CHAPTER FIVE

ENABLING TECHNOLOGIES

5.1 SEPARATION AND INTEGRATION

It is self-evident that many different sciences and technologies are involved in the conversion of all ideas, concepts, and visions into clinically relevant applications. These enabling technologies are described in this chapter. I discuss them under separate headings based on the principal focus of the applications, such as with prosthetics and orthotics in the next section, or on the underlying scientific / engineering principles, such as with biocompatibility or robotics later on. I emphasize that there is much overlap and success in any one of these areas, depending on the integration of principles. The section on biomechanically functioning implants, therefore, is largely based on principles of mechanical engineering and biomaterials science, but has to encompass those of biocompatibility, which are described in a different section, since no implantable device, however sound are the engineering details, will give acceptable performance without adequate biocompatibility.

5.2 CLINICAL TECHNIQUES FOR RECONSTRUCTION

5.2.1 Approaches to the Interior of the Body

Many reconstruction techniques require clinical access to the relevant part of the body. There are several ways in which this can be achieved, and it is unnecessary, and indeed irrelevant, to describe individual methods and approaches here. However, a few general principles must be mentioned since clinical outcomes often critically depend on the way that this access is achieved. One major innovation has involved the transition from open incisions to minimally-invasive procedures, this largely taking place in the mid-1980s[1]. Initially these methods were applied to the abdomen, replacing the conventional laparotomy with the so-called laparoscopy, and were mainly focused on the excision of tissues, such as hysterectomy, cholecystectomy (gall bladder) and bowel resection. Initially the technology and instrumentation did not allow for the insertion of reconstructive devices, but as noted below and in later sections of the book, this has change radically in recent years.

5.2.1.1 Open Incisions

A few specific situations are discussed here, especially in relation to implant placement.

[1] Philipose KJ and Sinha B, Laparoscopic Surgery, *Medical Journal of the Armed Forces of India*, 1994;50(2):137–43. doi:10.1016/S0377-1237(17)31019-5.

5.2.1.1.1 Abdominal surgery

By the year 2000, when the appeal of laparotomy techniques was at its highest, some 4 million such procedures were performed annually in the USA[2]. The outcomes of these procedures, whatever the medical rationale, naturally depends on the surgical skill, which itself encompasses the decision of where to make the incision. Within the abdomen, there are three primary choices, the vertical, transverse and oblique. A vertical (i.e., midline) incision through skin, subcutaneous fat, linea alba, and peritoneum, is easy to perform and results in minimal blood loss, because of the avascular nature of the linea alba, with excellent exposure of the abdomen. Extensions can be easily made, superiorly or inferiorly, if required. An alternative is the paramedian incision; there are two variants, the conventional paramedian incision, in which the rectus sheath and rectus muscles are transected close to the linea alba, and the lateral paramedian technique, where a longitudinal incision is made near the lateral border of the rectus sheath. A supraumbilical transverse incision gives good exposure of the upper abdomen, but extending the original incision is more difficult. With a full-length transverse incision, the oblique and transverse muscles and the rectus abdominis muscle and linea alba are cut in a horizontal plane. An infraumbilical transverse incision in the lower abdomen is the Pfannenstiel incision, which is often used for gynecological and obstetric procedures. Widely used oblique incisions are the subcostal, or Kocher, incisions which follow the profile of the costal margin, directed in a medio-proximal direction. Many segmental blood vessels and nerves are dissected, as well as the fibers of the external oblique, the transverse and the rectus abdominis muscles.

Complications that may be related to incisional technique include post-operative pain, wound infection, wound dehiscence and incisional hernia. There are possibly many confounding factors at play, so that it is difficult to generalize. It has been found that transverse incisions give rise to less post-operative pain than those of the vertical midline, but most studies reveal few statistically significant differences with respect to infection and dehiscence. With respect to incisional hernias, one of the most common complications of abdominal surgery, midline incisions are generally associated with higher hernia levels than the other techniques.

5.2.1.1.2 Total hip replacement (arthroplasty)

The surgical approach for total hip arthroplasty has been a matter of discussion for many decades and is an area of interest in the current orthopedic literature. There are three approaches that are universally popular[3, 4], the posterior, direct lateral and direct anterior approaches.

The posterior approach is probably the most common worldwide, although several iterations have been described. When first popularized in the early days of hip replacement, the intention was to limit bone and soft-tissue damage by sparing the abductor musculature while providing a wide exposure of the acetabulum and femur. The pelvis has to be stabilized properly when in the lateral decubitus position to avoid pelvic drift during the surgery since it can shift more than 10° anteriorly with the result of the acetabular component being placed in a relative retroversion. Lift-off of adhesive drape has to be avoided as this can facilitates bacterial entry into the wound. The direct lateral approach allows for significant exposure of both acetabulum and femur, with latitude for an extensible exposure of the femur if necessary; this has a low dislocation rate due to the preservation of the posterior stabilizers of the joint. The direct anterior approach has become popular in recent years, being performed in the supine position

[2] Burger JWA, van 't Riet M and Jeekel, J, Abdominal incisions: Techniques and post-operative complications, *Scandinavian Journal of Surgery*, 2002;91:315-21.

[3] Moretti VM and Post ZD, Surgical approaches for total hip arthroplasty, *Indian Journal of Orthopedics*, 2017;51(4):368-76. doi:10.4103/ortho.IJOrtho_317_16.

[4] Angerame MR and Dennis, DA, Surgical approaches for total hip arthroplasty, *Annals of Joint*, 2018;3:43. doi: 10.21037/aoj.2018.04.08.

so that intraoperative fluoroscopy can be used for optimal component positioning. It has a low dislocation rate and earlier functional recovery compared to other approaches.

The success of THA is confirmed by consistent, long-term survivorship of 89–94% and excellent patient satisfaction ranging from 87% to 95%. Infection is a rare but devastating complication in THA. Instability following THA is another complication of concern for patients and surgeons, with an overall dislocation of 3.9% in the US. Registry studies have demonstrated higher dislocation rates with the posterior approach. Abductor muscle insufficiency is common in the immediate post-operative period following the direct lateral approach since the gluteus medius and minimus are partially incised and repaired during the procedure, possibly leading to muscle weakness, pain, or abnormal gait mechanics.

Currently there is no consensus on the optimal approach as each exposure has a unique set of conditions and risks; all of the three common approaches are associated with very good results. Naturally, surgeons select their optimal exposure based on their comfort and experience with a given approach.

5.2.1.1.3 Breast enlargement

As discussed in several places in this book, breast enlargement involves the placement of an implant within the breast tissue to increase the size and shape of the breast, either for cosmetic purposes or for reconstruction after mastectomy. In the latter case, the surgical technique of the mastectomy is the primary arbiter of incision details. With augmentation, the implants are usually inserted using an incision placed under the breast, at the crease. The implants themselves can be placed either directly behind the breast on top of the chest wall muscle (sub-glandular placement), or behind the breast and chest wall muscle (sub-muscular placement). The former technique is the simplest and is less likely to cause discomfort; it is also effective in patients who have drooping of the breast. Placing implants behind the breast muscle gives more coverage, being useful for slender patients who have very little breast tissue.

5.2.1.1.4 Hernia repair

A hernia occurs when an internal organ or other structure protrudes through a muscular wall that normally contains it, most of these occurring within the abdominal cavity[5]. Although some hernias resolve spontaneously, many do not; some form of hernia surgery is then necessary. There are several different types of hernia, and each have their own challenges as far as technique is concerned. Inguinal hernias are the most common, with more than 20 million patients annually, worldwide. Inguinal hernia repair is one of the most often performed surgical procedures worldwide. There have been at least 100 different repair techniques described over the years, the majority now being classified as open mesh repair or laparoscopic mesh repair. The latter are discussed in a following section.

The most widely used open mesh repair method is the Lichtenstein technique introduced in the early 1990s[6]. Here, the patient is in the supine position. After incising the skin, subcutaneous tissue, and external oblique aponeurosis, the spermatic cord is elevated from the posterior wall of the inguinal canal. With indirect hernias, the hernial sac is identified, dissected and opened to allow examination of its contents. The sac can be ligated and the distal portion excised. With large inguinal hernias, the sac may descend down to the scrotum; the distal part of the sac may be left open to prevent the formation of a hydrocele. A generally accepted technique suitable for all inguinal hernias does not exist and it is commonly recommended that surgeons should provide both a Lichtenstein and a laparo-endoscopic approach option, so that the treatment can be based on expertise, resources, and patient- related factors.

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5 Köckerling F and Simons MP, Current concepts of inguinal hernia repair, *Visceral Medicin*e, 2018;34:145-50. doi:10.1159000487278.

6 Sakorafas GH, Halikias I, Nissotakis C, *et al,* Open tension free repair of inguinal hernias; the Lichtenstein technique, *BMC Surgery,* 2001:1:3. doi:10.1186/1471-2-2482-1-3.

5.2.1.1.5 Open heart surgery and heart-lung bypass

Techniques for access to the heart for reconstructive procedures have evolved over several decades. Many approaches now involve minimally invasive methods, as discussed in the next few sections, but some still require open access to the heart. So-called 'open-heart surgery' is considered to be any process where a relatively large incision is made in the chest after which the breastbone is cut and the rib cage opened to allow visual and manual access to the heart. For many procedures, a heart-lung machine is attached to blood vessels, which takes over the pumping action, allowing procedures to be performed in the absence of beating of the heart. With some procedures, notably coronary artery bypass, it may not be necessary to use this technique, the heart being steadied by a mechanical device in order to allow the surgery; this is called off-pump or beating heart surgery. The surgeon will consider relevant characteristics of the heart problem, including age and overall health to decide whether off-pump surgery is appropriate.

5.2.1.2 Minimally Invasive Procedures and Laparoscopic Techniques

(To be completed, Q2, 2024)

5.2.1.2.1 Transcatheter Technology

(To be completed, Q2, 2024)

5.2.2 Wound Closure, Sutures and Clips

5.2.2.1 Surgical Sutures

The first known document that described suturing techniques is the *Samhita,* by the Indian surgeon Susruta in 500 BC, who was mentioned earlier in this book. Susruta described the use of bow string made of sheep upper small intestine as a suture for procedures such as rhinoplasty and tonsillectomy; catgut was readily available from musicians who used it for stringed instruments, with 'kitgat' being the fiddle string of a three-stringed violin. Several centuries later, Hippocrates, Aurelius Cornelius Celsus and Galen refined the use of catgut, and also silk sutures for their surgical procedures[7].

Ambroise Paré, a French military surgeon, used linen and silk suture ligation methods after limb amputation. By the mid-nineteenth century the preparation of sterile catgut sutures, with more reproducible absorption times, was achieved. Even so, these natural materials did not perform well in the treatment of conditions such as vesicovaginal fistulas because of inflammation, and silver wire was introduced as an alternative. They were, however, difficult to tie, and their use decreased when synthetic pliable non-absorbable suture materials became available.

Sutured wounds often became infected, and many surgeons preferred to cauterize wounds, rather than risk the patient's death from infected sutures. In 1867, Lister was the first to make a connection between the presence of germs and infection. He speculated that if the bacteria in the interstices of suture material could be eliminated, the material could be safely left *in situ* with the ends cut short, and he noted that healing took place without any suppuration, and with remarkable absence of swelling or tenderness. He used carbolic acid to clean suture material, instruments, dressing materials, and wounds, He also steeped

[7] Muffy TM, Tizzano AP and Walters MD, The history and evolution of sutures in pelvic surgery, *Journal of Royal Society of Medicine,* 2011;104(3):107-12, doi:10.1258/jrsm.2010.100243.

catgut in a solution of carbolic acid in olive oil and developed chromic catgut to improve properties. Catgut was the main absorbable suture material through the early part of the next century, surgeons using silk and cotton when a non-absorbable material was needed.

In Europe, the occurrence of prion diseases in animals, especially bovine spongiform encephalopathy, and the possibility of infectivity of humans that were exposed to certain animal tissues, led to the withdrawal of catgut sutures, which by then were made of bovine intestinal tissues. The opinion of the European Commission in 1998[8], which I helped to write, determined that there were many alternative synthetic suture materials which were, indeed, superior to catgut, their preferred use obviating any infectivity risk. So-called 'non-absorbable' sutures included silk, nylon and some aromatic polyesters, while synthetic absorbable materials were largely based on the aliphatic polyesters, poly(lactic acid), poly(glycolic acid) and polycaprolactone.

5.2.2.2 Surgical Clips / Staples and Adhesives

In the 1980s there was a marked increase in attention given to alternative methods of wound closure, particularly with staples, or skin clips; one major potential advantage was the reduced operative time. Quite early on, some doubts were expressed about the nature of the putative benefits, Ranaboldo and Rowe-Jones showing in 1992 that although the operative time for closure of laparotomy wounds was shorter, this was off-set by the need for staple removal, and pain levels were higher in that group[9]. Although skin clips were recommended for closure of uncomplicated orthopedic incisions in 2004[10], many subsequent studies showed that, in hip and knee surgery, this optimism was unfounded[11]. Quite soon, staples were being used in simple procedures, such as cesarian section deliveries, Rousseau *et al* stating "*Staples are the method of choice for skin closure for elective term cesareans in our population*" in 2004[12]. However, several extensive reviews have again drawn attention to deficiencies of staple techniques, even in this uncomplicated area, MacKeen *et al,* for example, concluding that "*For patients undergoing cesarean, closure of the transverse skin incision with suture significantly decreases wound morbidity, specifically wound separation, without significant differences in pain, patient satisfaction, or cosmesis*". Suture placement does take 7 minutes longer than staples".[13] Overall there are few incentives for using staples in open incisions involving reconstructive devices. I should not be too surprised at this; at the time of increasing interest in skin clips / staples I published a paper, in conjunction with a surgeon colleague, about a comparison of these devices and sutures in an animal model[14] which showed good results with clips for a few days, but with a rapid decline in performance after 5-7 days when the clips compromised the microvasculature; the main thing I learned from these studies was the extreme difficulty of repeatedly examining wounds in rapidly growing pigs who had a good memory of me and my anesthetic skills every few days.

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[8] European Commissions, Scientific Committee on Medicinal Products and medical Devices, "*The Equivalency of Alternative Products to Intestines of Animal Origin for use as Surgical Sutures*", Opinion Adopted on 16 September 1998

[9] Ranaboldo CJ and Rowe-Jones DC, Closure of laparotomy wounds: skin staples versus sutures *British Journal of Surgery*, 1992;79(11):1172-3 doi:10.1002/bjs.1800791122.

[10] Murphy M, Prendergast P and Rice J, Comparison of clips versus sutures in orthopaedic wound closure, *European Journal Orthopedic Surgery Traumatology*, 2004:14:16–8. doi:10.1007/s00590-003-0121-2.

[11] Smith TO, Sexton D, Mann C, *et al*, Sutures versus staples for skin closure in orthopaedic surgery: meta-analysis, *British Medical Journal*, 2010;340:c1199. doi:10.1136/bmj.c1199.

[12] Rousseau J-A, Girard K, Turcot-Lemay L et al, A randomized study comparing skin closure in cesarean sections: staples vs subcuticular sutures, *American Journal of Obstetrics and Gynecology*, 2009;200(3):265.e1-4. doi:1-.1016/j.ajog.2009.01.019.

[13] MacKeen AD, Schuster M, Berhella V *et al,* Suture versus staples for skin closure after cesarean; A meta-analysis, *American Journal of Obstetrics and Gynecology*, 2015;212(5):621.e1-10.

[14] Williams, D.F. and Harrison, I.D. The variation of mechanical properties in different areas of a healing wound, *Journal of Biomechanics*, 1977; 10:633-42

An alternative wound closure technique to either sutures or staples (or in some cases as an adjunct to these methods) is that of tissue adhesives; this was also first investigated over 50 years ago. Early attempts, which are still used today, with some modifications, used chemicals of the cyanoacrylate family, especially n-butyl-2-cyanoacrylate. About one minute after application to wound edges, the molecules have polymerized to give good bond strength. Plasticizers, stabilizers, and other substances may allow for several different formulations for different clinical situations. Changes in the number of alkyl groups in the cyanoacrylates have been the most important, and octyl-2-cyanoacrylate became the dominant product, with four times the tensile strength of most other products, being granted FDA approval in 1998[15]. Although new formulations have increased tensile strength, these adhesives are often limited to use on low tension areas such as the face or scalp. Cyanoacrylates may also yield potentially toxic compounds as they resorb, and risks of infection may be increased. Several other polymerizable substances have been developed for assistance in wound closure, but few are attractive in areas of reconstructive technologies, apart from some roles in tissue grafts, which are discussed elsewhere in the book, as are some tissue sealant products.

5.2.2.3 Vacuum Assisted Closure

Delayed wound healing can be a major problem in some groups of patients, especially with the elderly and those with co-morbidities. Vacuum-assisted closure of surgical incisions can assist conventional methods of wound management in such cases[16]. Use of negative pressure optimizes the wound for spontaneous healing by increasing blood flow and reducing oedema. Once adequate hemostasis is achieved, and adjacent skin is dry, sterile foam dressings are applied to provide an even distribution of negative pressure over the whole wound bed. A fenestrated evacuation tube within the foam is connected to a vacuum pump. and wound sealed with an adhesive drape. The negative pressure mode can be either continuous or intermittent. Vacuum assisted closure is often used with diabetic foot ulcers, bed sores and other difficult conditions where increased blood flow is important; within reconstructive techniques it may be beneficial in skin graft fixation, flap salvage and similar procedures.

5.2.2.4 Hyperbaric Techniques

As an alternative to applying a vacuum to the wound site, the patient may be subjected to breathing oxygen at elevated pressure. Hyperbaric oxygen therapy is a treatment in which patients breathe 100% oxygen while inside a hyperbaric chamber, pressurized to greater than sea level; for clinical efficacy, the pressures applied are usually range 2 to 3 times that level. Depending on the indication, patients can be treated with up to 3 sessions of 2 hours daily. This therapy improves neovascularization, as increased oxygen leads to increased production of nitric oxide in the bone marrow, which appears to stimulate increased progenitor cell mobilization, leading to more stem cells recruited to skin wounds and accelerated blood vessel formation[17]. Although there are many who advocate this technique for treating severely compromised wounds, the evidence of clinical effectiveness varies and even in the situations

[15] Januchowski R and Ferguson WJ, The clinical use of tissue adhesives: A review of the literature, *Osteopathic Family Physician,* 2014;2:25-9.

[16] Agarwal P, Kukrele R and Sharma D, Vacuum assisted closure (VAC)/negative pressure wound therapy (NPWT) for difficult wounds: A review, *Journal of Clinical Orthopedics and Traumatology*, 2019;10(50:845-8. doi:10.1016/jcot.2019.06.015.

[17] Lam G, Fontaine R, Ross FL *et al,* Hyperbaric oxygen therapy: Exploring the clinical evidence, *Advances in Skin & Wound Care*, 2017;30(4):181-90. doi:10.1097/01.ASW.0000513089.75457.22.

where good results are most likely, as with the severe diabetic foot ulcer, the outcomes are very technique sensitive, with limited long-term benefits in many patients[18]

5.2.2.5 Wound Dressings

It is self-evident that once the surgical wound has been closed it has to be protected from the external environment to facilitate healing. This is true for all types of surgical wound, although conditions do vary from one type of site to another. Much of the discussion here is reserved for the section on infection control that follows, since it is the prevention of surgical site infections that is one of the most important factors, but the general nature of the materials used to cover the wound site, normally referred to as wound dressings, deserves come specific commentary. The type of dressings used is determined by the nature of the operative site and the preference and experience of the surgeon. In general terms, the environment promoting healing should be moist, warm, and clean, so that the dressing absorbs sufficient exudate, while being permeable enough to control a moist environment, acting as a watertight barrier against the external environment, while also allowing the wound to breathe.

Total joint arthroplasty wounds present morphologic specificities[19]; dressings over joints should accommodate motion allowing frictionless free range of movements, allowing for postoperative oedema fluctuations in the presence of potentially friable skin in elderly patients. Ideally dressings should allow wound inspection so that the number of dressings is minimized; changing dressings can be a painful procedure, which is time- and cost-consuming, and represents a contamination risk. Several dressing products, introduced over the last few decades are hydrophilic, with the ability to maintain a suitable moisture level around the wound. Such dressings are absorbent and do not need frequent changing. They are usually covered with a polyurethane film that protects the primary dressing against environmental contamination and, being transparent, enables both the wound exudate and the surrounding area to be inspected visually.

Wound dressings for most hernia repairs are straightforward, but large ventral hernias pose significant problems, where high morbidity and prolonged recovery time are major factors. Primary wound closure is often attainable even after large hernia repair and complex abdominal wall reconstruction, and the techniques of the two previous sections, especially vacuum or negative pressure, are valuable. When closure is possible, a non-adherent dressing, such as those made from knitted cellulose acetate fabric and impregnated with petrolatum emulsion, are effective, especially when used in association with negative pressure systems[20]. When it is impossible to achieve wound closure, the challenges for dressings are extreme.

[18] Thistlethwaite KR, Finlayson KJ, Cooper PD, *et al,* The effectiveness of hyperbaric oxygen therapy for chronic venous leg ulcers: A randomized, double-blind, placebo-controlled trial, *Wound Repair and Regeneration*, 2018;26(40:324-31

[19] Langlois J, Zaoui A, Ozil C, *et al,* Randomized controlled trial of conventional versus modern surgical dressings following primary total hip and knee replacement, *International Orthopaedics (SICOT*);39:1315–9. doi:10.1007/s00264-015-2726-6.

[20] Conde-Green A, Chung TL, Holton LH, *et al,* Incisional negative-pressure wound therapy versus conventional dressings following abdominal wall reconstruction: A comparative study, *Annals of Plastic Surgery*, 2013;71(4):394-7. doi:10.1097/SAP.0b013e31824c9073.

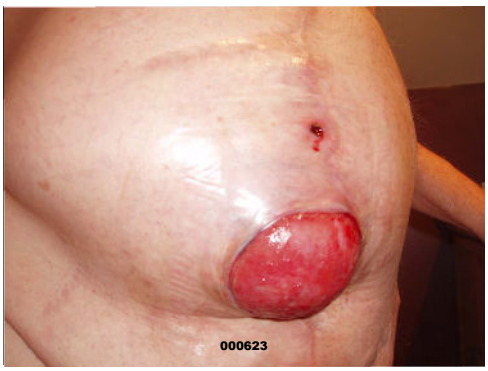

Figure 5.1, Challenges for wound closure and dressings in major ventral hernia repair.

5.2.3 Infection Control

5.2.3.1 Surgical Site Infections

The CDC healthcare-associated infection prevalence survey reported that there were about 110,800 surgical site infections associated with inpatient surgeries in the USA in 2015[21]. Although advances have been made in infection control practices, such as improved operating room ventilation, sterilization methods, barriers, surgical technique, and availability of antimicrobial prophylaxis, these infections are a substantial cause of morbidity, prolonged hospitalization, and death, with an estimated annual cost of $3.3 billion, extending hospital length of stay by 9.7 days, with cost of hospitalization increased by more than $20,000 per admission. Of course, not all of these procedures are reconstructive in nature, but many of the more complex reconstructive procedures, including transplants, have high rates. It is worth noting that the CDC report mentioned above classifies the nature of wounds (both surgical and traumatic) on the basis of risk of infection, with four categories: Clean, Clean-Contaminated, Contaminated and Dirty/Infected. Most surgical procedures involving reconstruction are performed on clean sites. Clean-contaminated wounds have no signs of infection at the time of surgery but do involve potentially contaminated internal tissues or organ, such as appendix and vaginal procedures. Contaminated situations involve an operation in which there is a major break in sterile technique or gross spillage from the gastrointestinal tract. Dirty or infected sites are rarely encountered in reconstructive techniques.

It should be of no surprise that surgical procedures that involve placing foreign material into the body are at a higher risk of infection than those that do not: this was made very clear by some elegant work by Elek and Conen over 60 years ago that simple surgical sutures place in tissues increase the risk of infection enormously[22]. This is not a theoretical position; it has considerable relevance to outcomes of reconstructive procedures. With knee reconstruction [23] periprosthetic infection occurs when the tissues surrounding the prosthesis become infected, and it accounts for 25.2% of revision procedures after knee

[21] Center for Disease Control and Prevention (CDC), National Healthcare Safety Network, Surgical Site Infection Event (SSI) Report, January 2023.
[22] Elek SD and Conen PE, The virulence of staphylococcus pyogenes for man. A study of the problems of wound infection, *British Journal of Experimental Pathology*, 1957;38(6):573-86.
[23] Mallon CM, Gooberman-Hill R, Moore AJ, Infection after knee replacement: a qualitative study of impact of periprosthetic knee infection, *BMC Musculoskeletal Disorders*, 2018;19:352. doi:10.1186/s12891-018-2264-7.

replacement with reported incidence in the UK and USA ranging from 0.5 to 2%. In 2015 in the UK, 6104 knee revision procedures were performed, of which nearly one quarter were for infection. Prosthetic heart valve infection, known as endocarditis, after surgical aortic valve replacement and transcatheter aortic valve replacement, carries significant morbidity/mortality. An analysis of large numbers of cases showed that with surgical valves the incidence of endocarditis was 0.3%–1.2% per patient-year while transcatheter valves procedures had rates of 0.6%–3.4%; there were key differences in pathogenesis, as the transcatheter approach has a specific set of infection risks related to entry site, procedure, and device, including non-standardized protocols for infection control, valve crimping injury, paravalvular leak, neo-leaflet stress, intact/calcified native leaflets, and intracardiac hardware[24]. When operative intervention is necessary for infection treatment, mortality is high, at 20% to 30%.

With kidney transplantation, a Canadian study showed that of close to 150 transplant patients, 31.0% had at least one infection, the incidence being 36.2 per 100 patient-years by 2 years post-transplant[25]. In the first 2 years, urinary tract infections had the highest incidence (18.1 per 100 patient-years) followed by skin infection, cytomegalovirus, and bacteremia. With hematopoietic stem cell transplantation, infectious complications account for most of the associated morbidity and mortality, occurring in pre-engraftment, immediate post-engraftment, and late post-engraftment periods. Risk factors of infectious complications differ according to the stem cell source, donor type, region, prophylaxis strategy, and comorbidities[26].

Diabetic foot infection is a limb and life-threatening condition if untreated. Acute infection may lead to tissue necrosis and rapid spread through tissue planes, especially in patients with poorly controlled diabetes; coexisting chronic osteomyelitis can serve as a persistent source of soft tissue infection recurrence. This is not associated with a primary reconstructive procedure but is highly relevant to the use of such procedures that may form part of the treatment plan. In the patient shown in Figure 5.2[27], infection from an early stage ulcer spread through the tendon sheaths; all muscle of the anterior compartment were affected. Three weeks after the first debridement, a split skin graft and second debridement were undertaken. One year later, the wounds had healed but a recurrent ulcer developed because of muscle-tendon imbalance; definitive reconstruction fusion surgery was then performed as there was considerable involvement of the hind foot and lateral plantar surface.

5.2.3.2 Device Sterilization

Any device or material that is inserted into the human body, whatever the intended duration, must be sterile, not introducing any unacceptable risk of infection. This implies that there are adequate methods to assure that devices meet the acceptable standards of sterility during production that these methods should not leave behind residues that could still act as antigens and cause an immune response, and they should not damage the materials used in the device.

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[24] Alexis, SL, Malik AH, George I, *et al,* Infective endocarditis after surgical and transcatheter aortic valve replacement: A state of the art review, *Journal of the American Heart Association*, 2020;9:e017347. doi:10.1161/JAHA.120.017347.

[25] Cowan J, Bennett A, Fergusson N, *et al*, Incidence rate of post-kidney transplant infection: a retrospective cohort study examining infection rates at a large Canadian multicenter tertiary-care facility *Canadian Journal of Kidney Health and Disease*, 2018;12(5):2054358118799692. doi: 10.1177/2054358118799692.eCollection 2018.

[26] Cho S-Y, Lee H-J and Lee D-G, Infectious complications after hematopoietic stem cell transplantation: current status and future perspectives in Korea, *Korean Journal of Internal Medicine*, 2018;33(2):256-76. doi:10.3904/kjim.2018.036.

[27] Ahluwalia RS and Reichert ILH, Surgical management of the acute severely infected diabetic foot – The 'infected diabetic foot attack'. *Journal of Clinical Orthopedic Trauma*, 2021;18:114-20. doi:10.1016/j.jcot.2021.04.012.

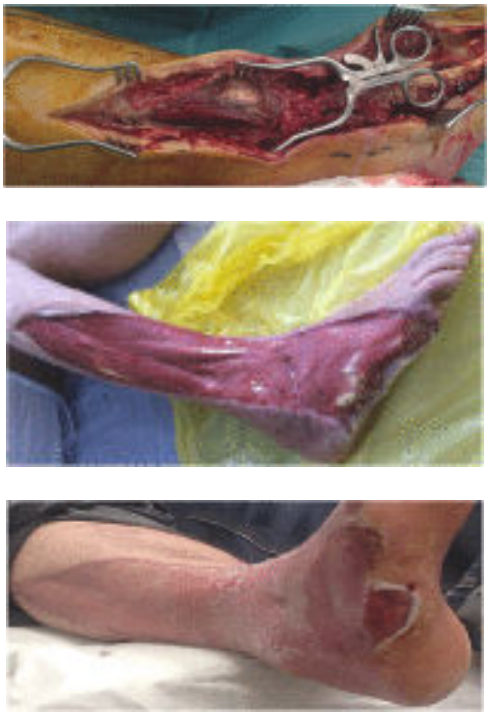

Figure 5.2. Infection of diabetic foot ulcer. See text for explanation.

Sterility is the absence of all living organisms, principally bacteria, fungi and viruses. In practical terms it may not be possible to remove each organism let alone be possible to give an assurance that all have been killed. Sterilization validation, which is an essential part of quality control, works through the use of a Sterility Assurance Level (SAL), which is the probability that a product will be non-sterile after exposure to a specified sterilization process. The accepted SAL for an implantable device is 10^{-6}. There are several standards that are used to inform the technical aspects of the sterilization of health care products, and this is one of the most important parameters of quality control in medical technologies.

Moist heat sterilization is the oldest method to be used and involves exposing the device to saturated steam, typically at 121°C; it is a simple process and leaves no residues, but many materials are unable to withstand these temperatures without undergoing unacceptable changes. A major alternative involves the use of ethylene oxide, a gas that affects the nucleic acids of microorganisms. Objects are placed in gas permeable packages, which are themselves placed in vessels with a relative humidity between 60 and 80 % and a temperature around 40-50°C for up to 15-20 hours. The process is compatible with many materials and devices and is very efficient. However, both ethylene oxide and the by-product ethylene chlorohydrin have toxicity and carcinogenicity profiles so that the processes must be strictly controlled with respect to environmental contamination.

Several sterilization methods involve irradiation. Gamma rays cause ionization of cellular components such as DNA, which readily causes cell death. The rays are highly penetrating and provide a very effective sterilization mechanism. Usually, the rays are generated by a ^{60}Co isotope source, which decays to ^{60}Ni, emitting the rays and electrons, and a dose of 25 kGy is sufficient to satisfy the implantable device SAL under most circumstances. Many materials, including most polymers, can be sterilized by this method, although some are too sensitive to radiation for this to be used. Electron beams provide an

alternative method of applying radiation energy. Penetration into objects is not so good and applications are limited. Nevertheless, many devices including surgical dressings, and wound care products, IV administration kits and cardiac catheters are routinely sterilized by electrons.

5.2.3.3 Operative Technique

Preoperative antibiotic prophylaxis, the administration of antibiotics prior to surgery is one of the most effective procedures to combat infection. AlBuhairan *et al* showed that with total hip and knee replacement, the absolute risk of wound infection was reduced by over 80% when using prophylaxis no prophylaxis[28]. The routine administration of prophylactic antibiotics is now standard in cases where a foreign body is implanted as part of the procedure, with bone grafting procedures, and where extensive dissections or high blood loss are anticipated. The timing of antibiotic administration may be important, with the goal of having the concentration in the tissues at its highest at the start and during surgery, generally starting between 30 and 60 minutes before the skin incision is made, usually with IV administration. The antibiotic should be effective against the most common organisms implicated as causes of surgical site infections, including Staphylococcus aureus, Staphylococcus epidermidis, Aerobic streptococci and Anaerobic cocci. The three antibiotics used in adult surgical prophylaxis, where weight-based dosing is recommended, are cefazolin, vancomycin, and gentamicin. Special attention is necessary where there is a high risk of MRSA infection. In all cases, meticulous attention has to be paid to skin care before the incision is made, with appropriate use of drapes etc. Unless there is a known infection, prophylactic antibiotics should be discontinued within 24 hours.

5.2.3.4 Anti-bacterial Coatings

There is no doubt that bacteria have an affinity for foreign surfaces and there are many reasons, both real and imaginary, about why this should be so[29]. It is natural, therefore, that there have been many attempts to minimize device-related infections by trying to prevent bacterial attachment by modifying surfaces to reduce this affinity; a wide variety of substances, usually referred to as anti-bacterial coatings, have been attached to biomaterial surfaces for this purpose. The reality is that little clinical success, as opposed to voluminous published academic papers, has resulted from this outlay of effort. One recent paper suggesting good clinical success with a 'novel' coating on surfaces of hospital equipment[30] was met with a rejoinder that the actual evidence did not support their 'success' criteria and optimism[31]. With implantable devices, including those used for reconstructive techniques, the majority of developments look good in the laboratory but fail to make clinical impact, no matter how authors try to embellish the potential and 'promise'[32,33] . There are many potential reasons for this, one major factor being that

[28] AlBuhairan B, Hind D and Hutchinson A, Antibiotic prophylaxis for wound infections in total joint arthroplasty: a systematic review, *Journal of Bone and Joint Surgery, British Edition*, 208;90 (7):915-9. doi:10.1302/0301-620X.90B7.20498.

[29] Kimkes TEP and Heinemann M, How bacteria recognise and respond to surface contact, *FEMS Microbiology Reviews*, 2020;4491):106-22. doi:10.1093/fensre/fuz029.

[30] Ellingson KD, Pogreba-Brown K, Gerba CP, *et al,* Impact of a novel antimicrobial surface coating on health care–associated infections and environmental bioburden at 2 urban hospitals, *Clinical Infectious Diseases*, 2020;71(8):1807–13. doi:10.1093/cid/ciz1077.

[31] Dancer SJ, How much impact do antimicrobial surfaces really have on healthcare-acquired infection? *Clinical Infectious Diseases*, 2020;71(8):1814–6, doi:10.1093/cid/ciz1078.

[32] Swartjes JJTM, Sharma PK, Van Kooten TG, *et al,* Current developments in antimicrobial surface coatings for biomedical applications, *Current Medicinal Chemistry*, 2015;22(18):2116-29.

chemical substances attached to a biomaterial surface with the intention of suppressing bacterial growth, including the killing of bacteria, may also have detrimental effects on the cells of the host tissue. A great deal of attention has been given to silver in this respect, which is known to have anti-bacterial properties, but which also may induce adverse effects in many mammalian cells by virtue of its affinity for some proteins[34].

5.2.4 Pain Control

This is a very brief section that deals with the control of pain during and after surgical procedures; it is not concerned with procedures that are intended to control painful conditions. Armstrong *et al* identified 7 potential risk factors that may lead to inadequate pain control postoperatively with orthopedic surgery, including a history of physical, emotional, or sexual abuse, history of anxiety or of drug or alcohol abuse, preoperative nonsteroidal anti-inflammatory drug, or disease-modifying antirheumatic drug use, current opioid use, and psychological conditions other than anxiety and smoking[35]. Anxiety, other psychological conditions, current opioid use, and current smoking were significantly associated with higher preoperative and postoperative pain scores. These results suggest that, unless the surgeon makes serious mistakes, the pain experienced post-operatively by patients (in these types of procedure) is largely associated with their own characteristics and pre-operative behavior, unrelated to the device in question. Much of the research in this area has been devoted to the reduction in reliance on opioids, because of serious addiction risks, and current evidence suggests that drugs such as intravenous acetaminophen is more effective than intravenous morphine in the majority of patients. Chronic pain after reconstructive surgery is a different matter; this tends to be procedure related and will be discussed in relation to individual situations in later sections.

5.3 PROSTHETICS AND ORTHOTICS

5.3.1 The Prosthesis of the Flesh; A Historical Perspective

In a fascinating essay on 'a medieval theory of prostheses', Walter refers to an early eighteenth-century definition of prosthesis as '*that which fills up what is wanting, as is to be seen in fistulous and hollow ulcers, filled up with the flesh by that art; also, the making of artificial legs and arms, when the natural ones are lost*'[36]. It is not necessary to go into some of the linguistic arguments contained in this essay, but the historical perspective is clear; centuries ago, absent parts of the body were considered to be unacceptable, from functional, psychological, sociological, spiritual, and aesthetic considerations, and many efforts were made to replace such absent parts by whatever technologies and substances were available. Thus, in medieval times, flesh was considered as a natural prosthesis of the body, fifteenth century records of surgical procedures indicating that there were three types of flesh, glandular, muscular, and 'simple' flesh, the latter having the capacity to fill up hollow spaces. Flesh and fat were determined to be radically different from tissues such as bones, nerves, and skin, being characterized as sanguine in

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[33] Guillaume O, Perez-Tanoira R, Forteiny R, *et al*, Infections associated with mesh repairs of abdominal wall hernias: Are antimicrobial biomaterials the longed-for solution? *Biomaterials,* 2018;167:15-31. doi: 10.1016/j.biomaterials.2018.03.017.

[34] Williams RL, Doherty PJ, Vince DG, *et al,* The biocompatibility of silver. *Crit Rev Biocompatibility, 1989;* 5: 221–43.

[35] Armstrong AD, Hassenbein SE, Black S, *et al,* Risk factors for increased postoperative pain and recommended orderset for postoperative analgesic usage, *Clinical Journal of Pain,* 2020;36(11):845–51. doi:10.1097/AJP.0000000000000876.

[36] Walter KL, Fragments for a medieval theory of prosthesis. *Textual Practice,* 2016;30(7):1345-1363. doi:10.1080/0950236X.2016.1235844.

contrast to spermatic, this difference then being crucial for medieval beliefs about the continuity and survival of the body.

There is ample evidence of the use of prostheses to replace extremities over several millennia[37]. Paleopathological evidence from graves at Turfan, in the Uygur Autonomous Region of China, dating from 300 – 200 BC, reveal a leg prosthesis on a male individual who had osseous ankylosis of the left knee; it was constructed of wood, sheep or goat horn, horse hoof and leather[38]. Thurston has documented the early history of artificial limbs[39], showing a prosthetic toe on an Egyptian mummy and Roman lower-limb prostheses dating from the same time as the Chinese example above. He recounts the stories of many famous surgeons who developed the skills of amputation and prosthetics, including Pare and Potts.

As this section clearly demonstrates, the parts of medical technology that relate to artificial limbs have received much impetus from the injuries sustained by the military during armed conflict, and this itself

Figure 5.3, Detail photographs of leg prosthesis showing (A) the outline of the knee, (C) thinning of the thigh plate by rubbing over a long period, and (B, D) fastening of the hoof with a leather strap penetrating the horn tip.

[37] Finch J, The art of medicine – The ancient origins of prosthetic medicine, *The Lancet*, 2011;377:548-549. doi:10.1016/s0140-6736(11)60190-6.
[38] Li X, Wagner M, Wu X, *et al,* Archaeological and paleopathological study on the third / second century BC grave from Turfan, China: Individual health history and regional implications. *Quaternary Internationa*l, 2013;290-1:335-343. doi:10.1016/j.quaint.2012.05.010.
[39] Thurston AJ, Pare and prosthetics: The early history of artificial limbs, *Australia and New Zealand Journal of Surgery*, 2007;77:1114-1119. doi:10.1111/j.1445-2197.2007.04330.x.

has reflected the development of advanced weaponry that has been designed to confer devastating injuries. Almost perversely, such powerful weapons have been matched by increasing skills in treating battlefield injuries, so that tremendous effort has had to be directed to treating those whose lives have been saved, albeit with parts of their bodies missing or functionally useless, rather than killed outright or soon afterwards. Such developments were, perhaps, first witnessed during the American Civil War, where the introduction of the Minié (or Minnie) ball, one of the early types of practical rifle bullets, changed the nature of injuries; the ball was made of soft lead with a hollow base that expanded when fired, causing large, irregular, slow-healing wounds. About 70% of Civil War wounds affected the limbs, primary amputation becoming the treatment of choice in battlefield surgery[40]. More than 30,000 Union and 40,000 Confederate soldiers lost limbs between 1861 and 1865. A massive industry arose out of the need for prosthetic limbs, and for improvements to the wood and steel structures that were initially available. The introduction of rubber components provided a significant advance. The same type of profile in the artificial limb business, and the development of specialized hospitals such as Roehampton in the UK, followed during the two world wars[41]. The Vietnam war spurred many developments in battlefield medicine and surgery, but also had a profound effect on the design of artificial legs, especially the effect of socket design and alignment on achieving proper adduction of the femoral stump in above-knee amputations, as eloquently described by King[42].

It has to be said that from a clinical perspective, in many parts of the world, in spite of the growing awareness of the importance of biomechanics and rehabilitation, the service provided to amputees was primitive and often disrespectful. I remember, as a trained metallurgist, during my first year in medical technology, trying to work with an 'artificial limb service', in the basement of an orthopedic outpatient clinic, where limb sockets were made of very poor quality, inexpensive, aluminum alloys that were prone to rapid corrosion and disintegration through continued contact with urine[43], the whole place, and every device, smelling dreadful; not a good insight into the potential benefits of advanced materials in reconstructing the body.

5.3.2 Rationale of Twenty-First Century Limb Prostheses

This section will concentrate on prostheses for the legs; this is not meant to denigrate prostheses for other limbs, but it is where much of recent technology has been focused. There are three specific features of lower limb prostheses that must be emphasized, integration with the body, control and power. Materials of construction are important, and play some role in these primary factors, especially integration, but the focus is on these three.

It should be noted here that this section, for the sake of completeness, refers to prostheses and orthotics. The latter are non-invasive devices that assist in body movements, including inserts for shoes and braces for limbs. They do not really qualify for inclusion in a discourse on reconstruction, but there are some commonalities. The closest involve what are referred to as exoskeletons, especially used in therapy for

[40] Hasegawa GR, Mending broken soldiers: The Union and Confederate programs to supply artificial limbs, Southern Illinois University Press, 2012, ISBN 978-0-8093-3130-y.
[41] Guyatt M, Better legs: Artificial limbs for British veterans of the First World War, *Journal of Design History,* 2001;14(4):307-325. doi:10.1093/jdh/14.4.307.
[42] King C, Modern research and the forgotten prosthetic history of the Vietnam war, *Journal of Rehabilitation Research and Development*, 2009;46(9):x1 – xxxvi. doi:10.1682/JRRD.2009.07.0092.
[43] Williams DF, Some problems associated with conventional artificial limbs, *Biomedical Engineering*, 1970, 5, 10-13.

patients with spinal cord injuries. Reference to a couple of recent good papers on these exoskeletons should suffice here[44,45].

5.3.2.1 Prosthesis – Body Interfaces

A variety of terms is used to describe the relationship between prosthesis and body; 'integration' is the key message here in relation to the metaphysical incorporation of the device into the well-being of the patient, including the possibility, although not of necessity, of the physical and permanent integration of the device within the skeletal structure. Whatever the precise mechanism used, it is the interface between the technology and the residual tissues that is critical[46]. The interface should provide a suitably stiff coupling to give control without causing pain and discomfort. This is not a trivial situation; the majority of prostheses use some type of socket for this interface, but up to 50% of those with transtibial devices do not use them because of socket problems, a figure which is even higher with transfemoral amputees. The design of sockets did not change for many years after the introduction of the patellar tendon bearing socket in the 1960s, but changes to elastomeric materials for the tissue-contacting surface and of vacuum-assisted socket suspension made significant improvements. One of the major problems relates to residual limb volume fluctuations, arising from weight and activity changes and factors such as perspiration. Routine measurement of limb geometry has proven difficult, due to the expense of imaging technology and the far lower clinical priority, especially as patients tend to be of lower socio-economic status; this remains a concern.

Several technologies are under investigation with respect to improvement of interface design and integration. Comotti *et al* have reviewed the potential of additive manufacturing (including 3D printing) on the basis that '*the socket represents a deformable interface between the residual limb and the artificial leg that must be optimized according to geometry and loads distribution of patients*'[47]. The percutaneous anchoring of femoral prostheses using so-called 'osseointegration', that is the direct and permanent attachment of titanium sections of the prostheses to residual femoral bone, has been used in some cases[48]. The materials and clinical technologies of osseointegration was developed specifically for dental implants, and this is discussed elsewhere in this book. Two aspects should be mentioned here. First, this is a complex method, largely reserved for difficult patients, more or less on a personal basis (for example, used experimentally in USA military medicine). Secondly, since the method involves the passage of metallic components through skin and into bone, infection is a constant threat, osteomyelitis being reported in 20% of cases over a ten-year period.

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[44] Baunsgaard CB, Nissen UV, Brust AK, *et al,* Gait training after spinal cord injury: safety, feasibility and gait function following 8 weeks of training with the exoskeleton from Ekso Bionics, Spinal Cord, 2018;56:106-116. doi:10.1038/s41393-017-0013-7.

[45] Alamro RA, Chisholm AE, Williams AMM, *et al,* Overground walking with a robotic exoskeleton elicits trunk muscle activity in people with high-thoracic motor-complete spinal cord injury, *Journal of NeuroEngineering and Rehabilitation*, 2018;15:109. doi:10.1186/s12984-018-0453-0.

[46] Safari R, Lower limb prosthetic interfaces: Clinical and technological advancement and potential future direction, *Prosthetics and Orthotics International*, 2010;44(66):384-401. doi:10.1177/0309364620969226.

[47] Comotti C, Regazzoni D, Rizzi C, *et al,* Additive manufacturing to advance functional design: An application in the medical field, *Journal of Computing and Information Science in Engineering*, 2017;17:031006-1. doi:10.1115/1.4033994.

[48] Tillander J, Hagberg K, Berlin O, *et al*, Osteomyelitis risk in patients with transfemoral amputations treated with osseointegration prostheses, *Clinical Orthopedics and Related Research*, 2017;475:3100-3108. Doi:10.1007/s11999-017-5507-2.

5.3.2.2 Prosthesis Control; Power and Sensors

Most prostheses, even today, are passive, requiring power from the patient to actuate movement. Some powered systems are available that use external power, with microprocessor control, either with data obtained from the prosthesis (e.g., acceleration or position) or from the user's own physiological system[49]. Different types of powered devices have been designed for foot, below-knee and above-knee amputations[50]. Many of these designs have only been introduced after 2010 and evaluations, and hence widespread use, is an evolving process. Some adaptive above-knee prostheses, actuated by combinations of hydraulic, pneumatic, and electromechanical power appear to have acceptable performance, as amputees are able to control the prostheses during ground level walking, although many types of movement may be difficult. There are still challenges with current control systems, such as finite state and impedance control.

At this point, it would be possible to describe individual devices and enumerate the reasons why many are still deficient in many patients. That is not a good use of time and effort. Instead, I use the review of Huang *et al*[51] to guide the arguments about the dichotomy between intelligent prostheses and human motor control, and then give a few examples of future perspectives. The basis of the Huang position is that while some lower limb prostheses can mimic the torque-generating capabilities of natural joints, even with the most common locomotor task, that of walking, such devices fail to show clear advantages over energetic passive devices; a plausible explanation is poor human-prosthesis coordination. By this, they mean that human locomotion is a dynamic process that involves coordination of many joints controlled by one system, the individual's nervous system, where musculoskeletal structure such as bi-articular muscles (i.e., those which cross two joints and influence both) contribute to overall coordination. With a robotic prosthesis, the innate mechanism for 'between-joint' coordination is altered. Current controllers are largely disconnected functionally, and do not consider factors such as motor impairment or compensatory strategies used by patients; they are not intrinsically designed to optimize the overall gait performance. The solution, albeit a very difficult solution, is for the user and robotic controller to function together.

For the prostheses, the controllers need to adapt to individual user impairments and motor behavior, sensing the overall system states, thus optimizing human-prosthesis gait performance outcomes. For the control of human movement, it is essential to communicate the prosthesis system states to the user to maximize the energy transferred from the robotic device. A major challenge here is that of identifying a paradigm that can promote human – prosthesis coadaptation, especially identifying whether this should be done concurrently or alternately. Merging human motor control with computerized prosthesis control could enable symbiosis but it cannot yet address situations in which immediate adaptation is required, such as obstacle avoidance.

As indicated by Simao *et al*[52]*,* although intuitive interfaces for prosthetic devices are still inaccessible to routine patients, the use of electroencephalography and, especially, electromyography (EMG) to decode user intentions is now very close. Surface EMG electrodes (sEMG) detect potential generated by muscle cells when excited by motor nerves; this has looked most relevant when addressing hand movement,

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[49] Wolf EJ, Cruz TH, Emondi AA, *et al,* Advanced technologies for intuitive control and sensation of prosthetics, *Biomedical Engineering Letters*, 2020;10:119-128. doi:10.1007/s13534-019-00127-7.

[50] Asif M, Tiwana MI, Khan US, *et al,* Advancements, trends and future prospects of lower limb prostheses, *IEEE Access*, 2021, 9, 85956. doi:10.1109/ACCESS.2021.3086807.

[51] Huang H, Si J, Brandi A *et al*, Taking both sides: seeking symbiosis between intelligent prostheses and human motor control during locomotion, *Current Opinion in Biomedical Engineering*, 2021;20:100314. doi:10.1016/j.cobme.2021.100314,

[52] Simao M, Mendes N, Gibaru O, *et al,* A review on electromyography decoding and pattern recognition for human-machine interaction. *IEEE Access,* 2019;7:39564. doi:10.1109/ACCESS.2019.2906584.

electrodes being placed on the skin near forearm muscles[53]. The challenges of using myoelectric control for robotic lower limb prostheses, of which there are many, have been recently reviewed by Fleming *et al*[54]. A very attractive option for use in such complex environments, which recognizes the significance of features that have been developed at enormous cost but which are applicable to very few patients is that of open source systems, involving, for example, a robotic knee-ankle prosthesis that facilitates the real-world testing of control strategies, including software for low-level control and communication with control systems, and hardware design that is customizable, enabling reduction in mass and cost, improvement in ease of use and independent operation of knee and ankle joints[55]. The objectives of developments such as these are to satisfy the need to recognize the user's intended movement, translate that movement into an appropriate pattern of effort, and execute the desired movements with close-loop control, noting that errors or failures at any of these levels may lead to falls, injuries, loss of confidence and reduced community mobility.

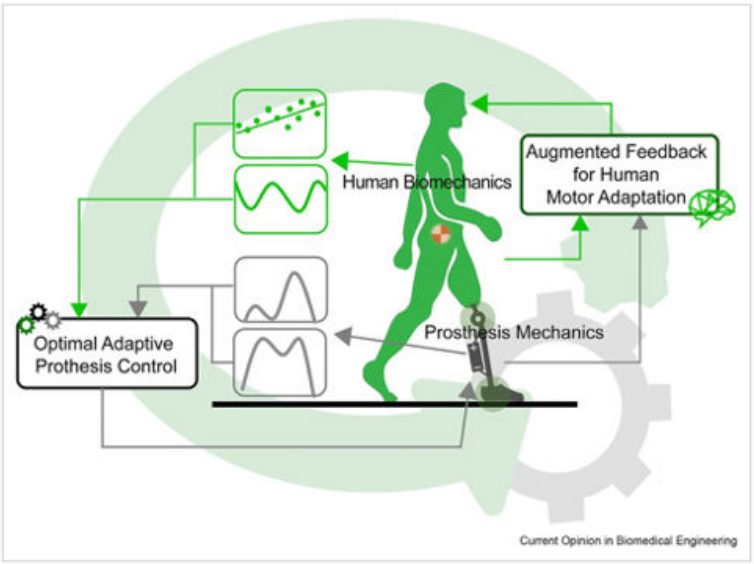

Figure 5.4, Human – prosthesis symbiosis requires seamless coordination and coadaptation between prosthesis control and human movement gait control. After Huang *et al.*

These practical objectives are at heart of the philosophical objectives of this book, which relate to the integration of every appropriate technology within reconstructive systems that can give performance to all individuals in need, irrespective of their circumstances.

[53] Tavakoli M, Benussi C and Lourenco JL, Single channel surface EMG control of advanced prosthetic hands: A simple, low cost and efficient approach, *Expert Systems with Applications,* 2017;79:322-332. doi:10.1016/j,eswa.2017.03.012.

[54] Fleming A, Stafford N, Huang S, *et al,* Myoelectric control of robotic lower limb prostheses: a review of electromyography interfaces, control paradigms, challenges and future directions, *Journal of Neural Engineering,* 2021;18:041004. doi:10.1088/1741-2552/ac1176.

[55] Azocar A, Mooney LM, Duval J-F, *et al,* Design and clinical implementation of an open-source bionic leg, *Nature Biomedical Engineering*, 2020;4:941-943. doi:10.1038/s41551-020-00619-3.

5.3.3 Psychological and Metaphysical Aspects

There are many different manifestations of attitudes of both individuals and societies to major disfigurement or dysfunction and to rehabilitation using prostheses. Leaving aside disfigurement of the face, which is covered elsewhere, this is most relevant in the case of the lower limb; few people can recognize that an individual has an implanted hip replacement, but it is often very obvious if that individual has one or two artificial legs. Societal aspects here range from those who, through sheer terror or paranoia will do anything to avoid amputation, to those who will do everything possible to acquire the world's best reconstructive technology to prove that they are even better than normal able-bodied individuals.

Two examples, one fictional but very realistic, one real but which appears fictional, demonstrate these scenarios. In the Second World War classic novel 'Whistle' by James Jones[56], himself a US Army soldier in the Pacific, one character, Bobby Prell, a corporal, had been seriously injured in both thighs while on patrol in Guadalcanal and was evacuated back to an army hospital in Tennessee. The travelling, by ship and train, gave him tremendous pain, and he knew that his legs were so badly wounded that they might never heal. Throughout this, he convinced himself that he would recover, even though the rumors were that he might lose one or both of his legs. A group of orthopedic surgeons, of varying rank, examined and treated him, the conclusion being reached by the ranking surgeon, a colonel, that amputation of the right leg was the only way to save his life. Prell was adamant that he would not agree to this, even in the face of the rebuke that such a clinical decision, in the army, could be taken without his approval. He understood that the splintered bone, which was not healing, was at mid-thigh, which meant sawing it off high, near the hip, so that there would be enough flesh to make a flap, which could support a full artificial leg. "*I don't think you understand*", said the colonel; "*I understand*", replied Prell, "*It's my leg*". The colonel carried on, "*The problem is your right leg is not healing. There is no infection, up to now. But that is because we are keeping you pumped full of sulfa. But you can't keep on taking sulfa forever. In the meantime, you are getting weaker and weaker, slowly. If you do infect, you're probably going to be dead. Do you understand that, soldier*?". "*I understand. The answer is still no. Better dead than no leg*". The irony (fictional, of course), was that Prell was being considered for the award of The Congressional Medal of Honor, the highest US military decoration, because of his bravery in the action during which he was so badly injured, but he could not contemplate living with a prosthesis in place of his natural right leg. I will not say any more about the subsequent fight over this particular amputation, the story being well-worth reading in its own right, but the point has been well made, I think.

With respect to the use of technology to enhance performance, a very interesting example is found with the South African athlete, Oscar Pistorius. A paper by Swartz and Watermeyer on this matter[57] was published in 2008, a little before it became clear that not all was well with this athlete. I will deal with the facts first and then come back to consider some psychological aspects. Oscar Pistorius was born in 1986, in Johannesburg, South Africa; he was born without a fibula in either leg and with deformed feet. His parents made the decision to have his legs amputated below the knee when he was 11 months old. He was fitted with prosthetic legs at 17 months and took to sports and outdoor activities with minimal difficulty. He took up serious running at the age of 16. He attended the University of Pretoria High Performance Centre and was fitted with so-called 'running blades'.

In 2004, he received his first set of carbon-fiber "Flex-Foot Cheetah" blades, with which he set new world-records mark and won medals at Paralympic Games. Much has been written about this type of

[56] James Jones, "*Whistle*", William Collins, 1978, ASIN B01B988XC8.
[57] Swartz L and Watermeyer B, Cyborg anxiety: Oscar Pistorius and the boundaries of what is means to be human, *Disability and Society,* 2008;23(2):187-190. doi:10.1080/09687590701841232.

materials technology[58,59]. His powerful ambition then carried him to competitions against able-bodied runners, his performances attracting scrutiny from those who thought he was getting an unfair advantage from his artificial devices. In 2008, the International Association of Athletics Federations announced that he was indeed benefitting from racing prostheses and banned him from all sanctioned events. The ruling was overturned on appeal to the Court of Arbitration for Sport, which concluded that any advantages gained with the blades were offset by the difficulties they presented on the starting block and curved sections of the track. He continued to win important races and collect medals, including World Championship and Paralympic victories in 2011 and 2012.

Figure 5.5, Flex foot Cheetah Running Blades

Unfortunately, the impact of his fame and over-riding ambitions led to violent behavior and several arrests, culminating in his fatal shooting of his girlfriend. His trials and appeals stretched out over many years, with much embarrassment to the South African legal system, with eventual intervention by the Supreme Court of Appeal and a conviction of murder and a long prison sentence. He is at the Attridgeville Correctional Centre and is eligible for parole in 2023.

The paper by Swartz and Watermeyer mentioned above comes from the psychology department of a top South African university, Stellenbosch, which is well-known for expertise in academic and practical aspects of sport. It starts with the statement that disabled people have a history of being viewed as not entirely human; this would align with the concepts of 'prostheses and flesh' mentioned earlier. The reader is encouraged to believe that 'the *idealized mythic valuing of the perfect body, with its association of personal virtue, carries as its counterpoint the denigration of persons with different bodies; the unspoken assumptions about these bodies, and their inhabitants, relate to undesirability, psychological damage, abjection and failure*'. The argument presented here is that someone like Pistorius is found on the brink of straddling these binary universes, and if he is allowed to do so may lead to the rendering of catastrophic questions regarding what we are striving for in terms of the attendant virtues of culturally designated bodily perfection. The discussion centers on a binary stereotype within which disabled people are snared, and which splits disabled people into two opposing, but inextricably linked, categories. These

[58] Curran SA and Hirons R, Preparing our Paralympians, *Prosthetics and Orthotics International*, 2012;36(3):366-369. doi:10.1177/0309364612453256.

[59] Ouarhim W, Ait-Dahi M, Bensalah M-O, *et al,* Characterization and numerical simulation of laminated glass-fiber – polyester composites for a prosthetic running blade, *Journal of Reinforced Plastics & Composite*s, 2012;40(3-4):118-133. doi:10.1177/0731684420949662.

are '*the invalide, dependent, incapable, damaged both inside and out and the celebrated media persona of the disabled person who has overcome adversity, unrestricted by his or her flaws, believing that everything is possible for those who work hard'*. A conclusion is that the case of Pistorius, who wishes to compete alongside able-bodied athletes, breaks entrenched boundaries, and lays bare core concerns in society about disability and the body. I doubt whether this is a widely-held view, although the extreme position taken by Pistorius is consistent with his later fall, not known to these authors at the time. The arguments are powerful and interesting.

5.4 INERT, INANIMATE SPACE FILLING OBJECTS

The technologies that are relevant here are those which allow an individual to change the shape, or possibly texture, of a part of the body. Various objects, in a range of physical forms, can be placed within the body, where they are intended to alter shape, with no other objective, and with no intentional biological interaction with the tissues of the body.

5.4.1 Changing Shape for Cosmesis

There are many specific,[60] reasons for the individual to want to change shape, or appearance, but they are largely based on their perceptions of how other people view them and / or form their opinions about them. It has become clear that impressions of personality traits are significantly affected by body shapes and facial appearances.

With respect to overall body shape, human bodies have been generally categorized as mesomorph (heavily muscled, broad shoulders, small waist, widely considered as energetic and desirable), ectomorph (tall and thin, fragile, considered as neurotic) and endomorph (round body, short neck, considered as lazy and undesirable). While most people accept their natural bodies, many would like to change their shape so that it was considered to belong to the more acceptable end of the spectrum; they may try to do by lifestyle issues such as control of diet and exercise, or by medical intervention to either remove unwanted tissue (e.g., breast reduction, liposuction) or to the increase apparent tissue volume or shape by implanted materials.

Leaving aside the face and skull, which are considered later, adding volume to tissues of the body is almost solely concerned with soft tissues, especially adipose tissue, muscle, fibrous tissue and cartilage. The descriptions of the specifications for shape-modifying materials are very simple to enumerate, but very difficult to achieve in practice. The materials have to exist within a normal biomechanical / physiological environment, but the requirements for mechanical functionality, such as parameters of strength are not onerous, nor are there any biophysical requirements. What are important, however, are the elastic, or possibly viscoelastic, properties, since the flexibility and softness must be as close as possible to the tissues the material is trying to emulate. Although there are several relevant properties here, the easiest to consider are the elastic moduli, best typified by the Young's modulus, which is a measure of rigidity, or its converse, flexibility. According to Akhtar *et al*[61] , the modulus for soft tissues

[60] Hu Y, Parde CJ, Hill MQ, *et al,* First impressions of personality traits from body shapes, *Psychological Science,* 2018;29(12):1969-83, doi:10.1177/0956797618799300.
[61] Akhtar R, Sherratt MJ, Cruickshank JK, *et al*, Characterizing the elastic properties of tissues, *Materials Today,* 2011;14(3):96-105, doi:10.1016/S1369-7021(11)70059-1.

ranges from 0.1 to 10 MPa. Subcutaneous adipose (fatty) tissue has a value around 2 kPa[62], fibroglandular tissue of the breast around 3 kPa[63] , nasal cartilage[64] and plantar fat[65] both around 3 MPa. A typical metallic biomaterial, such as a titanium alloy has a modulus of just over 100 GPa, that is 100,000 times greater than typical fibrous connective tissue. Many thermoplastic biomaterials such as high density polyethylene have a modulus of about 1 GPa, that is 1,000 times greater than that for the soft tissue, while natural rubber may be as low as 50 MPa, still substantially higher than tissues. The obvious conclusion is that there are no conventional biomaterials that have flexibilities and softness anywhere near those characteristics for the tissues of the body that we are trying to reshape.

The prospective solutions to this conundrum have followed several patterns. First, there were attempts to use polymeric sponges for breast reconstruction, such as those of polyvinyl alcohol, but uncontrolled tissue ingrowth, which often calcified, led to hardness and loss of volume and shape[66]. It was realized in the post second world war era that volume increases could also be achieved by injections of oils, waxes and gels, this use becoming quite widespread in Japan, but tissue responses and migration of the materials, which included paraffin and silicone fluids, was very problematic[67]. Some of these substances have also been used for augmentation elsewhere, especially for the buttocks; although, as Singh *et al* point out, liquid silicone is inexpensive, minimally antigenic and easy to inject, there continue to be problems of oil migration and granulomatous tissue reactions, so that their use is not widely recommended.[68].

The most widely used concept, in breast augmentation, calf and penis enhancement and other areas, is that of the encapsulation of a gel or fluid within a shell of an elastomer, almost invariably a silicone elastomer. The gel gives volume but not shape, while the shell constrains the gel within a pre-determined shape. These are not without problems and are very controversial; for this reason, discussion of shell-gel implants is reserved to the section on breast augmentation and reconstruction.

With respect to the face, there are two widely used soft but solid materials used in malar (cheek), chin and mandibular positions, these being silicone elastomers and polyethylene[69]. A typical malar implant is depicted in Figure 5.6.

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[62] Alkhouli N, Mansfield J, Green E, *et al,* The mechanical properties of human adipose tissues and their relationships to the structure and composition of the extracellular matrix, *American Journal of Physiology, Endocrinology and Metabolism,* 2013;305:E1427-35. Doi:10.1151/ajpendo.00111.2013.

[63] Briot N, Chagnon, Connesson N, *et al,* In vivo measurement of breast tissues stiffness using a light aspiration device, *Clinical Biomechanics,* 2011;99:105743, doi:10.1016/j.clinbiomech.2022.105743.

[64] Griffin MF, Premakumar Y, Seifalian AM, *et al,* Biomechanical characterization of the human nasal cartilage; implications for tissue engineering *Journal of Materials Science: Materials in Medicine,* 2016;27:11, doi:10.1007/s10856-015-5619-8.

[65] Kwak Y, Kim J, Lee KM, *et al,* Increase of stiffness in plantar fat tissue in diabetic patients, *Journal of Biomechanics,* 2020;107:109857, doi:10.1016/jbiomech.2020.109857.

[66] Peters W, The evolution of breast implants, *Canadian Journal of Plastic Surgery*, 2002;10(5):223-36, doi:10.1177/229255030201000508.

[67] Okubo M, Hyakusoku H, Kanno K, *et al,* Complications after injection mammaplasty, *Aesthetic Plastic Surgery,* 1992;16:18107.

[68] Singh M, Solomon S, Calderwood *et al,* Silicone-induced granuloma after buttock augmentation, *Plastic and Reconstructive Surgery- Global Open,* 2016;4(2):e624, doi:10.1097/GOX.0000000000000618.

[69] Rojas YA, Sinnon C, Colasante C, *et al,* Facial implants: controversies and criticism. A comprehensive review of the current literature, *Plastic and Reconstructive Surgery,* 2018;142:991, doi:10.1097/PRS.0000000000004765.

Figure 5.6. Positioning of solid malar implants

The demarcation between reconstructive procedures that are purely driven by cosmetic considerations and those that have additional functionality is rather blurred. In craniofacial, maxillofacial and orthognathic procedures within the head and neck, acceptable appearances are important but secondary to the effects on functions such as protection (as with cranioplasty plates after brain injuries or surgery[70]), breathing, mastication and so on. These technologies are considered in relevant parts of the text. So too are those procedures which use transplanted or transposed tissues or grafts.

5.5 BIOMECHANICALLY FUNCTIONING IMPLANTS

5.5.1 Some Essential Requirements

The biomechanical environment of the human body has been briefly discussed in an early chapter. There are many situations where the body is unable to function within the constraints of the applied forces, either because of age-related diseases, congenital defects, trauma, or other conditions. Implantable devices have been used for well over a century to provide or restore some mechanical functionality. This is rarely a trivial task; although the forces generated within the body are much lower and are experienced within a narrower frequency range, than with most non-medical engineering applications, the biomechanical system is, by definition, dynamic, living and often changing. It is necessary to consider not only how the implantable devices, and the materials of their construction, perform within these force systems, but also how the tissues of the body relate to the presence of the device, which inevitably alters the local, and possibly systemic stress systems.

This is one of the situations where early, historical uses of natural materials, such as ivory, cork and wood are not of much interest since they did not, and could not, work. The first real attempt to use engineering materials relates to bone fracture plates. Plating of fractures began in 1895 when Lane first introduced a metal plate for use in internal fixation[71]. These plates had problems with corrosion; subsequent attempts with marginally better materials also failed because of corrosion resistance and insufficient strength. Structural weakness and the resulting instability of the fixation remained problematic until the 1960s,

[70] Wiggins A, Austerberry R, Morrison D, *et al,* Cranioplasty with custom-made titanium plates – 14 years' experience, *Neurosurgery,* 2013;72(20:248-56, doi:10.1227/NEU.)b013e31827b98f3.
[71] Uhthoff HK, Poitras P and Backman DS, Internal plate fixation of fractures: short history and recent developments, *Journal of Orthopedic Science*, 2006, 11(2):118-26, doi:10.1007/s00776-005-0984-7.

when superior metallurgical quality (with stainless steel, cobalt-chromium and titanium alloys) and different designs and techniques, gave much better performance. Failure of fracture plates is rarely experienced today, as discussed in the next chapter.

Obviously, the function of a bone fracture plate is simply holding the bone in a stable position while new tissue forms and matures at the fracture interface(s). Starting in the 1950's devices were introduced to replace mechanically compromised tissues (e.g., joint replacement, heart valve prostheses, vascular 'grafts', etc.), to alter internal skeletal form (e.g., correction of spinal deformities) or assist healing (e.g., with abdominal hernia) and so on. In such cases, the mechanical requirements became more stringent.

There is no situation where fracture or rupture of a mechanically functioning implanted device is acceptable. Strength, in all of the manifestations highlighted in the next section, is therefore of paramount importance. Various terms are used to describe how a material deforms on applications of forces, including rigidity and flexibility; when the deformation is reversible, explained below, it is said to be elastic. There are time-dependent variations of elastic deformation, including viscoelasticity. In situations where there are moving parts, such as the components of total joint replacements or movable discs within rigid heart valve frames, all engineering aspects of those movements must be considered; these phenomena are described under the general term 'tribology' and relate to friction, lubrication and wear. Some applications have their own special requirements, including the need for intra-operative manipulation of shape to fit anatomical features, and the need to hold, without breakage or tearing, sutures within a fabric, as with hernia meshes.

All of these general and individual characteristics are discussed in the following sections. Many of the devices that rely on these enabling mechanical properties are described in the next chapter.

5.5.2 Strength, Including Plasticity and Elasticity

Just a few introductory definitions; these are straightforward but surprisingly misunderstood or mis-represented so often. When a force is applied to a material, it induces a stress in that material; that stress, which as a measure of the force exerted between the atomic or molecular entities of the material, is dependent on the amount of material present. There are several ways in which the force is applied, for example if the force is tending to pull atoms apart, it is a tensile force, if it pushes atoms together it is a compressive force, if it is twisting them, it can be a shear force. In a simple situation, the stress is determined to be the amount of force divided by the cross-sectional area of material over which the force is applied. The internal movement of atoms within a material that is subjected to stress produces a change in dimension, which is the strain, generally referred to as deformation. It is important to recognize that stress and strain are not synonymous; stress can be considered (albeit simplistically) as the cause, and strain as the effect in mechanical behavior.

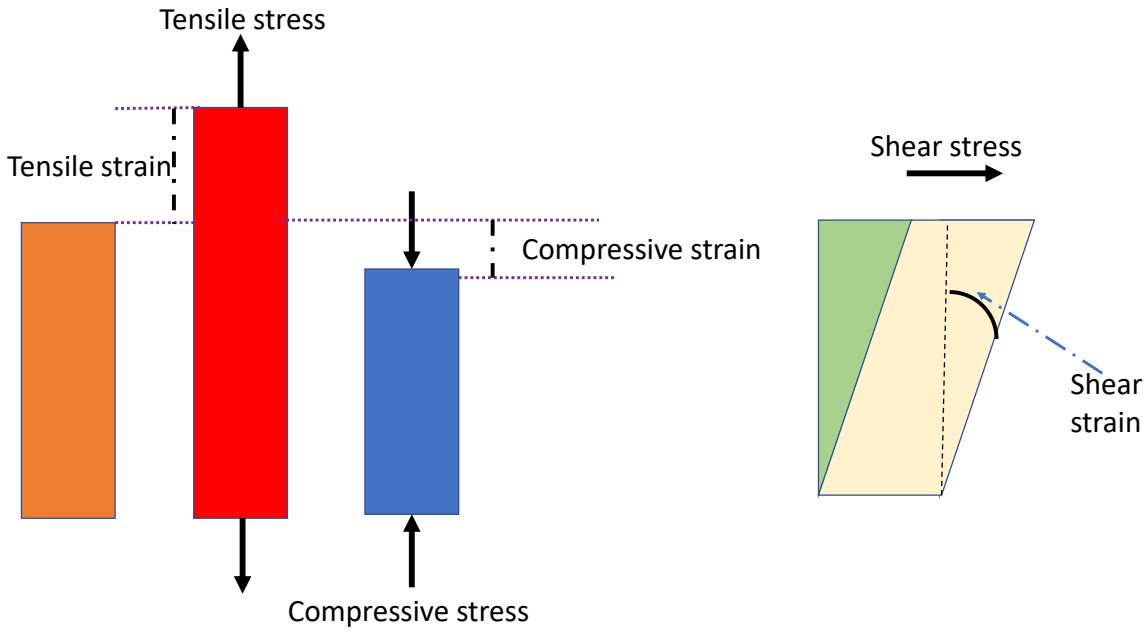

Figure 5.7, Stress and strain definitions in tension, compression and shear

5.5.2.1 Strength

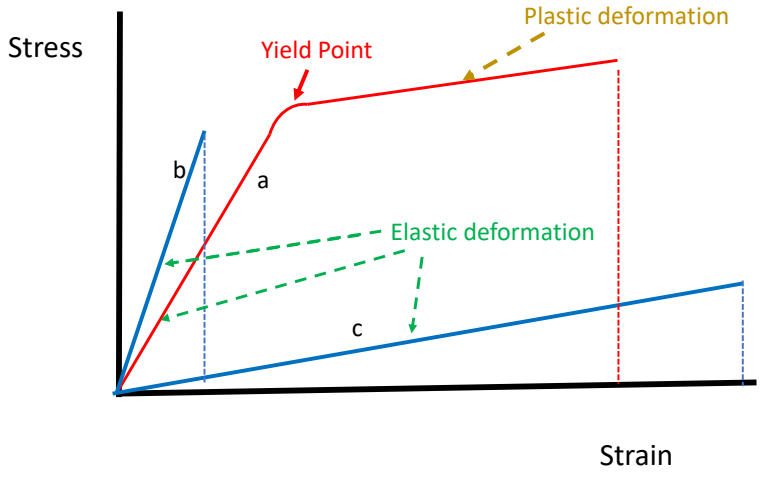

Figure 5.8, Stress – strain relationships for different materials

One term that is widely used to characterize this mechanical behavior is ‘strength’, but we must be very careful to define what is precisely meant by the term, since it is employed in everyday, non-engineering language (as in strength of character) as well as in many facets of engineering. Broadly speaking, strength is the quality of resisting an applied stress; a strong material exhibits minimal deformation. With many materials, that resistance depends on the nature of the applied stress, so that we can characterize the performance in terms of tensile, compressive or shear strength. Next comes the big question; what happens when the bonds between atoms (or molecules, or other microstructural features) are stretched in this way? For the moment, we can ignore the first stages since there is movement, i.e., strain, but not much else; these features are discussed in the following section. A critical point is reached when the forces between atoms becomes larger than the inherent strength of the bonds holding them together. This can happen at some local sites, in which case there is internal rearrangement of atoms, which gives a permanent change of shape. Alternatively, it can happen more or less simultaneously in a large region of the material such that the material breaks apart, or fractures.

5.5.2.2 Plasticity

The permanent change of shape can be considered first. Figure 5.8 shows the relationship between applied stress and resulting strain for different types of material. The curve (a) in red demonstrates plastic behavior, or plasticity. As stress is increased, so does the strain, until a point is reached where the local deformation mentioned in the previous section is initiated. The transition may be gradual or abrupt, the inflection point being described as the yield point. The stress level at which this happens is the first measure of strength, being referred to as the yield strength. To the right of the yield point, plastic deformation continues; this deformation is permanent, or irreversible. A material which deforms plastically extensively is said to be ductile; the term malleable is also used, which denotes that the material can be permanently shaped by applying the appropriate stress, either crudely by a blacksmith’s hammer, or in a refined way by an extrusion process to give wires, or a rolling process to give flat sheet. Ultimately, the material can undergo no further deformation (red dotted line) and fractures. The stress at which this happens is the second measure of strength, being referred to as the ultimate strength, usually measured in tension as the ultimate tensile strength. The blue lines (b and c) indicate materials that are unable to deform plastically, and fracture rather than yield to permanent deformation. A material represented by curve (b) is exemplified by glass; under normal circumstances glass cannot be deformed and is described as brittle, showing brittle fracture. Curve (c) represents materials that deform extensively, but reversibly, such as an elastic band, and ultimately will also fracture without permanent deformation.

5.5.2.3 Elasticity, Viscoelasticity and Creep

5.5.2.3.1 Elastic deformation

In all three examples above, the initial stress-strain behavior is seen to have a linear relationship, where strain is proportional to the stress; the diagram indicates that this is associated with elastic deformation. In contrast to plasticity, which is permanent deformation, elastic deformation is reversible, that is the material sample will return to its original form, and atoms and molecules will return to their original locations, once the stress is removed. The slope of the stress – strain relationship is a very important characteristic of the material, and is called the modulus of elasticity, which is quantitively, by definition, stress divided by strain. There is a limit to how much elastic deformation can be sustained, this limit being defined as the elastic limit, which is the case of the ductile material (curve b) is essentially the same as the yield point. Technically, the elastic modulus varies with the type of applied stress; traditionally, a

material is characterized by the modulus that related to tensile stress, which is referred to as the Young's Modulus.

The Young's Modulus, elastic limit and ultimate tensile strength of some conventional materials and some tissues are shown in Table 5.1. These are representative values, and there is much variability with strength data.

Material	Young's Modulus (GPa)	Elastic Limit / Yield Strength (MPa)	Ultimate Tensile Strength (MPa)
Diamond	1220	3000 [a]	3000
Alumina	340	400 [a]	400
Cobalt alloys	225	1700	1900
Stainless steel	195	290	580
Titanium alloy	110	400	1200
Tooth enamel	90	40 [a]	40
Bioglass	75	42 [a]	42
Magnesium alloy	45	400	500
Cortical bone	20	100	100
Hydroxyapatite	10	90 [a]	90
Achilles tendon	2	100	100
Polypropylene	1.3	30	300
High density polyethylene	1	30	40
Thermoplastic polyurethane	0.007	80	95
Skin	0.0005	[b]	20
Silicone elastomer	0.00005 – 1	0.05 – 140	1 – 150

[a] Brittle, no yield point
[b] Highly variable behavior

Table 5.1 Young's Modulus, elastic limit / yield Strength and ultimate tensile strength for selected materials and tissues

As a final point related to elasticity, the elastic behavior may depend on the orientation of the applied stress. If, with a cubic sample of the material, the elastic deformation is the same with all three orthogonal directions, the material is said to be isotropic. If, however, the deformation varies between these directions, the material is anisotropic. With some material microstructures, the Young's Modulus may vary by a factor of ten or more between these directions. This is particularly important when synthetic materials are replacing with, or augmenting, human tissues, which are often highly anisotropic.

5.5.2.3.2 Viscoelasticity

Most solid materials are obviously 'solid' and have characteristic properties, such as those given in Table 5.1. Other substances are obviously 'liquid', defined as something that flows freely but is of constant volume, such as water or oil. Some substances have some characteristics of a solid and some of a liquid. The solid characteristics are derived from their molecular structure, but the liquid features arise from the ability of molecules to slide past each other. Such substances possess the features of viscoelasticity, the 'visco' denoting the ability to flow and the 'elasticity' the ability to deform elastically. The contributions of elasticity and viscous flow vary considerably, especially depending on temperature and the cross-links that can be established between molecules. Almost all tissues in the human body have some viscoelastic component, including the vitreous humor in the eye and synovial fluid in articular joints. Many polymers exhibit viscoelasticity, including some silicone materials used in reconstructive surgery, these usually

being called silicone gels. Latex is a viscoelastic substance, based on polyisoprene, obtained from trees such as Hevea brasiliensis, which can be cross-linked, or vulcanized, to give soft latex rubber, formerly used in many medical devices and gutta percha, a much harder substance used in dentistry. The ability to use a substance that is viscoelastic such that it can be easily inserted into parts of the body, where it gels, or sets, to take on the characteristics of a solid, has been extensively used in medical technology. Many of the gels combine polymeric molecules with water, these being known as hydrogels, are similarly used as biomaterials. Most discussions about viscoelasticity involve complex mathematical modeling, which is outside the scope of this book. Those with a serious interest can read the work of Snoeijer *et al*[72].

5.5.2.3.3 Creep

As one might imagine for processes related to flow, this viscoelastic behavior is time dependent. Generally, purely elastic behavior is time-independent; a stress is applied and there is a resulting strain. The same situation applies to plastic deformation under most circumstances. However, it is possible for plastic deformation to occur at stress levels below the yield point. This is essentially equivalent to 'flow' in the sold state and arises because of situations where local stress concentrations allow for movement of material, which would not have been predicted from the computed average stress in the material. This process is known as creep. This is very much temperature-dependent, occurring in metals only at significantly elevated temperatures; there is very limited opportunity for metallic creep to occur in implanted devices at body temperature. The situation is different with many polymers since body temperatures are much closer to their melting points, and polymer molecules find it easier to migrate under the influence of relatively low stresses.

5.5.2.4 Fatigue

A further variable that has major implications for the performance of engineering alloys, including those used in medical technology, is the repetitive application of force. This gives rise to the phenomenon of fatigue, fatigue fractures often being the source of catastrophic failures, such as those of aircraft or civil engineering structures. In this mechanism, very small cracks can open up at stress discontinuities, and propagate across the material, or component, with each application of stress. It may take tens of millions of stress cycles for failure to occur, but it is easy to see how this happens in high stress – rapidly cycled structures such as aeroengines. In the average human patient, the heart beats about 35 million times per year, so that fatigue is an important consideration in cardiovascular devices; the number of force repetitions in the musculoskeletal system is much smaller but the stresses (for example in hip and knee joints) may be much higher. Bearing in mind that the fatigue limit, that is the stress level below which fatigue will not take place, may be only a small fraction of the yield strength, fatigue failures are still possible in these forms of reconstruction. Example are shown in Figure 5.9. The engineering science of fatigue mechanisms is very well understood these days, so that examples such as these should not be seen with current devices. However, the danger is always there, and the introduction of different technologies with different materials can produce unexpected surprises[73]. This is especially true with technologies that result in porous structures or surfaces, since it is discontinuities in stress in porous or irregular features that are usually the cause of fatigue crack initiation.

[72] Snoeijer JH, Pandey A, Herrada MA, *et al,* The relationship between viscoelasticity and elasticity. *Proceedings of the Royal Society, A,* 2020;476 (2243): 20200419. doi:/10.1098/rspa.2020.0419.

[73] Kelly CN, Evans NT, Irvin CW, *et al*, The effect of surface topography and porosity on the tensile fatigue of 3D printed Ti-6Al-4V fabricated by selective laser melting, *Materials Science and Engineering C,* 2019; 98:726-36,

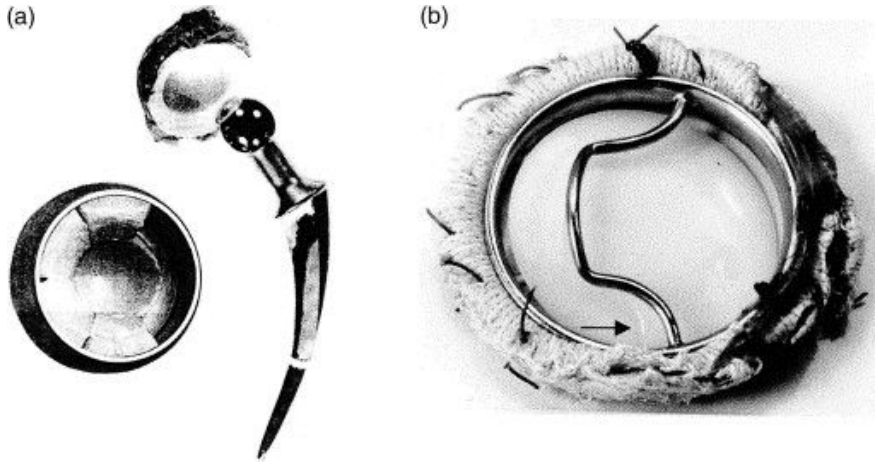

Figure 5.9, Some examples of fatigue failure of medical devices: (a) hip prosthesis; (b) explanted Björk–Shiley polyacetal disc mechanical heart valve (arrow indicates fatigue-wear mark)[74].

5.5.2.5 Toughness and Composite Materials

5.5.2.5.1 General Principles

It is instructive to compare the mechanical behavior of a high-purity, dense, alumina ceramic, of the type used in some total hip replacement prostheses, with that of a lightly cross-linked silicone elastomer, such as that used in some space-filling implants in soft tissue augmentation. The former has a very high compressive strength and high rigidity, but cannot deform elastically, that is, it cannot sustain high strain. The latter can deform considerably but cannot sustain high stresses. Both have their place as engineering materials, with several applications in medical technology, but these applications are curtailed by the inability to sustain, simultaneously, high stress and high strain. This relates to the property of toughness; which refers to the ability to deform plastically over large stress and strain conditions without fracture; perhaps put more simply, it relates to the ability to absorb mechanical energy without rupture.

Since fracture of a material must start with the initiation of a small crack, which could be induced at a pre-existing flaw arising from manufacturing or from localized deformation, an important element of making materials tougher involves minimizing the creation or propagation of the microcracks. One way of achieving this is to modify the material microstructure by inducing phase changes into the material matrix where phase boundaries blunt the progress of cracks, a process known as transformation toughening. The widely used zirconia biomaterials utilize this process through the use of minor additions of second phase-inducing agents such as yttrium oxide[75]. As is often the case, making minor modifications to materials that give generally good performance in order to improve one deficiency can lead to other problems; in this case the toughening process was very much dependent on precise temperature control during manufacture, where errors could lead to catastrophic failure[76].

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[74] Teoh SH, Fatigue of biomaterials: a review, *International Journal of Fatigue*, 2000;22(10):825-37, doi:10.1016/S0142-1123(00)00052-9.

[75] Piconi C and Maccauro G, Zirconia as a ceramic biomaterial, *Biomaterials,* 1999;20:1-25.

[76] Hummer CD, Rothman RH and Hozack, Catastrophic failure of modular zirconia-ceramic femoral head components after total hip arthroplasty, *Journal of Arthroplasty*, 1995;10(6):848-50, doi: 10.1016/s0883-5403(05)80085-3.

5.5.2.5.2 Composite materials

By far the most important way of producing toughness involves the use of composite materials, that is those materials that contain both rigid components and flexible polymeric matrices. This should not be surprising since so many of nature's tough materials are structured in this way. For example, the properties of bamboo are derived from the composite structure of cellulose microfibrils in a matrix of intertwined hemicellulose and lignin[77]; both silk[78] and, of course, bone, are good example of tough natural composites.

As their name implies, composites are materials made up from combinations of different types of substance; they are not random mixtures, nor are they combinations of quite similar but not exactly the same substances. Alloys involving different elements and phases are not composites, nor are polymer blends and copolymers. Composite materials are also bulk materials rather than standard materials with surface coatings – these may be composite structures but not composite materials. The real significance is that composites involve two, or occasionally three, different classes of materials where the structure of the composite has been designed to maximize the benefits of each component and, if at all possible, minimize their disadvantages. The majority of useful composites combine a ceramic phase with a polymer phase. Usually, the composite structure can be identified with one continuous phase and one dispersed phase, the continuous phase may be a polymer, while the discontinuous phase may be a dispersion of ceramic particles. A very good example in the biomedical field is the composite dental filling material. The polymer is usually a clear resin such as urethane dimethacrylate and the ceramic is often a form of silica. The resin, effectively a thermosetting material, is able to polymerize and cross-link within the tooth while the ceramic gives the material toughness and abrasion resistance. Other composite materials can be obtained by using different physical forms of the dispersed phase, the best example being seen with the use of fibers. Again, usually involving a thermosetting resin such as an epoxy or phenolic resin, these may contain high percentages of long fibers, usually made of a glass or carbon. Carbon fiber composites are amongst the strongest and toughest synthetic materials, especially on a strength-to-weight ratio basis. It is difficult to process thermoplastic materials with very long fibers, but very good properties can be achieved by cutting the fibers into short lengths. Some very good engineering thermoplastics, such as polyetheretherketone, which is used as a biomaterial in several areas, can have certain properties substantially improved by the incorporation of chopped carbon fibers.

Fracture occurs when cracks propagate through the bulk of a material. There are two basic ways of preventing fracture; the first involves preventing crack initiation, the second is preventing crack propagation, or at least preventing crack propagation throughout the material. Structural composite materials have been developed primarily to generate strong and tough materials by increasing the resistance to crack propagation. The ceramic fibers, which have a high elastic modulus, will sustain a much higher stress than the lower modulus polymer matrix. The ceramic, however, will be far more brittle and unable to sustain any plastic deformation, while the polymer is able to deform plastically, but will do so at low stress. We might expect, therefore, to see some cracks develop in the fibers but as soon as they reach the interface with the polymer, the latter will deform plastically at the point of interception with the crack, and dissipate the energy of that crack, preventing its further propagation. Herraez *et al* have given a good mathematical analysis of the toughening effect[79]

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[77] Youssefian S and Rahbar N. Molecular origin of strength and stiffness in bamboo fibrils. *Scientific Reports, 2015;* **5**: 11116. doi:10.1038/srep11116.

[78] Shah DU, Porter D and Vollrath F. Opportunities for silk textiles in reinforced biocomposites: Studying through-thickness compaction behavior, *Composites Part A: Applied Science and Manufacturing,* 2014:62:1-10. doi:10.1016/j.compositesa.2014.03.008.

[79] Herraez M, Ferandez A, Lopes, *et al,* Strength and toughness of structural fibres for composite material reinforcement. *Philosophical Transactions A, Mathematics, Physics and Engineering Sciences*, 2016;374(2071):20150274. doi:10.1098/rsta.2015.0274.

5.5.2.6 Stress-shielding

There is one major consequence of the disparity in the elastic moduli of bone and the engineering materials used within bone surgery. This is easiest to explain by reference to Figure 5.10 below.

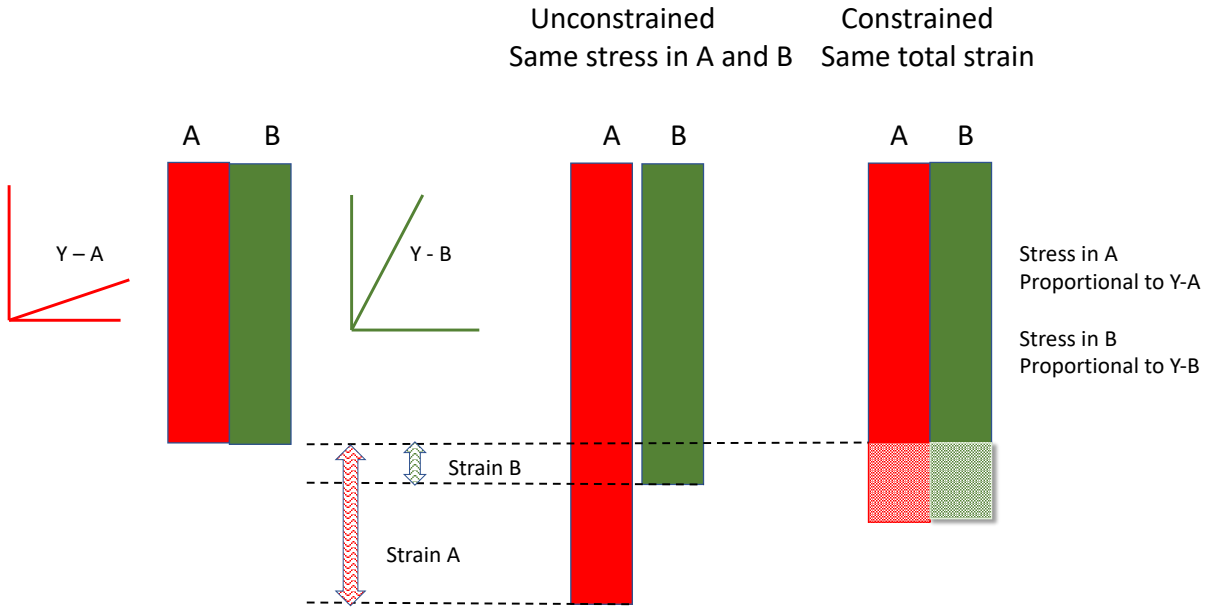

Figure 5.10 Principles of stress shielding.

Consider two identically shaped bars of two different materials (on the far left), where one, material A (in red) has a significantly lower modulus of elasticity that material B (in green). If these bars are subjected, independently, and unconstrained, by identical stresses, bar A, of lower modulus will show a significantly larger strain than the higher modulus B (center of diagram). If, however, the bars are rigidly attached to one another (far right) and subjected to stress, they will be constrained to deform (i.e., exhibit) the same strain. The stress in each bar will then be proportional to their respective modulus, so that the higher modulus component B will experience a significantly higher stress. In an explanatory, but practically unrealistic, scenario, material A could be cortical bone and material B, a cobalt-chromium alloy, the latter having a modulus 10 times the former. This means that the alloy will sustain about 90% of any applied stress; the bone is said to be stress-shielded by the alloy component[80].

The questions arise as to whether this is important, and if so, why? At the center of the debate is the physiological fact that bone metabolism is responsive to mechanical stress, although the mechanisms are not uniform and depend on bone location, age and other factors[81]. In general terms, if bone is not subjected to dynamic mechanical stress, then, over time, that bone may resorb, becoming less dense and

[80] Huiskes R, Weinans H, Grootenboer HJ, *et al*, Adaptive bone-remodeling theory applied to prosthetic-design analysis, *Journal of Biomechanics*, 1987;20 (11-12):1135-50. doi: 10.1016/0021-9290(87)90030-3.

[81] Pearson OM and Lieberman DE, The aging of Wolff's "law": ontogeny and responses to mechanical loading in cortical bone, *American Journal of Physical Anthropology*, 2004; Suppl 39: 63-99. doi:10.1002/ajpa.20155.

subject to mechanical failure. Under experimental conditions, it is certainly possible to demonstrate so-called disuse osteoporosis in relation to rigid biomaterials attached to bone; many years ago I was able to demonstrate significant differences between the bone response to rigid stainless steel fracture plates compared to less rigid carbon fiber plates in an animal model[82], but the translation of theoretical and pre-clinical laboratory data to clinical practice is difficult, and there is still controversy of how clinically relevant is this phenomenon[83].

5.5.2.7 Hardness

The hardness of a material is a measure of the resistance to abrasion or indentation. A very rough comparison of hardness is made by the ability of materials to scratch each other. In the Mohs' scale, a series of standard materials are arranged in order, with talc as No 1 and diamond as No 10. More conveniently for conventional engineering materials, the hardness is measured by the amount of deformation induced in a specimen by a standard indentation; the size of the indentation produced under a known load is measured and converted to a hardness value. High values indicate hard materials and low values, soft materials. Hardness is a good engineering parameter, but it is rarely critical in most reconstructive procedures.

5.5.2.8 Superelasticity and Shape Memory

Conventional elasticity is derived from the reversible movement of atoms or molecules within a material where the state of that material, determined by phase structure, is stable. Under some conditions, usually involving temperatures very close to the transition temperature between two phases, the application of stress stimulates a diffusionless, shear transition, which is accompanied by major deformation. This is reversible since it will revert once the stress is removed and hence it is deemed to be elastic, and here the effective modulus can be very low as these major changes in dimensions occur with very little increase in stress. It is, however, described as superelasticity, or pseudoelasticity, to indicate its unusual nature. It is best seen in nickel-titanium alloys, described in the next section, and is used in some health care applications[84], especially in orthodontics where it is effective in producing tooth movement at low applied forces. It is also associated with the phenomenon of shape memory. It would be possible to provide elegant mathematical and mechanistic explanations for this phenomenon, but those would be out of place here. Suffice it so say that shape memory alloys (of which there are very few) have a precise atomic arrangement at a specified temperature (say room or body temperature) but will spontaneously reconfigure the arrangement when the temperature changes, any object made of the material then taking a different shape. If the temperature is now changed back to the original, then the shape changes back with it; hence 'shape memory'. This effect is most widely used in those situations where an implantable device can be manufactured with a specific and complex shape that is required for clinical performance, but is then collapsed to a different shape, at a different temperature, for placement into a catheter. On insertion into the body, the original manufactured shape is reconstituted.

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[82] Williams DF, Gore LF and Clark GCF, Quantitative microradiography of cortical bone in disuse osteoporosis following fracture fixation, Biomaterials, 1983; 4(4);285-8. doi:10.1016/0142-9612(83)90029-7.

[83] Engh Jr CA, Young AM, Engh Sr CA, *et al*, Clinical consequences of stress shielding after porous-coated total hip arthroplasty, *Clinical Orthpaedics and Related Research*, 2003;417:157-63.

[84] Mantovani, D, Shape memory alloys: Properties and biomedical applications, *Journal of Materials*, 2000;52(10):36-44.

5.5.2.9 Friction, Wear and Lubrication

Many applications of biomaterials involve different components in contact with each other or in contact with tissues, where there is relative movement between them. The mechanical properties of materials under sliding conditions, collectively discussed under the term tribology, are very important; two features of the interactions at sliding surfaces are particularly relevant, the frictional forces that are generated and the wear or destruction of the surfaces during the movement.

5.5.2.9.1 Friction

If two solids are placed in contact, there will be some forces of attraction between their surface atoms or molecules. There is, therefore, some bonding at the interface, which implies that a force will be necessary to break the bonds if the materials are to slide over each other. This adhesion accounts for the frictional forces involved in surface movement. At the interface, however good the surface finish of the components, they will be atomically rough, so the actual, or real, area of contact is much smaller than the apparent area. The real area of contact is governed by the normal force acting on the surface and on the strength of the material. For two identical materials in contact the real area will be proportional to the hardness and the frictional force will be proportional to the shear stress and the real area. With two materials of quite different mechanical properties the frictional behavior will be controlled by the weaker of the two for it is this which will yield plastically in compression to give a larger real area, and this will also shear to produce the sliding. In the absence of lubrication, the coefficient of friction is basically independent of load, sliding speed, surface geometry and roughness. Since the friction is dependent on the ratio of hardness and shear strength, and since these two properties are related to the same basic material properties, forces of friction should be very similar for most materials. There is therefore a remarkably narrow range for the coefficients of friction for clean materials in sliding contact, usually in the range of 0.3 to 1.5. There are some exceptions, most notably polytetrafluoroethylene which is so chemically inert that forces of adhesion at an interface are minimal and hence the coefficient of friction is very low, around 0.04, hence its ‘non-stick’ characteristics.

5.5.2.9.2 Wear

Wear is defined as the removal and relocation of material arising from the contact of two solids. There are four distinct types of wear, adhesive, abrasive, corrosive and surface fatigue wear. Corrosive wear involves the wear of surface oxide films that would otherwise inhibit corrosion, thereby accelerating corrosion. Surface fatigue wear occurs under repeated loading and sliding cycles, which results in the formation of surface cracks and eventual breakdown of the surface. Abrasive wear occurs when a rough hard surface slides over a much softer surface and ploughs a series of grooves in it. The material from the grooves is displaced in the form of wear particles. Adhesive wear occurs when two surfaces slide over each other and fragments are sheared off at points within the real area of contact. During sliding there are several possibilities for the adhesive forces to be overcome. This could possibly happen along the interface itself, resulting in no loss of material on either side. Alternatively, shear could take place within the asperities of either side resulting in the release of fragments, or wear particles. Generally, the amount of wear is directly proportional to the load applied across the interface and to the distance of sliding, and is inversely proportional to the hardness of the surface being worn away. Wear, and the generation of wear particles, is of immense importance to the clinical performance of joint replacement prostheses[85].

5.5.2.9.3 Lubrication

Both friction and wear properties may be significantly altered if a lubricant is present between the surfaces. There are several different types of lubrication, ranging from situations in which a liquid film is

[85] Jacobs JJ, Shanbhag A, Glant TT, *et al,* Wear debris in total joint replacements, *Journal of the American Academy of Orthopedic Surgery*, 1994;2(4):212-20. doi:10.5435/00124635-199407000-00004.

thick enough to give complete separation of the components to those where the film is only of atomic dimensions. In many engineering situations, the lubricating film will be relatively thin, and the mode of boundary lubrication will apply. The sliding may also be accompanied by elastic deformation of the asperities, giving elastohydrodynamic lubrication.

5.5.3 Materials that Operate in a Biomechanical Environment

In this section, the biomaterials that are currently used in common structural implantable devices are described. Items of historical interest, and those of very limited use are not included.

5.5.3.1 General Principles

When implantable devices were first being considered for use inside the body, there weren't many obvious candidate materials. Synthetic plastics had not been invented, and glasses and traditional ceramics were too brittle and/or too difficult to fabricate. Some natural materials, such as bone, wood and ivory were considered, without much success, and so it is not surprising that metallic materials (some pure metals, but mostly combinations of metals in the form of alloys) were the principal focus; after all, the early ages of man were denoted by the dominant metallic materials, as in the bronze age starting 5,000 years ago and the iron age from 3,000 years ago. I wish I could remember where I heard this adage about metallurgy being the personification of old age (if I could, he or she would get the credit here), but this is very relevant to the use of metals is the body, for

As we get older,
We see silver in the hair,
Gold in the teeth,
Lead in the feet,
And iron the soul

Adage, unattributed

It rapidly became clear that all metals known to man suffer corrosion to a greater or lesser extent in the saline-based environment of the body, so that relative corrosion resistance became the main requirement, which would have to be coupled with adequate mechanical properties, especially strength / fatigue strength. In time, a range of polymeric, ceramic and composite materials were developed, many of which had superior overall properties to those of the original metallic systems, and some of which could compete with the best of the later systems.

5.5.3.2 Metallic Materials and Alloys

It will be seen from the following sections, that corrosion resistance (and its inevitable consequential characteristic of biocompatibility), coupled with appropriate mechanical properties have continued to dominate the selection of metallic biomaterials. The list of 'acceptable' materials in this category has declined in recent years, as improvements and refinements in those at the top end of the range have rendered some at the lower end to be of limited value.

5.5.3.2.1 Titanium alloys[86]

Over 50 years ago, soon after entering my first academic appointment in the Department of Orthopaedic Surgery at the University of Liverpool, I was asked by a supplier of implants what I thought of titanium

[86] Kaur M and Singh K, Review on titanium and titanium-based alloys as biomaterials for orthopaedic applications, *Materials Science and Engineering, C,* 2019;102"844-62. doi:10.1016/j.msec.2019.04.064.

as a suitable material for fracture plates and spinal instrumentation. Being trained as a metallurgist at the University of Birmingham (UK), where a senior professor was Alan McQuillan, author of the main textbook on titanium[87], and close to which was the premises of Imperial Metal Industries (IMI) a prominent developer of the commercial production of titanium, the workings of which I became quite familiar, it is of no surprise that I was very enthusiastic. I related my enthusiasm to some of my new orthopaedic colleagues in Liverpool who started to use titanium fracture plates; the literature coming from some US institutions were already alluding to the quality of titanium implants[88]. Problems arose when the surgeons went to remove the plates after the fractures had healed. I was not yet on first-name terms with these surgeons and started to get messages "Williams, the tissue around the plates is black". Also a few of them had trouble removing the screws, and several screw heads sheared off, leaving them with a serious problem as they could not leave the screw shank behind. The latter problem was quite easily solved as the manufacturer changed from a commercially-pure titanium to a titanium alloy with much better torsional strength. The black color remained controversial but with my orthopaedic pathologist colleague, George Meachim, we were able to show that this discoloration had no histological or clinical consequences[89]. I am pleased that I persevered with my enthusiasm, since my nascent reputation was saved, and I was able to continue with many years research on titanium and its alloys[90].

The main attribute of titanium is its corrosion resistance. Paradoxically, the element is very reactive with oxygen, but as soon as the metal surface is exposed to air, a thin but very tenacious oxide layer forms on that surface, which is self-limiting in thickness and extremely impervious to attack by most corrosive fluids, including saline solutions. Interestingly, this reactivity was a problem with the high-temperature processes used in extraction of titanium from its ores, and the production plant at IMI mentioned above had one of its four walls made of plastic, which could blow out relatively harmlessly should an explosion occur. One other attractive feature of titanium is its low elastic modulus, which minimizes the stress shielding effects when in rigid contact with bone. The mechanical properties of the commercially pure titanium are not outstanding, but there are several alloys with much better strength (especially the alloy of titanium with aluminum and vanadium) but comparable corrosion resistance, which are used extensively in biomechanically challenging situations. As we shall see with most commonly used biomaterials, standard specifications for those forms used in medical devices are available; the most widely used are those published by ASTM, including the specifications for titanium alloys[91].

Overall, these titanium alloys represent excellent choices for many implantable device applications, both in stress-bearing and non-stress-bearings situations. Very early on I decided that the element titanium could be considered 'physiologically indifferent', meaning it has no essential function in the body but had minimal adverse effects. I retain that opinion; thousands of academic papers have been published in the

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[87] McQuillan AD and McQuillan MK, *Titanium,* 1956, Butterworths, London, Bib ID 3118329.

[88] Hahn H and Palich W, Preliminary evaluation of porous metal surfaced titanium for orthopedic implants, *Journal of Biomedical Materials Research*, 1970;4(4):571-7. doi:10.1002/jbm.820040407.

[89] Meachim G and Williams DF, Changes in nonosseous tissue adjacent to titanium implants, *Journal of Biomedical Materials Research*, 1973;7(6):555-72. doi:10.1002/jbm.820070607.

[90] Williams DF, Titanium as a metal for implantation. Part 1: physical properties, Part 2: biological properties and clinical applications *Journal of Medical Engineering Technology,* 1977;1(4):195-8. doi:10.3109/03091907709160641and 1977;1(5):226-70. doi:10.3109/03091907709162192.

[91] ASTM International, Standard Specifications for Titanium and its Alloys for Surgical Implant Applications; ASTM F67-13(2017), Unalloyed Titanium (UNS R50250, UNS R50400, UNS R50550, UNS R50700); ASTM F136-13(2021)e1 Wrought Titanium - 6Aluminum - 4Vanadium ELI (Extra Low Interstitial) Alloy (UNS R56401); ASTM F1472-20a, Wrought Titanium -6Aluminum -4Vanadium (UNS R56400); ASTM F1295-16 Wrought Titanium - 6Aluminum -7Niobium Alloy (UNS R56700); ASTM F1713-08(2021)e1 Wrought Titanium - 13Niobium -13Zirconium Alloy(UNS R58130); ASTM F1813-21 Wrought Titanium -12Molybdenum - 6Zirconium -2Iron Alloy (UNS R58120): American Society for Testing and Materials International, 100 Barr Harbor Drive, PO Box C700, West Conshohocken, PA 19428-2959, USA.

intervening half-century exploring ways to 'improve' the biological performance, especially through surface treatments, but few of these have had any practical benefit in clinical applications[92].

5.5.3.2.2 Cobalt-chromium alloys[93]

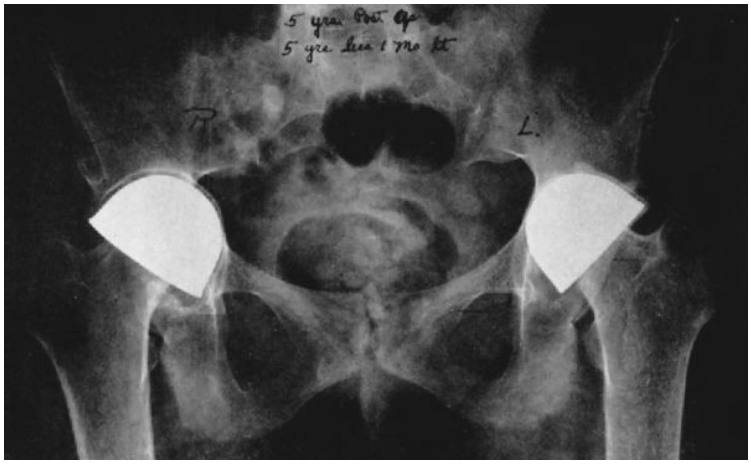

Fig 5.11, Vitallium arthroplasty cups, five years after implantation

Cobalt-chromium alloys are quite different to those of titanium; in general, they are harder and stronger, but much more brittle. However, the chromium present on these alloys, typically at 20-30% has a similar affinity for oxygen as does titanium, and it is able to render these alloys highly corrosion resistant. The fact that in early industrial uses of these alloys they stood out as retaining a lustrous appearance in many environments, led to the name 'Stellite', or star-like, being given to them; stellites were used in dentistry at an early stage[94]. The extreme hardness and brittleness were both good and bad features. The brittleness (of the early formats) made it difficult to mechanically work with them and so they had to be cast in most applications; this was fine for the use in dentistry, since the alloys were used for individually cast partial dentures (as shown much earlier in Figure 1 of the Preface), but mass production of components for orthopedic devices was very difficult; stellites themselves were used as cutting tools in metallurgical practice. The hardness, however, was a positive advantage for devices used in joint surgery. It has been shown way back in the 1920s that the tissue response to the alloys was exceptionally benign[95], and surgeons were very anxious to use them where sliding contact with bone was required. As manufacturers learned how to fashion some intricate shapes with the material, the alloy used for such applications was renamed as 'Vitallium', for obvious reasons and arthroplasty cups (in the days before total joint replacement techniques were developed) became popular, both in the USA and UK[96,97]. Today, there are

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92 Xue T, Attarilar S, Liu S, *et al*, Surface modification techniques of titanium and its alloys to functionally optimize their biomedical properties: Thematic review. *Frontiers in Bioengineering and Biotechnology, 2020;* 8:603072. doi:10.3389/fbioe.2020.603072.

93 Morral FR, The metallurgy of cobalt alloys—A 1968 Review, *Journal Of Materials, 1968;* 20, 52–9. doi:10.1007/BF03378733.

94 Riddihough M, Stellite as a wear-resistant material, *Tribology,*1970;3(4):211-5. doi:10.1016/0041-2678(70)90058-8.

95 Zierold A, Reaction of bone to various meals, *Archives of Surgery*, 1924, ID 72376611. doi:10.1001/ARCHSURG.1924.01120080133008.

96 Cole WH, The use of Vitallium in surgery with special reference to cup arthroplasty, *Proceedings of the Royal Society of Medicine*, 1941;34(12):779-82.

97 Gibson A, Vitallium cup arthroplasty of the hip joint, *Journal of Bone & Joint Surgery (American Volume*), 1949;31:861-72.

many varieties of cobalt-chromium alloys is use in several areas of surgery, including several designs of total hip prostheses. One aspect that is not shared with titanium is that the major alloying elements (cobalt, chromium, nickel) cannot be described as physiologically indifferent, and several forms of idiosyncratic adverse event, including hypersensitivity, can occur. Such events are discussed in a later section of the book. The full range of specifications for these implantable alloys is maintained by ASTM[98].

5.5.3.2.3 Stainless steels [99]

In 1913, in Sheffield (UK), the metallurgist Harry Brearley, added chromium to molten iron to produce a metal that did not rust; it also had good heat resistance, formability and weldability, durability, and was relatively inexpensive. He was trying to solve erosion problems on the inner surface of gun barrels as the First World War loomed but solved many more engineering challenges with this experiment; the history of metallurgy was changed, Sheffield itself becoming synonymous with steels and, especially, 'stainless steels'. As with the cobalt-based alloys of the previous section, the chromium content was sufficient to passivate the steel, producing its stainless epitaph. A wide variety of formulations was developed during succeeding years, most having some further alloying additions such as nickel. It was soon realized that about 18% chromium and 8-10% nickel yielded good quality steels, universally referred to as 18-8 stainless, these being used in many engineering and domestic (e.g., cutlery) applications. Some historical metallurgical literature suggests that surgical scalpel blades of stainless steel were introduced in 1915 and some 'surgical implants' in 1925, but many of the relevant citations are vague, and indeed circuitous, but the fine detail does not matter. It is clear that stainless steels were the materials of choice for orthopedic and other applications by the 1940s. Even then they did suffer from visible corrosion on some occasions, two developments improving the situation enormously, the addition of about 3% molybdenum, which increased the stability of the oxide layer, and the reduction of the maximum allowable carbon content from 0.08% to 0.03%, which reduced the chances of deleterious carbide formation. The resulting alloy, termed AISI 316L has been used ever since.

The popularity of stainless steels has decreased over several decades due to the improved benefits of the titanium and cobalt alloys. One aspect which is not in its favor is the presence of nickel, which, as we shall see decreases biological acceptability. Corrosion can still occur, with variable clinical consequences, and the combined presence of chromium and nickel debris can be harmful[100]. Some of the current specifications for surgical stainless steels are shown here[101].

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[98] ASTM International, Standard Specifications for Cobalt - Chromium Alloys for Surgical Implant Applications; ASTM F75-18, Cobalt - 28Chromium - 6Molybdenum Alloy Castings and Casting Alloys (UNS R30075); ASTM F688-19, Wrought Cobalt - 35Nickel – 20Chromium – 10Molybdenum Alloy Plate, Sheet and Foil (UNS R30035); ASTM F1537-20 and ASTM F799-19 Cobalt – 28Chromium – 6Molybdenum (UNS R31537, 31538, 31539); ASTM F90-14, Wrought Cobalt – 20Chromium – 15Tungsten – 10 Nickel (UNS 30605); ASTM F1377-21 Cobalt – 28Chromium – 6Molybdenum Powder (UNS R30075, R31537, 31538); ASTM F2886-17, Injection Molded Cobalt – 28Chromium – 6Molybdenum Components; ASTM F562-22, Wrought Cobalt – 35Nickel – 20Chromium – 10Molybdenum (UNS R30035); ASTM F961-20, Cobalt – 35Nickel – 20Chromium – 10 Molybdenum Forgings (UNS R30035). American Society for Testing and Materials International, 100 Barr Harbor Drive, PO Box C700, West Conshohocken, PA 19428-2959, USA.

[99] Walley KC, Bajraliu M, Tyler Gonzalez T, *et al*, The chronicle of a stainless steel orthopaedic implant, *The Orthopaedic Journal at Harvard Medical Schoo*l, 2016;17:68-74.

[100] Williams DF and Meachim GA, combined metallurgical and histological study of tissue-prosthesis interactions in orthopaedic patients, *Journal of Biomedical Materials Research,* 1974, Symposium No. 5, 1-9.

[101] ASTM International, Standard Specifications for stainless steels for surgical implant applications; ASTM F621-12(2021)e1, Stainless Steel Forgings; ASTM F138-19 Wrought 18Chromium -14Nickel -2.5Molybdenum Stainless Steel Bar and Wire (UNS S31673); ASTM F1314-18 Wrought Nitrogen Strengthened 22Chromium –13 Nickel–5Manganese –2.5Molybdenum Stainless Steel Alloy Bar and Wire(UNS S20910); ASTM-F1586 Wrought Nitrogen Strengthened 21Chromium -10Nickel -3Manganese -2.5Molybdenum Stainless Steel Alloy Bar (UNS S31675).

5.5.3.2.4 Nickel-titanium shape memory alloys[102]

Superelasticity and shape memory characteristics have been discussed in a recent section; as alluded to at that time, these properties are extremely useful in many medical applications, but there is only one significant biomaterial that possesses these properties. This is the alloy nitinol, named after the laboratory where it was developed, the Naval Ordinance Laboratories, and its composition, a nearly equiatomic alloy of nickel (Ni) and titanium (Ti); hence N-I-T-I-N-O-L. The unique thermomechanical behavior of nitinol made it an attractive option for many types of medical devices, and it was soon used in orthodontic archwires[103] and surgical instruments. Early recognition that the tissue response to nitinol was 'acceptable'[104] led to uses in several implantable devices, for example orthopedic fracture fixation, stents and transcatheter heart valves. Of great significance has been the development of minimally invasive procedures, discussed earlier, nitinol becoming an essential material due to its ability to return to its original shape after being mechanically deformed or after heat is applied. Clinical applications have been numerous for several decades[105] and there is an overarching ASTM standard specification for nitinol used in medical devices[106]. The corrosion resistance of nitinol is dependent on the passivity of titanium, which allows for the formation of a titanium oxide surface layer, the integrity of which is dependent on the quality of the surface after manufacturing processes. It is inevitable that some nickel ions diffuse out from this surface under some conditions, which has led to concerns of nickel toxicity, and especially hypersensitivity, with some medical devices, which is discussed elsewhere, indeed in several places.

5.5.3.2.5 Biodegradable magnesium alloys[107]

One of the most significant conundrums in the selection of technologies for reconstruction of the human body concerns the question of whether implantable devices should be permanent or should be degradable such that they could be replaced by reparative host tissue. Initially, I was quite in favor of the degradable concept, and wrote on this subject in the popular scientific press 50 years ago[108]. Over the subsequent years, the clinical evidence has not been very convincing about the performance of degradable systems, as I will show in the case of some degradable polymers. With metallic systems, a fundamental contradiction immediately arises with knowledge that the best biocompatibility performance of traditional devices is obtained when there is minimal ion or particulate release, but any putative degradable system would absolutely require such release. There would be no point in using systems where metals with overt toxicity were released (such as lead, arsenic or nickel), nor indeed with metals that had a very narrow therapeutic range between essentiality and excess, such as copper. There are a few metals that are well tolerated by the body, being essential nutrients with low toxicity. Magnesium is one such metallic element. The degradation of magnesium itself (which in engineering terminology is equivalent to

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American Society for Testing and Materials International, 100 Barr Harbor Drive, PO Box C700, West Conshohocken, PA 19428-2959, USA.

102 Shabalovskaya SA, Physicochemical and biological aspects of Nitinol as a biomaterial, *International Materials Reviews*, 2001;46(5):233-50. doi:10.1179/095066001771048745.

103 Burstone CJ, Qin B and Morton JY, Chinese NiTi wire--a new orthodontic alloy, *American Journal of Orthodontics*, 1985;87(6):445-52. doi:10.1016/0002-9416(85)90083-1.

104 Castleman LS, Motzkin SM, Alicandri FP, *et al,* Biocompatibility of nitinol alloy as an implant material, *Journal of Biomedical Materials Research*, 1976;10(5):695-731. doi: 10.1002/jbm.820100505.

105 Duerig T, Pelton A and Stöckel D. An overview of nitinol medical applications. *Materials Science and Engineering: A*. 1999;273:149-60.

106 ASTM F2063-18 Standard Specification for Wrought Nickel-Titanium Shape Memory Alloys for Medical Devices and Surgical Implants, 2018, American Society for Testing and Materials International, 100 Barr Harbor Drive, PO Box C700, West Conshohocken, PA 19428-2959, USA.

107 Persaud-Sharma D and McGoron A, Biodegradable magnesium alloys: A review of material development and applications, *Journal of Biomimetic Biomaterials and Tissue Engineering*, 2012;12:25-39. doi:10.4028/www.scientific.net/JBBTE.12.25.

108 Williams, D. F. Step nearer the redundant implant, *New Scientist*, April 1973, 221-3.

corrosion) is too fast, generates hydrogen bubbles and alters tissue pH, and is not suitable. Alloys can be created using other biologically acceptable metallic elements such as zinc and calcium, and occasionally with less acceptable alloys, although in small amounts, such as aluminum. There has been a massive amount of work performed on these alloys in the last decade, and products are queuing up to gain regulatory approval. Many studies point to the unresolved metallurgical problems[109] and many others report on modifications that are hoped to improve matters[110], but the case has not yet been made for a place for these alloys in major clinical practice.

5.5.3.3 Ceramics

As a reminder, metals, virtually all of which are crystalline, consist of three-dimensional arrays of positively charged metal ions. On the other hand, ceramics, many but not all of which are crystalline, consist of arrays of both negative metal ions and positive non-metallic ions, the ratio between these being determined by the respective valences. This structural fact provides the reason why ceramics can be so useful, but yet so useless. Figure 5.12 reveals why this is so. Part (a) is a two-dimensional representation of a metallic lattice, where each atom is identical, the distance between them being determined by the interactions between them and the intervening cloud of free electrons, each of which has been lost by an atom when the ion is formed, and the overall metallic bond is established. Part (b) shows the arrangement for a ceramic; in this simple example, both metal and non-metals have a valence of one, and the structure is formed by a transfer of an electron from one metal ion to a neighboring non-metal ion, establishing covalent bonds, which are highly directional. Part (c) shows the metallic structure after plastic deformation, involving the permanent movement of one layer over another, has taken place. Internally, after the ion movement has taken place is identical to the original. This plastic deformation is easy, which is why metallic materials are usually very ductile. Part (d) shows the hypothetical situation with the simple ceramic, but here the result would be the juxtaposition of like ions in the planes; because of the directionality of the metal to non-metal bonds, this would result in a structure of very high internal energy. In the vast majority of such situations, it is energetically more favorable for this ceramic to fracture than undergo such plastic deformation. Ceramics are usually, therefore, hard and brittle; this can be good for some situations, but not where plasticity and resilience is required, which is usually the case for biomaterials in biomechanically functional situations. Some ceramics can be modified or adjusted to allow for good functionality in selected applications.

(Fig 5.12 to follow here, Q1, 2024)

5.5.3.3.1 Alumina[111]

Alumina is the oxide of aluminum, Al_2O_3; it is a relatively simple oxide ceramic that can exist in crystalline or amorphous states. Natural crystalline forms include ruby and sapphire. Industrial, polycrystalline forms are the very hard corundum and solid structural grades of different purity and grain size that are used in many engineering applications, largely based on high hardness and high melting point. These general industrial grades have a purity between 85 and 99% Al_2O_3; materials from the higher purity end of this range were first used for implantable devices over 40 years ago but their mechanical properties, especially the brittleness and lack of toughness were not sufficient for reliable quality. Nevertheless, the hardness (and therefore wear resistance) and outstanding resistance to degradation (and therefore excellent biocompatibility) ensured further developments. Gradually the technology of alumina ceramics has improved and the material is now used in highly stressed orthopedic applications, including

[109] Peron M, Torgersen J and Berto F, Mg and its alloys for biomedical applications: Exploring corrosion and its interplay with mechanical failure, *Metals,* 2017, *7*, 252. doi:10.3390/met7070252.

[110] Rahman M, Dutta NK and Choudhury NR, Magnesium alloys with tunable interfaces as bone implant materials, *Frontiers in Bioengineering Biotechnology*,2020; 8:564. doi: 10.3389/fbioe.2020.00564.

[111] Nizard R, Pourreyron D, Raould *et al*, Alumina-on-alumina hip arthroplasty in patients younger than 30 years old, *Clinical Orthopedic and Related Research*, 2008;466(2):317-23. doi:10.1007/s11999-007-0068-4.

alumina-alumina bearing surfaces in total hip replacements. I mentioned earlier, in full disclosure, that I myself have multiple joint replacements; the first of these was a French-made alumina-alumina device, implanted in Paris in 2007. I have had no problems with this, although I should add that I am no longer playing rugby. The alumina used in such devices typically had a purity greater than 99.8%, a density of greater than 3.98 g/cm^3 and a grain size of 2-5 μm. Such materials have a compressive strength of 4500 MPa, with very good toughness and fatigue resistance. Standard specifications for high purity aluminum oxide materials for medical devices have been published[112]

Figure 5.13, Some alumina components of total hip replacements

5.5.3.3.2 Zirconia[113]

Zirconia, zirconium oxide, ZrO_2 is also a simple oxide ceramic that has several applications in structural healthcare products. It is hard, although not as hard as alumina, but can be made tougher by the use of additives. The qualities of zirconia are dependent on the fact that it is polymorphic; that is, it exists with different crystal structures at different temperatures, the stability of which depend on the presence of some additives, such as CaO, MgO, CeO and Y_2O_3. Zirconia has one crystal structure at room temperature, transforming to a different one at 1170ºC and yet to another one at 2370ºC (details of these crystal structures should not concern us here). The significance is that phase transformations are often accompanied by volume expansion, which can generate internal stresses and cracking. The additives mentioned above modify the mechanisms of phase changes and allow internal stresses to nullify the cracks, increasing the toughness. These structural changes take place during the heat treatment parts of manufacturing; the resulting materials are referred to as partially-stabilized zirconia and are the subject of various standard specifications[114] . It should also be noted that several composites of alumina and zirconia have been developed for orthopedic and dental applications[115].

[112] ASTM International, Standard Specification for High-Purify Dense Aluminum Oxide for Medical Applications, F603-12 (2020),, American Society for Testing and Materials International, 100 Barr Harbor Drive, PO Box C700, West Conshohocken, PA 19428-2959, USA.

[113] Chevalier J, What future for zirconia as a biomaterial? *Biomaterials,* 2006;27:535-43. doi:10.1016/j.biomaterials.2005.07.034.

[114] ASTM International, Standard Specification for High-Purity Dense Magnesia Partially Stabilized Zirconia (Mg-PSZ) for Surgical Implant Applications, American Society for Testing and Materials International, 100 Barr Harbor Drive, PO Box C700, West Conshohocken, PA 19428-2959, USA.

[115] Burger W and Kiefer G, Alumina, zirconia and their composite ceramics with properties tailored for medical applications. *Journal of Composites Science*, 2021;5(11):306. doi:10.3390/jcs5110306

5.5.3.3.3 Calcium Phosphate Materials[116]

The two sections above refer to a few oxide ceramic materials that make significant contributions to medical technology applications that operate in harsh biomechanical environments. It is not surprising that these crystalline materials involve simple molecular structures with very few ionic species. Materials with greater numbers of such species, while sometimes offering excellent non-mechanical properties, cannot usually sustain high loads, especially those that generate tensile stresses, and cannot be risked under most situations in implantable devices. There is one type of ceramic which is not an oxide structure that must be mentioned, very briefly, and that is the group of ceramics based on calcium phosphates. These are not particularly strong but have the perceived advantage of having similar chemical characteristics to the mineral phases of bones and teeth. There are many different forms of calcium phosphate biomaterials, which are mostly used in in-situ setting applications in contact with existing bone. There is considerable controversy over how important these apparent bone-like qualities are; such considerations are best left to those sections that deal with these applications, since their performance can rarely be discussed in generic terms and since their ability to sustain high stresses is very questionable.

5.5.3.4 Polymeric Materials

The third classical category of materials are those based on polymers. A polymer is generally considered to be a large molecule made up of chains or rings of linked monomer units. It is predominantly the four-fold vacancy and covalent bonding associated with the carbon atom that allows such linking to take place, so that most polymers are organic; there is an almost infinite number of possible combinations of carbon with other elements, and hence a large number of polymeric materials. Some of these occur naturally, including proteins and peptides, polysaccharides and lipids which, since they often form structural and functional components of the human body, have already been discussed in Chapter 2.

The first synthetic polymer, that of phenyl formaldehyde, was commercialized as Bakelite in 1909 and thousands of different forms of similar types of material, usually referred to as plastics, have been developed since then. Many of these have non-mechanical functionality, including those which are water-soluble, ionizable, environmentally-responsive or biodegradable, and these will be mentioned at appropriate places in this and succeeding chapters. Although the carbon-carbon bond is reasonably strong, most synthetic polymers do not have exceptional mechanical properties since the bonds between adjacent chains or rings are usually much weaker, and it is these that control the overall properties. A relatively small number of these polymers have good relevant properties to be considered for structural applications in reconstructive procedures.

5.5.3.4.1 Polyethylene[117]

Polyethylene is one of the best-known thermoplastic polymer, that is a structural polymer that softens on heating and which may, therefore, be shaped by heating. It is one of the polyolefins, which are based on olefin monomers, of general formulae C_nH_{2n}, such that the polymers have an all-carbon backbone with pendant hydrogen atoms; they are usually strong, light, flexible and environmentally stable. Polyethylene is the simplest of all polymers, being derived from ethylene, C_2H_4. There are three main determinants of the properties of the various forms of polyethylene. The first is the average length of the molecular chains, which determines molecular weight. The second is the amount of chain branching, which determines the closeness with which the molecules can be arranged and hence the resulting density, and the third is the degree of cross-linking established between the chains. Some forms of low and medium density polyethylene are used in medical products, such as syringes and bottles, but the most profound uses are reserved for the cross-linked, ultra-high molecular weight, high density material that is used in

[116] Lu J, Yu H and Chen C, Biological properties of calcium phosphate biomaterials for bone repair: a review, *Royal Society of Chemistry Advances*, 2018;8:2015. doi:10.1039/c7ra11278e.

[117] Paxton NC, Allenby MC, Lewis PM, *et al,* Biomedical applications of polyethylene*, European Polymer Journal,* 2019;118:412-28. doi:10.1016/j.eurpolymj.2019.05.037.

many, indeed most, types of joint replacement prostheses; several standard specifications exist for this material[118].

5.5.3.4.2 Polypropylene[119]

Polypropylene is another polyolefin that has some good mechanical characteristics and excellent biocompatibility. It also has a carbon backbone, but every other carbon atom has one methyl (CH_3) group and one hydrogen atom attached to it. These methyl side groups can have several different positions on either side of the chain, giving variable degrees of crystallinity. While the mechanical properties of solid pieces of polypropylene are good for general engineering applications, such as pipes, they are not good enough for most highly stressed medical devices; however, when the polymer is drawn into long filaments, the properties are very appropriate for fibres, as in sutures, and for surgical meshes and textiles. Polypropylene meshes, and some attending controversies, that have been widely used in hernia repair and incontinence treatment, are discussed in a later section.

5.5.3.4.3 Polyethylene terephthalate

Polyethylene terephthalate, commonly referred to as PET, is an aromatic polyester. It is widely used in domestic products such as plastic bottles, but the medical applications depend on its ability to be formed into textiles, the most obvious bearing the trade name Dacron. PET can be formed as knitted or woven fabrics, using multifilament yarns. Weaving tends to result in a tighter structure with relatively small spaces between yarns, knitting allowing looser patterns with larger spaces; these differences result in different biological performance. The most extensively used implantable device using Dacron is the vascular graft, especially for bypass grafting in peripheral arteries. Their performance is essentially equivalent to that seen with expanded PTFE discussed below[120]. Dacron has also been used in ligament and tendon reconstruction although, as noted later, with mixed results.

5.5.3.4.4 Polyetheretherketones

Polyaryletherketones comprise a family of high-performance thermoplastics that have widespread applications in many industrial area, including some in medicine and dentistry. The principal example of this family is polyetheretherketone, for which standard specifications of the polymers used for surgical implants have been published[121]. The version that is used in medical technologies is a pure semicrystalline homopolymer that consists of phenylene rings connected by ether and either carbonyl or ketone groups along the polymer chain. It is environmentally very stable and has excellent biocompatibility under many circumstances; I published one of the first papers on this material, and its potential orthopedic applications more than three decades ago[122]. The most relevant applications today are in spinal fixation devices, especially interbody fusion, and in craniofacial and dental reconstruction.

5.5.3.4.5 Fluorinated hydrocarbon polymers

Polytetrafluoroethylene (PTFE) is a very simple polymer, being analogous to polyethylene, where each pendant hydrogen atom in the polymer chain is replaced by a fluorine atom. The carbon – fluorine bond is

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[118] ASTM International, Standard Specification for Ultra-High-Molecular Weight Polyethylene Powder and Fabricated Form for Surgical Implants, American Society for Testing and Materials International, 100 Barr Harbor Drive, PO Box C700, West Conshohocken, PA 19428-2959, USA.

[119] Bellon JM, Contreras LA, Bujan J *et al,* Tissue response to polypropylene meshes used in the repair of abdominal wall defects, *Biomaterials*, 1998;19(7-90:669-75.

[120] Roll S, Muller-Nordhorn J, Kell T, *et al*, Dacron vs PTFE as bypass materials in peripheral vascular surgery _ systematic review and meta-analysis, *BMC Surgery*, 2008;8:22. doi:10.1186.1471-2482-8-22.

[121] ASTM International, Standard Specification for Polyetheretherketone (PEEK) Polymers for Surgical Implant Applications, F2026-17, 2017, American Society for Testing and Materials International, 100 Barr Harbor Drive, PO Box C700, West Conshohocken, PA 19428-2959, USA.

[122] Williams DF, McNamara A and Turner RM, Potential of polyetheretherketone (PEEK) and carbon-fibre reinforced PEEK in medical application, *Journal of Materials Science Letters,* 1987, 6, 188-90, doi:10.1007/BF01728981.

very strong so that degradation resistance is excellent, and indeed any interactions with other substances or surfaces are minimal, hence the industrial / domestic use of the trademarked version, Teflon. The lack of any significant tissue response to PTFE led many people to believe that it would be an ideal implantable material. The first of the modern generation of total hip replacements used the material for the acetabular component, but low friction was confused with low wear rate, and the overall poor mechanical properties led to catastrophic wear and the abandonment of the material in favor of the ultra-high molecular weight polyethylene[123].

Although the use of solid PTFE has been confined to a few applications of very low stress, a different form of the material is widely used. This is expanded PTFE, often referred to by its trade-name Gore-Tex. This is microporous, where the structure consists of a dense network of very fine fibrils that meet up at so-called nodes; these provide the material with unusual mechanical properties, which can give very good functionality to tubular structures such as vascular grafts[124].

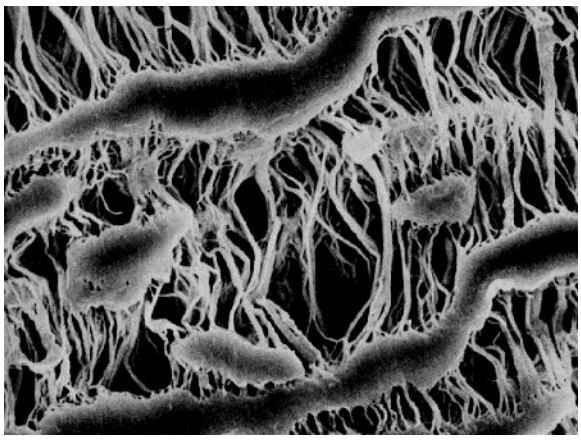

Figure 5.14, Microstructure of expanded PTFE

5.5.3.4.6 Polymethylmethacrylate and other acrylics

Polyacrylic acid, - CH_2–CHCOOH - is a reactive chemical used in the formulation of many dental materials and is the basis for a number of materials used in reconstructive surgery. Polymethacrylic acid is similar, with a methyl group in the structure, from which are derived some important acrylic polymers, including polymethylmethacrylate (PMMA). The real significance of these polymers is that they are often generated by polymerization of their precursors, such as methyl methacrylate, by free-radical initiated addition reactions that occur at around body temperature. They are therefore used as *in-situ* curing biomaterials, again in dental situations but most commonly today as bone cements[125], with appropriate standard specifications[126]. For over 40 years, the basis formulation of acrylic bone cement has stayed essentially the same, using pre-polymerized PMMA powder with a radio-opaque medium such as barium sulfate, and a liquid that has methylmethacrylate and an accelerator, typically N,N-dimethyl-p-toluidine.

[123] Charnley J, Using Teflon in arthroplasty of the hip joint, *Journal of Bone and Joint Surgery,* 1966;45(A):819.
[124] Roina Y, Auber F, Hocquet D, *et al,* ePTFE-based biomedical devices: An overview of surgical efficiency, *Journal of Biomedical Materials Research, B Applied Biomaterials*, 2022;110(2):302-20. doi:10.1002/jbm.b.34928.
[125] Lewis G, Properties of acrylic bone cement: State of the art review, *Journal of Biomedical Materials Research; B Applied Biomaterials,* 1997;38:155-82.
[126] ASTM International, Standard Specification for Acrylic Bone Cement, F451-21, 2021, American Society for Testing and Materials International, 100 Barr Harbor Drive, PO Box C700, West Conshohocken, PA 19428-2959, USA.

Mixing and delivery techniques have become quite sophisticated. Many varieties also contain an antibiotic such as gentamicin.

5.6 BIOPHYSICALLY FUNCTIONING IMPLANTS

(All to be completed, Q2, 2024)

5.6.1 Some Essential Requirements

5.6.2 Relevant Electrical, Electronic and Electromagnetic Properties

5.6.3 Sound Conduction

5.6.4 Light Transmission

5.7 EXTERNAL ARTIFICIAL ORGANS

(All to be completed, Q2, 2024)

5.7.1 Historical Perspective

5.7.2 Heart and Lung Assistance Technology

5.7.3 Liver Assistance Technology

5.7.4 Kidney Assistance Technology

5.7.5 Pancreas Assistance Technology

5.8 TRANSPLANTS AND GRAFTS

5.8.1 Historical Background

5.8.1.1 Barnard and the World's First Heart Transplant

I start here with one of my history of medicine sonnets that concerned the world's first heart transplant carried out by Christiaan Barnard in Cape Town, South Africa. I start each example with a brief backstory, followed by the sonnet:

> *Barnard's Fame*
>
> There are very many elements to this episode in history; and I do mean history and not just medical history. In the 1960's the country of South Africa powerfully embodied and formalized racism, the white Afrikaans dominating poorer black and colored communities. Apartheid, as this policy was known, caused the country to be shunned by much of the world, and this continued into the 1990s. In Cape Town a young cardiac surgeon was staking his claim as a pioneer and he

had his eye on that elusive first, the transplantation of a heart from a 'dead' donor to a living, critically ill patient. Barnard went to the USA, where some very famous surgeons were working on the same target, and learnt their techniques. They were very close to carrying out this procedure, and virtually all surgical challenges had been solved. There was one major issue, the ethical positions had not been fully worked out in America. There were rules in South Africa, but were more favorable to the transplanting surgeon, and in December 1967, Barnard was able, in the now famous Groot Schuur Hospital, to beat his US 'colleagues' with the transplantation of the heart of the young Denise Darvall into the elderly Louis Washkansky.

There was generous acknowledgement by many of the American surgeons, but also claims that Barnard had stolen their idea and rushed, heedlessly and unethically, to beat them. The reality is that Barnard had followed the local rules meticulously and results showed that his success in his procedures in subsequent years were better than anyone else in the world. His success was due to his own conviction and his courage. His arrogance and hubris, not to mention his divorces and affairs, eventually let him down, but it was early, chronic rheumatoid arthritis that stopped his career. He died in 2001, aged 78, a lonely miserable man.

As the history of medicine is writ,
The pen will linger over the theatre
Of life, or death, and to the benefit
With lasting fame or numbing disaster
Only the brave take the risk and the fear
Transfer from the dead a beating red heart
To the chest of a man in Groot Schuur
Part of history or history of a part
Would the handsome man win for Africa
The historic Atlantic transplant race
Defeating the favorites from America
Millions of dollars just left a red face
Welcome to Barnard's powerful new world
A lonely success for Apartheid unfurled

David Williams, *Barnard's Fame, in "A History of Medicine in Sonnets", Unpublished, 2020.*

5.8.1.2 The beginnings of the period of organ transplantation

It is ironic that I am drafting this section in the foyer of the Chris Barnard Memorial Hospital in Cape Town. While the achievements of Barnard were immense, they were based on major pre-clinical and clinical work by surgical and scientific pioneers across the globe. I discuss here the major factors that led to the ability to transplant the major organs between humans (i.e., heart, liver, lungs, and kidney), identifying the significant enabling technologies and scientific achievements. The first 'successful' organ transplants for the liver and lung in humans were reported in the same decade as that of Barnard's heart, with both Starzl *et al* for the liver[127] and Hardy *et al* for the lungs[128] publishing their findings in 1963. Because humans have two kidneys, allowing the possibility of using genetically identical donor and recipient for the transfer of one kidney between them, kidney transplantation preceded that of the other organs, the first live donor kidney transplant taking place in 1954, followed seven years later by the first

[127] Starzl TE, Marchioro TL, Von Kaulla KN, *et a*l, Homotransplantation of the liver in humans, *Surgery, Gynecology and Obstetrics*, 1963;117:659-76.
[128] Hardy JD, Webb WR and Dalton ML Lung homotransplantation in man, *Journal of the American Medical Association*, 1963;186:1065-74.

unrelated kidney transplant, both of these being performed by Murray[129], who received the Nobel Prize for Medicine in 1990 in recognition of this work.

Although the surgical techniques for organ transplantation may appear daunting, for the average patient these were not too difficult, and many teams around the world became quite proficient in them usually after many acute experiments in dogs. Having said that, there was one ground-breaking technique that underpinned organ transplantation (and also vascular and cardiovascular surgery); this was the end-to-end vascular anastomosis, the ability to sew blood vessels together, developed by Carrel at the beginning of the twentieth century, which also led to a Nobel Prize.

As an aside, Alexis Carrel had a controversial, to many people an unsavory, life. Born in 1873 in France, he qualified as a surgeon and moved to the USA to work in medical research at the Rockefeller Institute. There, he developed the techniques of vascular anastomoses which ultimately allowed surgeons to join vessels, both large and small, when undertaking experimental transplantations[130]. He teamed up with the famous aviator / engineer to develop a number of medical devices and cell culture techniques. However, he also held deeply illiberal views, and in his 1935 book "*Man, the Unknown"* (1935), he endorsed fascism and called for the elimination of the unfit through processes of forced sterilization so that the human gene pool could be improved[131]. In 1941, he went into the service of the French pro-German regime of Vichy, which appointed him to head an institution of eugenics research. He had a remarkable influence, affecting radical Islamic groups as well Le Pen's Front National. However, he extreme writings, including his endorsement of what became Nazi policy *(for those who have seriously abused the trust of the public, for them the establishment designed for euthanasia, provided with suitable gases, would allow for their disposal in a humane and economical way*) caused great problems in France, and he has been deliberately ignored since his death in 1944; had a lived, he could well have been indicted in post-war legal hearings.

Returning to the question of technique, there are some obvious differences between these major organs. With the heart, a major issue concerned the choice of orthotopic or heterotopic placement. Heterotopic heart transplantation allows the graft to be connected to the native heart in a parallel fashion, which effectively assists the patient's heart, maintaining circulation in the case of severe rejection. Although Barnard himself preferred this technique for some of his later patients, his first case used the orthotopic method, in which the recipient's heart is totally excised and replaced with the donor's organ; this is now the preferred option in most centers, especially being used in cases of end stage heart failure. A somewhat similar scenario exists with liver transplantation, where orthotopic techniques, with so-called classic caval reconstruction[132], which involves complete resection of the recipient inferior vena cava followed by donor inferior vena cava interposition, dominated clinical practice. So-called piggy-back techniques are now

[129] Tan SY and Merchant J, Joseph Murray (1919-2012): First transplant surgeon, *Singapore Medical Journal,* 2019;60:162-3.doi:10.11622/smedj.2019032.
[130] Aida L, Alexis Carrel (1873-19440; visionary vascular surgeon and pioneer in organ transplantation, *Journal of Medical Biography,* 2014;22(30:172-5. doi:10.1177/0967772013516899.
[131] Reggiani AH, God's eugenicist: Alexis Carrel and the sociobiology of decline, New York: Berghahn Books, 2006, ISSBN 978-1-84545-172-1. doi:10.3167/9781845451721.
[132] Chan T, DeGirolamo K, Chartier-Plante *et al*, Comparison of three caval reconstruction techniques in orthotopic liver transplantation: A retrospective review, *American Journal of Surgery,* 2017;213(50:943-9. doi:10.1016.amjsurg.2017.03.045.

very common[133]. These involve hepatectomy (removal of all or part of the liver) but with preservation of the native retrohepatic vena cava. Specific features of the techniques vary amongst the main centers[134].

In the case of the lungs, two major decision points arise at the very beginning of the discussions about suitability: are either one or two lungs involved, and is it appropriate to consider transplanting the heart as well as the lungs? The first of these decisions obviously depends on the condition of the patient; the first human case performed by Hardy, mentioned above, was a single lung transplant performed on a patient with a squamous carcinoma of the left main bronchus[135]. Techniques for both single-lung and double-lung transplantation have been described by Gust *et al*[136]. With respect to heart and lung transplants, the first significant outcomes were seen in a few patients in the 1980s, but the procedure was most effectively pursued in the UK by Sir Magdi Yacoub[137]. In particular, he pioneered the technique of domino transplantation in which a patient with end-stage lung disease but still adequate heart function would receive a combined heart-lung transplant from a deceased donor, while then using the recipient's heart in a different patient who had end-stage heart failure[138]. Interestingly, he carried out such a procedure on one of his colleagues at Imperial College, London. Dame Julia Polak, a pathologist and tissue engineer, suffered severe pulmonary hypertension, which he successfully treated with this method; in full disclosure, I knew both Sir Madgi and Dame Julia when I was working in the UK. The information about this transplant was included in her obituary in the Lancet in 2014[139], so it was already in the public domain.

As described by Ng *et al*[140], the basic technique of kidney transplant surgery is well established, involving both vascular and ureteric anastomoses. The common approach is to anastomose the renal vein to the external iliac vein first, followed by that of the renal artery to the external or internal iliac artery.

5.8.2 Definition of death

The definition, or determination, of death has important consequences in many situations, but probably none so crucial as with the decision when it is ethically acceptable to confirm end of life and remove tissues and organs for transplantation[141]. The nature of this decision belongs to the metaphysical sphere (see Chapter 2)), and specifically epistemology. To many people, and indeed to many faiths, death is considered to be the departure of the soul, but that is indeterminant and cannot form the basis of any medically-oriented, legally-valid, decisions.

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[133] Nishida S, Nakamura N, Vaidya A, *et al*, Piggyback technique in adult orthotopic liver transplantation: an analysis of 1067 transplants at a single center, *HPB (Hepato-Pancreato-Biliary Association Journal)*, 2006;8:182-8. doi:10.1080/13651820500542135.

[134] Czigany Z, Scherer MN, Pratschke J, *et al*, Technical aspects of orthotopic liver transplantation – A survey-based study within the Eurotransplant, Swisstransplant, Scandiatransplant and British Transplantation Society Networks, *Journal of Gastrointestinal Surgery,* 2019;23:529-37. doi:10.1007/s11605-018-3915-6.

[135] Blumenstock DA and Lewis C, The first transplantation of the lung in a human revisited, *Annals of Thoracic Surgery,* 1993;56:1423-5.

[136] Gust L, D'Journo X-B, Brioude G, *et al,* Single-lung and double-lung transplantation: technique and tips, *Journal of Thoracic Diseases*, 2018;10(4):2508-18. doi:10.21037/jtd.2018.03.187.

[137] Allvizatos PA, Sir Magdi H. Yacoub; the Leonardo da Vinci of cardiac surgery, *Proceedings of the Baylor University Medical Center*, 2019;32(1):146-51. doi:10.1080/08998280.2018.1532247.

[138] Klepetko W, Wollenek G, Laczkovics A, *et al*, Domino transplantation of heart-lung and heart: an approach to overcome the scarcity of donor organs, *Journal of Heart Lung Transplantation*, 1991;10:129-31.

[139] *The Lancet*; Obituary of Julia Margaret Pollak, 2014;9952:1342. doi: 10.1016/S0140-6736(14)61890.

[140] Ng ZQ, Lim W and He, B, Outcomes of kidney transplantation by using the technique of renal artery anastomosis first, *Cureus,* 2018;10(8):e3223. doi:10.7759/cureus.3223.

[141] Kirkpatrick JN, Beasley KD & Caplan AC, Death is just not what it used to be, *Cambridge Quarterly of Healthcare Ethics,* 2010;19:7-16. doi:10.1017/S0963118010999020X.

A heart passing through the sky
Blades overhead
Unsuspecting parties below

Beneficial carnage
Begins with a wreck
A straight line starts with death
Hopefully life at the other end

Permission tenderly sought
Distraughtly given
Kidneys to Winston
Liver to Charlotte
Heart to Philly
Brain going nowhere just yet
Except for the grave

But where is the soul?
Does it go to the grave as well,
Or to the life-support hospitals?

Can a soul be divided this way?
No-one knows
It surely wasn't consulted
Body partitioned
Soul forgotten

David Williams *"Life and Soul of the Party"* 2016, In 'A Decade of Transition, The Collected Poems of David Williams, 2004-2014'.

There was, therefore, a need for a far more objective criterion, and some consensus has been achieved, although difficulties and confusion still exist. The main discussion points have concerned definitions of cardiopulmonary death and brain death, the diagnostic tests used to determine death and the implications of advances in resuscitation techniques on the irreversibility of death. With cardiopulmonary criteria, cardiac arrest victims who do not show any spontaneous circulation after standard resuscitation efforts over 20 to 30 minutes are usually declared dead on the grounds of irreversible cessation of cardiopulmonary function. The main arguments about this simple concept center around the difference between presumed and actual death, since controlled reperfusion after much longer periods of cardiopulmonary resuscitation can result in reanimation.

With brain death criteria, there are differences of opinion about whether this applies to the whole brain or the brain stem. Most authorities consider that the diagnosis of brain death involves the irreversible loss of consciousness and brain functions that are essential to integrative functioning. However, certain brain functions continue to integrate and regulate body systems while still fulfilling whole brain death criteria. This has led to a broader, and not necessarily helpful, discourse about 'disintegration of personhood' as a criterion (or perhaps a conceptual criterion), this involving 'higher functions'. Since decisions about the use of organs for transplant have to be taken in short periods of time, such discussions, I believe, have little practical value. In situations where brain death cannot be confirmed by any recognized procedure, but cardiopulmonary function cannot be maintained without continued assistance, that cardiopulmonary support may be withdrawn, and after a period of time which depends on local jurisdictions, death of the

person may be declared. This satisfies the universal Dead Donor Rule that mandates that organs necessary for life can only be taken from dead people, but still leaves open the possibility of misuse. At a more philosophical level, these arguments have led towards the use of somatic integration as guidance on brain death, where the rationale for equating brain death with death follows the belief that the brain integrates parts of the body into a whole organism. However, as Shewmon has pointed out[142], many integrative functions of the brain are not somatically integrating, and the brain's role is more modulatory than constitutive. In other words, integrative unity of the human body is non-localizable, involving mutual interaction of all parts, rather than coordination by one part and multiple passivity by everything else. This view has been supported in the essay of Thomas[143], who has argued that, since there is strong evidence of the continuing functional integration in brain dead patients, the equation of death with brain death is essentially untenable.

The almost universal adoption of the concept of 'donation after circulatory death', DCD, has not resulted in much lessening of controversy about the details. A European panel[144] achieved reasonable consensus in 2013 when redefining the classification of DCD, which focuses on the circumstances of cardiac arrest, the initial therapeutic procedures used and the location of the cardiac arrest (i.e., in or out of hospital). In the USA, most states rigorously follow the Federal 'Uniform Determination of Death Act,' first passed in 1981 and updated in 2018; however, some organizations, such as the Catholic Church still have concerns over issues such as the moment of death, the departure from the unitary concept of death and the challenge to the standard of irreversibility[145].

5.8.3 Organ Donation, Transport and Storage

(To be completed, Q3, 2024)

5.8.4 Immunosuppression

(To be completed, Q3, 2024)

5.8.5 Decellularization and Recellularization

There is an interesting analogy of decellularization and recellularization within shamanism. Here there is a specific type of journey, known as the dismemberment journey, where the shaman recognizes a fear that impedes the expansion of their soul. To overcome this, they have to appeal to the laws and spirits of the 'Otherworld' for them to be healed of this condition; during this process, they undergo symbolic death, which gives way to a profound re-birth, a journey referred to as 'dismember and re-member', perhaps 'separate and recombine' or 'dissolve and coagulate'.

There are several spiritual consequences of this. To a shaman, whether or not the dismemberment, or transformation, was invited, and whatever the circumstances, the process is not random, and no-one can

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[142] Shewmon AD, The brain and somatic integration: insights into the standards biological rationale for equating 'brain death' with death, *Journal of Medical Philosophy,* 2001;26(5):457-78. doi:10.1076/jmep.26.5.457.3000.
[143] Thomas AG, Continuing the definition of death debate; the report of the president's council on bioethics on controversies in the determination of death, *Bioethics,* 2012;26(2):101-7. Doi:10.1111/j.1467-8519.2010.01812.x.
[144] Thuong M, Ruiz A, Evrard P, *et al*, New classification of donation after circulatory death donor definitions and terminology, *Transplantation International,* 2016;29:749-59. doi:10.1111/tri.12776.
[145] White FJ, Controversy in the determination of death; The definition and moment of death, *Linacre Quarterly*, 2019;86(4):366-80. doi:10.1117/0024363919876393.

afford to ignore or abuse the rules. The concepts of decellularization and recellularization of tissues or organs, say a kidney, is equivalent to its dismemberment and subsequent restoration. This is not a trivial process; to the kidney it is traumatic, it having lived within a live individual until a few hours before, when sudden death came to that person, the kidney living on in a confused state but with critical cellular components now moving towards death themselves. In the analogy, the kidney is moving towards the Otherworld of organs, potentially to be rescued, recombined and re-membered by recellularization.

5.8.6 Homograft Tissues

(To be completed, Q3, 2024)

5.8.7 Heterograft Tissues

(To be completed, Q3, 2024)

5.8.8 Xenogeneic Tissues

(To be completed, Q3, 2024)

5.9 PHARMACEUTICALS AND THERAPEUTIC AGENTS, INCLUDING OXYGEN-CARRIERS

(To be completed, Q4, 2024)

5.10 GENE THERAPIES AND GENE EDITING

(To be completed, Q4, 2024)

5.11 CELL THERAPIES

(To be completed, Q4, 2024)

5.12 TISSUE ENGINEERING

(To be completed, Q4, 2024)

5.13 3D PRINTING AND BIOPRINTING

(To be completed, Q4, 2024)

5.14 ROBOTICS AND ARTIFICIAL INTELLIGENCE

(To be completed, Q4, 2024)

5.15 BIOCOMPATIBILITY

(To be completed, Q4, 2024)