American Society of Anesthesiologists, Park Ridge, IL.)*

**Box 9.2** Contents of a Difficult Airway Cart

- Fiberoptic bronchoscope and video monitoring system (optional), adult and pediatric sizes
- Magill and Krause forceps
- Solution atomizer
- Ovassapian and Williams airways
- Video laryngoscopy (various products available) blades, sizes for neonate to large adult
- Direct laryngoscopy Miller and Macintosh blades, sizes 1–4
- Intubating laryngeal mask airways, sizes 3–5 (or equivalent)
- Standard laryngeal mask airways, sizes 3–5 (or equivalent)
- Esophageal-tracheal Combitube (or King LT or EasyTube by Rüsch)
- Gum elastic bougies (various manufacturers)
- Airway exchange catheters, multiple sizes
- Endotracheal tubes, sizes 6–9, standard and Evac types (pediatric sizes if appropriate)
- Capnometric devices
- Cricothyroidotomy kit (purchased or hospital standardized)
- Retrograde intubation kit (Cook Critical Care)
- Percutaneous tracheostomy kit
- Medications kit (etomidate, propofol, ketamine, succinylcholine, rocuronium, intravenous and viscous lidocaine, atropine)

an active heated humidifier or a passive heat and moisture exchanger (HME) (Figure 9.17) [121].

HMEs are typically cylindrical devices that are fitted to the ventilator circuit, usually just proximal to the ETT connector and the Y-piece, with limited changes on airway mechanics [122,123]. This is the most effective HME placement for maximizing humidity and temperature retention in the patient circuit [121,124]. The materials provide heat, humidification, and filtering properties, earning the device the nickname, "artificial nose" [125]. They are lightweight and inexpensive, require no power source, and reduce circuit condensation, making them attractive alternatives to the more expensive heated humidifiers.

Use of heated humidifiers is associated with the production of almost 100% humidity in the inspiratory gas and is thus more effective than use of HMEs. These units require an external power source and additional circuitry, increasing cost. Accidental overheating can occur and may create additional damage to the airway if temperatures are not frequently monitored. There is no consensus about the proper duration of use of these implements. Multiple studies have failed to show a correlation of increased incidence of pneumonia with heated humidifiers versus HMEs or with frequent changes of HMEs or heated humidifiers. Therefore, frequent changes (i.e., more often than every 7 days) of ventilator circuits, unless they are visually soiled, is neither cost-effective nor medically efficacious [73,126–129].



**Figure 9.17** A heat and moisture exchanger.

## 9.5.2 Suctioning

Perhaps the simplest and most logical means of assisting with secretion clearance is direct

suctioning. This modality is safe, but when it is performed carelessly, complications may occur, including soft tissue or airway trauma, aspiration, laryngospasm, increased intracranial pressure, bronchospasm, hypoxemia, and cardiac dysrhythmias [130]. Hypoxemia can be minimized with preoxygenation using a fraction of inspired oxygen ($F_{IO_2}$) of 100%. In patients with intracranial hypertension, mild hyperventilation or blunting of the cough reflex with instilled intravenous lidocaine just before suctioning may reduce the risks of additional increases in intracranial pressure. The evacuation procedure should be brief and intermittent. The vacuum should be applied only after the suction catheter has been advanced to its distal position. After each pass of the catheter, lung re-expansion with a few gentle manual breaths should be administered. Suctioning can be applied by a single-use open system in which the catheter is unprotected and open to the environment or by a closed system (Figure 9.18) that sheathes the catheter in a sterile protective covering.

Closed systems are usually incorporated into the ventilator breathing circuit at the junction of the Y-piece and the ETT or tracheostomy tube, allowing continued ventilation during suctioning with no need to disconnect the circuit. The advantage of not having to disconnect is important for patients who require aggressive ventilator management (e.g., high PEEP therapy), making them less susceptible to alveolar derecruitment compared with open suctioning. The retractable catheter does not add any additional restriction to airflow (when not deployed). There are concerns that colonization of these devices with aspiration of bacterial particles and cross-contamination may predispose to VAP [131]. Such concerns have led to differing opinions on the appropriate timing of any system changes. Kollef and coworkers randomly assigned patients to scheduled changes every 24 hours or to no change except when there was a malfunction or visible soiling [132]. In both groups, 15% of patients developed VAP. The only difference was in total cost: US$11,016 in the group with scheduled changes and US$837 in the group with no scheduled changes [132,133].

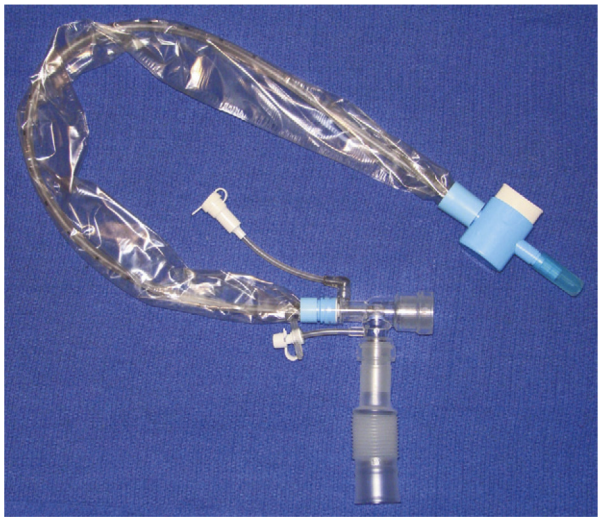


**Figure 9.18** The Ballard closed endotracheal tube suctioning system.

## 9.5.3 Subglottic Care

Secretion management has, by necessity, moved beyond the ETT lumen. Suctioning of secretions that are pooled above the ETT cuff, in the subglottic space, is an important step in good tracheal care and is paramount in the prevention of VAP [111,132–137]. Subglottic suctioning has been shown to decrease the incidence of VAP in the ICU from 16% to 4% [135]. Specialized ETTs with dedicated subglottic suctioning ports are more expensive ($15 compared with $1 for a standard ETT) [138]. An interesting cost analysis done in 2003 demonstrated that despite this increased cost, the estimated cost benefit of an ETT with a subglottic suction port was $4,992 per case of VAP saved [138]. The U.S. Centers for Disease Control and Prevention (CDC) universally recommends the use of subglottic suctioning tubes in the ICU to help reduce the rate of VAP [139].

Subglottic suctioning can be done with small suction catheters that are advanced down the trachea until resistance is met from the ETT cuff. Another option is using ETTs with a subglottic port positioned just above the cuff. These specialized ETTs are certainly not infallible and do not replace vigilant airway care. It has been demonstrated that dysfunction of the suction lumen can occur almost 50% of the time [140]. In 43% of cases, the cause of the suction loss was determined to be prolapse of the tracheal mucosa into the subglottic suction port [140].

## 9.5.4 Bronchoscopy

The use of fiberoptic bronchoscopy for routine secretion management is not advocated. It is expensive, requires proficient training, and may produce

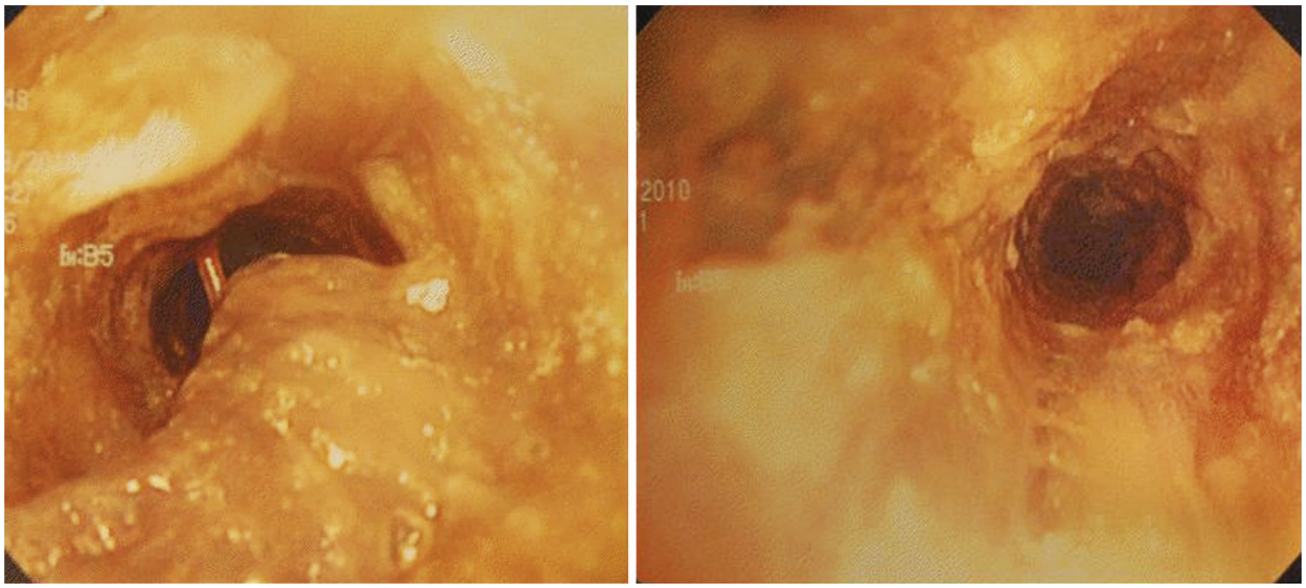



**Figure 9.19** Examples of biofilm accumulation inside the lumen of an endotracheal tube.

complications such as barotrauma secondary to a marked reduction or cessation in expiratory airflow (depending on the relative airway caliber) in intubated patients [4]. It should be reserved for assisting with lobar collapse caused by mucus plugging or inspissated secretions not amenable to conventional mucolysis, to perform so-called pulmonary toilet bronchoscopy that may be needed after an inhalation injury to evaluate for tracheobronchial injury, to aid in the diagnosis of significant hemoptysis, or to assist with specimen procurement when clinical suspicion merits sampling.

### 9.5.5 Biofilm Management

Biofilm and adherence of secretions (Figure 9.19) within the ETT have been implicated in the development of VAP, increased WOB, delays in extubation, and other complications [141–144]. Biofilm can easily be identified by bronchoscopy on insertion of the scope into the ETT. Newer technologies using acoustic reflectometry have also been developed to help with monitoring the accumulation of biofilm and evaluating the integrity of the intubated airway. The SonarMed airway monitoring device (SonarMed, Indianapolis, IN) employs this technology to assess ETT positioning and movement as well as ETT patency hampered by either internal or external agents.

Traditional methods used to manage biofilm include catheter suctioning, bronchoscopic lavage, and ETT exchange. Catheter suctioning is often ineffective for biofilm removal, because its presence frequently evades detection as the suction catheter navigates the patent channel formed by the biofilm concretions, thereby leaving the impression that the lumen is patent. Bronchoscopic lavage and ETT exchange are hampered by significant costs and hazards for both practitioners and patients. Another option is a device that essentially scrapes the biofilm from the luminal surface of the ETT. The Complete Airway Management (CAM) Rescue Cath by Omneotech (Tavernier, FL) (Figure 9.20) resembles a Fogarty catheter used to remove a thrombus. This product has an inflatable balloon at the distal end of a catheter that is encased in a latticed netting to provide "traction" and atraumatic "abrasion" of the lumen. It is introduced into the ETT and advanced to the distal end (based on ETT and CAM depth markings); the balloon is then inflated, and the catheter is fully withdrawn back out through the proximal end of the catheter, along with any luminal biofilm. This device and procedure may prove to be a useful option in already hypoxic or PEEP-dependent patients in whom time-consuming bronchoscopies could be hazardous. The CAM Rescue Cath is also a good option for patients with a potentially difficult airway, in whom ETT exchange can pose a considerable risk [145].

Information on the prevention of biofilm formation is rife with conflicting data. One study showed no difference in rate of *Pseudomonas aeruginosa*



**Figure 9.20** The Omneotech Complete Airway Management (CAM) Rescue Cath catheter. *(Courtesy of Omneotech, Tavernier, FL.)*

and *Staphylococcus epidermidis* biofilm formation among different ETT materials including PVC, silicone, stainless steel, and sterling silver [146]. More recently, however, ETTs coated in silver and chlorhexidine showed significantly reduced rates of biofilm colonization in a nonclinical setting [23,147]. The preventive management of biofilm may not be far in the future, but chlorhexidine-coated ETTs are currently not available. For now, the best strategy to manage biofilm is increased vigilance, fastidious respiratory care, and new technologies aimed at minimization and safe clearance.

## 9.6 Respiratory Therapies for the Intubated Patient

### *9.6.1 Secretion Clearance and Control Therapies*

#### 9.6.1.1 Mucolytic Agents

Agents used to decrease the viscosity of tracheobronchial secretions and assist with their reduction and clearance have been used for decades. The primary agent in use is *N*-acetylcysteine (NAC, Mucomyst). NAC is a sulfhydryl-containing compound; therefore, it is classified as a thiol. It has extensive first-pass metabolism in the gastrointestinal tract and liver when administered orally and is almost completely absorbed; only minimal amounts are excreted in the feces. The plasma half-life is approximately 2 hours, with virtually no detectable NAC at approximately 12 hours [148].

Most of NAC's biochemical effects appear to be related to its sulfhydryl group, which reduces the production hydroxyl radicals [148,149]. This effect has provided many uses for NAC beyond that of a mucolytic agent, including hepatic protection in acetaminophen overdose and renal protection against contrast-induced nephropathy [52,150]. NAC's effects on mucus viscosity result from its ability to disrupt the disulfide bridges and render them more liquid [133,148]. NAC is usually delivered by nebulizer in combination with a $\beta_2$-adrenergic agonist because it can induce bronchospasm [151]. Clinically, its effects have been variable in patients with chronic bronchitis, for whom oral NAC is used to assist with exacerbations and symptomatic relief [152–154]. Direct instillation of NAC during bronchoscopy may assist in secretion removal.

Another important factor in mucus viscosity is DNA content. DNA contributes to secretion viscosity because it accumulates from the degradation of bacteria and neutrophils. An agent that is considered mostly a mucokinetic agent, recombinant deoxyribonuclease (DNase, Pulmozyme), has been used in nebulized form in patients with bronchiectasis caused by cystic fibrosis with good results; however, it is expensive, and its use beyond this population of patients is not indicated [117,155,156].

One interesting therapy used in the population of burn patients who have an associated inhalation injury is nebulized heparin. Heparin assists with decreasing and removing bronchial casts that form with inhalation injury. Heparin's anticoagulant effects assist with removal of casts, and it may act as a free radical scavenger with anti-inflammatory effects. Although studies have not consistently shown a significant change in pulmonary function, cast formation and removal are favorably altered [157,158].

#### 9.6.1.2 Chest Physiotherapy

Chest physiotherapy encompasses a variety of techniques that include position changes, percussion

and vibration of the chest wall, and stimulation of a cough response. These are relatively dogmatic approaches that have historically provided poor results. They also tend to be burdensome to both the respiratory therapist and the patient. Newer, alternative techniques show promising results.

### *Percussion and Postural Drainage*

Used extensively in patients with cystic fibrosis, the technique of percussion with postural drainage utilizes external percussion of the chest wall overlying the affected lung region. Percussion can be applied manually with a cupped hand or by an automated, usually pneumatic, device. The application of percussion or vibration, or both, to the chest wall functions to loosen the secretions in the bronchi and facilitate their mobilization [94,159]. A steep Trendelenburg position of 25 degrees or more is employed—less if the patient cannot tolerate that angle—to facilitate the gravitational effects on mucus clearance [77,160].

Relative contraindications to the postural component of this therapy are the presence of increased intracranial pressure; the possibility of an unprotected airway and the potential for aspiration; recent esophageal, ophthalmic, or intracranial surgery; congestive heart failure; and uncontrolled hypertension [120]. As for the application of percussion or vibration, placement of the technique over recent surgical sites (e.g., split-thickness skin grafts, rib fractures or chest trauma, pulmonary contusions, burns, unstable spine fractures) or in the presence of coagulopathies, subcutaneous emphysema, or bronchospasm are all relative contraindications [160]. Hazards include hypoxemia and accidental extubation.

Clinically and experimentally, the use of percussion with postural drainage in cystic fibrosis patients is well supported [161–163]. However, patients' compliance remains a concern, because the technique is burdensome for patients and caregivers.

### *Positive End-Expiratory Pressure Therapy*

PEEP therapy, as a secretion clearance technique, creates a restriction to expiratory flow by means of a face mask or mouthpiece. The resistance is adjusted to 10 to 20 cm $H_2O$ of back pressure during expiration, which allows airflow to move into distal airways and associated lung units, forcing past secretions and causing them to move toward the larger airways, where suctioning is more feasible. The maneuver is used with gentle and forceful coughs lasting up to 20 minutes and aerosolized medications that can be administered concurrently. Patients with an increased WOB or severe dyspnea may have difficulty performing this technique due to temporary lapses in ventilation. PEEP therapy is at least as effective for secretion clearance as percussion with postural drainage, if not more effective, and patient satisfaction is markedly more favorable [125,164,165].

### *Intrapulmonary Percussive Ventilation*

Intrapulmonary percussive ventilation (IPV) can be delivered through a mouthpiece or to the end of the ETT. Its high-frequency percussive oscillations function to loosen retained secretions, expand airways and lungs, and reduce atelectasis. Conceptualized and designed by Dr. Forrest Bird, IPV uses a "phasetron"—a sliding venturi device capable of providing 5 to 35 cm $H_2O$ pressure during oscillations of 2 to 5 Hz [166]. Aerosolized medications may also be delivered during IPV treatments. Favorable results have been reported for secretion clearance and lung expansion in patients with cystic fibrosis, as well as in other disorders with an increased incidence of thickened secretions [167,168]. IPV offers an advantage to patients who lack the ability to perform percussion with postural drainage or high PEEP therapies.

### *High-Frequency Chest Wall Compression*

Therapy with high-frequency chest wall compression entails the wearing of an inflatable vest around the chest. Air is instilled into the vest bladder and then rapidly withdrawn in a cyclic manner, essentially creating an artificial cough. The high-frequency oscillations that are produced range from 5 to 25 Hz and can generate pressures as high as 50 cm $H_2O$. These oscillations create a gentle "squeezing" of the patient's chest that mimics small coughs. The frequency of the oscillations can be adjusted, and sensors in the vest can reduce the pressure delivered when the patient's chest expands (as with a sigh breath or a deep cough) [141]. Secretion clearance and improvement in mucus rheology have also been reported [169,170]. Perhaps the biggest drawback of this method is its cost, estimated at US$15,900 for each unit.

### 9.6.2 Overcoming Work of Breathing Imposed by Endotracheal Tubes, Tracheostomy Tubes, and Ventilator Circuits

With any translaryngeal intubation, the upper airway is bypassed and the resistance it imparts is thereby removed; however, there is still a substantial amount of work performed by the patient in an effort to ventilate. WOB is minimal during normal, quiet breathing, accounting for about 5% of the total oxygen consumption at rest. With increases in WOB, oxygen consumption can be markedly increased to as much as 30% or more [155]. This newly acquired increased demand may not be well tolerated by the critically ill patient. The additional WOB ($WOB_{add}$) imposed by the artificial airway and ventilator apparatus not only hinders weaning and liberation from mechanical ventilation but also impairs tissue oxygenation and alters critical blood flow, which may lead to worsened organ dysfunction [86]. To initiate a "breath" from the ventilator, a pressure differential across the ETT and circuit must be produced. The patient must overcome this resistance to initiate the demand flow needed for ventilation to occur. It has been shown experimentally that the ETT, the ventilator circuit, and the ventilator itself all add varying degrees of additional work for the patient to overcome, on top of the problems that initially necessitated intubation and mechanical ventilation [32,171].

#### 9.6.2.1 Pressure Support

Various modalities have been designed to overcome $WOB_{add}$ imposed by the artificial airway and ventilator [155]. One is pressure support (PS), which is used as either an adjunct or as a mode of ventilation to help the spontaneously breathing patient overcome the $WOB_{add}$ imposed by an artificial airway [21,168,172]. A preset, flow-triggered inspiratory pressure chosen by the clinician is added to the airway opening pressure when inspiration is triggered by the patient. Because it is flow cycled, the patient can control the duration and depth of inspiration, and the PS ceases when some preset gas flow has diminished, usually about 25% of the maximal peak flow achieved [173]. PS has been shown to decrease $WOB_{add}$ even with normal lungs [173,174]. However, in patients with obstructive pulmonary disease and expiratory flow limitation, breath stacking, or auto-PEEP, flow may not decelerate quickly enough, and active exhalation may be necessary to terminate the PS, thereby creating additional WOB [175]. The amount of inspiratory pressure added is usually 4 to 15 cm $H_2O$. Currently, it is recommended that PS be applied for all spontaneously breathing, intubated patients to assist with overcoming the resistance of the ETT or tracheostomy tube [176]. Additional PS may be necessary if tidal volumes or respiratory rates, or both, are inadequate to support oxygenation. Most patients tolerate PS well, but decreased tolerance in patients susceptible to expiratory flow limitation must be appreciated and accounted for in any management strategy.

#### 9.6.2.2 Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP) is applied at end-exhalation in spontaneously breathing patients. Much like PEEP, CPAP is designed to offset the degree of atelectasis that occurs inherently in the intubated, supine patient. CPAP ranging from 4 to 10 cm $H_2O$ should be provided for all spontaneously breathing patients in an effort to compensate for the loss of expiratory lung volumes and further promote oxygenation. So-called physiologic PEEP, an amount thought to rectify the aforementioned atelectasis, is theoretical but is estimated to be equivalent to 4 cm $H_2O$ in the normal lung. The reduction in WOB seen with CPAP has been appreciated primarily in the setting of expiratory airflow reductions; in such cases, CPAP offsets the auto-PEEP, thereby reducing the work required to generate the next inspiratory effort [177]. The type of flow-triggered mechanism and the location at which the flow differential is measured (typically at the tracheal end of the ETT) have been shown experimentally to decrease the inspiratory WOB as well [178]. CPAP is usually applied in combination with added PS.

#### 9.6.2.3 Automatic Tube Compensation

As stated previously, the ETT imposes a substantial degree of resistance to inspiration. The modalities described thus far assist with decreasing some of the work needed to overcome this burden. Added PS and PS ventilation help compensate for the resistance primarily encountered during

inhalation but not during exhalation, and they are not consistently provided because of the varying flow across the ETT during normal breathing [179]. Much resistance to exhalation is also produced by the presence of an ETT. Indeed, the internal diameter of the ETT greatly affects this phenomenon, as do other factors such as gas flow rates, gas density and viscosity, and luminal secretions adherent to the ETT wall. Automatic tube compensation (ATC) is a feature on some newer ventilators. It is designed to assist with the resistance imposed by the ETT or tracheostomy tube during both the inspiratory and expiratory phases of the respiratory cycle. By altering the PS delivered—raising it during inspiration and lowering it during expiration according to the pressure-flow characteristics of the ETT—ATC adjusts for the resistance and the pressure drop across the ETT during spontaneous breathing. A computer assists by calculating the pressure difference across the ETT ($\Delta P^{ETT}$) based on ETT size, measuring gas flow and airway pressure, and selecting the resistive properties of the ETT [179]. Unlike PS, ATC cannot be used as a ventilatory mode; it is merely an adjunct component to mechanical ventilation.

One drawback to ATC is the inability to correct for the reductions in airway diameter that can occur with secretions or kinking. This limitation results in an inaccurate measurement of $\Delta P^{ETT}$ such that ATC undercompensates for the pressure difference across the airway. A high index of suspicion is necessary to monitor for this possibility. Clinically, ATC has been shown to decrease the $WOB_{add}$ encountered with ETTs and tracheostomy tubes [28]. When these modalities were used to assist with weaning and extubation of patients in a T-piece trial, there was no difference in the workload encountered with ATC and T-piece alone, whereas adding PS to the T-piece trial at 7 cm $H_2O$ unloaded this additional work [180].

## 9.6.3 Pharmacologic Treatments

### 9.6.3.1 Inhalation Drug Delivery

The presence of an ETT does not limit drug delivery to the lungs and may actually enhance it. Many clinicians take advantage of this route of administration. The two predominant methods used to deliver agents are metered-dose inhalers (MDIs) and nebulizers. The drugs delivered by these devices are most commonly bronchodilators, mucolytics, corticosteroids, and antibiotics. For pulmonary ailments, inhaled drugs achieve efficacy comparable to or exceeding that of systemically delivered drugs with a smaller dose [181–183]. Tracheal administration of some traditionally systemic drugs often requires much higher doses to ensure absorption.

Inhalation drug delivery has other advantages over systemic administration. Systemic side effects can be reduced, because systemic absorption is markedly decreased. Variable reports regarding penetration and distribution of an aerosol to the lower respiratory tract range from 0% to 42% with nebulizers and 0.3% to 98% with MDIs. However, when the delivery method was standardized, the amount delivered in either method was similar, about 15% [184–186].

Particle size also plays an important role in delivery. The larger the particle, the less likely it is to be delivered distally to the alveoli. Aerosol particles ranging between 1 and 5 μm are optimal for proper deposition [181,182,185,187]. The density of the gas carrying the aerosol also influences the delivery in an inverse relationship. Improvement in delivery has been reported when a mixture of helium and oxygen was used in the ventilator circuits of both MDIs and nebulizers [183,188].

#### *Nebulizers*

The performance of a nebulizer depends on multiple factors including the model, operating pressure, flow rate, and volume of diluent utilized. Nebulizers are capable of generating aerosols with particle sizes of 1 to 3 μm, and the size produced is inversely influenced by the flow rate or pressure used: the greater the flow rate, the smaller the particle [181,182]. Nebulizers may be used continuously or intermittently. Intermittent use appears to be more efficient than continuous delivery, with less waste of aerosol demonstrated [189]. Placing a nebulizer upstream from the Y-piece and ETT also increases drug delivery [187,189,190]. Interestingly, the use of continuous drug nebulization may impair the ability of the patient to initiate a negative-pressure inspiratory effort in the PS mode of ventilation, thereby leading to hypoventilation [168,191].

#### *Metered-Dose Inhalers*

An MDI delivers medication in combination with a mixture of pressurized propellants, preservatives,

flavoring agents, and surfactants. The final concentration of active drug constitutes about 1% of the total volume in the canister [181]. When the stem on the MDI canister is depressed, a finite amount of drug is released at a certain velocity, and a spray cloud develops. Various adapters are available that fit in line with the ventilator circuit or on the end of the ETT as so-called elbow adapters to aid in the administration of inhalational therapies. Chambers or spacers appear to provide better delivery of aerosol compared with the more commonly used elbow adapters [192]. MDIs typically cause more aerosol deposition on the ETT than nebulizers do, decreasing the amount of drug delivered. These particles, in turn, adhere to the ETT. This problem can be reduced by using a spacer and performing the administration with meticulous attention to timing of the ventilatory cycle: it is most effective during inspiration and when synchronized with the patient's spontaneous effort. Dhand and Tobin reported excellent results with their technique of MDI delivery [189].

When comparing the overall efficacy of nebulizers versus that of MDIs, several factors favor the use of MDIs in mechanically ventilated patients. Nebulizers may become colonized with bacteria and help to deliver an aerosolized inoculum. Bowton and colleagues reported a potential saving of US$300,000 annually with the use of MDIs compared with nebulizers [193].

#### 9.6.3.2 Inhaled Bronchodilators

Airway reactivity is a ubiquitous consequence of airway manipulation that hinders respiratory function and prolongs the duration of mechanical ventilation. Additional pathophysiologic processes attributed to persistent bronchospastic disease that serve to prolong mechanical ventilation include mucosal inflammation that persists and promotes further mucus production, airway hyperemia and resultant edema, and the consequent narrowing of small airways leading to an increase in closing volume. These processes adversely affect oxygenation as functional residual capacity is decreased and $CO_2$ elimination, as expiratory flow, is limited. At extremes of expiratory flow limitation, generous amounts of intrinsic PEEP (auto-PEEP) are generated; this can impede cardiac filling by reducing preload, and hypotension and cardiac arrest may result. The physical effects of auto-PEEP are not limited to the cardiovascular system. The obvious effects of alveolar overdistention include an increased physiologic dead space and the potential for barotrauma, especially when controlled positive-pressure mechanical ventilation is instituted. Pneumothorax, pneumomediastinum, and pneumoperitoneum may all occur as a result, as may patient-ventilator dysynchrony.

Many maneuvers are available to reduce the effects of bronchospasm (and higher airway pressures), including decreasing the respiratory rate, prolonging the expiratory time, decreasing the tidal volume, and increasing the inspiratory flow rate. Pharmacologically, the use of β-adrenergic agonists, specifically $\beta_2$-agonists such as albuterol, is the mainstay therapy. $\beta_2$-receptors on bronchial smooth muscle promote relaxation and dilation of the airway diameter when stimulated. Systemic methylxanthines such as theophylline do not add much benefit in the acute stage of treating bronchospasm or reactive airways. Their narrow therapeutic window and vast side effect profile increase potential toxicity.

$\beta_2$-agonists also have a beneficial effect on respiratory cilia in that they cause an increase in ciliary beat frequency [194]. This phenomenon is mediated by β-adrenergic receptors and can be attenuated with nonselective beta-blocking agents. An increase in the frequency of ciliary beating promotes mucus clearance over the respiratory epithelium. Other effects include increased water secretion onto the airway surface, which facilitates mucus clearance [195]. Indeed, the beneficial effects of β-agonists on bronchial reactivity and mucociliary clearance are evident. However, there are data suggesting a more robust effect in healthier airways than in chronically diseased airways such as those seen in patients with chronic bronchitis, possibly due to downregulation and chronic attenuation [196]. Newer formulations of inhaled β-agonists such as levalbuterol may have reduced side effect profiles and possibly improved outcomes.

#### 9.6.3.3 Anticholinergics

Although inhaled β-agonists are pivotal in the reduction of airway reactivity, the use of inhaled anticholinergics such as ipratropium bromide or the newer tiotropium bromide needs to be emphasized, given their obvious synergistic effect with β-agonists. It is well appreciated that many of the mechanisms of

airway reactivity and inflammation associated with bronchospastic disease are cholinergically mediated. In patients with chronic obstructive pulmonary disease, the use of these agents alone or in combination with β-agonists is the foundation for rescue therapy and a mainstay in chronic management [183].

#### 9.6.3.4 Corticosteroids

Inhaled glucocorticoid therapy has become a mainstay of treatment in various obstructive respiratory ailments, including chronic obstructive pulmonary disease and asthma. This class of medicines unquestionably has disease-specific effects at the target organ. Equally interesting is the fact that administration in an aerosol preparation magnifies their effects while markedly reducing their side effect profile, leading to a lower risk-benefit value. Targeted efficacy with minimal adverse effects helps to quantify an appropriate risk-benefit value [197,198]. High lung deposition or targeting, high receptor binding, longer pulmonary retention, and high lipid conjugation are among the pharmacokinetic parameters that lead to improved efficacy of these compounds and should be considered. A low or negligible oral bioavailability, smaller particle size leading to a relatively inactive drug at the oropharynx, higher plasma protein binding, increased metabolism rates, higher clearances, and lower systemic concentrations are associated with lower risks for adverse effects [197–199].

For individuals who require long-term care with inhaled glucocorticoids during ventilator dependency, therapy should be continued to minimize the underlying disease process and thereby decrease the number of new variables, including adrenal insufficiency, in the treatment equation with inhaled or intravenous formulations [200]. Despite all of these perceived benefits, inhaled glucocorticoids do not seem to reduce mortality [201]. Acute exacerbations tend to be treated with intravenous or oral preparations due to the higher doses required.

#### 9.6.3.5 Inhaled Antibiotics

Inhaled antibiotics have been used for decades, falling in and out of favor over the years. They are used primarily for treatment and suppression of chronic airway bacterial colonization. Their theoretical advantages are improved drug delivery and higher concentrations at the site of infection, leading to improved efficacy and better bacterial eradication compared with systemic administration [90,202–204]. The primary concern with this therapy is development of bacterial resistance.

Results differ on efficacy. Inhaled antibiotics, mainly aminoglycosides, have been used extensively in cystic fibrosis patients with good results [90,202–205]. Palmer and colleagues reported a marked reduction in the volume of airway secretions and a decrease in the laboratory markers of inflammation in a prospective study of mechanically ventilated patients with chronic respiratory failure [90,205]. However, their study lacked power and was not randomized.

Other studies have failed to show similar benefits but rather have demonstrated poor, unpredictable drug delivery [206]. Unequal ventilation, atelectasis, lobar collapse, and consolidation impair even drug distribution. Bronchospasm with chest tightness has also been reported [134]. Use of inhaled antibiotics should be limited to selected patients, such as those with cystic fibrosis. Routine use to assist with secretion reduction and clearance in the mechanically ventilated patient is not recommended.

### 9.6.4 Positioning of the Patient

The appropriate position in which to maintain the patient requiring mechanical ventilation has been debated. Current recommendations from the CDC state that elevating the head 30 to 40 degrees reduces the risk of VAP. A study examining head elevation and the rate of VAP concluded early after interim analysis showed an incidence of microbiologically confirmed pneumonia of 5% in semirecumbent patients versus 23% in supine patients [207]. The semirecumbent position has also been supported with regard to facilitating nursing care and decreasing gastric reflux and resultant aspiration. It has not been shown to have an effect on the hemodynamic status of the patient, although this remains a common theoretical concern [208].

Special beds that provide continuous lateral rotation have been used for patients who cannot be repositioned easily, such as those with severe head or traumatic brain injury, bariatric patients, and those who are pharmacologically paralyzed (e.g., patients with acute respiratory distress syndrome [ARDS]). These beds are advertised to enhance skin care, reduce thrombotic events, and improve

pulmonary function. Their use is proposed to reduce atelectasis and, hence, pneumonia formation; however, studies' results have remained conflicting [209,210].

Occasionally, in severe cases of ARDS, alternative positioning (prone) may be necessary to facilitate ventilation and oxygenation. This method attempts to combat the physiologic shunt that is responsible for the observed hypoxemia. The prone position improves oxygenation by increasing lung volume, recruiting posterior lung fields, and redistributing perfusion [211]. No statistical difference was shown in a meta-analysis of the data for prone positioning of patients, although a small subset of patients with severe ARDS has been shown to benefit [212,213]. However, prone positioning is not without risks, particularly an increased risk for bed sores and ETT complications such as dislodgement [212]. Recently, a bed has become commercially available that possesses the ability to fully prone the patient, making use of this potentially beneficial intervention more dependent on necessity than caregiver feasibility. (Rotoprone, KCI Therapeutic Support Systems, San Antonio, TX.)

## 9.7 Conclusions

The establishment and maintenance of a secure and dependable airway is paramount in the care of the critically ill patient. From the very onset of admission to the ICU, care of the airway should begin with surveillance and a determination of which airways will be difficult to secure or difficult to maintain. The proper choice of an artificial airway not only facilitates ventilatory requirements for improved oxygenation but protects the patient from untoward iatrogenic problems encountered with instrumentation. Regardless of the intervention, an unfettered vigilance is the key to improved outcomes. Proper ETT care, early performance of a tracheostomy (when indicated), frequent pulmonary hygiene, and the use of established protocols and proven preventive measures should help to ensure safe and successful outcomes in critically ill patients.

## 9.8 Clinical Pearls

- Polyurethane endotracheal tube (ETT) cuffs that have high-volume, low-pressure (HVLP) cuffs are capable of conforming to the irregular borders of the tracheal lumen and therefore are more effective at preventing microaspiration.
- ETT placement has mechanical and physiologic consequences. Vigilant surveillance of skin hygiene, airway patency, cuff integrity, and ventilatory support must be realized to minimize injury and maximize support.
- Confirmation of ETT placement is necessary to aid in proper resuscitation efforts. Verification by the presence of end-tidal carbon dioxide, whether by capnography or capnometry or by direct or indirect visualization, is mandatory to ensure appropriate placement.
- Cuff leak evaluation is a multifaceted endeavor requiring vigilance, diligence, and skill. An appropriate analysis of the potential cause, scrutinized against the risks and benefits of ETT exchange, must occur with limited interference to homeostasis.
- ETT exchange, whether for biofilm accumulation and luminal obstruction, ETT cuff damage (cuff leak), or other ETT mechanical failure (e.g., kinking) is a high-risk ordeal. The decision to exchange an ETT should be assessed against newer, currently available technologies, such as biofilm extraction, that are designed to salvage damaged ETTs. Should the decision to perform an exchange arise, airway adjuncts such as an airway exchange catheter and video laryngoscopy have proved invaluable for achieving higher success rates.
- Once an ETT is in place, efforts must be aggressive and perpetual to decrease the risk of ventilator-associated pneumonia (VAP); these efforts range from acid-suppression therapies to use of specially designed ETTs to advanced nursing care regimens. VAP appears to be more multifaceted than previously believed. Subglottic suctioning and biofilm management are just the beginning steps.
- Any area of a facility that deals with intubated patients should have a readily accessible difficult airway cart. The cart should be well outfitted but tailored to the types of airways managed and familiar as well as specific for the providers who respond to such emergencies.

- As with pulmonary artery catheters, it is not the difficult airway cart that manages the airway but the personnel who utilize it.
- It is better to investigate any perceived ETT problem electively than to deal with its consequences after it becomes an acute emergency.
- The landscape of ETT design, construction, and maintenance has changed and will continue to change over the next decade. Not all variations will prove effective, but improved patient care will take place.

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# 10 Applications of Polyaryletheretherketone in Spinal Implants: Fusion and Motion Preservation

*Steven M. Kurtz, PhD*

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## 10.1 Introduction

The orthopedic and biomaterials literature of the 1990s reflects an early academic curiosity in implant applications of polyaryletherketone (PAEK) biomaterials [1,2]. However, widespread commercial applications for PAEK biomaterials in the human body were first realized with cage implants intended to promote intervertebral body (interbody) fusion of the lumbar spine. Success of PAEK with interbody implants would later inspire applications in a broad variety of spinal implant applications, including posterior fusion, dynamic stabilization, and disc arthroplasty.

Fusion is now considered a standard of care for intractable low back pain arising from degenerative disc disease and/or spinal instability. In the cervical spine, anterior decompression and fusion is the standard treatment for degenerative disc disease, myelopathy, and radiculopathy. Whether in the lumbar or cervical spine, fusion consists of first immobilizing the painful spine segments by encouraging bone growth across the immobilized level. Spine fusion was first performed without instrumentation using bone grafts, often obtained from the patient's own body, such as iliac crest. Harvesting bone from the patient was undesirable, because it is a second procedure and has associations with complications, including donor site pain. Also, the operated level was unstable until fusion occurred, and required local immobilization. Posterior instrumented fusion, using rods, plates, and screws, was developed to provide immediate rigid stability to the spine while the bone fused across the treated level [3].

Since the 1990s, the incidence of spinal fusion has grown substantially in the United States [4], reflecting both an increased prevalence of the degenerative disc disease and growing acceptance of the procedure (Figure 10.1). In 2008, an estimated 286,000 thoracolumbar fusions and 180,000 cervical fusions were performed in the United States based on the data from the Nationwide Inpatient Sample (NIS), and that the number is projected to increase to millions of procedures a year within the next two decades [5].

Polyaryletheretherketone (PEEK) interbody cages represent a considerable commercial, as well

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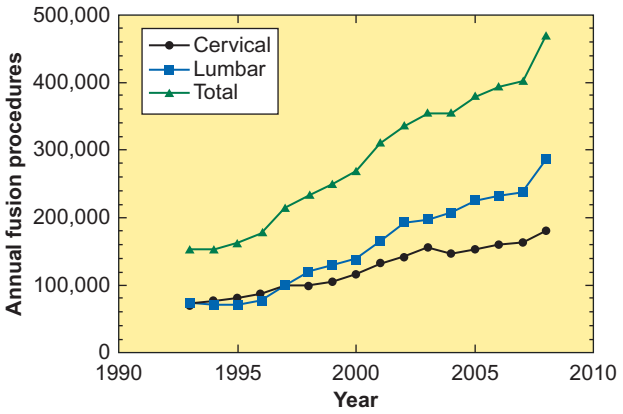



**Figure 10.1** Incidence of spinal fusions in the United States based on NIS data from 1993 to 2008. (*Source: http://hcupnet.ahrq.gov.*)

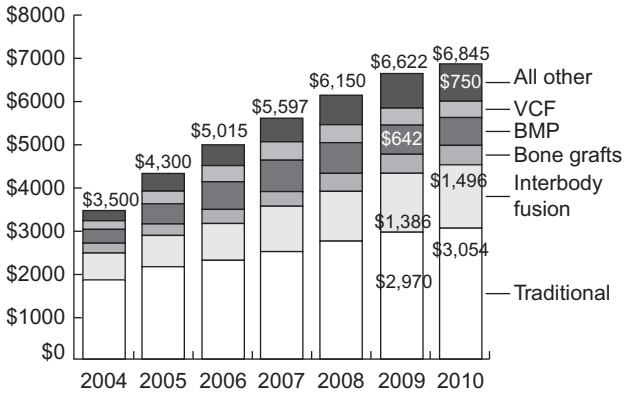



**Figure 10.2** 2004–2010 spinal implant US sales ($ millions) by segment. (*Reproduced with permission from the* Orthopedic Network News *[6].*)

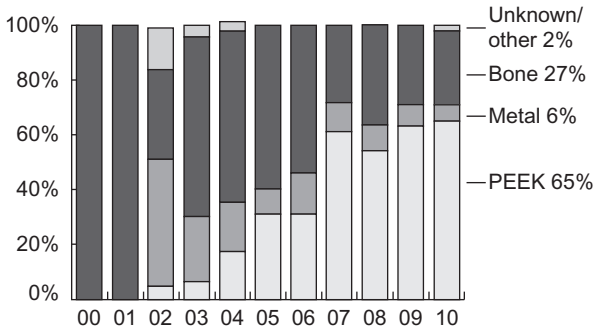



**Figure 10.3** Trends in materials used in interbody fusion devices, 2000–2010. (*Reproduced with permission from the* Orthopedic Network News *[6].*)

as clinical, success. The US market for interbody fusion products has increased from 0.6 billion US$ in 2004 to 1.5 billion US$ in 2010 (Figure 10.2) [6]. The positioning of PEEK cages within the interbody market has likewise expanded since Food and Drug Administration (FDA) approval in 2001. By 2010, PEEK cages accounted for 65% of interbody devices, representing a market of approximately 1 billion US$ in the United States alone (Figure 10.3) [6]. PEEK cages have also contributed to the growth of the $613 m recombinant human bone morphogenetic protein-2 (BMP) market (Figure 10.2). The use of BMP for facilitating interbody fusion was approved by the FDA in 2002 for the threaded titanium LT-Cage [7], but it has been increasingly used "off label" with other spinal fusion devices [8]. Metal cages, such as the LT-Cage fabricated from titanium, are estimated to constitute 10% of the interbody market (Figure 10.3) [6]. Thus, the vast majority of BMP use for interbody fusion is accomplished using PEEK rather than metal cages. Compared with other synthetic biomaterial solutions, PEEK biomaterials now dominate the design space for interbody cages and are the principal implant delivery system for BMP.

In recent years, there has been great interest in finding ways to halt the degenerative cascade following fusion surgery [9,10]. Because fusion results in unnatural motion at adjacent levels, researchers have proposed that preserving normal motion in the spine will help alleviate, and perhaps even prevent, adjacent segment degeneration. Consequently, a variety of new implant technologies have developed to preserve, limit, or enhance motion of the spine. Although previous fusion technologies have been referred to as "static" or rigid fusion, new fusion technologies that employ a more flexible instrumentation systems are gaining clinical acceptance. Interspinous implants, such as the X-STOP (Kyphon, Sunnyvale, CA), have been developed with PEEK-OPTIMA components to treat back pain caused by spinal stenosis [11]. Artificial discs, developed with PEEK components, represent another novel implant technology that is intended to preserve motion of the treated spine [12].

Motion preservation spine technology, while perhaps no longer in its infancy, still remains in the very early years of development and clinical acceptance. In 2008, an estimated 5000 interspinous process implants, 800 posterior pedicle-based stabilization devices, and 4900 total disc

replacements (TDRs, including both cervical and lumbar) were performed in the United States based on data from the NIS. Reimbursement for surgeons and hospitals for performing motion preserving spinal surgery continues to be extremely challenging in the United States. Thus, motion preservation should be viewed through the lens of an early development in the spine field; fusion procedures currently dominate the clinical practice of spine surgery.

This chapter focuses on the variety of spinal implant applications of PEEK. We begin with an overview of interbody fusion and historical development of the first carbon fiber-reinforced (CFR)-PEEK spinal implant, the Brantigan I/F lumbar fusion cage. More recent applications of PEEK in the spine, including dynamic stabilization devices and artificial discs, are also reviewed.

## 10.2 Origins of Interbody Fusion and the "Cage Rage" of the Late 1990s

Although lumbar and cervical fusions are today considered common procedures, the surgical techniques have evolved considerably since 1911 when fusion was first suggested as a treatment for Pott's disease [13]. During the first half of the 20th century, posterior fusion techniques for treatment of back pain included resection of the posterior elements and implantation of bone fragments harvested from the patient's pelvis [14]. Dissatisfaction with the stability and outcomes of these early posterior surgical techniques led to the development of interbody fusion between adjacent lumbar and cervical vertebral bodies during the 1930s and 1950s [15–17]. Early interbody fusions were accomplished by removal of the disc and implantation of bone graft, either from the patient or from newly created bone banks of cadaver bone [16]. However, the success of early interbody fusion surgery also proved to be variable [18]. A key limitation for interbody fusion remained the strength and stability afforded by the bone graft. Along with the development of posterior instrumentation, the invention of interbody implants, known as cages, would help expand the acceptance of both cervical and lumbar fusion surgery starting in the 1990s.

The first interbody implants were used in horses, not humans. George Bagby M.D. [19] developed a cylindrical stainless steel implant in 1982 known as the "Bagby Basket" to fuse unstable spine segments in race horses that had become paralyzed or otherwise neurologically impaired. The concept of an interbody implant for humans was developed in the 1980s and 1990s as the "Bagby and Kuslich" (BAK) technique. The BAK cage of the 1990s was a threaded, fenestrated titanium cylinder that could be filled with bone graft. The BAK cage was manufactured by Spine-Tech, Inc., Minneapolis, MN. The stand-alone threaded cage was approved by the FDA in 1996 after a rigorous multicenter clinical trial for implantation by a direct anterior approach, a posterior lumbar interbody fusion (PLIF), and a laproscopic approach [20]. In the FDA investigational device exemption (IDE) clinical trial, Kuslich et al. [20] reported that 91.7% of patients were fused at 2 years and 95.1% of patients were successfully fused at 4 years.

For a short time, the stand-alone BAK cage was widely used. However, the clinical results of the threaded cage after FDA approval did not match high expectations raised by the prospective clinical trial [21–23]. The poor results of the BAK cage that were reported following FDA approval are now thought to be largely due to poor patient selection by surgeons, technical difficulties with implantation, and its stand-alone indication [24]. Consequently, the period of the late 1990s is sometimes referred to as the "Cage Rage" by some members of the spine community. Regardless, Bagby and Kuslich are credited for developing the first FDA-approved interbody fusion cage as a stand-alone device in combination with bone graft. The second-generation threaded cage, the LT-Cage (Medtronic Spinal and Biologics, Memphis, TN), was approved in 2002 in combination with BMP. In retrospect, the Cage Rage of the late 1990s set the stage for the introduction of PEEK into this dynamic and growing field of spine surgery.

## 10.3 CFR-PEEK Lumbar Cages: The Brantigan Cage

In parallel with the development of threaded titanium cages, PAEK biomaterials for interbody spinal cages were also developed for posterior lumbar interbody fusion (PLIF) in the 1980s and 1990s



**Figure 10.4** CFR-PEEK lumbar fusion cage, used in concert with posterior screws and rods.

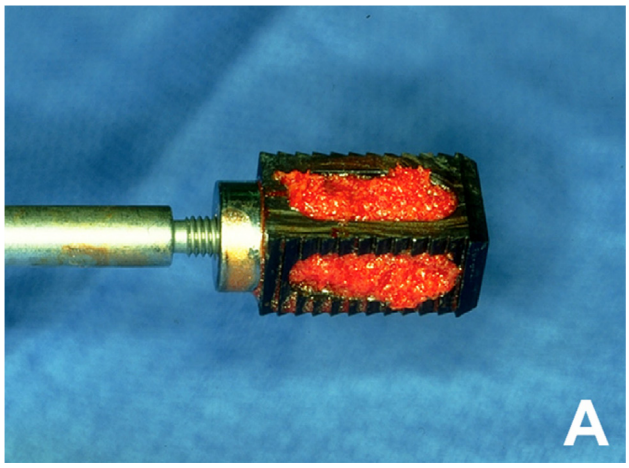



**Figure 10.5** CFR-PEEK lumbar fusion cage loaded with fragmented bone graft, prior to implantation. (*Image courtesy of Bill Christianson, DePuy Spine.*)

by AcroMed (Cleveland, OH, now DePuy Spine, Raynham, MA). The CFR-PEEK I/F lumbar fusion cage was approved by the FDA in 2001, following the aftermath of the Cage Rage. By this time, interbody fusion surgery had evolved from the experience with the stand-alone threaded cages. The CFR-PEEK cage has been described in a monograph by John Brantigan M.D., the lead surgeon inventor [25]. In this section, we provide an overview of the development history for the CFR-PEEK cage. Readers interested in a more detailed account are encouraged to read Brantigan's treatise [25].

In contrast with the initial stand-alone design of the threaded cage, the Brantigan cage was typically intended to be used in concert with posterior instrumentation for added stability. A model of a PLIF instrumentation system is illustrated in Figure 10.4. The PLIF procedure is conducted in two phases. In one phase of the surgery, a cage is placed anterolaterally between the vertebral bodies of the treated level. The cage may be packed with bone graft (Figure 10.5) or a sponge containing BMP (e.g., INFUSE bone graft [26]). The cage may be reinforced with an anterior plate, to prevent extrusion. In another phase of the surgery, posterior screws and rods are also typically placed to provide additional stability to the treated level (Figure 10.4).

Due to the mechanical loading requirements for these permanent implants, the surgeons who helped develop the PLIF cage, Arthur Steffee M.D. and John Brantigan M.D., initially conceived of a titanium device that would allow bone to grow through a columnar fenestration in the device [27]. There were two perceived drawbacks with the initial proposed design, the first being the stiffness of the titanium device, which might promote stress shielding and inhibit bone growth, and the second being the radiopacity of the device, which would hinder diagnostic assessment of the bone growth. Carl McMillin, a polymer engineer at AcroMed, was familiar with high-performance thermoplastics and recommended PAEKs for the cage to overcome both limitations [27,28]. The clinical and commercial success of this medical device, which came to be known as the Brantigan cage after its primary surgeon champion, lay the foundation for the current widespread use of PEEK in spine implants.

CFR-PAEK cages were subjected to an extensive in vitro biocompatibility and mechanical testing program, including pull-out tests in cadaver bone, static compression, static compressive shear, static torsion, and dynamic compressive shear testing (Figure 10.6). The mechanical behavior of the cages was found to be more than sufficient for the intended application [29]. Indeed, the mechanical strength of the CFR-PAEK cages, although not as strong as a metal cage, could support the weight of

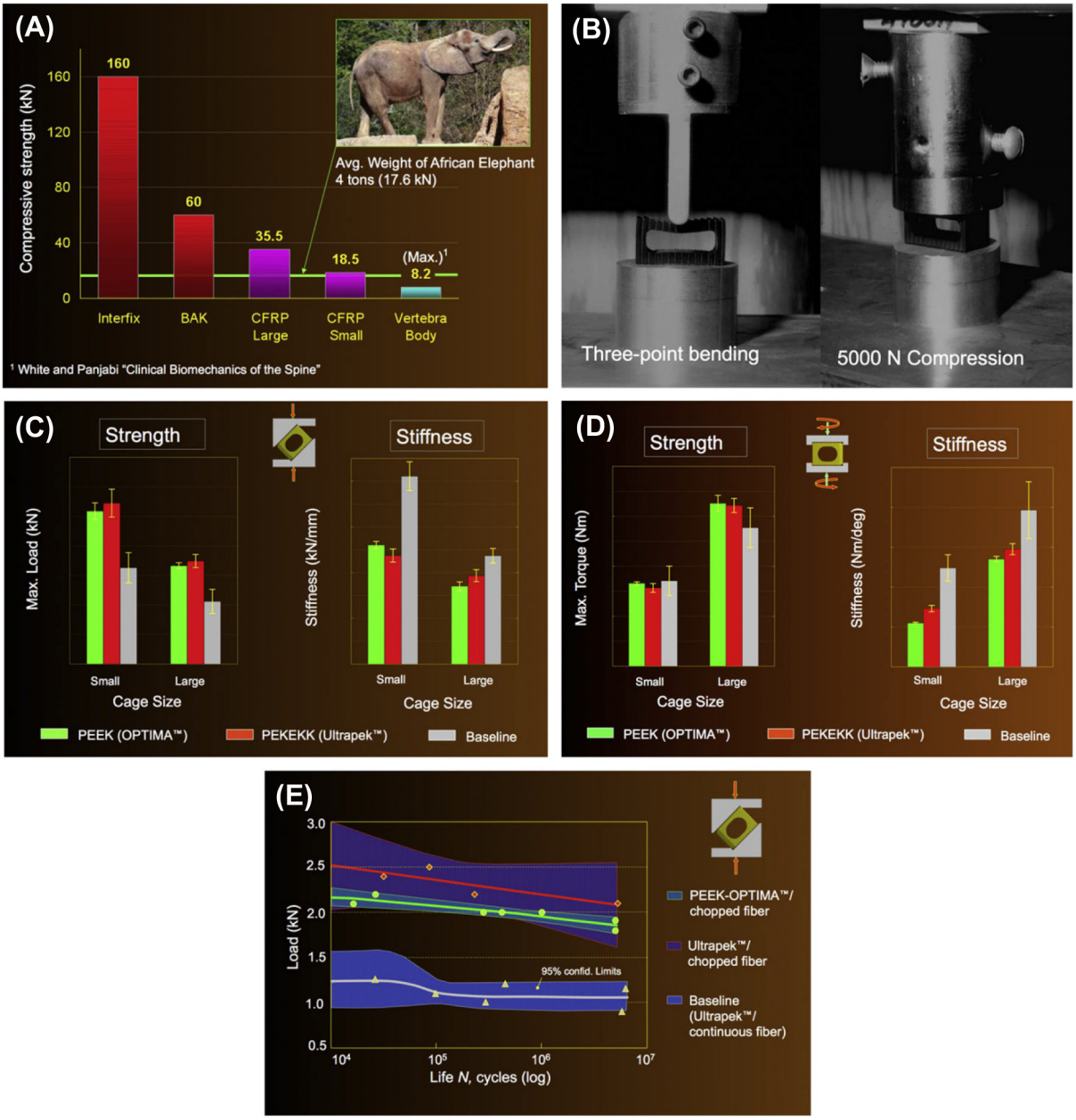



**Figure 10.6** CFR-PEEK and CFR-PEKEKK cages were subjected to an extensive in vitro mechanical testing program, including static axial compression (A, B), compressive shear (C), torsion (D), and fatigue testing (E). (*Image courtesy of Bill Christianson, DePuy Spine.*)

a full-grown elephant (Figure 10.6A). Initially, the full suite of biocompatibility testing, prescribed at the time under the Tripartite agreement, was also performed by the manufacturer; these tests were later repeated for PEEK-OPTIMA after the ISO 10993 standard was created [25]. The CFR-PAEK cages passed all of the biocompatibility tests prescribed by the Tripartite agreement and ISO 10993 [25].

Starting in May 1989, PEEK and PEKEKK were evaluated in a 2-year pilot clinical study of the spine cage for PLIF in 26 human patients [30]. Both implant materials were consolidated into plates with continuous 68% by weight carbon fibers for reinforcement, and the cages were subsequently machined from the plates into their final form. In the PLIF procedure, in addition to a cage or bone spacer, the spine is further stabilized by pedicle

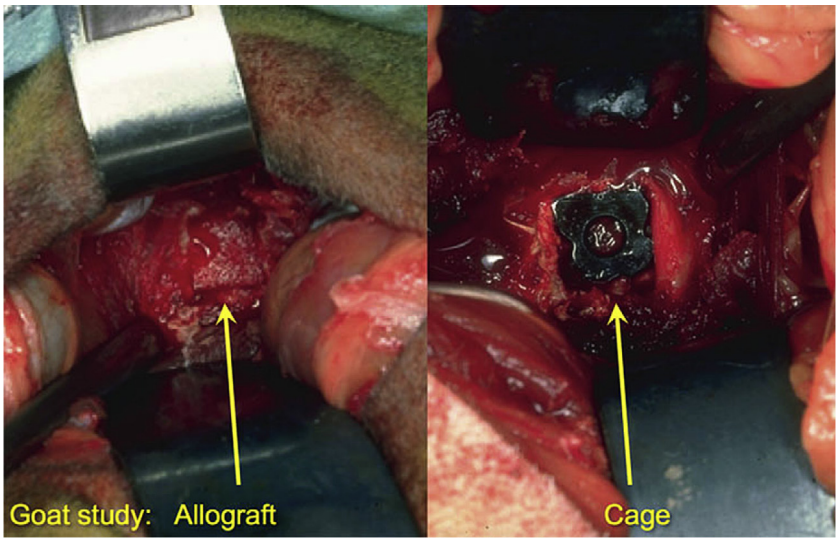



**Figure 10.7** PAEK cages were compared with sterilized allografts in a Spanish goat study. (*Image courtesy of Bill Christianson, DePuy Spine.*)

screws and axial rods or plates. In the 26 patients, the initial clinical trial evaluated 32 interbody cages (of two designs and two materials) and 31 alternative interbody fusion therapies, for a total of 63 total fusion levels. Thirty-one of the 32 cages survived 2 years of follow-up. Clinical results were good or excellent in 21 of the 26 patients, and fair or poor results were traced back to problems unrelated to the cage. Because of the radiolucency of the cages, interbody fusion could be identified in 100% (31/31) of the cage levels. Despite the problematic clinical research design, Brantigan's pilot clinical study [30] marks the first implantation of carbon-reinforced PEEK and PEKEKK in the human spine.

These excellent fusion results were also reflected in a 2-year study of reinforced Ultrapek cages in Spanish goats [31]. In this animal study, PAEK cages were compared with sterilized allografts (Figure 10.7). Additional goals of the study were to verify the biocompatibility of the device and potential wear debris in a functional animal model. Fusion was observed radiographically after 2-year follow-ups (Figure 10.8). Histology confirmed extensive growth of trabeculae into the cages (Figure 10.9) and the absence of an inflammatory reaction (Figure 10.10).

Based on the encouraging fusion results from the pilot clinical study and animal study [30,31], a prospective, multicenter IDE study was initiated for the FDA in November 1991 [32]. A total of 221 patients received a carbon-reinforced PEKEKK cage with posterior pedicle screw fixation. The authors reported successful fusion in 176 of the 178 (98.9%) patients who reached 2-year follow-up. Although there were no major device-related complications in the study, 23 major nondevice-related complications occurred (10.4%), including six deaths. These findings underscored the clinical difficulties associated with the PLIF procedure for spinal fusion.

The clinical limitations associated with PLIF were addressed with evolution in surgical technique to explore anterior lumbar interbody fusion (ALIF) with the Brantigan cage, as well as the more extensive "circumferential" or 360° fusion, involving an ALIF procedure and posterior instrumentation with pedicle screws. Two- and 5- to 9-year follow-up data for the ALIF Brantigan cage in a 360° fusion have been reported [33,34], with superior clinical outcomes as compared with posterolateral instrumented fusion.

In the mid 1990s, BASF decided to no longer produce PEKEKK and withdrew the UltraPek resin from the market. Although AcroMed stockpiled sufficient UltraPek to support their products, their cage products were transitioned to PEEK, produced by Invibio, to provide a long-term biomaterial supply [27]. Stockpiled UltraPek continued to be used in Brantigan cages distributed in Japan until February 2007 when DePuy received Japanese approval for a CFR-PEEK OPTIMA cage [27,35].

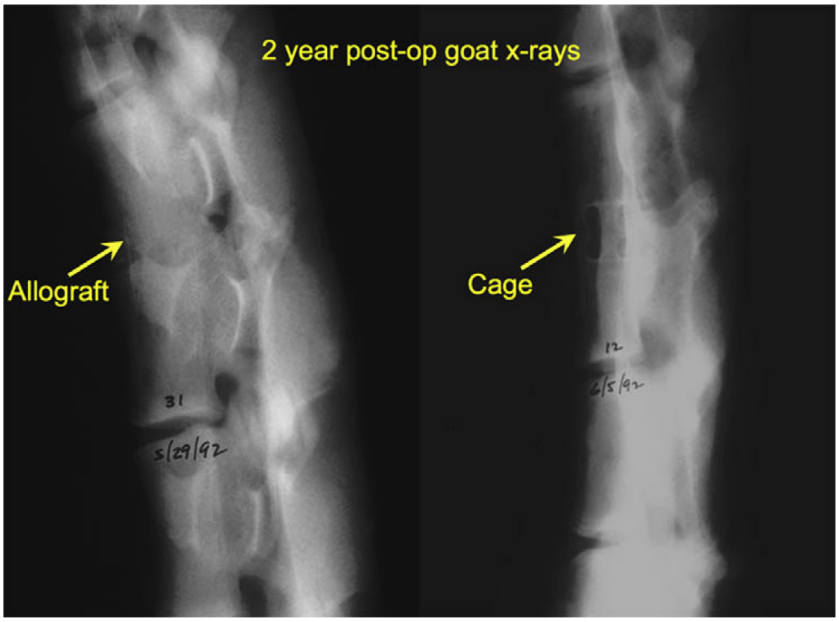



**Figure 10.8** Fusion was observed radiographically in the Spanish goats after 2-year follow-up. (*Image courtesy of Bill Christianson, DePuy Spine.*)

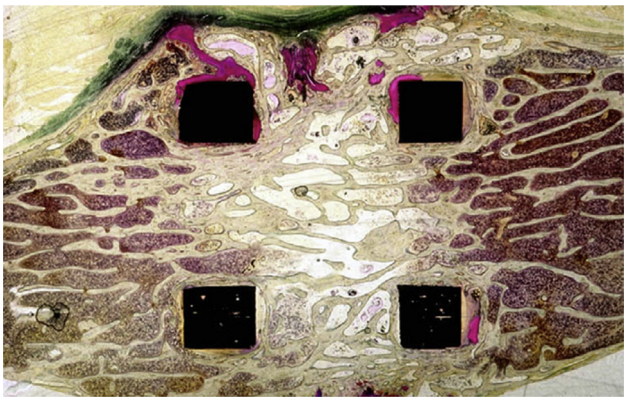


**Figure 10.9** Histology confirmed the radiographic findings of fusion in the cages of the Spanish goat study. Extensive growth of trabecular bone was observed through the cages. (*Image courtesy of Bill Christianson, DePuy Spine.*)

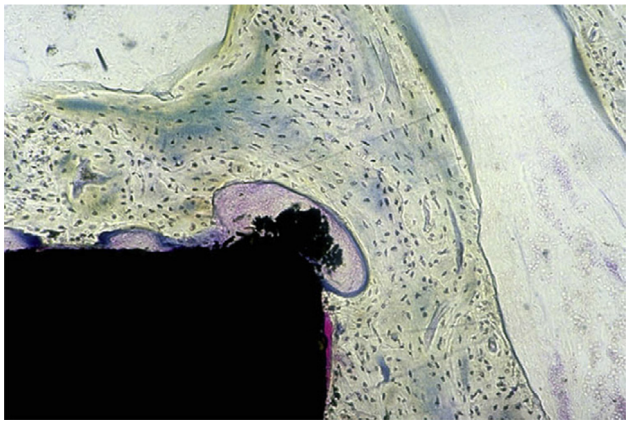


**Figure 10.10** Histology confirmed the absence of an inflammatory reaction to the CFR-PAEK in the Spanish goat model. The black particles at the corner of the cage strut may be polishing artifact, rather than wear debris. No foreign body reaction is observed. (*Image courtesy of Bill Christianson, DePuy Spine.*)

Brantigan cages were originally machined from CFR-PAEK plates. Both 30% PEKEKK and 70% continuous carbon fibers, as well as 70% PEKEKK with 30% carbon fiber, were originally used [36]. Today, these cages are fabricated more efficiently by injection molding CFR-PEEK OPTIMA (70% PEEK with 30% chopped carbon fiber) [36].

## 10.4 Threaded PEEK Lumbar Fusion Cages

Although many articles describe the use of CFR-PEEK for spine implants, many recent studies also involve the use of neat PEEK for both cervical and

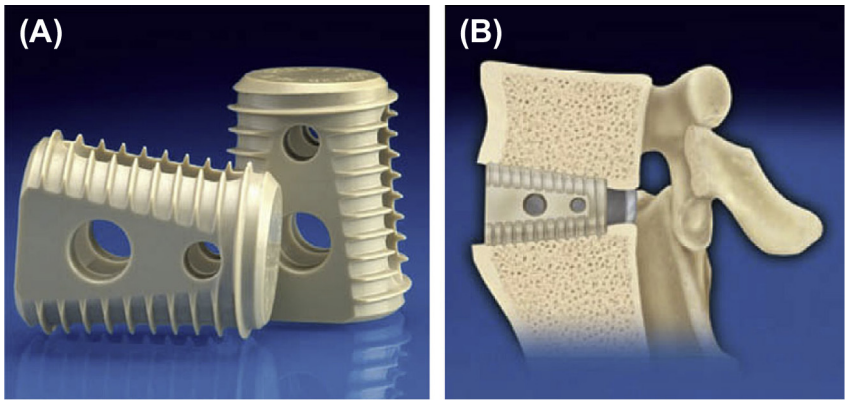



**Figure 10.11** Tapered PEEK cage for the lumbar spine (LT-CAGE System: Medtronic Spinal and Biologics, Memphis, TN).

lumbar spinal cages [37–47]. A tapered PEEK cage for the lumbar spine is shown in Figure 10.11. Because the use of neat PEEK for spine is a relatively recent development, the published literature is generally limited to in vitro biomechanical studies [43–45], or short-term outcomes in animal studies or human clinical trials [37–41,46,47]. Recent studies with PEEK cages have looked to improve or accelerate fusion performance by combining the devices with the use of hydroxylapatite [41], 40% β-tricalcium phosphate/60% hydroxylapatite [38], or rhBMP-2 on a collagen sponge [40].

A detailed animal study investigating PEEK interbody cages has recently been reported by Toth et al. [40]. Researchers studied the influence of rhBMP-2 on a collagen sponge (InFuse™: Medtronic Spinal and Biologics, Memphis, TN) on fusion with a PEEK-threaded cage in an ovine model. An autograft group served as a control (Figure 10.12). After 6 months, the biomechanical behavior of the treated level was measured. The cage group treated with InFuse™ was found to be significantly stiffer in flexion and left lateral bending than the control group treated using a PEEK cage filled with autografts. Histology and microradiographs were used to characterize the extent of fusion (Figure 10.13). All the PEEK cages with InFuse™ were diagnosed with fusion at 6 months radiographically and histologically. No evidence of wear debris or damage to the device was noted. Only mild inflammatory response was noted during histological evaluation of tissue adjacent to the PEEK implants, which the authors judged to represent "excellent" biocompatibility for the material.

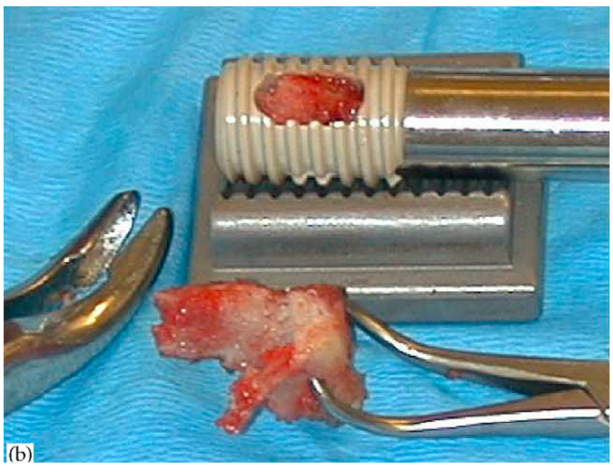



**Figure 10.12** Threaded PEEK interbody device filled with autograft prior to implantation into a goal animal model. (*Reproduced with permission from Ref. [40].*)

Intermediate-term clinical reports on the use of unfilled, neat PEEK cages are reported in the spine literature [48]. A retrospective study of neat PEEK cages used for circumferential lumbar fusion was reported by Rousseau et al. [48], who evaluated 57 consecutive patients after a mean follow-up of 5.7 years (range: 4–8 years). They observed fusion in 56 cases, but they were unable to maintain the desired curvature of the spine in 10 patients. They attributed the loss of spinal curvature correction to the order of implantation of the cages, which occurred after the spine was locked in place using a rigid posterior instrumentation system. The authors concluded that "lumbar circumferential arthrodesis using PEEK cages ... provided good clinical results and fusion rate."

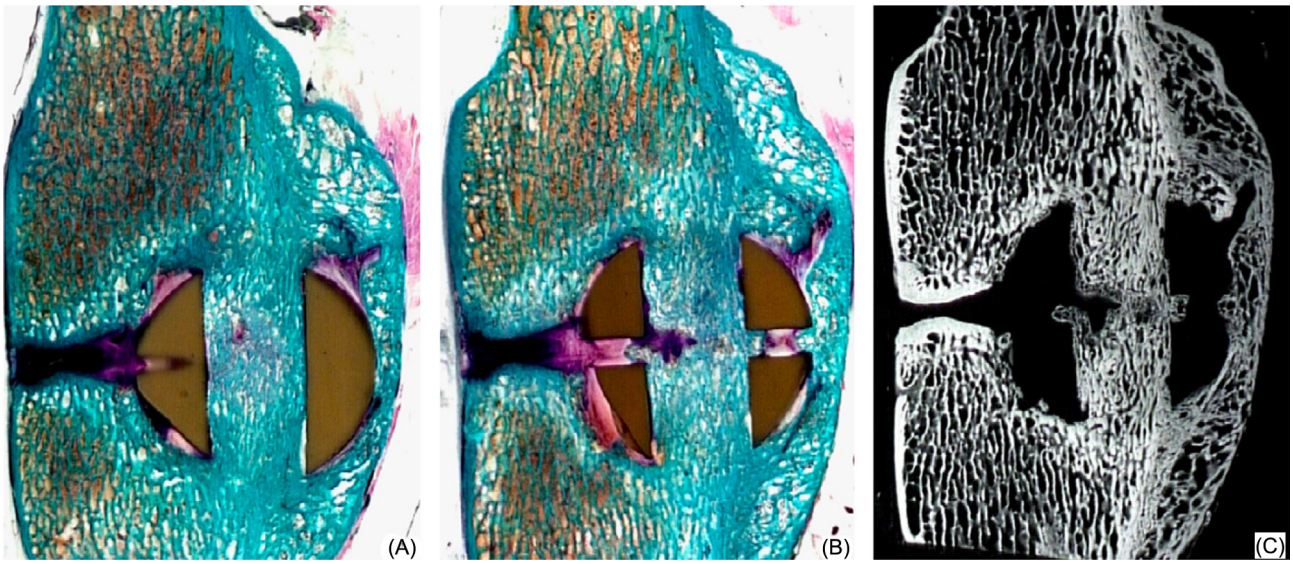



**Figure 10.13** Histological section of autograft-treated goats in a prospective study of threaded PEEK cages. (*Reproduced with permission from Ref. [40].*)

## 10.5 Clinical Diagnostic Imaging of PEEK Spinal Cages and Transpedicular Screws

The compatibility of PAEK polymers with clinical diagnostic imaging has been a major driver for the widespread adoption of this polymer family for spinal applications. Numerous studies have remarked upon the radiolucency of the neat and reinforced spinal implants fabricated from PEKEKK and PEEK, which have been found to greatly facilitate radiographic assessment of fusion in vivo [30–32,40,49]. Computed tomography (CT) generally provides a more reliable assessment of fusion than plane radiographs [49]. Figure 10.14 shows a representative lateral radiograph of a solid fusion in the lumbar spine through the fenestrations of a Brantigan cage.

CFR-PEEK is also used for transpedicular fusion in the cervical spine, where radiographic imaging is crucial to permit safe insertion of the devices using computer-assisted navigation with fluoroscopic guidance (Figure 10.15). The CFR-PEEK screws also contain 0.5% tantalum fibers to provide sufficient visualization using fluoroscopy [50]. In vitro studies have confirmed the feasibility of using CFR-PEEK screws for transpedicular fixation [50],



**Figure 10.14** Radiograph of a fused lumbar spinal segment using a Brantigan CFR-PEEK cage. (*Image courtesy of DePuy Spine.*)



**Figure 10.15** CFR-PEEK transpedicular screw and a radiograph of a fused cervical spinal segment. The screws are radiolucent because of the addition of 0.5% tantalum fibers. (*Images courtesy of Invibio.*)

but clinical results using these devices have not yet been reported in the literature.

## 10.6 Subsidence and Wear of PAEK Cages

Although most of the literature for PAEK biomaterials in the spine focuses on biomechanical stability or clinical outcomes such as fusion, relatively few studies provide insight into the unique limitations of the material when used in cage implants. The potential for some implant complications of PEEK cages, such as subsidence, are shared with metallic cages, and thus are not unique to the use of PEEK [51]. As with any load-bearing implant, wear and fracture are also concerns with PEEK spinal implants. Our experience with these implant-related complications is largely drawn from the Brantigan cage, because of its extensive clinical history. As of 1998, no implant-related complications of carbon fiber cages had been reported in the literature. Tullberg [52] described the fracture of a Brantigan cage in a case study of a failed fusion. Togawa et al. [53] studied biopsy samples from radiologically successful fusions with Ti alloy or Brantigan cages. Researchers noted particles of debris in biopsies from four of the five carbon fiber cages and in one of the four titanium cages, but no evidence of an inflammatory reaction to the particles was seen. The overall clinical significance of particulate debris and fracture is unclear for the Brantigan cage, given the strong evidence of long-term successful fusion using this design and similar findings to those in metal cages.

Nevertheless, due to the loading demands in the spine (especially in the lumbar region) and the competing design goals of strength and thin implant cross-sections to promote internal bone growth, the literature suggests that implant fracture and debris production could be considered important potential failure modes for PEEK biomaterials in the spine. Finite element analysis, in particular, has proven to be an effective tool to evaluate the fracture risk of PEEK implant designs in the spine [45]. The effect of wear debris on the spinal cord has been investigated in a rabbit model [54]. After injecting particle loads into the spinal canal of rabbits, researchers have concluded that PEEK particles appear "harmless" to the spinal cord.

## 10.7 Posterior Dynamic Stabilization Devices

The continued availability, radiolucency, and biomechanical success of PEEK in spinal fusion applications have stimulated interest in using the biomaterial in posterior dynamic stabilization devices. In contrast with fusion, which aims to stabilize a painful and diseased spinal unit by eliminating motion, the general aim of dynamic stabilization is to restrict motion and forces in directions that cause pain, while allowing motion in the asymptomatic directions [11,55]. Posterior dynamic stabilization devices were developed to treat the degenerated lumbar spine, but the precise indications for treatment are extremely broadly advocated in the literature, ranging from discogenic back pain,

spondylesthesis, and spinal stenosis [11,55]. Although the specific biomechanical mechanisms whereby posterior dynamic spinal devices are intended to function vary by design, the devices themselves fall into two general categories depending on whether they are implanted between the spinous processes or are installed as flexible members using pedicle screws. PEEK has been successfully incorporated into both types of spinal dynamic stabilization devices, most notably as a replacement for metallic interspinous process spacers (ISPs) or metallic fusion rods.

### 10.7.1 Interspinous Process Spacers

Several different designs of ISPs have been developed in recent years and are currently under clinical evaluation [11,55,56], but their gross biomechanical function in the spine appears to be fairly similar [57]. By distracting the posterior elements to insert the ISP, the posterior intervertebral disc is placed into flexion (or local kyphosis), the spinal canal is locally widened, and the pressure on the posterior disc is relieved [57]. Thus, ISPs are intended to stabilize the spine in extension, but provide little to no resistance to flexion, axial rotation, and lateral bending [57]. The posterior distraction created by implanting an ISP also relieves nerve root impingement, one of the causes of low back and leg pain.

ISPs were initially designed and fabricated from Ti alloy, serving as rigid or "static" spacers between the interspinous processes. Examples of rigid ISPs initially fabricated from Ti include the Wallis and X-STOP posterior dynamic stabilization systems [55,56]. As PEEK gained widespread exposure to the spine community through interbody fusion, ISP implant designers developed second-generation devices in which Ti was replaced with PEEK. For example, Senegas [58] noted that the developers of the Wallis devices converted their titanium interspinous component to PEEK in 2004. The St Francis developed X-STOP also converted from Ti alloy to PEEK-OPTIMA as a spacer for its Interspinous Process Decompression System (Figure 10.16) [11]. The X-STOP is currently produced by Medtronic Spinal and Biologics (Memphis, TN).

Among ISPs, the X-STOP has the most extensive track record in the clinical and biomechanical literature, as summarized recently by Kabir et al. [56], including a 2-year multicenter randomized control trial that was performed as an Investigational Device Exemption study in support of its Premarket Approval (PMA) application for

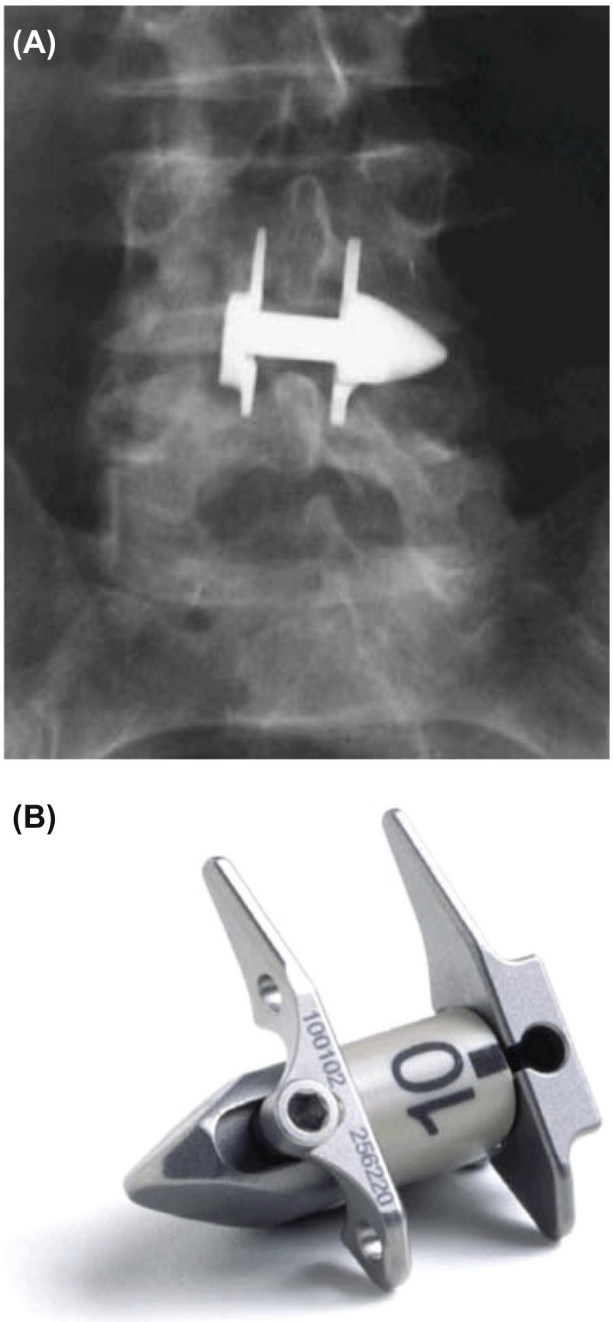



**Figure 10.16** Extension-limiting, interspinous device, incorporating a PEEK spacer, and an anterior–posterior radiograph showing the device implanted in the lumbar spine (X-STOP, Medtronic Spinal and Biologics, Sunnyvale, CA).

the FDA [59]. At the time of this writing, the X-STOP is the only FDA-approved posterior dynamic stabilization device that can be legally marketed as such in the United States. The approved indications for the X-STOP include treatment of a confirmed diagnosis of lumbar spinal stenosis in patients aged 50 years or older [60].

The designs of ISPs vary from rigid or static devices, like the X-STOP, to so-called "dynamic" designs that are capable of deformation during extension. Examples of dynamic ISPs include the Co-Flex device, fabricated from Ti alloy (Paradigm Spine), and the DIAM device, fabricated from silicone encased within a woven polyethylene terepthalate fiber jacket (DIAM: Medtronic Spinal and Biologics) [11,55,56]. Dynamic ISPs are currently under clinical evaluation in IDE studies for PMA applications for the US FDA [11,55,56].

As the use of ISPs has grown in the United States following FDA approval of the X-STOP in November 2005 [60], reports of complications, including early revision and spinous process fractures, are beginning to surface in the literature [61–63]. For example, Verhoof et al. [63] reported poor results when the X-STOP was implanted in patients with degenerative spondylolisthesis. Using a biplanar radiographic and CT examination protocol, Kim et al. [62] observed a higher spinous process fracture rate (22% of treated levels) than was previously reported (1%) in the randomized clinical trial that was performed for the FDA [59].

The recent reports of complications underscore the importance of better understanding the indications and contraindications for ISP implantation. At present, it still remains under clinical debate which symptomatic spine patients are most likely to obtain lasting pain relief from the targeted benefits of ISPs. Although patient selection criteria for ISP utilization are currently open to debate, the role of PEEK as a suitable biomaterial for this application remains unquestioned.

## *10.7.2 Pedicle-Based Posterior Stabilization (PEEK Rods)*

Pedicle-based systems represent another major design category for posterior dynamic stabilization systems. In this motion-preserving design paradigm, a flexible (or "semiflexible") element is substituted for the metallic rod that is fixed to the posterior spine by pedicle screws. The shift away from rigid instrumentation using metallic rods was driven by the desire to reduce increased stress on adjacent discs and facet joints that were thought to contribute to the degeneration of adjacent levels [64]. In addition, stress shielding of the vertebral column at the level of rigid instrumentation using metal rods was considered to result in decreased stimulus for bone growth during fusion. As a result, there has been growing interest in using flexible or semiflexible posterior fusion constructs to provide increased mobility and allow load sharing while stabilizing the spine [64–68].

### 10.7.2.1 Early Pedicle-Based Systems: Graf Ligaments and Dynesys

In the 1990s, flexible posterior stabilization systems emerged in Europe. One such device, referred to as the Graf ligament system, consisted of braided polypropylene (PP) bands connected to Ti pedicle screws [69]. Thus, the Graf ligament system was a tension-only device; the PP bands could not support compression. The long-term clinical results of this system were mixed [69–72], and Graf ligaments never gained widespread clinical acceptance, nor were these devices approved for use in the United States.

Another early pedicle-based design developed in the 1990s was the Dynesys system, consisting of polyethylene terepthalate (PET) cord and a cylindrical polycarbonate urethane bumper spanning Ti alloy pedicle screws. In the Dynesys design, the PET cord resists tension and the PCU bumper provides resistance to compressive and lateral loading. Initially commercialized by Sulzer Spine, Dynesys was acquired by Zimmer Spine (Minneapolis, MN) who currently markets the device. The Dynesys system has been widely used in Europe and the United States [73–76].

Dynesys became available on the US market in 2005 after receiving FDA clearance as an adjunct to fusion. However, this 510(k) clearance did not include nonfusion applications of Dynesys, which were included as a PMA application to the FDA. In November 2009, an FDA Panel convened to evaluate Zimmer Spine's PMA did not recommend approval for a variety of reasons, including concern over the proposed indications for use and complications related to screw loosening and breakage.

Since that time, several studies in the clinical literature have reported screw complications with Dynesys [77–80]. Examination of retrieved Dynesys explants has also demonstrated macroscopic creep of the PCU components (on average, 4.3° of angular deformation), and beyond 5 years of implantation evidence of surface degradation was observed on the PCU where it was exposed to bodily fluids [79]. Zimmer Spine developed a modification to Dynesys with the introduction of hydroxyapatite-coated screws. As of this writing, Dynesys has not been granted FDA approval as a dynamic stabilization device, and therefore cannot be legally marketed for nonfusion indications in the United States.

### 10.7.2.2 PEEK Rods

PEEK rods were developed for both fusion and nonfusion applications [64–68,81], but today only have FDA clearance as adjuncts to fusion. In contrast with the polymers previously considered for posterior spine implants, PEEK exhibits outstanding creep and degradation resistance under in vivo conditions. During cadaver-based biomechanical studies, PEEK rods have been shown to offer comparable stability as Ti rods [65–67]. In addition to radiolucency, the anticipated clinical benefits of PEEK rods are hypothesized to include improved load sharing with bone to promote fusion, as well as decreased stresses at the pedicle screw interface during bone healing [64,67].

PEEK rods are currently available for fusion in the United States from two major manufacturers (CD HORIZON LEGACY: Medtronic Spinal and Biologics, Memphis, TN; EXPEDIUM: DePuy Spine, Raynham, MA). The rods differ in terms of their PEEK formulation and design. EXPEDIUM rods are fabricated from image contrast grade PEEK and have a circular cross-section (Figure 10.17). The CD HORIZON LEGACY is fabricated from unfilled PEEK-OPTIMA and has an elliptical cross-section (Figure 10.18). The LEGACY rods have metallic end caps for visualization in radiographs. If the physician wants to directly visualize the rods, they can be detected using CT scans [82]. A description of the rationale, surgical technique, and case studies of the CD HORIZON LEGACY system have been published [64].



**Figure 10.17** PEEK rod system for posterior lumbar fusion (EXPEDIUM System: DePuy Spine, Rayhnam, MA).

Fatigue testing of PEEK rod systems is challenging because of their flexibility and notch sensitivity [83,84]. Care should be taken in the design of the tulip and set screw where the PEEK rod is connected to the pedicle screw. In addition to the tulip and set screw design, the screw tightening torque can also influence the fatigue behavior of PEEK rods [85]. The interaction between the tulip, set screw, and PEEK rod creates a geometric stress concentration and potential initiation site for fatigue failure [67].

Conventional standardized fatigue test methods (i.e., ASTM F1717 [86]) for metallic fusion rod systems need to be modified for flexible fusion constructs incorporating PEEK rods. Specifically, ASTM F1717 provides a basis for both static and dynamic characterization of fusion constructs, but the fatigue test methods specified in the standard recommend load-controlled testing based on static failure. Previous studies suggest that displacement control may be a more relevant method for testing semirigid fusion constructs incorporating PEEK rods [67,68]. Furthermore, while these studies have documented that a PEEK rod construct assembled with traditional titanium polyaxial pedicle screws can survive up to 5 million cycles of loading, the failure location for subendurance limit tests appears to be at the set screw–rod interface.

Thus, current test methods based on ASTM F1717 for PEEK rods appear to challenge the set screw–rod interface and provide limited insight

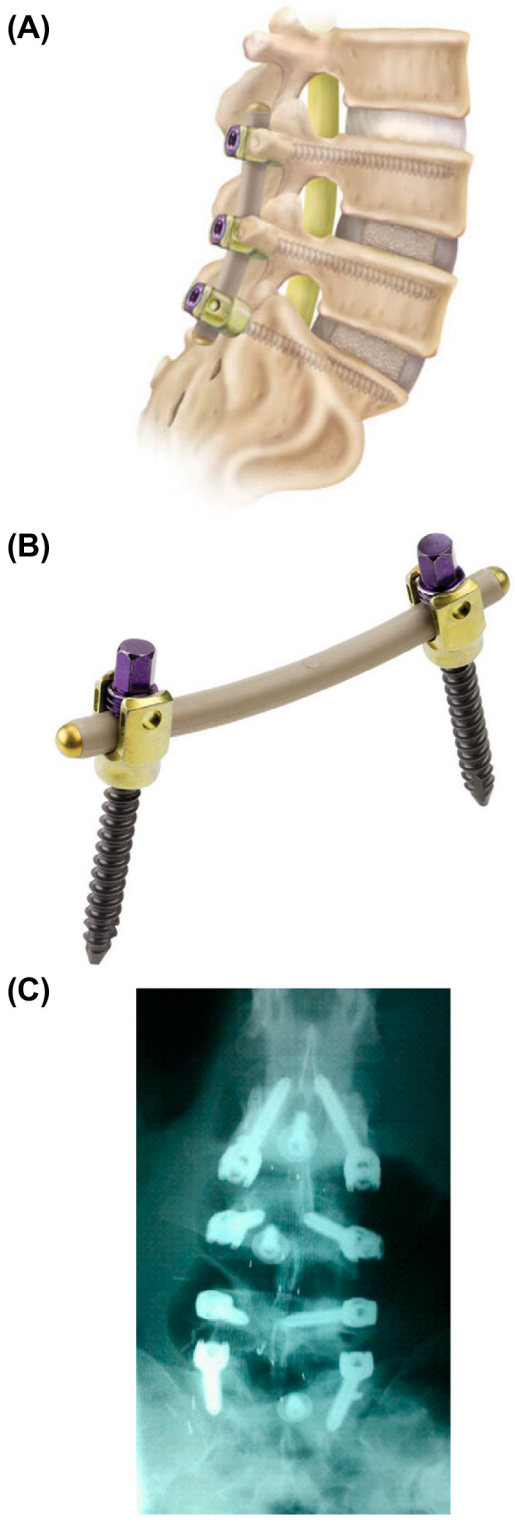



**Figure 10.18** (A, B) PEEK rod system for posterior lumbar fusion (CD HORIZON LEGACY System: Medtronic Spinal and Biologics, Memphis, TN). (C) Radiograph of a CD HORIZON LEGACY PEEK rod system, courtesy of Dr. Todd Lanman. Note that PEEK rods are radiolucent and not visible on X-ray, except for the metal end caps.

into the fatigue strength of the PEEK rods themselves. PEEK rod systems currently under development for spinal applications differ considerably in terms of the biomaterials employed (e.g., unfilled vs. radio-opaque grades of PEEK), implant dimensions, and rod cross-sectional geometry. Test method development is currently under way under the auspices of ASTM to create a general test method for evaluating the fatigue strength of PEEK rods that would allow for comparisons of the properties of the rod rather than the set screw−rod interface. By applying greater rotational constraint to the rods at the set screw−rod interface, it is possible to shift the fatigue failure location during the test away from the set screw to the center of the rod [87].

PEEK rod systems are currently evaluated not only in terms of their static and fatigue performance in standardized experimental protocols but also in more clinically relevant biomechanical models, such as cadaver spine and finite element models [65−68]. Both experimental and analytical techniques can thus be used to evaluate load sharing between a PEEK rod system and the thoracolumbar spine. These experimental and analytical techniques are also essential to better understand the ability of the PEEK implant system to resist motion and stabilize the spine.

Clinical data on the performance of PEEK rods are currently very limited [64,67,88], both for fusion and nonfusion applications. A conference poster at Eurospine in 2009 described a clinical series of 120 lumbar fusion patients, in which 60 patients were treated with Ti instrumentation and 60 with PEEK rods [88]. Both groups were only followed up for 6 months and generally comparable outcomes were observed in this preliminary investigation [88]. At present, detailed clinical data for PEEK in these novel and demanding spinal applications are not yet available in the peer-reviewed scientific literature and are eagerly anticipated by the spine implant community.

## 10.8 Cervical and Lumbar Artificial Discs

All-polymer artificial discs fabricated from PEEK biomaterials have attracted growing interest from the research community as a second-generation alternative to contemporary TDRs,

which are now most often fabricated from UHMWPE and CoCr alloys. Polymer bearings are considered promising for artificial discs due to a favorable combination of mechanical strength, wear resistance, radiolucency, biocompatibility, and manufacturability that is unique to the family of PEEK biomaterials [89,90]. Initial investigations of all-polymer PEEK bearings were performed for the lumbar spine [90–96], but recently the focus of scientific and commercial inquiry has shifted to cervical spine applications [89,97,98], which experience lower loads and are biomechanically less demanding. Mirroring the increased interest in all-polymer disc arthroplasty bearings, several basic science, pin-on-disc research studies of PEEK-on-PEEK articulations have also recently been completed [99,100]. In this section, we review the latest advances in all-polymer PEEK bearings for disc arthroplasty.

The first artificial disc fabricated entirely from unfilled, PEEK-OPTIMA LT1 was the NUBAC intradiscal arthroplasty device for the lumbar spine (Pioneer Surgical Technology, Marquette, MI) [90–96]. The design consists of a semiconstrained ball-and-socket joint and is intended to serve as an intradiscal, load-sharing device, analogous to a nucleus replacement (Figure 10.19), with an intact and a competent annulus fibrosus.

The preclinical mechanical testing for the NUBAC has been summarized in a review article [90], as well as in several conference abstracts [92–95]. The purpose of this battery of testing was to confirm the preclinical safety and effectiveness of the lumbar PEEK-on-PEEK artificial disc. Several wear studies of the NUBAC artificial disc have been conducted [93–95]. Initially, the NUBAC was tested for 40 million cycles with unidirectional motion; these tests generated the lowest amount of wear when later compared with multidirectional test conditions, but did not display the marked orientation softening behavior characteristic of UHMWPE tribology [94]. Researchers also conducted three multidirectional, 10 million cycle tests in accordance with ISO/DIS 18192-1, in which the loading was adjusted to account for the load sharing between the annulus and the nucleus in the lumbar spine. In one series of tests, the components were gamma irradiated in air with 200 kGy and accelerated aged in accordance with ASTM F2003 for 40 days [93,94]. ASTM F2003 was developed for gamma-irradiated UHMWPE the protocol is



**Figure 10.19** PEEK-on-PEEK Lumbar Nucleus Replacement (NUBAC: Pioneer Surgical Technology).

conducted at 70°C and is too low to influence PEEK. Regardless of the testing protocol, and including the standardized UHMWPE oxidative challenge, the average wear rates for the NUBAC experiments were relatively insensitive to changes in testing parameters, and fell within the range of 0.4–1.0 $mm^3$ per million cycles [94]. Overall, the wear values for the NUBAC were judged by the authors to be comparable with the rates for other metal-on-metal and metal-on-polymer artificial discs [101–103].

An international multicenter prospective clinical trial of the NUBAC is currently under way. At the 2009 meeting of the Spine Arthroplasty Society, it was announced that 225 NUBAC devices had been implanted since December 2004 [91]. The authors reported that "good pain relief and improvement in function" was achieved for up to 2 years [91]. At the time of publication, only 15 of the 225 devices (6.7%) had reached the 2-year milestone of the ongoing clinical study [91].

A cervical all-PEEK TDR, known as the NUNEC, was also developed by Pioneer Surgical Technology [97,98]. According to a recent conference abstract, the cervical TDR was tested for 10 million cycles in accordance with ASTM F2423, followed by an additional 10 million cycles in accordance with ISO 18192 [98]. The wear rates were found to be, on average, 0.3 $mm^3$ per million cycles for both test methods, and these rates were judged to be comparable with other cervical TDRs. The clinical results of the NUNEC are currently being evaluated by a pilot study. At the 2009 SAS annual meeting, clinical data were reported for 17 patients at 3–6 months of follow-up [97].

In the first full-length journal article dedicated to wear in PEEK cervical discs, researchers from Aesculap AG compared contemporary CoCr/UHMWPE couples with PEEK-OPTIMA LT1, CFR-PEEK (30% PAN fibers), and polyaryletherketone (PEK) all-polymer articulations [89]. The study by Grupp et al. [89] provides the most extensive and detailed peer-reviewed data available to date on the wear test methods, rates, and wear particle characteristics for three groups of all-polymer PEEK and PEK articulations intended for the cervical spine. All the polymer bearings used in this study were based on the design of the Activ-C cervical artificial disc. The UHMWPE was GUR 1020 gamma sterilized in nitrogen (30 kGy). Testing was conducted in accordance with ISO 18192. The PEEK and PEK bearings exhibited comparable wear rates to CoCr/UHMWPE, whereas the CFR-PEEK bearings had significantly lower wear rates (Figure 10.20). The size and morphology of the PEEK and PEK wear particles fell within the range previously observed for CoCr/UHMWPE articulations.

Considered together, recent studies suggest that PEEK biomaterials provide new design opportunities for all-polymer disc arthroplasties. Both cervical and lumbar PEEK artificial discs are currently in clinical trials; however, these studies are still in progress, and final data have yet to be published in peer-reviewed journals. Although the first designs in clinical use were fabricated from unfilled PEEK, there is not yet consensus on the optimal PEEK biomaterial for all-polymer disc bearings. Basic science pin-on-disc studies [99,100] suggest that all polymer CFR-PEEK articulations fabricated with PAN carbon fibers generate less wear than unfilled PEEK articulations and these findings are corroborated by recent cervical TDR tests conducted in a multidirectional spine wear simulator (Figure 10.20) [89]. Similarly, whether evaluated on a pin-on-disc experiment or in a spine wear simulator (Figure 10.20) [89], all-polymer PEK bearings appear to offer relatively modest improvements relative to PEEK. It remains to be seen if all-polymer PEEK bearing performance is design specific, or whether all-polymer disc replacements are equally well suited to the cervical and lumbar spine. Although scientific debate is sure to continue on these topics for years to come, currently available data would suggest that PEEK biomaterials are strong candidates for disc arthroplasty applications.

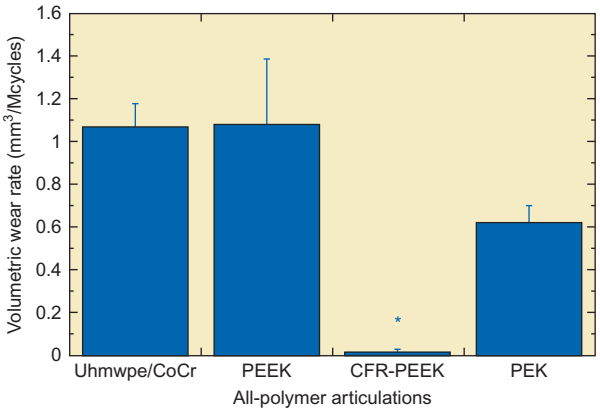



**Figure 10.20** Comparison of volumetric wear rates for all-polymer PEEK and PEK articulations with conventional, gamma nitrogen-sterilized UHMWPE/CoCr cervical TDRs. Adapted from Ref. [89]. *CFR-PEEK bearings were significantly lower than the other cervical disc combinations tested ($p < 0.05$).

## 10.9 Summary

In summary, PEEK biomaterials have over a decade and a half of successful clinical history in load-sharing, fusion applications in the spine. Thus, the clinical history of PEEK biomaterials is heavily weighted by the cage experience from the spine fusion literature. PEEK is playing a growing role in spine implants for a combination of reasons, including the clinical need for improved treatments for operative treatment of persistent low back pain. The radiolucency of PEEK is another key advantage over metals, allowing visualization of the critical soft tissue structures, such as the spinal cord, adjacent to the implant components. Finally, the versatility of PEEK biomaterials allows for spinal devices to be designed with a tailored range of stiffnesses, depending on rigidity desired for a particular spine implant application.

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# 11 Microbubble Applications in Biomedicine

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## 11.1 Introduction

Microbubbles are small (<10 μm), gas-containing spheres with a lipid, protein, or polymer shell [1] (Figure 11.1). Microbubbles provide a means for contrast-enhanced ultrasound imaging, targeted drug delivery, and other diagnostic and therapeutic applications.

The developmental history of microbubbles as ultrasound contrast agents is summarized in Figure 11.2. The first indirect mention of the use of microbubbles in medical diagnostics was in 1968, when Gramiak and Shah demonstrated that intracardiac injections of saline-containing small air bubbles significantly increased ultrasound contrast and improved aortic delineation [2]. Given the dissolution time of nonencapsulated air bubbles (dependent on bubble size, but generally a few seconds), the next step was to create a vehicle that would entrap gas and offer enough stability for prolonged ultrasound exposure. In 1984, Feinstein et al. showed that a more stable microbubble could be formed using sonication of various sugar derivatives as a technique to entrap gas within a solid-state shell [3]. From this concept, microbubbles were developed to have protein, polymer, or lipid shells. Variations on the microbubble construction/design increased its utility in the world of ultrasound imaging. In the early 1990s, it was discovered that microbubbles could be targeted by taking advantage of ligand/receptor interactions [4]. By the year 2000, microbubbles had proven to be not only useful contrast agents, but also powerful vehicles for targeted drug and gene delivery. Microbubbles were also proven to have therapeutic applications in thrombus treatment [5]. Currently, the first clinical trials are under way to evaluate the efficacy of VEGFR2-targeted microbubbles (BR55; Bracco, Milan, Italy) in monitoring anti-angiogenic effects of prostate cancer treatment [6].

Microbubbles serve the purpose of providing a relatively inexpensive, bio-inert, and metabolically inert method for increasing ultrasound contrast [7,8]. Both the micron-scale size and the gas core

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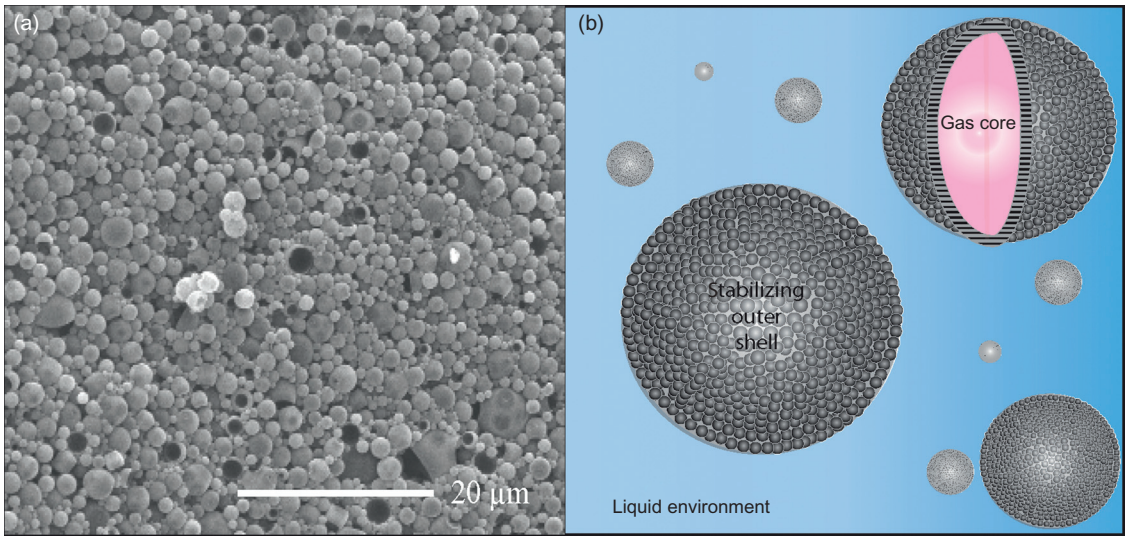



**Figure 11.1** Microbubble structure and components. (a) SEM image of polymer-shell microbubbles (PLA) diameter 1−10 μm. (b) The basic structure of microbubbles—outer shell, gas core, liquid environment. *(Courtesy: Dr. Margaret Wheatley, PhD, for providing the SEM image.)*

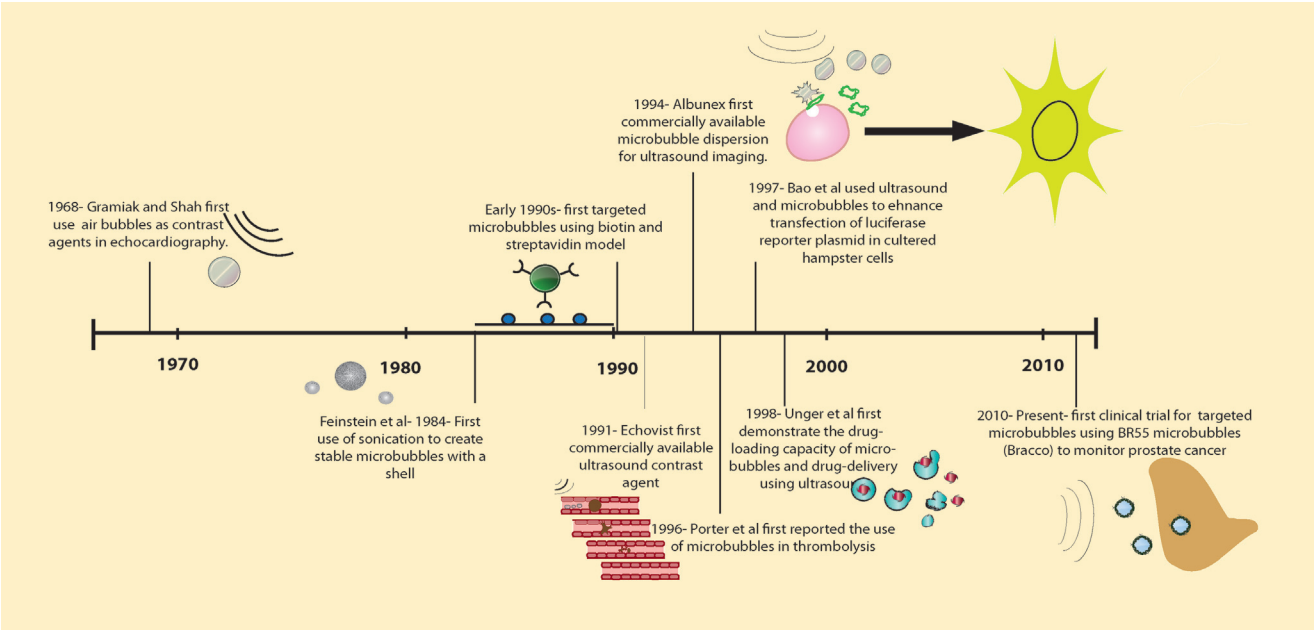



**Figure 11.2** Microbubble timeline.

of the microbubbles are key features for their utility in ultrasound imaging. Firstly, microbubbles are small enough to traverse the human circulatory system without causing blockage, or producing physiologic aberrations, but are generally too large to escape out of the vasculature [3]. Second, the difference between the acoustic properties of the gas core of the microbubble and the surrounding medium allows for clinicians to more effectively visualize the cardiovascular system [9].

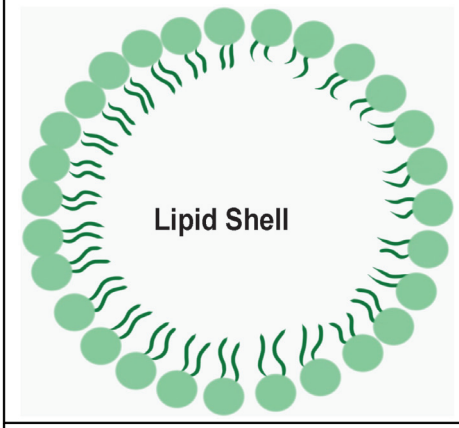
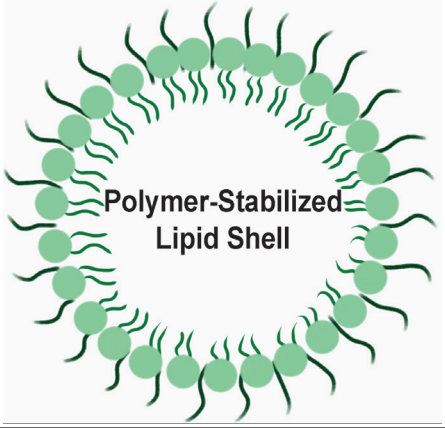
Microbubbles in solution provide a substantial mismatch in acoustic impedance, which is highly conducive for providing reflection in ultrasound imaging. Soft tissue is nearly homogeneous in

acoustic impedance when compared to a gas-phase/filled contrast agent. Ultrasound scanners use a transducer to emit sound energy as well as to collect returning signal [10]. As the sound waves reach the microbubble surface, the microbubble undergoes compression and rarefaction, generating both linear and nonlinear signals which return to the transducer and are processed to form ultrasound images [11].

Microbubbles have been fabricated using several individual gases and may have protein, lipid, surfactant, or polymer shells that are thin (5–10 nm) or thick (up to 250 nm). The microbubble shell provides stability, but also dampens the oscillatory motions of the microbubble when activated. Furthermore, microbubbles can have modified extruding surfaces such as polyethylene glycol (PEG) brushes and ligand attachments [12]. Table 11.1 gives the various microbubble shell types along with the potential benefits each modification imparts.

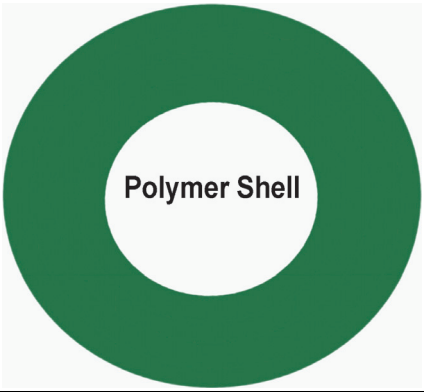
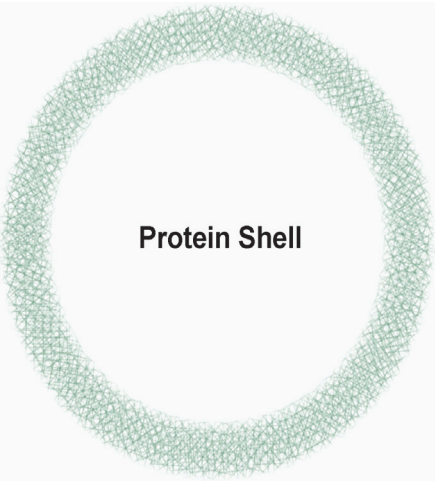
Clinically, microbubbles are administered via intravenous injection [3]. Once they enter the bloodstream, they can circulate without disrupting normal blood flow. The residence time of microbubbles in circulation is less than 1 h as the shells of the microbubbles are typically removed from the bloodstream by the liver and spleen, while the gas is exhaled [1]. The incorporation of high molecular weight perfluorocarbon gases in microbubbles has ensured that gas exchange is negligible *in vivo* when compared to clearance time of the microbubble injection [18]. Once in circulation, microbubbles may be either imaged using low-power ultrasound (generally with mechanical indexes $< 0.4$) or burst using localized higher power ultrasound (generally with mechanical indexes $> 0.7$) to facilitate microbubble

**Table 11.1** Table of Microbubble Structure and Function/Use

| Microbubble Type | Description |
|---|---|
|  | Phospholipids, such as phosphatidylethanolamine, spontaneously self-assemble into a spherical monolayer, wherein the hydrophilic polar head groups are oriented towards the liquid environment and the hydrophobic acyl chains face the gaseous core of the microbubble. Lipid-shelled microbubbles are highly echogenic due to the flexibility of the lipid shell, which allows the microbubbles to resonate under ultrasound stimulation with minimal damping [13]. |
|  | Lipid shells are often stabilized by a thick shell of polymer. A polymer brush, normally polyethylene glycol (PEG), lends rigidity to the microbubble, however it reduces the echogenicity [14]. PEG coatings have also been shown to increase targeting efficacy and decrease complement activation *in vivo* [15]. |

(*Continued*)

**Table 11.1** Table of Microbubble Structure and Function/Use—*Cont'd*

| Microbubble Type | Description |
|---|---|
|  | Polymer microbubbles can be made of synthetic polymer such as PLGA, or naturally occurring polymers such as sugar derivatives. At a lower ultrasound pressure intensity, the polymer microbubble has a reduced oscillatory activity when compared with its lipid and albumin counterparts. At higher ultrasound pressure, the polymeric shell will form cracks and disassemble [16]. |
|  | Albumin-coated microbubbles were the first commercially available micro-bubbles (Albunex™, GE Healthcare). The albumin shell is stabilized by disulfide bonds between cystein residues in the shell [17]. |

destruction-based imaging modes or local drug/gene delivery [19].

One particular advantage of microbubbles as a contrast and drug-delivery agent is that microbubbles are highly shelf-stable when the gas headspace is maintained and are manufactured at a relatively low cost and in high quantities [20,21]. Industry has taken advantage of microbubble technologies, making them commercially available and readily accessible by clinicians and researchers alike. Table 11.2 lists current commercially available ultrasound contrast agents which are approved for human use, particularly in left ventricular opacification (LVO) for the diagnosis of coronary artery disease.

It should be noted that the safety of microbubble administration has been questioned at several points in the short history of their clinical use. The bursting of microbubbles has emerged as a double-edged sword. On the one hand, microbubble cavitation is central to microbubble drug-delivery applications. On the other hand, it is known that microbubble destruction as a result of high-powered ultrasound can cause rupturing of microvessel walls and subsequent extravasation of the blood [7]. Though rare, serious adverse reactions generally involve anaphylaxis [22]. A post market study of SonoVue by the European Medicines Agency revealed a nonfatal reaction rate of 0.012% and a fatal reaction rate of 0.002% [22]. Thus, microbubble use in echocardiography was branded as causative for rarely observed cardiopulmonary and hypersensitivity reactions, garnering a Food and Drug Administration (FDA) black box warning. Main et al. demonstrate that it is important to put these rates of adverse reaction in perspective, pointing out the mortality rates of coronary angiography and exercise treadmill testing are 0.1% and 0.04%,

**Table 11.2** Table of Commercially Available Microbubble Preparations

| Microbubble Preparation | Microbubble Type | Details on Use |
|---|---|---|
| Definity (Lantheus Medical Imaging) | Phospholipid Shell octofluoropropane-filled | Available worldwide. Approved for use in the USA (cardiac imaging) |
| Sonazoid (GE healthcare) | Phospholipid Shell perfluorobutane-filled | Approved and marketed in Japan, South Korea, Taiwan, and China |
| Sonovue (Bracco) | Phospholipid Shell sulfur hexafluoride-filled | Approved and marketed in European countries, China, South Korea, Hong Kong, and Singapore. |
| Optison (GE healthcare) | Albumin Shell perfluorobutane-filled | Approved and marketed in European countries. Approved for use in the USA (cardiac imaging) |

respectively [23]. This safety issue has also been well addressed by Blomley et al., who point out that the increased enhancement in endocardial border delineation and cardiac perfusion well outweighs the minor side effects (mainly temporary headache and altered sensation at the injection site in roughly 2% of patients) [24]. As a result of the outcry from cardiologists, radiologists, and researchers, as well as the publication of numerous large clinical studies showing both the benefits and safety of microbubbles, the FDA's warning has since been softened [23–25].

In this chapter, microbubble use in medical diagnostics are briefly reviewed as well as additional emerging roles in surface targeting, drug and gene delivery, pressure estimation, and other future potential clinical applications.

## 11.2 Microbubbles for Ultrasound Imaging

### 11.2.1 Interactions of Microbubbles with Ultrasound

Clinical ultrasound imaging continues to increase in popularity due to its superior safety (it uses non-ionizing radiation), real-time imaging, cost, and portability relative to other imaging modalities [26]. It is estimated that there are 75,000 ultrasound machines compared to only 5000 magnetic resonance imaging (MRI) machines in the United States and this disparity is expected to increase over time [27]. During an ultrasound scan, acoustic waves are transmitted through the body, some of which are reflected back to the transducer due to differences in acoustic impedance. Reflected waves are then used to generate images. Acoustic impedance ($z$) is defined as:

$$z = \rho \times c, \tag{11.1}$$

where $\rho$ is the density of the medium (kg/m$^3$) and $c$ is the speed of sound in the medium (m/s). The degree of reflection an ultrasound wave undergoes when passing from one medium to a second medium is defined by the reflection coefficient ($R$) as:

$$R = \frac{z_2 - z_1}{z_2 + z_1}, \tag{11.2}$$

where $R = 1$ denotes 100% wave reflection, while $R = 0$ denotes 100% transmission of the wave.

The utility of microbubbles in ultrasound imaging was first discovered incidentally by Gramiak and Shah in 1968 [2]. While injecting indocyanine for an X-ray study of the aorta under ultrasound guidance, the group observed that the small gas bubbles at the syringe tip produced noticeable ultrasound enhancement. Later it was discovered that the gas within the microbubbles provided a substantial impedance mismatch between the blood and gas interface, reflecting the ultrasound waves. For air at atmospheric pressure and 20°C [28]:

$$z_{\text{air}} = 415\ \text{Pa}\cdot\text{s/m} \tag{11.3}$$

while for distilled water (similar to blood and tissue) at 1 atm and 20°C,

$$z_{\text{water}} = 1.48 \times 10^6\ \text{Pa}\cdot\text{s/m} \tag{11.4}$$

Substituting these impedance values into equation (11.2) results in $R \approx 1$, explaining the near

perfect reflection of the acoustic wave by gas within the microbubble. Additionally, microbubble scattering or reflection can be categorized by the effective scattering cross section ($\sigma$) of the microbubble. The scattering cross section reflects the scattered ultrasound intensity related to the incident intensity and distance from the transducer, and can be calculated as:

$$\sigma = \frac{4\pi}{9} K^4 r^6 \left[ \left( \frac{\kappa_s - \kappa_f}{\kappa_f} \right)^2 + \frac{1}{3} \left( \frac{3(\rho_s - \rho_f)}{2(\rho_s + \rho_f)} \right)^2 \right] \tag{11.5}$$

where $K$ is the wave number, $r$ is the bubble radius, $\kappa_s$ is the compressibility of the scatterer, $\kappa_f$ is the compressibility of the fluid, $\rho_s$ is the density of the scatterer, and $\rho_f$ is the density of the fluid [29–31]. It is important to note from the bracketed portion of this equation that while the density (and thus impedance) portion of this term plays a central role in the cross scattering area, the difference in compressibilities is more than 10,000 times larger that of the difference in densities [32]. Thus, while the impedance mismatch is important for providing a reflective surface for the ultrasound wave, the differences in compressibility are what truly account for microbubbles having effective backscattering radii several orders of magnitude larger than the bubble itself [31].

As the acoustic wave propagates through the gas microbubble, the gas within the microbubble expands and contracts according to the pressure rarefaction and compression of the sound wave as shown in Figure 11.3. These oscillations result in both a linear and nonlinear response, as shown in the frequency spectrum from an ultrasound contrast agent (Targestar-B; TargesonInc, San Diego, CA) insonated at 4 MHz presented below in Figure 11.4. Note that the strongest frequency response occurs at the fundamental insonation frequency ($f_0 = 4$ MHz), while there are also significant signal components at the subharmonic

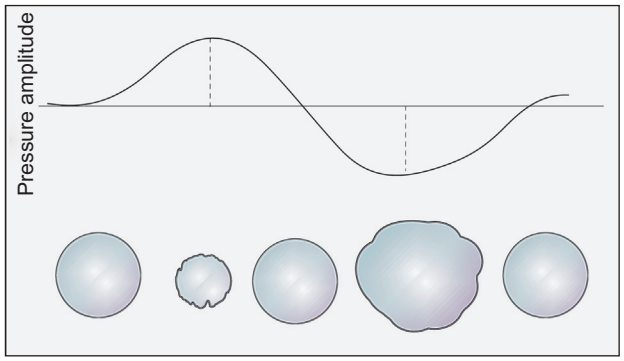



**Figure 11.3** Microbubble compression and rarefaction. Illustration of a microbubble undergoing expansion and contraction during the pressure rarefaction and compression phases of the ultrasound pulse.

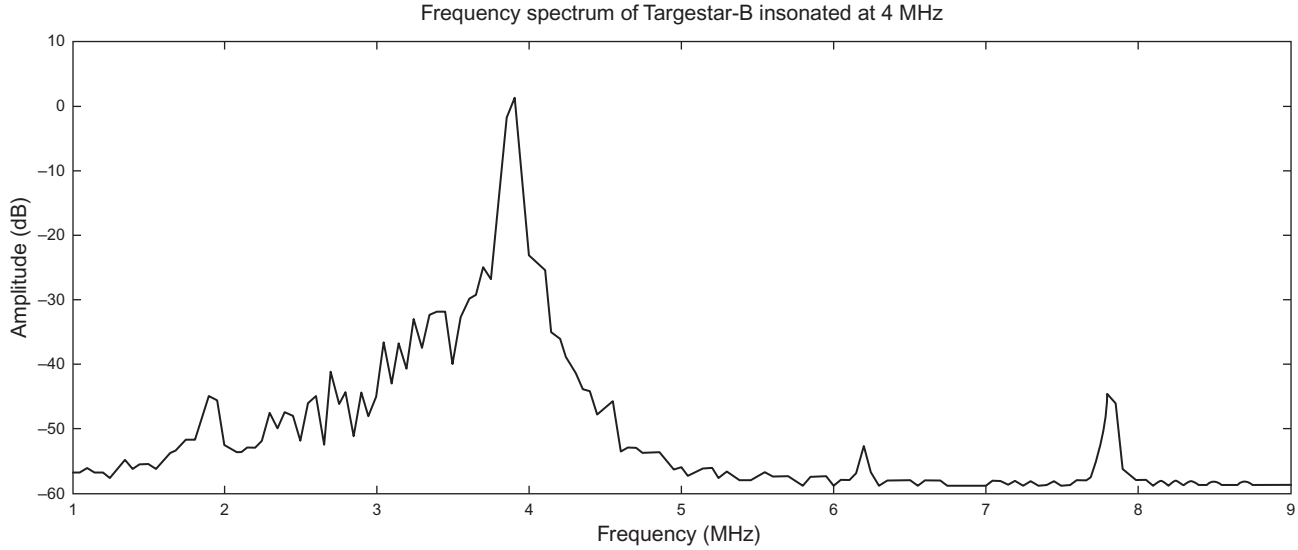



**Figure 11.4** Frequency response of the ultrasound contrast agent Targestar-B (Targeson Inc., San Diego, CA). Microbubbles insonated at 4 MHz show a nonlinear response of the microbubble population.

($f_0/2 = 2$ MHz), higher harmonics ($n \cdot f_0$; 8 MHz), and ultraharmonic frequencies ($((2n-1)/2 \cdot f_0$, $n > 1$; 6 MHz). This nonlinearity forms the basis for microbubble-specific imaging modes.

### 11.2.2 Microbubble-Specific Ultrasound Modes

Microbubbles were initially used with grayscale B-mode ultrasound (i.e., a linear imaging mode) to improve contrast and contour detection [33]. However, these improvements were incremental due to a low detection sensitivity and blood volume relative to tissue [32].

The addition of microbubbles to Doppler imaging (which detects changes in relative movement, generally blood) has proven more advantageous due to this mode's ability to detect microvasculature and has been used for the imaging of a variety of clinical applications [32–37]. In conjunction with Doppler ultrasound, microbubbles are frequently used in echocardiography in the diagnosis and interpretation of cardiac defects such as hypertrophic cardiomyopathy, chest-wall deformities, coronary artery disease, and for the evaluation of heart valves [38–41]. However, the use of contrast microbubbles with Doppler is also associated with significant imaging artifacts such as "blooming" and shadowing of signal below areas of contrast which make smaller, deeper vessels difficult to image [41,42].

Specific microbubble imaging modes have been and are currently being developed to exploit the nonlinearity of these agents. Harmonic imaging relies on the ability of microbubbles to reflect signal at twice the insonation frequency by removing all other frequency components. Additionally, pulse inversion and amplitude modulations can be applied to transmit multiple, inverted pulses which are subsequently summed to further remove linear components and designed to specifically make the microbubbles resonate [43]. Contrast packages involving some variation of these techniques are now commercially available on most scanners and have been shown useful for a variety of applications [44–49].

Despite these advances, tissue itself has also been shown to produce lower amplitude harmonic echoes due to the distortion of the ultrasound wave as it propagates through the tissue, thus limiting the ability of the mode to isolate microbubble signals [50,44]. One emerging attractive alternative to harmonic imaging is subharmonic imaging due to a lack of subharmonic generation in tissue [50]. While still in a research phase, subharmonic imaging has now been implemented on modified commercial scanners [51–55] and used for numerous imaging applications [51,54–58]. Additionally this mode has been implemented in 3D to provide complete visualization of a vascular region [56,59]. Figure 11.5 shows an example of a canine kidney during open abdomen scanning with 3D subharmonic and harmonic imaging [54]. Note the improved levels of tissue suppression in subharmonic mode (evident before contrast arrival at baseline) and the improved visualization of the renal vasculature that this tissue suppression offers relative to the harmonic case. While this mode is still in research phases, this or other improved contrast imaging modes may further improve the utility of microbubbles in contrast ultrasound imaging.

A final class of microbubble imaging modes involves the destruction (using high-intensity ultrasound pulses) of the agent, followed by imaging of the reperfusion into the vasculature. These techniques, such as contrast burst imaging and microflow imaging, have been used to image microvasculature in a variety of applications, particularly in the estimation of blood flow perfusion [60–63] and have also been well reviewed in the literature [32,64].

### 11.2.3 Current Clinical Uses of Microbubbles

The full extent of microbubbles in clinical imaging (contrast-enhanced ultrasound) is beyond the scope of this chapter but has been well reviewed in the literature [32,65–68]. Additionally, ultrasound and echocardiography professional societies also routinely publish consensus statements on clinical guidelines for the use of ultrasound contrast agents [69–71].

Within the United States, microbubbles are only approved by the FDA for use in echocardiography. Suggested uses include improved visualization for the assessment of cardiac structure and function (particularly in hard to image patients), improved accuracy and decreased variability in stress echocardiography, to assist in the detection and classification of intracardiac masses, and to enhance spectral Doppler signals for the evaluation of diastolic and valvular function [69]. The use of these agents has been demonstrated in large-scale clinical trials. For example, a Phase III study of Optison for left

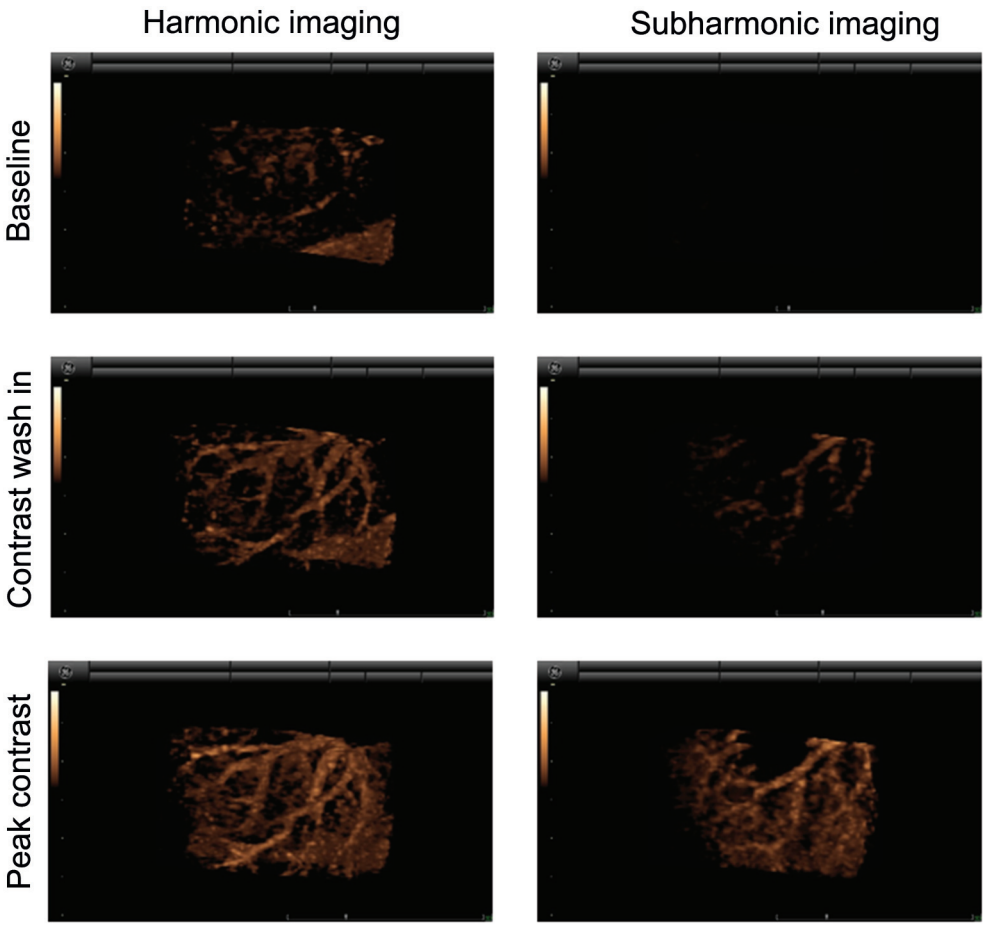



**Figure 11.5** Ultrasound image of a canine kidney. Example images obtained from a canine kidney during baseline (top row) and contrast arrivals (bottom row) using 4D harmonic imaging (left column) and 4D subharmonic imaging (right column).

ventricular endocardial border delineation was able to convert 74% of non-diagnostic ultrasound scans to diagnostic, thus providing potentially lifesaving information to physicians [72]. While the initial FDA black box warnings discussed in the introduction section severely dampened the usage of contrast-enhanced echocardiography, usage has increased with the subsequent clarification and abundant published safety studies, and is expected to further increase in the future [73–77].

Microbubble-based ultrasound contrast applications are approved for general vascular imaging in most countries outside the United States and used frequently in abdominal imaging, and clinical guidelines are available [70,71]. The real-time nature of contrast imaging allows detection of microbubble perfusion during the vascular phase within the liver. As a result, one of the largest abdominal applications is for the detection and characterization of focal liver lesions [70,78]. Large clinical trials have shown these techniques to correlate well with contrast-enhanced computed tomography (CT) [32,47,70,79] and this has become the clinical standard of care in many countries. As FDA approval extends to other applications of contrast-enhanced ultrasound, this technology will become a standard clinical tool for both therapeutics and diagnostic applications.

## 11.3 Targeted Microbubbles

Once microbubbles have entered the circulatory system, they can freely circulate throughout the vasculature with a residence time on the order of 10 min [80] and will typically accumulate in the liver and spleen [1]. Clinically, ultrasound is used on freely circulating microbubbles for contrast

imaging purposes (as discussed in the imaging section above) where visualizing physiology is the only objective. In other cases, it might be necessary to direct microbubble accumulation toward a certain pathological manifestation. Once microbubbles have been targeted to the affected area, ultrasound can be used to better image the delineated area. Methods of microbubble targeting include ligand/receptor "pairing" and magnetic guidance [4,81]. Due to the size of the microbubbles, potential targets are currently limited to those expressed within the vasculature. However, the advent of nanobubbles (discussed later in the chapter) may further diversify these targets as smaller bubbles are able to extravasate out of the blood supply.

### 11.3.1 Ligand/Receptor Targeting

The most common method of targeting microbubbles is through passive targeting, either through ligand-receptor specificity or through organ-specific accumulation.

One of the first reports of targeted microbubbles used biotinylated microbubbles to target a streptavidin-coated surface [4]. Another early study by Unger et al. explored the *in vitro* targeting of microbubbles using a thrombus-specific hexapeptide coupled to microbubbles and showed improved microbubble targeting to blood clots *in vitro* [21,82]. Figure 11.6 depicts the targeting of a biotinylated microbubble onto a streptavidin-coated agar surface. From these experiments, it became apparent that an antigen-coated surface can be targeted and subsequently imaged with increased microbubble accumulation. It therefore follows that disease states such as inflammation and cancer can potentially be targeted using ligand-conjugated microbubbles.

For example, microbubbles can be targeted to specific inflamed areas within blood vessels allowing for visualization of the diseased state. Most notably, microbubbles have been shown to be able to target atherosclerotic disease markers, such as VCAM-1 using an anti-VCAM-1 antibody that is conjugated to the surface of the microbubble [6]. Once microbubbles have honed in on the inflamed area, ultrasound imaging will reveal the highlighted atherosclerotic plaque. Figure 11.7 illustrates the targeting of microbubbles to atherosclerotic lesions or plaques within the vasculature.

The targeting of neoplasia using microbubbles has become an area of interest in recent years. Pysz et al. developed microbubbles to target human kinase insert domain receptors and/or VEGFR2 receptors using microbubbles conjugated with VEGF [83]. Generic-targeted microbubbles (mainly for angiogenesis or atherosclerosis markers) or kits for preparing microbubbles for specific targets are now commercially available from several companies for research purposes in animals. Recently, the first clinical trial with targeted microbubbles BR55 (Bracco), a VEGFR2-targeted microbubble (which does not use an avidin–biotin linkage, making it suitable for

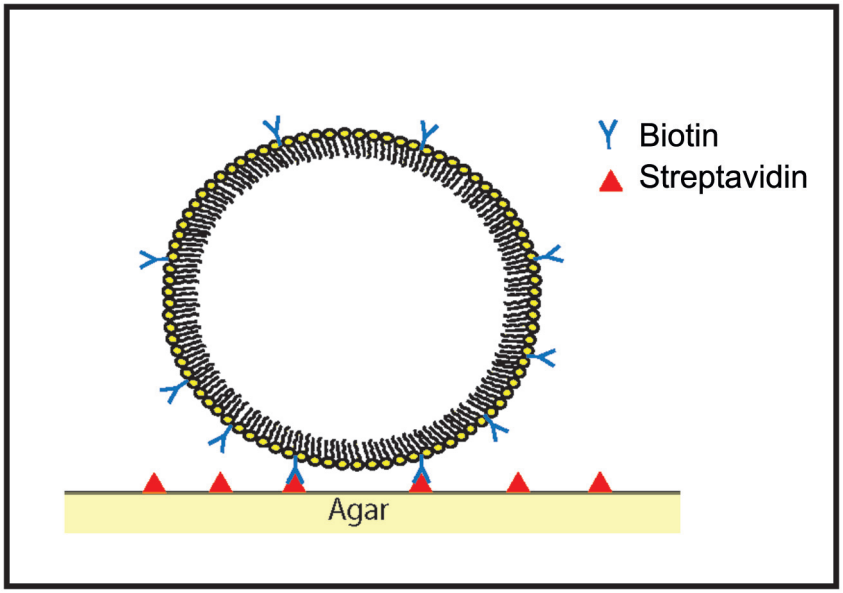



**Figure 11.6** Biotinylated microbubble targeted to a streptavidin-coated surface.

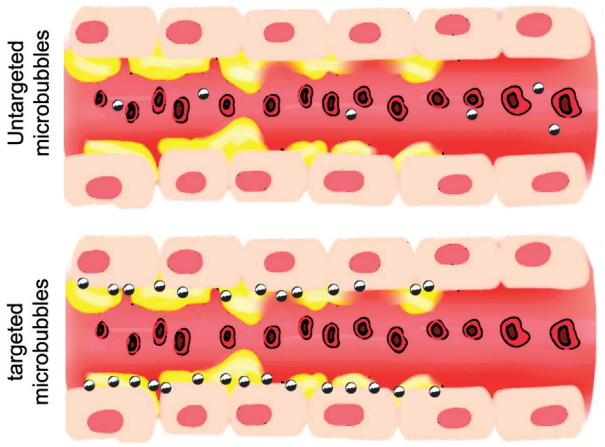



**Figure 11.7** Targeting atherosclerosis with microbubbles. Endothelial cells in atherosclerotic areas express up-regulated levels of adhesion molecules such as P-selectin, E-selectin $\alpha 5\beta 3$ integrin, and V-CAM. Targeting microbubbles to these markers allows for enhanced microbubble accumulation as well as identification of specific disease markers.

human use), was employed to evaluate angiogenesis in prostate cancer [6].

Another form of passive targeting is based on the inherent characteristic of microbubbles, wherein they accumulate in the liver and spleen. When those organs are the desired targets for microbubble-assisted drug delivery or contrast-enhanced microbubble imaging, microbubbles can simply be administered and left to self-congregate prior to insonation with low-power imaging [1]. In the liver, contrast-enhanced ultrasound can be particularly useful for the evaluation of hepatic portal vein thrombus, facilitating differentiation between benign and malignant thrombosis [84]. The splenospecific properties of microbubbles also allow for identification of splenic infarcts and the imaging of splenic abscesses and tumors [85].

These methods of passive targeting provide methods of delineating disease processes that may otherwise not be easily detected and/or evaluated.

### 11.3.2 Identification and Quantification of Microbubble Attachment

Identifying areas of successful microbubble targeting and accumulation typically involves a "flushing" period wherein unadhered microbubbles are allowed to exit the circulation (generally over 5–10 min). Additionally, before and after, images can be processed in order to determine microbubble attachment following ultrasound-mediated bursting of microbubbles.

For a real-time approach with fewer artifacts, Needles et al. used subharmonic imaging (to identify microbubbles while suppressing tissue) combined with an interframe filtering technique to identify stationary bubbles [55]. Groups have also investigated both the effects of attachment on the acoustic properties of the microbubbles and the strength of these attachments. Attached microbubbles can be characterized *in vitro* under high flow and shear stress, although the strength of adherence is largely related to the ligand receptor pair binding kinetics as well as ligand/receptor concentration [86].

### 11.3.3 Active Targeting

One method for improving microbubble targeting is through active targeting. Microbubble adhesion can be further improved using acoustic radiation forces, whereby the ultrasound beam pushes microbubbles toward the vasculature wall resulting in more ligand–target interaction [87]. These forces are useful for improving microbubble accumulation, but may also confound identification of receptor attachment.

The use of an external magnetic field has also been shown to redirect modified microbubbles to a desired region in tissues proximal to a magnet. In 2008, Kaminski et al. showed that microbubbles loaded with magnetic nanoparticles can be localized using magnetic guidance in a mouse model [88]. More recently, Wu et al. demonstrated the synergistic effects of targeting when magnetic guidance was used in conjunction with ligand targeting of microbubbles in a mouse model [89].

## 11.4 Microbubbles in Drug and Gene Delivery

Microbubble-assisted drug and gene delivery has been explored for over 20 years. This research has focused on improving efficacy while also limiting systemic side effects. These approaches utilize the biomechanical effects of both the microbubble as they interact with the ultrasound beam and the physical structure of the agent itself, which allows

encapsulation or attachment as a means of drug transport. Microbubble-aided drug delivery has been extensively reviewed in the literature [6,90–92]. In this section, we present a small sample of previous and ongoing research efforts in microbubble-aided drug delivery. These samples are categorized by microbubble-aided delivery of free (unattached) therapeutics or microbubble-transported (attached or encapsulated) drug delivery.

### 11.4.1 Microbubble-Assisted Delivery of Free Drug

Ultrasound by itself has already been proven as an effective aid for drug delivery through increased drug retention at the tumor site and transient membrane permeability [93]. For example, studies have shown systemic administration of doxorubicin combined with low-intensity ultrasound (0.25–2 W/cm$^2$) leads to increased drug efficacy *in vivo* [93,94]. The benefits of ultrasound with drug delivery appear to become even more significant in the presence of microbubbles. Several studies have shown that peptides, genes, and other small molecules can be delivered out of the vasculature and into the intracellular space with the help of ultrasound and microbubble cavitation, and that this phenomenon also transiently increases cell permeability [95–97].

Microbubble cavitation can be classified as either stable (repeatable oscillations during insonation) or inertial, in which the bubble violently collapses [98]. Inertial cavitation of a gas bubble produces brief (<1 ms) shock waves, and extreme localized temperatures and pressures (>5000°C and 500 atm) [99]. Linear oscillations of microbubbles during stable cavitation have been shown to be strong enough to rupture lipid-based cellular membranes [97]. Using high-speed imaging of oscillating microbubbles against endothelial cells, van Wamel and colleagues were able to show uptake of propidium iodide and increased membrane permeability as cells became deformed from contact with vibrating phospholipid microbubbles [100]. Additional work using the same high-speed photography setup showed that jetting from inertially cavitating gas microbubbles in the close vicinity (<2 bubble diameters) of a cellular boundary resulted in detachment of roughly 5 cells/localized ultrasound contrast agent *in vitro* [101]. These experiments demonstrate the benefit of using microbubbles to improve drug delivery on a cellular level.

On a more macroscopic level, inertial cavitation of microbubbles within the vasculature has been shown to change the tissue transport properties, allowing transport of large (up to 500 nm) particles out of the vasculature. Price et al. showed they could deliver 200 and 500 nm fluorescent particles out of the capillary vasculature and into the interstitial space when combined with phospholipid ultrasound contrast agent cavitation by 2.3 MHz, 4 cycle pulses of ultrasound at a mechanical index of 0.7 (well within the FDA pressure guidelines for clinical ultrasound scanners) [102]. While the gap junctions within the vasculature are generally quite small (<50 nm in normal tissue) and prevent transport of larger particles, Price was able to show these particles could extrasavate in a time window of up to 5 s after ultrasound contrast agent cavitation [102]. Therefore, ultrasound-triggered destruction of microbubbles may be used to temporarily increase vasculature permeability for increased particle transport as well as increased cellular permeability.

Numerous studies and reviews have been published showing the synergy of these bioeffects when combined with traditional chemotherapy *in vitro* and *in vivo* [20,102–108]. One earlier *in vivo* example of microbubble destruction-aided cancer therapy showed that the cavitation of microbubbles when combined with the anticancer drug bleomycin significantly retarded growth of B-16 melanoma tumors in mice compared to drug alone [109]. Additionally, the group showed that a lower overall dose was required (nearly 10% of the effective dose with ultrasound alone) when combined with microbubble destruction to generate tumor shrinkage [109]. In another cancer therapy application, Sorace et al. showed that ultrasound-triggered microbubble disruption increased delivery and efficacy of Taxol in 2LMP breast cancer tumors in mice [105].

These bioeffects have also been used to deliver drugs and larger particles across the blood–brain barrier, which generally restricts passage of molecules larger than a few nanometers. The cavitation of microbubbles using focused ultrasound near the blood–brain barrier has been shown to transiently increase the gap junctions within this barrier to allow transport of larger therapeutics [110–114]. Potential clinical applications of drug delivery using this technique include treatment of

Alzheimer's, schizophrenia, and other cerebral disorders. In light of the obvious safety concerns, research in this area has progressed incrementally. However, Konofagou's group recently showed that the blood–brain barrier could safely and transiently be opened using microbubble cavitation in primates by monitoring gadolinium perfusion with MRI after cavitation of definity as well as an in house-fabricated agent [115]. While future safety studies will be required, this pilot study was a major milestone toward future human clinical trials.

In cases of blood clots causing blockage to the cerebrovascular system, stroke patients rapidly lose brain function due to ischemia in the brain. Thrombolysis can be performed if the condition is detected recently (generally within 3–6 h) using tissue plasminogen activator (tPA), but this treatment carries major side effects and has varied results. Studies have shown that ultrasound with and without tPA can help disrupt blood clots [116]. This inclusion of microbubbles has been shown to further enhance this phenomenon and spurred an entire field termed "sonothrombolysis" [116–118]. While the majority of results in this field are still at an animal model stage, results have been promising showing that cavitating microbubbles can significantly help clot disruption with and without coadministration of tPA [119–122].

## 11.5 Microbubbles in Gene Delivery

Gene delivery is another ongoing area of research exploiting the bioeffects of cavitating microbubbles for improved delivery. Previous approaches for delivering genetic material to cells relied on transfection via viral vectors. However, this approach is often associated with low transfection efficiency, immuno-response issues, and may be difficult to pass regulatory approval [123]. Several groups have shown that gene transfection is possible in the presence of cavitating microbubbles without viral vectors [124–128]. Figure 11.8 shows breast cancer cells in the presence of free DNA with and without ultrasound treatment, where ultrasound treatment shows a clear increase in plasmid uptake. Similar to work with the blood–brain barrier, results have progressed gradually due to safety concerns with the technique. Chai et al. recently showed the cavitation of lipid microbubbles can be used to selectively transfect islet cells in the pancreases of rats with rat insulin promoter for potential treatment of type II diabetes [129]. This ongoing work is currently being translated to a baboon model and may ultimately result in future human clinical trials for the treatment of diabetes [130].

### 11.5.1 Microbubbles as Drug Carriers

The size of microbubbles (<10 μm in diameter) makes them small enough to freely traverse the microcirculation, yet large enough to prevent them from extravasating out into the tissue [32]. Additionally, microbubbles are one of the only medical contrast agents whose destruction can be triggered by the imaging modality [32]. These factors make microbubbles an ideal platform for drug delivery, in that drug can be attached to the microbubble, retained during circulation through the

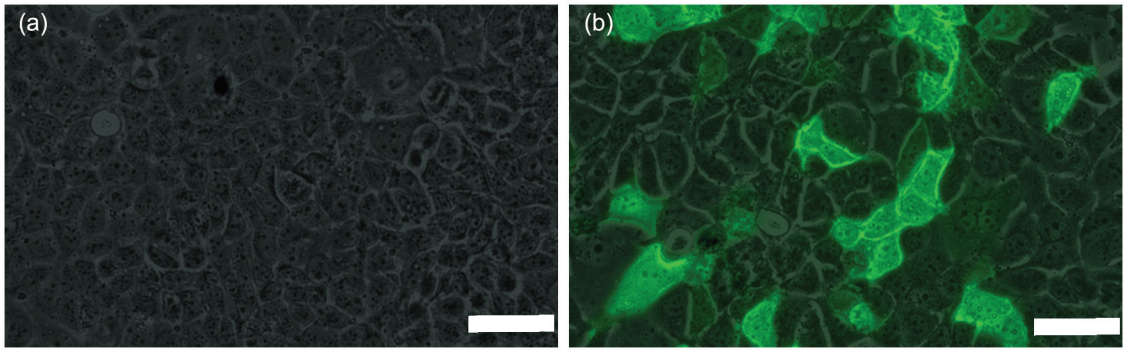



**Figure 11.8** MCF 7 cells treated with microbubbles and 10 μg/mL EGFP plasmid. (a) No ultrasound, (b) (1 × treatment) 15 s of ultrasound at 1 MHz (scale bar = 50 μm). (*Courtesy: Dr. Margaret Wheatley, PhD, and Dr. Michael Cochran, PhD.*)

vasculature, and then locally released upon ultrasound-triggered destruction. A great deal of research has been invested in loading strategies and applications for drug-loaded bubbles and this concept has been extensively reviewed [11,19,20,92,131–133]. Figure 11.9 summarizes demonstrated loading strategies for both polymer and lipid microbubbles. Drug payloads can be attached to the microbubble surface, incorporated within the shell itself, encapsulated within the gas core of the microbubble (either in solid or aqueous phase), or encapsulated in nanoparticles and attached to the surface for improving drug payload.

One of the first reports of drug-loaded microbubbles was published by Unger's group who encapsulated paclitaxel in an oil layer within phospholipid-stabilized microbubbles [21]. After fabrication, the group showed that drug could be locally released using 100 kHz pulsed wave therapeutic ultrasound and significantly reduced toxicity in mice relative to unencapsulated drug [21]. Since then, numerous drug-loaded liposomal microbubbles have been fabricated [134–138]. Despite these advances, the relative space within the phospholipid shell or microbubble core (at least some gas is required to maintain acoustic activity) is limited, thus hindering extensive drug payload. One potential solution to this problem is to attach drug-containing nanoparticles to the surface of the microbubble (as illustrated in Figure 11.9(d)) to increase drug payload while still maintaining the required size and acoustic properties [139,140]. As an example, Lentacker et al. formulated microbubbles loaded with nano-sized liposomes-containing doxorubicin and showed that when insonated these particles delivered higher drug concentrations to the nucleus of melanoma cells relative to both nanoliposomal drug and free drug delivered with lipid microbubbles [140]. This may be a useful strategy for increasing the drug payload of microbubbles.

Polymer-shelled microbubbles offer an attractive alternative to lipid-based microbubbles for drug delivery due to their improved stability and thicker shells (which in turn may house/carry more drugs). Similar to previous work by Unger with phospholipid microbubbles, de Jong et al. showed that a paclitaxel/oil mixture can be encapsulated within polylactic acid (PLA) microbubbles and that these can be triggered with ultrasound to slow growth of colon adenocarcinoma in a mouse model [141]. Wheatley's group showed that doxorubicin could either be encapsulated within the shell or electrostatically attached to the surface of PLA microbubbles [142]. These agents were shown to become more toxic to breast cancer cells *in vitro* after ultrasound triggering [143], and that locally triggering these agents *in vivo* led to a 110% increase in drug delivery to a liver tumor model in rabbits via a microbubble fragmentation mechanism [144]. Tumor necrosis factor-related apoptosis-inducing

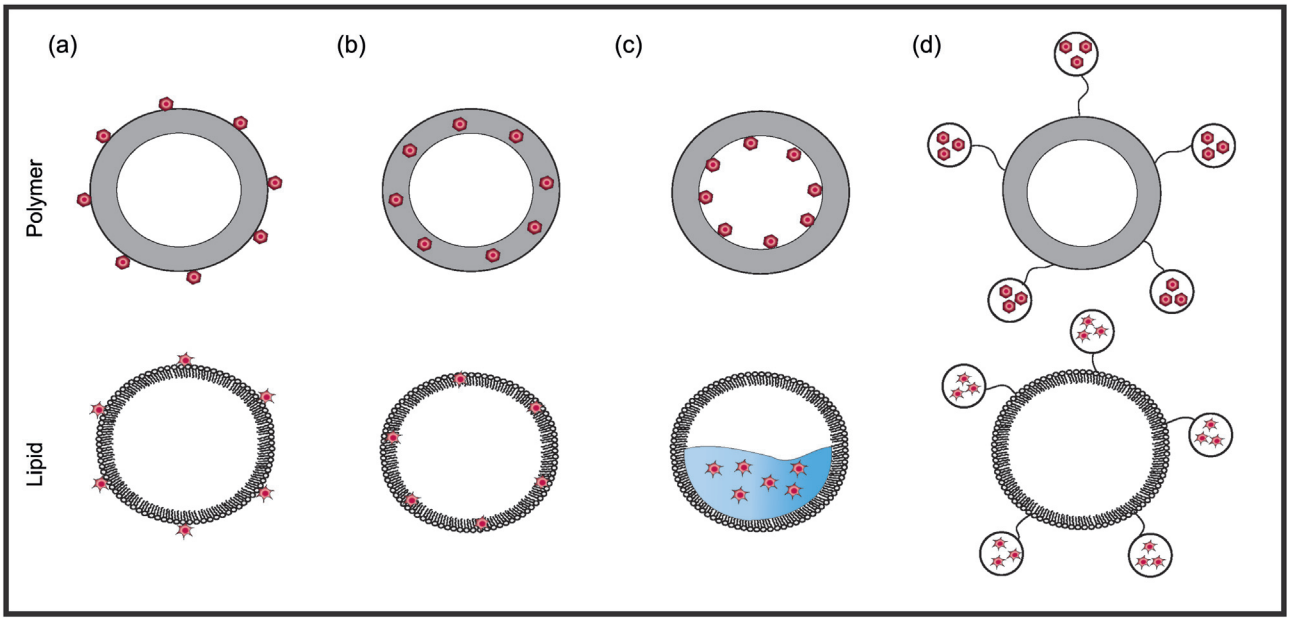



**Figure 11.9** Drug loaded polymer and lipid microbubbles. Various microbubble drug-loading conformations.

ligand and genetic material have also been attached to the surface of these agents, demonstrating the flexibility of the platform [145,146].

## 11.6 Other Emerging Applications

Currently, microbubbles are mainly used as ultrasound contrast agents; however, they have shown utility in several other applications. As previously discussed, targeted drug and gene delivery is a widely recognized emerging microbubble application. Other applications of microbubbles in earlier phases/stages of development include biofilm destruction, pressure estimation techniques, tissue engineering applications, concomitant imaging with MRI through the use of iron-oxide nanoparticles in microbubbles, and lymphosonography [147–151]. As with the general trend in modern science, the scale of technology decreases with time. Accordingly, nanobubbles have emerged as a contrast agent concept with similar (albeit smaller-scale) characteristics and uses as microbubbles. Here, we discuss each of these less developed applications.

### 11.6.1 Biofilm Destruction

Bacterial infection, particularly of implantable materials, often leads to biofilm formation, which is difficult to treat and can lead to repeated surgical interventions, ultimate removal of the implant, and further health problems [152,153]. Biofilms are inherently resistant to even the most potent antibiotics due to their protective niche, which also evades immune surveillance [154]. Microbubbles have recently been shown to improve biofilm treatment by improving their drug susceptibility. He et al. showed that vancomycin treatment is significantly more effective at decreasing *Staphylococcus epidermidis* biofilm on polyethylene implants, when SonoVue microbubbles insonated in conjunction with free antibiotic over a 10 min ultrasound exposure in a rabbit model (80 KHz, 0.5 W/cm$^2$, 50% Duty Cycle) [147]. Figure 11.10 depicts increased antibiotic sensitivity of biofilms in the presence of microbubble insonation. Cavitation nuclei formed by microbubble destruction in proximity to a biofilm allow for the entrance of small molecule drugs, such as vancomycin, rendering the biofilm more susceptible to antibacterial activity [155].

### 11.6.2 Noninvasive Pressure Estimation

Several groups have investigated the use of microbubbles for noninvasive hydrostatic pressure estimation [148,156–159]. Clinically these measurements are currently performed via pressure catheter threaded through the vascular system or a direct wick in needle approach, both of which are moderately invasive and carry significant risk [160–162]. Because applied force will influence the behavior of microbubbles, it was anticipated that a microbubble's response may be useful in evaluating hydrostatic pressures noninvasively. Early efforts focused on measuring changes in bubble resonance frequency [157], microbubble size changes through the use of dual frequency excitations [158], dissolution time of free gas after microbubble rupture [159], and changes in amplitude from single microbubbles [163]. However, these

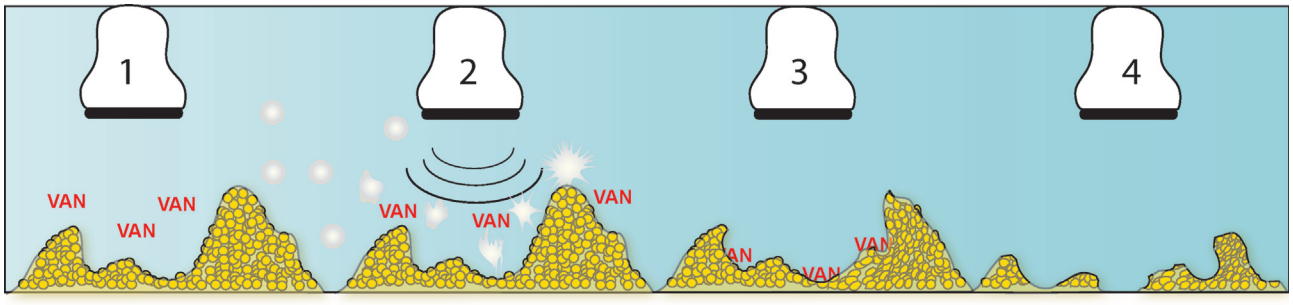



**Figure 11.10** Biofilm destruction using microbubbles and ultrasound. 1—Vancomycin (VAN) cannot penetrate biofilm, 2—insonation of microbubbles causes cavitations in the biofilm surface allowing, 3—VAN penetration into the biofilms, and 4—destruction of biofilm architecture.

efforts fell short before reaching *in vivo* trials due to an inability to identify signal from individual bubbles and the inherent polydispersity of microbubble populations. More recent advances have focused on a technique termed subharmonic-aided pressure estimation (SHAPE) in which the subharmonic amplitude at a particular stage (the stage at which point the subharmonic amplitude is most sensitive to changes in applied acoustic pressure) decreases linearly with increases in surrounding hydrostatic pressure [148]. As a result of this technique's *in vitro* validation [164,165], it has successfully been applied *in vivo* to measure left and right ventricle pressures in canines [166,167], intratumoral fluid pressures in swine melanoma (changes of which provide an early indication of treatment response) [168], and hepatic pressures in both canines [169,170] and patients with chronic liver disease [171]. In a recent, first in humans, study, SHAPE was shown to accurately detect portal hypertension (defined as a hepatic-venous pressure gradient $> 10$ mmHg) in patients with chronic liver disease with a sensitivity of 89% and specificity of 88%, indicating it may be a noninvasive alternative to transjugular catheter-based pressure measurements [171].

### 11.6.3 Tissue Engineering

Microbubbles have recently been incorporated into tissue engineering technologies. Polymeric tissue engineering scaffolds can be limited in their biomolecular delivery [172]. The use of microbubbles as porogens and growth factor carriers promotes bioactivity in degradable scaffolds [150,173,174]. Nair et al. showed that the incorporation of insulin growth factor-loaded microbubbles in the production of a porous scaffold provides larger pores and a nontoxic biocompatible mode of incorporating growth factors [150]. Microbubbles may therefore result in tissue engineered scaffolds which may foster host in-growth and promote cell survival and proliferation. In another tissue engineering application, microbubbles have shown promise in the targeting of stem cells to areas where regeneration may be required. Toma et al. demonstrated that mesenchymal stem cells conjugated to microbubbles can be targeted and delivered to areas of arterial injury using acoustic radiation force under physiologic flow rates [175].

### 11.6.4 Magnetic Resonance Imaging

Although microbubbles were originally intended as contrast agents for ultrasound, the potential for microbubbles as contrast agents in MRI has recently been realized. Contrast agents for MRI include gadolinium chelates and superparamagnetic iron oxide particles [176,177]. Microbubbles have been prepared as dual contrast agents for ultrasound and MRI through the incorporation of superparamagnetic iron oxide nanoparticles in polymeric shells [178]. More recently, He et al. demonstrated that polymeric microbubbles with nitrogen gas cores and superparamagnetic iron oxide particles conjugated to the polymeric shell surface rather than incorporated within the shell provided further MRI and ultrasound imaging enhancements [179]. The fusion of MRI and ultrasound imaging could provide more efficient imaging and diagnostics.

### 11.6.5 Nanobubbles

While technically not microbubbles, several groups have worked to develop nanobubbles using either size separation techniques or modifications to the microbubble fabrication process [180–182]. These bubbles are supposed to offer better penetration into tumor interstitial for drug-delivery purposes, but may not be ideal for imaging purposes (as shown in equation (11.5), the effective cross scattering area is proportional to the bubble radius to the sixth power) [183,184]. Nano-sized ultrasound contrast agents have been fabricated using polymer [181], surfactant [185], and lipid shells [186]. Similar to microbubbles, these agents have also been loaded with drug or had the surface modified with targeting ligands for targeting and drug delivery [183,184,187]. While these agents are still in bench top or early *in vivo* trials, improved tumor penetration is expected to be a major advantage for drug and gene delivery.

### 11.6.6 Lymphosonography

The identification of sentinel lymph nodes is often required for surgical biopsy or removal and is currently performed using injection of a radioactive tracer or methylene blue dye immediately prior to resection surgery. The ability to noninvasively trace lymphatic channels and identify connected sentinel

lymph nodes using microbubbles was first demonstrated by Mattrey et al. [188]. The application has been expanded by Goldberg et al., who showed visualization of these structures using subcutaneous, submucosal, and parenchymal injection of Sonazoid in swine, canines, rabbits, and a monkey [151]. Since then lymphosonography has been shown useful in porcine models for identification of nodes connected to the supraglottis, thyroid, and melanomas [187,189,190]. Sever et al. showed that this technique can be applied to humans by successfully identifying sentinel lymph nodes (with 89% sensitivity in one study) for biopsy and staging in patients with breast cancer prior to surgery [185,191]. Despite these advances, no microbubble is currently approved for subcutaneous injection or use in lymphosonography, but may gain approval in the future.

## 11.7 Conclusion

The ongoing research on microbubbles continues to result in the discovery of new potential clinical applications. Past research has already established microbubbles as a safe method for contrast-enhanced ultrasound imaging with significant improvement over conventional (non-enhanced) ultrasound imaging.

Polymer, protein, and lipid microbubbles provide a means of increasing contrast within the vasculature, even at the capillary level. As each microbubble undergoes compression and rarefaction upon exposure to ultrasound, the nonlinear oscillations of the microbubble generate signals which return to the transducer, increasing the contrast significantly compared to the surrounding tissue. The pliability of the encapsulating shell allows for microbubble destruction upon an increase in the ultrasound power, creating transient holes in the membranes of neighboring cells and thus potential windows for drug and gene delivery. The engineering of microbubbles as drug carriers either conjugated to or incorporated within the microbubble shell provides a method of more efficient localized drug and gene delivery. Targeted microbubbles may identify specific markers expressed on a desired tissue type as well as a method for increased microbubble accumulation, leading to significantly enhanced contrast in the area.

Microbubble use in medical diagnostics continues to grow and evolve in the United States and is already well established in the majority of other countries. As microbubbles become a more accepted tool for diagnostic imaging, there will be an increase in the ability of ultrasound to aid in the accurate diagnosis and treatment of patients and a more rapid adoption of emerging microbubble applications.

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# 12 Hydrogels in Regenerative Medicine

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## 12.1 Introduction: Relevance of Hydrogels to Regenerative Medicine

Hydrogels are crosslinked polymeric networks containing hydrophilic groups that promote swelling due to interaction with water [1]. While hydrogels are heavily used in the field of regenerative medicine, their application to biomedical systems is not new. In fact, it has been suggested that they were truly the first polymer materials to be developed for use in man [2]. They have been in use for clinical applications since the 1960s, initially for use in ocular applications including contact lenses and intraocular lenses due to their favorable oxygen permeability and lack of irritation leading to inflammation and foreign body response, which was observed with other plastics [3]. Before the concept of tissue engineering and regenerative medicine had gained traction, hydrogels were used for cell encapsulation [4]. They have also been utilized extensively in the clinic for wound healing applications due to their oxygen permeability, high water content, and ability to shield wounds from external agents. Perhaps the largest research focus and utility of hydrogels has been found in their use as controlled release systems. This combination of controlled release and cell encapsulation has led to increasing uses of hydrogels in regenerative medicine applications.

Hydrogels used in regenerative applications can be based on naturally or synthetically derived polymers. By most definitions, native tissues, particularly the extra-cellular matrix, are hydrogels and derivatives of these and other naturally based systems are in widespread use. Natural hydrogels are generally regarded as having favorable biodegradation products compared to some synthetic polymers as the monomeric degradation products are typically amino acids or saccharide units. In contrast, synthetics offer wide flexibility in terms of mechanical properties, water swelling, degradation rates, ionic charge, and other important parameters. Table 12.1 describes several prominent synthetic and natural hydrogels. These natural systems are derived from mammals, crustaceans, plants, and bacteria and are typically polypeptides or polysaccharides. Table 12.1, which highlights uses of hydrogels in regenerative

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**Table 12.1** Hydrogels Used in Regenerative Medicine and Medical Technology Applications

| Hydrogel Material [Abbreviation] | Description | Examples of Applications | References |
|---|---|---|---|
| Poly(ethylene glycol) diacrylate [PEG] | Widely used, flexible synthetic polymer with low protein adsorption that is photo-crosslinkable | Neural<br>Cartilage | [5]<br>[6] |
| Poly(2-hydroxyethyl methacrylate) [pHEMA] | Non-degradable polymer modifiable for degradation [7] | Intraocular lenses<br>Nerve guidance | [3]<br>[8,9] |
| Oligo-(polypropylene fumarate) [OPF] | | Bone<br>Cartilage<br>Nerve | [10]<br>[11]<br>[12,13] |
| Poly(*N*-isopropylacrylamide) [pNIPAAM] | Synthetic material with lower critical solution temperature (LCST) near physiological temperature | Corneal sheets | [14] |
| Collagen | Most prevelant protein in mammals characterized by proline-lysine-glycine repeating units and various isoforms | Bone<br>Tendon | [15]<br>[16] |
| Fibrin | Protein involved in clot formation and platelet binding in blood coagulation cascade | Surgical glue<br>Neural regeneration<br>Bone<br>Cartilage | [17]<br>[18]<br>[19–21]<br>[22] |
| Keratin | Protein derived from intermediate filaments of eukaryotes | Neural regeneration<br>Hemostasis | [23]<br>[24] |
| Silk | Biopolymer derived from spiders, *Bombyx mori*, and other sources | Cartilage<br>Bone | [25]<br>[26] |
| Agarose | Thermoreversible linear polysaccharide derived from red algae | Cartilage<br>Neural regeneration | [27,28]<br>[29,30] |
| Alginate | Second most abundant polysaccharide on earth; derived from seaweed and contains β-D-mannuoronate and β-L-guluronate sub-units (1,4 linkage) | Cell encapsulation<br>Bone<br>Ovary follicles | [4]<br>[31]<br>[32] |
| Chitin | β-(1,4)-*N*-acetyl glucosamine polysaccharide | Neural regeneration<br>Cartilage | [33]<br>[34] |
| Chitosan | Deacetylated chitin | Wound dressings | [35,36] |
| Hyaluronic acid | β-(1,3) glucuronic acid and β(1,4)-*N*-acetylglucosamine glycosaminoglycan found in connective tissue | Cartilage<br>Vocal cord<br>Bone<br>Wound healing | [37]<br>[38]<br>[39]<br>[40] |

(*Continued*)

**Table 12.1** Hydrogels Used in Regenerative Medicine and Medical Technology Applications—*Cont'd*

| Hydrogel Material [Abbreviation] | Description | Examples of Applications | References |
|---|---|---|---|
| Methyl cellulose | Cellulose (polysaccharide) with hydroxyl groups substituted with methoxyl groups to disrupt cellulose crysallinity and provide solubility | Neural regeneration<br>Nucleus pulposa | [41]<br>[42] |
| Bacterial cellulose | Non-degradable cellulosic material produced by *Acetobacter xylinum* | Vascular graft<br>Bone | [43]<br>[44] |

medicine, primarily shows the use of single-component systems. However, combinatorial uses of hydrogels to obtain desirable properties of each component are widely investigated.

The diversity and flexibility of natural and synthetic hydrogels makes it impossible to consider every type of hydrogel. The goal of this chapter is to provide an overview of the basic theory of hydrogels, describe important uses and applications in regenerative medicine, and consider their continued importance in research and the clinic.

## 12.2 Background and Theory

### 12.2.1 Classification

Several methods can be used to classify hydrogels including network structure or porosity, physical structure, source, and crosslink type [45]. In tissue engineering and regenerative medicine, the porosity of the scaffold materials is often of considerable importance. Hydrogels can be classified according to their *network structure* as macroporous (pores of $\sim 10-200\,\mu m$), microporous (pores of $\sim 1-10\,\mu m$), and non-porous (pores of $<1\,\mu m$). Clearly, if used for approaches in which cells must infiltrate the scaffold, macroporous scaffolds must be used. Non-porous scaffolds have low rates of diffusion, making cell viability a significant concern and preventing infiltration of cells not pre-encapsulated in the hydrogel.

Classification by *physical structure* is also fairly intuitive for regenerative applications. Hydrogels can be considered amorphous, semicrystalline, hydrogen bonded, or complexation products. They can be classified according to their *source*, that is, whether they are naturally derived or synthetic. Synthetic systems have a plethora of options and may be homopolymer or copolymer systems. Further, synthetic polymers can also be synthesized to form interpenetrating polymer networks in which the two polymer sheets are physically entangled. Naturally derived systems may be polysaccharide or polypeptide-based and derived from numerous sources.

More common in the polymer chemistry literature is classification according to the *ionic charge* of the hydrogel. The gels may be neutral, anionic, cationic, or ampholytic. The charge properties become crucial in considering their interaction with physiological environments and cells. Ionotropic gels are ionic polymers that contain a balancing multivalent counterion. One example of this is an alginate hydrogel. Alginate in its native form is anionic but is not a hydrogel. In the presence of calcium counterions it forms a physical hydrogel through ionic interactions.

Hydrogels can also be classified according to the type of *crosslink*. The two broadest categorizations are chemical or physical crosslinks. In general, a chemical crosslink is defined as a covalent interaction at a point of overlap or junction (see below). Physical crosslinks may be the physical entanglement of the polymer chains, interpenetrating polymer networks, and other secondary forces (e.g. hydrophobic interactions, hydrogen bonding, ionic interactions, electrostatic interactions) [46].

### 12.2.2 Theory

An in-depth description of the polymer science theory governing the formation and behavior of hydrogels is beyond the scope of this text. Below we briefly describe several of the key parameters that are of particular importance to scientists working with hydrogels in regenerative medicine applications. More complete descriptions of the theoretical

polymer science basis for hydrogels are given in several other locations [1,47]. Nonetheless, the principles that govern their formation are highly relevant to regenerative medicine applications as these properties control (among other things) swelling, interaction with cells, and drug delivery kinetics.

Numerous mathematical models have been developed to estimate the properties of hydrogels and to predict processes related to controlled release (e.g. diffusion parameters and rates of release). Much of the discussion below is taken from review articles on the topic [47].

Three important parameters to consider in defining hydrogels are: (1) the *volume fraction* in the swollen state, (2) the *crosslink density*, and (3) the *porosity of the hydrogel*. These parameters can be described mathematically.

The volume fraction is simply the volume fraction occupied by the polymer and gives a sense of the amount of water in the gel. Mathematically, it has been defined as:

$$\upsilon_{2,s} = \frac{\text{Volume of polymer}}{\text{Volume of swollen gel}} = \frac{1}{Q}$$

where $Q$ is another useful parameter known as the volume degree of swelling. Although the polymer volume can be estimated from the density of the polymer, it is sometimes easier to determine the polymer weight. A second set of parameters based on the weights can therefore be defined akin to the volume fractions above:

$$m_{2,s} = \frac{\text{Mass of polymer}}{\text{Mass of swollen gel}} = \frac{1}{q}$$

The effective molecular weight between crosslinks can be inferred from the description in Figure 12.1. This figure shows a schematic of a hydrogel polymer network [48]. Areas of "overlap" in Figure 12.1 are known as junctions and indicate either physical or chemical crosslinks. The average molecular weight between crosslinks is known as the effective molecular weight between crosslinks, $M_c$. This value can be used to determine the crosslink density based on the known molecular weight of the polymer repeat units, $M_o$, as:

$$X = \frac{M_c}{M_o}$$

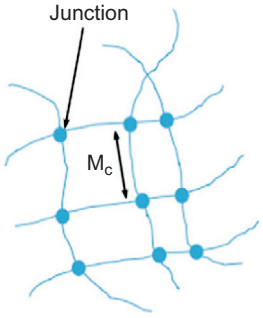



**Figure 12.1** Simplified schematic of hydrogel structure. Junctions indicate points of crosslinks, with the distance between the junctions indicating the molecular weight of between crosslinks, $M_c$. Junctions may be physical entanglements or chemical or ionic crosslinks. *(Adapted from Peppas and Barr-Howell [48], with permission.)*

Several other parameters of interest are those of porosity, tortuosity, and the diffusion coefficients through the gel. Porosity is the volume of the gel that is not physically occupied by the polymer itself. This parameter is often of particular interest to tissue engineers working with macroporous or microporous gels as the porosity is an indication of the volume of the material available for cell infiltration or seeding. Within regenerative medicine, the role that cells play in remodeling a matrix is often important, so materials with higher porosity are viewed as favorable, potentially allowing a larger number of the cellular ("functional" units) of the system to be present. Tortuosity is the path that a molecule or cell must navigate in order to penetrate the gel. Both the porosity and tortuosity are important in determining the rate of diffusion within hydrogels. Diffusion is the main transport mechanism of nutrients and oxygen to cells within the gel, of metabolic waste products out of the gel, as well as the release of therapeutic agents from the gel or from cells within the gel.

## 12.3 Utility in Regenerative Medicine

Hydrogels currently have a wide range of applications from consumer products to electronics and biosensors. Within the biomedical field, the earliest applications of hydrogels were for ocular applications

including intraocular lenses [49], soft contact lenses [3,50], and corneal repair [51]. They have also been used as suture, as dental materials, in biosensors, and as coatings for catheters and defibrillators, and for wound care products.

The original use of hydrogels came as stand-alone biomaterials or as devices for controlled release applications. Later, they became the focus of cell-encapsulation approaches. The wedding of these three uses for hydrogels has propelled their use in the field of regenerative medicine as scientists use their properties to direct cell attachment, migration, and differentiation. The application of these individual roles of hydrogels and their combinatorial approaches in regenerative medicine are described in more detail below.

### 12.3.1 Hydrogels as Biomaterials

Although the field of biomaterials is clearly moving from the use of inert materials that minimize host response to more bioactive and integrative materials, the original use of hydrogels came as stand-alone biomaterials for ophthalmic and blood-contacting applications. Indeed these applications remain important in the biomedical field. At the time of their discovery, one of the appealing aspects of hydrogels was their minimal foreign body response compared to other semi-crystalline polymers (Wichertle and Lim, 1960). This stems from the observation that hydrogels typically have low levels of protein adsorption. For example, poly(ethylene glycol) (PEG) is widely used on drug delivery vehicles due to its ability to provide long circulation times, likely through steric effects on complement proteins. Similarly, PEG-diacrylate gels are known to have low protein adsorption [52], as are various other synthetic-based hydrogels [53] due to steric effects and possibly their hydrophilic surfaces. Low protein adsorption is generally associated with poor cell attachment. Further, synthetic hydrogels and many natural hydrogels (particularly polysaccharides such as alginate and agarose) lack peptidic sequences that would promote cell attachment via integrin binding.

While this lack of biological activity seems counter-intuitive in regenerative medicine, hydrogels are highly labile in terms of chemical and physical modifications that can be used to modulate cellular response in a more bioactive fashion (see below). Thus, while hydrogels remain highly significant as stand-alone biomaterials in minimizing host response, they are also useful for the direction of cell response to materials in a more bioactive fashion.

The method of hydrogel formation is particularly important for maintaining bioactivity of molecules and for minimizing any detrimental effects to cells associated with the gels. Typically, a monomer or non-crosslinked polymer is found in the solution (sol) phase. Upon application of some initiation conditions, the sol phase forms the hydrogel (gel) phase; that is, it undergoes the sol-gel transition. For hydrogels containing bioactive molecules or cells, it is clear that high temperatures and many monomers, solvents, and polymerization initiators cannot be used due to inactivation of bioactives or cytotoxicity. Therefore, approaches that achieve the sol-gel transition with minimal effect on bioactive molecules and cells have been developed and are described here and in other sections of this textbook.

Photopolymerization is commonly used to achieve gelation for regenerative medicine applications. Photopolymerization reactions for hydrogel formation have been performed for poly(vinyl alcohol) [54], polysaccharide-based materials, poly(2-hydroxyethylmethacrylate) [55–57], and modified PEG-collagen [58] among others. Poly(ethylene glycol) or PEG diacrylate gels are the most common gel systems used for the formation of photopolymerized hydrogels [59]. The presence of pi bonds in the diacrylate terminal ends of PEG provides the chemical moieties for the reaction. Photoinitiators used for biomaterial applications have been classified as photolytic or hydrogen abstraction [60]. Photolytic groups include free radical initiators including acetophenone derivatives widely used for hydrogel formation. One advantage of photopolymerizable hydrogels is their ability to be polymerized *in situ*. Materials that spontaneously undergo the sol-gel transition in response to light or physiological temperature can be maintained in solution phase until *in vivo* injection followed by gel formation at the desired location. Other more robust forms of achieving gelation have been described, such as the use of click chemistry [61–63]; however, the effects of this chemistry and the copper initiators on cells have not been established.

Hydrogels have been coupled with most modern approaches to biomaterial scaffold fabrication.

Cell-hydrogel constructs with alginate or poly(ethylene oxide)-pluronic-poly(ethylene oxide) block polymer as the hydrogels have been used with BioPlotter and solid free-form fabrication systems [64,65]. One drawback to hydrogel systems is a lack of mechanical integrity associated with certain applications.

Non-woven electrospun fibers [66] and woven hydrogel/cell mixtures [67] have been reported that may allow for materials of greater mechanical integrity. More complex approaches to achieving spatial regulation of cells within hydrogel biomaterials include photopatterning and photolithographic techniques of cell adhesion and migration molecules to direct cell attachment and material response (see below) [68,69]. The role of topographical cues in cell fate is becoming well established and hydrogels are useful for the creation of three-dimensional topographical cues such as nanopillars [70] to promote cell migration, and recently through the introduction of enzyme-assisted photolithography to achieve spatial functionalization of hydrogels that may provide insight into the topographical designs necessary for larger tissue constructs [71].

### 12.3.2 Hydrogels for Controlled Release

Over the past 30 years, numerous systems have been developed for delivery of therapeutic agents within the context of the medical device field with the goal of achieving long-term, zero-order release of therapeutic agents. These systems can generally be classified as swelling-controlled, diffusion-controlled, or chemically controlled. Examples include osmotic pumps (swelling-controlled), transdermal patches (diffusion-controlled reservoir matrix), and drug eluting stents (chemically controllable erodible system).

Within the field of regenerative medicine, it desirable to have release of therapeutic agents occur from a system that degrades with time so that secondary retrieval and removal of a device (e.g. osmotic pump) is not required. As such, those systems described above as medical devices are usually not employed within the context of regenerative medicine. Rather, implantable or injectable bulk hydrogels are a preferential alternative. The primary therapeutic agent of interest is the release of growth factors. However, the delivery of small molecules (e.g. antibiotics) and nucleic acids have also been widely employed, often in conjunction with cell therapies.

A drawback to this bulk hydrogel approach is that the complexity provided by a device (e.g. an osmotic pump) is lost, making zero-order release difficult to achieve over the time periods that can be achieved with medical devices. However, in principle, regenerative medicine approaches seek to stimulate a physiological response to a chemical cue such as growth factor release. Following the initial stimulus, the regenerated tissue should move toward normal physiological function, thereby obviating the need for long-term release of the chemical cue as is desirable in the traditional medical device field.

As a controlled release platform, several parameters can be used to modulate the release of the therapeutic agent. Because these systems are examples of diffusion-mediated release, the porosity and tortuosity of the system significantly affect the release of therapeutic agents. The ionic nature of many hydrogel systems also lends itself to the sustained release of counter-charged molecules. More generally, affinity between the hydrogel and therapeutic agent (whether through ionic charge, hydrophobic effects, or protein-protein interactions) can be used to modulate the rates of release.

The ability to modulate the release through external control is also of considerable importance. Examples of these types of systems include increasing binding between the gel and therapeutic, the use of environmental controls such as temperature, pH, or enzymes, or the application of external energy sources such as ultrasound, light, or electrical fields to promote or mitigate release. Such approaches allow for the tunable, responsive, and/or pulsatile release profiles.

The hydrophilic groups of hydrogels that lead to high water content and therefore low protein adsorption or cell binding also provide chemical flexibility for the covalent binding of molecules to the hydrogel backbone. This is described in more detail below for matrix-immobilized ligands. However, this approach can also be used to control the rate of release of therapeutic agents. One example of this approach is in making use of the heparin-binding domains found on many growth factors. By coupling heparin to the hydrogel via these reactive groups, it is possible to maintain the association of heparin-binding growth factors with the hydrogel for a longer timeframe than achieved with diffusion-mediated release [72].

A more sophisticated controlled release system applicable to hydrogels and other polymers is that of cell-demanded liberation and is akin to a pendant-chain system [73]. The premise of this approach is that growth factors can be tethered to the backbone of the hydrogel [19]. The backbone of the hydrogel or the pendant-chain tether itself can contain sequences cleavable by matrix-metalloproteases (MMPs). Diffusion-mediated release from the hydrogel or cleavage of the growth factor from the tether occur only as cells infiltrate the scaffold, hence the term cell-demanded liberation. In one version of this system, the 121 isoform of VEGF was engineered to contain the factor XIII substrate amino acid sequence, for binding to a fibrin hydrogel, and an $\alpha 2$ plasmin-inhibitor that is MMP-cleavable [74]. As cells infiltrate the scaffold, they produce MMPs, leading to cleavage of the VEGF from the hydrogel to promote vascularization of the construct in conjunction with cell infiltration.

The most well known and studied thermally responsive system is the *N*-isopropylacrylamide or pNIPAAM. pNIPAAM has a lower critical solution temperature (LCST) of approximately 32°C (for the linear form). Therefore, below 32°C the polymer is hydrophilic and promotes cell attachment and adhesion. Above 32°C, the polymer becomes hydrophobic, leading to detachment of cells. This approach has therefore been exploited for use in the creation of cell sheets for various tissue engineering applications including cornea [14,75–77], cardiac grafts [78–80], urothelium [81,82], and skin [83], among others.

In addition to intrinsic physiological control mechanisms such as pH, enzymes, and temperature, release of therapeutic agents can also be controlled through extrinsic mechansisms or energy sources. In one example of these systems, pHEMA has been used as the drug reservoir for the release of small molecules (ciprofloxacin antibiotic, molecular weight $\sim$330 Da) and pHEMA/2-hydroxyethyl-acrylate PEG-dimethylacrylate has been used to release larger molecules (insulin, molecular weight $\sim$5.8 kDa). This system used a coating of methylene chains to prevent passive diffusion of drug during periods without the application of ultrasound and was compatible with ultrasonic energies that are clinically relevant (43 kHz and 1.1 MHz) [84]. Electrically responsive hydrogels are also an active area of research. Although an important area of research for drug delivery applications, the use of electrically responsive hydrogels has not found widespread use in regenerative medicine due to the need for application of electrical field and/or electrode implantation [85]. Nonetheless, extrinsically mediated systems and feedback-controlled systems provide added control and sophistication that may find utility, particularly in endocrine-related tissues.

In summary, hydrogel systems can provide a mechanism to achieve near zero-order release for finite time periods, which is advantageous as a secondary procedure for device removal is not required. Hydrogels can also be used to achieve on-demand or pulsatile release. Because they can serve as a physical matrix for cells or for cell encapsulation, they can also be considered controlled release systems by slowly releasing therapeutic agents produced by cells.

## 12.3.3 Cell Association with Hydrogels

### 12.3.3.1 Cell Encapsulation

Hydrogels have been in use for nearly 30 years as a system to encapsulate cells [86]. For example, endocrine disorders such as diabetes that result from autoimmunity against hormone-secreting cells are intensely studied for regenerative therapies. The ability to achieve a functional effect may be attainable not through whole organ replacement but through delivery of cells microencapsulated in hydrogels (Figure 12.2), which can promote cell viability, controlled release, and protection from immune response to implanted cells. While the spatial distribution of cells is clearly important in the engineering of *de novo* functional tissues, the more general non-spatially controlled encapsulation of cells still provides the potential for a significant clinical impact.

The incorporation of cellular components provides the opportunity to achieve zero-order or physiologically responsive release over prolonged periods of time. Alginate microspheres are among the most studied hydrogel carriers for microencapsulation of cells. The mechanical properties of these gels can be modulated depending on the divalent cation used to achieve crosslinking. For example, the use of barium or strontium instead of calcium leads to more rigid gels. These systems also provide a barrier to immune

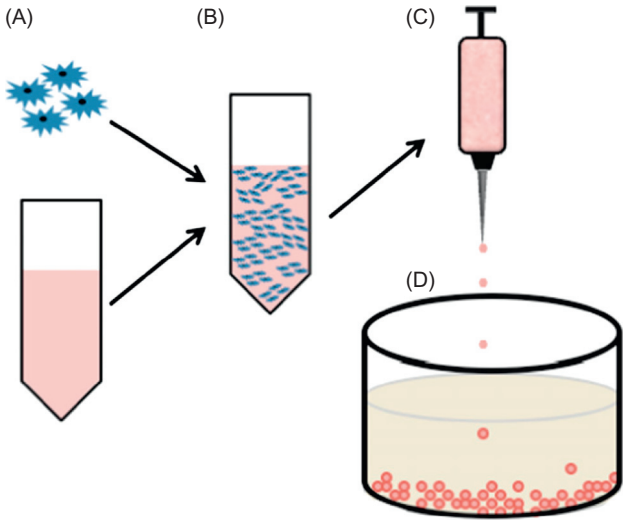



**Figure 12.2** Schematic of the process of cell microencapsulation with sol-gel transition of hydrogels. (A) In this process, cultured or isolated cells are dissolved in a solution-phase hydrogel (e.g. alginate) and (B) mixed into a viscous cell suspension. (C) The solution-phase hydrogel/cell mixture is then extruded (e.g. by pressure) from a droplet microencapsulator (typically a syringe, possibly with some electric field applied to regulate droplet size). (D) The droplets are collected in a solution promoting gelation (e.g. calcium-containing solution for alginate). Regulation of drop size allows single or multiple cell encapsulation and mechanical properties can be regulated through the hydrogel precursor concentration or the gelling agent.

response, providing the potential to use autologous stem cells, allogeneic differentiated cells, or even xenografted cells. They can also be coated with polycations such as poly-L-lysine or poly-ornithine for stabilization and to regulate solute release from the capsules [87]. With these semi-permeable membrane coatings, the encapsulated cell/microbead system becomes akin to the traditional reservoir drug delivery systems but with the ability to respond to physiological stimuli. Problems with foreign body response and issues of achieving sufficient nutrient supply and waste removal remain challenges to long-term patency of these systems, but many of the approaches to achieve vascularization currently under investigation may provide more immediate benefit to these types of cell-encapsulation therapies for numerous hormone-related deficiencies.

Within the last decade, approaches have been developed to provide more control over methods to achieve encapsulation of cells. Two particularly important approaches include *in situ* gelation and photoencapsulation. In situ gelation systems may depend on pH, temperature, or light as the initiating species. Temperature and light are the primary mechanisms of *in situ* gelation initiators used in regenerative medicine with pH systems being used less frequently to avoid exposing cells to caustic environments. Particularly advantageous for regenerative medicine applications are reverse thermogelation compounds that are in solution at low temperatures but gel at higher temperatures, preferably in the physiological range. That is, compounds that undergo the sol-gel transition with increasing temperature. Important natural hydrogels that are reverse thermogelation compounds include collagen, carboxymethylcellulose, and certain combinations of hydrogels. Important synthetic hydrogels known to undergo *in situ* gelation include poly (*N*-isopropylacrylamide) and block co-polymer systems consisting of poly(ethylene glycol) in combination with Pluronic or PLGA [88]. The ability of hydrogels to undergo sol-gel transitions at increasing temperatures depends on the balance of intermolecular forces including hydrogen bonding and hydrophobic interactions as well as water content and crosslinking density. The applications of these systems are numerous, but include both hard and soft tissues [89,90].

Photo-encapsulation can be a subclass of *in situ* gelling materials. Photo-initiators are widely used in dental applications to cure resins. Photo-initiators have also been used for the formation of hydrogels for approximately 20 years [91] as a solution-phase material can be injected and then cured to the gel phase *in situ*. Various initiators have been employed, but those that are active in the ultraviolet range are most widely reported in part because they are less likely to polymerize in response to ambient light and have higher reported crosslinking efficiencies [92]. The use of polymerization initiators as well as the use of UV-light have been shown to have detrimental effects on cells [93]. However, alternate initiators such as those active in the infrared range may mitigate some of the UV effects, and the ability to achieve spatially controlled encapsulation of cells within hydrogels is clearly important for achieving structure-function relationships [94,95].

#### 12.3.3.2 Spatial Patterning

As described above, hydrogels can be utilized to achieve three-dimensional spatial patterning of cells. One important development in the use of hydrogels has been the advent of inkjet printing technology, first described by Boland's group in 2004 [96,97]. Originally used for high-throughput screening of drug compounds [98] and then for the printing of nucleic acids to solid substrates [99], this approach has since garnered more attention for the spatial patterning of cells that may resemble native tissue. In the initial iterations of this work, ink from inkjet printer cartridges was replaced with cells suspended in a non-crosslinked polymer solution. Alginates in the absence of calcium is the most common gel system although there are reports using collagen [97], fibrin [100,101], polyurethanes [102], and polyacrylamide [103]. In each case, the cells are suspended in a non-crosslinked form of the polymer solution and printed into a solution containing the crosslinking agent. In the case of alginate this involves printing into a calcium solution whereas fibrinogen can be printed into a thrombin solution. Cells are printed in a two-dimensional pattern, and three-dimension structures are formed through a layer-by-layer approach. More recently, true three-dimension bioprinters have been developed [104] and the ability to print from an array of cartridges is also under development. The role of gradients in directing migration and/or differentiation is an area of interest in many aspects of regenerative medicine. Inkjet printers provide a medium for the development of these types of gradients [103,105,106]. Current drawbacks to this approach are the lack of mechanical integrity and questions regarding the thermal effects on cells. Although the technology has not shown a noticeable effect on cell viability [107], more subtle effects on gene regulation through the heat shock protein (HSP) family are yet to be fully characterized.

Dielectrophoresis is an approach useful for screening and may also be applicable to the formation of scaffold materials on scales relevant to organ engineering [108]. This approach allows for the patterning of cells within hydrogel constructs via the application of uniform electrical field. One drawback to the approach is that relatively weak hydrogels are required to allow manipulation and patterning of the cells for the dielectrophoretic field. An approach has been described to overcome this, which treats hydrogels as a composite system wherein cells are patterned via electrical field within an agarose or PEG gel and surrounded by a bulk-phase material with the desired mechanical properties, thus providing an approach to scale up this technique to larger-sized constructs [109]. It is unclear whether the application of electrical field or the application of high temperatures in inkjet printing will be less deleterious to cells, but the approach demonstrates the ability to achieve spatial patterning through other approaches.

The ability to spatially pattern cells on or within hydrogels is also important in considering approaches to achieve high-throughput screening of hydrogels to assess the role of hydrogel type, topographical signals, soluble chemical cues, immobilized chemical cues, mechanical properties, and other parameters on cells. Several approaches have been developed toward this end and will likely be important tools in providing more systematic study of the role of hydrogels (and other biomaterials) on cell phenotype and genotype. One approach to high-throughput analysis is the use of the dip pen lithographic technique with hydrogels [110]. This technique allows for the rapid printing of gels with or without cells and is compatible with soluble and matrix-immobilized chemical cues. While this technique is likely limited to screening assays, the knowledge imparted is important for a rational approach to the design of larger-scale constructs.

#### 12.3.3.3 Hydrogels as Substrates for Promoting Cell Attachment, Growth, and Differentiation

It is increasingly clear that both physical (e.g. mechanical properties and topographical cues) as well as chemical cues have a significant impact on cell functions such as attachment, proliferation, migration, and differentiation. As described above, one advantage of hydrogel systems is the ability to achieve three-dimensional constructs of materials and cells that begin to recapitulate the architecture of native tissue. Because their high water content and low protein adsorption typically lead to poor cell attachment (in the absence of native or added binding motifs), these systems also provide the ability to isolate specific effects such as a particular ligand or a range of mechanical properties. That is, they provide the means to conduct systematic evaluations of certain biological ligands, combinations of ligands, or the effects of specific mechanical

properties on cell response. Hydrogels have many parameters than can be altered to modulate and study the environmental cues associated with the material. These alterable parameters can generally be divided into chemical and physical parameters. A summary of approaches to modulate these parameters is shown in Figure 12.3.

There are two basic methods to provide chemical cues to cells via hydrogels: soluble factor delivery and matrix-immobilized presentation. Parameters and methods that control soluble factor delivery are described on pages 284–285. The primary function of matrix-bound cues is to promote cell attachment and to provide signaling cues to direct cell behavior. The role of specific ligands is discussed elsewhere in this text, but Table 12.2 lists specific examples of matrix-immobilized molecules on hydrogels.

It is noteworthy that most of the gels shown in Table 12.2 are based on poly(ethylene glycol) or other gels to which cell attachment is poor. One approach to achieving better cell attachment and biological function is to mix hydrogels that have some inherent biological activity with those that do not to provide a type of composite material that has desirable properties [123]. An approach that is slightly more complex but can provide greater control over the presentation of binding molecules is to incorporate cell binding motifs or other cell-guiding peptides via surface immobilization into gels that lack these components. It should be noted, however, that hydrogels based on natural materials that provide good cell attachment (e.g. collagen) can benefit from several of these techniques. For example, the use of gradient techniques should be more broadly applicable to all hydrogels in an effort to direct cell migration, and photolithographic approaches to pattern hydrogels are important for achieving spatial organization of multiple cell type tissue constructs. Lastly, the spatial distribution of specific cell types is an important consideration in attempts to create *de novo* complex tissues due to well-known physiological structure-function relationships. The ability to achieve cell-specific attachment in a spatially defined fashion is key to achieving this physiology. As such, spatial distribution of peptides or proteins that promote the selective (or preferably specific) attachment of certain cell types based on the principles highlighted in Table 12.2 is also of considerable importance [59,124].

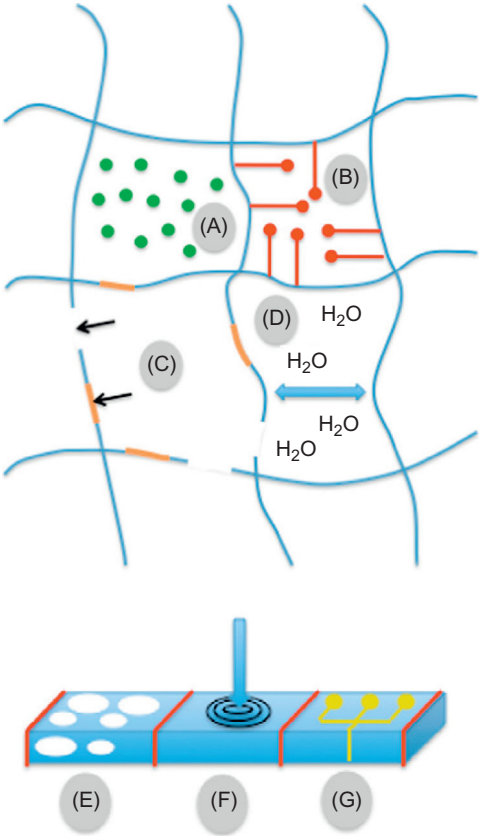



**Figure 12.3** Schematic highlighting several key mechanisms and properties of hydrogels important in regenerative medicine applications. Additional details of these are provided in the text. Delivery of growth factors and other compounds may be provided via soluble factors (A) or matrix-bound cues (B). Delivery of soluble factors may also be controlled by the rate of degradation of the hydrogel (C) through hydrolysis of certain regions (arrows) or other specific enzymatic mechanisms. The water content and swelling (D) also affect soluble factor delivery, protein adsorption, and cell attachment. The porosity of the scaffold (E) and mechanical properties (F) such as compressive modulus are known to have significant effects on cellular infiltration. Lastly, hydrogels can be modified through numerous patterning techniques such as photolithography to provide micropatterned substrates to assess and regulate the microenvironment of cells.

Approaches to achieve surface immobilization include selective adsorption and covalent crosslinking. Selective adsorption is difficult to achieve for protein molecules on hydrogels due to their low

**Table 12.2** Examples and Applications of Matrix-immobilized Ligands with Hydrogel Systems

| Application | Hydrogel Component(s) | Ligand and Immobilization Method | Reference(s) |
|---|---|---|---|
| Cell attachment | Poly(ethylene glycol) (PEG) | Arginine-glycine-aspartic acid (RGD) modified with acryol groups for reaction with poly(ethylene diacrylate) hydrogel | [111] |
| Vascularization of three-dimensional constructs | Collagenase-degradable PEG | Vascular endothelial growth factor (VEGF) and arginine-glycine-aspartic acid-serine (RGDS) covalently coupled to PEG by attaching acry-moiety to ligand for reaction to PEG during polymerization | [112] |
| Improve cell adhesion to non-adhesive gels | PEG | Collagen-mimetic peptide co-polymerized into hydrogel | [113] |
| Delivery of plasmid DNA transgene growth factor expression | Hyaluronic acid/ PEG-collagen | Polyethylenimine-DNA complexes coupled via neutravidin-biotin or non-specific adsorption | [114] |
| Delivery of plasmid DNA transgene growth factor expression | Fibrin | Polyethylenimine-DNA complexes adsorbed non-specifically with high affinity | [115] |
| Guided tissue regeneration with focus on bone | Oligo-poly (ethylene glycol)-fumarate | Osteopontin-derived peptide covalently coupled to hydrogel via PEG linker | [116] |
| Cell attachment to hydrogels | Proteolytically-degradable PEG | RGDS and other cell-adhesive peptides conjugated to PEG linker and photocoupled to hydrogel | [59,117] |
| Cell attachment for soft tissue constructs in trauma applications | Alginate | RGD covalently coupled to alginate backbone | [118] |
| Osteoblast adhesion for bone tissue engineering | Poly(propylene fumarate-co-ethylene glycol) | RGDS covalently coupled to hydrogel via PEG linker | [119] |
| Directing cell attachment and migration | PEG | RGDS or basic fibroblast growth factor (bFGF) covalently immobilized to hydrogel in gradient fashion | [52,120] |
| Cell adhesion and neurite outgrowth | Agarose | RGDS covalently immobilized to hydrogel via photo-cross-linking | [121] |
| Cell binding and vascularization of tissue constructs | PEG | RGDS and vascular endothelial growth factor covalently coupled to hydrogel via photo-cross-linker in pattern defined by photo-masking lithography | [122] |

protein adsorption. Certain hydrogels may allow adsorption through electrostatic interactions and larger particles (see PEI−DNA complexes in Table 12.2) allow more interactions with the material surface, thereby promoting adsorption through multiple weak interactions. Non-covalent but strong interactions such as avidin-biotin crosslinking has also been used as it is a straightforward process without reaction by-products. However, covalent crosslinking is clearly the most widely used approach to achieving matrix immobilization of bioactive molecules.

For covalent crosslinking, the molecule of interest may be reacted with a chemically labile side group on the hydrogel in the solution phase prior to gelation. Photo-crosslinking is now more widely used, particularly for cellular applications to avoid chemical reaction by products and to prevent loss of activity of the bioactive molecule during the gelation process. Most hydrogels are compatible to some degree with photo-crosslinking as they are somewhat translucent. Thicker constructs, however, may require the use of layered constructs to achieve desired coupling throughout the hydrogel. Photo-crosslinking is also useful as it is compatible with lithographic techniques that allow control over cell spatial distribution. References to representative papers on these approaches are provided in Table 12.2.

In addition to their compatibility with soluble and matrix-bound chemical cues, parameters of hydrogels can be altered to change the mechanical properties of the gel. Table 12.3 lists several of these parameters. Changes in these parameters clearly affect the mechanical properties of the gels, which in turn affect cell systems. For example, low moduli PEG gels have been shown to promote markers of early cardiomyocyte differentiation in an embryonal carcinoma cell model [133]. Proliferation of neural stem cells has been shown to be inversely proportional to the matrix modulus of alginate hydrogels [134]. Matrix modulus in conjunction with mechanical stimulation has been shown to have effects on chondrocyte morphology in PEG gels [6,128]. Other parameters that affect the mechanical properties and the cellular response include the porosity of the hydrogel, which can be modulated through the use of porogens. Effects of the porosity have also been demonstrated to affect mesenchymal stem cell proliferation [135] and mineralization in osteogenic medium [136]. Thus, although chemical regulatory mechanisms are perhaps better understood, it is clear that the mechanical nature of the materials must be given equal consideration.

## 12.4 Applications of Hydrogels in Regenerative Medicine

As described above, hydrogels are applicable for fundamental studies on the role of topographical patterning, microfluid flow, and high-throughput screening. They are also in use or under investigation as a repair or replacement strategy for virtually all tissues including both hard and soft tissues. It is not possible to describe every tissue and application, but the goal of this section is to highlight several areas in which hydrogels are used in a translational light.

### 12.4.1 Skin and Wound Healing

The FDA's searchable database (1979 to present) indicates that more than 510,000 applications have

**Table 12.3** Effect of Hydrogel Parameters on Mechanical Properties

| Parameter | Effect | Relevant Reference(s) |
|---|---|---|
| Water content | Inversely correlated with crosslink density. Decreased water content leads to increase in compressive modulus | [125,126] |
| Crosslink density | Inversely correlated with water content. Increased crosslink density leads to increase in compressive modulus | [6,125,127,128] |
| Degradation | Decrease in compressive modulus as gel degrades | [126] |
| Molecular weight | Increase in molecular weight for oligo(polyethylene glycol) leads to decrease in tensile modulus, increase in toughness, and a higher percent elongation | [129] |
| Charge | For anionic hydrogels, increasing surface charge leads to swelling and decrease in modulus | [130]; [131][a]; [132] |
| Electrical field | Hydrogel deswells with application of electrical field leading to increase in modulus | [131][a]; [132] |

[a] *[131] is a theoretical model based on experimental results from [130].*

been granted for the use of hydrogels in treating wounds than any for other medical device application. This is in part due to the shear number of wound healing products as well as the overlap in mechanical property similarities between skin and most hydrogels. Beyond the mechanical properties, there are numerous advantages to the use of hydrogels in these systems. Namely, hydrogels for wound healing applications are:

- Permeable to oxygen to prevent necrosis of remaining and newly forming tissue.
- Able to retain moisture at the site of injury to promote healing.
- Compatible with therapeutic agents important to wound healing including antimicrobials, steroids, and growth factors.
- Able to stimulate cellular response and infiltration with minimal foreign body response and subsequent scarring.

An FDA-approved dressing that makes use of a number of concepts described earlier is Oxyzyme, and there are other similar market-approved products. This proprietary hydrogel contains glucose oxidase, which, in the presence of oxygen, leads to the formation of gluconic acid and hydrogen peroxide. The hydrogen peroxide decomposes to water and oxygen, thereby further improving the oxygenation of the tissue. This product also contains iodine to inhibit bacterial growth and contamination of the wound [137,138]. Preclinically, bilayered chitosan hydrogels have been used in a third degree porcine burn model [139] and the application of matrix-immobilized fibronectin on hyaluronic acid has been shown to promote fibroblastic wound healing response [40]. These studies indicate that the next generation of clinical hydrogel wound dressings will utilize current-generation research principles.

### 12.4.2 Musculoskeletal

Some of the earliest-envisioned applications for hydrogels in tissue engineering involved replacements for gel-like tissues such as articular cartilage [140–142]. These tissues have high levels of glycosaminoglycans and therefore have a high water content, making them a type of natural hydrogel. Hydrogels encapsulating chondrogenic cells are a promising approach to cartilage repair. Examples of chondrocyte-encapsulating materials include alginate [143], oligo(polyethylene glycol) fumarate (OPF) with soluble TGFβ1 delivered from gelatin microspheres [144], and fibrin-PEG-poly(lactic acid) hydrogels, which are currently in large animal trials [145]. Indeed, for articular cartilage, an extremely wide range of hydrogels has been used, in part because suitable treatments have not be found. An interesting approach that is applicable to cartilage repair is the use of adhesive hydrogels that contain chondroitin sulfate in combination with methacrylate and aldehydes to bridge the material with native tissue [146].

Hydrogels do not possess the mechanical properties of native bone tissue and are not applied directly for bridging critically sized gaps without fixation. However, the controlled release capabilities of hydrogels have been widely exploited for the delivery of growth factors (and plasmid DNA encoding for growth factors) that promote robust bone formation. For cell-free hydrogels, this generally involves delivery of bone morphogenetic protein 2 (BMP-2) or 7 (BMP-7 also known as OP-1) as these compounds are FDA approved. Recent examples of this approach include delivery of BMP-2 via an *in situ* gelling hyaluronic acid/polyvinyl alcohol hydrogel [147], and BMP-2 delivery from a gelatin hydrogel for a rabbit segmental bone defect model [148] and regeneration of skull tissue in non-human primates [149]. It might be argued that any material that delivers the potent mitogen BMP-2 will lead to successful bone regeneration. However, hydrogels or other materials that minimize ectopic bone formation meet an important criteria for bone regeneration systems. The controlled release of BMP-2 on timescales most beneficial for promoting regeneration is also important. Unfortunately, this timescale is not well defined, though it appears that there exists a threshold level of BMP-2 that can achieve bone regeneration.

### 12.4.3 Neural Regeneration

Hydrogels are becoming more widely used with encapsulation of Schwann cells and neural progenitor cells to promote neural regeneration via cell-based trophic support. However, hydrogels have been and remain widely investigated as standalone materials for neural regeneration applications as well. This is because the regeneration of neuronal axons is different from many other tissues in

that the cell body is typically located proximally to the site of injury, requiring migration of a part of the cell (i.e. the axon) to and then through the site of injury.

In the peripheral nervous system, hydrogels are under investigation as fillers for nerve conduits composed of natural materials such as collagen (e.g. Neuragen Nerve Guide) or synthetic materials (e.g. Silastic). Examples of hydrogels used as fillers include agarose, fibrin, and keratin, among others. The role of charge [150] and mechanical properties [151] have been elucidated for peripheral nerve systems. Some natural materials appear to promote regeneration simply through the provision of the physical matrix [23], which allows for Schwann cell infiltration and axonal extension through gels. Others have developed hydrogel scaffolds of higher mechanical integrity that are also promising for neural regeneration through the provision of physical guidance cues [8,152]. Glial and neuronal axon migration through hydrogels has also been enhanced through delivery of soluble growth factors such as NGF from fibrin [153] as well as through the presentation of laminin or laminin-based peptides that are matrix-immobilized [29,154]. Hydrogels have also been created to provide topographical cues in three dimensions alone or in combination with matrix-bound ligands [8,155], indicating the integration of chemical and mechanical properties in guiding neural regeneration.

These principles are also applicable to spinal cord injuries (SCIs). However, injectable gel systems are advantageous in the case of SCIs as complete transection of the spinal cord is rare and materials that can be injected in a less invasive fashion are desirable. Those hydrogels that can gel *in situ* may be particularly appealing as they are injectable yet provide additional mechanical integrity [90].

### 12.4.4 Liver

The mechanical properties of hydrogels could indicate that they would be best suited to the development of the visceral organs. Indeed, hydrogels are widely used both for fundamental studies at the cell level and in more translational applications toward the development of functional units. As indicated in the previous sections, hydrogels are used extensively as controlled release systems, often for the delivery of factors to promote angiogenesis. Due to diffusional limitations in large tissues, one approach has been the formation of smaller functional constructs. The simplest example of this is the microencapsulation approach described above.

More complex approaches are being developed toward the creation of functional tissues through provision of the correct structural properties of these tissues. In one example of this, hepatocytes encapsulated in thin collagen gel sheets have been shown to be vascularized and demonstrate functional markers [156]. In a more sophisticated approach, PEG hydrogels were functionalized to promote cell adhesion and processed into complex shapes reminiscent of native liver structure, demonstrating functionality [157]. In each case, the hydrogels serve the role of promoting cell engraftment through encapsulation and also likely provide for improved diffusional profiles to allow for bioreactor perfusion [157] and vascularization [156]. These approaches are certainly applicable to other visceral organs. Recently, multi-layered hydrogels have been developed from natural hydrogels such as alginate and hyaluronic acid [158] as well as synthetic materials [159]. Such multi-layer systems provide the opportunity to juxtapose cells in structural orientations that mimic native tissue.

The ideal approach to the generation of complex tissues such as the liver and other visceral organs certainly remains in doubt, but it is clear that hydrogel-based technologies such as these of creating small functional units as well as other encapsulation and printing technologies provide potential solutions alone or in combination with other approaches.

### 12.4.5 Reproductive Medicine

An area in which the mechanical properties of hydrogels has recently proven useful is in the tissue engineering of ovarian follicles. Females facing radiotherapy or chemotherapy are at increased risk of future infertility. The ability to grow and preserve immature ovarian follicles in culture has been suggested as an approach to minimize the risk of reintroducing cancer cells to patients as may occur with the use of ovarian tissue cryopreservation [160]. Alginate hydrogels have been used to provide three-dimensional context to immature ovarian follicles, allowing growth *in vitro* and also allowing for stable cryopreservation [161]. This approach

has resulted in the live birth of fertilized embryos in a mouse model [160]. Early studies have utilized alginate due to its mechanical properties and compatibility with cell encapsulation as described above. Recently, alginate-fibrin hydrogels have shown increased numbers of meiotically competent oocytes [162], indicating that optimization of the hydrogel chemical and mechanical properties may lead to further improvements in this promising technique.

## 12.5 Prospects and Conclusions

Hydrogels are clearly an important component in the repertoire of biomaterial approaches to regenerative medicine with applications in nearly every organ system currently under exploration. The ability to modify hydrogels with bioactive molecules has proven fortuitous in the era of bioactive compound delivery as it allows for the integration of mechanical properties that mimic native tissue with bound and soluble chemical cues. In looking to the future of hydrogels in regenerative medicine applications, there are several opportunities for the development of these systems.

It should be clear from this chapter that there is a very large number of material parameters that can be altered for numerous applications. While many hydrogels allow a systematic evaluation of these parameters in isolation, the ability to compile a set of parameters that are optimal or near optimal for a particular application is not readily accomplished. The use of statistical analysis and parametric analysis, and the development of sophisticated engineering models in combination with some of the high-throughput screening methods described will be important in the design of regenerative medicine therapies involving hydrogels [163].

The use and characterization of hydrogels for the delivery of therapeutic agents that behave differently from traditionally delivered molecules is also of increasing importance. Examples include the use of hydrogels for the delivery of nucleic acids or gaseous materials. The advent of the gene-activated matrix (GAM) has spurred methods to achieve delivery of DNA, RNA, antisense, siRNA, or other nucleotides from hydrogels. Efficient delivery of these molecules to their cellular site of action has been of interest to the gene delivery community, and recent approaches to promoting viral [164] or non-viral [114] delivery of nucleic acids from hydrogel scaffolds [165] will likely take on increasing importance. The lack of oxygen and nutrient supply to tissue-engineered constructs is also well documented [166]. While delivery of factors promoting vascularization is widely studied, other alternatives such as the direct delivery of oxygen have been investigated more recently [167]. The role of hydrogels in regulating release of these types of molecules will also be an important consideration.

Another challenge in regard to hydrogels is obtaining the mechanical integrity necessary for tissue engineering applications. As described previously, one advantage of hydrogel systems is that they provide a matrix comparable in modulus to native extracellular matrix for many soft tissues. However, the mechanical integrity of many commonly used biodegradable hydrogels diminishes with time and the starting properties may be insufficient to withstand mechanically challenging bioreactor systems that are increasingly used for perfusion as well as mechanical and electrical stimulation. Increasing the polymer concentration within the gels provides additional mechanical support but reduces nutrient and oxygen diffusion, thereby inhibiting cell viability with the material. One approach to providing mechanical stability while promoting cell infiltration into hydrogels is through the use of templating approaches. These approaches include the use of micellar structures [168] and sacrificial polymer beads [169], or other geometries [8,170] that mimic native tissue architecture. This approach promotes cell infiltration or encapsulation throughout the scaffold and allows diffusion to occur in a fashion similar to macroporous hydrogels. This approach may provide the mechanical integrity necessary for bioreactors such as those used for ligament [171,172], tendon [173], and muscle [174]. To date, limited hydrogels have been used in these mechanically challenging systems [175,176]. However, modifications to natural polymers to allow bioreactor pre-conditional in conjunction with their advantageous cell adhesion and differentiation motifs may prove of great utility in regenerative medicine applications.

It is difficult to generalize the host response to hydrogels due to differences in the chemistry of the materials, leachates, processing techniques, and methods of sterilization. However, most experts

would agree that the difference in the host response to hydrogels compared to traditional polymer systems was and remains a key point of interest for these materials. Monocyte and macrophage response to traditional polymers involves protein adsorption, monocyte/macrophage response, and (typically) fibrous encapsulation. This is generally considered an acceptable response for a material [177]. However, hydrogels may be well positioned to exploit the body's native machinery to achieve a more desirable host response to the material and cells or tissues associated with it. For example, it has been suggested that certain biological hydrogels and porous hydrogels may promote an alternative macrophage phenotype that is anti-inflammatory and may even lead to recruitment of progenitor cell populations that can transdifferentiate for the promotion of tissue remodeling within and around the hydrogel [178–180]. While further studies are needed to elucidate the mechanisms, the methods described in this chapter provide the tools to harness and manipulate these processes.

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# 13 Biodegradable Polymers

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## 13.1 Introduction

The design and development of tissue-engineered products has benefited from many years of clinical utilization of a wide range of biodegradable polymers. Newly developed biodegradable polymers and modifications of previously developed biodegradable polymers have enhanced the tools available for creating clinically important tissue-engineering applications. Insights gained from studies of cell-matrix interactions, cell-cell signaling, and organization of cellular components, are placing increased demands on medical implants to interact with the patient's tissue in a more biologically appropriate fashion. While in the twentieth century, biocompatibility was largely equated with eliciting no harmful response, the biomaterials of the twenty first century will have to elicit tissue responses that support healing or regeneration of the patient's own tissue.

This chapter surveys the universe of those biodegradable polymers that may be useful in the development of medical implants and tissue-engineered products. Here we distinguish between biologically derived polymers and synthetic polymers. The materials are described in terms of their chemical composition, breakdown products, mechanism of breakdown, mechanical properties, and clinical limitations. Also discussed are product design considerations in processing of biomaterials into a final form (e.g., gel, membrane, matrix) that will effect the desired tissue response.

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In this chapter, we follow the official polymer nomenclature conventions adopted by the International Union of Pure and Applied Chemistry (IUPAC). According to these rules, the correct naming of a polymer requires the simple addition of the prefix "poly" in front of the monomer name, *if the monomer name consists of a single word*. For example, the polymer made of ethylene is simply polyethylene. There is no space between poly and ethylene. When the monomer name consists of two or more words, it is important that the entire monomer name be enclosed in parentheses. This is needed to avoid ambiguity. For example, the polymer made of lactic acid is correctly named as poly (lactic acid). Note the absence of a space between the prefix poly and the parenthesis. Polymers made of amino acids are sometimes referred to as peptides, proteins, or poly(amino acid)s. When referring to one polymer that is made of one type of amino acid, IUPAC rules require this material to be named as a poly(amino acid). When referring to several such polymers, the plural of poly(amino acid) is poly(amino acid)s. Note the placement of the plural "s" outside of the parenthesis. When a polymer is made of several different amino acids, then that polymer would be referred to as a poly (amino acids). Note the placement of the plural "s" inside the parenthesis, indicating that this is a single polymer that contains more than one type of amino acid as monomer. Unfortunately, these rules are often violated in the contemporary literature.

## 13.2 Biodegradable Polymer Selection Criteria

The selection of biomaterials plays a key role in the design and development of medical implants and tissue-engineering products. While the classical selection criterion for a safe, stable implant dictated choosing a passive, "inert" material, it is now understood that any artificial material placed into the body of a patient will elicit a cellular response [1,2]. This means that there are in fact no artificial materials that are totally "inert", and some of the chemically least reactive materials, such as polyethylene or polysiloxane, can cause significant inflammatory responses. Therefore, it is now widely accepted that a biomaterial must interact with tissue in a biologically appropriate manner rather than act simply as an inert body. Consequently, a major focus of biomaterials science centers around harnessing control over cellular interactions with biomaterials. Researchers now tend to explore ways to manipulate the cellular response by including biologically active components in the design of biomaterials. Specific examples of such biologically active components include protein growth factors, anti-inflammatory drugs, and gene delivery vectors [3].

It is important for the tissue-engineering product developer to have many biomaterials options available, as each application calls for a unique environment for cell-cell interactions. Such applications include:

1. Support for new tissue growth (wherein cell-cell communication and cells' access to nutrients, growth factors, and pharmaceutically active agents must be maximized);
2. Prevention of cellular activity (where tissue growth, such as in surgically induced adhesions, is undesirable);
3. Guided tissue response (enhancing a particular cellular response while inhibiting others);
4. Enhancement of cell attachment and subsequent cellular activation (e.g., fibroblast attachment, proliferation, and production of extracellular matrix for dermis repair) [4];
5. Inhibition of cellular attachment and/or activation (e.g., platelet attachment to a vascular graft);
6. Prevention of a biological response (e.g., blocking antibodies against grafted cells used in organ replacement therapies).

Biodegradable polymers are applicable to those tissue-engineering products in which tissue repair or remodeling is the goal, but not where long-term materials stability is required. Biodegradable polymers must also possess:

1. Manufacturing feasibility, including availability of sufficient commercial quantities of the bulk polymer;
2. The capability to form the polymer into the final product design;
3. Mechanical properties that adequately address short-term function and do not interfere with long-term function;

4. Low or negligible toxicity of degradation products, in terms of both local tissue response and systemic response;
5. The capability to be formulated as a drug delivery system in applications that call for prolonged release of pharmaceutically active compounds.

## 13.3 Biologically Derived Polymers

Biologically derived polymers are materials created by living organisms, as opposed to synthetic materials which are man-made. This distinction divides the universe of medically useful, biodegradable polymers into two large subgroups. However, the delineation between these groups is not always clear-cut. For example, glycolic acid is a natural metabolite and poly(glycolic acid) is naturally produced by many organisms. However, glycolic acid can also be created synthetically from oil-derived starting materials. Currently, poly(glycolic acid) is produced commercially by both fermentation and synthetic processes. Both production pathways result in the same final product, making poly(glycolic acid) either a biologically derived polymer or a synthetic polymer. A similar situation exists in regard to polymers derived from hydroxybutyric acid and hydroxyvaleric acid. Commonly referred to as polyhydroxyalkanoates, these polymers can be derived from bacterial fermentation, as well as purely synthetic processes. In this chapter, polyhydroxyalkanoates are included among the biologically derived polymers (since the most prevalent mode of commercial production is based on bacterial fermentation), while poly(glycolic acid) and the closely related poly(lactic acid) are introduced to the reader as synthetic polymers (since the predominant mode of commercial production is currently based on oil-derived starting materials and synthetic polymerization reactions).

The biologically derived polymers can be further classified into peptides and proteins, polysaccharides, polyhydroxyalkanoates, and polynucleotides. Each of these subgroups will be discussed separately.

### *13.3.1 Peptides and Proteins*

Peptides and proteins are polymers derived from naturally occurring $\alpha$-L-amino acids. Peptides are usually shorter chains of dozens of amino acids linked together via amide bonds, while proteins are longer chains of hundreds of individual amino acids. The amino acids are connected via hydrolytically stable amide bonds. Therefore, these materials are usually degraded via enzymatic mechanisms. The major shortcoming of peptides and proteins as starting materials for the fabrication of any medical implant is their lack of "processibility". This term refers to the ability of creating a shaped device by any of the conventional polymer processing methods used in the plastics industry: compression molding, extrusion, injection molding and fiber spinning. Another important limitation of peptides and proteins as biomaterials is their inherent immunogenicity. Any peptide or protein carries the risk of being recognized as foreign by the patient's immune system. For example, for many years, the safety of using bovine collagen was a hotly debated topic because of fears that the implantation of bovine collagen could provoke an immune response and predispose the patient to autoimmune diseases.

On the other hand, peptides and proteins can have outstanding biological properties and can help the tissue engineer in designing a polymer with desirable biological activities. This fact has been the driving force behind the long-standing interest in using peptides and proteins as starting materials for medical implants or tissue-engineering products. Unfortunately, most peptides and proteins have mechanical properties that are not conducive for their use in medical implants, resulting in the utilization of only a very small number of proteins as biomaterials (Table 13.1).

#### 13.3.1.1 Collagen

Collagen is the major component of mammalian connective tissue, accounting for approximately 30% of all protein in the human body. It is found in every major tissue that requires strength and flexibility. Fourteen types of collagens have been identified, the most abundant being type I [5]. Because of its abundance and its unique physical and biological properties, type I collagen has been used extensively in the formulation of biomedical materials [6]. Type I collagen is found in high concentrations in tendon, skin, bone and fascia, which are consequently convenient and abundant sources for isolation of this natural polymer.

**Table 13.1** Proteins Used as Degradable Biomaterials in Medical Implants

| Type of protein | Source | Function |
|---|---|---|
| Collagen | Isolated from cattle, fish, and other species | Key component of tissue architecture, provides mechanical strength, supports cell attachment and growth, provides a biocompatible matrix for cell transplantation. Used extensively as a tissue expander and bulking agent in cosmetic products |
| Gelatin | Partially hydrolized collagen | Used in food industry, widely explored by researchers as a matrix for three-dimensional cell culture and as a component of tissue-engineering scaffolds |
| Elastin | Isolated from elastic tissues of cattle and birds | Key component of tissue architecture, provides elasticity to tissues |
| Keratin | Isolated from skin, hair and nails of cattle and birds | Key structural component of outer skin, hair and nails. Used as a matrix for cell growth and as a component in wound dressings and skin care products |
| Silk | Isolated from insect larvae | Used in the textile industry because of its extraordinaty strength. Also studied as a component of tissue-engineering scaffolds and as a cell culture substrate |
| Proteoglycans | Various tissue extracts | Used in research of cell-matrix interactions, matrix-matrix interactions, cell proliferation, cell migration |

**Table 13.2** Widely Investigated Polysaccharides

| Type of polysaccharide | Source | Function |
|---|---|---|
| Cellulose | Cell wall of green plants | Main structural component of plants which keeps the stems, stalks and trunks rigid |
| Starch (amylose and amylopectin) | Present in all staple foods | Important in plant energy storage |
| Alginate | Found in the cell walls of bacteria | Protects bacteria from engulfment by predatory protozoa or white blood cells (phagocytes) |
| Glycosaminoglycans | Widely distributed | Cell-matrix interactions, matrix-matrix interactions, cell proliferation, cell migration |
| Chitin/chitosan | Major component of the exoskelton of insects, shells of crustaceans, cell walls of fungi | Structural component |

The structure, function, and synthesis of type I collagen has been thoroughly investigated [7]. Because of its phylogenetically well-conserved primary sequence and its helical structure, collagen is only mildly immunoreactive [8]. However, many human recipients of medical or cosmetic products containing bovine collagen have anti-bovine collagen antibodies. The clinical significance of this finding is not yet fully understood.

The individual collagen molecules will spontaneously polymerize to form strong fibers that form larger organized structures. Collagen exists in tissue

in the form of collagen fibers, fibrils, and macroscopic bundles [9]. For example, tendon and ligaments are comprised mainly of oriented type I collagen fibrils, which are extensively crosslinked in the extracellular space.

*In vitro*, collagen crosslinking can be enhanced after isolation through a number of well-described physical or chemical techniques [10]. Increasing the intermolecular crosslinks:

1. Increases biodegradation time, by making collagen less susceptible to enzymatic degradation;
2. Decreases the capacity of collagen to absorb water;
3. Decreases its solubility; and
4. Increases the tensile strength of collagen fibers.

The free amines on lysine residues on collagen can be utilized for crosslinking, or can similarly be modified to link or sequester active agents. These simple chemical modifications provide a variety of processing possibilities and consequently the potential for a wide range of tissue-engineering applications using type I collagen.

It has long been recognized that substrate attachment sites are necessary for growth, differentiation, replication, and metabolic activity of most cell types in culture. Collagen and its integrin-binding domains (e.g., RGD sequences) assist in the maintenance of such attachment-dependent cell types in culture. For example, fibroblasts grown on collagen matrices appear to differentiate in ways that mimic *in vivo* cellular activity and to exhibit nearly identical morphology and metabolism [11]. Chondrocytes can also retain their phenotype and cellular activity when cultured on collagen [12]. Such results suggest that type I collagen can serve as tissue-regeneration scaffolds for any number of cellular constructs.

The recognition that collagen matrices could support new tissue growth was exploited to develop the original formulations of artificial extracellular matrices for dermal replacements [1,2,13–15]. Yannas and Burke were the first to show that the rational design and construction of an artificial dermis could lead to the synthesis of a dermis-like structure whose physical properties "would resemble dermis more than they resembled scar" [15]. They created a collagen–chondroitin sulfate composite matrix with a well-described pore structure and crosslinking density that optimizes regrowth while minimizing scar formation [16]. The reported clinical evidence and its simplicity of concept make this device an important potential tool for the treatment of severely burned patients [17].

The advantageous properties of collagen for supporting tissue growth have been used in conjunction with the superior mechanical properties of synthetic biodegradable polymer systems to make hybrid tissue scaffolds for bone and cartilage [18,19]. These hybrid systems show good cell adhesion, interaction and proliferation compared to the synthetic polymer system alone. Collagen has also been used to improve cell interactions with electrospun nanofibers of poly(hydroxy acids) such as poly(lactic acid), poly(glycolic acid), poly(ε-caprolactone) and their copolymers [18–22].

In recent years, the combination of collagen scaffolds with active biological entities, such as cells, growth factors, platelet rich plasma [23] and various autologous or allogenic cell types [24] have provided significant opportunities for researchers to achieve tendon and ligament regeneration.

#### 13.3.1.2 Gelatin

Gelatin is commonly used for pharmaceutical and medical applications because of its enzymatic biodegradability and biocompatibility in physiological environments [25–27]. Of the two types, acidic and alkaline gelatin, the former has an isoelectric point similar to collagen. The isoelectric point depends on its extraction procedure from collagen, and variations in it allow gelatin to bind with either positively or negatively charged therapeutic agents. Based on this, the acidic gelatin, with an isoelectric point of 5.0, could be used as a carrier for basic proteins *in vivo,* while basic gelatin, with an isoelectric point of 9.0, could be used for the sustained release of acidic proteins under physiological conditions. The advantage of gelatin as a carrier for controlled drug release is that the therapeutic agent can be loaded into the gelatin matrix under mild conditions. Gelatin hydrogels have been used as controlled release devices for a variety of growth factors known to enhance bone formation. Yamada et al. successfully incorporated bFGF (basic fibroblast growth factor) into acidic gelatin hydrogels, which were implanted into a

rabbit skull defect to allow for the localized release over 12 weeks [28,29].

#### 13.3.1.3 Elastin

Elastin is an extracellular matrix protein and is most abundant in tissues where elasticity is of major importance, such as blood vessels (50% of dry weight), elastic ligaments (70% of dry weight), lungs (30% of dry weight) and skin (2−4% of dry weight) [30,31].

The incorporation of elastin into biomaterials was a major topic of research in the 1970s and 1980s. The basic structure-function-activity correlations of various elastin sequences were discovered by Urry and his associates [32]. It is important to note that elastin is not a single, well-defined molecule. Rather, the name "elastin" is associated with a wide range of elastic peptide and protein sequences that exist in different lengths and with different compositions. A common feature of all elastin sequences is that they are rich in glycine, proline, and lysine. In humans, elastin is synthesized early in life. By age 40 (approximately) elastin biosynthesis in humans slows down to a trickle. The appearance of skin wrinkles and other aging processes are directly related to the loss of elastin biosynthesis. This fact has been exploited as a marketing gimmick by cosmetic companies, who add elastin to a wide range of anti-aging products. However, there is overwhelming evidence that externally applied elastin is not able to pass through the skin and is not able to slow the loss of elastin from aging tissues.

When elastin was used as a component in heart valve prosthetic devices, the deposition of calcium-rich precipitates was a significant problem. This process, often referred to as "calcification", limited the utility of elastin-containing biomaterials in cardiovascular prosthetic implants [33]. This experience illustrates that the use of natural substances is not necessarily a guarantee for clinically successful device performance.

Another important point is that not all biologically derived polymers are good cell growth substrates. While collagen is highly cell adhesive, elastin tends to discourage cell attachment and growth. This has been a concern in the biomedical community, since many potential applications of elastin (for example in blood vessel and ligament regeneration) would require a highly cell adhesive surface. This challenge can be addressed using the tools of protein engineering to incorporate cell adhesive peptide sequences within the elastin structure [32].

Overall, elastin is a highly versatile biomaterial that continues to inspire the imagination and curiosity of biomedical engineers. Recently, the ability of elastin to self-assemble into large supramolecular structures was used to fabricate sponges, scaffolds, sheets and tubes from human tropoelastin [34]. These promising studies are still ongoing.

#### 13.3.1.4 Keratin

Keratin is the name for a family of structural proteins which are abundant in the outer layer of human skin, in hair, and in nails. Keratin is rich in the amino acid cysteine, and it has the ability to self-assemble into bundles of fibers. Within these fiber bundles, individual strands are further cross-linked through S-S (sulfur-sulfur) bonds involving the cysteine side chains. In this way, keratin forms particularly tough, insoluble structures that are among the strongest non-mineralized tissues found in nature. The only other non-mineralized tissue that resembles the toughness of keratin is chitin (the material found in the exoskeleton of insects and the outer shell of shellfish).

Since human hair is rich in keratin, this protein is added to many hair care products. However, as in the case of the misleading marketing claims made for elastin-containing anti-aging skin products, there is no evidence that externally applied keratin can penetrate into the hair structure. While keratin was mostly studied for use in cosmetic (hair care) products, the exploration of keratin's properties also led to the development of keratin-based biomaterials for use in biomedical applications. The unusual mechanical properties and strength of keratin and its ability to self-assemble were the driving force for these biomedical studies.

The history of keratin research illustrates another major challenge when using biologically derived polymers as biomaterials. Based on the animal source used, and depending on the exact extraction procedure employed, individual keratin preparations can differ significantly from each other. The variability and irreproducibility of individual preparations is a general feature of most biologically derived polymers. Early research, mostly by Yamauchi's laboratory, focused on the preparation

of protein films from keratin extracted from wool and human hair. These pure protein films were brittle and weak. The researchers could not reproduce in the laboratory the outstanding strength of keratin formed *in vivo*. Only when glycerol was added as a plasticizer, could keratin films be obtained that were relatively strong and flexible [35]. Fujii et al. also demonstrated that hair keratins were useful for preparing protein films and described a rapid casting method [36]. This research also revealed the feasibility of incorporating bioactive molecules such as alkaline phosphatase into the keratin films for controlled release applications. The films, however, had poor strength and flexibility [36]. Recently, significant progress was made by researchers at Wake Forest University, where keratin extracted from human hair was used as a matrix for the regeneration of peripheral nerves. This is currently one of the most advanced applications of keratin as a biomaterial [37].

#### 13.3.1.5 Silk

On a weight basis, natural silk fibers can be stronger than high-grade steel. However, the strength of natural silk fibers is difficult to reproduce in the laboratory once pure silk has been extracted from the cocoons of silkworm larvae or from spider's webs. Still, the unique mechanical properties of natural silk fibers have fascinated scientists for more than a century. Recent work has demonstrated the biocompatibility of various silk protein preparations [38]. Another very interesting fact is that the degradation rate of laboratory-made silk fibers can be tailored to be from months to years after implantation *in vivo*, based on the processing procedure employed during the material's formation [39]. Finally, the thermal stability of silk biomaterials allows processing over a wide range of temperatures up to about 250°C, as evidenced by the ability to autoclave silk biomaterials without loss of functional integrity. Min and colleagues investigated the potential of electrospun silk matrices for accelerating early stages of wound healing [40]. In another study, chitin was blended with silk fibroin to fabricate composite fibrous scaffolds for skin tissue engineering. The rationale of these experiments was to combine the good mechanical properties of silk fibers with the wound healing effects of chitin [41]. The chitin/silk fibroin blends were electrospun to form nanofibrous matrices and evaluated for initial cell attachment and spreading [42]. *In vitro*, increased adhesion of keratinocytes was observed on chitin/silk blend matrices compared to pure chitin matrices, but the significance of these results for wound healing *in vivo* has not yet been established.

Overall, the exploration of silk as a biomaterial has not yet produced any commercially available medical products. While silk is a fascinating material, the studies performed so far have not discovered truly compelling reasons for the use of silk as a medical implant material.

#### 13.3.1.6 Proteoglycans

Proteoglycans (PGs) are a major component of the extracellular matrix (ECM). They consist of one or more glycosaminoglycan (GAG) chains that are attached, via a tetrasaccharide link, to serine residues within a core protein [43,44]. GAGs are long chains of repeating disaccharide units that are variably sulfated. There are four main classes of GAGs—hyaluronan (HA), chondroitin sulfate (CS) and dermatan sulfate (DS), heparan sulfate (HS), and keratan sulfate (KS). PGs exhibit great structural diversity because each type of PG may contain different kinds of GAGs, different numbers and lengths of GAG chains, modifications in the repeating patterns of the disaccharides by a complex pattern of sulfate groups, and a different core protein structure. PGs can be present in monomeric form or can form very large aggregates. Both the core protein and the GAG chains of PGs play key roles in tissue remodeling, intracellular signaling, uptake of proteins, cell migration, and many other crucial functions in native tissues [43,44]. The fact that PGs seem to be involved in so many crucial cell signaling pathways is the main reason for the intense interest of biomedical engineers in understanding their properties.

To replicate the biological functions of PGs in tissue scaffolds, PGs or their GAG chains have frequently been grafted to the polymers used in fabricating tissue scaffolds, or they have been grafted onto the surface of tissue-engineering scaffolds. Most notably, chondroitin sulfate GAGs have been used to create collagen−GAG hybrid materials which seem to be particularly effective in skin regeneration.

PGs are sometimes used alone or in combination with other matrix proteins such as fibrin, collagen,

or chitosan to create hybrid materials [45–47]. The rationale for exploring such complex mixtures is usually an attempt to "mix and match" biological properties with appropriate mechanical properties. For example, a mixture of PGs and extracellular matrix proteins are part of the widely used Matrigel™ scaffold. Among the various combinations, collagen–GAG scaffolds are often preferred for tissue-engineering applications, because collagen provides a very cell friendly matrix environment and the specific GAG used can affect (and regulate) cell behavior. Collagen–GAG hybrids can be readily sterilized using heat, and can be manufactured with a variety of pore structures and a wide range of degradation rates [48]. The first commercially used tissue-engineered product, an artificial skin scaffold, developed by Integra LifeSciences, a New Jersey company, is a collagen–GAG hybrid.

### 13.3.2 Biomimetic Materials

Biomimetic materials are synthetic (man-made) materials that mimic natural materials or that follow a design motif derived from nature. In the previous section, a number of peptides and proteins were discussed. In general, peptides and proteins are isolated from natural sources and are therefore listed among the biologically derived polymers. However, significant research breakthroughs were made when scientists started to create mimics of natural polymers by semi-synthetic or totally synthetic means. An excellent example for this type of research approach is the work of Urry and coworkers, who used peptide synthesis methods to create artificial variants of elastin [49,50]. Using a combination of solid-phase peptide chemistry and genetically engineered bacteria, they synthesized several polymers which contained homologies of the elastin repeat sequences valine-proline-glycine-valine-glycine (VPGVG). These biomimetic polymers had better engineering properties than their natural equivalents, making it possible to create films and fibers that could then be further modified by cross-linking. The resultant films had intriguing mechanical responses, such as a reverse phase transition which results in contraction with increasing temperature [50], resembling the action of muscles. The exact transition temperature could be varied by variations in the polymer's amino acid composition [50]. Several medical applications are under consideration for this system, including musculoskeletal repair mechanisms, ophthalmic devices, and mechanical and/or electrically stimulated drug delivery.

Other investigators, notably Tirrell and Cappello, have combined techniques from molecular and fermentation biology to create novel protein-based biomaterials [51–54]. These researchers had the remarkably innovative idea of creating genetically-engineered microorganisms that would produce exactly those polymers that the researchers liked to study. In this way, completely new variations of biologically derived peptides and proteins could be prepared. These protein polymers were based on repeat oligomeric peptide units, which were controlled via the genetic information inserted into the producing bacteria. It has been shown that the mechanical properties and the biological activities of these protein polymers can be pre-programmed, suggesting a large number of potential biomedical applications [55].

Another approach to elicit an appropriate cellular response to a biomaterial is to graft active peptides to the surface of a biodegradable polymer. For example, peptides containing the RGD sequence have been grafted to various biodegradable polymers to provide active cell-binding surfaces [56]. Similarly, Panitch et al. incorporated oligopeptides containing the REDV sequence to stimulate endothelial cell binding for vascular grafts [57].

### 13.3.3 Polysaccharides

Polysaccharides are polymers made of various sugar (saccharide) units. The most common monosaccharides are glucose and fructose. Sucrose is the chemical name of the widely used table sugar. Sucrose is a disaccharide composed of glucose and fructose. Scientists who are not experts in sugar chemistry are often unaware of the exquisite structural variability of these molecules. For example, the important human food, *starch*, and the structural polymer of all plants, *cellulose*, are both polymers of glucose. The only difference between starch and cellulose is the way in which the individual glucose units are linked together. Considering the many different isomeric variations possible for saccharides, and the different chemical bonds that can be used to link individual saccharide units together, the number of structurally different polysaccharides is extremely large. In fact, the chemistry of

polysaccharides is as rich in diversity and variability as protein chemistry. It is therefore not surprising that various saccharides and polysaccharides play an important role in fine-tuning the responses of cells to their environment. As outlined above, proteoglycans (PGs) and glucosaminoglycans (GAGs) are critical in regulating key cell functions. In contrast, the industrially used polysaccharides (such as starch and cellulose) are polymers comprising exclusively various sugar (saccharide) units as monomers. These polysaccharides can be extremely large polymers containing millions of monomers, and they are mostly used in nature for cellular energy storage or as a structural material. As a general rule, most of the natural polysaccharides are not biodegradable when implanted in any mammalian species due to the lack of digestive enzymes. Therefore, without further chemical modification, most polysaccharides are not obvious material choices for use in biomedical applications.

#### 13.3.3.1 Cellulose

Cellulose is the most abundant polymeric material in nature. In its most common form, it is a fibrous, tough, water-insoluble material that is mostly found in the cell walls of plants, mainly in stalks, stems or trunks. Cellulose is the major ingredient of wood. Cellulose is composed of D-glucose units that are linked together by β-(1→4) glycosidic bonds. In nature, cellulose is formed by a simple polymerization of glucose residues from a substrate such as UDP-glucose [58]. Cellulose possesses high strength in the wet state [59]. The major commercial applications of cellulose are in the paper, wood, and textile industries [60] where millions of tons of cellulose are processed annually worldwide.

The major limitation of cellulose as a biomaterial is that it is not biodegradable, due to the lack of digestive enzymes for cellulose in the human organism [61,62]. However, a number of cellulose derivatives, such as methylcellulose, hydroxypropylcellulose and carboxymethylcellulose are used as biomaterials, due to the useful material properties exhibited by these synthetically created derivatives [63].

Cellulose is not an obvious choice for biomedical applications and there is no scientific rationale to expect cellulose to have unique or useful properties as a cell growth substrate or tissue-regeneration scaffold. This, however, has not prevented a number of laboratories from exploring cellulose or cellulose derivatives as a drug delivery implant, as a barrier for the prevention of surgical adhesions, or as a scaffold in cartilage tissue engineering [64,65]. *In vivo* studies have been performed to assess the biocompatibility of a bacterial cellulose scaffold by subcutaneous implantation in rats. While there were no macroscopic or microscopic signs of inflammation around the implants, and no fibrotic capsule or giant cells were observed, the limited biodegradability of cellulose will most probably prevent the use of this material in most biomedical applications [65].

#### 13.3.3.2 Starch

Whereas cellulose is composed of D-glucose units that are linked together by β-(1→4) glycosidic bonds, starch is composed of D-glucose units that are linked together by α-(1→4) glycosidic bonds. This change makes starch digestible, allowing its use as a major human nutrient. The chemistry of starch is complicated by the fact that starch consists of linear and branched chains, referred to as amylose and amylopectin respectively [66]. The relative abundance of these two natural ingredients can significantly influence the material properties of starch. Consequently, literally hundreds of different starches exist, each with its own particular composition of amylose and amylopectin.

Starch can be totally water insoluble, or partially soluble at room temperature, depending on the proportions of amylose and amylopectin present. Water-soluble starches can be dispersed in water, forming clear solutions upon heating. Upon cooling, soluble starch forms a highly viscous solution at low concentrations and a stiff hydrogel at higher concentrations. This is the basis of the thickening action of soluble corn starch, which is used extensively in the food industry.

Although enzymes present in the human gut can digest starch, it is not readily biodegradable when implanted into human tissues. The cellular energy storage polymer in humans is glycogen and not starch. Consequently, starch is not an obvious choice for biomedical applications. However, some starch-based polymers are biodegradable in human tissues and biocompatible. Among many potential applications, starch-based polymers were used to prepare scaffolds for cartilage regeneration [67].

These scaffolds did not perform better than other types of scaffolds. Starch was also used for the design of implantable drug delivery systems. In spite of the research conducted by several laboratories worldwide, starch-based polymers are not likely to find major biomedical applications in the near future.

#### 13.3.3.3 Alginate

Alginate is a natural anionic polysaccharide found in seaweed, which is composed of β-(1−4) linked D-mannuronic acid and α-L-guluronic acid units. Along its polymer chain, alginate has regions rich in sequential mannuronic acid units, guluronic acid units and regions in which both monomers are equally prevalent.

The most important use of alginate in biomedicine is as a cell-compatible hydrogel. Alginate can form strong hydrogels in the presence of divalent cations (such as $Ca^{2+}$ or $Ba^{2+}$) that interact with the carboxylic groups present in the alginate backbone to form ionic crosslinks. In a typical experiment, a solution of alginate is added to cells suspended in physiologic buffer solution. This mixture is then dropped slowly into a solution of calcium chloride. As each drop of the cell suspension touches the calcium chloride solution, the alginate forms a hydrogel that encapsulates and captures the suspended cells. This process has been used *in vitro* to encapsulate human articular chondrocytes in the presence of recombinant human BMP-2 [68].

Alginate has a well-characterized structure, which allows for a range of comparative studies to be performed. Cells do not readily attach and grow on or within alginate hydrogels. This is a common feature of most unmodified polysaccharides. However, the carboxylic groups in its guluronic acid residues provide an easy handle for the chemical modification of alginate [69]. This feature makes it possible to attach biologically active ligands (such as the important RGD peptide) to the alginate backbone [69].

Alginate's major disadvantage is the difficulty of its isolation from contaminated seaweed, which leads to the presence of mitogenic, cytotoxic and apoptosis inducing impurities in the final processed material. Although such molecules can be removed by further purification steps, it is a time consuming and costly process [70].

#### 13.3.3.4 Gellan Gum

Gellan gum is another anionic polysaccharide, similar in utility profile to alginate. Gellan gum can be easily processed into transparent gels that are resistant to heat. Gellan gum is not cytotoxic [71]) and can be injected into tissues. It has been used *in vivo* in humans as an ocular drug delivery vehicle [4]. Gellan gum is still relatively unknown in the biomedical community and only a few studies have explored this material for tissue engineering [72]. Like alginate, gellan gum can be used for the encapsulation and *in vitro* culture of cells [71]. Gellan gum hydrogels were able to support the development of nasal chondrocytes, and injectable gellan gum hydrogels were efficient in the encapsulation and support of human articular chondrocytes, while also enabling active synthesis of ECM components.

#### 13.3.3.5 Glycosaminoglycans

Glycosaminoglycans (GAGs), which consist of repeating disaccharide units in linear arrangement, usually include a uronic acid component (such as glucuronic acid) and a hexosamine component (such as N-acetyl-D-glucosamine). The predominant types of GAGs attached to naturally occurring core proteins of proteoglycans include chondroitin sulfate, dermatan sulfate, keratan sulfate, and heparan sulfate [73,74]. The GAGs are attached to the core protein by specific carbohydrate sequences containing three or four monosaccharides.

The largest GAG, hyaluronic acid (hyaluronan), is an anionic polysaccharide with repeating disaccharide units of N-acetylglucosamine and glucuronic acid, with many unbranched units ranging from 500 to several thousand. Hyaluronic acid can be isolated from natural sources (e.g., rooster combs) or via microbial fermentation [75]. Because of its water-binding capacity, dilute solutions of hyaluronic acid form viscous solutions.

Like collagen, hyaluronic acid can be easily chemically modified, for instance by esterification of the carboxyl moieties, which reduces its water solubility and increases its viscosity [75,76]. Hyaluronic acid can be crosslinked to form molecular weight complexes in the range 8 to 24 $\times$ $10^6$ or to form an infinite molecular network (gel). In one method, hyaluronic acid is crosslinked using aldehydes and small proteins to form bonds between the C—OH groups of the polysaccharide

and the amino or imino groups of the protein, thus yielding high molecular weight complexes [77]. Other crosslinking techniques include the use of vinyl sulfone, which reacts to form an infinite network through sulfonyl-bis-ethyl crosslinks [78]. The resultant infinite network gels can be formed into sheaths, membranes, tubes, sleeves, and particles of various shapes and sizes. No species variations have been found in the chemical and physical structure of hyaluronic acid. The fact that it is not antigenic, eliciting no inflammatory or foreign body reaction, makes it desirable as a biomaterial. Its main drawbacks in this respect are its residence time and the limited range of its mechanical properties.

Because of its relative ease of isolation and modification and its superior ability in forming solid structures, hyaluronic acid has become the preferred GAG in medical device development. It has been used as a viscoelastic during eye surgery since 1976, and has undergone clinical testing as a means of relieving arthritic joints [79]. In addition, gels and films made from hyaluronic acid have shown clinical utility in preventing formation of postsurgical adhesions [80–82].

The benzyl ester of hyaluronic acid, sold under the trade name HYAFF-11, has been studied for use in vascular grafts [83–88].

#### 13.3.3.6 Chitosan

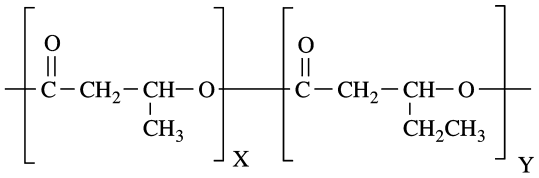
Chitosan is a biosynthetic polysaccharide that is the deacylated derivative of chitin. Chitin is a naturally occurring polysaccharide that can be extracted from crustacean exoskeletons or generated via fungal fermentation processes. Chitosan is a β-1,4-linked polymer of 2-amino-2-deoxy-D-glucose; thus it carries a positive charge from amine groups [89]. It is hypothesized that the major path for chitin and chitosan breakdown *in vivo* is through lysozyme, which acts slowly to depolymerize the polysaccharide [90]. The biodegradation rate of the polymer is determined by the amount of residual acetyl content, a parameter that can easily be varied. Chemical modification of chitosan produces materials with a variety of physical and mechanical properties [91–93]. For example, chitosan films and fibers can be formed utilizing crosslinking chemistries adapted from techniques for altering other polysaccharides, such as treatment of amylose with epichlorohydrin [94]. Like hyaluronic acid, chitosan is not antigenic and is a well-tolerated implanted material [95].

Chitosan has been formed into membranes and matrices suitable for several tissue-engineering applications [96–99] as well as conduits for guided nerve regeneration [100,101]. Chitosan matrix manipulation can be accomplished using the inherent electrostatic properties of the molecule. At low ionic strength, the chitosan chains are extended via the electrostatic interaction between amine groups, whereupon orientation occurs. As ionic strength is increased, and chain-chain spacing diminishes; the consequent increases in the junction zone and stiffness of the matrix result in increased average pore size. Chitosan gels, powders, films, and fibers have been formed and tested for such applications as encapsulation, membrane barriers, contact lens materials, cell culture, and inhibitors of blood coagulation [102].

### 13.3.4 Polyhydroxyalkanoates

Polyhydroxyalkanoates (PHA) are a group of copolymers of hydroxybutyric acid and hydroxyvaleric acid. These linear polyesters are intracellular energy storage polymers whose function is to provide a reserve of carbon and energy [103] in certain microorganisms. These polyesters are slowly biodegradable, biocompatible, thermoplastic materials [104,105]. Depending on growth conditions, bacterial strain, and carbon source, the molecular weights of these polyesters can range from tens into the hundreds of thousands. Although the structures of PHA can contain a variety of *n*-alkyl side chain substituents (see Structure 13.1), the most extensively studied PHA is the simplest: poly(3-hydroxyburtyrate) (PHB).

ICI developed a biosynthetic process for the manufacture of PHB, based on the fermentation of sugars by the bacterium *Alcaligenes eutrophus*. PHB homopolymer, like all other PHA homopolymers, is highly crystalline, extremely brittle, and relatively hydrophobic. Consequently, the PHA homopolymers have degradation times *in vivo* on the order of years [106,104]. The copolymers of PHB with hydroxyvaleric acid are less crystalline, more flexible, and more readily processable, but suffer from the same disadvantage of being too hydrolytically stable to be useful in short-term applications, in which resorption of the degradable polymer within less than one year is desirable.




**Structure 13.1** Poly(b-hydroxybutyrate) and copolymers with hydroxyvaleric acid. For a homopolymer of HB, Y = 0; commonly used copolymer ratios are 7, 11, or 22 mole percent of hydroxyvaleric acid.

PHB and its copolymers with up to 30% of 3-hydroxyvaleric acid are now commercially available under the trade name Biopol, and are mostly used as environmentally friendly polymers that degrade slowly when disposed of in a landfill. It was previously found that a PHA copolymer of 3-hydroxybutyrate and 3-hydroxyvalerate, with a 3-hydroxyvalerate content of about 11%, may have an optimum balance of strength and toughness for a wide range of possible applications. PHB has been found to have low toxicity, in part due to the fact that it degrades *in vivo* to D-3-hydroxybutyric acid, a normal constituent of human blood. Applications of these previously tested polymers, and others now under development, include controlled drug release, artificial skin, and heart valves, along with industrial applications such as paramedical disposables [107–109]. Among the biomedical applications, sutures are the main product where polyhydroxyalkanonates are used, although a number of clinical trials for other applications may still be ongoing [110].

### 13.3.4 Polynucleotides

Gene delivery from the surfaces of tissue scaffolds represents a new approach to manipulating the local environment of cells [111]. Gene therapy approaches can be employed to increase the expression of tissue inductive factors or block the expression of factors that would inhibit tissue formation [112]. A biomaterial can enhance gene transfer by localized expression of the genetic material and by protecting the genetic material against degradation by nucleases and proteases. Sustained delivery of DNA from a polymer matrix may transfect large numbers of cells at a localized site and lead to the production of a therapeutic protein that could enhance tissue development. The work by Yao [113] serves as a specific example for this approach: Yao investigated the potential of chitosan/collagen scaffolds with pEGFP-TGFβ1 as a gene vector candidate in cartilage tissue engineering.

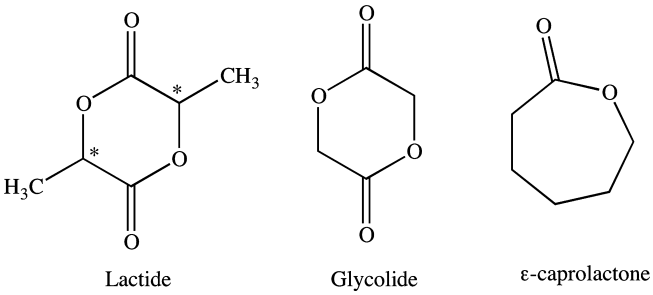
## 13.4 Synthetic Polymers

The concept of a "polymer" evolved from the study and commercial development of biologically derived macromolecules such as cellulose derivatives (celluloid, cellulose acetate) and vulcanized rubber in the nineteenth century. In 1907, the first totally synthetic polymer, Bakelite, was invented. At that time, the macromolecular structure of Bakelite and all other polymers was still not understood. It was only in 1922 that Hermann Staudinger proposed that the properties of polymers can be best explained by assuming that they consist of long chains of monomers linked together via regularly repeating bonds. The shortage of natural materials (in particular rubber) during World War II was the driving force behind the development of totally synthetic polymers. During World War II, Nylon, Teflon, various polyesters, and synthetic rubber emerged. The tremendous improvements in virtually all consumer products since 1945 would not have been possible without the development of hundreds of specialized polymers.

World War II left an additional legacy: the medical needs of millions of injured war fighters across the globe stimulated the development of new surgical procedures and innovative medical devices. Often, advances in the material sciences produced and enabled commensurate advances in medical practice. A new polymer, referred to as "Vinyon N", was developed during World War II for use in parachutes. In 1952, vascular surgeons noticed the stretchiness and elasticity of this material and developed the first vascular graft using Vinyon N. This effort became the starting point for the development of polymer-based medical implants and devices.

The systematic development of polymers for medical implants started with a focus on inert, biostable materials to be used in implants that lasted for the lifetime of the patient. It was only in 1969 that the first biodegradable polymer, poly

(glycolic acid), was used to create the first, synthetic degradable suture line—a breakthrough that ended the use of suture lines made from the intestines of animals. Due to the efforts of many research groups, a number of different polymeric structures and compositions have been explored as degradable biomaterials. However, commercial efforts to develop these new materials for specific medical applications have been limited. Thus, detailed toxicological studies *in vivo*, investigations of degradation rate and mechanism and careful evaluations of the physicomechanical properties have so far been published for only a very small fraction of those polymers. This leaves the tissue engineer with just a relatively limited number of promising polymeric compositions to choose from. The following section is focused on a review of the most commonly investigated classes of biodegradable, synthetic polymers.




**Structure 13.2** Cyclic esters used in ring-opening polymerizations. *Lactide has two optically active carbon atoms in the ring.

## 13.4.1 Aliphatic Polyesters

Aliphatic polyesters made of hydroxy acids, such as glycolic acid, lactic acid, and ε-hydroxy-caproic acid, have been utilized for a variety of medical product applications. As an example, bioresorbable surgical sutures made from poly(α-hydroxy acids) have been in clinical use since 1969 [114–116]. Other implantable devices made from these versatile polymers (e.g., internal fixation devices for orthopedic repair) are now part of standard surgical protocol [56,117,118].

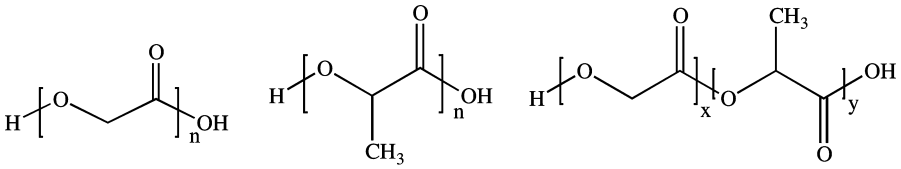
Although polyesters can be synthesized by polycondensation of hydroxy acids such as lactic acid [119], it is difficult to achieve high molecular weights and control the molecular weight, molecular weight distribution, and architecture of the polymer in this process. In most cases, biodegradable polyesters are synthesized in a two-step procedure: first, the hydroxy acids are transformed into intramolecular lactones (see Structure 13.2), which are then used as monomers in ring-opening polymerizations.

The ester bond of the aliphatic polyesters is cleaved by hydrolysis, which results in a decrease in the polymer molecular weight of the implant [120]. This initial degradation occurs until the molecular weight of the resulting oligomers is less than 5000 Da, at which point the oligomers become water soluble and the degrading implant starts to lose mass as well. The final degradation and resorption of the polyester implants may also involve inflammatory cells (such as macrophages, lymphocytes, and neutrophils). Although this late-stage inflammatory response can have a deleterious effect on some healing events, these polymers have been successfully employed as matrices for cell transplantation and tissue regeneration [121,122]. The useful lifetime of implants made from these polymers is determined by the initial molecular weight, exposed surface area, crystallinity, and (in the case of lactide-glycolide copolymers) by the ratio of the monomers.

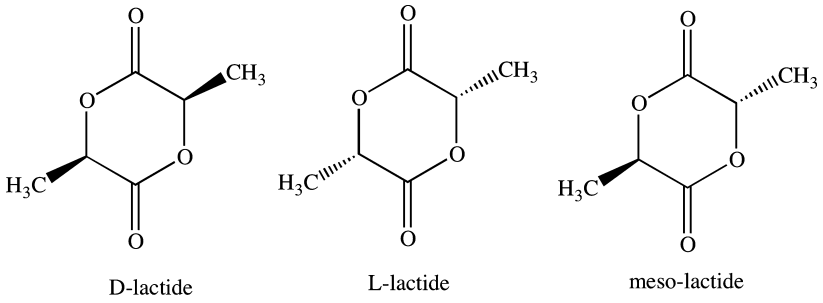
Aliphatic polyesters have a modest range of thermal and mechanical properties and a correspondingly modest range of processing conditions. The polymers can generally be formed into films, tubes, and matrices using such standard processing techniques as molding, extrusion, solvent casting, and spin casting. Ordered fibers, meshes, and open-cell foams have been formed to fulfill the surface area and cellular requirements of a variety of tissue engineering constructs [56,117,123]. The aliphatic polyesters have also been combined with other components, e.g., poly(ethylene glycol), to modify the cellular response elicited by the implant and its degradation products [124].

### 13.4.1.1 Poly(glycolic Acid), Poly(lactic Acid), and their Copolymers

Poly(glycolic acid) (PGA), poly(lactic acid) (PLA), and their copolymers poly(lactic acid-co-glycolic acid) (PLGA) are the most widely used synthetic degradable polymers in medicine (see Structure 13.3). Of this family of linear aliphatic polyesters, PGA has the simplest structure and is more hydrophilic than PLA. Since PGA is highly




**Structure 13.3** Poly(glycolic acid), poly(lactic acid) and their copolymer.




**Structure 13.4** Lactide enantiomers: d-lactide, l-lactide and meso-lactide.

crystalline, it has a high melting point and low solubility in organic solvents. PGA was used in the development of the first totally synthetic absorbable suture [114]. The crystallinity of PGA in surgical sutures is typically in the range 46–52% [125]. Due to the hydrophilic nature and quick water uptake, surgical sutures made of PGA lose their mechanical strength typically over a period of 2 to 4 weeks post implantation [126].

In order to adapt the materials properties of PGA to a wider range of possible applications, researchers undertook an intensive investigation of copolymers of PGA with the more hydrophobic poly (lactic acid) (PLA) (see Structure 13.3). Alternative sutures composed of copolymers of glycolic acid and lactic acid are currently marketed under the trade names Vicryl.

Due to the presence of an extra methyl group in lactic acid, PLA is more hydrophobic than PGA. The hydrophobicity of high molecular weight PLA limits the water uptake of thin films to about 2% [125] and results in a rate of backbone hydrolysis lower than that of PGA [126]. In addition, PLA is more soluble in organic solvents than PGA.

It is noteworthy that there is no linear relationship between the ratio of glycolic acid to lactic acid and the physicomechanical properties of their copolymers. Whereas PGA is highly crystalline, crystallinity is rapidly lost in PGA-PLA copolymers. These morphological changes lead to an increase in the rates of hydration and hydrolysis. Thus, copolymers tend to degrade more rapidly than either PGA or PLA [125,126].

Since lactic acid is a chiral molecule, it exists in two stereoisomeric forms that give rise to four morphologically distinct polymers. D-PLA and L-PLA are the two stereoregular polymers, D,L-PLA is the racemic polymer obtained from a mixture of D- and L-lactic acid, and meso-PLA can be obtained from D,L-lactide. The polymers derived from the optically active d and l monomers are semicrystalline materials, while the optically inactive D, L-PLA is always amorphous (Structure 13.3).

The differences in the crystallinity of D,L-PLA and L-PLA have important practical ramifications: Since D,L-PLA is an amorphous polymer, it is usually considered for applications such as drug delivery, where it is important to have a homogeneous dispersion of the active species within a monophasic matrix. On the other hand, the semi-crystalline L-PLA is preferred in applications where high mechanical strength and toughness are required—for example, sutures and orthopedic devices [127–129].

L-PLA (PLLA) and D-PLA (PDLA) are semicrystalline polymers with a glass transition temperature (Tg) of approximately 60°C, and a peak melting temperature (Tm) of approximately 180°C. D,L-PLA (PDLLA) is amorphous with a Tg of

approximately 55°C. Both semi-crystalline PLLA and amorphous PDLLA polymers are rigid materials. Their Young's modulus and stress at break values are close to 3.5 GPa and 65 MPa, respectively. However, these polymers are relatively brittle with an elongation at break of less than 6% [130–132].

These polymers degrade by hydrolysis in which naturally occurring lactic acid is formed. Degradation of the polymers starts with water uptake, followed by random cleavage of the ester bonds in the polymer chain. The degradation is throughout the bulk of the material [133]. Upon degradation, the number of carboxylic end groups increases, which leads to a decrease in pH and an autocatalytic acceleration of the rate of degradation [134]. During the degradation of semi-crystalline PLLA, crystallinity of the residual material increases as hydrolysis preferentially takes place in the amorphous domains [135]. In general, the rate of degradation and erosion of amorphous PDLLA is faster than that of PLLA [136].

Ikada et al. were the first to report on the stereocomplexation of enantiomeric PLLA and PDLA polymers during co-precipitation of mixed polymer solutions in non-solvents [222]. Since then, they have shown that stereocomplexation of PLLA and PDLA can take place in dilute and concentrated solutions, during solvent evaporation and spinning, and during annealing of their mixtures prepared in the melt [137]. Other groups have also reported the formation of poly(lactic acid) stereocomplexes [138,139].

Upon stereocomplexation, the melting temperature of the poly(lactide) stereocomplexes increases to about 230°C. This is 50°C higher than the melting temperature of the enantiomeric PLLA and PDLA polymers. Stereocomplexation influences the mechanical properties of poly(lactide) films [133]. When stereocomplexes were formed from PLLA and PDLA their films were stiffer, stronger, and tougher than films prepared from the enantiomeric polymers. In addition, under hydrolytic degradation conditions, the degradation of thin films of stereocomplexes of PLLA and PDLA is slower than that of the enantiomeric PLLA and PDLA homopolymers [140]. These findings are of great interest to biomedical engineers as they provide a simple way to increase the mechanical strength of these polymers with a concomitant increase in hydrolytic stability.

Recently, PLA, PGA, and their copolymers have been combined with bioactive ceramics, such as Bioglass particles or hydroxyapatite, that stimulate bone regeneration while greatly improving the mechanical strength of the composite material [141]. It was also reported that composites of polymer and Bioglass are angiogenic (e.g., they supported the growth of blood vessels), suggesting a novel approach for providing a vascular supply to implanted devices [142].

Some controversy surrounds the use of these materials for orthopedic applications. According to one review of the clinical outcomes for over 500 patients treated with resorbable pins made from either PGA or PGA:PLA copolymer, 1.2% required reoperation due to device failure, 1.7% suffered from bacterial infection of the operative wound, and 7.9% developed a late noninfectious inflammatory response that warranted operative drainage [143]. This delayed inflammatory reaction represents the most serious complication of the use of PGA or PLA in orthopedic applications. The mean interval between device implantation and the clinical manifestation of this reaction is 12 weeks for PGA and can be as long as three years for the more slowly degrading PLA [143]. Whether avoiding reoperation to remove a metal implant outweighs an approximately 8% risk of severe inflammatory reaction is a difficult question; in any event, an increasing number of trauma centers have suspended the use of these degradable fixation devices. It has been suggested that the release of acidic degradation products (glycolic acid for PGA, lactic acid for PLA, and glyoxylic acid for polydioxanone) contributes to the observed inflammatory reaction. Thus, the late inflammatory response appears to be a direct consequence of the chemical composition of the polymer degradation products [143]. The incorporation of alkaline salts or antibodies to inflammatory mediators may diminish the risk of a late inflammatory response [144]. A more desirable solution to these problems for orthopedic (and perhaps other) applications requires the development of new polymers that do not release acidic degradation products upon hydrolysis.

Using biodegradable PGA mesh scaffolds and a biomimetic perfusion system, Niklason et al. have successfully engineered small-diameter vessel grafts using either endothelial cells (ECs) and smooth muscle cells (SMCs) obtained from vessels in various species, or mesenchymal stem cells

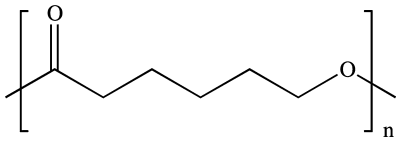
derived from adult human bone marrow [145,146]. In this approach, *ex vivo* culture resulted in the formation of a tissue-engineered vascular structure composed of cells and ECM while the PGA degraded during the same period. Cellular material was removed with detergents to render the grafts non-immunogenic. Tested in a dog model, grafts demonstrated excellent patency and resisted dilatation, calcification, and intimal hyperplasia [147].

### 13.4.1.2 Poly(ε-caprolactone)

Poly(ε-caprolactone) (PCL) (Structure 13.5) is an aliphatic polyester that has been intensively investigated as a biomaterial. The discovery that PCL can be degraded by microorganisms led to evaluation of PCL as a biodegradable packaging material; later, it was discovered that PCL can also be degraded by a hydrolytic mechanism under physiological conditions [148–150]. Under certain circumstances, crosslinked PCL can be degraded enzymatically, leading to what can be called enzymatic surface erosion [148,149]. Low molecular weight fragments of PCL are reportedly taken up by macrophages and degraded intracellularly, with a tissue reaction similar to that of the other poly (hydroxy acids) [150]. Compared with PGA or PLA, the degradation of PCL is significantly slower. PCL is therefore most suitable for the design of long-term, implantable systems such as Capronor, a one-year implantable contraceptive device [151].

Poly(ε-caprolactone) exhibits several unusual properties not found among the other aliphatic polyesters. Most noteworthy are its exceptionally low glass transition temperature of about −60°C and its low melting temperature of 57°C. Another unusual property is its high thermal stability. Whereas other tested aliphatic polyesters had decomposition temperatures (Td) between 235 and 255°C, poly(ε-caprolactone) has a Td of 350°C, which is more typical of poly(ortho esters) than aliphatic polyesters [152].

A useful property of PCL is its propensity to form compatible blends with a wide range of other polymers [153]. In addition, ε-caprolactone can be copolymerized with numerous other monomers (e.g., ethylene oxide, chloroprene, THF, δ-valerolactone, 4-vinylanisole, styrene, methyl methacrylate, vinylacetate). Particularly noteworthy are copolymers of ε-caprolactone and lactic acid, which



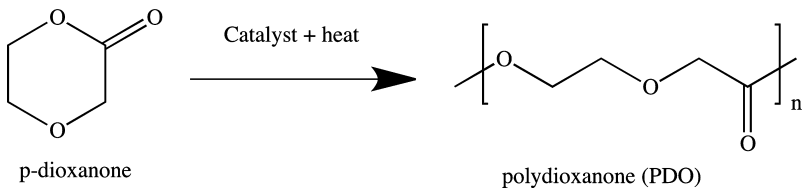

**Structure 13.5** Poly(ε-caprolactone).

have been studied extensively [149,154]. PCL and copolymers with PLA have been electronspun to create nanofibrous tissue-engineered scaffolds that show promise for vascular applicaions [155,20–22]. The toxicology of PCL has been extensively studied as part of the evaluation of Capronor. Based on a large number of tests, the monomer ε-caprolactone, and the polymer PCL, are currently regarded as non-toxic and tissue compatible materials. Early clinical studies [156] of the Capronor system were started around the year 2000 and resulted in a commercial implant used in Europe, but not in the USA.

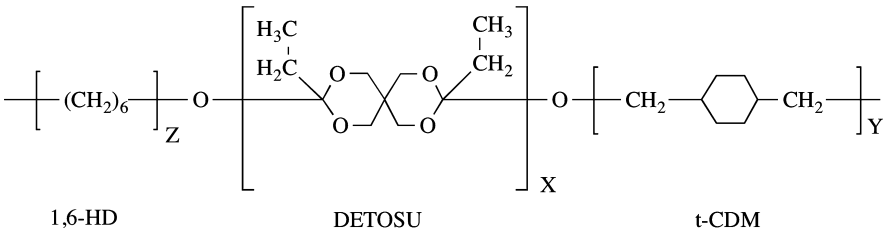
### 13.4.1.3 Poly(p-dioxanone)

Poly(p-dioxanone) (PDS) is prepared by the ring-opening polymerization of p-dioxanone (Structure 13.6). It is a relatively weak, rapidly biodegrading polymer that was introduced into the market in the 1980s as a new degradable suture material. When compared on a weight basis (for example per 1 gram of implant), poly(p-dioxanone) releases degradation products that are less acidic than the degradation products released by PGA or PLA. This is a potential advantage for orthopedic applications, which led to the development of small bone pins for the fixation of fractures in non-load bearing bones. Bone pins based on poly(p-dioxanone) are marketed under the trade name Orthosorb in the USA and under the name Ethipin in Europe. Poly(p-dioxanone) is also found in suture clips.

Unfortunately, poly(p-dioxanone) is relatively weak and lacks the stiffness and strength required for most orthopedic applications. Its range of applications is therefore limited. Academic laboratories have investigated poly(p-dioxanone) mostly as a polymer for implantable drug delivery applications. Little work has been done to explore this polymer as a scaffold for tissue engineering, probably because the polymer offers no clear advantages in terms of cell attachment and tissue compatibility over the widely used poly(lactic acid) and the copolymers of lactic and glycolic acid.




**Structure 13.6** p-Dioxanone and polydioxanone.




**Structure 13.7** Poly(orthoesters). The specific composition shown here is a terpolymer of hexadecanol (1,6-HD), trans-cyclohexyldimethanol (t-CDM), and DETOSU.

#### 13.4.1.4 Poly(ortho Esters)

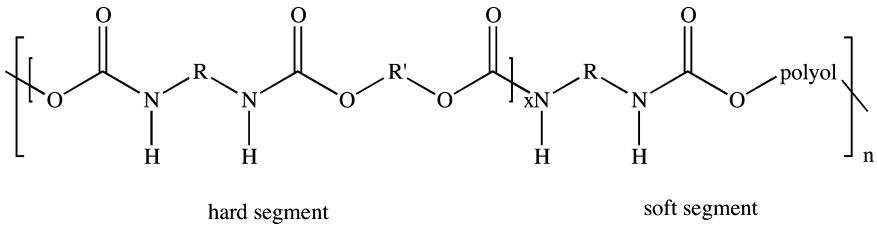
Poly(ortho esters) are a family of synthetic degradable polymers that have been under development since 1970 [157,158]. Devices made of poly (ortho esters) can be formulated in such a way that the device undergoes surface erosion—that is, the polymeric device degrades at its surface only and will thus tend to become thinner over time rather than crumbling into pieces. Since surface-eroding, slab-like devices tend to release drugs embedded within the polymer at a constant rate, poly(ortho esters) appear to be particularly useful for controlled release drug delivery [159]; this interest is reflected by the many descriptions of these applications in the literature [160].

There are two major types of poly(ortho esters). Originally, poly(ortho esters) were prepared by the condensation of 2,2-diethoxytetrahydrofuran and a dialcohol [161]) and marketed under the trade names Chronomer and Alzamer. Upon hydrolysis, these polymers release acidic by-products that autocatalyze the degradation process, resulting in degradation rates that increase with time. More recently, Heller et al. [162]) synthesized a new type of poly (ortho ester) based on the reaction of 3,9-bis(ethylidene 2,4,8,10-tetraoxaspiro {5,5} undecane) (DETOSU) with various dialcohols (Structure 13.7). These poly(ortho esters) do not release acidic by-products upon hydrolysis and thus do not exhibit autocatalytically increasing degradation rates. By selecting diols having different degrees of chain flexibility, polymers can be obtained that range from hard, brittle materials to materials that have a gel-like consistency. A drug release system for mepivacaine (a treatment for post-operative pain), was tested in Phase 2 clinical trials between 2000 and 2005 [158], and as of 2012, a fourth generation, poly(ortho ester)-based drug delivery system for prevention of chemotherapy-induced nausea and vomiting was in Phase 3 clinical trials.

### *13.4.2 Biodegradable Polyurethanes*

Polyurethanes, polymers in which the repeating unit contains a urethane moiety, were first produced by Bayer in 1937. These polymers are typically produced through the reaction of a diisocyanate with a polyol. Conventional polyols are polyethers or polyesters. The resulting polymers are segmented block copolymers with the polyol segment providing a low glass transition temperature (i.e., $<25°C$) soft segment and the diisocyanate component, often combined with a hydrocarbon chain extender, providing the hard segment (Structure 13.8). A wide range of physical and mechanical properties have been realized with commercial polyurethanes.

Polyurethanes have been used for nearly 50 years in biomedical applications, particularly as blood-contacting material in cardiovascular

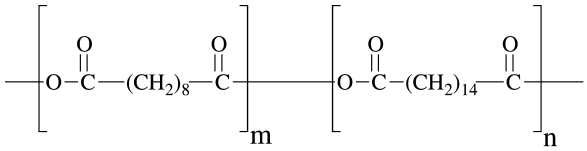



**Structure 13.8** General structure of a segmented poly(urethane) prepared from diisocyanate, OCN-R-NCO; chain extender, HO-R′-OH; and polyol building blocks.

devices. Intended as non-biodegradable coatings, polyurethanes fell out of favor with the failure of pacemaker leads and breast implant coatings. Subsequent studies, as reviewed by Santerre et al., have clarified much about the behavior of polyurethanes in biological systems [163]. Elucidation of the biodegradation mechanism and its dependence on the polyurethane structure and composition have led to the development of biodegradable polyurethanes for a variety of tissue-engineering applications such as meniscal reconstruction [164], myocardial repair [165] and vascular tissues [166]. Design of biodegradable polyurethanes has required alternative diisocyanate compounds. The traditional aromatic diisocyanates are putative carcinogenic compounds. Biodegradable polymers are made from biocompatible diisocyanates such as lysine-diisocyanate or hexamethylene diisocyanate that release non-toxic degradation products.

The urethane bond is essentially non-degradable under physiological conditions. Therefore, biodegradable poly(urethane)s can only be obtained when the employed soft polyol segments are degradable [163]. As an example, aliphatic poly (ester urethane)s containing random 50/50 ε-caprolactone/L-lactide copolymer segments, 1,4-butanediol and 1,4-butanediisocyanate were synthesized and used to prepare porous structures for meniscus reconstruction [167]. In these polymers, the biodegradation mechanism involves the hydrolytic cleavage of the ester bonds in the ε-caprolactone/L-lactide copolymer segments, resulting in the formation of low molecular weight blocks of the non-degradable hard segments which are ultimately excreted from the body via the liver and/or kidney.

An interesting applicaton of polyurethanes was developed by Santerre et al. where fluoroquinolone antimicrobial drugs were incorporated into the polymer as hard-segment monomers [163]. This led to the design of drug polymers (trade name: Epidel)




**Structure 13.9** Poly(SA-HDA anhydride). This composition represents one of many polyanhydrides that were explored. The clinically relevant polyanhydrides are copolymers of sebacic acid and p-carboxy-phenoxypropane.

that release the drug when degraded by enzymes generated by an inflammatory response. This is an example of a "smart" system in that antibacterial agents are released only while inflammation is present. Once healing occurs, the enzyme level drops and the release of drug diminishes.

### 13.4.3 Polyanhydrides (Structure 13.9)

Polyanhydrides were first investigated in detail by Hill and Carothers [168] and were considered in the 1950s for possible applications as textile fibers [169]. Their low hydrolytic stability, the major limitation for their industrial applications, was later recognized as a potential advantage by Langer et al. [170], who suggested the use of polyanhydrides as degradable biomaterials. A study of the synthesis of high molecular weight polyanhydrides has been published by Domb et al. [171].

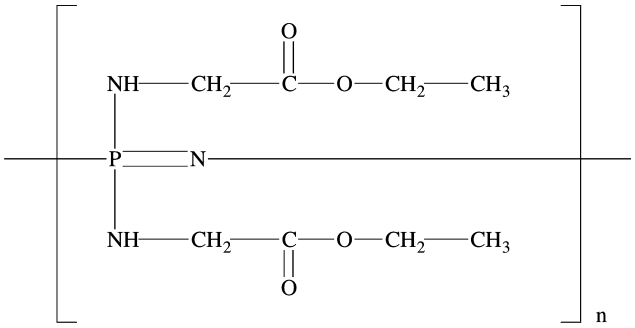
A comprehensive evaluation of the toxicity of the polyanhydrides showed that, in general, they possess excellent *in vivo* biocompatibility [172]. Their most immediate applications are in the field of drug delivery, although tissue-engineering applications are also being developed. Drug loaded devices are best prepared by compression molding or microencapsulation [173]. A wide variety of

drugs and proteins, including insulin, bovine growth factors, angiogenesis inhibitors (e.g., heparin and cortisone), enzymes (e.g., alkaline phosphatase and b-galactosidase) and anesthetics have been incorporated into polyanhydride matrices, and their *in vitro* and *in vivo* release characteristics have been evaluated [174]. One of the most aggressively-investigated uses of the polyanhydrides is for the delivery of chemotherapeutic agents. An example of this application is the delivery of BCNU (bis-chloroethylnitrosourea) to the brain for the treatment of glioblastoma multiformae, a universally fatal brain cancer [175]. For this application, polyanhydrides derived from bis-p-(carboxyphenoxy propane) and sebacic acid received Food and Drug Administration (FDA) regulatory clearance in the fall of 1996 and are currently being marketed under the name Gliadel®.

### 13.4.4 Polyphosphazenes (Structure 13.10)

Polyphosphazenes consist of an inorganic phosphorous-nitrogen backbone, in contrast to the commonly employed hydrocarbon-based polymers [176a]. Consequently, the phosphazene backbone undergoes hydrolysis to phosphate and ammonium salts, with the concomitant release of the side group. Of the numerous polyphosphazenes that have been synthesized, those that have some potential use for medical products are substituted with amines of low pKa, and those with activated alcohol moieties [177–179]. Singh and colleagues have modified the side groups to tune polyphophazine properties such as glass transition temperature, degradation rate, surface wettability, tensile strength and elastic modulus, enabling these polymers to be considered for a wider range of biomedical applications [180]. The most extensively studied polyphosphazenes are hydrophobic, having fluoroalkoxy side groups. In part, these materials are of interest because of their expected minimal tissue interaction, which is similar to Teflon.

Aryloxyphosphazenes and closely related derivatives have also been extensively studied. One such polymer can be crosslinked with dissolved cations such as calcium to form a hydrogel matrix because of its polyelectrolytic nature [181]. Using methods similar to alginate encapsulation, microspheres of aryloxyphosphazene have been used to encapsulate hybridoma cells without affecting their viability or




**Structure 13.10** Polyphosphazene. Shown here is a polymer containing an amino acid ester attached to the phosphazene backbone.

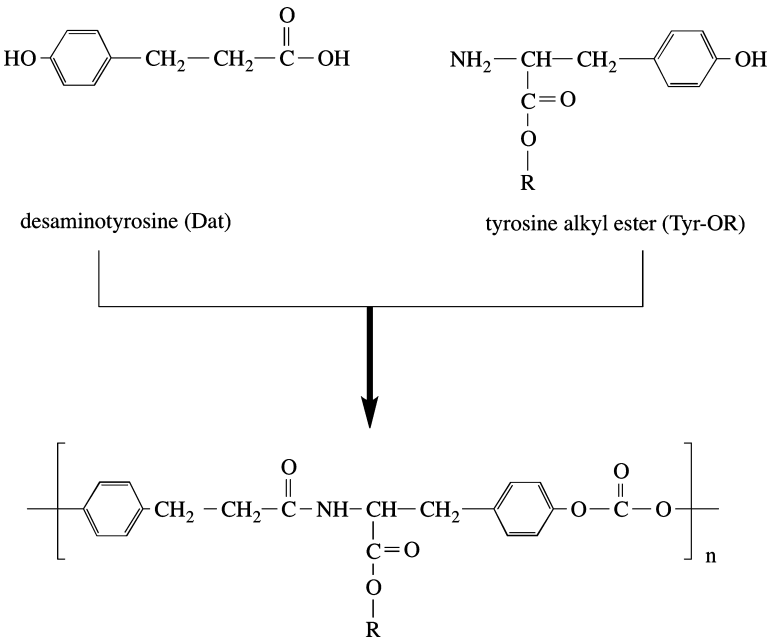
their capacity to produce antibodies. Interaction with poly(L-lysine) produced a semi-permeable membrane. Similar materials have been synthesized that show promise in blood contacting and with novel drug delivery applications.

### 13.4.5 Poly(amino Acids) and "Pseudo"-poly(amino Acids)

Since proteins are composed of amino acids, many researchers have tried to develop synthetic polymers derived from amino acids to serve as models for structural, biological and immunological studies. In addition, many different types of poly (amino acids) have been investigated for use in biomedical applications [176]. Poly(amino acids) are usually prepared by the ring-opening polymerization of the corresponding *N*-carboxy anhydrides, which are in turn obtained by reaction of the amino acid with phosgene [182].

Poly(amino acids) have several potential advantages as biomaterials. A large number of polymers and copolymers can be prepared from a variety of amino acids. The side chains offer sites for the attachment of small peptides, drugs, crosslinking agents, or pendant groups that can be used to modify the physicomechanical properties of the polymer. Since these polymers release naturally occurring amino acids as the primary products of polymer backbone cleavage, their degradation products may be expected to show a low level of systemic toxicity.

Poly(amino acids) have been investigated as suture materials [178], as artificial skin substitutes [183] and as drug delivery systems [184]. Various drugs have been attached to the side chains of poly(amino acids), usually via a spacer unit that




**Structure 13.11** A poly(amide carbonate) derived from desaminotyrosyl tyrosine alkyl esters. This is an example for a group of new, amino acid derived polymers.

distances the drug from the backbone. Combinations of poly(amino acid)s and drugs that have been investigated include poly(L-lysine) with methotrexate and pepstatin [185], and poly(glutamic acid) with adriamycin and norethindrone [186]. Short amino acid sequences such as RGD and RGDS, strong promotors of specific cell adhesion, have been linked to the polymer backbone to promote cell growth in tissue-engineering applications [187,188].

Despite their apparent potential as biomaterials, poly(amino acids) have actually found few practical applications. *N*-carboxy anhydrides, the starting materials, are expensive to make and difficult to handle because of their high reactivity and moisture sensitivity. Most poly(amino acids) are highly insoluble and non-processible materials. Since poly (amino acids) degrade via enzymatic hydrolysis of the amide bond, it is difficult to reproduce and control their degradation *in vivo,* because the level of relevant enzymatic activity varies from person to person. Furthermore, the antigenicity of poly(amino acids) containing three or more amino acids limits their use in biomedical applications [176]. Because of these difficulties, only a few poly(amino acids), usually derivatives of poly(glutamic acid) carrying various pendent chains at the $\gamma$-carboxylic acid group, have been identified as promising implant materials [189].

As an alternative approach, Kohn et al. have replaced the peptide bonds in the backbone of synthetic poly(amino acids) by a variety of "nonamide" linkages such as ester, iminocarbonate, urethane, and carbonate bonds [190,191]. The term *pseudo-poly(amino acid)* is used to denote this new family of polymers in which naturally occurring amino acids are linked together by nonamide bonds (Structure 13.11).

The use of such backbone-modified pseudo-poly (amino acids) as biomaterials was first suggested in 1984 [192]. The first pseudo-poly(amino acids) investigated were a polyester from *N*-protected trans-4-hydroxy-L-proline and a poly(iminocarbonate) from tyrosine dipeptide [193,194]. Several studies indicate that the backbone modification of conventional poly(amino acids) generally improves their physicomechanical properties [190,195,196]. This approach is applicable to, among other materials, serine, hydroxyproline, threonine, tyrosine, cysteine, glutamic acid, and lysine; it is only limited by the requirement that the nonamide backbone linkages give rise to polymers with desirable material properties. Additional pseudo-poly(amino acids) can be obtained by considering dipeptides as monomeric starting materials. Hydroxyproline-derived polyesters [194,197], serine-derived polyesters [198], and tyrosine-derived polyiminocarbonates

[199] and polycarbonates [200] represent specific embodiments of these synthetic concepts.

## 13.5 Combinations (Hybrids) of Synthetic and Biologically Derived Polymers

Biologically derived polymers have important advantages over synthetic materials. These advantages often include reduced toxicity, since they generally originate from molecules that occur naturally in the body and biodegrade under physiological conditions [201,202], and they also exhibit improved *bioactivity*. In this context, the term bioactivity refers to the ability of a material to elicit specific cellular responses. Collagen, for example, is a bioactive material because of its ability to support cell attachment, growth and differentiation. However, the usefulness of biologically derived polymers is often limited by their poor engineering properties. Important disadvantages of biologically derived polymers are:

1. High batch-to-batch variability due to complex isolation procedures from inconsistent sources,
2. Poor solubility and processibility, preventing the use of industrial manufacturing processes,
3. Risk of contamination by pyrogens or pathogens,
4. Poor or limited materials properties such as strength, ductility, elasticity, or shelf life, and
5. Their high cost.

In overall terms, synthetic materials offer a wider range of useful engineering properties (polymer composition, architecture, mechanical properties, etc.) but they generally fail to promote cell growth and differentiation to the same degree as some of the biologically derived polymers [203]. To address these shortcomings, it is an obvious idea to combine biologically derived polymers with synthetic materials. As a general rule, the purpose of such hybrid materials is to combine the bioactivity of biologically derived polymers with the superior engineering properties of synthetic materials.

As an example, a clinically useful cornea replacement material was obtained when collagen was incorporated into a synthetic, polyacrylate-based hydrogel [204]. Another example of this approach is provided by a hybrid material derived from silk fibroin (as the hydrophobic, bioactive material) and poly(vinyl alcohol) (as the hydrophilic, synthetic component) [205]. Poly(vinyl alcohol) (PVA) can be crosslinked under mild conditions by exposure to UV (ultraviolet) radiation. This crosslinking method allows PVA and fibroin to form a highly biocompatible hydrogel with adjustable engineering properties [205].

A final example of this approach is provided by a hybrid material composed of poly(N-isopropylacrylamide) (pNIPAM) as the synthetic component and various natural polysaccharides as the biologically derived component. pNIPAM undergoes a thermally induced phase transition around 32°C that causes the soluble material to precipitate. This property allows the design of a product that is liquid and injectable at room temperature and that precipitates and forms a hydrogel at body temperature, facilitating the formation of a solid implant while eliminating the need for surgical insertion. The disadvantage of pNIPAM as a biomaterial is its inability to support cell growth and its lack of biodegradability. This can be overcome by crosslinking pNIPAM with natural polysaccharide precursors, leading to cell-permissive formulations that will biodegrade *in vivo*.

## 13.6 Using Polymers to Create Tissue-Engineered Products

The medical implant of the future will not be an artificial prosthetic device that replaces tissue lost due to trauma, disease, or aging, but a tissue scaffold that integrates with the surrounding healthy tissue and assists in the regeneration of lost or damaged tissue. As one possible implementation of this concept, the biomedical literature currently envisions such tissue scaffolds as consisting of bioactive polymers that may be shaped as porous sponge-like structures. These tissue scaffolds may either be preseeded with specific cell populations outside of the body of the patient prior to implantation into the patient, or the tissue scaffolds may be implanted into the body of the patient first, and then be colonized by the patient's own cells, leading to the regeneration of the desired tissue. In

either case, one can formulate several design criteria that can guide the biomedical engineer in the process of selecting an appropriate biomaterial for the intended application.

First and foremost, one must be concerned with the bulk polymer properties. The biomaterial must have an appropriate range of physicomechanical properties, biodegradation rates, and biocompatibility appropriate for the intended application. Next, it must be possible to create the desired tissue scaffold. This requires that the desired device shape and architecture can actually be created by cost-effective fabrication methods. For example, electrospinning may be the preferred fabrication method to create an ECM-like scaffold that consists of nano-sized fibers. Since electrospinning requires that the biomaterial is soluble in non-toxic solvents, any insoluble biomaterial would not meet a key design requirement. Finally, it is important to consider the biological properties of the biomaterial. Tissue-engineering products require specific cellular responses. For example, in a bone regeneration scaffold, the ability to support the attachment and growth of osteoblasts in combination with the ability to adsorb and concentrate endogenous bone morphogenic protein on the polymer surface may be important design requirements (Figure 13.1). There is a wide range of additional requirements that impose further limitations on the selection of the biomaterial and/or the architecture of the implant. For example, whenever functional tissue has to form within the tissue-engineering scaffold, a lack of proper vascularization will impede a favorable tissue response. For encouraging angiogenesis within the scaffold, details such as pore size, pore structure and pore connectivity are often critical [206].

Once an appropriately shaped tissue scaffold has been conceptionalized, it is time to consider a wide range of secondary design criteria relating to device shelf life, ability of the device to be sterilized and packaged for clinical use, and overall cost. Here, being able to create a terminally sterilized device is a factor often overlooked by academic researchers, who fail to consider the fact that most FDA-recognized sterilization methods cannot be applied to products that contain living cells. Thus, the requirement to ensure device sterility has been a major hurdle in translating research concepts from the laboratory to clinical practice.

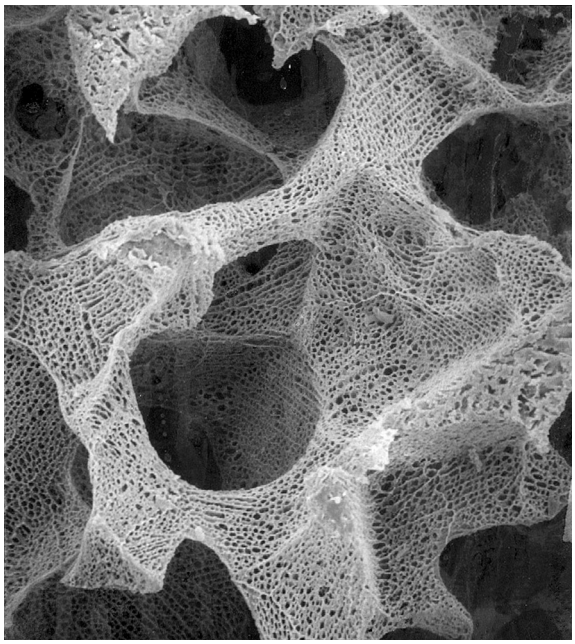


**Figure 13.1** Bone regeneration scaffold from the New Jersey Center for Biomaterials. The scaffold has a delicate and carefully optimized pore structure consisting of large macropores (200–400 μm) and linearly aligned micropores (5–20 μm). This particular pore architecture is believed to facilitate the regeneration of bone *in vivo*. *(Photo: Courtesy of the Laboratory of Professor Joachim Kohn, Rutgers-the State University of New Jersey)*

### 13.6.1 Barriers: Membranes and Tubes

Design formats requiring cell activity on one surface of a device while precluding transverse movement of surrounding cells onto that surface calls for a barrier material. For example, peripheral nerve regeneration must allow for axonal growth, while at the same time precluding fibroblast activity that could produce neural-inhibiting connective tissue. Structures such as collagen tubes can be fabricated to yield a structure dense enough to inhibit connective tissue formation along the path of repair while allowing axonal growth through the lumen [207]. More recently, conduits composed of a silk fibroin scaffold coupled with biologics have shown improvement in performance [208]. Similarly, collagen membranes for periodontal repair provide an environment for periodontal ligament regrowth and attachment while preventing epithelial ingrowth into the healing site [209]. Anti-adhesion formulations using hyaluronic

acid, which prevent ingrowth of connective tissue at a surgically repaired site, also work in this way [80].

### 13.6.2 Gels

Gels are used to provide a hydrogel scaffold, encapsulate, or provide a specialized environment for isolated cells. For example, collagen gels for tissue engineering were first used to maintain fibroblasts, which were the basis of a living skin equivalent [210]. Gels have also been used for the maintenance and immunoprotection of xenograft and homograft cells such as hepatocytes, chondrocytes, and islets of Langerhans used for transplantation [211–213]. Semi-permeable gels have been created to limit cell-cell communication and interaction with surrounding tissue, and to minimize movement of peptide factors and nutrients through the implant. Injectable biodegradable gel materials that form through crosslinking *in situ* show promise for regeneration of bone and cartilage. Temenoff and Mikos review a number of injectable systems that demonstrate appropriate properties for these applications [214]. Lee and colleagues discuss the use of biodegradable polyester dendrimers (highly branched, synthetic polymers with layered architectures) to form hydrogels for tissue-engineering applications such as corneal wound sealants [215]. In general, non-degradable materials are used for cell encapsulation to maximize long-term stability of the implant. In the future, however, it may be possible to formulate novel "smart" gels in which biodegradation is triggered by a specific cellular response instead of simple hydrolysis.

### 13.6.3 Matrices

It has been recognized since the mid-1970s that three-dimensional structures are an important component of engineered tissue development [13,14]. Yannas and his coworkers were the first to show that pore size, pore orientation, and fiber structure are important characteristics in the design of cell scaffolds. Several techniques have subsequently been developed to form well-defined matrices from synthetic and biologically derived polymers, and the physical characteristics of these matrices are routinely varied to maximize cellular and tissue responses [216–219]. Examples of engineered matrices that have led to several resorbable templates are oriented pore structures designed for regeneration of trabecular bone [220,221].

## 13.7 Conclusion

Research using currently available biomaterials and research aimed at developing novel biodegradable polymers has helped to advance the field of tissue engineering. Throughout most of the twentieth century, most research and development efforts relied on a small number of biodegradable polymers that had a history of regulatory approval, making poly(lactic acid) the most widely used biodegradable polymer. Research in the twenty first century aims to develop advanced biodegradable polymers that elicit predictable and useful cellular responses. To achieve this goal, current research efforts focus on creating bioactive materials that combine the superior engineering properties of synthetic polymers with the superior biological properties of natural materials. The extremely complex material requirements of tissue scaffolds pose significant challenges and require a continued research effort toward the development of new bioresorbable polymers.

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# 14 Regulations for Medical Devices and Application to Plastics Suppliers: History and Overview

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## 14.1 History and Introduction

Over the past 2000 years, many devices have been developed and used in the mitigation and diagnosis of diseases. The materials used in these devices have ranged from stone, wood, metal, ceramics, and most recently plastics. Medical devices have also evolved in sophistication and complexity over time. With the formalization of the scientific method in the seventeenth century such devices became more prevalent [1]. Many medical devices were manufactured by doctors or small companies and sold directly to the public with no government standards or oversight. With the explosion of medical technology in the early twentieth century, several intermediaries had evolved between the medical device industry and the public. In 1879, Dr E.R. Squibb, in an address to the Medical Society of the State of New York, proposed the enactment of a national statute to regulate food and drugs [2]. It was not until 27 years later that the Food and Drug Act of 1906 was introduced into the Congress and signed into law by President Theodore Roosevelt [3]. At that time, devices that were harmful to human safety and health proliferated the market but regulation of medical devices by the Bureau of Chemistry (the precursor to the Food and Drug Administration—FDA) was limited to challenging commercial products only *after* they had been released into the market. Devices in the marketplace that were defective, adulterated, or misbranded were seized and the device manufacturers were prosecuted in a court of law, but only *after* the products were sold in the market and caused harm to the end users. Thus, there was a strong need for regulating the devices *before* they entered the marketplace. An FDA report [4], issued in September 1970, detailed as many as 10,000 injuries and 731 deaths from ineffective medical devices. The report recommended the formation of a regulatory system and body that would enforce the production and sale of safe and effective devices to the public. All medical devices already on the market would be inventoried and classified into a three-tiered system based on their criticality of end use. It also detailed requirements for records and reports, registration and inspection of establishments, and uniform quality assurance programs called good manufacturing practices (GMP). After much lobbying by the FDA, Senate bill SR 510,

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"The Medical Device Amendments of 1973" was introduced by Senator Edward M. Kennedy and was passed by the Senate in 1975. House bill HR 11124, introduced by Representative Paul Rogers, was passed by the House in 1976. These bills eventually became the Medical Device Amendments of 1976, and were signed into law by President Nixon. The Medical Device Amendments of 1976 became the basis for the medical device regulation in the United States to control and regulate the production of finished devices and thus the device manufacturers themselves.

The GMP requirements for medical devices came into effect on December 18, 1978. This regulation was designed to specify general requirements for all manufacturers as well as special requirements for what were termed "critical devices." Yet, between 1978 and 1990 a number of studies and data from recalls of medical devices [5,6] indicated that a significant number of recalls were due to improper, faulty, or ineffective designs. On November 28, 1990, Congress passed the Safe Medical Device Act (SMDA), providing the FDA with the authority to add pre-production design controls to the GMP regulation. This meant that device manufacturers would need to have controls over their design and development processes including strict controls of the raw materials and components used to manufacture the finished device. It also incorporated a provision to include the oversight of foreign countries selling products into the United States. Quality System Regulation 21 CFR Parts 820 [7] was then drafted. Efforts were made to harmonize this regulation with both the ISO 9001:1994 entitled "Quality systems: Model for quality assurance in design, development, production, installation and servicing" and with ISO 13485:1996 entitled "Quality Systems—Medical Devices—Particular requirements for the application of ISO 9001." This new regulation removed the term "critical devices" and allowed manufacturers to tailor their quality systems commensurate with the risk associated with their device during end use. For example, an implantable device will need more stringent (design, development, and production) controls compared to a simple tongue depressor and these will differ in the level of detail and complexity of their respective quality system requirements.

The purpose of the regulations is to ensure that manufacturers of medical devices have the appropriate procedures and processes in place to design, develop, and produce consistent, safe, and effective devices for their intended use. The regulations are a framework for manufacturers and are flexible enough to allow them to formulate and implement those parts of the regulation that are applicable to their products and processes and the risk of their products.

## 14.2 United States Regulations

The design, development, production, distribution, and use of medical devices in the United States of America are regulated by the Federal Drug and Cosmetics Act in the Code of Federal Regulations (CFR)—21 CFR Parts 820 [7]. This regulation is entitled "The Quality System Regulation." To sell medical devices in the United States of America, all (domestic or international) finished medical device manufacturers must register with the Federal Drug Administration (FDA), must be willing to comply with the regulation, and must be willing to let the FDA inspect their facilities.

The intent of 21 CFR Parts 820 is that "quality must be designed and built into components through the application of proper quality systems" [8]. The regulation requires that medical device manufacturers establish and implement an appropriate quality system that encompasses the design, manufacture, packaging, labeling, storage, installation, and servicing of the finished device intended for commercial use and distribution in the United States. Effective quality systems will ensure that manufacturers are in a "state of control" and produce consistent, safe, and effective devices for their intended use. The FDA monitors and inspects the complaints, data, and records from both end users and manufacturers to track and determine the safety and efficacy of a device.

Table 14.1 details the various sections of the regulation with a brief description of each section. This regulation pays particular attention to the design controls that were added to the latest (1997) version.

Suppliers of raw materials or components do not have to comply with the regulations, but are subject to the *purchasing controls* of the regulations. Finished device manufacturers must establish procedures and controls with their suppliers for essential raw materials that include quality metrics, material performance and purity specifications, assurance of supply, and notification of any formulation or process changes.

**Table 14.1** FDA 21 CFR Part 820 and Its Subsystems

| Section | Title | Description |
|---|---|---|
| Subpart A | General requirements | Defines the scope and applicability requirements for the quality system. Who needs to comply? |
| Subpart B | Quality System requirements | Outlines the methods of formulating, implementing an effective quality system via management reviews, quality audits, and appropriate personnel. |
| Subpart C | Design controls | Describes the process and controls during the various stages in design and development of a medical device from design inputs, design outputs, design verification and validation, design reviews, and effective design transfers. |
| Subpart D | Document controls | Review, approval, retention, accuracy, and accessibility of appropriate documents. |
| Subpart E | Purchasing controls | Controls and processes all raw materials, components, products, and services. |
| Subpart F | Identification and traceability | Documentation and process to identify and trace incoming, in process, and finished device products and components, especially those of high-risk devices. |
| Subpart G | Production and process controls | The development, monitoring, and control of all processes used in production of the finished device. |
| Subpart H | Acceptance activities | Establishing and using acceptance criteria for the control of incoming, in-process and finished device performance, quality, and consistency. |
| Subpart I | Nonconforming product | Developing and implementing procedures to assess and control all products and processes that do not meet specified requirements. |
| Subpart J | Corrective and preventive action | Establishing and implementing procedures and processes for sustainable corrective and preventive action of identified issues. |
| Subpart K | Labeling and packaging | Ensuring that there are procedures and processes in place to include the requirements, design, production, and control of device packaging and labeling into the quality system. |
| Subpart L | Handling, storage, distribution, and installation | Having procedures for the handling and storage of all incoming, in-process, and finished device products. Ensuring proper distribution procedures for finished devices and if applicable, procedures and processes for the installation of finished devices at the end user's facility. |
| Subpart M | Records | Documents specific to this regulation include the Design History File (DHF), the Device Master Record (DMR), the Device History Record (DHR), and complaint files. |
| Subpart N | Servicing | If needed, maintenance and servicing procedures and processes must be included to continue and to ensure safety and efficacy of devices at the end user. |
| Subpart O | Statistical techniques | The regulation encourages the use of statistical techniques (like sampling, data analysis, design of experiments) where appropriate. |

### 14.2.1 FDA Master Files

For the submission of a Premarket Approval (PMA) [9], a 510(k) [10] for substantially equivalent devices or an Investigational Device Exemption (IDE) [11] a finished device manufacturer submits an application to the FDA containing substantive data of the finished device including performance, chemical resistance, biocompatibility, toxicity, and clinical data. In many cases, the finished device or components are made from a supplier's product or raw materials. In order that a sound scientific evaluation may be made of the PMA, 510(k) or the IDE, a review of data and other information related to the supplier's product, facility, or manufacturing procedures is required. While suppliers may be willing to have the FDA review this information, they may not want their proprietary information in the hands of their customers (the finished device manufacturers). A system for the submission of Master Files was developed by the FDA to permit the suppliers of the materials to provide confidential product information directly to the FDA for its review without disclosing the confidential information to the customer or manufacturer. If the same raw material is used in various applications, components, or devices, only one Master File is required.

There are various types of master files depending upon the intended use.

- Device master files (MAF)—Supporting data on material used in medical devices (information for pre-manufacturing notices, 510(k)s and Investigational Device Exemptions);
- Drug Master File (DMF)—Supporting data on material used in drugs; (information for Investigational New Drug Applications (IND), New Drug Applications (NDA), and Abbreviated New Drug Applications (ANDA));
- Biologics Master Files—Supporting data for material used in applications contacting blood or blood products (information for notices of claimed Investigational Exemption for an Investigational New Drug (IND) for biologics and biologic licenses);
- Food Master Files (FMF)—Supporting data material used in food applications (information for Food Additive and Color Additive Petitions); and
- Veterinary Medicine Master Files—Supporting data for materials used in animal drug and devices (Investigational New Animal Exemptions (INAD) and New Animal Drug Applications (NADA)).

The content of a Master File includes the following:

- Company Name,
- Product Name,
- Manufacturing Address,
- Statement of Commitment,
- Product Formulation,
- Product Specification, and
- Test methods and results (physical, chemical, biocompatibility, and toxicity).

The information provided in the master file gives the device manufacturer and the FDA a level of comfort that the raw material being used in the device will pass the specific physical, chemical, biocompatibility, and toxicity tests. The FDA must be notified of any changes to the formulation and subsequent properties of the material and the Master File must be updated. Failure to notify and comply will render the finished device "adulterated" and may not be subjected for sale or use.

MAFs may be submitted for various types of operations and products and can be grouped by the following types:

- facilities and manufacturing procedures and controls;
- synthesis, formulation, purification, and specifications for chemicals, materials (e.g., an alloy, plastic, etc.), or subassemblies for a device;
- packaging materials;
- contract packaging and other manufacturing (e.g., sterilization);
- nonclinical study data; and
- clinical study data.

## 14.3 ISO 13485 (European and Global Standard)

The international standard for medical devices is ISO 13485:2003 entitled "Medical devices—Quality

management systems—Requirements for regulatory purposes" [12]. Though geared specifically toward medical device manufacturers, the ISO 13485 standard is harmonized with ISO 9001:2000 with some differences. ISO 13485:2003 includes particular requirements for medical devices and excludes some of the requirements of ISO 9001:2000 that are not appropriate as regulatory requirements with respect to medical devices. Thus, organizations which conform to ISO 13485:2003 cannot claim that they conform to ISO 9001:2000 or vice versa unless their quality management systems conform to *all* the requirements of ISO 9001:2000. Risk management is a key part of ISO 13485 [13]. Terms like customer satisfaction and continuous improvement have been removed from this document (compared to ISO 9001:2000). The regulation consists of the sections as described in Table 14.2. An ISO technical report (ISO/TR 14699) [14] provides guidance for the application of ISO 13485.

The primary objective of the regulation is to provide harmonized guidelines to organizations so that they can consistently meet end user and regulatory requirements. Compliance with ISO 13485 is recognized as a first step in achieving compliance with European regulatory compliance. Certification of the Quality Management System allows the manufacturer to sell medical devices in the European Union.

### 14.3.1 European Union Medical Device Directive

There are three directives for medical devices in the European Union.

**Table 14.2** ISO 13485:2003 Sections and their Descriptions

| Section | Title | Description |
|---|---|---|
| 1 | Scope | Defines the scope of the regulation, describes the requirements for exclusion to design and development where appropriate, and the applicability of the regulations |
| 2 | Normative references | References ISO 9001:2000 |
| 3 | Terms and definitions | Provides the terms and definitions used in the regulation |
| 4 | Quality management system | Focuses on procedures and processes for the implementation of an effective quality management system including the review, approval, and control of records and documents |
| 5 | Management responsibility | Emphasizes the involvement of management in the entire process, from customer needs, to product planning and product realization. Use of effective reviews, communication to ensure implementation and effectiveness of the quality system |
| 6 | Resource management | Ensures that there are adequate resources that include personnel, infrastructure, and the work environment |
| 7 | Product realization | A significant part of the regulation, includes product planning, product design and development, purchasing process and controls, production and service validation and controls, and, the identification and traceability of all products and components used in the production of devices |
| 8 | Measurement analysis and improvement | A separate section is devoted to the importance of good measurement systems, monitoring products and processes, controlling nonconforming products, analysis of data, and corrective and preventive action |
| 9 | Annex A | Differences between ISO 13485:2003 and ISO 13485:1996 |
| 10 | | Differences between ISO 13485:2003 and ISO 9001:2000 |
| 11 | Bibliography | References |

- The Active Implantable Medical Device (AIMD) Directive—90/385/EEC;
- The Medical Device Directive (MDD)—93/42/EEC; and
- The In Vitro Diagnostic Directive (IVD)—98/79/EC.

After June 14, 1998, medical devices could not be offered for sale in the European Union without "CE marking" and a "declaration of conformity." The letters CE stand for "Conformité Européene" in French literally meaning "European Conformity." For many products CE marking and a declaration of conformity may only be affixed with proof of a certified quality system and/or product testing based on its end use. The quality systems certification, the CE marking, and the declaration of conformity are provided by a "Notified Body" which is an organization appointed by the national accreditation authorities and which "notifies" the European Commission to approve products covered by the Medical Devices Directive. All medical device manufacturers must designate a notified body to certify and register their products. For all classes of devices, a detailed technical file must be submitted providing objective evidence demonstrating compliance with the Medical Device Directive's essential requirements and with appropriate harmonized standards which include ISO 13485:2003 and ISO 10993 standards [8].

Products shipped must bear the CE marking to show compliance with the directive (Figure 14.1). If a Notified Body is involved in the approval, the number of the Notified Body must also appear adjacent to the CE marking.

Additionally, the product must be shipped with a Declaration of Conformity, an example of which is shown in Figure 14.2.

Documentation can include the following:

- Evidence demonstrating compliance with essential requirements detailed in the directive for the particular product's end use;
- Demonstration of design verification and validation;
- Risk assessment and analysis;
- Clinical evidence demonstrating effectiveness of the device;
- Procedures for post-market surveillance;



**Figure 14.1** The CE mark.

**EC Declaration of Conformity**

**Council Directive 93/42/EEC concerning medical devices**

We *(Name and address of manufacturer)*

Certify that the product described is in conformity with the applicable provisions of Council Directive 93/42/EEC concerning medical devices.

*(Name, type or model, lot, batch or serial no. etc.)*

*(Description)*

*(Name of Responsible Person)* *(Signature of Responsible Person)*

*(Date)*

**Figure 14.2** CE marking declaration of conformity.

- Complete declaration of conformity;
- Technical information of the finished device—including toxicity and biocompatibility studies;

- Accurate product identification, labels, procedures, and user instructions; and
- CE mark or label on product or packaging.

## 14.4 Other Countries

### 14.4.1 Japan

The Japanese government, through the Ministry of Health, Labor, and Welfare (MHLW), regulates all medical devices, whether manufactured in Japan or imported from other countries. In Japan, the term "medical device" is used for any instrument, apparatus, or material as designated by the Japanese government that is used in diagnosing, treating, and/or preventing diseases in humans or animals and which can be used to affect the structure and functions of humans or animals. The Pharmaceutical Affairs Law (PAL) is the primary governing law for medical devices in Japan. Medical devices must undergo thorough safety examinations and demonstrate medical efficacy before they are granted approval, or "*shonin*," to be sold in Japan. PAL regulations specify very detailed requirements for companies that manufacture or import medical devices for sale in Japan, ranging from infrastructure and facilities to personnel and processes. For new medical devices for which there are no equivalent products already approved in Japan or for devices that have been improved or modified that might affect device safety and efficacy, clinical trials are required. Clinical trials must be conducted to demonstrate the safety and efficacy of the product under strict Good Clinical Practice (GCP) standards, and must be followed by standard Post-Marketing Assessment (PMA) reporting and a follow-up program.

In April 2004, the Pharmaceuticals and Medical Devices Agency (PMDA) was established in an effort to create a more efficient and transparent medical device registration review process. The PMDA was formed by merging three already existing organizations: (1) the Pharmaceuticals and Medical Devices Evaluation Center (PMDEC), (2) the Organization of Pharmaceutical Safety and Research (OPSR), and (3) the Japan Association for the Advancement of Medical Equipment (JAAME). Two of these three agencies (PMDEC and JAAME) were previously involved in the medical device approval process, including the review of product registration applications and clinical trial consultations. Prior to the creation of the PMDA, the application and review process for *new* devices could take as long as 2 years. Over the next several years, the PMDA intends to shorten this process, although it has not had success in doing so thus far.

Under the New PAL, the Quality Assurance Controller will be responsible for ensuring compliance with the new Good Manufacturing Practice (GMP) requirement, based on Japan's own adaptation of ISO 13845:2003, as well as Good Quality Practice Ordinance (GQP) standards [15]. The Standard Operating Procedures (SOPs) for GQP include product storage controls, the release of products into the market, quality control at local offices, ensuring the maintenance of all quality assurance documents and reports, the handling of product recalls, and audits.

Necessary Governmental Authorizations (for sale of devices into Japan):

- Manufacturing (or import) approval ("*Shonin*") which guarantees the safety and efficacy of the device, obligatory for every product;
- Manufacturing (or import) license ("*Kyoka*") of a device, which the Japanese manufacturer and importer hold, renewable every 5 years; and
- Reimbursement listing approval.

### 14.4.2 China

There are two main agencies in China that regulate medical devices, the State Food and Drug Administration (SFDA) and the Department of Medical Devices. The State Food and Drug Administration (SFDA) is the Chinese equivalent of the FDA in the United States. All imported medical devices must be registered with the SFDA. The Department of Medical Devices under the SFDA is responsible for the standardization, product registration, safety, and supervision of all imported devices into China. Some of the standards used by the agency are ISO 10993 (Biologic Evaluation of Materials and Medical Devices), ISO 14971 (Risk Management), and ISO 13485 (Medical Devices—Quality Management Systems).

### 14.4.3 Australia

The medical device legislation has been established by the Therapeutic Goods Act 1989 as

amended by the Therapeutic Goods Amendment (Medical Devices) Bill 2002 and the Therapeutic Goods (Medical Devices) Regulations 2002. The new framework also adopts the philosophies of the Global Harmonization Task Force on medical devices.

The new regulatory system has the following features:

- a device classification scheme based on different levels of risk for each class of device;
- essential principles for the quality, safety, and performance of the medical device that must be complied with before the product can be supplied;
- options as to how compliance with the essential principles can be satisfied and assessed;
- manufacturer quality systems, type testing, and design evaluation;
- the use of recognized standards to satisfy the requirements of the essential principles;
- a comprehensive post-market surveillance and adverse incident reporting program;
- appropriate regulatory controls for the manufacturing processes of medical devices;
- the continued use of the Australian Register of Therapeutic Goods as the central point of control for the legal supply of medical devices in Australia; and
- chemical, physical, and biological properties.

### 14.4.4 India

The Central Drugs Standards Control Organization (CDSCO) under the Ministry of Health and Family Welfare regulates the licensing, import, manufacture, and sale of medical devices into the country. Approvals can be facilitated by evidence of approval from the US FDA, the EU MDD (CE certificate), and approvals from Australia, Canada, Japan, and other countries. ISO certification for specific manufacturing facilities (ISO 13485) is also accepted. Device master files must contain details of good manufacturing practices including components and materials used in the device. It must also include the manufacturing and quality assurance processes, risk assessment, design verification, sterilization, stability, biocompatibility, and toxicological data associated with the materials and production of the finished device.

### 14.4.5 South America

For most companies the access point to South America is Brazil. Brazil has the second largest healthcare market in the Americas (bigger than Canada and second only to the United States). It is a member of Mercosur—the South American Free Trade Area that includes Brazil, Argentina, Uruguay, and Paraguay. Separate submissions have to be made in each country. Registration of products or product families must contain information on the manufacturer, the materials and composition used, and the intended use.

Mexico has patterned its regulations after the US FDA and ISO requirements under the Secretaría *de Salud*.

## 14.5 Global Harmonization Task Force (GHTF)

The GHTF was conceived in 1992 and is an informal grouping that was formed to respond to the growing need for the international harmonization of regulations in medical devices. The members of the GHTF include government and industry officials from the European Union, Japan, Canada, Australia, and the United States. These representatives working with medical device manufacturers and other organizations related to medical devices try to harmonize global approaches to the safety, efficacy, clinical performance, and quality of medical devices with the goal of protecting public health, promoting innovation, and facilitating international trade. Global harmonization is the aligning of the different regulatory systems of the world making them globally on par with each other to manufacture and sell safe and effective devices. The GHTF is committed to developing guidelines accepted in all GHTF countries and gives technical guidance toward a more coherent approach on the interpretation of technical and quality requirements for medical devices. It has four study groups, dealing with product approval-related issues, post-market surveillance, quality system requirements, and audits of quality systems.

## 14.6 Applicability of the Regulations to Material Suppliers

The regulations (FDA 21 CFR Parts 820 and ISO 13485:2003) are applicable to the manufacturers of "finished devices." Suppliers of raw materials are not expected to comply with these regulations but must meet acceptable material requirements set forth by the device manufacturers (as per their purchasing controls). Finished device or component manufacturers expect their material suppliers to have consistently good quality and process control in their facilities.

In July 1998 in the United States, the Biomaterials Access Assurance Act—BAAA (HR 872) was signed into law by President Bill Clinton. The purpose of the act was to "establish rules governing product liability actions against raw materials and bulk component suppliers to medical device manufacturers, and for other purposes" [16]. This was a very important bill, as it protects the suppliers of biomaterials or components of implanted devices from liability if an entire device results in injury or death, provided it was not the fault of the material or component. This act was in response to a very serious concern expressed by suppliers following many expensive lawsuits where it was found that the eventual cause of the problem was not with the material but with the finished device itself. Many plastics suppliers are willing to supply materials as long as their materials are used in devices that are in contact with the human body for less than 29 days (minimal contact with and minimal residence time within the body). A few plastics suppliers are willing to recommend their products for implants and devices that are in the body for more than 29 days (implantable devices) based on the extensive studies and data that show their materials pass all physical, chemical, biocompatibility, hemocompatibility, and toxicity tests required for implantable devices.

Finished device manufacturers are expected to establish purchasing controls [17], providing material suppliers with acceptance criteria and material specifications and requirements needed for their specific devices and applications. Such requirements might include the following:

- Raw material performance specifications,
- Biocompatibility,
- Sterilization requirements,
- Material purity,
- Chemical resistance,
- Toxicity requirements,
- Product quality and consistency,
- Notification of formula changes,
- Adherence to good manufacturing practices, and
- Assurance of supply.

## 14.7 Conclusion

The purpose of regulations for medical devices is to ensure that the products are consistent, safe, and effective for their intended use. The two major regulations are the 21 CFR Parts 820 Quality Systems Regulations enforced by the Food and Drug Administration in the United States and the global standard by the International Organization of Standards ISO 13485:2003 "Medical devices—Quality management systems—Requirements for regulatory purposes" enforced by the European Union. Most countries have adopted modified versions of the ISO 13485 and/or the FDA regulations. Finished device manufacturers need to comply with the regulations. Suppliers of raw materials and components do not need to comply with the regulations, but are subject to the purchasing controls of the finished device manufacturers. Finished device manufacturers must have stringent supplier qualification procedures that include supplier audits, incoming raw material and component specifications, and quality metrics. Plastic material suppliers must provide appropriate data and information about their products that the regulatory bodies and the finished device manufacturers can use to assess the performance and viability of the raw materials for their specific devices. This is only required for high-risk devices. Such information includes the formulation, the performance specifications, the test methods and release criteria, the quality metrics, material characteristics (physical, chemical, biocompatibility, and toxicity), the assurance of supply, and the notification of any formulation changes. This information is typically maintained by the regulatory bodies in master files, is kept confidential, and is accessible only to the regulatory bodies but not to the finished device manufacturers or the public at large.

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[7] 21 CFR Part 820—Quality Systems Regulation.

[8] 21 CFR Parts 808, 812, 820 Medical Devices; Current Good Manufacturing Practices (CGMP); Final Rule; October 7, 1996, p. 52606, response #7.

[9] Premarket Approval (PMA)—is the FDA process of scientific and regulatory review of devices "that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury."

[10] 510(k) application and submission—is the FDA scientific and regulatory approval process of devices that a manufacturer thinks is "substantially equivalent" to a similar device that was on the market prior to May 28, 1976. This is less involved than the premarket approval defined in reference 9.

[11] Investigational Device Exemption (IDE) is issued by the FDA to allow the use of investigational devices in human subjects for clinical trials and investigation in order to evaluate the safety and effectiveness of the investigational medical device.

[12] ISO 13485:2003, Medical devices—Quality management systems—Requirements for regulatory purposes.

[13] ISO 14971:2007, Medical devices—Application of risk management to medical devices.

[14] ISO/TR 14969:2004, Medical devices—Quality management systems—Guidance to the application of ISO 13485:2003.

[15] Ministerial Ordinance on Standards for Quality Assurance for Drugs, Quasi-drugs, Cosmetics, and Medical Devices MHLW. Ordinance Number 136; September 22, 2004.

[16] Public Law 105–230, sect. 1, 112 Stat. 1519 codified in 21 U.S.C. 1601–1606, 1999.

[17] Quality Management System—Medical Devices—Guidance on the Control of Products and Services Obtained from Suppliers.

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