

Textbook of Oral and Maxillofacial Surgery

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Chapter 16

Tissue transplantation

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Research achievements in immunology and related disciplines combined with sophisticated improvements in surgical techniques have made possible innovative organ and tissue transplantation procedures in many different surgical specialties. These scientific advancements have produced the successful application of improved techniques of bone, tooth, and skin grafting to oral and maxillofacial surgical practice. Many oral surgeons have adapted these new grafting principles in the development of more efficient procedures in preprosthetic surgery, in the treatment of congenital defects and orthodontic deformities, and in the reconstruction of jaws after oncological surgery. These developments have made possible a health care service that gives every indication of increasing in significance in the future.

Of the various types of transplantable tissues available, *bone* is the most commonly utilized in oral surgical procedures, although skin grafting is becoming increasingly popular in some areas of preprosthetic surgery and in postoncological restorative procedures. Cartilage, fascia, and dura mater are more rarely used as tissues grafts in oral surgical procedures.

In the grafting of intact *organ systems*, oral surgeons have adapted immunological research to the transplantation of viable teeth with incompletely formed roots. (The grafting of endodontically treated nonviable teeth constitutes a *tissue* rather than an organ transplant inasmuch as such teeth do not function as viable organs after surgical transplantation.) Although the viable tooth bud graft constitutes the principal organ transplant system with which oral surgeons are concerned, it should be remembered that the grafting of fresh autogenous marrow within a cancellous bone graft constitutes an intact organ system, with the marrow organ being involved in the process of hemopoiesis as well as osteogenesis.

In an organ- or tissue-grafting procedure, the transplanted substances are classified according to their immunologic origins:

1. Autogenous grafts composed of tissues taken from the same individual.
2. Allogeneic grafts (allografts) or implants composed of tissues taken from an individual of the same species who is *not* genetically related to the recipient.
3. Isogeneic grafts or implants (isografts or syngenesioplasmic grafts) composed of tissues taken from an individual of the same species who *is* genetically related to the recipient.

4. Xenogeneic implants (xenografts that are composed of tissues taken from a donor of another species, for example, animal bone grafted to man).

Generally, the term "implant" applies to the transplantation of nonviable tissues. The term "graft" is usually reserved for a true transplantation of living tissue with the success of the grafting procedure depending on the survival of the transplanted cells.

Immunological Concepts Applied to Oral Surgical Transplantation Procedures

The various methods of transplanting living *autogenous* tissues, although frequently presenting surgical and technical problems, do not as a rule involve immunological complications. However, graft rejection phenomena must be given serious consideration when allografts or xenografts of bone and cartilage are used in oral surgery. The basis for these rejection phenomena is reviewed in the following discussion to more fully identify the clinical response to various graft materials.

The immune response

The process by which the host rejects foreign graft material is a manifestation of an immunologically specific tissue reaction called the *immune response*. In the past it has been customary to explain the immune process within the context of disease susceptibility. The human body does not possess a natural immunity to many types of invading organisms. The immune process is initiated by exposure of the human host to invading bacteria, viruses, or parasites. The initial invasion of the host by these agents results in the production of specific substances in the tissues and body fluids that are capable of reacting with and destroying the invading agents. The invading agent causing the initiation of the immune response is called an *antigen*. The specific protein developed in the body in response to the antigen is called an *antibody*, or an *immune body*. This specific protein antibody is available to combined with the initiating antigen should it again invade the host organism. This reaction between the antigen and the antibody, which occurs on subsequent exposure or invasion by the antigenic substance, is called the *immune response*.

Tissue immunity and humoral immunity

Two types of immunity are described in relationship to the mechanism of antibody release in the host. The cell most often implicated in antibody production is the plasma cell. Large lymphocytes and reticulum cells are also known to produce moderate amounts of antibody. These cells are capable of releasing their formed antibody into the circulatory body fluids; hence the name *humoral immunity*.

Other cells of the invaded host may also respond to foreign antigens. These cells, however, do not release antibody into the intercellular fluids of the host but do react, often violently, with foreign material containing the antigens, giving rise to the so-called *tissue immunity*, which as the name implies operates at the cellular level. Humoral immunity lasts only as long as the specific antibody persists in the body fluids. Tissue immunity may last indefinitely.

Immune response applied to tissue transplantation

Because there is a tendency to think of the immune response in terms of infectious disease processes, it is not always appreciated that organic material taken from one person as

part of a tissue graft may be foreign to another individual. The rejection of tissue grafts made between unrelated members of the same species is called an *allograft response*. This rejection of a living homogenous or allogeneic graft is the result of the cellular reaction of the host to the transplanted antigens. Such rejection is not immediate, however, and an allogeneic homograft transplanted into a normal animal enjoys an immunological latent period during which its healing is indistinguishable from that of an autograft.

The length of this latent period depends on the disparity between donor and host, that is, the genetic relationship of the two. Genetic similarity between the donor and recipient of a transplanted tissue appears to be the major factor responsible for the success of the graft. For example, skin allografts transplanted between closely related mice (isografts in inbred strains) may remain in place for over a month; skin allografts between different lines of mice may, on the other hand, be destroyed in an acute inflammatory reaction within a few days.

The second set response

The destruction of a tissue allograft leaves the recipient host in a specifically immune state, which is a condition of heightened resistance that may last for months. A second allograft from the same donor transplanted within this period is destroyed much more rapidly than its predecessor; indeed, these second transplants (the so-called white grafts) are even rejected with little or no evidence of beginning revascularization. This is called a *second set* reaction and has been demonstrated in most tissue transplants, including bone and teeth.

All available evidence at present indicates that humoral or circulating antibodies do not play a significant part in solid tissue homograft rejection.

Methods used to attenuate the immune response in grafting

In attempting to solve problems of incompatibility in grafting from one individual to another, three approaches have been used. One approach attempts to modify the host's immune mechanisms to block the rejection of the graft. Various methods have been used to effect this modification in experimental animals, including thymectomy, the use of high and low dosages of antigen, the use of irradiation, and the employment of immunosuppressive drugs. A second approach attempts to alter the inherent graft antigenic properties so that normal immune defenses of the host will not be stimulated. (For example, irradiation, freezing, and freeze-drying tend to diminish graft antigenicity of bone.) A third method of attenuating or altering the antigenic properties of a graft by storage of the transplant organ in an intermediary host has been used experimentally. (Kidneys, for example, have been stored in intermediary host animals that have been given immunosuppressive drugs for the storage time period. The organ is then retrieved and transplanted into a third animal recipient.)

The first of the approaches just listed has been used largely in the form of immunosuppressive drugs in major organ transplants (for example, kidney and heart). This type of treatment has not been used clinically in oral surgical transplantation procedures. The second method of pretreating the graft material to alter its antigenicity has, however, been used successfully in the storage and preservation of allogeneic bone and cartilage for use in oral surgery. The third method remains highly experimental.

Tissue typing procedures by which individual donors may be identified as having tissues histocompatible with a given recipient have produced marked advancement in certain organ transplant surgery such as kidney transplantation. Characterization of HL-A locus in

genetic distribution and the matching of this genetic material, particularly in lymphocyte cytotoxicity testing, and other serological techniques have produced effective laboratory procedures for histocompatibility evaluation.

Bone Grafting

Historically attempts have been made for centuries to employ bone graft materials in surgical procedures. In 1668 Van Meekren is recorded as having successfully transplanted heterogenous bone from a dog to man in restoring a cranial defect. Hunter conducted experiments in the eighteenth century on the host response to bone grafts, noting the phenomena of resorption and remodeling of the graft matrix. The first successful autogenous bone graft was reported by Merrem in 1809. Macewen reportedly transplanted allogeneic bone successfully in clinic patients in 1878.

Various forms of devitalized bone from an animal source (xenografts) have been used clinically during the past half century. Orell in 1938 produced a graft material from bovine bone by the use of strong alkalis. Boiling and defatting procedures have been employed in the treatment of animal bone prior to its use in xenogeneic grafting. Bovine osseous tissue grafts treated with chemicals such as ethylenediamine, hydrogen peroxide, and strong detergents have also been used clinically.

Attempts have been made to preserve allogeneic bone by the use of chemical agents. Thimerosal (Merthiolate) coagulation was employed for some time as a method of storing bone taken at autopsy. The drastic treatment of human (allogeneic) bone by physical or chemical agents, however, is now generally thought to be an inferior method of preservation in comparison to cryogenic methods of tissue preservation. Cryobiological methods of storage were first employed by Inclin, who is credited with developing the first modern bone bank in 1942. Following the use of refrigeration (above-freezing temperatures) for the preservation of bone. Wilson developed a bone bank using freezing techniques.

Criteria used in bone graft evaluation

In evaluating the clinical and histological effectiveness of various bone graft materials, the following criteria are usually employed:

1. The graft must be biologically acceptable to the host (that is, it must not elicit an adverse immunological response).
2. The graft must *actively* or *passively* assist osteogenic processes of the host.
3. The graft material or its accompanying metallic or nonosseous supporting implant should withstand mechanical forces operating at the surgical site and contribute to internal support of the area.
4. Ideally the graft ultimately should become completely resorbed and replaced by host bones.

Allogeneic bone

Storage and preservation of allogeneic bone for grafting

The most successful tissue storage methods used in the banking of allogeneic bone have been cryobiological in nature, that is, by use of cooling, freezing, or freeze-drying environments. Bone grafts preserved by cryogenic methods are more rapidly and completely revascularized, resorbed, and remodeled than are allografts that have been deproteinized, boiled, or otherwise drastically treated.

The application of cryobiological techniques to bone preservation is predicated on the unique histological nature of osseous tissue. Unlike many soft tissue and organ systems having large cell populations, bone and cartilage are composed of relatively small numbers of living cells with large amounts of calcified and noncalcified intercellular matrix, which is considered to be nonviable. Since the survival of the cells of an allogeneic bone graft is not necessary or even desirable because of the previously discussed immunological factors, a method of storage that will bring about this cellular death without deleteriously altering the remaining osseous structure of the graft material is considered to be essential for the development of an effective graft substance. This is accomplished by freeze-drying and by most controlled methods of freezing at low temperatures. Since cells of a cryobiologically preserved bone graft do not survive, the assistance on the part of the graft to osteogenic processes of the host is purely *passive*. No active osteogenic stimulation is expected of these grafts. Such grafts offer their extracellular matrix as a system of absorbable surfaces over which new bone of the host may grow to reconstruct the grafted defect.

Although clinical evaluation of freeze-dried allogeneic bone has indicated that implants preserved in this manner are highly acceptable allografts, disadvantages associated with freeze-drying techniques have interfered with a more generalized use of this osseous material. These disadvantages relate to equipment costs and to the relatively large personnel requirements necessary for the performance of aseptic autopsies and for the processing and storing of the bone product. Efforts to minimize these disadvantages have been directed toward eliminating the need for aseptic autopsies by sterilization of the bone after its procurement by less time-consuming, nonsterile procedures. Sterilization methods employed have been in the form of irradiation from cathode and cobalt sources and chemical sterilization with such agents as ethylen oxide and betapropiolactone.

Clinical use of allogeneic banked bone

Freeze-dried and frozen allogeneic bone can be produced in various anatomical forms to conform to the needs of different oral surgical procedures.

Cancellous iliac crest bone can be ground into particles having a diameter of approximately 2 to 10 mm for use in confined intrabony defects after cyst enucleation. Smaller cancellous particles may be used in periapical areas after curettage, and larger cancellous chips may be used in recontouring procedures of the alveolar ridge. Some surgeons have also utilized cancellous allogeneic freeze-dried chips in the treatment of nonunion of fractures of the mandible.

Frozen or freeze-dried, split-rib grafts may be used as onlays to improve *width* and *contour* of deficient edentulous ridges and to cosmetically restore other facial bone deficiencies. Although freeze-dried allogeneic allografts of bone may be used in recontouring

procedures to improve the width of deficient edentulous alveolar ridges, autogenous iliac crest bone is recommended for rebuilding the *height* of deficient ridges. (See section on autogenous bone grafts.)

It may appear paradoxical that banked allogeneic bone will at times produce a better recontouring onlay implant for rebuilding deficient mentum areas than will an autogenous graft. The slow remodeling rate of the allogeneic bone in comparison to the fresh cancellous autograft permits the onlay graft to maintain the desired contour for longer periods of time postoperatively. Fresh autogenous bone grafts placed in this area not infrequently resorbed rapidly with no accompanying replacement of the graft by host osseous tissue to maintain the correct contour. The disadvantage of using banked allografts in the mentum area, of course, relates to the slow acceptance and slow bonding to the host bone, thus prolonging the postoperative period when slight trauma could completely dislodge the graft from the host bone, leading to failure of the procedure.

Although considered to be second-rate graft materials, cryobiologically preserved bone allografts are used in the surgical treatment of the indicated minor defects and can be used in selected cases as substitutes for larger autogenous bone transplants in patients for whom the operation necessary to obtain an autogenous graft is contraindicated.

A recent application of banked cryologically preserved allogeneic bone has been in certain orthognathic surgical sites following osteotomy procedures. If the surrounding musculature is conducive to good revascularization of the host bone and the graft recipient site, a banked bone implant will accomplish the desired surgical result as readily as an autogenous fresh graft. Such favorable orthognathic surgical sites primarily are in the ramus where the pterygomasseteric sling affords good vascularity to both the medial and the lateral aspects of the ramus and to any graft placed in this area. Additionally, allogeneic bone has been placed in Le Forte I osteotomy sites along the lateral aspect of the horizontal osteotomy and in the maxillary tuberosity-pterygoid space. It appears clinically that such banked implants do as well as fresh autogenous bone, and the application in the future for this type of implant-grafting procedure appears to be most promising.

Experimentally, allogeneic bone has been used in the attempted reconstruction of edentulous ridges; however, at this time the long-term effect of prosthetic function over such osseous restorations has not substantiated the ability of such grafts to withstand resorptive forces.

Another experimental way in which allogeneic banked bone has been used is as an interpositional graft after splitting the body of the mandible and raising the superior portion of the alveolar ridge, interposing the allogeneic graft between the raised superior portion of the ridge and the base of the mandibular bone. Again, the long-term response of such implant-grafts after the clinical application of prosthetic forces has not been determined. These types of procedures indicate the interest of surgeons in finding new applications and more effective procedures for bone grafts and implants in orthognathic surgery and in maxillofacial reconstruction.

Banked allogeneic bone may be subjected to various surface decalcification procedures as well as enzymatic treatment in order to render the surface of the graft more amenable to remodeling and eventual replacement with new host bone. The use of surface decalcified allogeneic bone appears to have application at the clinical level. The effect of such surface

treatment generally is to enhance the graft's acceptance through increasing the chance of resorption and remodeling of the surface-altered matrix of the osseous implant.

Clinical use of allogeneic banked cartilage

Cryobiologically preserved allogeneic cartilage has been utilized in restoring contour defects of facial bones. If the cartilage allograft is placed supraperiosteally within a soft tissue pocket (as in the mentum area), fibrous encapsulation and a prolonged resorption of the implant occur. This host reaction in certain soft tissue implant areas restoring facial defects is considered to be advantageous, since the cartilage graft will remain in place for longer periods of time, maintaining the desired postsurgical contour.

Cartilage placed subperiosteally that is well immobilized will unit with the underlying bone by the formation of reactive osseous tissue. Such grafts are so slowly revascularized, however, that they are subject to complete rejection and loss if only a slight dehiscence of the overlying soft tissue occurs postoperatively. Normally, the cartilage implant in such a recipient site will gradually be replaced with host bone. The bone replacement rate as well as the revascularization of cartilage onlays placed subperiosteally on edentulous alveolar ridges is generally slower than that of similarly implanted bone grafts. Thus in the selection of the graft material to be used in these areas, the disadvantage of the slow remodeling and replacement of subperiosteally placed implants of allogeneic cartilage must be weighed against the advantage of ease of manipulation of the cartilaginous tissue as opposed to the more rigid allogeneic bone graft material.

Xenogeneic bone

Attempted preparation of xenogeneic bone for grafting

Although properly preserved hard tissue allografts have a place in oral surgical procedures, the expense of preparing allogeneic bone in an acceptable manner has not been conducive to the widespread establishment of tissue banks in hospital centers. For this reason a continuing effort has been made through the years to develop an acceptable xenogeneic bone graft material.

As one would expect, cross-species bone and cartilage transplants stimulate an immune response on the part of the host. Studies have shown that in the case of bone allografts the main antigens are associated with nucleated marrow and bone cells contained in the transplant, whereas in the case of xenografts the osseous matrix and the serum proteins are also potentially highly antigenic. As a result the problem of rendering animal bone acceptable to the human host becomes increasingly difficult. Since the major antigenic component of animal bone is contained within the organic fraction of the tissue, this portion of the bone must either be altered or removed to render the product acceptable to the human host.

The problem of cross-species antigenicity in bone xenografting procedures has been approached for the most part by treating animal bone material with vigorous chemical measures to remove, alter, or destroy the organic portion of the osseous tissue. Consequently, although many chemical techniques have been described in the literature for processing of xenografts, relatively few reports have appeared describing the use of freezing and freeze-drying in xenogeneic bone preservation and storage.

As previously mentioned, the treatment of bovine bone by boiling in water, boiling in alkalies (such as potassium hydroxide), macerating in hydrogen peroxide, and extracting with ethylenediamine has been used in the past to render potentially antigenic xenografts acceptable to the host. The preservation of beef bone by storage in alcohol and in ether also has been described. However, extensive clinical and histological evaluations of most of these methods have indicated serious disadvantages that preclude the clinical use of these materials.

Attempts to produce an acceptable xenograft from calf bone, using a process that included treatment with chemical detergents and freeze-drying, resulted in a product that, although acceptable as a space-occupying implant in certain minor osseous defects, did not develop into an effective substitute for autogenous or even preserved allogeneic bone.

Animal cartilaginous tissue treated by various means has also been investigated as a xenogeneic implant material. Such materials have not enjoyed significant clinical acceptance.

Various organic extracts of animal bone have been used in the past in an effort to produce an inductor substance that would stimulate bone formation. Such studies have involved evaluation of the properties of the mucopolysaccharide fraction of bone and effects of chondroitin sulfates on bone repair. Results of these studies have been at best equivocal, and, to date, no clinical application is apparent.

This research efforts have not at the present time produce a clinically acceptable xenogeneic bone graft material.

Autogenous grafts

It is obvious that the most optimal type of bone graft material should be autogenous in origin. While there is general agreement among surgeons that autogenous bone is a superior graft material, there has been considerable disagreement as to the optimal anatomic form that this type of graft should take. Autogenous grafts are usually employed to restore large areas of lost mandibular bone following surgery or trauma. Restoration of the traumatically avulsed or the surgically resected mandible has been of paramount clinical concern for many years. Of all the facial bones resected in oncological surgery, the mandible is the most frequently removed. It is paradoxical that the most frequently resected facial bone is also the most difficult to reconstruct surgically. The constant movement of the mandible in swallowing and in speech and the unprotected contours of the mandible in the facial skeleton coupled with the relative paucity of blood supply to the area and the minimal amount of muscular tissue surrounding the structure make the mandibular bone one of the most difficult to esthetically and functionally reconstruct through osseous grafting. Reconstruction procedures are not only technically difficult but their prognosis is most uncertain. Since the degree of surgical difficulty attending the restoration of a resected or lost mandible is great, it is appropriate that the determination of maximum effectiveness of any graft material in maxillofacial surgery should be based on its ability to reconstruct this particular facial bone.

Some surgeons have preferred to use rib grafts for spanning such large defects, fabricating the transplant to the desired shape by notching and cutting the rib in order to bend the graft to the appropriate contour of the maxillofacial defect. Rib grafts also may be placed in an onlay position overlying the host bone, either on a decorticated or nondecorticated recipient site. For production of angle grafts to replace a disarticulated mandible, a costochondral rig graft may be employed with the cartilaginous portion simulating the temporomandibular joint and condyle. The overall postoperative results of the use of rib grafts

in large discontinuity defects of the mandible in general have not been consistently rewarding. Autogenous ribs, however, may be used to reconstruct smaller missing segments of the mandible with a fair degree of success.

Other surgeons have preferred to take solid, one-piece grafts from the iliac crest, cutting these to desired form and shape. Many types of mortising "carpentry" are performed to make the graft interface with the host bone in an onlay, inlay, or combination of forms of attachment with the remaining host bone fragments. The iliac crest graft also can be cut to simulate the angle of the mandible.

Additionally, a cut from the inner table of the iliac crest may give a curvature that, to a limited extent, simulates that of a mandibular hemisection. Such grafts, however, during the first 3 postoperative months tend to resorb at the interface between the grafts and the host bone. Such resorption leads to immobilization problems. Grafts utilized in this manner have a tendency to become mobile, displaced from their anatomical sites, and to undergo extensive resorption. In the use of solid one-piece grafts, care must be taken by the surgeon to effect maximal intermaxillary immobilization to avoid failure caused by the phenomenon of interface resorption.

Particulate autogenous marrow-cancellous bone grafting

Recently, experimental studies have demonstrated the marked osteogenic potential of hemopoietic marrow. Marrow taken from the iliac crest can be transplanted autogenously to effect new bone formation in various types of osseous defects. Autogenous hemopoietic marrow and autogenous cancellous bone containing marrow appear to be the only types of bone graft material that are capable of actively inducing osteogenesis. (As mentioned previously, properly preserved allogeneic bone in certain graft sites can passively assist the osteogenic process of the host, but this type of graft material is not actively osteogenic.)

The clinical exploitation of the marked osteogenic potential of hemopoietic marrow and cancellous bone has been impeded in the past by the lack of development of a satisfactory method of containing the graft within the surgical site and of preventing the ingrowth of fibrous tissue, which has a tendency to insinuate between the individual particles of the graft material, producing a fibrous union. Recent studies, however, have developed a technique whereby these particulate marrow grafts may be applied to many areas of oral surgical treatment. The technique that has been developed is one in which autogenous bone and marrow taken from the iliac crest is placed in a metallic chrome-cobalt or titanium mesh implant. The metallic mesh serves to span the discontinuity defect of the mandible or maxilla, contain the graft material, and immobilize the host bone fragments.

The use of autogenous rib grafts in restoring similar large areas of lost mandibular bone has not been particularly successful. Massive resorption of the rib grafts frequently results. In cases in which the surgeon can be confident of having a complete intraoral closure of healthy mucosa a cellulose acetate filter may be placed within the troughlike metal implant. The filter serves to further contain the graft and to prevent ingression of fibrous tissue into the graft area. The use of this type of autogenous graft material in the surgical system described was found to have several advantages over the solid one-piece autograft in the regeneration of large discontinuity defects of the mandible.

This technique has been used successfully in restoring large areas of the mandible, including the entire body of the mandible in cases of traumatic loss after gunshot wounds and

other types of injuries. More recently the technique has been applied to the reconstruction of resected mandibles after oncological surgery. The procedure is also used for the treatment of nonunion of the body of the mandible, particularly in cases of old nonunion or malunion of *atrophic* edentulous mandibles. The procedure may additionally be used for smaller traumatic or surgical defects.

The procedure of using autogenous particulate marrow in this system has the following advantages:

1. The particulate graft of marrow and cancellous bone is easily obtained by making only a small opening along the lateral surface of the iliac crest rather than taking a large portion of the ilium or a rib to effect the desired surgical result.

2. Complete healing of the grafted defects with viable bone is more rapid than when the solid one-piece autograft is used.

3. The need for intermaxillary fixation can be greatly reduced because of the rapid spanning and osseous regeneration of the defect by new bone and because immobilizing support of the host bone fragments is provided by the metal implant itself.

Treatment of the edentulous atrophic alveolar ridge. The use of surgical procedures to correct atrophied, deficient, alveolar ridges has included both soft tissue, ridge-extension-type surgery and the use of bone graft material to increase the osseous alveolar base. A technique employing the marrow-cancellous bone graft system has been utilized to extend the height of atrophic deficient alveolar ridges. It was found in a long-term, follow-up study of these types of grafts in clinical human patients that approximately 35% of the alveolar height restored at surgery was resorbed at the end of a 3-year period. It is believed that this technique compares favorably with the use of rib grafts to restore the edentulous alveolar ridge, in which, based on my experience and the observations of others, approximately 50% of the graft is lost during this same 3-year period. Neither of these two types of autografting procedures would appear to be completely feasible for the long-range treatment of the deficient edentulous alveolar ridge.

A more recent application of the marrow grafting principle to the treatment of deficient edentulous ridges has been the combination of marrow cancellous bone grafts with a subperiosteal metal implant used for the attachment of semiburied posts for implant denture construction. This new technique has resulted in a clinical application that has been used initially with considerable success. The patients are being observed on a long-term basis to determine whether the usual stresses transmitted directly through the posts to bone by way of the subperiosteal metal implant will produce the same degree of resorption as the mucosally transmitted forces of the conventional denture.

Treatment of maxillary clefts. Another application of the autogenous marrow and cancellous bone particulate graft has been in the secondary grafting of residual clefts of the alveolar ridge and the palate in congenital cleft palate cases. It was found that in children between the ages of 8 and 12 with residual osseous clefts of the alveolar ridge and anterior palate, the autogenous cancellous bone graft may be used effectively. It was found that the permanent cuspid and lateral incisor teeth on either side of the previously existing cleft may be moved into the cleft area orthodontically within 2 or 3 months of the time of grafting. Additionally, the maxillary arch may be expanded orthodontically to improve the occlusion after the bone grafting of the clefts. Thus the responsiveness of the viable marrow graft to

changes in function is well demonstrated by this particular grafting technique. It has been shown in the past that rib grafts in the same types of residual clefts were not successful because teeth could *not* be moved into the grafted area postoperatively, and considerable constriction of the lateral expansile growth of the maxilla sometimes occurred.

It is clear that in areas of the oral cavity in which a viable graft is necessary to respond to the forces of function and orthodontic movement, the autogenous particulate marrow-cancellous bone graft is the transplant of choice.

More recently, autogenous marrow grafts have been used in periodontal therapy by the placement of grafts in intrabony pockets. The same type of graft material is used in these smaller defects, with the grafting material being taken by a trephine biopsy needle from the iliac crest while the patient is under local anaesthesia. This technique of taking a small amount of the highly osteogenic graft material from the iliac crest using local anesthesia offers a new opportunity for the oral surgeon to obtain a maximally osteogenic graft with a minimal amount of trauma and inconvenience to the donor.

The use of autogenous particulate marrow and cancellous bone grafts in areas adjacent to the roots of erupted teeth must be accompanied by the caveat that the highly cellular pluripotentiality of living marrow grafts may stimulate an adverse cellular response and result in a clinical failure even though the osseous defect itself may be regenerated. The cellular marrow graft has the capacity to form osteoclasts that have as their function the resorption of nonvital bone and hard tissue trabeculae. This resorptive process leads to remodeling and paves the way for viable osseous regeneration. Such osteoclasts, however, may also attack other hard tissue matrices such as the cemental surfaces of roots of adjacent teeth and cause massive root resorption leading to the exposure of the pulps and complete loss of teeth. For this reason, in periodontal therapy, killed cell suspensions and nonvital allogeneic grafts that have been preserved by freezing usually are used instead of fresh marrow transplants.

The same precautions must be used in grafting in cystic areas next to the cervical portions of roots of adjacent teeth and in the use of marrow in palatal cleft grafting in adults. In cleft bone grafting, it does not appear that the placement of autogenous viable marrow against the roots of unerupted teeth in children leads to any resorptive process. In the adult patient, however, root resorption may occur in teeth located along the margins of the cleft after grafting.

Treatment of cystic bone cavities. Autogenous marrow and cancellous bone have also been utilized in large cystic cavities after the enucleation of keratinizing cysts or after removal of benign but locally aggressive tumors, such as ameloblastomas. It is found that in large cystic areas, the autogenous graft produces a more rapid regeneration of the defect and a more acceptable postoperative result than the banked homograft. Banked, freeze-dried allografts, however, continue to remain an acceptable graft material in the treatment of moderately sized cystic bone defects.

Autogenous bone chips obtained at operation from the oral cavity are usually qualitatively and quantitatively poor. Little cancellous bone is present at the operative sites of common oral surgical procedures. Most osseous specimens obtained from alveolectomies, ostectomies, and osteotomies are composed of cortical or lamellated bone. Such cortical chips are of little osteogenic value. They may, however, be used as an acceptably banked allograft that would be employed to fill well-demarcated intrabony defects and to restore contour to deficient osseous areas.

Summary of graft evaluation

Based on both experimental laboratory procedures and clinical experience it is possible to offer an overall evaluation of the surgical use of most types of bone graft materials. The relative effectiveness of the most common types of graft materials is given in the following outline. This evaluation is based on repeated experiments with laboratory animals, using various test systems and extensive clinical observation.

First-rate grafts

1. Viable autogenous marrow.
2. Viable autogenous cancellous bone.
3. Viable autogenous osteoperiosteal grafts.
4. One-piece, autogenous cortical-cancellous bone (iliac crest or rib).

Second-rate grafts

1. Autogenous cortical bone.
2. Banked, allogeneic freeze-dried bone.
3. Banked, allogeneic frozen bone.

Third-rate grafts (unacceptable)

1. Detergent-treated, freeze-dried xenogeneic bone.
2. Ethylenediamine-treated xenogeneic bone.
3. Fat-extracted xenogeneic bone.
4. Improperly preserved allogeneic bone.

Composite allografts-autografts

Current research studies indicate that a promising graft material for intraoral and extraoral use may be some combination of an acceptably preserved allograft and autogenous marrow. Marked osteogenic properties have been observed with the use of this combination of tissues in experimental animals.

The use surface-decalcified allogeneic bone combined with autogenous hemopoietic marrow has produced an acceptable composite graft material. The advantage of using such a composite allograft-autograft lies in the fact that the amount of autogenous graft tissue may be reduced to a minimum. With this combined graft, a much smaller extraction of marrow and cancellous bone from the iliac crest is necessary, with a lessening of postoperation complications. It was found that in the reconstruction of entire mandibles after oncological surgery for eradication of malignancies of the oral cavity, often an insufficient amount of hemopoietic marrow and cancellous bone could be obtained from one iliac crest. This necessitated the taking of autogenous marrow and cancellous bone from both ilia. In an effort to prevent the necessity of bilateral use of donor sites, a technique has been devised, utilizing a graft of allogeneic, surface-decalcified mandibular bone that has been "hollowed out" to enable the allograft to contain autogenous marrow within its troughlike structure. Initial experimental work with this technique has been most successful. It would appear to be an acceptable method of reducing the amount of autogenous graft material necessary to regenerate a given area of mandibular or maxillary bone.

The combining of recently acquired knowledge about graft materials with results of present studies on osseous repair phenomena offers exciting areas for future surgical techniques.

Experimental studies related to bone graft procedures

Some promising bone grafting procedures in oral surgery have evolved from investigations of normal osseous healing mechanisms. By means of appropriate intravital labeling with tetracycline, it has been possible to delineate and predict areas of enhanced osteogenic activity after injury or surgical trauma to the facial bones. These areas of osteogenic potential have been intensively investigated to determine the feasibility of utilizing these regions as sites for developing new oral surgical procedures and new bone-grafting techniques.

One area of enhanced osseous reparative response was found to occur along the lingual aspect of the mandible after removal of buccal or lateral osseous tissue in alveolectomy procedures in dogs and monkeys. This subperiosteal lingual area has been found to be an excellent site for onlay implantation of grafts.

It has been found, however, that in experimental fractures of the body of the mandible in rhesus monkeys, callus formation in *endosteal* (marrow-vascular space) areas predominates over *subperiosteal* callus proliferation in effecting bony union. Experimental comparison of gap-spanning grafts of the mandible placed in various positions in an effort to obtain the most optimal anatomical placement of grafts at surgery indicated that the best graft placement was in an onlay position adjacent to the marrow-vascular spaces of the host bone fragments and not in an overlapping onlay position.

Another aspect of the relationship of osseous repair to grafting procedures involves the optimal time for bone implantation. Important studies have been made of the histological effect of delayed grafting procedures in which bone implants were placed several days after an initial surgical trauma.

An important peripheral application of the experimental studies of bone healing phenomena has been in understanding more fully the postsurgical osseous repair responses in the normal mandible and maxilla. Following surgical osteotomy of the alveolar crest or the removal of teeth or both, it was found that in addition to the proliferation of bone along the lingual subperiosteal aspect of the mandible, considerable bone formation occurred surrounding, and at the superior portion of, the underlying mandibular canal. Since this phenomenon was observed repeatedly in experimental animals, especially in fully adult rhesus monkeys, it is felt to be significant in explaining the occasional paresthesia that is observed following the removal of third molar teeth in clinical patients in whom no direct communication to the underlying mandibular canal was seen at the time of surgery. It is now believed that a normal healing response to the removal of third molar teeth is the formation of a certain amount of bone around the mandibular canal. In certain instances, representing possible individual variance, this formation of bone may be excessive. Such excessive bone formation may conceivably cause changes in the neurovascular bundle and result in paresthesia. Further work on these healing responses will undoubtedly elicit valuable information for the clinician in understanding and managing various postoperative complications.

Another important finding resulting from research of healing responses of the mandible has led to a more efficacious treatment of patient with osteoradionecrosis or postirradiation osteomyelitis requiring surgery and bone grafting procedures. It was found in experimental animals following irradiation and surgery, that of the two main areas of repair existing in the mandible, that is, the subperiosteal-lingual component of repair and the marrow-vascular repair component, the subperiosteal component of repair is the more severely damaged by the radiation process. With the passing of time after irradiation, the marrow-vascular component of repair returns partially with revascularization of the obtunded vasculature of the marrow-vascular spaces. However, the periosteum rarely regains its preirradiation capacity of osseous repair potential and does not form bone in response to a surgical procedure or assist in the acceptance of a bone graft. Therefore, the surgeon, in undertaking sequestrectomies, saucerization procedures, or bone grafting procedures in the postirradiated mandible, should develop surgical techniques that rely on the marrow-vascular component of the patient's remaining osseous structure to revascularize and to assist in the healing process. Procedures that rely on the subperiosteal component of repair, such as placing only one-piece onlay grafts along the lateral surface of an irradiated mandible, will result in failure because the patient's subperiosteal component of repair will not return following irradiation and, in the case of the onlay graft, no bonding of the graft to the host bed will occur. This is an extremely important point in undertaking osseous surgical operations or grafting procedures in the irradiated patient.

Skin Grafts

Autogenous skin grafts have been used in oral surgery for some time. Recently, the use of split-thickness skin grafts in preprosthetic surgery has received additional emphasis with the development of more efficient surgical techniques. Skin grafts used in oral surgery may be of two types: full thickness and split thickness.

Full-thickness grafts are generally used in plastic surgical reconstruction of large facial defects and may be employed to line the oral or nasal cavities in such facial reconstruction procedures. However, for the most part, autogenous skin used in oral surgery is of the split-thickness type, ranging from 0.015 to 0.022 inch in thickness. When used in the oral cavity, such a graft survives and becomes an integral part of the mucosal surface. In addition to the use of such grafts in preprosthetic vestibuloplasty surgery, split-thickness skin transplants may be used to cover a primary dressing over a stent after resection of various areas of the mandible or maxilla in eradication of tumors. The split-thickness skin graft is placed over a stent that is secured in place for approximately 7 to 10 days; at the end of this period, the obturator or stent is removed and the graft is trimmed. This graft material then serves as a soft tissue covering, supporting the surgical site. The split-thickness graft may later be reconstructed with a larger, thicker skin graft if necessary or with a composite bone and skin transplant procedure.

Allogeneic split-thickness skin obtained from the tissue bank and preserved by cryogenic means may be used as a *temporary* dressing for burns and skin abrasions. Oral surgeons have found this material an excellent dressing for facial abrasion contaminated with debris as a result of automobile accidents. After the debris-tattooed areas are vigorously scrubbed, the allogeneic skin is placed over the bleeding surface and kept in place for 7 to 10 days. Although these grafts later slough and are removed, they leave a clean, granulating surface, which is optimal for maximum epithelization.

Tooth Transplantation

During the past quarter of a century, research investigation of allogeneic tooth transplantation procedures has greatly increased. This renewal of interest in the centuries-old surgical exercise of dental transplantation was occasioned by the advent of antibiotic therapy and the almost simultaneous development of tissue banking and histocompatibility testing procedures.

Good evidence supports the view that teeth are capable of being antigenic. The failure of tooth transplants to elicit overt immune responses may be the result of several factors. One interesting theory proposes to explain this lack of detectable immune response on the basis of the alveolus being a site of immunological privilege not subject to the usual laws of transplantation. Further work has tended to disprove this reasoning, however. The immune response phenomenon after tooth transplantation, although not of the same magnitude as that elicited by other types of tissues, may be evidenced by the following:

1. A chronic inflammatory infiltration of cells surrounding the transplant and infiltrating the pulpal tissue.
2. Failure of the pulp to function as a dentin-forming agent and failure to assist in the completion of the structure of the tooth root.
3. Fibrous encapsulation and root resorption with replacement by osseous tissue.

It has been suggested that the following two phases are present in the immune response of the host to allogeneic homografts of teeth:

1. An early phase that is part of a reaction to the soft tissue portion of the transplant.
2. A later, weaker phase in reaction to the less antigenic hard structure of the tooth.

Allogeneic tooth transplantation

Many attempts have been made to preserve tooth buds by refrigeration, by various freezing techniques, and by tissue culturing. In the final evaluation, these attempts have generally been unsuccessful. Clinical acceptance without immediate rejection has been recorded after the transplantation of allogeneic teeth previously stored under these various conditions. However, no tissue culture or cryobiological method has been able to preserve the pulp so that it could assume a functional state subsequent to transplantation. Necrosis of transplanted pulpal tissue invariably occurs after the storage of developing teeth by freezing and tissue culturing. Such necrosis results, of course, in a failure of further root development, and the pulp is gradually replaced by host fibrous and osseous tissue.

In the transplantation of pulpless, fully matured teeth from a homogenous allogeneic source, initial apparent acceptance has been obtained. However, ankylosis and progressive root resorption are the almost universal sequelae of such surgical procedures.

Although experimental work continues in evaluating the effects of histocompatibility testing of donor material, the pretransplantation treatment of the root with fluoride and other agents, and the cryobiological storage techniques of tooth banking, the present level of

investigation does not support the extensive clinical use of homogenous allogeneic tooth transplantation.

Autogenous tooth transplantation

Although experimentation with tooth homografts has not been productive clinically, autogenous transplantation of teeth has during the past several years enjoyed a measure of success. A resurgence of clinical research in this area has occurred, with new surgical techniques developed in an effort to improve the transplantation success rate. A detailed surgical procedure has been described by Hale and others for the transplantation of developing third molars to the first molar position in the younger age groups. Proper patient selection is considered to be most important. Adequate mesiodistal width of the host implant site, absence of acute periapical or periodontal inflammatory states, and general oral health of the patient are emphasized. The optimal root development of the tooth to be transplanted is approximately 3 to 5 mm of root growth apical to the crown. The recipient site is prepared surgically by removing the interseptal bone at the crest of the ridge to produce the proper size of alveolus to receive the transplant. The transplant is removed from the donor site by elevator and forceps. In one technique the portion of the dental follicle surrounding the transplant may be removed. Damage to the soft tissue of the root sac, however, must be avoided. The tooth is placed in the recipient site just below the level of occlusion and stabilized with stainless steel wire ligatures crossed over the occlusal surface of the transplanted crown. Surgical cement is packed around the transplant and the crossed wire ligatures. Some surgeons prefer to use an acrylic splint for stabilization. The surgical cement splint is usually allowed to remain in place for 14 days; acrylic splints may be employed for longer periods.

In another technique the developing third molar tooth is removed with the operculum, gubernaculum, and follicle intact and transplanted to a first or second molar recipient site beneath a mucogingival flap. An acrylic splint is also constructed in this procedure to maintain the intercoronal space and to prevent occlusal drift of the teeth mesial and distal to the transplant. As the transplant erupts into position, the splint is trimmed to permit proper tooth movement.

Various success rates using this procedure have been reported in the literature, with 5-year successes observed in 50% of cases. Failure of complete root formation frequently occurs, and root resorption is not uncommon. The cause of such resorption has often been attributed empirically to damage to surrounding periodontal structures in the surgical transplantation procedure. Root resorption phenomena in autogenous tooth transplants have been studied by various techniques. Some investigators have found that the presence of periodontal ligament surrounding a transplanted tooth inhibits root resorption if a portion of the accompanying alveolar bone is implanted along with the grafted tooth. Others have shown that the transplantation of teeth together with surrounding periodontal ligament and bone has resulted in an extensive root resorptive process.

The autotransplantation of fully developed teeth has been attempted using various surgical techniques. The transplantation of fully matured, impacted maxillary cuspid teeth has been effected in a one-stage procedure. Initial attachment of the periodontal ligament after surgery can be demonstrated, and the transplanted tooth may be retained as a member of the dental arch for varying periods of time. Root resorption eventually occurs, however, and rarely do these transplants remain in place for longer than 5 years postoperatively.

Reimplantation

Reimplantation refers to a dental procedure that is in reality a form of autogenous transplantation in which the avulsed or extracted tooth is returned to its original alveolus. Reimplantation of avulsed or partially avulsed teeth with incompletely formed roots and with or without a concomitant fracture of the surrounding alveolar bone may be undertaken in many cases. Proper splinting is essential in retaining the reimplanted tooth in the dental arch, although in some cases the reimplanted tooth can be digitally repositioned in such a manner as to make further mechanical splinting unnecessary. Root canal therapy may become necessary if revascularization of the pulpal tissue does not occur postoperatively.

Immediate endodontic therapy is necessary in reimplantation surgery involving completely avulsed teeth with fully formed roots and in all cases in which considerable time has elapsed between the accidental avulsion of the teeth and the institution of treatment.

Of the dental transplantation procedures used at the present time, the autogenous grafting of the developing third molar appears to be the most successful. Good evidence supports the autogenous transplantation of the third molar tooth as a practical procedure in well-selected cases.

Summary

Current and projected investigations of bone and tooth transplantation are directed toward solving clinical oral surgical problems that are immunological, anatomical, and physiological in nature. Research in these problem areas must of necessity bring to bear the work of other disciplines in evolving new and effective clinical procedures. Root resorption after both homogenous and autogenous tooth transplantation, rejection of chemically treated osseous xenografts, the response of grafted areas to occlusal and prosthetic function, and the determination of the optimal time and anatomical location for grafting are all problems that must be solved to evolve more efficacious oral surgical transplantation procedures of the future.