

Chapter 1

Evolution of Allograft Transplantation

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Introduction

To everyone who reads this book and endeavours to master the operation of a tissue bank, it is important to first understand the history behind bone and skin allograft transplantation.

The history of bone and skin allograft is replete with controversies due to the radical nature of the procedure in earlier times. Understandably, the act of transferring bone or skin from one person to another invited much public contention on social, ethical and religious grounds. The many works to advance the field of allograft transplantation were likewise, often frowned upon by the public and the medical authorities (Bradley and Hamilton, 2001). Furthermore, considering the dearth of knowledge on the subject in the past, failure of a study was as much an outcome as success. It is therefore not beyond our imagination to understand how these factors would have deterred the progress of allograft transplantation in earlier times.

At other times, however, events served as impetus to the progress of allograft transplantation. World War II, for example, resulted in large numbers of casualties. Losses of bone, fractures or burn wounds in victims of the War compelled surgeons of their time to come up with methods to repair these defects (bone-grafting and bone-transplantation; Lancet, 1918). Indeed, necessity is the mother of invention.

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Regardless of circumstances and public opinion, the pioneers have undertaken research to shed light on allograft techniques and their significance in the realm of medicine. Their motivation for doing so would perhaps be aptly expressed by Gaspare Tagliacozzi of Bologna (1546–1599), pioneer of the autologous procedure known as the “Forearm Flap”. He wrote, “We reconstruct and complete parts which nature had given but which were destroyed by fate, and we do so, not so much for the enjoyment of an eye, as for psychic comfort to the afflicted” (Ben-hur and Converse, 1980; Ang, 2005).

The Early Miracles of Transplantation

The early history of transplantation was marked by accounts of transplantation that carried with them an element of wonder. One such famous account was that of the legend of Saints Cosmas and Damian. Born in the third century as sons of a physician, these two Christian Arab twins became physicians and practiced the art of healing across Turkey, Rome and Greece, all the while providing their services for free. They were subsequently martyred in 287 AD during the persecution of Christians by the Emperor Diocletian and were buried in their hometown of Egea. Two centuries later, in ancient Rome, the Deacon Justinian was so exhausted by the pain from his ulcerated leg that he fell asleep during his prayers. In his dream, the twin physicians came to him and replaced his diseased leg with that from a recently deceased Moor (Julien *et al.*, 1987; Rinaldi, 1987; Mankin, 2002; Mankin *et al.*, 2005). The successful transplantation, later called the “black leg miracle”, has since been depicted in many paintings (Fig. 1) and decorations in religious manuscripts.

History of Skin Allograft Transplantation

The practice of skin grafting originated in India — as described in the *Sushruta Samhita* (ca. 600 BCE) — for the purpose of nasal reconstruction. The mutilation of the nose was rampant as a form of punishment in the past and this necessitated skin grafting for the repair of the mutilated nose (Sushruta, 1907; Nichter *et al.*, 1983; Ang, 2005). With time, the applications of skin grafting evolved to include reconstruction after



Fig. 1. Saints Cosmas and Damian performing the “miracle of the black leg”. This painting is attributed to Master of Los Balbases, Burgos, Spain, c. 1495. Reproduced from the Wellcome Institute Library, London (reference L0014276).

surgery, treating patients with burn wounds and patients with epidermolysis bullosa, treatment of chronic ulcers, and hair restoration to areas of hair loss (Herman, 2002).

The early recorded attempts at skin transplantation were made by Branca de Branca, an Italian, who in 1442 AD, employed the binding of the patient’s arm to the site of skin graft to transplant a slave’s nose to his master’s. While Branca pioneered the use of surgical flap for nasal reconstruction, credit went to his compatriot, Gaspare Tagliacozzi, instead. (Davis, 1941; Herman, 2002).

Tagliacozzi’s work came over a hundred years later, and was described in his publication *De Curtorum Chirurgia per Institutionem* (*Surgery of the Mutilated by Grafting*) in 1597. The procedure, called the “Forearm Flap”, was likewise used for nasal reconstruction using a graft

harvested from the inner arm. The difference between the work of Tagliacozzi and Branca, however, was that the former's technique was autologous, whereas the latter's was allogenic. Unfortunately, this difference was not apparent to the many intellectuals of the 17th and 18th century who despised Tagliacozzi's work. Many satirical stories about the use of noses from slaves were propagated. The Church was also against such work and hence exhumed Tagliacozzi's body from its burial site lest it desecrate the holy ground (Koch, 1941; Gina, 2005). It is therefore ironic when we learn that Tagliacozzi was himself against the idea of using allografts because of considerations about the "force and power" of the individual. It would be another 400 years before this "force and power" was to be recognised as a major biological phenomenon (Phillips, 1998).

The First Skin Allograft

In 1869, Jacques-Louis Reverdin (1842–1929) of Switzerland performed the first skin allograft transplantation with the use of epidermal grafts, otherwise known as split thickness skin grafts (Reverdin, 1869). He described this technique during a meeting of the Société Impériale de Chirurgie during the same year (Freshwater and Krizek, 1978; Ang, 2005) and was hailed as the father of skin transplantation due to his work in this area (Hauben, 1985; Ang, 2005).

In 1871, the Englishman George Pollock (1897–1917) introduced the idea of treating burns patients with epidermal grafts. He purportedly donated small pieces of his own skin and used it together with skin from the patient in the treatment process (Pollock, 1871; Freshwater and Krizek, 1978; Herman, 2002). His first patient was an 8-year-old called Anne T, who had severe burns on her thighs from having caught fire on her dress (Freshwater and Krizek, 1971; Ang, 2005).

A year after, in France, Louis Xavier Édouard Léopold Ollier (1830–1900) reported the successful transplant of skin using the entire epidermis and a portion of the dermis (Ollier, 1872). In the United States, John Girdner (1881) described the first allograft skin transplantation using skin from a human cadaver (Herman, 2002). Girdner procured skin from the inner thigh of a young German boy within 6 hours of his death and transplanted the skin onto the shoulder blade of a 10-year-old boy

who had been struck by lightning (Obeng *et al.*, 2001). And in 1886, following Thiersch's method of removing split-thickness grafts, the use of new and improved skin grafting methods spread (Phillips, 1998).

The Discovery of Immunogenicity

The progress of skin allograft techniques and applications made a significant impact on the treatment of skin and burns patients. However, it was observed that all allografts, despite starting out well initially, would ultimately fail to integrate into the recipient's body. The concepts that explained the loss of grafted tissue were still unknown at that time. It was not until 1920 that the experiments of Emile Holman in Baltimore hinted at the first signs of what would become the concept of rejection. Holman, a surgeon at John Hopkins, transplanted the skin of a mother onto a badly burnt child. The subsequent grafting of more skin onto the child a few days later resulted in the inflammation of both the mother and the child's own skin. The implications of immunogenicity from this experiment, though noted by Holman, were not fully explored at that point of time (Holman, 1924; Hakim, 1997).

In 1927, the German Karl Bauer performed a successful skin allograft between identical twins and the skin on the twins stayed on indefinitely. With our current knowledge of the mediation of the body's immune system, such a result is hardly surprising (Bauer, 1927; Lytton, 2005).

Yet it was only in 1943 that the physiology of graft survival was unravelled. World War II had resulted in many victims of the war, amongst them the sufferers of massive burns. After seeing a seriously burnt patient in an Oxford hospital, a young zoologist, Peter Medawar, became interested in the problems of skin grafting. Following the establishment of the Burns Unit at Glasgow, he was asked by the British Medical Research Council to collaborate with Glasgow surgeon Thomas Gibson to perfect skin grafting, and in doing so, discovered the "Second Set Response". When transplanting skin allograft onto a burnt patient, they observed the hastening of the rejection of a second set of allograft. Medawar returned to Oxford and experimented on rabbits (Tilney, 2000). He observed that when skin was transplanted from animal A onto animal B, the graft survived about 7 days. However, when the same transplantation

was carried out a second time, the graft was rejected in half that period. From this discovery, Medawar drew the link between the body's immune system and the rejection of grafted tissue (Gibson and Medawar, 1943; Hakim, 1997) and termed the rejection mechanism as "actively acquired immunity".

Further Developments

In 1944, Jerome Pierce Webster (1888–1974), a Professor of Surgery at Columbia University Hospital, described the use of refrigerated skin as a temporary dressing to treat burns patients (Webster, 1944; Herman, 2002). A few years later, in 1949, the first proper skin bank, the US Navy Skin Bank, was established (Trier and Sell, 1968; Herman, 2002). In that same year in England, a doctoral student Christopher Polge and his mentors Parkes and Smith discovered the way to preserve tissues for transplantation with cryopreservatives (Polge *et al.*, 1949; Herman, 2002).

The second half of the twentieth century marked even more developments in the application and understanding of skin allografts. Skin from human cadavers was used as biological dressings in burn patients. In 1958, Eade discovered the use of skin grafts in controlling surface wound infection (Eade, 1958; Herman, 2002). By 1968, cryopreserved skin was successfully used as skin allografts. (Cochrane, 1968; Herman, 2002) In 1971, O'Donoghue and Zarem described the stimulation of neovascularisation by skin grafts (O'Donoghue and Zarem, 1971; Herman, 2002).

In 1975, Rheinwald and Green developed a method of producing cultured epithelial sheets from human keratinocytes (Rheinwald and Green, 1975; Herman, 2002). Following this, in 1981, O'Connor reported the successful use of cultured epithelial autografts (CEA) (O'Connor *et al.*, 1981; Brychta *et al.*, 1994). However, as cultured epithelial autograft took a long time for culture, and cultured epithelial allograft was, in contrast, a readily available source for recipients, the latter became widely used as well (Matouskova *et al.*, 2002).

More recently, in 1993, Kirsner described the ability of skin allografts to release growth factors as well as to act as pharmacologic agents (Kirsner *et al.*, 1993; Herman, 2002). Fortunato Benaim and Alberto Bolgiani, both leaders in the realm of burn care in Latin America, also

reported in 1993 that skin allografts provided by tissue banks were routinely used in burns centre as a temporary cover for serious burn wounds (Bolgiani and Benaim, 1993; Bourroul, 2002).

From repairing mutilated noses to becoming an important means of wound care in burn patients, the field of skin allograft has witnessed a giant leap since Branca's time, and it will no doubt continue to be invigorated by the continuing research and development in this field.

History of Bone Allograft

The earliest work that demonstrated the viability of bone allograft was that by the Scottish surgeon and anatomist, John Hunter. In 1770, Hunter transplanted the spur of a cock into its comb. The spur, being an outgrowth of the tarsometatarsus, contained a solid mass of bone within it (Lancet, 1918). In 1771, Hunter described in his book, the *Treatise on the Natural History of the Human Teeth*, the successful reimplantation of a premolar that was lost through trauma. Thereafter, he conducted his famous experiments on the transplantation of human tooth into the comb of a cock. Hunter's work had intrigued others into conducting experiments on tooth transplantation. Unfortunately, those experiments often exploited the poor as donors and placed their lives at the mercy of infections, and hence abated in the latter half of the eighteenth century (Tilney, 2000).

The Problem of Osteogenesis

In the eighteenth century, the fate of allografts and their role in bone formation became of interest to many orthopaedic surgeons. A controversy over the science of osteogenesis — the formation of bone — had emerged following the opposing views of Duhamel and von Haller.

In 1739, Duhamel performed an experiment in which he implanted silver wires subperiosteally. Weeks later, he found that the wires were buried in bone and concluded that the periosteum had led to new bone formation (Duhamel, 1739). Duhamel went on in 1742 (Duhamel, 1742) and 1743 (Duhamel, 1743) to repeat and extend the madder feeding experiments of Belchier (Belchier, 1736a; Belchier, 1736b). He noted that

madder (the root of *rubria tinctoria* giving a red dye) stained only growing bone, and distinguished between two layers of the periosteum — a superficial supporting layer and a deep osteogenic layer, which he termed the “cambium layer” (cambium meaning a layer of cells between bark and wood) (Chase and Herndon, 1955; Bassett, 1962).

However, von Haller (1763), the professor of John Hunter, claimed the opposite: the periosteum was not osteogenic. According to von Haller, the periosteum merely acted as the support for blood vessels, and it was the exudation from arteries that caused osteogenesis (Chase and Herndon, 1955; Bassett, 1962).

The views of these two men soon led to two opposing schools of thought and formed the basis of the aptly named “Duhamel-Haller Controversy”. Hunter joined in the conflict and performed a number of experiments to substantiate his professor’s claim (Bassett, 1962). On the other hand, Heine (1836) described findings that lent support to Duhamel’s claim — he removed ribs subperiosteally and found that they grew back. However, it was Flourens (1842) who went a long way in settling the controversy when he conclusively showed that periosteum was osteogenic and was the chief agent in the healing of bone defects (Chase and Herndon, 1955).

In 1858, Ollier took what was arguably the first really scientific approach to tackle the problem of osteogenesis (Ollier, 1858; Chase and Herndon, 1955). Despite the lack of modern histological techniques or aseptic surgery, he performed comprehensive studies on the periosteum. Ollier’s experiments were published in two volumes entitled “*Traite Experimental et clinique de la regeneration des os*” in 1867. His conclusion was that transplanted periosteum and bone survived and could become osteogenic under proper circumstances. Additionally, Ollier believed that periosteum-covered transplants were the best bone grafts for use, and that the contents of the Haversian canals and the endosteum were also osteogenic (Chase and Herndon, 1955).

Owing to the thoroughness of Ollier’s work, his views remained almost indisputable for the following decades. Then in 1893, Barth, a student of Marchand, began to challenge those views with his numerous papers. By basing his work almost solely on replanted discs removed by trephine from the skull, Barth claimed that all transplanted bone, marrow

and periosteum would eventually die and be replaced by surrounding tissue, and that bone grafts were but a form of passive scaffolding. In response to this challenge, scores of papers were written by others to defend each side of the argument (Chase and Herndon, 1955).

Axhausen entered the debate with his thorough and scientifically rooted studies on osteogenesis and bone transplantation (Axhausen, 1907; Axhausen, 1909a; Axhausen, 1909b; Axhausen, 1909c). He showed that the survival and osteogenic property of the periosteum varied between different types of graft: they were highest in autografts; significantly less so in allografts and null in xenografts. He also believed that most of the periosteum would survive and lead to osteogenesis while the transplanted bone would die. Hence, like Ollier, Axhausen preferred bone grafts with attached periosteum. His evidence was so convincing that in 1908, Barth, influenced by Axhausen's findings and similar findings by others, rescinded his views and accepted Axhausen's principles (Chase and Herndon, 1955).

Then in 1912, Macewen in his work "The Growth of Bone" contradicted Axhausen's views. He denied that periosteum was osteogenic and regarded it as only a limiting membrane. Macewen ascribed all the phenomenon of bone graft repair to osteoblasts. The cause of this contradiction was due to Macewen's failure to recognise the cambium layer as part of the periosteum (Chase and Herndon, 1955). Ollier had shown that periosteum without the deep layer did not produce bone. Axhausen had also showed that osteogenesis in the graft occurred beneath the periosteum. The confusion arose due to the anatomical description of the periosteum. Hey Groves (1917) suggested using the term "epiosteal" to denote structures on the surface of the bone but beneath the periosteum. Thus, Axhausen showed it was the epiosteal layer which was osteogenic. In fact, Macewen's work showing that periosteum was useless, unless the underlying surface of the cortex was attached, formed the basis for the present day concept of the osteoperiosteal graft.

In 1914, Phemister performed a series of experiments in dogs to further investigate osteogenesis. His findings showed that other than the periosteum, the endosteum, and the contents of the Haversian canals also had the capacity for osteogenesis. He explained that the surface location of the periosteum and endosteum allowed it to receive sufficient nutrition

for survival and proliferation. However, the great mass of bone cells that were separated from the surface by an impermeable calcified matrix would eventually be necrotised and absorbed. A few bone cells lying about the periphery and lining the larger vascular spaces as well as the fibrous elements of the latter might survive and proliferate. Blood-forming cells of the marrow, despite their favourable nutrition, would necrotise because of their higher degree of specialisation (Phemister, 1914). Hence, Phemister proved that Axhausen's claim that osteogenesis did not occur from transplanted bone devoid of periosteum and endosteum was incorrect. The old view of Barth, later advocated by Murphy (1913), that there is no osteogenesis from a transplant, and that substitution occurs entirely from the ingrowth of new bone from the host fragment ends, was also proven wrong.

Still, the basic principles advocated by Axhausen have largely been corroborated by later investigators. The wide acceptance of Axhausen's views has thus brought an end to the debate over the role of the periosteum in osteogenesis.

The First Bone Allograft

Other than his work on osteogenesis, the Scottish surgeon William Macewen was also the first to perform a bone allograft. In 1879, using the tibia of a child with rickets, he transplanted the allograft onto the humeral shaft of a young boy whose humerus was lost through osteomyelitis. This work was later described in 1881 in a paper called "Observations concerning transplantation of bone. Illustrated by a case of inter-human osseous transplantation, whereby over two-thirds of the shaft of a humerus was restored" (Jones, 1952; Macewen, 1881). The allograft was a success because Macewen operated under antiseptic conditions as introduced by Lister. Furthermore, the transplanted tibia was, by chance, subjected to muscular stress and this encouraged the osteoblasts present to form bones (Burwell, 1994).

Developments in the Use of Bone Allograft

In 1908, Erich Lexer described the first massive allograft, in which tissue harvested from amputees were used to restore motion to joints following

osteomyelitis and to reconstruct defects following resection of bone tumours (Lexer, 1908a; Lexer, 1908b; Burwell, 1994; Enneking, 2005). A year later, in 1909, Judet reported a whole-joint transplantation — femur, tibia and patella — in the knee joint of man. The procedure, as he described, could be carried out to treat the trauma of infective arthritis or tuberculosis (Judet, 1909; Burwell, 1994).

Use of Fresh Bone Allograft

Before advancements in refrigeration techniques, fresh bones were used for most allografts. In 1915, Trout reported the successful bone transplantation between father and child to treat spina bifida, with the use of fresh bone allograft (Trout, 1915; Burwell, 1994). The trend of using fresh bone allografts continued through the 1930s and 1940s, mainly in cases of bone transplants from parent to child to treat pseudarthrosis, cysts and tumours. In 1948, Alldredge described the treatment of nonunion in adults using fresh bone allograft (Alldredge, 1948). However, the development in the use of fresh bone allografts took a turn in the 1950s. It was reported that fresh allografts produced a strong immune response within the body (Bonfiglio *et al.*, 1955; De Boer, 1988). The use of fresh bone allografts has since dwindled to a stop with the increased understanding of immunogenicity (Burwell, 1994).

Preservation of Bone Allografts

In 1910, Bauer demonstrated the successful transplantation of bones stored by refrigeration for as long as three weeks (Bauer, 1910; Burwell, 1994). A year later, Tuffier described the use of thin bone slices refrigerated for as long as five days in the treatment of patients (Tuffier, 1911; Burwell, 1994). Then in 1912, Albee, an American orthopaedic surgeon, recommended that all tissues — bones included — be stored at 4–5°C (Albee, 1912; Tomford, 1994). In 1942, Inclan reported the successful storing of autologous bones by refrigeration. Following the report, the idea of bone banking received much mention in various publications (Inclan, 1942; De Boer, 1988; Donati, 2007).

Influenced by the success of Inclan, Bush and Wilson independently described the preservation of bone grafts at -20°C and the building of a bone bank for small fragments (Bush, 1947; Wilson, 1947; Donati, 2007). After Wilson's report, many orthopaedic surgeons across the United States followed suit. They stored femoral heads collected from their patients in freezers in their own hospitals, and used these small bones on an individual basis (Tomford, 1994), much like the practice of a cottage industry.

Establishment of Tissue Banks

Spurred by the needs of the wounded following World War II and encouraged by the climate of interest surrounding bone banking, George Hyatt, an orthopaedic surgeon, founded the US Navy Tissue Bank in Bethesda, Maryland in 1949. Hyatt developed a system for procuring tissue, with a focus on bones, from cadavers in operating theatres, and employed freeze-drying to store bones. These helped to increase the availability of allogenic bones. (Hyatt, 1950; Hyatt *et al.*, 1952; Tomford, 2000).

Many other banks were also founded in Europe during this period. In 1952, Rudolph Klen set up the Hradec Kralove Tissue Bank in the old Czechoslovakia. In the UK, the Leeds Tissue Bank was founded in the city of Leeds, Yorkshire, in 1955 with Frank Dexter managing the day to day running of the bank (Kearney, 2006). In 1956, the Central German Tissue Bank was set up in Charité University Hospital in Berlin, the old East Germany. The bank has since been re-established as the German Institute for Cell and Tissue Replacement in 1994 by Rudiger von Versen. In Athens, Greece, the Demokritos Human Tissue bank was set up by Nicholas Triantafyllou (Phillips, 1998).

In Poland, the Central Tissue Bank was set up at the Medical University of Warsaw in 1963. Under the leadership of Janus Komender and Kazimierz Ostrowski, followed by Anna Dziedzic-Goclawska, the tissue bank went on to become the oldest tissue bank in the world to employ radiation technology in the sterilisation of tissue grafts.

In 1965, the activities in Leeds Tissue Bank were shifted following a decision to centralise all tissue banking activity within the Yorkshire region. The Yorkshire Regional Tissue Bank was thus established at the Pinderfields Hospital in Wakefield, with Frank Dexter appointed as the head of the bank (Kearney, 2006).

Allograft Immunogenicity

Since the 1950s, there has been much research into the antigenicity of the various types of allograft bones. Herndon and Chase noted that freezing allogenic bones could reduce immune response to it (Chase and Herndon, 1955; Hubble, 2001) Curtiss made similar observations in his animal studies and agreed that freezing cadaveric bones would reduce the immune response and hence also reduce the rejection rate (Curtiss *et al.*, 1959; Mankin *et al.*, 2005).

In the 1960s, Geoffrey Burwell, an orthopaedic surgeon in Leeds, embarked on a series of experiments on bone transplantation which led to his discoveries in allograft immunogenicity. He showed that the bone marrow was responsible for the immune response to fresh allogenic bone and that frozen bones performed better compared to fresh allogenic bones (Phillips, 2008). More significantly, his experiments shed light on the science of bone preservation and led to the development of the protocol for bone preservation we use today (Burwell, 1962; Burwell, 1963; Burwell, 1964a; Burwell, 1964b; Burwell, 1965; Burwell, 1966; Burwell and Gowland, 1961; Burwell and Gowland, 1962; Burwell *et al.*, 1963; Kearney, 2006).

Many other investigators sought to understand the immunology behind allografts and most reached the same conclusion, as summarised here by Friedlaender: fresh bone allografts were the most immunogenic; freeze-drying dramatically reduced the immune response and frozen bones had an immunogenicity that was between that of the former two (Friedlaender, 1976; Friedlaender *et al.*, 1983; Burwell, 1994).

The growth in knowledge of allograft immunogenicity proved to be instrumental in influencing the decline in the use of fresh bone allograft and the development of freezing and freeze-drying techniques for use in bone banks.

The Discovery of the BMP

The journey that led to the discovery of bone morphogenetic protein (BMP) started in 1965, when Marshall Urist made the discovery that demineralised bone matrices stimulated ectopic bone induction in his experiment using rats (Urist, 1965; Glowacki, 1992). The discovery

prompted Urist to study the mechanism behind the stimuli, and finally led to his identification of BMP as the protein responsible for bone induction activity in 1971 (Urist and Strates, 1971; Meikle, 2007).

The significance of this discovery lies in the field of possibilities BMP opens up for the study of bone development through all stages, from beginning to the end. BMP can be manipulated to initiate bone development (Urist, 1994). However, the amino acid sequence of BMP needed identification before BMP can be easily manipulated. It was in the late 1980s that the purification and sequencing of bovine BMP and human BMP was finally achieved (Wozney *et al.*, 1988; Luyten *et al.*, 1989; Wozney, 1992; Chen *et al.*, 2004). Since then, 20 BMPs have been identified. The clinical applications of BMP have also been widely studied.

Further Developments in the Use of Bone Allograft

Following his classic work on massive bone allograft transplantation in 1908, Lexer described in 1925 the results of using fresh cadaveric tissue on 11 half joints and 23 whole joints and reported a reasonable success rate (Lexer, 1925; Mankin *et al.*, 2005).

Operations using massive bone allograft were far and few between until the 1970s, when Volkov in Russia expanded on Lexer's work with a large series on transplanting whole joints and articular surfaces (Volkov, 1970). At around the same time, Carlos Ottolenghi in Buenos Aires, Argentina, reported his use of deep frozen allografts for mostly bone tumours (Ottolenghi, 1966). Together with his successor, Luis Muscolo, he later presented the results of a series of long-term follow-ups on massive bone allografts transplanted (Ottolenghi *et al.*, 1982). In Houston, Texas, Frank Parrish, upon learning of Volkov's reported success, performed a series of experiments on the use of frozen massive osteoarticular allografts in reconstructing defects following the removal of tumour (Parrish, 1973; Enneking, 2005). The efforts of these surgeons across the region inspired other groups to look towards bone allograft as an alternative to metallic implants. One of these group, led by Henry Mankin at the Massachusetts General Hospital, reported the largest clinical series on the use of bone allografts in bone tumour surgery and

showed success in three quarters of the patients (Mankin *et al.*, 1976; Tomford, 2000).

With the development of chemotherapy, imaging and surgical reconstruction techniques, the use of allograft in limb-sparing procedures became adopted in the early 1980s (Enneking, 2005). Since then, the procedure has offered patients with bone tumours a much-needed alternative to amputation.

Development of the Living Bone

While the use of massive bone allografts gained impetus in the 1980s, it was during this same period that the problems with allografts were reported. Enneking, with the help of Burchardt, performed a series of experiments to investigate the fate of large bone allografts and found that the allografts were often poorly incorporated into the host bone and were vulnerable to infection and fatigue fractures (Enneking *et al.*, 1975; Burchardt *et al.*, 1983; Tomford, 2000). Solutions were needed to overcome the histoincompatibility of bone allografts and to improve allograft incorporation. One such solution came in the form of a living bone.

The possibility of a living bone was first raised by Curtis in 1893, when he described the ideal “living bone which will exactly fill the gap and will continue to live without absorption” (Curtis, 1893; De Boer, 1988). This ideal living bone inched towards reality with the birth of vascular surgery through the work of Alexis Carrel (Carrel, 1908), then with further developments in microsurgery in the 1960s. In 1975, the first free vascularised graft was performed by Ostrup (Ostrup and Frederickson, 1974; De Boer, 1988). Following that, the technique of revascularising bone with anastomosis became adopted in transplants for treating bone tumours in the 1980s (Weiland *et al.*, 1983; Wood and Cooney, 1984; Wood *et al.*, 1984; Wood *et al.*, 1985; De Boer, 1988). During the same period, the technique of transplanting both allograft and vascularised graft was also introduced to improve the success of transplantation (Gross *et al.*, 1984; Bieber and Wood, 1986; De Boer, 1988). The living bone proved successful in reducing graft fractures, nonunion between the graft and host bone, resorption of bone and infection (De Boer, 1988).

The Issue of Disease Transmission

The first case of AIDS surfaced in 1981 (Centers for Disease Control, 1981; Tomford, 2000) and the first case of HIV-1 transmission in bones was reported in 1984, followed by a second case in 1985 (Centers for Disease Control, 1988; Tomford, 2000). The transmission of disease came at a time when proper screening methods were yet to be developed. Two cases of hepatitis C transmission were also reported in the 1990s, the second case occurring despite the existence of a first-generation screening test (Eggen and Nordbo, 1992; Conrad *et al.*, 1995; Tomford, 2000).

The occurrence of disease transmission prompted the development of proper donor-screening and bone preparation and processing methods. When Kenneth Sell became the head of the US Navy Tissue Bank, he started a programme in which a group of fellows researched on graft technology. Many prominent investigators, including Andrew Bassett, Gary Friedlaender, Theodore Malinin, William Tomford, and Michael Strong, were recruited. The findings of the programme helped immensely in advancing the knowledge in ensuring the safety of allografts and the prevention of disease transmission in the field of tissue banking (Lord *et al.*, 1988; Buck *et al.*, 1989; Tomford *et al.*, 1990; Strong *et al.*, 1991; Lietman *et al.*, 2000; Quinn *et al.*, 2001; Mankin *et al.*, 2005).

Developments in Tissue Banking

With the development in the use of bone and other allografts, it became imperative to move away from the “cottage industry” model that had continued well into the latter half of the twentieth century. Not only was the practice unreliable for preservation of bone, it was unsafe for surgeons to simply retrieve the bones they stored in their private freezers for transplantation purposes. However, there were exceptions to the model, of which includes the US Navy Tissue Bank (1949). From those first yawnings of activity, tissue banks began its slow sprouting across the world.

In the United States, the Boston group, led by Henry Mankin, researched extensively on tissue banking. It seems as though there was a gestation period, which in due course exploded. In 1976, in a meeting of

a group of 26 individuals with backgrounds ranging from the sciences to the clinical to tissue banking, the American Association of Tissue Banks (AATB) was established (Phillips, 1998). The AATB was to “facilitate the provision of transplantable tissues of uniform high quality in quantities sufficient to meet national needs”. Kenneth Sell was elected as the first president of AATB in 1977 (Joyce, 2000). In 1990, there were 30 tissue banks in the United States (Phillips, 2008).

The situation was similar in Europe. There had been a period during which tissue banks had very little contact with one another. Europe was divided into East and West. The East, with its more liberal tissue donation laws, had generally progressed faster than the West. In the UK, for example, while Geoffrey Burwell collaborated with Frank Dexter and supplied bones to orthopaedic surgeons in the North of England, there was no movement to extend the progress to the remainder of the country. The principal reason was that orthopaedic surgeons had not been convinced of the value of allografts for their procedures. Then in 1991, an International Conference in Tissue Banking was held in Berlin, and only then did the various centres realise the full extent of participation. The following year, in June 1992, the European Association of Tissue Banks (EATB) was set up in Marseilles, France, with Rudiger von Versen elected as the first president (Phillips, 1998).

In the Asia-Pacific region, tissue banking began in a few countries as early as the 1980s. In 1981, the Burma Tissue Bank was set up by Dr U Pe Khin at the Rangoon Orthopaedic Hospital in Rangoon, Burma. In 1984, Dr Yongyudh Vajaradul set up the Bangkok Biomaterial Centre at Siriraj Hospital in Bangkok, Thailand. Tissue banks sprouted across the Asia-Pacific region over the next few years. In October 1988, the Asia Pacific Association of Surgical Tissue Banks (APASTB) was established in Bangkok, Thailand, with Vajaradul as its first president and Aziz Nather as its first vice president (Nather *et al.*, 2005).

A New Beginning

Five associations have now come together once every three years to run a World Congress. They include the AATB, EATB, APASTB, ATBF (Australasian Tissue Banking Forum) and ALABAT (Latin America

Association of Tissue Banks). At the Fifth World Congress, held in Kuala Lumpur, Malaysia from 2–6 June 2008, a World Union of Tissue Banks was set up on 4 June 2008 with representatives from all five associations. The Sixth World Congress will be held in 2011 in Portugal by the EATB.

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