CHAPTER SIX

SPECIFIC CLINICAL EXAMPLES

6.1 INTRODUCTION

In this Chapter, the specific therapeutic modalities that are available for the treatment of diseases and conditions of different parts of the body are described.

I make one general point at the outset. This Chapter is based on clinical reality and not on science fiction or even speculation about future possibilities. The latter may be mentioned if they represent a logical extension or improvement of existing therapies. However, I do not dwell on *in vitro* or *in silico* observations, nor on data derived from pre-clinical animal studies. Far too often we hear of the 'amazing potential' of a new technology based on some laboratory results, but never to hear of it again. I try to avoid that speculation whilst at the same time expressing the excitement of where we are and the direction where we are going.

When dealing with each set of circumstances, the following points will be covered, since they all impact on the choice(s) available to clinician and patient (or their caregiver):

- Contribution of genetic factors to the etiology of the condition,
- Known environmental or life-style factors in causation of the condition,
- Palliative or conservative methods of treatment, including 'alternative' approaches,
- Pharmacological methods, including drug action and drug delivery,
- Surgical procedures, including grafts and transplants but excluding devices,
- Medical device options,
- Regenerative medicine options, including cell and gene therapy.

It is necessary to have some structure to this Chapter, rather than providing a random walk through diseases and therapies. For this type of discussion, there are several ways in which the body can be divided, into, for example, systems or compartments. I hesitate to use the word 'classify' since there are so many overlaps and multiple functions. I also prefer to avoid any format that is dependent on disease types. Instead, I prefer a simplified categorization based on systems and their functions. This is set out briefly below.

- Cardiovascular system,
- Musculoskeletal tissues,
- Nervous systems and sensory organs,
- Respiratory system,
- Digestive systems,
- Endocrine organs,
- Urinary system,
- Reproductive systems,
- Blood and immune system,

6.2 THE CARDIOVASCULAR SYSTEM

The cardiovascular system is comprised of the heart and the blood vessels. Mechanistically this system is quite simple since the heart is required to pump blood to all parts of the body *via* a network of blood vessels, providing oxygen and nutrients to cells and removing the metabolic wastes from the tissues.

The complexity of this system, and hence the frequent need for some form of therapy or reconstruction in order to maintain the expected lifespan of 80 or so years, is seen from the following characteristics:

- At an average heart rate of 70 beats per minute, the heart needs more that 4,000 beats per hour or over 40 million per year, or 3 billion for the 80 years; that is a profound engineering feat with respect to endurance,

- This activity is achieved by means of specialized muscles in the heart wall (a type of muscle not seen elsewhere in the body) and these muscles need a non-interrupted supply of oxygenated blood,

- The blood flow is not continuous, and its uni-directionality has to be controlled by valves, of which there are four main types, within the heart itself,

- The pumping action requires electrical energy for this performance, the pulses associated with this energy having a complex waveform; this has to be supplied and regulated through the heart's own conduction system,

- Both the heart musculature and the blood vessels change their characteristics over time, which can have a marked influence on the hemodynamic characteristics of the system. The inner lining of blood-contacting tissues, the endothelium, plays an important role here,

- The blood itself is not a simple inert fluid, as a complex mixture of fluids (that contain proteins and ions) and suspended blood cells; disorders within the blood cause many serious conditions; these are discussed in their own section at the end of this Chapter.

This is, therefore, an integrated system of fatigue-resistant cardiac muscles, a combination of valves that work synchronously with these muscles, a complex electrical power generator and control system, and specialized tissues that interface with and control flowing blood. Each of these components and their functions are now considered in turn.

6.2.1 The Heart as a Pump

The essential features of the heart are as follows; there are four chambers, i.e., two atria and two ventricles, the former of which collect blood and the latter pump it. The atria are thin walled, but the ventricles have thicker muscular walls in view of their pumping requirements. The right atrium collects blood from the systemic circulation, primarily from the superior and inferior vena cava – this blood is relatively de-oxygenated. This blood passes through the tri-cuspid valve into the right ventricle, from where it is pumped, *via* the pulmonary valve into the pulmonary arteries. This blood circulates through the vessels of the lungs, where it picks up oxygen and passes back to the left atrium. From here it is

pumped into the left ventricle via the mitral valve and is then ejected into the major blood circulatory system, initially through the aorta, this flow being controlled by the aortic valve. The two atria and the two ventricles are separated from each other by septae, the atria septum being a fibrous membrane and the ventricular septum being a muscular membrane.

The muscular heart wall is called the myocardium. This consists of cardiac muscle tissue, which is different from skeletal muscle; the muscle fibers are short, containing a single nucleus but many mitochondria that allow for continuous energy production *via* ATP. The cells are branched and interconnected so that they can contract with a wave-like pattern to give the pumping action. The myocardium requires a very effective supply of its own blood, provided by a series of coronary arteries, which are branches of the descending aorta. The heart itself is covered by the pericardium, a multi-layered sac, with a double serous membrane on the inner aspect and a fibrous membrane on the outside. The sac contains some serum-derived fluid that acts as a lubricant. The electrical activity of the heart commences with a stimulus being generated by the sinoatrial node, (SA node), a small mass of tissue located in the right atrium. As the atrium is activated, the stimulus travels down through the conduction pathways *via* the Bundle of His to the atrioventricular node (AV node), and causes the ventricles to contract and pump out blood. The atria contract a fraction of a second before the ventricles, so their blood empties into the ventricles before the latter contract.

These, then, are the functional parts of the heart, which we must address with respect to disease and reconstruction. We will deal with the myocardium and its blood supply first, then the septae, followed by the valves and then the electrical conduction system. This section will conclude with a discussion of end-stage heart failure and treatment options.

Before we look at the technicalities, let us take a brief look at how the non-clinical world looks at this system, especially the heart:

Working in South Africa on pediatric heart problems, I started to think how the complexity, but fragility, of the heart interfaced with literature.

He can live forever in the persistent but euphemistic vegetative state
Death does not come easily to the ailing brain,
Traumatic disturbance of the spine kills feeling, but not life,
Cirrhosis takes years to wither the final stages of gin
Loss of hearing and vision inconvenience but do not fatally maim
But missing a single heartbeat is the beginning of the end, a quick ending of life

That degenerate brain keeps the heart alive
Often giving perverse succor where it is no longer respected
You have to mend a broken heart quickly
Since it strokes the genius and then the life out of the white matter above,

A mass of muscle, a bundle of nerves,
Shimmering, pulsating, the essence of life,
Architectural similes, of arches, atria, portals and septa
Activities fundamental for living, rhythm, pulse, beat,
Its deficiencies initiate the decline, dissent and incipient death,
Murmur, attack, occlusion, clot,
The adjectives and nouns of the incompetent and dying

A heart, broken, forever denied the power of recovery
The epitome of irrecoverable traumatic decline
Heart wrenching, tearing, stopping phenomena,
No soothing words, no emollient of help.

Why has God ordained it thus, that the
Incompetent and incontinent live forever
But the transient infarct in the life and soul of the party
Kills both instantly?

Can this change, can the glue be found to mend the broken heart?
Not the machine to replace it; that is no answer,
A technical chance for the few, to be sure, but
Of no affordable value to the hearts of the many.

No, the death of the heart, which brings death to the soul, starts with the death of some cells,
The primordial cells of the pulsating beat
Can we bring them back to life, can we regenerate
The few, can we persuade the body
To heal itself, in that moment of time,
In that deliciously delicate of all places,
Through that molecular glue of cellule souche?

Of course we can,
With care, humility, and no heroics.

David Williams; "*Mending a Broken Heart*" 2016, In 'A Decade of Transition, The Collected Poems of David Williams, 2004-2014'.

6.2.2 Congenital Defects

(To be completed, Q4, 2024)

6.2.3 The Myocardium And Its Blood Supply

(To be completed, Q4, 2024)

6.2.3.1Anatomy and Function

(To be completed, Q4, 2024)

6.2.3.2 Myocardial Infarction

(To be completed, Q4, 2024)

6.2.3.3 Pharmaceutical options

(To be completed, Q1, 2025)

6.2.3.4 Cell therapy

(To be completed, Q1, 2025)

6.2.3.5 Gene therapy and gene editing

(To be completed, Q1, 2025)

6.2.3.6 Interventions in coronary arteries

(To be completed, Q1, 2025)

6.2.3.6.1 General schemes

(To be completed, Q1, 2025)

6.2.3.6.2 Angioplasty and related techniques

(To be completed, Q1, 2025)

6.2.3.6.3 Intravascular stents

I start here with a contribution from the History of Medicine in Sonnets

> Backstory
>
> As discussed elsewhere in this collection, coronary artery disease (CAD) has been the leading cause of morbidity and mortality in developed regions for many years. Since coronary artery replacement techniques are thoroughly invasive, there has been a sequence of innovations aimed at minimally invasive therapies. Dr. Andreas Gruentzig, a German cardiologist, whose work was based on that of the American Charles Dotter, performed the world's first coronary angioplasty on an awake human in 1977; in this he expanded a short section of the left anterior descending artery, that had 80% stenosis. Whilst this was a revolutionary step, the elastic recoil of the arteries and the formation of a neointima caused re-stenosis within six months in 30% of cases.
>
> The stage was therefore set for the introduction of the 'stent', a device that could be left inside the artery to maintain patency. The origin of this word is unclear, some believing it was based on an earlier invention by an English dentist, Dr, Charles Stent who designed apparatus for taking dental impressions, while others believe it

was derived from an old Scottish term Extentus, to extend or stretch. Various so-called bare-metal stents were invented and patented in the middle 1980s, including those of Sigwart and Palmaz. These, however, did not totally solve the problem, as restenosis, the in-stent re-stenosis, still occurred in a finite number of patients. The next development was the drug-eluting stent, where a powerful agent (such as a chemotherapeutic agent was attached to, and eluted from, the stent surface, their anti-proliferative properties reducing the hyperplasia.

Stretching Extentus

Some people like a plaque, maybe on a wall
To show to others what their life's about
Plaque on a wall in the heart may forestall
All future life and hope, as time runs out.
Keep the channels open, inflate balloons
But borrowed time it is, as vessels recoil
Need stronger stuff in there, just read the runes
Stretch the vessel, leave behind metal coil
Stents these were named, but why, we're not so sure
When naked they were good, but not for long
Need drugs to keep awake, failure abjured
Stopping proliferation can't be wrong
Some years on, patents galore won and lost
Stents stretching our futures, no little coct

David Williams, *Stretching Extentus, From 'A History of Medicine in Sonnets',* Unpublished, 2020

(To be completed, Q1, 2025)

6.2.3.6.4 Coronary artery by-pass

I also start this section with a poem from The History of Medicine in Sonnets

Backstory

Angina pectoris, the clinical manifestation of myocardial ischaemia, was described in some detail, and given its name, by William Heberden in 1772. It is a consequence of coronary artery disease (CAD), which is now prevalent on an almost global scale. For the first 50 years of the twentieth century, many physicians and surgeons offered theories and experimental techniques to treat CAD, including Alexis Carrel, Claude Beck and Arthur Vineberg, the latter using ligation of the right internal mammary artery to increase blood flow to the coronary circuit. A major advance was made with the direct coronary anastomosis of the left internal thoracic artery to the left anterior descending artery (LAD) to enhance this flow.

A major difficulty related to the inability to picture the coronary arteries. This was resolved in an accidental manner when Mason Somes inadvertently injected a contrast dye into the right coronary artery of a patient; this was in the Cleveland

Clinic in 1958. The technique of coronary angiography resulted from this error, and this had a major impact on the treatment of CAD. Many surgeons were able to capitalize on this, including Michael DeBakey in Houston who grafted a saphenous vein onto the LAD in 1964. Most would agree that real progress was not really made until Rene Favaloro, an Argentinian surgeon working at the Cleveland Clinic perfected the use of the saphenous vein graft using by-pass surgery and end -to-end anastomoses, in the late 1960s. This technique of coronary artery by-pass surgery (CABG) was used in hundreds of thousands of patients in the following years. The technique soon become known by the 'Cabbage' derivative of its acronym.

Cabbages in the OR

Angina pectoris, the frightening
Chest pain, as coronary arteries
Denuded of blood are not nourishing
Heart muscles, too weak, too many pastries
And foods of fats, no oxygen for life
Death awaiting those who ignore the signs
If only we had new parts, and a knife
A stich, to cut and paste, a new design
Take a vein from your leg, will do just fine
The angiogram says where it should go
Single or quadruple, get it in time
Add twenty more years, and the blood will flow
A coronary artery by-pass
Cabbages for short, fittest of the class

David Williams, *Cabbages in the OR, From 'A History of Medicine in Sonnets',* Unpublished, 2020

(To be completed, Q1, 2025)

6.2.3.6.5 Tissue engineered coronary arteries

(To be completed, Q1, 2025)

6.2.4 Heart Valves

(To be completed, Q1, 2025)

6.2.4.1 Anatomy and Function

(To be completed, Q1, 2025)

6.2.4.2 Valve Diseases

(To be completed, Q1, 2025)

6.2.4.3 Aortic Valve Surgical Replacement

(To be completed, Q1, 2025)

6.2.4.4 Aortic Valve Transcatheter Replacement

(To be completed, Q1, 2025)

6.2.4.5 Mitral Valve Replacement and Repair

(To be completed, Q1, 2025)

6.2.4.6 Pulmonary and Tricuspid Valves

(To be completed, Q1, 2025)

6.2.4.7 Tissue Engineering Heart Valves

6.2.5 Arrhythmias

One of the poems fromA history of medicine in Sonnets is relevant here:

> Backstory
>
> Dr. Mark Cowley Lidwell, a physician and anesthetist at the University of Sydney, Australia, started work on a machine that could apply an electric current to resuscitate neonates who presented with asystole. His first patient was treated in 1926 using a transcutaneous needle and mains electricity. This achievement received much attention but did not gain acceptance clinically; nor did the efforts of Albert Hyman in New York and Wilfred Bigelow in Toronto over the next two decades. It was not until the 1950s that the technique, which became known as cardiac pacing, came into prominence.
>
> Dr. Paul Zoll, a Boston physician and electrophysiologist, started work on an external pacemaker in 1950, and over the next few years successfully used his devices to resuscitate a variety of patients with heart block. These devices were rather cumbersome and stimulation was painful, requiring sedation. Dr. C. Walton Lillehei, cardiothoracic surgeon in Minnesota, and engineer Earl Bakken worked on alternative technologies, sewing pacemaker leads directly onto the myocardial surface, pulling these leads through the skin for connection to an external pacemaker. Bakken, who went on to found the Medtronic company, developed the battery powered pacemaker but this still required transcutaneous access. It was the Swedish physician and biomedical engineer, working at the Elema-Schonander company that developed and used the first fully implantable pacemaker in the late 1950s. There have been many refinements of this technology over

the years, especially with the transvenous pacing technique developed by Dr, Seymour Furman, and the lithium – iodine battery introduced by Wilson Greatbach, and today some 600,000 pacemakers are implanted annually world-wide.

Pacing Leads to Victory

Jumping frogs of Luigi Galvani
Evinced animal electricity
Muscles still twitching way down the valley
Of death, elegant synchronicity
As applied to the beating of the heart
Nature signals the myocardium
Atria and ventricles play their part
But when volts are curbed, replacement paths hum
Half-century of research around the world
Led to Boston, an external pacemaker
Stimulated rhythms and life unfurled
Then devices implanted, much smaller
Batteries and leads for a lifetime's charging
Controlled power keeps those muscles pulsing

David Williams, *Pacing Leads to Victory, From 'A History of Medicine in Sonnets',* Unpublished, 2020

6.2.5.1 Clinical Scenarios

(To be completed, Q2, 2025)

6.2.5.1 Pharmaceutical Options

(To be completed, Q2, 2025)

6.2.5.3 Cardiac Pacing

(To be completed, Q2, 2025)

6.2.5.4 Defibrillation

(To be completed, Q2, 2025)

6.2.5.5 Other technologies

(To be completed, Q2, 2025)

6.2.6 Total Heart Failure

(To be completed, Q2, 2025)

6.2.7 Major Circulatory System

(To be completed, Q2, 2025)

6.2.7.1 Atherosclerosis

(To be completed, Q2, 2025)

6.2.7.2 Aneurysm

(To be completed, Q2, 2025)

6.2.8 Microvasculature

(To be completed, Q2, 2025)

6.2.9 Blood Transfusions and Blood Substitutes

(To be completed, Q2, 2025)

6.2.9.1 The Essential Enigma that is Blood

Replacement, or supplementation, of blood may seem to lie at the extreme end of the definition of 'reconstruction of the body' but I think that it is an appropriate inclusion. Within the Christian religions, of course, the blood and body of Christ were inseparable (Matthew 26: 26-28: '*As the disciples sat together, Jesus said, 'Take it and eat it, for this is my body'. He then gave thanks and offered them the cup and said, 'Each of you drink from it, for this is my blood, which seals the covenant between God and his people*.'). The human body needs, and is acutely dependent on, oxygen and blood, and especially uses the latter to deliver the former to all of its constituent parts; vascularization is a key factor in many reconstructive procedures, as noted throughout this book and it would be perverse, I believe, not to consider the role of blood here.

As we shall see in this section, blood is an enigma, albeit an essential one. Rapid blood loss can be fatal, such that medical attention to this phenomenon should have been a priority since the dawn of the profession. However, blood is such a complex liquid that it has proved virtually impossible to replicate. Biochemically it is well understood, but that hasn't helped much. Blood has an important place in Chinese medicine, blood (xue) and qi, life force, being two interrelated vital substances considered to

control yin-yang systems; qi-xue interactions are implicated in current Traditional Chinese Medicine[1], but practical consequences are difficult to identify. In Ayurvedic medicine, blood was recognized as critical but, although invasive procedures were developed millennia ago for many conditions, treatment of disorders of the blood were not included. As mentioned by Valiathan[2] the only direct practices were those of blood letting (Rakta visravana, in Sanskrit), using forms of venesection or leeches, for the treatment of inflammatory and other diseases.

In many ancient civilizations, the removal of blood was far from therapeutic, as many of them used human (and animal) sacrifices in order to please or feed gods and deities. Even with more structured groups within the last millennium, such as the Aztecs in South America, regular sacrifice of human blood and delivery to the gods allowed life to continue; this, and many other aspects of the historical and current implications of blood, especially sacrifices and transfusions, have been recently discussed by Garraud and Lefrere in an exceptionally good essay[3]. Aztec theology justified ritual human sacrifice through consideration of human bodies as having two selves, a shell and a divine spark. The gods and the universe needed to be regenerated through the sacrifice and release of the divine sparks within the bodies of humans. Blood is one of the carriers of this divine spark; perhaps not too different to the xue in China, or one of the four humors (along with yellow bile, black bile and phlegm) in Egyptian and Mesopotamian medicine.

There is one modern application of blood-letting, which I know personally very well. The genetic condition of hemochromatosis is associated with dysfunction of iron metabolism and in particular results in the accumulation of ferritin in the body, with significant effects on the liver. I have such a condition, the only therapy for which is regular venesection (or phlebotomy). For over 35 years I have had a blood-letting session every few months, wherever I am in the world. It is an interesting paradox that in most jurisdictions this blood has to be discarded as medical waste and cannot be used for transfusion.

Blood has therefore played a central role in the spiritual and mythological aspects of medicine without really giving away its secrets. This may be best seen with the concept of the Holy Grail, which is usually identified as the cup that Jesus drank from at the Last Supper and which Joseph of Arimathea used to collect his blood when he was crucified. It became an important theme in King Arthur, as a divine object in the early 12th century romantic poems of Chrétien de Troyes and in the poem "Joseph d'Arimathie," by Robert de Boron who claimed the holy grail's origins at the Last Supper and Christ's death. Some scholars believe that the holy grail is not entirely mythical, and that Joseph of Arimathea took it to Glastonbury. The water runs red where he buried the grail, running through Christ's blood. The Knights Templar are also said to have seized the holy grail from Temple Mount during the Crusades. There is no better enigmatic analogy to blood than the holy grail.

Perhaps not surprisingly, blood, as this enigmatic substance, whose only visual attribute is its vivid red color, has not figured much in art and literature. There are plenty of simple poems about the gory aspects of injury and the loss of blood, but few about the blood itself. William Butler Yeats did contribute a few of the better ones:

[1] Yao W, Yang H and Ding G, Mechanisms of Qi-blood circulation and Qi deficiency syndrome in view of blood and interstitial fluid circulation, *Journal of Traditional Chinese Medicine,* 2013;33(4):538-44. doi:10.1016/s0254-6272(13)60162-4.

[2] Valiathan MS, *The Legacy of Susruta*, Orient Longman, Hyderabad 2007.

[3] Garraud O and Lefrere J-J, Blood and blood-associated symbols beyond medicine and transfusion: far more complex than first appears, *Blood Transfusion* 2014;12:14-21, doi:10.2450.2013.0131-13.

In tombs of gold and lapis lazuli
Bodies of holy men and women exude
Miraculous oil, odour of violet.
But under heavy loads of trampled clay
Lie bodies of the vampires full of blood;
Their shrouds are bloody and their lips are wet.

William Butler Yeats, *Oil and Water*[4]

6.2.9.2 Blood Substitutes

Also not surprisingly, the need for a supply of blood to replace that lost in trauma or surgery has provided a significant stimulus for innovation in medical science. The complexity discussed above, however, has powerfully inhibited progress. Supplementation of blood was attempted in the sixteenth century, The British doctor Richard Lower experimented with dog-to-dog transfusion, with occasional success, and even tried lamb – to - human transfer, although such procedures were soon outlawed. The Frenchman Jean-Baptiste Deny, physician to King Louis XIV also performed sheep – to – human transfusions at that time. These procedures were abandoned since they usually produced death of the donor, which tended to dissuade use in human-to-human transfusion.

Figure 6.1,Transfusion of blood from lamb to human, 16th Century

Since the existence of blood groups was not discovered until 1901[5] it is understandable that many attempts at blood transfusion during the 18th and 19th centuries resulted in fatalities[6]. Because of this there were numerous attempts to use other fluids (some biological such as milk and urine) over the years. Milk was the most popular, the first recorded attempt being in 1854 in Toronto, when it was assumed that fatty particles in milk would be transformed into 'white corpuscles'. As with blood transfusion, these occasionally did not kill the patient, but usually they did.

[4] William Butler Yeats, *Oil and Water,*
[5] Landsteiner K (1901). *Ueber Agglutinationsersche inungen normalen menschlichen Blutes*. Wien. Klin. Wschr. 14, 1132.
[6] Farhud DD and Zarif Yeganeh M, A brief history of human blood groups, *Iran Journal of Public Healt*h 2013;42(1):1-6.

Blood typing and cross matching between donors and patients remarkedly improved success with transfusions in the early twentieth century. This was further enhanced by the observation of Adolph Hustin in Brussels in 1914 that sodium citrate could inhibit clotting of the blood during collection and the work of Richard Lewisohn in New York on the practical aspects of transfusion processes. Development of these technologies, including the use of PVC bags for storage, and screening methods to avoid disease transmission over the next several decades led to the establishment of successful national blood banks across the world.

Nevertheless, the availability of donated blood, both with respect to the willingness of altruistic donors and the limited shelf life of stored blood, has encouraged the search for synthetic or artificial blood substitutes[7]. This is, of course, not a trivial matter since such a substitute should have the functional attributes of the ability to transport oxygen and carbon dioxide and an extended half-life in the circulation but ultimate total excretion, while avoiding the negatives of the need for cross-matching and blood typing, potential contamination and infectivity, toxicity, biopersistence and accumulation in tissues, immunogencity and carcinogenicity. It would also be helpful if storage was convenient and the whole process was cost-effective.

The fact is that this search has not been very rewarding. Two possibilities have been extensively evaluated, perfluorochemical - and hemoglobin- based substitutes.

6.2.9.2.1 Perfluorochemicals

Perfluorochemicals (PFCs) were shown to be capable of carrying oxygen back in 1996[8]. PFCs have the generic formula C_nF_{2n+2} and may have either straight or cyclic hydrocarbon chains. From the beginning they possessed some disadvantages, including the fact that they are not metabolized in the human body and are insoluble in aqueous phases such they have to be solubilized using an emulsifying agent before application. There were many positively-looking papers on these materials for quite a while[9], and even 'second generation' versions were introduced[10] but clinically safe products have been elusive, and several clinical trials stopped because of adverse events.

6.2.9.2.2 Hemoglobin-based Substitutes

The main alternatives to PFCs have been those derived from hemoglobin[11]. Several chemically or genetically engineered hemoglobin oxygen carriers (HBOCs) have been developed, including human and animal derived substances and recombinant varieties. Genetic or chemical modifications have been aimed at stabilizing the hemoglobin molecule in tetrameric or polymeric form and improving oxygen carrying capacity. Yet problems remain, with several adverse effects reported in clinical trials; these effects include cardiac and renal injury, pancreatic and liver enzyme elevation, gastrointestinal problems and

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[7] Moradi S, Jahanian-Najafabadi A and Habbi-Roudkenar M, Artificial blood substitutes: First steps on the long route to clinical utility, *Clinical Medicine Insights: Blood Disorders* 2016;9:33-41, doi:10.4137/CMBD.S38461.

[8] Clark LC and Gollan F, Survival of mammals breathing organic liquids equilibrated with oxygen at atmospheric pressure, *Science* 1966;152(3730):1755-6. doi: 10.1126/science.152.3730.1755.

[9] Lowe KC, Perfluorinated blood substitutes and artificial oxygen carriers, *Blood Reviews* 1999;13(3):171-84. doi:10.1054/blre.1999.0113.

[10] Riess JG and Blanc ML, Solubility and transport phenomena in perfluorochemicals relevant to blood substitution and other biomedical applications, *Pure and Applied Chemistry, 2*013;54(12):2383-1406. doi:10.1351/pac198254122383.

[11] Alayash AI, Mechanisms of toxicity and modulation of hemoglobin-based oxygen carriers, *Shock* 2019;52(1S):41-9. doi:10.1097/SHK.0000000000001044.

transient hypertension. Even though increasingly sophisticated techniques, including those of nanotechnology such as liposome delivery, are under development, no system has yet been approved by the FDA in the USA.

I have written a sonnet to reflect on these issues:

Enigmatic Blood

Ayurvedic sages were very smart
Flesh and blood, treat the flesh, but let the blood
To avoid the pressure on organs and heart
Thicker than water, better than mud
Corpuscular fluid, nowhere repeated
Newtonian movement through fissures and valves
Nourishing tissues, from standing to seated
Heals the injured, as God's own salve
Redress the redness, alveoli exchanges
Globulins, like goblins, power immunity
Phages, as pages turn over the dangers
Sanguineous liquid deals all with impunity
No man-made solution can ever claim
The enigma of crimson, the eternal flame

David Williams, *Enigmatic Blood, Unpublished poem, 2020*

6.3 THE MUSCULOSKELETAL SYSTEM

6.3.1 Muscles

(To be completed, Q2, 2025)

6.3.1.1 Cardiac

(To be completed, Q2, 2025)

6.3.1.2 Smooth

(To be completed, Q2, 2025)

6.3.1.2 Skeletal

(To be completed, Q2, 2025)

6.3.2 Bones

(To be completed, Q2, 2025)

6.3.2.1 Appendicular skeleton

(To be completed, Q2, 2025)

6.3.2.2 Axial skeleton

(To be completed, Q2, 2025)

6.3.3 Joints

(To be completed, Q2, 2025)

6.3.3.1 Synarthrosis

(To be completed, Q2, 2025)

6.3.3.2 Diarthrosis

(To be completed, Q2, 2025)

As an introduction to the clinical examples of joint replacement, I include a poem from the History of Medicine in Sonnets; I should add that Professor Sir John Charnley carried out his groundbreaking work on the hip in Wrightington Hospital, which was not far from Liverpool. Without claiming to have a close relationship with him, we did talk of arthroplasty materials now and then; his over-riding objective was to provide treatment for the old ladies in Lancashire towns, who we so disabled by osteoarthritis.

> Backstory
>
> John Charnley, later Professor Sir John Charnley, was an orthopedic surgeon based in the north-west of England, spending much of his career at Wrightington Hospital, just outside Manchester. He initially specialized in the treatment of fractures but soon turned his attention to osteoarthritis, especially of the hip. Although in early days he favored treatment by arthrodesis, that is by producing fusion in the hip joint, he soon saw the potential of arthroplasty, that is the replacement of the diseased joint by a structure that would permit complete movement. There had been attempts to use hemi-arthroplasty, replacing just one side of the joint, but this had serious limitations. Although it is fair to say that Charnley was not the first to replace hips by a total arthroplasty, a few others using all-metal structures, he had the vision to develop replacement joints that mimicked the natural joint as far as possible. He noted that the hip joint has a remarkably low coefficient of friction, and he assumed that he could replicate this with a low friction plastic, such as the recently invented Teflon, or poly(tetrafluoroethylene), PTFE. He also developed the concept of using an acrylic ‘bone cement’ to attach prosthetic components to the remaining bone of the femur and pelvis.

Charnley's experience involved a combination of significant setbacks and remarkable success, a classic example of 'if at first you don't succeed, try, try again'. The PTFE did not work well, as it wore-out fast leaving significant bone destruction behind. He turned to a special type of polyethylene, which is still used, in modified form, today. Several early patients died on the operating table because of the toxicity of the acrylic, and he and his anaesthetists had to develop new procedures. Infection was a major problem, so he developed new anti-bacterial operating techniques. Almost all of the world's hip replacement devices used today are derivatives of the Charnley prosthesis, and very few surgeons are capable of achieving his success rates, once he had solved the early problems. His vision was to restore pain-free movement to the many older people, especially women, who he would see every day in his clinic; many people around the world today are grateful for that vision.

Sir John's Materiel,

He stood and watched old women from the shires
Hobbling, nay crying their way to his room
Bone upon grating bone, hip joint on fire
Seeking an answer, not a witch's broom
Nature's perfect, near frictionless couple
Synovia glide over each other
Hips rotate and revolve, when young and supple
Till the grind of aging defeats this mother
He cut through the thigh bone, leaving a gap
Reamed a socket in the pelvic domain
Polished steel for the femur, a new cap
His own fine plastic, cemented his name
Sir John's rightly receiving of the fame
Movement, slow but no pain, up-stairs again

David Williams, *Sir John's Materiel, From 'A History of Medicine in Sonnets', Unpublished, 2020*

(To be completed, Q3, 2025)

6.3.4 Tendons and Ligaments

(To be completed, Q3, 2025)

6.3.5 Teeth

One of the major successes in implant surgery was that of the replacement of teeth, pioneered in the Swedish city of Gothenburg;

Backstory

The biblical expression ‘An eye for an eye, tooth for a tooth’ has been frequently misquoted and abused, but taken literally, the last part of the phrase has been the ultimate objective of the dental profession for many years. For a long time, attempt were made to transplant teeth, from willing or unwilling donors, and some were successful for a short while, but the lack of a reliable, long-lasting, independent, tooth replacement has meant that dentists have had to use a tool-bag of metals, ceramics, plastics and composite to patch up diseased teeth or structures such as bridges and dentures that try to mimic the functionality of teeth. The main difficulty that arises when attempts are made to provide a tooth replacement that is fully integrated into the facial skeleton, is that the natural tooth is attached to the bone of maxilla or mandible *via* a thin layer of an exquisitely functioning shock-absorber, the periodontal ligament, that allows force transmission and provides stability to the tooth-bone complex. Simply inserting an artificial tooth into a socket without either providing an equivalent ligament or producing direct and permanent attachment to the bone, will result in failure.

The Swedish professor of anatomy, Per-Ingvar Brånemark was investigating the response of rabbit bone (in the legs) to various substances, and found that the metal titanium rapidly and strongly bonded to the bone. This was in the mid 1960’s and he realized that this could be of clinical relevance. Working with dental colleagues, he designed a dental implant made of this same titanium that could, provided great care was taken during insertion, and provided that too much force was not applied to the structure during the healing phase, result in permanent attachment. He called this process ‘osseointegration’ and this is the principle that revolutionized dentistry, with close to a million patients being treated each year.

Integration in Gothenburg

Visits to dentists rank up with the worst
Experiences that most people had
Root canals and carious crowns were cursed
Bleeding gingivae both messy and bad
Fillings, crowns, bridges, the tools of the trade
How simpler it would be, tooth for a tooth
An argument the bone was too afraid
To accept metal, too far from the truth
A doctor from Sweden showed us the way
The alveolus loves titanium
Plant carefully, treat well, it will stay
Integration, the coveted premium
Millions of patients now have brighter smiles
Swedish crowns stronger and healthy in style

David Williams, *Integration in Gothenburg, From ‘A History of medicine in Sonnets’, Unpublished, 2020*

(To be completed, Q3, 2025)

6.4 CENTRAL AND PERIPHERAL NERVOUS SYSTEMS

6.4.1 Brain

(To be completed, Q3, 2025)

6.4.2 Spinal Cord

(To be completed, Q3, 2025)

6.4.3 Peripheral Nerves

(To be completed, Q3, 2025)

6.5 SENSORY ORGANS

6.5.1 Eyes

(To be completed, Q3, 2025)

6.5.1.1 Vision Correction

(To be completed, Q3, 2025)

6.5.1.2 Cataracts

Backstory

Cataracts are areas of protein deposition within the eye that lead to increasing cloudiness and blurring of vision. Although they may involve genetic factors, or be associated with certain diseases such as diabetes, or with life-style matters such as smoking, they are essentially a consequence of ageing. Until the late 1940's, the end stage of cataract treatment was simple removal of the affected lens and 'correction' of vision by eye-glasses. Around 1946, Harold Ridley, an ophthalmologist in London, considered the possibility of replacing the lens with a pieced of transparent plastic. He had observed that RAF pilots in the second world war often sustained eye injuries because of shattered cockpit windows, and fragments of the plastic material used for these structures, made of polymethylmethacrylate (usually known as Plexiglas or Perspex) remained in the eye and were well tolerated. He arranged for lenses to be made from this material, and the Intraocular Lens was introduced into ophthalmological practice. By 2020 over 20 million IOLs were being implanted annually, with a market size of around $5 billion. The technique of implantation was improved by the introduction of phacoemulsion, that simplified and enhanced lens removal, by the use of foldable silicone lens that allowed for insertion through

smaller incisions, and by the development of specialized implants for use in astigmatism and other rarer conditions. Today, in excess of 95% of treated patients have remarkably improved vision through the use of the IOL.

Opaqueness of Ageing,

Forgive the cliché, eyes are a window
Out of which we see all around, we take
This for granted, till age muddies the glow
As the lens becomes cloudy, then opaque
Like church's stained glass, slowly vitrifies
And cataracts disturb the flow of light
Eyes being surrogates for our body's demise
Can we reverse the trend, restore the sight?
Emulsify the cloud, remove the blur
A rolled implant through a slit is placed
Unravels in the capsule, vision clear and pure
A new lens, advancing blindness replaced
In so many people, this plastic pane
Darkness becomes lightness, a window again

David Williams, *Opaqueness of Ageing, From 'A History of Medicine in Sonnets' Unpublished, 2020*

(To be completed, Q4, 2025)

6.5.1.3 Glaucoma

(To be completed, Q4, 2025)

6.5.1.3 Retina

(To be completed, Q4, 2025)

6.5.1.5 Eye Prostheses

(To be completed, Q4, 2025)

6.5.2 Ears

6.5.2.1 External Ear

(To be completed, Q4, 2025)

6.5.2.2 Hearing Aids

(To be completed, Q4, 2025)

6.5.2.3 Middle Ear

(To be completed, Q4, 2025)

6.5.2.4 Cochlear

Backstory

The history of the cochlear implant is confusing and, in contrast to many other items in this series, it is difficult to pinpoint any one event or inventor that unequivocally marks the birth of this particular medical technology. The cochlear implant is intended to apply electrical stimulation to the ear in order to produce the sensation of sound. The implant bypasses damaged parts of the ear to deliver sound signals to the auditory nerve. They have a sound processor behind the external ear which captures the signals and sends them to a receiver implanted under the skin. This receiver sends the signals to electrodes implanted in the cochlea within the inner ear. These signals stimulate the auditory nerve, directing them to the brain. Early attempts to create a sound simulating system date back to the mid-nineteenth century, but it was a French team (Djourno and Eyrès) that were the first to implant a device in 1957. It was several years before the next steps were taken, by House and Doyle in Los Angeles; a series of arguments about patents and inventors, and the less-than-successful outcomes, delayed widespread endorsement of this technology, which did not happen until Graeme Clark implanted the first multi-electrode hearing prosthesis, in Melbourne, Australia in 1978, which was commercialized by the Cochlear company.

One of the most profound consequences of the invention and clinical application of the cochlear implant concerns the use of device in young children who are born with profound deafness. There are strict guidelines on this use (it was approved by the FDA in the USA in 1990) since the child has to be of the right age for maximal benefit, and the involvement of child psychologists, speech therapists, audiology professionals and many others is essential. It is a remarkable experience to watch a two-year old child, up to then without hearing, listening to sounds for the first time in their life, with the help of a cochlear implant.

Sounds After Silence

A beautiful child born, smiles all around
Soon sees, gurgles, moves fingers and toes
But through its ears, no parent's coos, no sound
Reaches the brain, no friendly ahs and ohs
The fetus forgot this critical probe
No auditory nerve to take signals
To cochlear and temporal lobe
No hearing, just deafness to calls
A device now replaces natures part

Mic, processor, transmitter, receiver
Enter sound waves and pulses depart
Towards the cortex, the brain's vibrator
Take that child, who has never heard before
And carefully control its behavior

David Williams, *Sounds After Silence, From 'A History of Medicine in Sonnets, Unpublished, 2020*

6.5.3 Nose

(To be completed, Q4, 2025)

6.5.4 Mouth

6.5.4.1Tongue

(To be completed, Q4, 2025)

6.5.4.2 Salivary Glands

(To be completed, Q4, 2025)

6.5.4.3 Speech and Vocal Cords

(To be completed, Q4, 2025)

6.5.5 Skin and Hair

Backstory

During the First World War, new weapons such as heavy artillery, created battlefield injuries that had never been seen before. Shrapnel-filled shells caused immense damage in facial and head wounds. These injuries were not easily treated on the front line, and any emergency wound closure that was possible usually resulted in scarring and flesh tightening, which, along with massive tissue lost, pulled faces into a hideous configurations, leaving men unable to eat or drink, or even breathing normally. Into the horrendous hospital environment for the war-wounded back in England, came the New Zealander, surgeon Harold Gillies; he set up a special ward for facial wounds at the Military Hospital in Aldershot, and then at The Queen's Hospital where he was able to reconstruct wounded men's faces as fully as possible. This was the beginning of military plastic and reconstructive surgery.

Fast forward a quarter of a century. Another world war, fighting across and over the English Channel, more massive injuries, another New Zealander to the rescue, a cousin of Gillies. His name was Archibald McIndoe. He specialized in injuries to airmen, not men from the trenches. Their wounds were caused by exploding fuel tanks in their Spitfires; the same but different, burns not shrapnel, but horribly disfigured faces nevertheless. McIndoe pioneered plastic surgery for burns of the face, upper body and hands. He recognized, as had Gillies, the importance of social acceptance of these victims. His special hospital, in East Grinstead, became the focus of his experimental work with massive burns on his patients, the 'McIndoe's guinea pigs'. He personally talked to the townsfolk and urged them not to stare but embrace these guinea pigs, which they did very generously.

The Town That Did Not Stare

An injured fighter pilot walks into town
Not knowing their secret, himself he has none
Neither eyes, ears, nose or mouth of his own
Townsfolk can see, hear, talk to him as one
Of them; do not stare, just treat as normal
Asks McIndoe, surgeon extraordinaire
Who crafted new faces for those burned by fuel
Exploding in the sky, leaving lives all bare
These men, his 'guinea pigs' gave themselves
To his creative techniques and grafts
Returned to life and love at the front of shelves
Not back streets, disfigured, outcast on rafts
A Kiwi, he came from lands of white cloud
Dispersed dark clouds from all airmen he found

David Williams, *The Town That Did Not Stare, From 'A History of Medicine in Sonnets', Unpublished 2020.*

(To be completed, Q4, 2025)

6.6 URINARY SYSTEM

6.6.1 Kidney

(To be completed, Q4, 2025)

6.6.2 Bladder

(To be completed, Q4, 2025)

6.6.3 Ureter

(To be completed, Q4, 2025)

6.6.4 Urethra

(To be completed, Q4, 2025)

6.7 RESPIRATORY TRACT

6.7.1 Bronchus

(To be completed, Q4, 2025)

6.7.2 Lungs

(To be completed, Q4, 2025)

6.8 DIGESTION AND GASTRO-INTESTINAL SYSTEM

6.8.1 Liver

(To be completed, Q4, 2025)

6.8.2 Esophagus

(To be completed, Q4, 2025)

6.8.3 Stomach

(To be completed, Q4, 2025)

6.8.4 Small Intestine

(To be completed, Q4, 2025)

6.8.5 Large Intestine

(To be completed, Q4, 2025)

6.8.6 Rectum

(To be completed, Q4, 2025)

6.9 IMMUNE SYSTEM

6.9.1 Spleen

(To be completed, Q4, 2025)

6.10 ENDOCRINE SYSTEM

6.10.1 Pancreas

(To be completed, Q4, 2025)

6.11 ABDOMINAL CAVITY

6.11.1 Diaphragm

(To be completed, Q4, 2025)

6.11.2 Peritoneal Cavity

(To be completed, Q4, 2025)

6.12 REPRODUCTIVE SYSTEM

6.12.1 Penis

(To be completed, Q4, 2025)

6.12.2 Prostate Gland

(To be completed, Q4, 2025)

6.12.3 Testicles

(To be completed, Q4, 2025)

6.12.4 Vagina

(To be completed, Q4, 2025)

6.12.5 Womb

(To be completed, Q4, 2025)

6.12.6 Uterus

(To be completed, Q4, 2025)