Bone grafting in the pre-antiseptic era (historical review): Creation of the first theories related to bone grafting: 1860-1880

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Abstract. This article examines the period of formation of the theoretical foundations of bone plastic surgery and the ideas about bone regeneration in general, which predetermined the development of this branch of medical science in the following decades. The work covers the period from L. Ollier's experimental work to W.Macewen's operation (1881). At the time, there was a lively debate in the scientific literature regarding the fate of the transplanted bone fragment and the sources of bone tissue regeneration.Microscopic techniques have been used for the first time to study this process, albeit in a limited number of observations.The article analyses the arguments of each of the parties involved in the debate. Although no general concept was developed at that time, the accumulated facts formed the basis for subsequent clinical experiments made possible by the introduction of an antiseptic approach to surgical practice.

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

Introduction

It is fair to begin a new chapter in the history of bone grafting with the work of Louis Léopold Ollier, a physician from Lyon. In 1858-1860, he conducted several series of bone graft experiments in various animal species (1,2). In the first series of experiments, bone fragments were taken from living or recently killed animals, with or without periosteal preservation, and immediately transplanted into animals of the same species. In the second series, the bone sections before transplantation remained in the air for 10-75 minutes, or were taken from the animal after the same time after its killing, after which they were also transplanted to animals of the same species. In the third series, the bone was transplanted into animals of different species. Fragments of the humeral, peroneal, ulnar, radial, and metatarsal bones were used. The follow-up period was 2-7 months. The results of the study showed that in most cases bone fragments removed with the periosteum and transplanted into animals of the same species engrafted successfully. During the injection of arteries with cinnamon solution, the filling of the graft vessels was also noted. However, there were some cases of graft suppuration or graft encapsulation and resorption, which were more common in the second series of experiments.The author sometimes observed that, in his opinion, the periosteum remained viable even in the presence of bone necrosis. The grafts transplanted into animals of a different species, in all cases, either died or were absorbed. The same results were observed when transplanting bone fragments deprived of the periosteum (1,2).

On the basis of the data obtained, the author drew the following conclusions: the success of bone grafting was possible only with auto- or homotransplantation (i.e., transplantation into animals of the same species); the transplanted fragment retained its viability; its engraftment occurred due to the periosteum. As proof of its leading role, Louis L. Ollier transplanted the periosteum under the skin of animals and, in some cases, observed the formation of a bone plate corresponding to the shape of the periosteal fragment. He also drew attention to the fact that the medullary cavity of the graft did not correspond to that of the bone in the area of the defect margins, and was already undergoing secondary reconstruction. The author observed vascular ingrowth into the graft but assigned this phenomenon only an auxiliary value (1). Louis L. Ollier believed that the main reason for the failure of Pierre-Francois Percy operation, which we described in our previous publication (3), was the use of animal bone instead of human bone (2).

Evstafij Ivanovich Bogdanovskij, Ivan Gavrilovich Karpinskij (1861) experimented with the transplantation of diaphyseal bone in 8 dogs. In some cases suppuration was observed followed by bone necrotization, in others a capsule was formed around the transplanted fragments containing bone layers and being in close contact with the periosteum at the edges of the defect. Confident in the success of the subsequent osseointegration of the grafts, the authors formulated the following requirements necessary for the success of bone grafting:

1. The transplanted fragment must exactly match the size of the defect in size and shape. In this way, its tight contact with the walls of the perceiving bed is created.
2. The graft must be immobilized to prevent its mobility ordislocation.
3. Transplantation should be performed in cases where the tissues surrounding the defect are viable and well supplied with blood. Although the engraftment of the transplanted fragment occurs through the periosteum, it is in turn nourished by the surrounding tissues. With the so-called "sanatio per granulationem", the graft is inevitably deprived of nutrition and dies (4).

Yakov Nikiforovich Yakimovich (1863) also noted the importance of fixing a transplanted bone fragment (5).

Ivan Aleksandrovich Bredihin (1862) studied the process of regeneration of bone tissue using the microscopic technique. He noted an important role played by capillaries growing into the defect area from the side of the osteotomised surfaces of the defect edges. The author went on to conclude that the "bone scar" was formed not only by the periosteum, but also by growth from the edges of the bone. In the latter case, both the "soft parts" (bone marrow and its membrane, blood vessels) and the actual bone matter were involved in this process (6).

In turn, Julius Wolf (1863) argued that no reliable evidence of the viability of the bone graft had been provided. Foreign bodies (for example, bullets) can remain in body tissues, including bones, for decades, being surrounded by a connective tissue capsule, without causing inflammation. The mummy's bone looks the same as alive. Even filling the graft vessels with cinnabar proves nothing. According to the author, the dye can enter the lumen of mummified vessels. The restructuring that the graft undergoes in the body rather speaks not of its viability, but of degeneration. The thickening of the graft, which Louis L. Ollier considered to be the bone growth, in fact, according to Julius Wolf, was due to the presence of fragments of the connective tissue capsule. This is evidenced by the uneven, bumpy nature of its surface, while the normal bone should be smooth. Staining with madder could be proof of the viability of the transplanted fragments, but no appropriate experiments were performed. Another sign Julius Wolf believed to be reliable was the ability of the tissue to respond to external irritation. For this purpose, the author placed a metal plate on the bone surface of the graft and did not observeits fouling, which occurred on the intact bone (7).

Louis L. Ollier, responding to Julius Wolf, referred to Paul Burt's experiments (1864) on the transplantation of rat tails, which grew as well after transplantation as before, and to his own research on the introduction of periosteum into soft tissues, which caused bone formation.In parallel, he performed experiments with subperiosteal osteotomies. The author reported a complete recovery of the bone if the periosteum was preserved. If some of its fragments were left, then in the regenerate the corresponding areas of ossification were observed. In the case of the periosteum removal, bone was not formed (1).

Periosteal transplantation experiments, however, were not always successful. Reinhold Buchholz (1863), while transplanting the periosteum of the skull, both into soft tissues and into the area of the defect, had not observed bone formation, and concluded that the pericranium is unlikely to have the same osteogenic capacity as the rest of the periosteum (8). Louis L. Ollier himself failed to transplant a periosteum from one part of the human body to another (9).

In his classic work *Traité experimental et clinique de la régénération des os et de la production artificielle du tissuosseux* (1867), Louis Léopold Ollier summarised his earlier and later observations. On the basis of the experimental data obtained, he argued that the periosteum plays a crucial and determining role in the process of bone tissue regeneration. The author attributed only the auxiliary value to the bone marrow, as he did not observe the formation of a new bone during its transplantation into soft tissues. Although Louis L. Ollier was able to induce the formation of new bone by inserting the glass tube into the bone marrow cavity, he believed that this phenomenon was due to the artificial stimulation of the bone marrow cells. In clinical practice this method is unacceptable, since in case of excessive irritation the bone marrow substance is easily inflamed (1). The presence, allocated by some anatomists of that time, "internal periosteum", i.e., the shell of bone marrow (which now, according to F. Jackson (1904), is called endosteum [cited by 10]), he denied, admitting its existence only for the hollow bones of birds. He introduced the term medullization, which was understood as the gradual absorption of the inner layers of bone-by-bone marrow cells. Its final stage, according to Louis L. Ollier, is the filling of the enlarged bone marrow cavity with adipose tissue in mammals, or with air in birds. Even though the author, when studying the patterns of fracture healing, reported the formation of a strong bone adhesion between the edges of fragments formed due to the bone marrow, he argued that "although individual elements of bone tissue can produce bone to a more or less limited extent and under certain circumstances, neither of them nor all together, without a periosteum" cannot be said to "cause the true regeneration of previously removed bone" (1).

In the periosteum, in turn, Louis L. Ollier isolated an inner layer, which he called "osteogenetic", capable, in his opinion, to adhere to the surface of the bone, allowing it to regenerate even if the periosteum was scraped off (1, 2). A similar opinion was expressed by Rudolf Virchow, who called the inner layer of the periosteum "osteoplastic" (11). Carl von Rokitansky believed that dura mater also had bone-forming potential, making its preservation even more important than the "outer periosteum" (12). This view was confirmed by Forster (1863) and Aeby (1871), who found osteophytes in the cranial cavity of elderly people and mental patients (13). P. Florence wrote that both the periosteum and dura mater are equally important for the healing of a bone wound of the skull (14).

In 1869 Julius Wolf recognised the viability of the replanted bone fragments, having achieved their staining with madder. In his opinion, the surgical technique was of fundamental importance. In a new series of experiments, he used a chisel and sharp scissors instead of a cutting crown, which destroyed the ends of the bone fragment and prevented them from attaching firmly to the edges of the defect. The studies were carried out on the vault of the skull. The bone fragment was sharply separated from the surrounding bone on 3 sides, and broken on the 4th side, so that it was connected to the rest of the skull by a periosteal bridge.Julius Wolf performed experiments on pigeons, chickens, rabbits and dogs. At the same time, he concluded that rabbits were the best experimental model (15).

Julius Wolf did not carry out experiments on tubular bones in principle because he believed that bone transplantation would be impossible here, since no one had ever succeeded. As Mihail Fedorovich Rudnev has rightly pointed out, Julius Wolf ignored the study described by Louis Léopold Ollier on the successful transplantation of a rabbit radius fragment from the right forearm to the left (15).

A year earlier, under the direction of Christian Albert Theodor Bilroth, experiments had been carried out on the replantation of a fragment of the diaphysis of the radius of a pigeon after subperiosteal resection (1868). The removed bone was pre-crushed and placed under the periosteum "like in a bag". Necrosis of the grafted bone occurred in all cases (15).

Andrei Ivanovich Bajkov (1870) conducted experiments on transplanting bone marrow from one dog under the skin of another. They were all unsuccessful. However, in another series where bone marrow was taken from the femur or tibia and implanted under the skin of the same dog, the formation of bone tissue of varying degrees of maturity was observed in 50% of cases - from the initial stages to a fully formed bone with a lamellar structure containing the Haversian canals and marrow cavities. The author noted that his data directly contradicted Louis L. Ollier's results. He also observed an interesting phenomenon, the significance of which would be understood more than a century later: in some experiments, bone marrow cells developed into a cartilage-like substance which then transformed into bone, and in others, much less frequently, directly into bone tissue (16).

The next year, 1871, Yulian Aleksandrovich Kosmovskij, observing the regeneration process in the area of the skull defect in rabbits, concluded that the bone marrow was the only source of bone growth. Neither pericranium nor dura mater was involved in this process. As far as the "ossification points" are concerned, a more careful analysis shows that they were all associated with the regenerate growing from the edges of the defect. In addition, the author observed that, unlike the bones of the trunk, where cartilaginous tissue is initially formed, bone is immediately formed during the healing of defects in the cranial vault (17). In 1873, he also experimented with replanting trepanned skull fragments on 4 rabbits.In two cases the Julius Wolf method was used, in the third case the fragment was separated on all four sides by the acute route, and in the fourth case the entire outer cortical plate was separated. In the last two cases, the periosteum was completely removed, both from the graft itself and from the surrounding bone surface. In all cases, osseointegration of the replanted fragments was observed. This led the author to reaffirm his conclusion that, contrary to Louis Léopold Ollier, it is not the periosteum but the bone marrow that plays a decisive role in the process of bone regeneration (18). A similar conclusion was reached by F. Bush (1876), who observed a slowing of bone regeneration in the presence of bone marrow destruction. He also defended the view that osteoblasts are derived from embryonic cells of the bone marrow and not from "white blood beads", as Julius Friedrich Cohnheim believed (19).

The last experimental work within the time frame we are considering is the study by Mihail F. Rudnev (1880) (15). In the first series of experiments, he reproduced the conditions of Yulian A. Kosmovskij's experiment (18), followed by microscopic examination of the replants. After 5.5 months, the bone of the transplanted fragments had a normal structure in all cases. Further, the author completely replanted the metatarsal bones to the rabbits. Their structure was also fully preserved, including the periosteum and cartilaginous tissue. In both sets of experiments, the bone of the replanted fragments had a normal structure when examined under the microscope. However, they were not stained with madder. Mihail F. Rudnev pointed out that microscopic examination gives a much more reliable result than madder staining.Experiments on the transplantation of fragments of the diaphysis of long bones showed either resorption (in rabbits) or suppuration (in pigeons). However, the author believed that the presence of the transplanted bone fragment contributes to the restoration of bone tissue in the defect area, sharing the ideas of Bernhard Heine about "necrohormones". Moreover, Mihail F. Rudnev advanced the proposition that, even in the case of necrosis of the transplanted bone, the periosteum can connect to the surrounding viable tissues, and, subsequently, produce bone (15).

Such intensive experimental and theoretical work did not receive its clinical embodiment in the considered period. Louis L. Ollier, together with Charles-Emmanuel Sédillot, was awarded a special prize, established by the French Academy of Sciences after the end of the Italian War in 1859, for the development of the subject of "preservation of limbs by preservation of the periosteum", the amount of which was doubled by Napoleon III (20). However, this decision was taken primarily for the justification and improvement of the technique of operations of subperiosteal resections, which remained the main type of surgical intervention undertaken to preserve and restore bone. Bernard Rudolf Konrad Langenbeck (1877) urged that such operations be carried out step by step if possible, leaving the fragments of healthy looking bone connected to the periosteum, which will become the centre of new bone formation in the future. The author argued that in this way it is possible to restore bone even in the area of defects of significant size (21). However, as early as 1871, Yulian A. Kosmovsky, in an experiment, examined the tissue filling the defect of the skull vault, which he initially took to be bone; during the microscopic examination, he discovered connective tissue structures, calcified in some places. He also cited an earlier observation by L.

Martini (1856) in a 22-year-old girl with a skull defect caused by a bull's horn. The tissue filling the defect was as hard as bone, but post-mortem examination revealed it to be a cicatricial membrane (22). However, these works were not noticed by the general medical community at the time.

On the other hand, the use of cutaneous-periosteal flaps was becoming increasingly popular in medical practice at the time. New modifications of Nikolaj Ivanovich Pirogov's surgery for bone-plastic elongation of the foot was proposed: Leon Clement Le Fort (1873), Nikolaj Vasil'evich Sklifosovskij (1876), Jan Mikulicz-Radecki (1881) (operation by Vladimirov–Mikulicz) (23). Hardie (1875) proposed to sew the patient's index finger onto the nasal defect area. After engraftment, the finger was cut off and used for rhinoplasty [cited by 24]. Of course, the methodology did not get widespread, because it was associated with severe functional deformity of the hand. In the author's own observation, the finger underwent necrosis after being cut off.

Despite the unequivocal opinion of Louis L. Ollier on the inadmissibility of animal bone grafting in humans, Paterson (1874) used a canine radius fragment to replace the corresponding defect in humans after subperiosteal resection. After some time, the graft had to be removed due to the development of a purulent process (9). Nevertheless, Mihail F. Rudnev believed that the result was generally positive, as the graft contributed to independent bone formation in the defect area (15). In the same year, William Macewen replaced the patient's skull defect with a similar fragment from the dog's skull. One-third of the graft had to be removed because of suppuration, however the wound later healed and a solid substance was found on palpation in the defect area. The author also quoted a letter from Louis L. Ollier, who had attempted to use the periosteum of convicted criminals to close granulating wounds. After some time, a hard tissue of cartilaginous consistency was formed, but no further result could be traced (9).

The widespread use of bone grafting in clinical practice in the era of pre-antiseptic surgery was a high probability of developing inflammatory complications, and both clinical and experimental reports cited in this paper consistently describe cases of "sanatio per granulationem". Even amputation was then considered a "murderous operation". Eduard P.-M. Chassaignac (1866) wrote that "before asking how the patient would walk, one must know if he would walk" (23). For example, Yurij Karlovich Shimanovskij (1868) referred to data according to which during the Crimean War, the mortality during the performance of hip amputation in battlefield settings was 62.9% (25). Nikolai Ivanovich Studensky recalled the state of the surgical clinic at Kazan University: "There was neither a reception room nor an operating theatre in the clinic. Patients were examined in the ward, and operations were performed immediately in front of the patients… Instruments, bandages and charpie (threads obtained by unravelling old linen cloth, used instead of cotton wool - author's note) were kept in the ward, and charpie was prepared there and by the patients themselves; it lay on the table…A similar order of things existed at that time in all clinics and hospitals" (23).

Joseph Lister's ideas on the development of an antiseptic approach to surgery, first expressed in 1867 (26), were not immediately recognised by the medical community and did not become generally accepted until the mid-1880s (27), following the publication of Robert Koch (1878), who demonstrated the infectious nature of the wound process (28). It is therefore no coincidence that William Macewen's operation (9), which ushered in a new era in the history of bone grafting, was performed in the Glasgow hospital where Joseph Lister began to introduce his antiseptic surgical system, while for other medical centers, this approach was still innovative.

Conclusion

Although in clinical medicine free bone grafting (L. Ollier called it "direct or proper bone grafting") remained at the level of isolated experiments, the period under consideration was of great importance for its development. The main results were as follows:

1. The possibility of bone transplantation was conceptually justified. While Johann Friedrich Dieffenbach, describing the first attempts to perform osteoplastic operations at the beginning of the 19th century, called them "meaningless" (13), by the end

of the 1870s their clinical and biological relevance was proven, and no one had any doubts.

2. In fact, it was at that time that work began to study the osteoinductive potential of osteoplastic materials on a model of ectopic osteogenesis in experimental animals (1,2,16), although these terms themselves appeared much later (29). The possibility of transforming bone marrow mesenchymal cells into both cartilage and bone tissue was discovered (16).
3. The leading role of the periosteum in the process of bone regeneration remained the prevailing view. Henri-Louis Duhamel du Monceau should be considered the founder of this concept (30), but it was only in the 19th century that it received a fundamental theoretical justification, thanks to which it was able to dominate for such a long time. As noted by Ivan Ivanovich Grekov, the main role in this belonged to the works of Louis L. Ollier, who formed a solid foundation for this point of view (13). This was probably due to the fact of methods of stable fixation of bone fragments had not yet been developed, and clinicians could not fully assess the regenerative potential of endosteum. As noted by Ivan Ivanovich Grekov, it was the works of Louis L. Ollier that provided a solid foundation for this view (13), probably due to the fact that methods of stable fixation of bone fragments had not yet been developed and clinicians could not fully appreciate the regenerative potential of the endosteum. Even in the mid-1980s, recommendations were made to be radical with the bone when treating wounds, but sparing with the periosteum and preserving its fragments (31). The use of microscopic techniques in the study of biological processes in the historical period considered in this article was not yet widely recognised, which led to the persistent dissemination of ideas about the independent regeneration of bone from the periosteum (21). At the same time, the experimental work of Louis L. Ollier (1,2) not only studied the role of the periosteum in the process of bone growth, but also demonstrated the possibility and practical importance of its transplantation, both together with the bone and separately, which stimulated a series of researches in this direction.
4. However, there were alternative views on this issue. In the middle of the 19th century, the role of bone marrow structures, blood vessels and oppositional growth of bone tissue in the process of regenerative bone regeneration was convincingly demonstrated (6,13,16-18). The significance of these works was appreciated by the general medical community much later - after the discovery of the phenomenon of primary bone fusion (32), the separation of osteogenic precursor cells into deterministic and inducible (such as pericytes contained in the periosteum) (33).
5. It was during this period that the requirements were first formulated that are now considered a prerequisite for the success of bone grafting (stable fixation of the graft, its close contact with the edges of the recipient bed, adequate vascularisation of the surrounding tissues, etc.) (4).
6. The idea of including bone in the composition of complex flaps on the feeding leg was further developed in clinical practice. It has found application mainly in amputations of limbs (23).

Thus, by the beginning of the era of antiseptic surgery, a systematic approach to bone plastic surgery was developed, based on the scientific study of the process of bone regeneration. Although it was not possible to create a unified concept at that time, and the dispute was destined to drag on for another century, the results of the research works discussed in this article predetermined the active development of methods and materials for replacing bone defects that began in the 1880s.

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