International Orthopaedics (SICOT) (2015) 39:193–204
DOI 10.1007/s00264-014-2578-5

ORTHOPAEDIC HERITAGE

Bone transplantation and tissue engineering. Part II: bone graft and osteogenesis in the seventeenth, eighteenth and nineteenth centuries (Duhamel, Haller, Ollier and MacEwen)

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Received: 18 October 2014 / Accepted: 20 October 2014 / Published online: 15 November 2014
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Abstract In the 18th 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. Duhamel noted that the periosteum had a deep osteogenic layer, which he termed the "cambium layer". However, von Haller claimed the opposite: the periosteum was not osteogenic. In the 19th century, Ollier 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 conditions. The controversy was furthered by MacEwen who believed, contrary to Duhamel and Ollier, that the periosteum had no osteogenetic power and was purely a limiting membrane giving direction to bone growth but taking no active part in it. This manuscript describes this period of controversies about the osteogenesis of the transplanted bone, marrow and periosteum that would eventually die or not and be replaced by surrounding tissue or be active for osteogenesis. Whether bone grafts are a form of passive scaffolding or active in osteogenesis was the main question about auto and allografts in the 18th and 19th centuries. In response to this challenge, many papers were written to defend each side of the argument.

Keywords Bone graft · Autograft · Allograft · Vascularised graft · Tissue engineering · History of orthopaedic surgery · History of bone graft

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Introduction to the first xenograft in human with Job van Meekerenk

After a first period of mythology, miracles and fantasy [14], bone graft became reality in the 17th century. The modern age of bone grafts begins with the report of the surgeon Job van Meekeren. Job van Meekeren (1611–1666 in Amsterdam) was a Dutch surgeon. Van Meekeren became a surgeon in Amsterdam in 1635. He wrote a book (Fig. 1), which gives a good representation of the state of the art of surgery in the 17th century in Amsterdam. Names and addresses of patients are fully documented, so even today we know exactly where they lived and where the events took place. He is credited to have performed the first heterologous graft by inserting a fragment of dog skull into the skull of an injured soldier. In reality, Meekeren was only the first to record a bone graft. Ultimately it is Meekeren's report that has become the reference point for the story and thus immortalized in the annals of the history of medicine. His report appears in the first chapter of his book, *Observationes Medico-Chirugicae* [25], which was published in 1682 (Fig. 2). In chapter 1 of this book he states that he read a report of it in a letter received by the Reverend Engebert Sloot of Slooterdijk from John Kraanwinkel, a missionary in Russia, where the operation had been performed. Johannes Kraanwinkel, a missionary and member of the Moscow Evangelical Society, witnessed the event. Kraanwinkel related the "amusing tale" in a letter to a Reverend named Engebert Sloot of Slooterdijk. Sloot, in turn, shared the tale with Job Janszoon van Meekeren, a Dutch surgeon from Amsterdam.

In 1668, a Russian nobleman named Butterlijn had his scalp denuded and a section of his cranium removed after a sword fight with a Tartar. The surgeon, so that he might refill the empty space, selected a section from the cranium of a dead

JOBI à MEEK'REN
Chirurgi Amstelodamensis
OBSERVATIONES
Medico-Chirurgicæ,
Ex Belgico
In latinum translatæ
ab
ABRAHAMO BLASIO, Ger. Fil.
Medicinæ Studioso.

AMSTELODAMI,
Ex Officina HENRICI & Viduæ THEODORI BOOM, 1682.

Fig. 1 The German edition of Meekren's book, first published in Dutch in 1668 as Heel- en geneeskonstige aanmerkkingen. There was also a Latin edition in 1682

dog, answering in size and shape to that which had been carried off by the sword from the nobleman's head, and he adapted it to the wounded place. And by this method the nobleman was restored to complete health. He miraculously restored, exulting joyously, and told the things done to his friends or rather his acquaintances, who passed the same thing on to the clerics and, through them, to the Archbishop. The operation (transplantation of a piece of bone from a dog's skull) was successful but, because an animal graft was being used on a Christian, there were religious repercussions, and the soldier was excommunicated. Although healing was perfect, the Church ordered the removal of the graft. Because an excommunication had been pronounced, entry to those places where Christians gathered throughout all Russia would be denied to the aforesaid nobleman, as long as the forbidden section from the bones of the dog's head should remain united to the bones of a Christian man's head.

The success of the operation was testified by the fact that when the soldier asked the surgeon to remove the fragment so that he could be readmitted into the church, the fragment had been fully incorporated. The manner in which this story was transmitted through history has helped to create some inaccuracies that are often perpetuated. First of all, Meekeren only reported the case and did not perform the surgery as he is often credited for. Secondly, Meekeren was Dutch and not Russian as is commonly stated. Finally, it was only the patient that was threatened with excommunication. It is interesting to note that the surgeon who performed the operation was not similarly threatened.

The structure of bone and Anton van Leeuwenhoek

In the 17th and 18th centuries orthopaedic surgeons focused their attention on the structure of bone, which was described for the first time in 1674 by Anton van Leeuwenhoek (1632-1723) in Philosophical Transactions.

Leeuwenhoek, a son of a craftsman, was born in Delft in 1632 and died in 1723, at the age of 91 years. At the age of 22, he was married to Barbara and got involved in commerce. Widowed 12 years later, he did not remarry for several years. Of the five children from his first marriage, only his daughter Maria died after him and stayed with him until his last breath. After his death, Maria erected a monument to his memory that can still be visited in Delft. Although he lacked a formal education, Leeuwenhoek was a man respected in his hometown for his integrity. His passion was microscope observation and even on the verge of death he begged his doctor to translate into Latin some letters he had not yet sent to *The Royal Society.*

Several years before his death, Leeuwenhoek had built a nice wooden cabinet (Fig. 3) with shelves designed to accommodate 26 different models of microscopes [24]. After his death, his daughter sent the precious furniture to *The Royal Society of London*, where it remained for a century before disappearing mysteriously. Except for the microscopes (Fig. 4) that were sent to London, Leeuwenhoek possessed another 247, as well as 172 lenses mounted in gold, silver or copper frames.

In anatomy, he studied the epidermis, the hair, the nails, the teeth and the bone structure. He noted the fascicular nature of nerves and described the striation of muscular fibres, the internal structure of the crystalline as well as that of the optic nerve. In the 17th and 18th centuries orthopaedic surgeons focused their attention on the structure of bone, which was described for the first time in 1674 by Anton van Leeuwenhoek in Philosophical Transactions, concerning what would become known as Haversian canals. The concepts of bone callus, implant and resorption began to be outlined.

Wunder-Anmerckungen. 187

konnte/ überdeckete: Und was noch mehr zu verwundern war/ ſo fiel die Haut/ wann er ſie ſin-

-cken oder fahren lieſſe/ Augenblicks wieder dergeſtalt über den gehörigen Ort/ als ob ſie niemals berührt wordē: Und auf eben dieſe Weiſe zog er die Haut vom rechten Knie auf eine halbe Elle hoch/ auf-

Fig. 2 Among the numerous and unusual cases reported and illustrated by 60 engravings; two of the remarkable engravings (frontispiece and p 187) show abnormal elasticity of the skin

Duhamel and Haller and the problems with growth of bone, osteogenesis and periosteum

In 1739, Henri Louis Duhamel [7] 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. In 1742 Duhamel went onto repeat and extend the madder feeding experiments of Belchier [5, 6]. He noted that madder (the root of rubbia 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). Duhamel had studied the uptake of dye 'madder' by bone and found it was only deposited where osteoblast activity was present.

Fig. 3 Portrait of Anton van Leeuwenhoek; Leeuwenhoek manufactured his own microscopes himself and ended up in the possession of several similar microscopes

Duhamel [7–10] was a natural research worker delighting in his self-described role as 'Nature's detective'. He found that only parts of the bone became stained. The younger the animal the more bone would be stained because the madder was only deposited in newly formed active bone. By alternating a madder treated with a normal diet, he could produce successive layers of dyed bone, proving that bone grew by interstitial formation. By drilling holes in bone a measured distance apart, he proved that growth took place from the ends of long bones.

Albrecht Von Haller (Fig. 5), the professor of John Hunter [15], claimed the opposite, namely, that the periosteum was not osteogenic. According to von Haller [26], the periosteum merely acted as the support for blood vessels, and it was the exudation from arteries that caused osteogenesis. 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”. Albrecht von Haller made the then extravagant suggestion that the vascular system was responsible for osteogenesis. In his book *Experimentorum de ossium formatione* (1763) he stated that "the origin of bone is the artery carrying the blood and in it the mineral elements", and he had the courage of opposing Duhamel's periosteal theory of bone formation. For, he wrote, "vessels are found in the cartilage and without any doubt they *are* shown in the periosteum by the injection of coloured fluids." Thus, even in the periosteum the vessels were considered by Hailer to be responsible for laying down bone. Haller’s conviction soon found a supporter of the calibre of John Hunter, probably about 1754, as shown in the first edition of his collected works (1835). Hunter joined in the conflict and performed a number of experiments [14] to

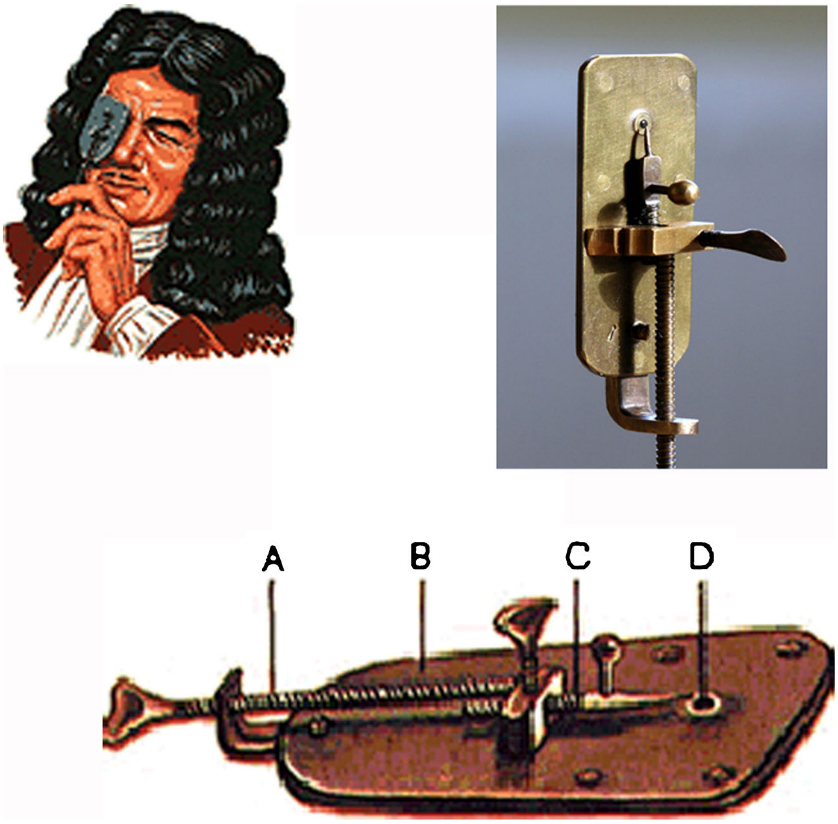


Fig. 4 Basic in design, van Leeuwenhoek's instruments consisted of simple powerful magnifying glasses. Compared to a modern microscope, van Leeuwenhoek's design is extremely simple, using a single lens mounted in a tiny hole in a brass plate that makes up the body of the instrument. The specimen was then mounted on a sharp point that sticks up in front of the lens. Its position and focus could be adjusted by turning the two screws. The entire instrument was only 3–4 in. long, and had to be held up close to the eye, requiring good lighting and great patience to use. Leeuwenhoek's microscope consisted simply of a screw for adjusting the height of the object being examined (*A*), a metal plate serving as the body (*B*), a skewer to impale the object and rotate it (*C*), and the lens itself, which was spherical (*D*)

Fig. 5 Portrait of Albrecht Von Haller

substantiate his professor’s claim. His work [14] demonstrated the viability of bone allograft. John Hunter [15] was a boy while Duhamel's numerous papers on bone growth were being published.

However, it was Jean Pierre Marie Flourens [13] who went a long way in settling the controversy when he conclusively (1842) showed that periosteum was osteogenic and was the chief agent in the healing of bone defects. Most operations requiring bone resection were for nonunion, which was often treated by amputating the limb. A technique called “subperiosteal resection”— based on Duhamel’s theory of the importance of the periosteum in bone regeneration—was widespread until halfway through the 19th century, and it was used by many surgeons for the treatment of nonunion.

Louis Léopold Ollier, periosteum and xenografts in animals

Louis Léopold Ollier, whose full name was Louis Xavier Édouard Léopold Ollier (2 December 1830 until 26 November 1900), was a French surgeon [11, 12] born in Les Vans, department of Ardèche. His father and grandfather were also physicians. His ancestors, who originally spelled their name Olier, had come from Malzieu in the neighbouring Département of Lozère. Initially he studied natural sciences at Montpellier. His early interest, as an undergraduate at Montpellier, was in botany. He was made a demonstrator (1849), and involved in the teaching of the subject at the famous botanical garden of the medical school. Perhaps it was a detailed study of the bark of certain trees that led him later to look more closely at the periosteum. In 1851, he began work as medical interne at Lyon Hospital. In 1857 he earned his medical doctorate in Paris; Ollier himself came to be appointed Chief Surgeon at the Hôtel-Dieu Hospital in Lyon in 1860. In 1877, he became a professor of clinical surgery.

As early as 1858, Ollier (Fig. 6) decided to devote his life to research into this process of ossification induced by different components of bone and by whole bone. In due course, he was able to show that joint repair was predicated upon the preservation of the joint capsule and periosteal sheath, and on keeping the tendons, ligaments and muscles in situ. He also studied bone growth in general, establishing the laws of long-bone growth. He looked into the effects of irritation of the various components of bone; and studied bone grafts using periosteum, periosteum plus the osteogenetic layer immediately beneath the periosteum, bone marrow, and whole bone. Ollier recalled the dictum of Claude Bernard that "there could be no scientific medicine without experimental medicine." Experimental research became the ruling passion of his life. His first experiments were conducted on his father's farm in the Ardèche mountains. The animal work done in chickens (Fig. 7), pigeons, rats, rabbits, cats, and dogs allowed Ollier to extend his osteotomies from the upper ends to the shafts of bones, the ribs, etc. He took a piece of periosteum from the long bone of a rabbit or a cockerel and wrapped the flap around the adjacent muscles. Similarly, he took a flap of periosteum from a rabbit tibia and transplanted it to the skin of the forehead. These two initial experiments later came to be repeated many times, when Ollier was working in Chauveau's laboratory at the Lyon Veterinary College.

Between 1850 and 1868, Ollier showed that the periosteum and the subperiosteal osteogenetic layer allowed joint excision to be performed underneath the periosteum or underneath the

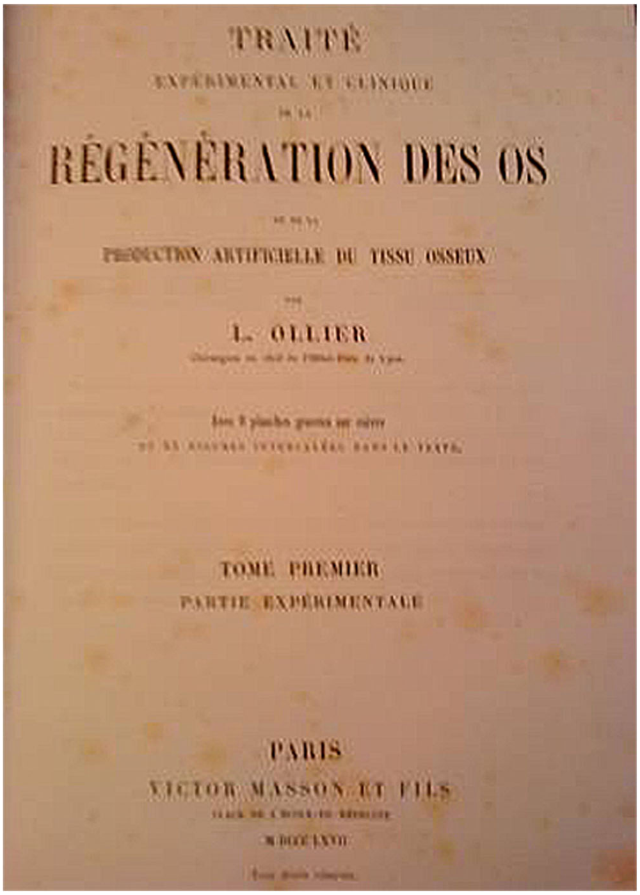
Fig. 6 Portrait of Louis Leopold Ollier

Fig. 7 One of Ollier's early experiments, some of which were conducted in the poultry yard on his father's farm at Les Vans (Ardèche). Heterotopic bone formation obtained after transplanting a piece of periosteum from the tibia (chicken). This experience was influenced by the experience of Hunter on the cock [14]

capsule and periosteum, in cases of severe inflammation of the joints, which, in those days, would either be fatal or require amputation to save the patient's life. In the shaft of an animal bone, the bone formed after the periosteum had been incised and, "somehow stripped off with an elevator", was found to be quite unlike normal bone. These experiments and findings were reflected in his Traité de régénération osseuse chez l'animal.

In 1858, Ollier took what was arguably the first really scientific approach to tackle the problem of osteogenesis. 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. For his textbook [20] called Traité expérimental et clinique de la régénération des os et de la production artificielle du tissu osseux (Fig. 8), Ollier was awarded the Great Prize for Surgery instituted by Napoleon III (sharing the prize with his opponent Sédillot, who had written a Traité de l'évidement des os).

Around 1885, Ollier decided to go back to work on xenografting, in order to see whether the aseptic techniques introduced meanwhile at the Hôtel-Dieu hospital had changed the dire outlook of these grafts. He found that grafts between mammals and birds (rabbit or cat bone grafted into a chicken host) did not work. However, in some cases, chicken bone was successfully grafted into rabbits. Grafts were found to work better where the recipient (rabbit or cat) belonged to a higher species than the donor (chicken). Grafting from the higher to the lower species was found to be less successful. When grafting between mammals, Ollier found that rabbit bone would take well in the cat host. However, often the graft would provide only temporary support, and eventually disappear. He concluded that there was no certainty of a graft taking in humans even if the material had come from "an animal very closely related to man, such as monkeys." Ollier used dowels of dead or living bone in the treatment of non-union in human patients, in particular in six cases of non-union of the tibia. The donors of the fresh bone were rabbits, calves, sheep, and humans. At the same time, Ollier used metal nails and ivory pins. The bone grafts invariably resorbed. The only advantage seen by Ollier was the stimulation of the host bone's osteogenetic potential. In conclusion, Ollier wrote that "it is mainly interhuman transplants (autografts or homografts) that provide a means of repairing certain bone defects. Xenografts between different animal species will give only incomplete


TRAITÉ
EXPÉRIMENTAL ET CLINIQUE

RÉGÉNÉRATION DES OS

PRODUCTION ARTIFICIELLE DU TISSU OSSEUX

L. OLLIER

TOME PREMIER
PARTIE EXPÉRIMENTALE

PARIS
VICTOR MASSON ET FILS

Fig. 8 Title page of Volume 2 (1872) of the *Traité expérimental et clinique de la régénération des os et de la production artificielle du tissu osseux* by L. Ollier, Chief Surgeon at the Hôtel-Dieu in Lyon (two volumes, octavo, with nine copper engraving plates and 45 illustrations in the text, V. Masson, 1867) and transient results." Ollier was able to show that autografts (where the bone came from the same subject) and homografts (between two human subjects) would take, whereas xenografts were short-lived at a time when antisepsis had not yet been introduced, and would ultimately be rejected. Ollier went on to become a celebrity, not only in Lyon, but also in Paris, and Europe-wide. He was particularly famous in Berlin and in Edinburgh, where his Traité des résections (published between 1867 and 1891) was highly appreciated. On 24 June 1894 Ollier was awarded commander of the Légion d'Honneur by French president Marie-François-Sadi Carnot. Ironically, later that evening Carnot [16] was stabbed by an assassin, and Ollier was summoned to tend to the dying president's wounds (Fig. 9). Today, the museum of pathological anatomy at the University of Lyon is named in Ollier's honor.

Sir William MacEwen and the first human bone allograft

Sir William MacEwen (Fig. 10) was one of the most versatile of British surgeons. He watched the dawn of antisepsis, grasped its implications and eagerly played a leading part in the romantic expansion of surgery that followed. Many of his widespread contributions [17–19] were of fundamental importance. He was born on June 22, 1848, at a house called "Woodend" on the Port Bannatyne side of Skeoch Wood, Isle of Bute. He was the youngest of the 12 children of John and Janet (née Stevenson) MacEwen. His father was a marine trader doing business in sailing ships plying from Rothesay, but family fortune ebbed and flowed like the tide. At one time he was master of the "Breadalbane," a yacht that ferried Free Church Ministers to and from the islands of the West Coast of Scotland. The boy, brought up in a seafaring atmosphere, felt the call of the sea all his life, returning to it whenever he could conveniently flee the city. Later in life he bought a small estate on the coast of Bute, engaging in experimental farming and yachting. John MacEwen retired to Glasgow in 1860 and William attended the Collegiate School, Garnett Hill. He was a big, bright and lively boy, displaying more prowess in the gymnasium than the classroom, skilful with the single stick. Passing on in 1865 to the university, he arrived at a time when the professors in the faculty of medicine were of unusual distinction: there was Allan Thomson in anatomy, Buchanan in physiology, Gairdner in medicine and Lister in surgery. It was the moment when Lister began tentatively to apply carbolic acid to compound fracture wounds, so that in the Glasgow Royal Infirmary MacEwen witnessed the birth of an antiseptic system that revolutionized surgery. For four years he watched its unfolding, part of which time he was Lister's dresser.

Fig. 9 Ollier was awarded commander of the Légion d'Honneur on 24 June 1884 by French president Marie-François-Sadi Carnot. Ironically, later that evening Carnot was stabbed by an assassin, and Ollier was summoned to tend to the dying president's wounds. He is represented in the drawing with the Légion d'Honneur award

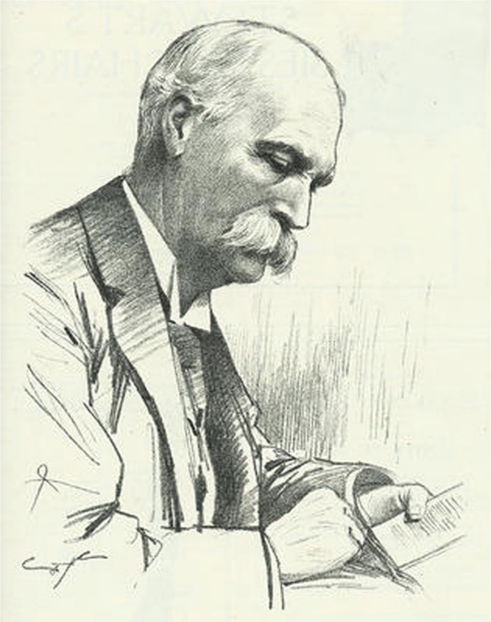


Fig. 10 Portrait of Sir William MacEwen

MacEwen graduated as Bachelor of Medicine and Master of Surgery in 1869, just after Lister had left Glasgow to succeed Syme as Regius Professor of Surgery at Edinburgh. After qualifying, he served as house surgeon and house physician before becoming superintendent of Glasgow Fever Hospital at Belvedere for a short period, an appointment notable for MacEwen's introduction of intubation of the larynx through the mouth instead of by tracheotomy or laryngotomy—a procedure that aroused interest at home and abroad whereby he anticipated O'Dwyer's tubes. In 1871 he was appointed district medical officer, a post that enabled him to gain experience in practical surgery at the parish hospital in Parliamentary Road. Also the same year he became casualty surgeon to the Central Police Division of Glasgow, an office offering him rich experience in emergency surgery and enabling him to contribute many original papers to medical journals (Fig. 11).

He proceeded to the degree of Doctor of Medicine in 1872 and the following year was elected to the important office of dispensary surgeon to the Western Infirmary, from which he resigned within a year on appointment to a similar post at the Royal Infirmary. In 1874 he was elected into the Fellowship of the Faculty of Physicians and Surgeons of Glasgow. MacEwen was now well set for a surgical career. He started consulting practice at 73 Bath Street, in the center of Glasgow. In 1876, when he was only 28 years old, he was promoted to full surgeon with charge of wards. In 1875 he became an assistant surgeon at the Royal Infirmary, Glasgow, being promoted to full surgeon in 1877.

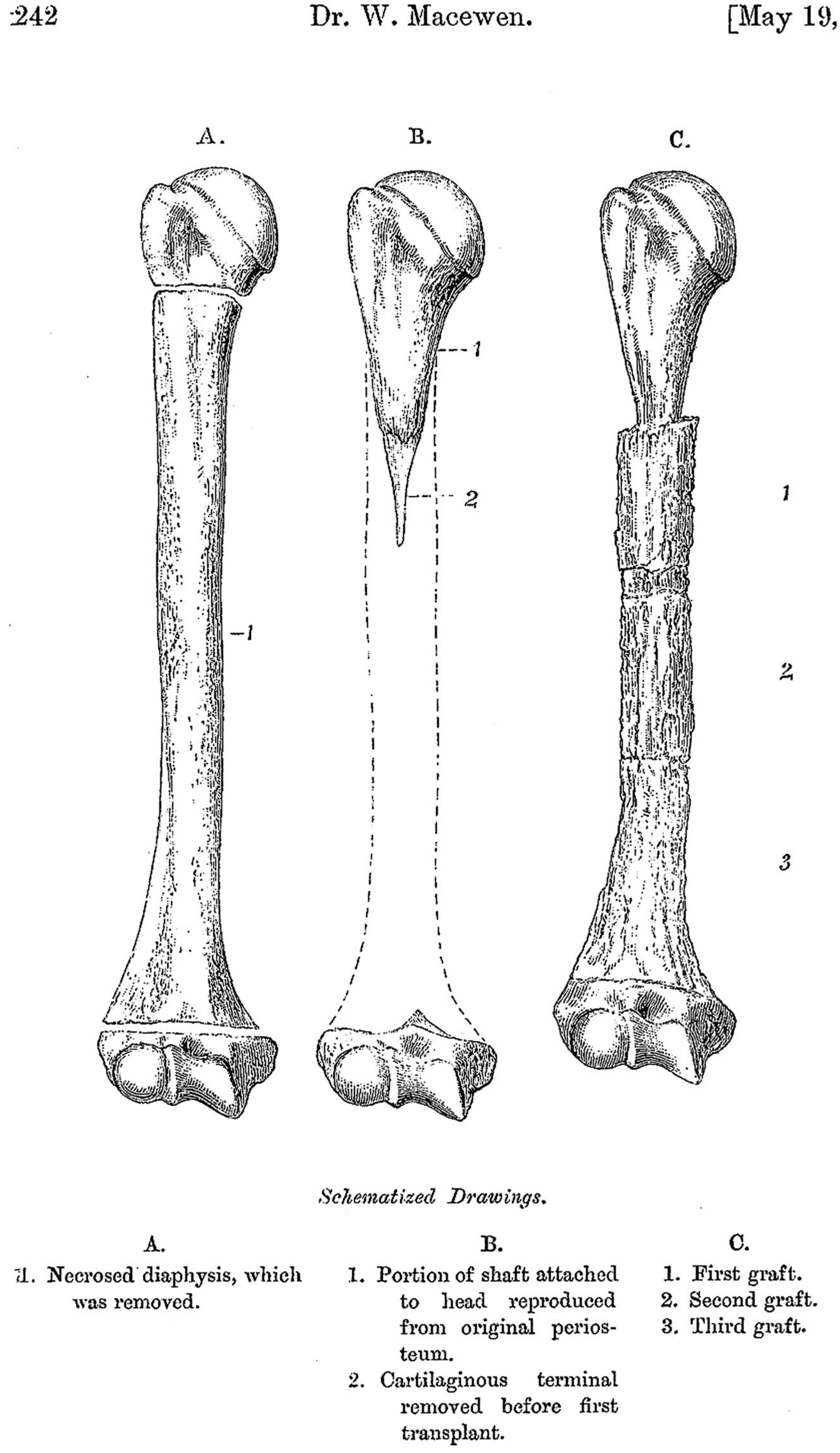
In 1879, MacEwen was the first to transplant bone in a human being successfully. One of the first cases which was treated in 1874 was a three-year-old boy with an osteomyelitis of the right humerus. The necrotic bone was removed surgically resulting in a deformed and useless humerus after a 15-month follow-up. The boy's parents wanted MacEwen to have the boy's arm amputated. MacEwen however performed a bone allograft transplantation to reconstruct the humerus (Fig. 12) in three stages over a period of five months.

It was a great pioneering achievement for at once it opened up a new field in bone surgery. The work was described in a communication to the Royal Society in 1881 entitled "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." This paper is a landmark in surgery; it received the enthusiastic commendation of Professor T.H. Huxley, secretary of the Society, who clearly saw the significance of successful human bone grafting.

Fig. 11 Photograph of Sir William MacEwen. MacEwen was Regius Professor of Surgery at Glasgow University (1892–1924) and knighted in 1902. He was Honorary Surgeon to his Majesty and Surgeon General for the Royal Navy in Scotland. He's the one that is on your right

MacEwen carried out many successful bone transplantations after his first classic case. In 1903 he succeeded in restoring the transverse ramus of one half of the jaw by transplantation of bone in a girl 15 years of age who had the horizontal ramus of the lower jaw on one side extirpated for a diseased condition several years previously. He was particularly gratified with the result, for the girl had been restored to her natural good looks from what was a hideous saliva-pouring disfigurement.

MacEwen, by his extended researches in the physiology of bone, greatly advanced our knowledge of its growth. He proved that bone was a living tissue capable of transplantation; he believed the graft played a vital part during the process of incorporation. In his operative and experimental work he was impressed by the efficacy of multiple small grafts. They provided a greater surface than the massive graft, each forming a centre of ossification that threw out osteoblasts from its whole periphery. Herein he displays a remarkable insight, for this seems to provide an explanation of the quickened osteogenetic power of small medullary bone grafts, which have found such favour in this last decade. The growth of a long bone occurred at the diaphysis, for he believed that the cartilaginous growth disc belonged to the diaphysis and not to the epiphysis. He showed experimentally that the disc was only concerned with the growth of the shaft. He also believed, contrary to Duhamel and Ollier, that the periosteum had no osteogenetic power; it was purely a limiting membrane giving direction to bone growth but taking no active part in it. He excised bone shafts with the epiphyses in dogs but left the periosteum intact and found that there was no periosteal reproduction of the shafts. In another animal a flap of periosteum was lifted from a radius, detached at its lower end, brought around some muscle fibers and reattached to the intact periosteum, but the strip produced no bone. Again he removed part of a radial shaft and inserted a glass tube between the remaining segments to exclude the periosteum and found that osseous tissue invaded the tubes from the severed ends. "The potency of the periosteum as a limiting membrane is seen when, in cases of fracture, it is torn up and stretched across the fractured surface of one of the fragments. It here forms an effective barrier against osseous union, the ossific formation being absolutely limited by the periosteum and fibrous union results." On the other hand, stripping or tearing of periosteum in a fracture allows outpouring of osteoblasts from broken surfaces into the gap between the bones and into the



242 Dr. W. Macewen. [May 19,

Schematized Drawings.

A.	B.	C.
1. Necrosed diaphysis, which was removed.	1. Portion of shaft attached to head reproduced from original periosteum. 2. Cartilaginous terminal removed before first transplant.	1. First graft. 2. Second graft. 3. Third graft.

Fig. 12 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”

surrounding tissues to form binding osseous deposits. Bone deprived of periosteum will live and grow. Growth and reproduction are an inherent property of the osseous elements themselves.

From 1881 to 1889 he was a lecturer at the Royal Infirmary School of Medicine, and later on a Professor of Clinical Surgery. On this appointment he had to transfer his surgical activities from the Royal to the Western Infirmary. In 1883 he was appointed as Surgeon to the Royal Hospital for Sick Children in Glasgow. He also helped to found in 1916 the Princess Louise Scottish Hospital for Limbless Sailors and Soldiers in Erskine (now the Erskine Hospital, near Glasgow, which was urgently needed to treat the thousands of military that lost their limbs in the First World War. The result of 30 years’ clinical and experimental investigation was published in 1912 in a book entitled, *The Growth of Bonen*

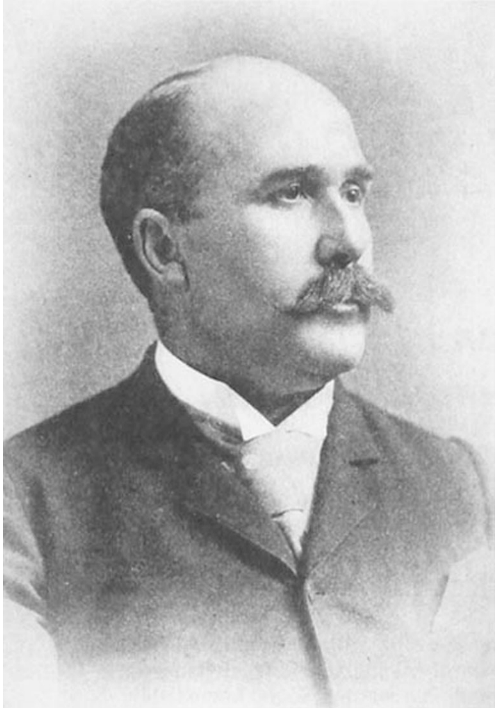


Fig. 13 Portrait of Abel M. Phelps

Observations in Osteogenesis. This was followed in 1921 by another work, *The Growth and Shedding of the Antlers of the Deer*. The casting of the antlers in early spring followed by the growth of a new pair provided him with the opportunity of closely studying rapid massive osteogenesis in nature.

Abel M. Phelps and the first vascularised graft (cross leg human dog)

Abel M. Phelps (1851–1902) is another important contributor (Fig. 13) to the development of bone grafting technology. In 1891, Phelps published a landmark review of two cases of bone transplantation that he performed at Charity Hospital in New York City [22]. One case was a young male (named John Gethins) with ununited leg fractures who had been operated on several times without success. After the failed surgeries, the patient's parents had appealed to Phelps' sense of humanity and repeatedly requested that he do everything possible to save the limb from amputation. As a last resort, Phelps transplanted a portion of bone from the foreleg of a dog (a black spaniel named Yig) to the patient. Like Meekeren, the transplant was xenograft and taken from dog. Similarly, his

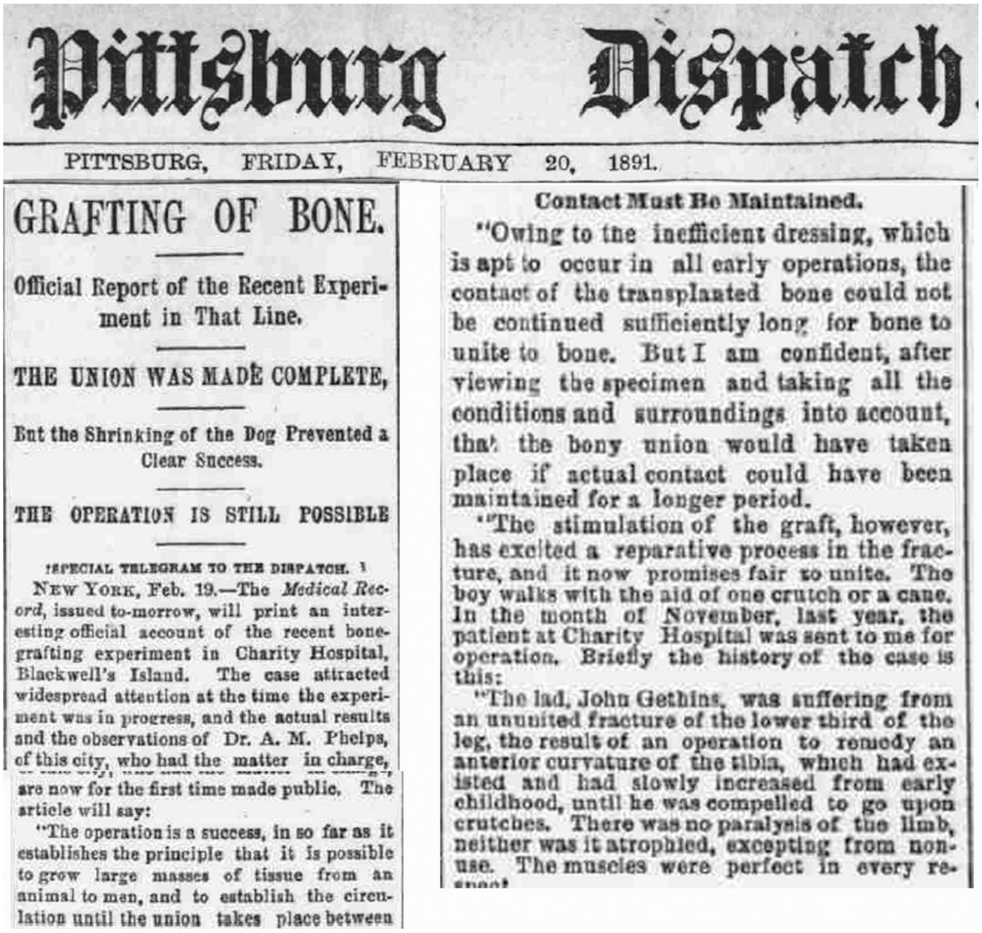


Fig. 14 History of the boy and graft is particularly well described in the Pittsburgh dispatch of Friday 20 February 1891

Pittsburg Dispatch

PITTSBURG, FRIDAY, FEBRUARY 20, 1891.

GRAFTING OF BONE.

Official Report of the Recent Experiment in That Line.

THE UNION WAS MADE COMPLETE,

But the Shrinking of the Dog Prevented a Clear Success.

THE OPERATION IS STILL POSSIBLE

[SPECIAL TELEGRAM TO THE DISPATCH.]

NEW YORK, Feb. 19.—The *Medical Record*, issued to-morrow, will print an interesting official account of the recent bone-grafting experiment in Charity Hospital, Blackwell's Island. The case attracted widespread attention at the time the experiment was in progress, and the actual results and the observations of Dr. A. M. Phelps, of this city, who had the matter in charge, are now for the first time made public. The article will say:

"The operation is a success, in so far as it establishes the principle that it is possible to grow large masses of tissue from an animal to men, and to establish the circulation until the union takes place between

Contact Must Be Maintained.

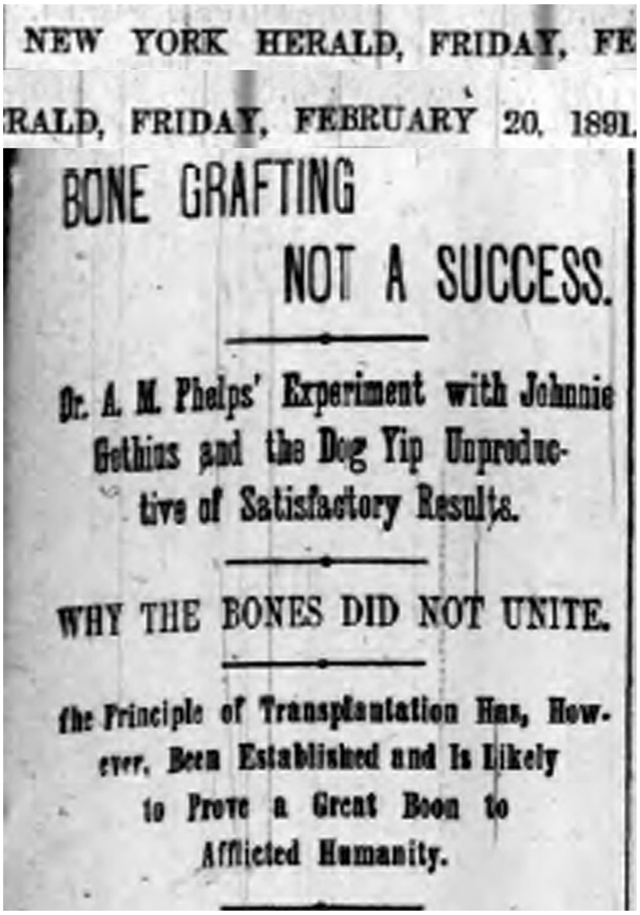
"Owing to the inefficient dressing, which is apt to occur in all early operations, the contact of the transplanted bone could not be continued sufficiently long for bone to unite to bone. But I am confident, after viewing the specimen and taking all the conditions and surroundings into account, that the bony union would have taken place if actual contact could have been maintained for a longer period.

"The stimulation of the graft, however, has excited a reparative process in the fracture, and it now promises fair to unite. The boy walks with the aid of one crutch or a cane. In the month of November, last year, the patient at Charity Hospital was sent to me for operation. Briefly the history of the case is this:

"The lad, John Gethins, was suffering from an ununited fracture of the lower third of the leg, the result of an operation to remedy an anterior curvature of the tibia, which had existed and had slowly increased from early childhood, until he was compelled to go upon crutches. There was no paralysis of the limb, neither was it atrophied, excepting from non-use. The muscles were perfect in every reprocedure brought much attention from persons praying that the effort to save the patient’s limbs would result in failure as the use of animal parts for humans was considered unnatural and against the church. Both donor and host were attached to each other for two weeks (Fig. 14) so that the blood could circulate between the two patients; then, by remaining vascularized, the graft could activate the growth of new bone in the boy’s limb. After about 15 days, the two patients were separated. The boy’s bone graft was irregularly covered in new bone, and both patients had a brief convalescence.

His operation is considered a landmark due to the fact that he left the vascular supply of the grafted bone intact. In fact, he effectively connected the patient to the dog such that the grafted bone would maintain a supply of nourishment during which time the patients’ blood vessels would grow into the graft. Although he provides no specific references, Phelps claimed: “Observation made in my studies during the past two years convinced me that the circulation between opposite species could be established with safety”. He goes on to reason:…"the capillary loops growing into the new cell formation. These finally unite and the circulation is established between opposite sides of the wound. The interchanging of blood between opposite species whose corpuscular elements differed in size, introduced a serious question. But it was reasonable to suppose that the dog would construct capillaries of natural size which might be a little larger than those of the patient. This would prevent the corpuscular elements of the blood from entering the capillaries of the patient, and then, secondly, the corpuscles, being protoplasm and possessed of amoeboid powers, would accommodate themselves to the smaller capillaries of the human being, and not be arrested in the circulation of the brain or other internal organs. If contact could be maintained bone ought to be united to bone as kindly as muscle to muscle or skin to skin—a fact which I had already demonstrated. The conditions favourable to the union being absolute rest of the wound, perfect coaptation, thorough drainage, and scrupulous cleanliness combined with antisepsis."

In the end, it must be mentioned that both operations resulted in failure. However, being a scientist, careful documentation and observation helped Phelps describe the reasons for the failures, which he blamed entirely on the manner in which the surgical wounds were dressed. He goes on to make a case for the experience of the surgeon being fundamental for troubleshooting and configuring solution strategies for unforeseen circumstances. Although the outcomes were failures, Phelp's work is nevertheless an important milestone in plastic surgery and was reported in many daily journals with different comments (success or failure) on the same day (Figs. 14, 15). Although Phelps stressed the use of animals to save human



NEW YORK HERALD, FRIDAY, FE

RALD, FRIDAY, FEBRUARY 20, 1891.

BONE GRAFTING NOT A SUCCESS.

Dr. A. M. Phelps' Experiment with Johnnie Gethins and the Dog Yip Unproductive of Satisfactory Results.

WHY THE BONES DID NOT UNITE.

The Principle of Transplantation Has, However, Been Established and Is Likely to Prove a Great Boon to Afflicted Humanity.

Fig. 15 On the same day as in Fig. 17, The New York Herald announces the failure of union

Fig. 16 Portrait of Dallas Burton Phemister

life and limb, the concept of vascularized grafts is prolific in plastic surgical techniques and Phelps' experience with these grafts made for a scientific landscape with increased interest and excitement in pursuit of success in this field rather than abandonment.

Beginning of the 20th century

Georg Axhausen [1–4] continues the debate in the beginning of the 20th century with studies on osteogenesis and bone transplantation. 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.

In 1914, Dallas Burton Phemister (Fig. 16) performed a series of experiments [23] 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 necrotize because of their higher degree of specialization. Hence, Phemister was preparing the modern concept of tissue engineering [21].

References

1. Axhausen G (1907) Histologische untersuchungen uber knochentransplantation am menschen. Duetsche Zeitschr F Chir 91:388–428
2. Axhausen G (1909) Die histologischen und klinischen gesetze der freien osteoplastik auf grund von thierversuchen. Arch F Klin Chir 88:23–145
3. Axhausen G (1909) Zur frage der freien osteoplastik. Zentralbl Chir 36:133–134, Beilage
4. Axhausen G (1909) Ueber den vorgang partieller sequestrirung transplantierten knochengewebes nebst neuen histologischen untersuchungen uber knochentransplantation am menschen. Arch F Klin Chir 89:281–302
5. Belchier J (1736) An account of the bones of animals being changed to a red colour by aliment only. Philos Trans R Soc 39:287–288
6. Belchier J (1736) A further account of the bones of animals being made red by aliment only. Philos Trans R Soc 39:299–300
7. Duhamel, HL (1742) Sur le developpement et la crue des os des animeaux. Histoire et memoiresde l'academie des inscriptions et belles lettres 2, 481
8. Duhamel HL (1739) Sur une racine qui a la faculte de triendre en rouge les os des animaux vivants. Mem Acad Roy des Sci Paris 52:1–13
9. Duhamel HL (1742) Sur le developpment et la crue des os des animaux. Mem Acad Roy des Sci Paris 55:354–370
10. Duhamel HL (1743) Quatrieme memoire sur les os dans lequel on se propose de rapporter de nouvelles preuves qui etablissent que les os croissent en grosseur par l'addition de couches osseuses qui tirent leur origine du perioste. Commun L'Acad Roy des Sci Paris 56:87–111
11. Fischer LP, Ferry MH, Begui J, Chavanne H, Papin P, Chotelet JC, Eyraud G (1995) Ollier, the father of bone and joint and of reconstruction surgery 1839-1900. Maîtrise Orthopédique 47
12. Fischer LP, Chatin B, Neidhard JC et al (2000) Centenaire d'Ollier créateur de la chirurgie orthopédique et de la chirurgie expérimentale (1830-1900). Conférence de l'Institut d'Histoire de la Médecine; cycle 1999-2000. Collection Fondation Marcel Merieux, Lyon, pp 77–91
13. Flourens JPM (1842) Recherches sur le developpement des os et des dents. Gide, Paris
14. Hernigou P (2014) Bone transplantation and tissue engineering, part I. Mythology, miracles and fantasy: from Chimera to the Miracle of the Black Leg of Saints Cosmas and Damian and the cock of John Hunter. Int Orthop 2014 Sep 9. PMID: 25201179. doi:10.1007/s00264-014-2511-y
15. Hunter J (1835) Works, vol 1. Longman, Rees, Orme, Brown, Green, and Longman, London, p 502
16. Le petit journal (1884) Supplément illustré du lundi 3 juillet, 1894
17. MacEwen W (1881) 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. Proc R Soc (Lond) 32:232–247
18. MacEwen W (1909) Intrahuman bone grafting and reimplantation of bone. Ann Surg 50:959–963
19. MacEwen W (1912) The growth of bone. Observations on osteogenesis. J. Maclehose & Sons, Glasgow
20. Ollier l (1867) Traité expérimental et clinique de la régénération des os et de la production artificielle du tissu osseux, two volumes. Victor Masson, Paris
21. Pecina M, Vukicevic S (2014) Tissue engineereng and regenerative orthopaedics (TERO). Int Orthop 38(9):1757–1760. doi:10.1007/s00264-014-2477-9
22. Peltier LF (2000) Transplantation of tissue from lower animals to man. Clin Orthop 371:3–9
23. Phemister DB (1914) The fate of transplanted bone and regenerative power of its various constituents. Surg Gynecol 19:303–333
24. Van Leeuwenhoek A (1677) Letter to Oldenburg dated 9 October 1676. Philosophical Transactions 12:831
25. van Meekren (1668) Heel- en geneeskonstige aanmerkkingen; German edition of Meekren's only and richly illustrated book, first published in Dutch (Latin edition in 1682)
26. Von Haller A (1763) Experimenta de ossium formatione. in Opera minora. 1763. Francisci Grasset, Lausanne, pp 1763–400