1 The clinical necessity of biomaterials in the twenty-first century

In this opening chapter you will be introduced to the extent to which health care products contribute to the delivery of therapeutic and diagnostic procedures across a massive array of clinical problems and solutions. Included here are examples of long-term implantable devices, procedures of regenerative medicine, the diagnosis of disease and injury, and the specialized delivery of drugs and genes. You will then see how biomaterials science has evolved in order to optimize the performance of these products. The concepts of biomaterials science are introduced, along with a general discussion of the requirements of biomaterials and their essential characteristics.

1.1 Health care products in medical practice

You are an observer in a busy doctor's clinic on a Monday morning during a cold wet month of the winter. This is a large polyclinic, which includes not only primary care physicians but a plethora of specialists, who deal with the diagnosis and uncomplicated treatments for a variety of conditions, ranging from dental and ophthalmological conditions, to neonatal care, trauma, geriatric complaints and common infectious diseases. A few hundred meters away is a major teaching hospital, able to deal with virtually every acute and chronic condition that is likely to be seen in this mid-size industrial city, which encompasses people of all ages and genetic background.

The doctors and their colleagues deal with regular, routine patients who have regular routine non-emergency, but increasingly complex, chronic conditions. They also deal with patients who present with recently acquired illnesses and are in urgent need of a diagnosis and referral, with those who have minor and moderate trauma, those who suffer from degenerative diseases that either before, after or instead of major therapeutic or surgical intervention require ameliorative or rehabilitation therapies. There are those who have acquired (by whatever route, perhaps while travelling overseas, through lifestyle decisions or just by living next door to someone) infections by bacteria, viruses, fungi or prions. They see children and adolescents who need ongoing support for the corrective therapies that changed their physical appearance when they were young. There are those who have no illness at all, but just think that they have, or who might have in the future if something is not done now. And of course they have to deal with those who are sensible enough to undertake regimes of preventive medicine, perhaps through vaccines, prophylactic drugs or physiotherapy.

The medical practitioners in this clinic clearly wish to provide the best service to these patients and in order to do this they need the best tools of their trade. First and foremost, of course, are the skills and knowledge that they themselves bring, a point which we shall

return to several times in this book. In addition, however, they need a variety of products, often called health care products, which allow them to deliver the required therapy or make the correct diagnosis. These could be drugs and vaccines, simple clinical sundries such as needles, scalpels and bandages, or more complex instruments or devices.

Let us follow some of these patients as they pass through the various offices in the clinic, often being referred onwards to the specialist clinics of the adjacent hospital.

1.1.1 The ubiquitous low back pain

The first patient is one of those individuals who experiences low back pain. The primary care physician sees many such people; the diagnosis may be complex since pain is difficult to quantify and there may be few indications on an X-ray that there is anything present other than normal ageing tissues. A prescription of anti-inflammatory agents and pain medication may be all that is necessary. This particular patient has been to the doctor before, however, and the condition is getting worse; there is chronic continuous pain with frequent spasms that leave him immobile and scared to try any movement. The time has come for more extensive diagnostic tests, where CT and MRI scans reveal that there are irreversible changes to one of the intervertebral discs in the lower, thoracic, part of the spine. The disc is a flat cylindrical piece of cartilage, which has an outer tough membrane, the annulus fibrosus, which encloses a viscous gel-like mass, the nucleus pulposus. This disc separates adjacent vertebrae and allows for bending and rotational movements of the spine. It is subject to degenerative changes over time and may, suddenly or gradually, be displaced from the intervertebral space, causing intense pain as two vertebrae now come into contact and interfere with nerves. This cartilaginous mass does not heal very well, and although the spinal doctors and neurologists know that efforts are being made to use stem cells to regenerate such discs, they are only too aware that, at this time, they have limited options.

The preferred treatment involves total removal of the disc and the intentional fusion of the two adjacent vertebrae. This results in some loss of mobility at that part of the spine, but with a total of 24 movable bones in the cervical, thoracic and lumbar sections of the spinal column, this is a small price to pay for the relief of the pain that accompanies the elimination of bone-to-bone sliding. The obvious practical question is how to produce this fusion. The surgeon has available to him/her a few devices which he/she can place, or implant, in the affected area to produce this fusion. The most common is a metal or plastic cage that is filled with bone grafts and secured between the vertebrae; this bone remodels over a short period of time to produce bony continuity and fusion (Figure 1.1). In some cases, this process is speeded up or enhanced through the use of a growth factor that is added to the bone graft. Our patient here is scheduled for this procedure a few weeks later. The doctors know he has at least a 75% chance of a good fusion and relatively pain-free back movements over the next 10 years.

Figure 1.1 Device for spinal fusion surgery. The illustration shows an Infuse® Bone Graft with an LT-Cage® used in the lower part of the spine. This device consists of titanium cages that contain collagen sponge mixed with recombinant Bone Morphogenetic Protein-2 (BMP-2); this system incorporates technology developed by Gary K Michelson MD. Image provided by Medtronic, Inc.

1.1.2 Sporting injuries and arthritis

Also in the doctor's office that morning are several patients who received sporting injuries over the previous weekend. Knees are common sites of injury, especially to the cartilage or ligaments. Small cartilage lesions and ligament tears will heal over time without too much intervention, but assistance may be required, especially if the injury is extensive or if there is an overwhelming reason for the patient to be repaired as quickly as possible, as with valuable sportsmen and women. Cartilage is a difficult tissue as far as healing is concerned and quite small lesions can lead to progressive destruction. One patient has a relatively small lesion but it is in a central area of the knee joint, on one of the condyles at the end of the femur, and the doctors agree to carry out a relatively new technique called mosaicplasty. This is suitable for small but painful injuries. It attempts to encourage the cartilage to heal by drilling a small hole at the site of the lesion through to the bone, and taking a graft from an undamaged, peripheral area of the joint and inserting this into the drilled hole. The drilling causes some local bleeding which helps with the healing process. The procedure is carried out with minimally invasive techniques rather than major surgery and it is very convenient. The doctors are very confident with this process, as they have done it many times, and they know from published studies that over 90% of patients have very good outcomes, without any recurring problems over 10 or more years.

With another patient, the doctor knew, from previous experience, that one knee joint did show signs of localized arthritis, but the patient still carried on playing various sports and now had some acute damage in the area of the lesion. The doctor did not believe that this patient was a good candidate for mosaicplasty, but instead thought that it was worth trying an alternative method, which had been used since the mid 1990s in such patients; it is, however, considerably more expensive and involves far longer rehabilitation. This is the technique of autologous chondrocyte implantation (ACI). This is a type of cell therapy, for it involves harvesting some of the patient's own cartilage cells, the chondrocytes, culturing them in a special laboratory such that they expand and form a significant mass of cells, which can then be re-injected into the site of the lesion, where they generate new cartilage. The first stage with this patient had been completed several weeks ago and now, in the hospital, he was to receive this injection of cells. This is a major surgical procedure that has to be carried out with great care since these chondrocytes are very sensitive and easily damaged. The surgeon prepares the site of the injection in the cartilage very carefully and uses a layer of the patient's own periosteum, the thin outer lining of bone, to cover the site, using fine sutures and a special surgical adhesive to make a tight seal. They are all aware that success is far from guaranteed with this procedure and experimental work is still under way with different materials and techniques that will minimize chondrocyte damage and leakage, and maximize new cartilage generation. Around 80% of patients report good results after 5 years, but this is very much dependent on the co-operation of the patient over a full year of rehabilitation.

Still on the subject of cartilage and joints, since in some countries more than half the population over the age of 60 have signs and symptoms of osteoarthritis, it is not surprising that the doctors in this clinic will see quite a few arthritic patients in one session. They will be at different stages of the disease. Today there are a couple of patients, in their seventies, with fairly early stage arthritis, one of the hip and the other of the knee, who are going through the routine of trying the various pain and anti-inflammatory medications, under medical supervision, in order to achieve the right balance of good results without too many side effects. Another patient, although under 60 years of age, has a more advanced stage of arthritis in one hip. He has had the usual radiographic diagnostic examinations and is now visiting the primary care physician for the last time before being admitted to the orthopedic clinic for the surgical solution to his problem – total hip replacement. Next week, he will receive a metal-on-plastic combination that will replace the top end of his femur and a small part of the pelvis. This is a routine

operation, the orthopedic surgeons carrying out this procedure on a daily basis, expecting to get a lifetime of 15–20 years with the device in 95% of patients.

That is a very good success rate, but does, of course, imply that 5% will not be so successful and also that after 20 years of function we might expect more problems. Unfortunately, on this particular day one of that 5% turns up at the hospital, in a wheelchair. Her device, after only 8 years, is clearly not working well and has become loose, giving extreme pain. She had not received this device in this hospital, having only moved to the neighborhood recently. The surgeons cannot readily identify the device on X-rays. The lady is obese and not in good shape. There is only one option, and that is to carry out a revision procedure, in which the old device is removed and a new one inserted, but the surgeons are well aware that, since the bones and joint have already been damaged, the chances of a really good outcome are not high.

Box 1.1 Glossary of terms

In each chapter, a brief glossary of (mainly) biological or clinical terms that have been introduced but not explained in detail will be provided. In some cases, the opportunity is used to define related or similar terms that have not specifically been introduced here, but will be in later chapters. The majority of definitions are taken from *The Williams Dictionary of Biomaterials*, published by Liverpool University Press, 1999.

agonist a drug that has an affinity for, and stimulates physiological activity at, cell receptors.

angina paroxysmal pain in the chest usually due to interference with the supply of oxygen to the heart muscle.

antibody an immunoglobulin protein with a site able to combine specifically with the antigenic determinant on an antigen; an *antigen* is any molecule that is capable of being recognized by the immune system, for example T-cell receptors.

artery any vessel in which blood flows away from the heart; a *vein* is any vessel in which blood flows towards the heart in the major circulation.

arthritis inflammation of a joint; *osteoarthritis* is primarily a degenerative disease, while *rheumatoid arthritis* has immunological origins.

atrium a chamber affording entrance to another structure or organ, especially the upper, smaller cavities on either side of the heart; *ventricles* are the lower chambers in the heart.

autograft a graft taken from a source in the individual who receives it; an *allograft* is a graft taken from another individual of the same species as the recipient and a xenograft is taken from a different species altogether.

cancer a general term used to refer to a malignant tumor.

cardiology that part of medical science that is concerned with the function and diseases of the heart.

cartilage the hard, compliant form of connective tissue, in which cells are embedded in chondroitin, and which is extensively distributed around the musculoskeletal system.

cataract opacity of the lens sufficient to cause visual impairment.

clinical trial a controlled study involving human subjects, designed to evaluate prospectively the safety and effectiveness of new drugs or devices.

Computerized Axial Tomography (CAT or CT) an imaging method in which the cross-sectional image of the structures in a body plane is reconstructed by a computer from X-ray absorption data.

condyle the smooth, rounded protuberance at the end of a bone.

disease the condition in which the normal function of some part of the body is disturbed.

echocardiography examination of the structure and function of the heart using reflected pulsed ultrasound.

etiology study of the causes of medical conditions.

ex vivo performed outside of the body; *in vivo* signifies something that takes place inside the body and *in vitro* refers to activities in solution or culture outside of the body.

growth factor one of a family of polypeptide hormones that regulate the growth, division and maturation of cells.

immunohistochemistry pathological technique for the microscopic examination of cells or tissues that have been stained by specific immunological markers in order to identify discrete cellular features.

lesion any pathological or traumatic discontinuity of tissues or loss of function of part of the body.

ligament bands of fibrous tissue that connect bones and cartilage and serve to support joints.

Magnetic Resonance Imaging (MRI) the use of nuclear magnetic resonance of molecules to produce images of the human body.

mutation sudden random change in the genetic material of a cell that may cause it to differ in appearance or behavior from the normal type.

neurotransmitter chemical that mediates the transmission of a nerve impulse across a synapse; a *synapse* is the site of functional apposition between neurons.

plaque a superficial, solid, elevated lesion, including the plaque that forms on the inner wall of arteries or the bacterial plaque that forms on teeth.

prophylaxis the use of methods to prevent the occurrence of disease, including *prophylactic drugs*.

receptor a molecule on the surface or within a cell that recognizes and binds with specific molecules, producing a specific effect in the cell.

sphincter a ring-like muscle that closes a natural orifice or passage.

stenosis the narrowing or contraction of a duct or canal.

thalamus either of the two large ovoid masses, consisting mostly of gray matter, forming part of the lateral wall of the third ventricle.

trauma injury.

vaccine a suspension of attenuated or killed microorganisms, or antigenic proteins derived from them, administered for the prevention, amelioration or treatment of an infectious disease.

1.1.3 The end of the road for cataracts

The next lady has a much better story. She is the same age, around 70, and is visiting the ophthalmologist. A few months ago, she was very depressed because of failing eyesight. Gradually she was losing the ability to see clearly, either near or far, and even recognising the faces of her five grandchildren had become impossible. She was otherwise very healthy, and never needed doctors and it took a great deal of persuasion by her children to seek help. She was petrified of needles and other medical paraphernalia and simply would not consider anyone going near her eyes with a surgical instrument. But now she had no choice, she had cataracts in both eyes; her natural lenses had become very cloudy and she was nearly blind. She could not believe it when, a few days after her first appointment she had a minor procedure under local anaesthetic, hardly noticing what was going on, and a piece of plastic was placed in each eye, in the form of intraocular lenses. Although such lenses had been used for a few decades, the ones she was fitted with were the relatively new self-accommodating lenses, and her vision was now truly excellent. Today the ophthalmologist was telling her that the results of the procedure were ideal and she could resume swimming and taking her grandchildren out.

1.1.4 The challenge of Parkinson's disease

Females around the age of 70 are frequent visitors to the clinic, and not all are so lucky as the lady with cataracts. Neurodegeneration is a massive problem in many countries. Although Alzheimer's disease is usually the major factor here, Parkinson's disease is also of huge significance. This disease has a complex aetiology, is progressive, incurable and difficult to treat. The incidence rises with age, from roughly 20 in 100 000 person years between 50 and 59 years of age, to over 90 in 100 000 person years between 70 and 79 years. Naturally as life expectancy in many countries is increasing, so the incidence of Parkinson's is increasing, and it will shortly affect around 1 in 800 people. The impact of the disease is therefore profound. It is caused by the failure of cells in that part of the brain known as the substantia nigra to produce adequate levels of dopamine, a neurotransmitter, with the result that the body experiences tremors, stiffness, slow movements and a loss of balance. These symptoms are not themselves life-threatening but collectively have a significant effect on the quality of life. Patients with Parkinson's have a median life expectancy of around 15 years following diagnosis, death often being due to complications of these physical limitations, such as pneumonia.

Why these dopaminergic neurons fail is still not clear. Most cases of Parkinson's disease are considered to be sporadic, occurring in individuals with no apparent history of the disease in their family, probably as the result of a complex interaction of environmental and genetic factors. Certain drugs may cause Parkinson-like symptoms, and various environmental toxins have been claimed to be associated with the disease. Approximately 15% of those diagnosed with Parkinson's have a family history of the disease, these familial cases often being caused by mutations in several genes.

Two patients, at different stages of disease progression attend the clinic. One, in the early stages, is solely on medication. It is not possible to supply dopamine directly to the body by a drug, but the molecule levadopa can be given orally, which is converted to dopamine within the brain. Levadopa can be converted too rapidly to dopamine outside of the brain, and has some unpleasant side effects, and so is usually combined with carbidopa. This combination is the major Parkinson's drug and it is this that has been prescribed for this first patient. However, it loses effectiveness over time and symptoms gradually reappear, even with increased dose levels. Other drugs include dopamine agonists, which mimic the function of dopamine, monoamine oxidase B inhibitors, which slow down the degradation of dopamine, and anticholinergics, which help to control the tremors. Her doctors know

that she has only a few years left during which the drug will be really effective.

As with many conditions, doctors know that their remedies are not always beneficial over the long term, but they await new developments that will take over and give new hope. The slow progressive loss of dopamine-producing neurons suggests that an alternative strategy may be based on neuroprotection through the delivery of neurotrophic factors, which could protect the neurons from cell death and promote their regeneration. Neurotrophic factors derived from glial cell lines do have the ability to promote such repair, but limited clinical trials have not been very successful as yet, since there are problems with the optimal delivery of the molecules and with the apparent development of anti-neurotrophic factor antibodies in recipients. The concept is still valid, however, and we should expect to see better results when superior delivery systems involving the incorporation of these factors into biomaterial-based systems, possibly in the form of nanoparticles, are developed.

A further alternative is to alter the cells such that they themselves produce such a neurotrophic factor *in situ*. This is the basis of gene therapy, where the delivery of the appropriate gene would allow the cells to constantly express that factor. There are still serious issues to resolve as far as safety is concerned. Again, alternatives may eventually be found through the use of new materials, either in the form of non-viral polymeric vectors for the genes, or through the use of microencapsulated, *ex vivo* genetically modified cells that have been programmed to express a neurotrophic factor. These developments will probably not occur in a time frame that will help this particular lady.

The next approach involves the transplantation of immature dopamine-producing cells into the brain, a type of cell therapy. This was actually first started over 20 years ago, through the use of embryonic or fetal neurons obtained at abortion. Leaving aside the ethical issues, there have been many problems with this, and although some patients have considerably improved following this transplantation, success is very difficult to achieve because so many of the cells are lost during sourcing and implantation procedures. It is possible that types of stem cells may be beneficial in this therapeutic approach in the future.

The second Parkinson's patient is being treated by a relatively new method that is proving effective. This involves the deep brain stimulator, and is generally used as an adjunct to medication. The goal of the procedure is primarily to improve the condition in the "off" medication state. Patients with Parkinson's disease have both "on" and "off" states. The "on" state is when the medications appear to be working and when the patient is reasonably mobile. The "off" state is when the patient is slower and stiffer. Deep brain stimulation does not usually improve the "on" state, which is the best condition, but improves the patient when they are in their worst state.

This technology requires the placement of an electrode deep inside the brain, which is attached to a subcutaneously placed electronic device that generates electrical signals that stimulate the brain and counter those effects which produce the Parkinson's symptoms (Figure 1.2). There are several locations in which the electrode can be placed, most involving either the thalamus or the sub-thalamic region. The procedure, which is more complex for the sub-thalamic stimulation device, is usually performed in two stages, the first involving the placement of the electrode and the optimization of its position, and the second involving implantation of the stimulator and connections. The procedure appears to have significant beneficial effects in addition to those achieved with medication by itself, and there is good evidence that the benefits last at least five years. There are indications that these benefits may be reduced at longer periods of time and it is clear that not all patients will benefit from this treatment. Obviously it is not inexpensive. This particular lady had the device fitted one year previously and this routine examination today shows that the treatment is going well. It took a few months for her to adjust to the "feel" of the system, but her quality of life has been immeasurably improved.

Figure 1.2 Deep brain stimulator. The deep brain stimulator used in the treatment of Parkinson's disease. The device has an outer casing of titanium and provides stimulation to specific parts of the brain by stereotactically implanted electrodes. Image courtesy of Medtronic, Inc.

She is aware that this may not last, but prefers to be very positive for her future.

1.1.5 The cath lab and beyond

Most people are fully aware that the major cause of death in developed countries is heart disease. In the USA there are close to half a million deaths a year from it, which accounts for one in every six deaths. No wonder there is such an emphasis on the prevention, diagnosis and treatment of this disease, and our clinic is heavily involved in all such aspects.

The heart is a magnificent engineering and physiological structure, but there is much to go wrong, especially as individuals get older, when changes to the structure of valves, coronary arteries and other parts cause loss of function. Sometimes the symptoms are dramatic, with sudden collapse from a heart attack. Often there are early signs of disease, usually ignored by the individual, which lead to discomfort, difficulties with breathing and movement, and chest pain, but most people will seek some form of help sooner or later. A whole variety of non-invasive tests are available to give some indication of the presence of heart disease, including exercise stress tests, echocardiograms, MRI scans and nuclear imaging. If there are signs of serious disease, more advanced tests are required and several treatment options may be considered. This hospital, as with most major hospitals, has full facilities to conduct such diagnostic tests and deliver various therapies. The main facility is the catheterization laboratory, known as the cath lab, in which the state of blood flow in arteries can be assessed, especially in the coronary arteries which are themselves supplying blood to the muscular walls of the heart. If it is obvious that one or more of the coronary arteries are blocked, either following the onset of certain symptoms or immediately following a heart attack, consideration may be given to the use of a percutaneous coronary intervention, often referred to as angioplasty. Here a catheter is placed, under sedation, through an incision in the groin and along the femoral artery into the area of the blockage. The catheter has a balloon attached to its end and once it reaches the blockage, the balloon is expanded and compresses or dislodges the plaque that has slowly built up on the inner surface of the artery, opening the artery up again.

One such patient attends the cath lab this morning. He is in his sixties, has had angina for some time, and tests have determined that he has coronary artery disease that should be amenable to angioplasty. The cardiologists have, as always, been very truthful, and have said that although the angioplasty works very well, the effects may not last and the blockage may return, perhaps as soon as within one year. They do have an alternative, which doctors have been using for some 20 years. This involves using the

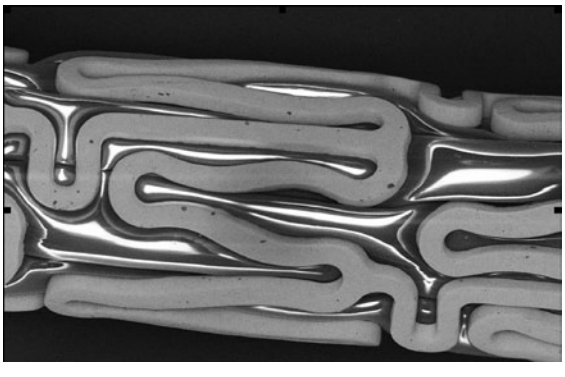

Figure 1.3 Intravascular stent. Scanning electron micrograph (original magnification ×200) of a stainless steel intravascular stent mounted on an expandable balloon.

same type of procedure but instead of simply compressing the plaque and then leaving it alone, a small metal device, known as a stent, is left behind, in the hope that it can hold the vessel open permanently (Figure 1.3). The patient is asked to give permission for the cardiologists to use a stent if they think that is the best thing to do. The story is a little more complex. It has become obvious that even with a stent in place there is no guarantee that the vessel will not close up again. Many of the stents now available have an additional component that is meant to address this problem. This component is a thin layer of a polymer on the surface of the metal; this polymer contains a minute amount of a very powerful drug, in fact a chemotherapy drug, which stops the cells in the blood vessel wall from proliferating (just as it normally stops cancer cells from proliferating). Our clinic is taking part in a clinical trial to assess the latest design of a drug-eluting stent, and our patient is asked to give informed consent to take part. He will not know before he is sedated whether he will receive the original type of stent (the bare metal stent), a new drug-eluting stent, or no stent at all.

One other patient in the hospital wasn't quite so lucky. He had ignored the warning signs and went straight to the heart attack. He had too many arteries blocked, in poor configurations, and was not suitable for the angioplasty and stent. He was admitted to the emergency room at dawn, a common time for heart attacks, and it was decided that he had to have a coronary bypass. In this, the blocked parts of the coronary arteries are bypassed by a segment of a tube, which allows the blood to flow freely.

In this situation, there is no magic piece of synthetic material for the tube. The coronary arteries are rather small, usually less than 5 mm in diameter, and no one has yet made a synthetic tube that works in this position – they would block rather quickly. Interestingly it is different when arteries in some other parts of the body become diseased, for example in the upper part of the leg, for these arteries are larger, and synthetic replacements made out of common textiles such as polyesters work quite well in these positions. A number of patients in the vascular ward of this hospital have had such procedures this week, most of them suffering from the consequences of lifetimes of smoking, since atherosclerosis, which is the blocking of arteries by plaque, is one of the major sequelae of this habit. Instead, with the coronary arteries, the surgeon will use one of the patient's own veins for the bypass, having determined that he has a good-quality greater saphenous vein in one of his legs that can be used. This is a relatively superficial vein that runs from just above the ankle to the top of the thigh. Removing this vein is not a problem for the long-term survival of the leg since there are several other veins that compensate as far as the major circulation is concerned, but it is not a trivial process removing it, usually with an incision running the whole of the length of the leg. The best sections of the vein are cut and trimmed and used for the bypass; in the case of this patient three of the coronary arteries are involved. When he comes around from the operation and recovers from the ordeal over the next few days, the patient will be concerned about his future, but the cardiac surgeons are very confident and positive. Many famous and active individuals have gone through this procedure and had very successful and rewarding lives afterwards. The British explorer

Sir Ranulph Fiennes had a double bypass in 2003 and went on to climb Mount Everest in 2009 at the age of 65. Well-known figures in the USA, such as Bill Clinton and Larry King, have had successful bypasses, so our patient is in good company. This area poses several difficult questions in relation to the preferred treatment modality. At one time drug-eluting stents appeared to offer the best prognosis, but as the results of long-term follow-ups are analyzed, the outcomes may not be better that coronary artery bypass surgery.

1.1.6 Pulses and shocks in the heart

The heart is not only about blood flow through tubes and valves; it needs to be driven in some way. The driving force is based on electrical signals; these are generated in the sinus node at the top of the right atrium of the heart and in healthy individuals the pulses produced trigger regular movements of the heart wall muscles, with a frequency (the heart rate) that is responsive to conditions such as exercise. One of our patients in attendance this morning had experienced some difficulties with his heart rate and rhythm a number of years ago and it was clear that his natural pacemaker was not functioning correctly. He was fitted with an artificial pacemaker (Figure 1.4).

This implantable device has two main components. One is the pulse generator, which is a small hermetically sealed metal container that is placed under the skin in the region of the shoulder. It contains the generator circuitry and the power supply. It is connected to electrodes in the heart by fine metallic wires that conduct and deliver the impulses to the muscle. Pacemakers are configured in different ways depending on the precise condition of the patient. This patient has a dual chamber pacemaker with leads going both to atria and ventricles. It is a demand pacemaker that does not work all the time; it senses the heart rhythm and switches itself on when the heart rate drops below a pre-determined level. These patients are routinely monitored and all have a device at home, linked

Figure 1.4 Cardiac pacemaker. Structure of an implantable cardiac pacemaker. The device has a chamber encased with titanium, two leads with electrode tips and a header through which the leads enter the chamber. This particular device has been designed to be MRI-compatible since many patients with pacemakers often require imaging and conventional pacemakers are not compatible with the magnetic fields used in MRI. Image courtesy of Medtronic Inc.

through a computer, which can send information about the state of the pacemaker over the phone to the clinic every three months. Once a year our patient comes into the clinic for a physical check and for inspection of the battery condition. Depending on the amount of time that the pacemaker is actually generating signals, a battery may last between 5 and 15 years; our patient had had the pacemaker for 7 years and today the tests show that he will need the device changed sometime in the near future and so he arranges the necessary appointment. The leads and electrodes look fine and so this will be a simple outpatient procedure.

Another patient with heart rate problems is not so confident. He has a history of arrhythmic episodes, where his heart beats irregularly, and he has been on anti-arrhythmic medication for a couple of years. The cardiologists are worried, however, and he does seem to be at risk of ventricular fibrillation, in which

the ventricles quiver instead of contracting, so that no blood is pumped from the heart. It is fatal unless treated immediately. There is one type of treatment involving an implantable device rather similar to a pacemaker, but this has been much more controversial. This is the implantable cardioverter-defibrillator (ICD). Most people are familiar with the normal defibrillator, the device with two big pads that can be placed on the chest of a victim of acute ventricular fibrillation and which deliver a massive electrical shock that stops the irregular beat and returns the heart to normal – it is often portrayed as the exemplary dramatic medical intervention and defibrillators are installed in many public places such as airports. The chances of being close to a defibrillator when an attack happens are usually rather small, however, and the possibility of personalizing this device was behind the development of the ICD. It does look similar to a pacemaker in terms of combinations of generator and electrodes, and has some similar functions, but with a big difference. The ICD can deliver pacing signals if required. It can also deliver cardioversion, which controls a heart beat that has become too fast – this is a mild electrical shock, detected by the patient as equivalent to being thumped in the chest. If ventricular fibrillation is detected, then a much stronger shock is delivered, this being powerful and unpleasant. In the early days, ICD was seen as a treatment of last resort, one of the issues being that they were not 100% reliable in the detection of ventricular fibrillation, and the powerful shock could be given when it wasn't required. Living with a system that could, without warning, deliver a massive shock – equivalent, some people say, to a horse kicking you in the chest – was psychologically disturbing to many people, and even more so when you were aware that often the horse had no reason at all to kick you. Depression and anxiety are not uncommon experiences in these patients. The situation has become far more reliable in recent years and almost all relevant medical authorities worldwide have concluded that ICD therapy is effective. The cardiologists here have concluded that this patient should be placed on the list for this treatment, and he now awaits this with just a little trepidation.

1.1.7 Care of the newborn

Not all patients in this medical facility are old and in need of care because of disease; many are very young and in need of care because of just that, they are too young to care for themselves. The Neonatal Intensive Care Unit (NICU) in this hospital is there to assist in supporting extra young individuals who have been born under less than optimal conditions. Prematurity and low birth weights have become significant problems. Prematurity is usually defined as delivery at less than 37 weeks pregnancy, and very premature at less than 32 weeks. Low birth weight is considered to be less than 2500 grams (around 5½ pounds) and very low birth weight is around 1500 grams (3½ pounds). Over 12% of American babies are born prematurely, with figures elsewhere ranging from 5% in Ireland to 17% in southern Africa. Risk factors for prematurity include diabetes, smoking, drug habits and infertility treatments in the mother. Just being born early is not necessarily a problem, it is more the health status of the baby, often reflected in the birth weight. According to the Center for Disease Control in Atlanta, 7% of babies are of low birth weight and 1% of very low birth weight.

Our maternity unit has its fair share of premature and low birth weight babies, some of whom have to spend time in the NICU – about 2000 per year, either premature or with life-threatening conditions, spend their first few days of life here. They are supported in their fight for life by a variety of machines and devices that allow them to breathe and feed.

Much of the equipment involves small disposable but life-saving items such as tubes, sensors and routine monitoring equipment. Babies that cannot be fed have catheters to assist in nutrition – we have one very low birth weight infant that needs all its nutrition delivered this way, a procedure known as

total parenteral nutrition (TPN), and has a catheter placed directly into a central vein for this purpose. It may take several weeks for him to be strong enough to be weaned off this system. The lungs and respiratory system are also vulnerable in premature infants and respiratory stress syndrome is the most common cause of death. These infants have to be assisted in their breathing by use of a ventilator, with constant monitoring of oxygen levels and other vital signs.

One of the infants is in quite a bad way, suffering from persistent pulmonary hypertension (PPHN), which arises from a failure of the babies' own circulation to successfully take over from that of its mother. This is life-threatening and the pediatricians have already placed the baby on the best ventilator for this purpose, the high frequency oscillation ventilator, but the results have not been good enough and now they have decided to place the baby on extracorporeal membrane oxygenation (ECMO). This is the equivalent to the so-called heart–lung machine used in major cardiac operations in adults, and takes the babies' blood from the heart and lungs and passes it through a machine where oxygen is added to the blood and carbon dioxide is removed, and then the blood is passed back to the major circulation. This baby will need to stay on ECMO for a few days before it is well enough to take over the heart and lung functions itself. The introduction of neonatal ECMO in the 1980s saved many infant lives, although fewer babies need it now because of advances in ventilation, including the use of nitric oxide in the ventilator, which improves the response from the lungs.

1.1.8 Diagnosing and treating breast cancer

According to the World Health Organization (WHO), there are around 8 million deaths annually worldwide from cancer, and this is increasing. Developed countries have a high prevalence of prostate, breast and colon cancer, while developing countries see high rates of liver, stomach and cervical cancer. With the very mixed population in our city, we see many different forms of cancer, and rather too many cases altogether. Since many cancers are preventable through lifestyle choices, there is a big emphasis in the community on prevention, while within the hospital itself early detection of cancer and the various forms of therapy that can be delivered after diagnosis are very important.

Breast cancer is a major problem, but there have been significant advances recently and our hospital is at the forefront of progress. Breast cancer screening is a politically sensitive issue in many parts of the world since the success rates of detection through screening processes such as mammography are controversial and, of course, there are difficult balances to make with respect to the health economic issues involved. We are more concerned here with what to do once a tumor is suspected. Of particular relevance is the fact that it is the nature of the tumor that may be as important as its presence.

Of special relevance here is the so-called HER-2 type of breast cancer. In some breast cancers, the cancer cells have an unusually large number of Human Epidermal Growth Factor 2 receptors on their surface. This occurs because of a gene mutation and causes the tumor to be more aggressive. Fortunately, there are some treatments specifically directed at HER-2 positive tumors, but the tumors need to be identified in the first place. Usually the front-line treatment will be surgical removal of the tumor and at that time a biopsy will be taken. There are two good tests for HER-2 positivity, one being immunohistochemical and the other involving the technique of fluorescence *in situ* hybridization (or FISH). Our laboratory uses the latter, and it is very effective, but it does take a little time. The oncologists are aware, however, of some new techniques that are in advanced stages of development that should be able to give real-time assessment of the presence of these receptors, especially using highly fluorescent nanoparticles called quantum dots. There is an international effort to develop these tests, and our group is liaising with groups in China, Japan and Singapore on these.