

Review article: history of medicine

Bone grafting in the pre-antiseptic era (historical review): Beginning of the journey. From antiquity to the 1860

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Abstract. This work presents a systematic review of the state of bone plastic surgery before the antiseptic approach was widely introduced into world clinical practice. The experience of the first bone tissue transplantation operations is analyzed in their relationship with the development of ideas about regenerative bone tissue regeneration. It is shown that, contrary to generally accepted ideas, it was at that time that the theoretical and practical foundation was laid, without which it would have been impossible to develop bone grafting in the following decades, discoveries were made, the significance of which could only be understood a century later. The authors describe the period of primary accumulation of facts, starting with the earliest archaeological finds dating back to the II millennium BC, until the early 1860s, when it became possible to systematize accumulated observations and create the first scientific theories

Key words: bone graft, periosteum, ossification, transplantation, amputation, bone defect, regeneration process, replantation

Introduction

Currently, more than 2 million operations associated with the use of certain methods of replacing bone defects are performed worldwide annually (1), which differ significantly in size, spatial configuration, the likelihood of developing an inflammatory process, and the degree of the functional load falling on the corresponding area. In fact, the creation of osteoplastic materials has turned into a kind of industry area, and bone grafting, issues of managing the process of bone tissue regeneration have become an independent area of modern clinical practice, affecting the professional interests of a significant number of medical specialties. It originates from the ancient dream of mankind, reflected in many legends. The most famous of them is perhaps "Miracle of the Black Leg" by Saints Cosmas and Damian being a plot that inspired many artists to create their masterpieces (2). In that case, it was a question of transplanting a limb entirely, i.e. a bone with a complex of soft-tissue structures surrounding it. Humanity was able to reproduce such an operation only in the 21st century, but the first research work on this problem began to be carried out much earlier.

Of course, the success of tissue transplantation and bone grafting, in particular, as well as surgery in general, largely depended on the progress of asepsis, antiseptics, analgesia. In this regard, until now, the prevailing opinion (3-7) is that genuine bone plastic surgery begins with the works of F.H. Albee (1915) (8), V. Putti (1912) (7) or, at best, W. Macewen (1881) (9), while in previous years, only haphazard attempts were made with unpredictable results. In our opinion, these representations exist because the reports available in the literature on the state of the issue before the end of the 19th century are fragmentary, limited to listing individual facts. As a rule, several fundamental works of well-known authors are briefly cited, while most of the documents related to the corresponding time period still remain without the attention of researchers. A true idea of the epoch can only be given by a comprehensive description of the formation of the doctrine

of bone regeneration and its development, which must be considered in relationship with the formation of clinical practice of the first osteoplastic operations.

In fact, it is with bone transplantation that the history of transplantology begins, as a separate branch of medical knowledge. But here we are faced with the following paradox. From an ethical point of view, in the era of early Christianity, the very idea of organ and tissue transplantation did not cause any objections, as evidenced by the authority of such great saints as Cosmas and Damian. Nowadays, when this idea has been put into practice, the situation does not seem so unambiguous. According to a survey conducted among dental patients, 17% consider it wrong to use bone material from another, especially a deceased person (10). With bone materials of animal origin, the situation is even worse. Only 60.1% of respondents agreed to them, and 84.6% of people rejected the possibility of using implants obtained from pigs in principle (11). In 2005, according to the decision of the District Court of Stuttgart (Germany), the dentist had to pay an amount of 5,000 Euros as compensation for moral damage caused to a patient who, according to his statement, was not provided with adequate information about the origin of Bio-Oss xenogenic bone material before implantation (12). But even autotransplantation of bone tissue was refused by 11.3% of respondents (11).

Thus, using the example of bone grafting, one can judge the history of the development of transplantation, not only as a medical, but also as a social phenomenon.

Considering the above, the goal of this work was to conduct a detailed analysis of the beginning of the path on which vague dreams about the very possibility of bone transplantation for the first time began to acquire some real form, in an era when surgery itself has only just experienced the period of its formation.

First attempts and their characteristics

Bone grafting has a more ancient history than previously thought. According to A. Jagharian during archaeological excavations in the Armenian Highlands near Lake Sevan, undertaken to study the burials of the Hurrians, people who lived in these places since the II millennium BC and whose descendants contributed to the formation of the modern anthropological so-called "Armenoid race", a woman's skull was found with a defect of 7 mm in diameter, closed by an animal bone. The transplanted graft has integrated with the bone surrounding the defect (7).

The first written report of a bone graft is a recently discovered text prepared by an Ottoman military surgeon Ibrahim bin Abdullah in the book *Alaim-I Cerrahin (Wonders of Surgeons)*, dated to 1505. It contains a recommendation to close a skull defect with a similar fragment of the goat's skull if such defect occurs during the surgical treatment of the wound. In the absence of this animal, it was possible to use the skull of young Kangal dogs, which usually accompanied the Janissary army. They were used to protect against a sudden attack of the enemy, which they warned about by barking, and, if necessary, as a source of food (13). Around the same time, a similar method became known in the army of Kyzylbash Iran, which was in a state of prolonged military confrontation with Ottoman Turkey. It is described by a Persian physician Baha al-Dowleh Razi in *Khulasat al-Tajarib (Summary of Experiences)* (14). Unfortunately, we do not have information about how often medieval Turkish and Iranian surgeons resorted to performing this surgical intervention, and what was the outcome of the surgeries.Similarly, we cannot judge the attitude of patients and their environment to the possibility of transplanting animal bones to humans.

In Europe, the first operation performed using bone grafting was described in 1668. The patient was a nobleman from "Muscovy" (i.e., Russia) whose surname was Buterlein (possibly distorted Buturlin that was an old Russian boyar family, known since the end of the XIV century). During the battle with the Tatars, this officer was hit on the head with a saber, which resulted in a scalped wound with a defect in the bones of the cranial vault. The soft tissue flap was used to close the wound, which engrafted, but the bone defect remained. While on a trip to Europe, aiming to invite foreign military engineers to the tsarist service, the nobleman sought medical help from the famous Dutch surgeon J.J. van Meekeren, who closed the defect with a fragment of a dog's skull. The

compatriots, however, did not understand this action, telling the officer that he thus humiliated his human dignity. Threatened with excommunication after returning to his homeland, the patient again turned to J.J. van Meekeren with a request to remove the transplant. On repeat surgery, it was found that the transplanted fragment partially integrated with the surrounding bone, which allowed the surgeon to consider the experience as a successful one (15).

Nevertheless, the method did not find followers, remaining for a long time the only message of this kind. However, its reliability based on the testimony of a certain priest Kraanwinkel, made after the death of J. Makeeren (1666), is questioned by many authors. For example, W. Macewen, calls him "fabulous" (9), L. Ollier – "fable" (16).

At the same time, the spread and improvements of armament have increasingly resulted in bone defects, which have led to the development of their repair methods. On the other hand, the ideas of the Enlightenment have contributed both to removing some moral and ethical restrictions on the means and goals of medical care and to increasing the importance of scientific knowledge based on direct observation and experience. An important event was the invention of the microscope by A. van Leeuwenhoek, which made it possible to study the histological structure of bone tissue,which was first carried out by C. Havers (1691) (17). Even earlier, J.Scultet (1653) noted the high ability of bone to regenerate, observed in clinical practice and the potential of its growth (16).

In 1684 A. de Heide was the first to study the process of callus formation during the healing of a fracture from a hematoma formed between the ends of bone fragments during their fracture under experimental conditions (16). The author used frogs as a model.

In 1743, a member of the Royal Academy of Sciences (France) and, subsequently, its president, H.L. Duhamel du Monceau, published his studies on the patterns of bone growth in the fundamental work *Quatrieme memoire sur les os.* Being a botanist by nature of his main occupation, he consistently defended the concept of the similar physiology of the animal bones and stems of plants' growth. In this regard, the author assigned the key role, by analogy with the bark of trees, to the periosteum, more precisely to its inner layer, which he called cambial, believing that over time it is transformed into bone. As proof of his theory, H.L. Duhamel du Monceau fed experimental animals food mixed and unmixed with madder(16) (a pigment extracted from the madder plant (Rubia tinctorum)), which, as A. Belchier's studies (1736) have shown, can accumulate in growing bone tissue (18). In a *postmortem* study of bones, he found in them an alternation of white and red stripes, which he considered to be similar to the annual rings of trees (16).

This point of view was opposed by M. de Haller (19,20) and M. Bordenave (21), who believed that the periosteum performs only a retaining function, and the leading role in the regeneration process belongs to "bone juice", which flows out of the vessels and bone matter along the edges of the defect. A similar opinion was expressed by M. Troja (1775), who considered the source of bone regeneration to be a jelly-like substance formed between the edges of bone fragments and the periosteum(16). Their position had many supporters. Among them was in particular, D.J.Larrey, the physician of Napoleon I, who wrote in 1818 that by this time already "... in all schools, in all audiences, the mistakes of Duhamel were abandoned" (22).

However, his claim was far from the truth. De Coutavoz (1752), David (1770) de Vigarous (1778) defended the theory of the leading role of the periosteum in the process of bone regeneration. The concept of H.L. Duhamel du Monceau served as the basis for the development of technology for the operation of subperiosteal bone resection. It was first described in 1694 by Delamotte, a surgeon from Normandy, but became famous after publication by Professor M. Sabatier (1771). In a surgical procedure performed in a patient with a comminuted tibial fracture complicated by osteomyelitis, six inches of the diaphysis were removed. The periosteum was preliminarily dissected from the sequesters and left in place. After 8 months, the author reported the replacement of the postoperative defect with newly formed bone tissue (16). A similar finding was reported by E.O. Muhin, who claimed that he observed 2 cases of spontaneous bone regeneration of significant bone defects in the limbs, commenting that the young age of the patient was of fundamental importance (23). In clinical practice,

the technique became widespread in the early 19th century (B. Heine) (24). In the opinion of its supporters, the preservation of the periosteum is a major condition for the regeneration of bone tissue in the defect area. At the same time, methods of amputation were proposed, in which osteotomized bone surfaces were covered with flaps from the periosteum (Brunningauzen, Walter) (25).

However, this concept turned out to be far from always applicable in practice, since in many cases, the periosteum has been damaged as a result of trauma or pathological process. Moreover, as subsequently recognized by N.I. Pirogov (1866), even the presence of a healthy intact periosteum may not always guarantee the formation of a new bone (26). New and more reliable treatment options were required.

On the other hand, the ideas of H.L. Duhamel du Monceau, led to the formulation of experiments on the "grafting" of different parts of the body of one animal to another, in analogy with plants based on the idea of the common physiology of their growth processes. The beginning was laid by Hunter (1797), who transplanted the spur of a rooster onto its own comb, onto the comb of another rooster, and onto the leg of a chicken. Subsequently, there were transplantations of bird claws (Dieffenbach), goat's horn on the head of a sheep (Gassendus), a wing of a siskin on a cock's comb (Baronio), a cat's tail on a rooster's comb (Brown-Sequard) (27) and others. J. Wolf reported a case of a Dalmatian merchant who bought a rooster from J.Hunter, on whose crest two spurs were transplanted, for public performances. The first attempt failed and he was expelled from Corfu as a warlock. Then, however, the merchant toured Russia, successfully demonstrating the rooster at fairs (28). The main significance of these works consisted in the demonstration of the possibility of transplanting biological tissues, drawing attention to it anddirecting the scientific thinking accordingly. Experiments on animal models, in turn, have become a recognized way to study biological processes.

Thus, by the beginning of the 19th century, the development of medicine came close to the idea of starting experiments with transplanting organs and tissue fragments, including bone for clinical purposes.

The period of evidence accumulation. 1800 - 1860

As W. Macewen noted, the first reliably documented osteoplastic surgery was performed by P. F. Percy, one of the leading surgeons of the Napoleonic army, at the very beginning of the 19th century (9). He tried twice in a row to repair a human tibial defect with bone fragments of the forearm of the bull that had just been killed. The result was unsuccessful. Moreover, when removing bone fragments, P.F. Percy noted that their prolonged stay in the wound even harmed vascular growth. The only positive aspect of the surgery was the fact that bone grafts prevented the ingrowth of scar tissue into the defect, which could lead to shortening of the limb (26). J.F. Dieffenbach pointed out that a similar operation was performed by Larasc when repairing a defect resulting from a complicated comminuted fracture of the arm. Finally, the graft also had to be removed (25).

However, in 1810 Merrem in an experiment on a dog in which a fragment of the skull was removed with the preservation of pericranium and dura mater, and then replanted to the old place after 22 days observed reliable signs of osseointegration. Later, he performed a similar operation on a cat, and also got a positive result on the 14th day of the experiment (25).

Since 1820, a series of related human interventions have been performed by Ph. Walter. His first patient was a wounded man after a saber blow to the head. A fragment of the occipital bone was placed on a soft tissue flap, which was put in place and sutured, after which complete healing was observed (27). Encouraged by this success, the author performed the replantation of an already completely detached skull fragment with preserved periosteum in a bricklayer injured during construction. In the postoperative period, a suppurative process developed, resulting in the formation of sequestration of the area of the outer compact plate of the transplanted fragment, which was removed 4 months after the intervention. The rest of the replanted bone was engrafted successfully. A year later, he also performed a similar operation on a man suspected of having a brain abscess. There was no pus in the supposed place, and therefore the bone fragment was put in place, and the skin wound was sutured. The patient died 36 hours after surgery. At the autopsy Ph.

Walter discovered the first signs of bone engraftment, which manifested itself in the adhesion of the edges of the dura mater, and confidently argued that replantation would be successful if the patient survived. At the same time, he experimented on a dog in which a fragment of the skull was removed with a preserved periosteum and then laid in place. A year later, complete osseointegration of the replanted bone was observed. The difference between it and the surrounding bone tissue was difficult to determine. The author believed that the transplanted bone fragment retains its viability and can grow independently with the edges of the defect (24,25).

The next operation using this technique was performed by Wedermeyer. The patient died 7 years later from peritonitis. The autopsy revealed complete integration with the edges of the defect over the entire width of the transplanted fragment (24,25). Finally, A.A. Abrazhanov reported that in the 1830s another successful similar operation was performed by Dr. Wolf in St. Petersburg(28) (possibly referring to the doctor of the Obukhov hospital A.M. Wolf, known for the fact that, for the first time in Russia, he performed a blood transfusion).

However, B. Heine, summing up a series of his own experiments, noted that success in bone transplantation is not always observed. The same conclusion was reached by Klenke and Wiesmann, based on their work with experimental animals carried out in the 1840s. B. Heine (1836) observed that the replanted rib fragment remained in the cavity washed by pus, while near it was found the "restored" bone in the area of the defect. Hence, the author concluded that the transplanted or replanted bone fragments die and gradually dissolve, but they have an "irritating" effect on the edges of the defect, from where the growth of the new bone originates. A decisive role in the process of bone regeneration, he assigned to the periosteum. Thanks to this work, the opinion was established that bone grafting is, in a way, an addition, playing an auxiliary role, when performing a subperiosteal resection operation. Thus, for example, H.J. Paul in 1854 reported that in order to stimulate bone formation in case of sluggish bone wound healing after sequestration, the Heine method was successfully used (24,25).

On the other hand, B. Heine, following P.F. Percy, believed that the presence of a transplanted bone fragment prevents scar tissue from growing into the defect. Observing in the experiment over the healing of the trepanation wound in the "empty control" of the skull, he noted the formation of adhesion between pericranium and dura mater, which led to subsequent scarring. As a result, the growth of bone regenerate, which began from the edges of the defect, reaches a certain value and ends. Vrolik (1837), Rokitanskiy (1847), Bruns (1854), Langenbeck(1859) disagreed with this opinion. In their opinion, the source of regeneration is the ossification points associated with the periosteum, which appear in the scar tissue in the form of separate foci or plates. Their arguments were based on cases of spontaneous bone replacement of cranial vault defects described by Scarger 30 years later, Walter 22 years later, Fritze and Bruns 3 years after injury (29).

The dissemination of these views was facilitated by the work of P. Fluorance (1847) *Theorieexperimentale de la formation des os*, dedicated to the memory of H.L. Duhamel. In it, the author argued that the bone grows out of the periosteum, increasing in thickness in layers stacked on top of each other. As the bone grows in thickness, resorption of its inner layers occurs, which leads to an increase in the diameter of the medullary canal. But, in addition, the work makes an important conclusion that the bone tissue is in a state of constant self-renewal (30).

To resolve the issue of the viability of the bone graft, Middeldorph (1852) transplanted fragments of the diaphysis of a pigeon into the abdominal cavity of another pigeon, Jouck (1853) transplanted fragments of calf bones into the abdominal cavity of chickens and rabbits. In both series of experiments, encapsulation of grafts, replacement of bone marrow cavities with adipose tissue and a gradual decrease in the weight of grafts were observed (25). The data obtained were interpreted, rather, in favor of the thesis that the transplanted bone fragments to some extent retain their biological activity. This was consistent with the opinion of G. Gulliver (1838) on the inability of completely dead bone to change when interacting with body tissues (31). Based on this concept, L. Ollier (1867) considered sequesters, although separated, but not completely dead tissue, the presence of which contributes to the formation of new bone (26).

On the eve of the Crimean War, in 1852 N.I. Pirogov in the clinic of the Medical-Surgical Academy of St. Petersburg performed surgery for osteoplastic lengthening of the lower leg during amputation of the foot. During this surgery, a fragment of the calcaneus, included in the flap on the feeding pedicle, was moved to the osteotomized surface of the leg. The method was described in 1854 (32), and in 1855 already, it was performed by M.P. Dzemeshkevich, in the military field hospital settings. The operation quickly became popular. In 1866, Weber reported 40 patients treated with this technique, and Kestner reported 16 men. Perrie (1860), Hahncocc (1866), Vladimirov (1872) announced their own modifications of this surgical technique (33).

The idea of using skin-periosteal-bone grafts has spread to other parts of the human skeleton. In 1857, Milan surgeon R. Gritty proposed to move the patella included in the soft tissue flap to the osteotomized surface for low femoral amputation performed at the level of the distal epiphysis (34). Yu.K. Shimanovskij, based on the results of a series of experiments on corpses, in 1859 proposed similarly, when performing a low shoulder amputation, to preserve the olecranon of the ulna and, together with the radial tubercle, to transfer it on the feeding stem to the osteotomized surface(35). In the clinic, such an operation was performed in 1865 (19).

B.R.C. Langenbeck (1859) proposed that the flap used for rhinoplasty should include the periosteum of the frontal bone, thereby hoping to achieve bone formation (36). In the same year, he performed a temporary maxillary resection to gain surgical access to the base of the skull when removing a tumor. The osteotomy line roughly corresponded to the fracture configuration described, nowadays, as Le Fort I (at present, osteotomy carried out along this line is widely used when performing orthognathic operations – author's note). The displaced fragment was nourished by the soft tissues of the cheek and palate. As shown by microangiographic studies carried out already in 1975, adequate perfusion is achieved by virtue of the ascending palatine and ascending pharyngeal arteries. After the tumor was removed, the upper jaw fragment was returned to its place and fixed in the correct position. In 1861, B.R.C. Langenbeck again reproduced his surgery (37), calling it a bone-plastic one. This term, which is not quite correct, has long been used to refer to surgical interventions associated with temporary bone resection (19).

In 1859, R. Flourens, in an experiment, performed craniotomy of two guinea pigs, followed by transplantation of trepanned bone fragments, together with the periosteum, into the defect area to each other. In both cases, the grafts survived, and, according to the author, the periosteum and the dura mater initially fused, and only then the bone substance did. According to the author, this again proves the leading role of the periosteum in the process of bone regeneration (24,25). This work marked the return of interest in free bone grafting as an independent method for replacing skeletal defects, which was further developed in the following decades.

Conclusion

As follows from the presented review, in fact, until the early 1860s, attempts at free transplantation of bone fragments were isolated and did not have a systematic character. But, nevertheless, they proved the very possibility of success of bone plastic surgery, both in the experiment and in the clinic, which served as the basis for subsequent studies. Since the middle of the 19th century, bone fragments have been actively included in the composition of complex flaps on the feeding leg during limb amputations, as well as during replantation. This idea (L. Ollier would later call it "indirect bone grafting") quickly began to gain popularity, which, in many ways, was facilitated by the military conflicts of that time.

The first half of the 19th century was characterized by the spread of theoretical ideas about the leading role of the periosteum in the process of bone regeneration. This was due, firstly, to frequent observations of pronounced periosteal calluses in places of bone fusion, and secondly, to cases of "spontaneous bone formation" with preserved periosteum, which sometimes even gave rise to ideas about the "redundancy" of bone grafting. Microscopic technique has not yet been used to study the processes of bone regeneration, which was carried out solely on the basis of visual macroscopic

observations. However, the facts accumulated by that time were already enough to begin their serious theoretical understanding, which characterized the work of subsequent years.

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