THE MINIMIZATION OF MORBIDITY IN CRANIO-MAXILLOFACIAL OSSEOUS RECONSTRUCTION
Bone graft harvesting and coral-derived granules as a bone graft substitute

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OU LU 2003
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Bone graft harvesting and coral-derived granules as a bone graft substitute

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Abstract

Reduction of morbidity in osseous reconstruction of cranio-maxillofacial bony defects could come from development of less invasive bone graft harvesting techniques or by elimination of bone graft donor sites using a bone graft substitute. This work studies outcomes and morbidity associated with these two approaches.

A power-driven trephine was used to harvest bone from the anterior iliac crest using a minimally invasive surgical technique. Initially the safety of the technique was evaluated in a cadaver model. Twenty-five freshly preserved adult cadavers had a total of 250 cancellous cores of bone harvested from 50 anterior iliac crest sites. Twenty intentional perforations were made to the maximum depth possible with the instrumentation tested. No encroachment upon the peritoneum was found.

A total of 84 patients had 333 cores of cancellous bone harvested using the same approach with a complication rate of 3.6% and a patient satisfaction rate of 98.8%. In a further 76 patients the motorized trephine method was compared to traditional open iliac crest corticocancellous block harvesting. The trephine group ambulated earlier, required fewer days of hospital stay and had significantly lower pain scores than the open iliac crest group.

Coral-derived granules were used as a xenograft bone graft substitute to treat bony defects in the cranio-maxillofacial skeletons of 36 patients with 54 sites and followed for 12 to 36 months. The augmentations produced satisfactory results with the following complications noted: overt wound infection 1.8%, wound irritation 3.8% and clinically evident resorption in 9.3% of augmented sites.

Coral-derived granules were then used to treat 48 dento-alveolar defects in 21 growing patients with trauma induced tooth-loss in the anterior maxilla and elective ankylosed tooth removal in the posterior maxilla and mandible. Coral granules were significantly more efficacious in reconstructing alveolar defects in the posterior maxilla or mandible (93.5%), than the anterior maxilla (17.6%).

The minimally invasive technique using a power driven trephine was successful at reducing morbidity from bone graft harvesting at the anterior iliac crest. Coral-derived granules can be used in selected situations as a bone graft substitute and minimize post surgical morbidity by eliminating the bone graft donor site.

Keywords: anterior iliac crest, autogenous bone grafts, bone graft substitutes, trephine
To My Dear Children, Kinga, Eniko and Hunor,
For yours are the many wonderful future goals to strive for...
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Oulu, April 2003

George Kálmán Béla Sándor.
(Sándor György Kálmán Béla).
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ASIS</td>
<td>anterior superior iliac spine</td>
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<tr>
<td>BMP</td>
<td>bone morphogenetic protein</td>
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<tr>
<td>CA</td>
<td>carbonic anhydrase</td>
</tr>
<tr>
<td>CC</td>
<td>cancellous cores</td>
</tr>
<tr>
<td>CCBG</td>
<td>corticocancellous block grafts</td>
</tr>
<tr>
<td>CDG</td>
<td>coral-derived granules</td>
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<tr>
<td>DBM</td>
<td>demineralized bone matrix</td>
</tr>
<tr>
<td>DO</td>
<td>distraction osteogenesis</td>
</tr>
<tr>
<td>FGF</td>
<td>fibroblast growth factor</td>
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<tr>
<td>GBR</td>
<td>guided bone regeneration</td>
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<tr>
<td>HA</td>
<td>hydroxyapatite</td>
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<tr>
<td>IGF</td>
<td>insulin-like growth factor</td>
</tr>
<tr>
<td>PDGF</td>
<td>platelet-derived growth factor</td>
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<tr>
<td>PGA</td>
<td>polyglycolic acid</td>
</tr>
<tr>
<td>PLA</td>
<td>poly lactic acid</td>
</tr>
<tr>
<td>PRP</td>
<td>platelet-rich plasma</td>
</tr>
<tr>
<td>PSIS</td>
<td>posterior superior iliac spine</td>
</tr>
<tr>
<td>rhBMP</td>
<td>recombinant human BMP</td>
</tr>
<tr>
<td>TCP</td>
<td>tricalcium phosphate</td>
</tr>
<tr>
<td>TGF-β</td>
<td>transforming growth factor β</td>
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**Glossary of terms**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Allograft</td>
<td>A graft derived from tissue taken from another individual of the same species.</td>
</tr>
<tr>
<td>Alloplast</td>
<td>Synthetically derived reconstructive material.</td>
</tr>
<tr>
<td>Anterior superior iliac spine</td>
<td>The most anterior superior point of the ilium which gives attachment for the inguinal ligament and sartorius muscle.</td>
</tr>
<tr>
<td>Autograft</td>
<td>A graft derived from tissue of the same individual.</td>
</tr>
<tr>
<td>Bone graft</td>
<td>Bone material used to replace bone tissue in a defect.</td>
</tr>
<tr>
<td>Bone graft substitute</td>
<td>A material other than bone used to replace bone tissue in a defect with the purpose of avoiding a donor site.</td>
</tr>
<tr>
<td>Graft</td>
<td>Transferable material derived from living cells that can be surgically moved from one location to another for the purposes of reconstruction.</td>
</tr>
<tr>
<td>Iliac crest</td>
<td>The superior most curved border of the fan-shaped ilium which connects the anterior to the posterior superior iliac spine and provides attachment as part of the insertion of the external oblique muscle.</td>
</tr>
<tr>
<td>Iliac tubercle</td>
<td>A widening of the iliac crest at the insertion of the iliotibial band two to three centimetres posterior to the anterior superior iliac spine.</td>
</tr>
<tr>
<td>Osseointegration</td>
<td>The formation of a direct bone to biomaterial interface without any interposed fibrous connective tissue.</td>
</tr>
<tr>
<td>Osteoconduction</td>
<td>The ability to guide bone formation on the surface of a material or scaffold in a bony environment.</td>
</tr>
<tr>
<td>Osteogenesis</td>
<td>The formation of new bone from osteocompetent cells.</td>
</tr>
<tr>
<td>Osteoinduction</td>
<td>A process whereby one tissue or a product derived from it causes another undifferentiated tissue to differentiate into bone.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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<tr>
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</tr>
<tr>
<td>Posterior superior iliac spine</td>
<td>A sharp spine which forms the posterior end of the iliac crest.</td>
</tr>
<tr>
<td>Xenograft</td>
<td>Bone material or a graft derived from an individual of a different species.</td>
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List of original papers

The thesis is based on the following original articles, which are referred to in the text by numerals I to V:


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Contents

Abstract
Acknowledgements
Abbreviations
Glossary of terms
List of original papers
Contents
1 Introduction .................................................. 19
2 Review of the literature ......................................... 22
   2.1 Structure, function and physiology of bone ......................... 22
   2.2 Bony defects in the cranio-maxillofacial skeleton ...................... 23
   2.3 Unique aspects of alveolar ridge defects and resorption ............... 24
       2.3.1 Prevention of alveolar ridge resorption ..................... 24
   2.4 Methods to augment deficient bone ............................. 25
       2.4.1 Processes of bone healing .................................. 25
           2.4.1.1 Osteoinduction ........................................ 26
           2.4.1.2 Osteoconduction ........................................ 26
       2.4.2 Local procedures to augment existing alveolar bone ............ 27
       2.4.3 Autografts ................................................ 29
       2.4.4 Allografts ................................................ 30
       2.4.5 Xenografts ................................................ 31
       2.4.6 Synthetic bone substitutes .................................. 32
       2.4.7 Osteoactive agents ....................................... 33
           2.4.7.1 Bone morphogenetic protein ............................ 34
           2.4.7.2 Transforming growth factor β .......................... 35
           2.4.7.3 Platelet-derived growth factor .......................... 36
           2.4.7.4 Bioactive polypeptides ................................. 36
           2.4.7.5 Stem cells ............................................. 37
   2.5 Harvesting autografts ....................................... 38
       2.5.1 Vascularized versus non-vascularized bone grafts ............... 38
       2.5.2 Potential non-vascularized donor sites .......................... 38
   2.6 Bone graft harvesting methods at the iliac crest ..................... 39
       2.6.1 Minimally invasive surgery .................................. 39
       2.6.2 Trephines and the iliac crest ................................ 40
   2.7 Coral-derived granules ....................................... 42
3 Aims of the study ................................................................. 45
4 Materials and methods ......................................................... 46
  4.1 Subjects and grafts ......................................................... 46
  4.2 Methods and techniques ................................................ 49
    4.2.1 Surgery ................................................................. 49
      4.2.1.1 Cadaver iliac crest harvest .................................. 49
      4.2.1.2 Patient iliac crest harvest ................................... 53
      4.2.1.3 Cranio-maxillofacial coral-derived granule reconstruction . 56
      4.2.1.4 Dento-alveolar coral-derived granule reconstruction ......... 57
  4.2.2 Evaluation of the surgical outcomes ................................. 58
    4.2.2.1 Cancellous core dimensions ................................... 59
    4.2.2.2 Questionnaire .................................................... 59
    4.2.2.3 Post-operative clinical examination, gait and discharge criteria .............. 60
    4.2.2.4 Visual analogue scale ......................................... 60
  4.2.3 Statistics .............................................................. 60
5 Results .................................................................................. 62
  5.1 Cadaveric and patient cancellous core dimensions and perforations of the medial iliac cortical plate .......... 62
  5.2 Clinical course of anterior iliac crest harvesting methods ................................................. 63
  5.3 Cranio-maxillofacial reconstruction with coral-derived granules .............................. 65
  5.4 Dento-alveolar reconstruction with coral-derived granules ......................................... 66
6 Discussion ............................................................................. 68
  6.1 General comments .......................................................... 68
  6.2 Methodological aspects ...................................................... 70
  6.3 Reduction of morbidity ....................................................... 71
    6.3.1 Safety of trephine harvesting of the anterior iliac crest ......................... 71
    6.3.2 Morbidity with trephine harvesting .................................... 72
    6.3.3 Morbidity with coral-derived granules in the cranio-maxillofacial skeleton .......... 74
    6.3.4 Morbidity with coral-derived granules in the dento-alveolar area ........ 76
  6.4 Clinical implications and recommendations ........................................ 77
  6.5 Future prospects ............................................................ 78
7 Summary and conclusions .................................................... 80
8 References ............................................................................ 81
Original papers
1 Introduction

Bony defects in the cranio-maxillofacial skeleton may arise as a result of congenital areas of failed development such as in patients with cleft lip and palate, the results of ablative surgery in which segments of bones are resected to treat tumours, and due to trauma in which case osseous tissue may have been traumatically avulsed. Such osseous defects can be reconstructed by bone grafts or hopefully, in the future, using bone graft substitutes or by modulating bone regeneration using a variety of osteoactive agents.

In the future, the ideal clinical scenario would have a surgeon identify an osseous defect, reach up to a shelf for a container of a reliable bone graft substitute, obviating the need for a second surgical site, and sparing the patient a donor site defect. However that day has not yet arrived, as autogenous bone still remains the gold standard for maxillofacial osseous reconstruction (Clokie et al. 2000). Bone grafting studies have shown, that autogenous cancellous bone produces the most successful and predictable results (Marx 1994). Therefore, the ability to harvest and graft autogenous bone using a minimally morbid technique would greatly enhance the success and patient acceptance of oral and maxillofacial reconstructive surgery by reducing morbidity.

Sources of non-vascularized autogenous bone for grafting can be broadly divided into local and distant sites, and their successful application to maxillofacial reconstructive surgery is well documented (Marx 1993). If the defect requiring a graft is small, often local or intra-oral donor sites are sufficient (Kainulainen et al. 2002a). When a moderate to substantial amount of bone is required, the distant or extra-oral sites are usually employed. Of these distant sources, the iliac crest has become a favoured donor site because of the relative ease of surgical access and the quantity of bone available (Dingman 1950, Converse & Campbell 1954, Flint 1964, Levy & Siffert 1969, Crockford & Converse 1972, Mrazik et al. 1980, Hall & Smith 1981).

The anterior ilium provides an adequate volume of bone for many of the cranio-maxillofacial reconstructive procedures that require grafting. While a variety of techniques have been devised with the intent to reduce morbidity (Wolfe & Kawamoto 1978, Mrazik et al. 1980, Grillon et al. 1984, Tiley & Davis 1984, van der Wal et al. 1986), the most commonly employed and least complex technique is to harvest a corticocancellous block through either a medial or lateral approach to the anterior ilium. In 1994 Tayapongsak et al. found no significant difference in morbidity in a comparative
study of lateral versus medial surgical approaches to the anterior ilium. However, these very routine standard approaches can still produce significant morbidity for the patient (Cocklin 1971, Wolfe and Kawamoto 1978, Marx & Morales 1988, Tayapongsack et al. 1994). Because of this degree of morbidity clinicians have been hesitant to adopt bone grafting as a treatment option and patients have been reluctant to accept such treatment. Thus, there is an advantage to developing a method for obtaining bone from the anterior ilium, which creates less morbidity for the patient than the traditional method.

The use of trephines in other fields of surgery has been shown to be safe (Duncan et al. 1980, Kreibich et al. 1994). The technique of using a trephine to harvest bone specimens from the anterior iliac crest for the purpose of biopsy has been used with minimal morbidity (Waldman & Kleinfeld 1970, Smirnov & Baranov 1971, Johnson, Kelly & Jowsey 1977, teVelde et al. 1978, Schuyl, Meulmans & van Eek 1979, Minns & Sher 1983, Faugere & Malluche 1983). The use of a power-driven trephine to procure bone from the anterior iliac crest is a simple technique, and should be adaptable to a minimally invasive surgical approach for the purposes of bone graft procurement with the intent to minimize morbidity.

Alternatively, a bone graft substitute would be ideal in minimizing post surgical morbidity by eliminating the donor site, thereby decreasing post-operative discomfort and saving the surgeon the time required to harvest bone. The ideal bone graft substitute should be biologically inert, readily available, easily adaptable to the site in terms of size and shape, biodegradable and replaceable by host bone (Bajpai 1983).

Many materials have been used as bone graft substitutes in the past. One formerly popular material, hydroxyapatite (HA), had been used extensively. Studies have demonstrated that the porous form of HA allows rapid fibrovascular tissue ingrowth which may stabilize the graft and help resist micromotion (Jarcho 1986, Alexander et al. 1987, Kenny, Lekovic & Caranza 1988, El Deeb & Holmes 1989, Ricci et al. 1989). However, HA may not undergo appreciable resorption. Furthermore, histological studies have shown that HA does not completely ossify, but rather, becomes encapsulated with fibrous tissue (Rosen & McFarland 1990, Byrd, et al. 1993).

On the other hand, coral-derived granules (CDG) do exhibit some of the characteristics described by Bajpai in 1983, including being completely resorbable and replaceable by host bone (Chiroff et al. 1975, Guillemín et al. 1987, Roux et al. 1988a).

CDG consist of natural coral skeletons from the genera Acropora, of the group Madrepora, collected from the French part of the Great Barrier Reef in New Caledonia (Guillemín et al. 1987). The process of coral resorption has been shown to be related to the action of carbonic anhydrase (Chétail & Fournié 1969, 1970), an enzyme contained in osteoclasts (Simasaki & Yagi 1960 and Gay & Miller 1974), which may act on the calcium carbonate in the coral skeleton. CDG are completely resorbable and replaceable by bone (Ouhayoun et al. 1991). Implanted coral is well tolerated in a variety of animal models (Issahakian et al. 1987a, Shabana et al. 1991), and also in humans (Souyris et al. 1985, Issahakian & Ouhayoun 1988, Ouhayoun et al. 1992). Prior to this present work, longer term experience and follow-up in augmenting defects of the human cranio-maxillofacial skeleton with CDG had been lacking.

One other novel application of CDG might be the preservation of the alveolar ridge after tooth-loss in a paediatric population. In 1994, Ostler and Kokich investigated changes in alveolar ridge width after removal of retained primary molars in patients who
were congenitally missing mandibular second premolars. They have shown that the alveolar ridge width decreases 25% within 3 years after extraction of the retained primary molars, and diminishes a further 4% over the next 3 years (Ostler & Kokich 1994). Our own experience at the Hospital for Sick Children in Toronto suggests that the premature loss of permanent maxillary incisors due to trauma, removal of retained ankylosed primary molars, and other ankylosed and submerged teeth results in the development of alveolar ridge defects. Alveolar ridge defects compromise the suitability of these sites for future restoration with dental implants, or impair the aesthetics of the restorative solutions.

Augmenting these types of alveolar defects with CDG may preserve bone volume until such time as the patient is ready to undergo definitive restoration with a dental implant when skeletal growth has ceased (Kurol & Ödman 1996). An alveolar sparing procedure using a bone graft substitute could be beneficial to such patients. The time required for wound healing and incorporation of the coral granules could advantageously allow for the completion of jaw growth, all the while preserving the dimensions of the residual alveolar ridge. The goal would be to allow the placement of a dental implant, in an uncomplicated manner, without the need to harvest a bone graft from a second anatomic location, thereby minimizing post-operative morbidity.

The present study therefore focuses on two aspects of minimizing the morbidity of cranio-maxillofacial osseous reconstruction. Firstly, the development of more conservative but effective harvesting techniques should reduce patient post-operative morbidity in those situations where autogenous bone graft material is deemed necessary. Secondly, the use of an effective bone graft substitute, where deemed appropriate, should diminish post-operative morbidity by eliminating the bone graft donor site while accomplishing a satisfactory reconstructive result.
2 Review of the literature

2.1 Structure, function and physiology of bone

Bone is a specialized connective tissue with a mineralized extracellular matrix that functions to provide support, form and rigidity for the human skeleton and supplies a vast store of calcium necessary for calcium related homeostasis (Roberts et al. 1987, Gielinski & Marks 1994, Buckwalter et al. 1995a, Buckwalter et al. 1995b, Hansen et al. 1996, Whybro et al. 1998). Fossil records date the evolution of bone to the Paleozoic era some 300 million years ago. Since then bone has evolved to play a significant role in the vertebrate (Bourne 1976).

Embryologically, bone is formed by two separate developmental processes described as intramembranous and endochondral ossification (Craft & Sargent 1989, Bortell et al. 1990). When ossification has occurred directly, it is classified as being intramembranous in character. Embryonic mesenchymal cells with an abundant vascular supply develop loci of intracellular collagen deposition. Osteoblasts begin secreting osteoid into which calcium salts are deposited. Such direct bone formation is responsible for the genesis of the cranial vault, the facial skeleton and parts of the mandible, scapula and clavicle. Endochondral bone formation, involves a cartilaginous phase, where embryonic mesenchymal stem cells differentiate into a primitive hyaline cartilage. Blood vessels and bone forming units resorb the cartilage and replace it with osteoid while invading this matrix. Weight-bearing bones and those terminating in joints comprise most of this group of bones. In addition, most of the cranial base and a portion of the mandible are thought to have an endochondral origin (Frost & Jee 1994).

Irrespective of embryonic origin, bone is composed of four cellular types; osteoblasts, osteocytes, osteoclasts and bone lining cells (Marks & Poppof 1988). Osteoblasts are cuboidal cells having a prominent Golgi apparatus and well-developed rough endoplasmic reticulum, a histological sign of protein production. These fully differentiated cells secrete both the type I collagen and the non-collagenous proteins of bone’s organic matrix. They will also regulate the mineralization of this matrix. The osteocyte is thought to be a mature osteoblast that becomes trapped within the bone matrix. While their primary function is maintenance, they have demonstrated abilities to
both synthesize and resorb bone (Martin & Ng 1994). Bone lining cells are flat, fusiform cells that are found covering inactive bone surfaces. Little is known about the function of these cells; however they may be precursors of osteoblasts. It is understood that certain cells (osteoprogenitor cells) are programmed to become bone cells and their origin is believed to lie with the primitive mesenchymal stem cells (Drivadahl et al. 1981). Osteoclasts, unlike the other bone cells, which have local origins, arise from the fusion of mononuclear precursor cells originating in the hematopoietic tissues. They function to resorb bone. Histologically, they have been characterized as having a ruffled border, where bone resorption is thought to occur. Coupling describes a process, which combines all of the above elements, whereby bone formation and resorption are maintained in balance (Farley et al. 1982). Once this balance is disrupted, excessive osteoclastic activity may lead to problems such as osteoporosis whereas increased osteoblastic activity may reflect bone growth, healing or pathological responses.

The architecture of bone is such that the outer shell of bone, referred to as cortical or compact bone, provides the mechanical support. It is composed of concentric sheets of collagen fibrils in the form of lamellar bone. Metabolic functions of bone are controlled by the centrally located cancellous, trabecular or spongy bone. In contrast to the densely packed fibrils of the cortical bone, the matrix of cancellous bone is loosely organized. Macroscopically, this bone appears as a honeycomb lattice in which hematopoietic elements are located. Bone is composed of 65–70% crystalline salts by weight, primarily in the form of hydroxyapatite, with the remaining 30–35% being composed of organic matrix. The organic matrix consists primarily of type I collagen (90–95%) interspersed with non-collagenous proteins such as osteopontin, osteonectin, and various growth factors (Robey et al. 1993).

### 2.2 Bony defects in the cranio-maxillofacial skeleton

Bony defects in the cranio-maxillofacial skeleton can cause severe functional and aesthetic deformities. They can arise from congenital malformations, traumatic avulsions or be the result of ablative tumour surgical resections. Surgeons have tried a variety of materials and methods to restore such defects. In Mayan times nacre or mother of pearl was used to try to reconstruct bony defects and as implants into the tooth bearing areas of the jaws (Lopez et al. 1995). The first recorded use of an alloplast to restore a skull defect was by Fallopis in 1600, who used a gold plate to reconstruct a calvarial defect (Moghadam 2002). Autogenous bone grafting was reported in 1890 to restore a skull defect by harvesting bone from the cranium (Muller 1890). Since that time autogenous grafts have continued to be used, although there has been a search for substitute materials. In order to decrease the morbidity of bony reconstruction both less invasive harvesting methods, which aim to reduce post-operative donor site morbidity, or agents that would substitute as bone grafts and would replace the donor site all together, have been sought.
2.3 Unique aspects of alveolar ridge defects and resorption

Alveolar bone is that specialized part of the cranio-maxillofacial skeleton that forms the primary support for the teeth. Alveolar bone is composed of bundles of bone which is built up in layers in a parallel orientation to the coronal-apical direction of the tooth. The anterior maxillary bone is less dense than mandibular bone but more dense than maxillary posterior bone (Truhler et al. 1997).

Alveolar ridge defects and deformities can be the result of congenital maldevelopment, trauma, periodontal disease or surgical ablation, as in the case of tumor surgery. Resorption after tooth-loss has been shown to follow a predictable pattern: the labial aspect of the alveolar crest is the principal site of resorption, which first reduces first in width and later in height (Atwood 1971, Tallgren 1972, Cawood & Howell 1988).

Alveolar bone is resorbed after tooth extraction or avulsion most rapidly during the first years. Non-traumatic loss of anterior maxillary teeth is followed by a progressive loss of bone mainly from the labial side (Lam 1960, Atwood 1973, Cawood & Howell 1988). The magnitude of bone loss is estimated to be 40–60 % during the first 3 years following tooth-loss and then decreases to 0.25–0.5 % annual loss thereafter (Ashman & Rosenlicht 1993, Ashman 2000). In the deciduous paediatric dentition, loss of a retained second deciduous molar, which has no succedaneous permanent tooth to replace it, is also associated with bone loss. The rates of bone loss at these sites have manifested as alveolar ridge width decreases of 25% within 3 years after extraction of the retained primary molars, and this continues to diminish by a further 4% over the next 3 years (Ostler & Kokich 1994). The cause for resorption of alveolar bone after tooth-loss has been assumed to be due to disuse atrophy, decreased blood supply, localized inflammation or unfavorable prosthesis pressure (MacKay et al. 1979, Ashman 2000).

2.3.1 Prevention of alveolar ridge resorption

One strategy to deal with alveolar bone loss without resorting to a bone graft is to prevent its occurrence. A number of methods have been tried including the retention of tooth roots to help maintain the alveolus. These retained tooth roots can be used as abutments for overdentures for example and are effective at halting the process of alveolar ridge resorption (Shykoff et al. 1978). Malmgren et al. have introduced a method in which the alveolar ridge is preserved by removing the crown and filling the root of an ankylosed and infrapositioned tooth. The decoronated root is left in situ for slow resorption (Malmgren et al. 1984, Filippi et al. 2001). Other treatment alternatives to preserve alveolar bone without the use of bone grafts include autotransplantation of teeth (Clokie et al. 2001) and orthodontic space closure (Ostler & Kokich 1994). Simply adding a bone graft to alveolar bone and allowing it to function by loading it with a dental prosthesis will also lead to further resorption of alveolar bone (de Koomen, 1982). The placement of dental implants into alveolar bone or grafted alveolar bone has also been shown to prevent further alveolar resorption (Zarb & Schmitt 1993, Zamb & Schmitt 1996, Satow et al. 1997, Stoelinga et al. 2000, Marx et al. 2002). However the timing of dental implant treatment is most important. Dental implant placement in young growing patients is
contraindicated because of the interference with alveolar growth in such patients (Kurol & Ödman 1996). However, dental implants can be placed in young patients once growth has ceased (Kurol & Ödman 1996).

2.4 Methods to augment deficient bone

The reconstructive options in the osseous reconstruction of the cranio-maxillofacial skeleton include autogenous bone grafts harvested from local or distant sources (Kainulainen et al. 2002a). Allogeneic bone from another individual may also be considered, as might xenogeneic bone from another species. Because the possibilities of immunogenic problems exist, such grafts were first treated with a freezing technique (Herndon & Chase 1954). Later other methods to deal with immunogenicity were developed such as freeze drying, deproteinating and demineralizing techniques (Buchardt 1983). Alloplasts have also been developed to replace bone. In addition a number of surgical procedures have been designed to increase the amount of bone available locally without bone grafting (Dahlin et al. 1988, Gaggi et al. 2000, Oikarinen et al. 2003). Bone reconstruction is best understood if the process of bone healing is first considered (Hollinger & Wong 1996).

2.4.1 Processes of bone healing

Bone is a unique tissue. It can be injured and then can repair itself and return to full function without scarring or deformity (Salter 1983). Embryonic bone development is repeated in the healing of bone. The pattern of bony healing is dictated by the host bed, vascular supply, oxygen tension and the stability of the bone segments (Buckwalter et al. 1995a). Healing can occur either directly as primary bone healing or secondarily, demonstrating an intermediate cartilaginous phase (Hollinger et al. 1994).

Bone healing can be illustrated using the model of the healing bone graft. It is important, when discussing healing in relation to bone reconstruction to differentiate between a graft and an implant. A graft may be defined as a transferable material that contains living cells and can be used for reconstruction. An implant is differentiated from a graft in that it does not contain any living cells. When the stages of graft or implant incorporation are examined, the presence of viable cells that are transferred in a graft will usually differentiate the two (Gray & Elves 1982). A graft of autogenous bone will contain bone-forming cells, fibrin and platelets. The endosteal osteoblasts and hematopoietic cells will survive as long as five days post transplantation due to their ability to absorb nutrients from the surrounding tissues (Marx 1994).

Within hours of placing a graft the initial regenerative process begins (Garge et al. 1998). Entrapped platelets degranulate releasing potent growth factors such as platelet-derived growth factor (PDGF) from their alpha granules and transforming growth factor-beta 1 (TGF-β1) (Caplan 1995). Endothelial cells initiate capillary ingrowth as they bind PDGF. Next endosteal osteoblasts and hematopoietic stem cells are stimulated to initiate
mitosis increasing their numbers. These cells also commence their production of osteoid (Friedenstein et al. 1996). This is mediated by the binding of TGF-β1 to cell receptors. After the third day, the influence of the growth factors transplanted with the graft is replaced by the action of locally induced macrophages (Knighton et al. 1983). They efficiently synthesize growth factors and will regulate bone healing from this point. By the end of the second week, the graft will demonstrate complete revascularization. Endosteal osteoblasts from the transplanted bone will begin laying down osteoid and stem cells will begin differentiating into osteoblasts. Resultant islands of bone formation are then seen developing within the graft. Once the graft has become revascularized and stem cells, attracted to the wound, may also transform into bone forming units (Marx 1994).

This initial bone formation, which occurs as a result of the transfer of osteocompetent cells contained within the graft, has been referred to as Phase I bone (Axhausen 1956). Complete by six weeks, graft viability is maintained as sufficient quantities of newly mineralized matrix have been deposited. The bone that has formed does so without initial cartilaginous deposition and is referred to as woven bone. This bone is extremely cellular and disorganized but does not demonstrate any independent structural integrity. During the second phase of healing, bone will undergo a remodelling phenomenon referred to as lamellar compaction. The resultant lamellar bone will be less cellular, more mineralized and is highly organized (Buckwalter et al. 1995b). As with all bone, this newly formed matrix will mature as it responds to the physical demands placed upon it. Finally, it will enter into a remodelling phase similar to normal skeletal turn-over (Marx 1994).

2.4.1.1 Osteoinduction

Osteoinduction describes a process whereby new bone is produced in an area where there was no bone before, where one tissue or its derivative causes another undifferentiated tissue to differentiate into bone. The phenomenon of osteoinduction was first described in the classic works of Urist (Urist & McLean 1952, Urist 1965, Urist et al. 1977). Bone matrix was shown to induce bone formation within muscle pouches of many species of animals. Later a specific extract from bone, a protein now referred to as Bone Morphogenetic Protein (BMP), was identified as that factor which caused the phenomenon (Urist et al. 1979, Mizutani & Urist 1982). Since then a great deal of research has resulted in the discovery of a variety of entities having different effects on bone (Goldring & Goldring 1996). These compounds may be classified as osteoinducers, osteopromoters or bioactive peptides (Hauschka et al. 1988).

2.4.1.2 Osteoconduction

Osteoconduction describes bone formation by the process of ingrowth of capillaries and osteoprogenitor cells from the recipient bed into, around and through a graft or bioimplant. Therefore the graft or bioimplant acts as a scaffold for new bone formation
(Buchardt 1983). Unlike osteoinduction, this process occurs in an already bone containing environment. Osteoconduction describes the facilitation of bone growth along a scaffold of autogenous, allogenic or alloplastic materials.

### 2.4.2 Local procedures to augment existing alveolar bone

There are a number of techniques, which enable the surgeon to maximize the available bone in the cranio-maxillofacial skeleton without harvesting a bone graft. These techniques serve to minimize reconstructive morbidity, as there is no graft donor site. Osteocondensation is one such technique. It can reshape the alveolar bone of the maxilla for example, to more optimally house a dental implant, resulting in better primary stability in areas of poor bone quality. Orthopaedic surgeons have practiced osteocondensation since the early 1960s (Valen & Locante 2000). The major advantage of this technique is that an implant bed is created with either minimal drilling or no bone removal (Syrakas et al. 2000) and with osteotomes, which compress the bone. There are implants, which produce osteocondensation and are called press-fit fixtures (de Wijs & Cune 1997, Valen & Locante 2000). In the cranio-maxillofacial skeleton, osteocondensation is best performed in the maxilla.

The major proponent of osteocondensation in the cranio-maxillofacial skeleton has been Summers who described a method to increase the width of alveolar bone and to facilitate sinus floor elevation, without opening the lateral sinus wall (Summers 1994a,b,c, Summers 1995). The technique was further developed to include the use of D-shaped osteotomes and chisels which produced lateral widening of the alveolar ridge and osteocompression, increasing the density of cancellous bone (Tatum 1986, de Wijs & Cune 1997). This ridge expansion osteotomy is achievable using osteotomes which have concave tips and sharpened edges. The instruments are shaped to allow progressively larger osteotome tips to fit into the opening created by the previous osteotome. Instruments are sensitive to changes in bone texture and density and allow excellent tactile sensation for the surgeon (Summers 1994a). The minimum alveolar width necessary for lateral alveolar widening by compression is 2–3 mm assuming that spongious bone is found between cortical layers (Summers 1994b, Sethi & Kaus 2000). Alveolar ridges can also be widened using the crestal split technique using osteotomes and chisels to produce a “greenstick fracture” at the base of the alveolus. The remaining periosteum is left intact and attached to the bone. This pedicled buccal cortex is repositioned and a new implant bed is created without any drilling. Lateral widening by completely exposing the labial cortex has also been introduced (Duncan & Westwood 1997). The major benefit of crestal widening is that it allows the thin alveolar bone to be utilized for implantation without grafting (Oikarinen et al. 2003). Esthetics and implant positioning are improved and wider implants can also be used. The bone can be moulded to some extent due to its viscosity (de Wijs & Cune 1997). Bone compression is achieved along with an increase in the density of trabeculations of the adjacent site (Komarnyckyj & London 1998). In addition the resulting gap can, if desired be covered by a
nonresorbable membrane (Simion et al. 1992, Engelke 1997) and filled with allogenic material (Engelke 1997). Interpositional autogenous bone grafts have been used to improve bony healing in the gap (Lustman & Lewinstein 1995).

Guided bone regeneration (GBR) has been used for minor augmentation procedures in the cranio-maxillofacial skeleton and prior to dental implant placement (Dahlin et al. 1988, 1989, Borgner et al. 1999, Buser 1990, Simion et al. 2001). GBR is a technique in which bone growth is enhanced by preventing soft tissue ingrowth into the desired area and utilizes either resorbable or nonresorbable membranes. Metallic membranes (von Arx et al. 1996) or membranes supported by a titanium frame (Simion et al. 1994, 1998, 2001) have been tested and have been successful. An acellular dermal matrix has been used as a barrier membrane with demineralized freeze-dried bone allograft (Fowler et al. 2000).

The use of membranes is a controversial issue in implantology and their use is certainly very technique-sensitive (Chiapasco et al. 1999). Nonresorbable membranes need a second operation for their removal (von Arx et al. 1996). Resorbable membranes can be associated with inflammation (Yoshinari et al. 1998). Intact periosteum, a split palatal or gingival flap are regarded by some as natural membranes and their use may obviate the need for a membrane (Ylimaz et al. 1998). Nevertheless, good results with augmentation procedures using membranes have been presented (Buser 1990, Simion et al. 1992, 1994, Lustmann & Lewinstein 1995, Lekovic et al. 1998, Simion et al. 2001). Vertical increase of a narrow alveolar crest has been shown to be possible with membranes (von Arx et al. 1996, Simion et al. 1998).

Distraction osteogenesis (DO) of the long bones in growing children has been used for decades to gradually lengthen osteotomized bones without a bone graft. The resulting distraction gap is initially filled with callus, which later matures into bone (Ilizarow 1989). DO has also been adapted to the maxillofacial area and special devices and implants are being developed for that purpose (Gaggi et al. 2000, Watzek G et al. 2000).

The DO technique has also been adapted for limited augmentations of the alveolar crest prior to implantation. Some systems use hardware, which expands the jaw over time, and then is removed at the time of dental implant placement (Watzek et al. 2000). Some have tried to utilize the implant itself as the distraction device (Chin & Toth 1996, Gaggi et al. 1999, 2000). The daily rate of alveolar crest distraction ranges from 0.25–0.5 mm and is initiated from two days to one week after the primary osteotomy. DO is continued up to 30 days and the final gain will be between 4 and 7 mm (Gaggi et al. 2000, Urbani et al. 1999). In some cases overcorrection is recommended (Gaggi et al. 2000). However some local limitations due to the lack of stretching of the palatal tissues, may not allow the distracted segment to move exactly as planned and then only in two dimensions (Chin & Toth 1996). Appliances intended to allow three-dimensional DO have been introduced (Ylimaz et al. 1998, Watzek et al. 2000). The benefits of DO are that donor site morbidity from harvesting of bone grafts and dehiscences of grafted bone are avoided (Chin & Toth 1996). However, a second surgery to remove and perhaps replace hardware is needed if implant-based distraction is not used. While DO could eliminate a donor site and thereby limit morbidity, it is so labour intensive that the patient trades the morbidity of the bone graft donor site for the inconvenience of wearing and tolerating potentially cumbersome hardware for longer periods of time.
2.4.3 Autografts

At the present time, autogenous bone grafting is the gold standard by which all techniques of osseous reconstruction of the cranio-maxillofacial skeleton must be judged. Autogenous cancellous bone grafts produce the most successful and predictable results (Marx 1994). Free bone grafts act mostly as scaffolds and are thus more osteoconductive than osteoinductive even though osteogenic activity may have remained in the spongy part of the graft (Buchardt 1983). The major disadvantage of autogenous grafts is the need for a second surgical site and the morbidity resulting from harvesting. The source of autograft, however, is not limitless for the patient. A point may be reached in reconstruction where the donor site morbidity may exceed the discomfort of the presenting complaint.

There are essentially two forms of nonvascularized free autogenous bone grafts: cortical and cancellous (Bonutti et al. 1998, Keller et al. 1998, Vinzenz et al. 1998). Buchardt has summarized the three essential differences between the two. Cancellous grafts are revascularized more rapidly and completely than cortical grafts. Creeping substitution of a cancellous graft initially involves an appositional bone formation phase, followed by a resorptive phase, whereas cortical grafts undergo a reverse creeping substitution process. Cancellous grafts tend to repair completely with time whereas cortical grafts remain as an admixture of necrotic and viable bone (Buchardt 1983).

Cortical grafts are able to withstand mechanical forces earlier, however, they take more time to revascularize. Cortical grafts are useful for filling defects where early mechanical loading is required (Boyne 1997). The cortical component can be incorporated into the fixation of the graft and can consequently be used in situations where bone is comminuted or where there are bony voids. In the cranio-maxillofacial skeleton these forms of grafts may also be used to onlay areas such as decreased vertical or horizontal alveolar ridges, to improve facial contours or they can be inlayed within bone to fill bony voids. Common sites for the harvesting of cortical grafts are the cranial vault, ribs and the medial or lateral table of the anterior aspect of the iliac crest, the posterior iliac crest as well as the mandibular symphysis (Kainulainen et al. 2002b).

Cancellous grafts have more widespread applications, are generally easier to manipulate and revascularize more rapidly (Marx 1993). The most abundant source of cancellous bone is the anterior or posterior iliac crest. Cancellous bone imparts no mechanical strength. When cancellous bone is used to reconstruct large continuity defects additional stability and rigid fixation is required, such as that which is afforded by using a titanium mesh system (Tideman et al. 1998). In the cranio-maxillofacial skeleton these grafts are packed into bony defects such as alveolar clefts and maxillary sinus floor augmentations (Boyne & James 1980, Merkx et al. 2003). The corticocancellous graft usually produces the best results by combining the attributes of both graft forms and can be placed easily into an interpositional location (Stoelinga et al. 1978, Egbert et al. 1986). These grafts allow for mechanical stabilization while at the same time providing for good revascularization. Others will particulate corticocancellous bone creating a mixed graft which can be used for the restoration of continuity defects in the jaws (Clokie & Sàndor 2001).
2.4.4 Allografts

Allogeneic bone is non-vital osseous tissue taken from one individual and transferred to another individual of the same species. There are three forms of allogeneic bone: fresh frozen, freeze-dried and demineralized bone matrix (DBM). Fresh frozen bone is rarely used today for the purposes of bony reconstruction in the cranio-maxillofacial skeleton because of concerns related to the transmission of viral diseases (Buchardt 1983). The risk of transmitting HIV with a properly screened demineralized freeze-dried bone allograft has been calculated to be 1 in 2.8 billion (Russo & Scarborough 1995). Bone harvested from a patient who died from AIDS related disease and was tested for the p24 core protein and reverse transcriptase and has been found to be positive. When this same bone was processed to make DBM, no evidence of either was found (Mellonig et al. 1992). It is therefore assumed that the process to make DBM eliminates or inactivates the p24 core protein and reverse transcriptase.

Freeze-dried allogeneic bone is processed to remove the moisture from the bone. This results in an implant with mechanical strength that can be used to onlay areas or as a crib to retain autogenous bone (Marx 1993). This implant, while osteoconductive, has no osteogenic or osteoinductive capabilities and consequently requires a source of osteocompetent cells. Therefore freeze-dried allogeneic implants are usually placed in conjunction with autogeneic grafts when reconstructing the cranio-maxillofacial skeleton.

By demineralizing the freeze-dried bone to create DBM, the implant loses its mechanical strength but may retain some osteoinductive properties (Urist 1965, Zhang et al. 1997a, b). Removal of the mineral component from the bone matrix may expose native proteins, such as bone morphogenetic protein (BMP). The potential osteoinductive capabilities of DBM make it a valuable tool for the surgeon.

Recent advances have seen DBM incorporated into various carriers such as collagen or selected polymers (Helm et al. 1997, Babush 1998, Morone & Boden 1998). These forms are either sponge-like or gel/putty-like in consistency. Putties are simple to apply and are well retained within the recipient tissue bed. These products could potentially be used in the treatment of periodontal infrabony defects, extraction sites to prevent ridge resorption, alveolar ridge reconstruction, bone reconstruction associated with dental implant placement, bone reconstruction associated with dental implant complications and cysts or bony defects of the jaws (Caplanis et al. 1997, Becker et al. 1998, Campbell 1998, Caplanis et al. 1998, Kim et al. 1998, Kumta et al. 1998, Parashis et al. 1998, Rosenberg & Rose 1998, Wiesen & Kitzis 1998). If larger volumes of bone are required, such as in maxillary sinus floor augmentation prior to dental implant placement, then DBM may be used as a bone graft expander to reduce the volume of bone graft required to fill an osseous defect (Blomqvist et al. 1998, Goldberg & Baer 1998, Stevenson 1998). This reduced graft volume may allow the use of a less morbid intra-oral harvest site. While reducing patient morbidity by potentially avoiding an extra-oral donor site, the major disadvantage of this technique is the cost of the DBM material.
2.4.5 Xenografts

Xenogeneic bone grafts consist of skeletal tissue that is harvested from one species and transferred to the recipient site of another species (van den Bogaerde & White 1997, Hammer et al. 1998). These grafts can be derived from mammalian bones and coral exoskeletons. Bovine derived bone has been commonly used (Block & Posner 1995, Jensen et al. 1996), even though other sources are such as porcine or murine bone are available. Xenogeneic bone was popular in the 1960's but fell into disfavour due to reports of patients developing autoimmune diseases following bovine bone transplants (Pierson et al. 1968, Buchardt 1983). The re-introduction of these products in the 1990's comes after the development of methods to deproteinate bone particles (Iwamoto et al. 1997). This processing reduces the antigenicity making these implants more tolerable to host tissues (Basle et al. 1998). The result is that the organic component of bone, referred to at the beginning of this chapter, is almost completely removed.

This inorganic bone matrix then has the structure of bone making it osteoconductive without the osteoinductive abilities imparted by the organic elements. Eventually xenogenic bone should be replaced by host tissue, which would make it useful for defect or extraction site filling in the alveolus prior to dental implant placement or prosthetic rehabilitation (Chappard et al. 1996, Berglundh & Lindhe 1997, Hurzeler et al. 1997, Merkx et al. 1997, Schmitt et al. 1997, Skoglund et al. 1997, Valenti et al. 1998). Resorption of bovine derived bone has been observed in animals studies (Merkx et al. 1997) but not consistently in human clinical trials (Hallman et al. 2001a, Valentin 1998, Skoglund 1997). Since the material is usually a powder it may require some form of retentive structure such as a membrane to keep the xenograft in the desired location (Avera et al. 1997, Zitzman et al. 1997, Hurzuler et al. 1998, Lorenzoni et al. 1998). While bovine xenografts may reduce morbidity by eliminating the donor site, their disadvantage is the concern with the possibility of future bovine spongiform encephalopathy due to potential slow virus transmission in bovine-derived products (Bons et al. 2002, Hunter 2002). Since other alternative biomaterials exist, bovine-derived products should probably be avoided until the concerns regarding potential slow virus transmission are clearly addressed.

One interesting xenogeneic transplant, Biocoral, is derived directly from the exoskeletons of corals from the Group Madrepora of the genus acropora (Guillemin et al. 1987). These corals are harvested from the relatively unpolluted waters of the reefs off New Caledonia, a point of importance since corals from contaminated waters can contain petrochemical impurities. Both solid blocks and particulated implants fashioned from this material are composed largely of calcium carbonate and are osteoconductive. When implanted, they are simultaneously incorporated into the human bony skeleton and replaced by human bone. The enzyme carbonic anhydrase, liberated by osteoclasts is responsible for the breakdown of this material. The time for total replacement of this implant by bone in the human craniofacial skeleton is approximately 18 months (Roux et al. 1988b). Since the use of coral-derived granules gives rise to bone with the material’s eventual replacement, it could decrease morbidity by avoiding a bone graft harvest donor site.
2.4.6 Synthetic bone substitutes

Alloplastic bone substitutes are synthetic substances that have been processed for clinical use in osseous regeneration. There are three types of alloplastic substances in clinical use today: hydroxyapatite, other ceramics and polymers.

Hydroxyapatite (HA) is a ceramic. HA can be divided into two groups depending upon its ability to resorb (Jarcho 1986, Alexander et al. 1987, Ricci et al. 1989, Brown & Constanz 1994). Some refer to the internal pore size as a means of differentiating between various types of hydroxyapatite (Holmes 1979, Guillemin et al. 1989, 1995). The porous form of HA allows rapid fibrovascular tissue ingrowth, which may stabilize the graft and help resist micromotion (Kenny et al. 1988, El Deeb & Holmes 1989). HA can be machined to many shapes or consistencies (Schliephake & Neukam 1991, Frayssinet et al. 1992, Marchac 1993). HA has several potential clinical applications including the filling of bony defects, the retention of alveolar ridge form following tooth extraction and as a bone expander when combined with autogenous bone during ridge augmentation and maxillary sinus floor augmentation procedures (Stoelinga et al. 1986, Bifano et al. 1998, Haas et al. 1998a,b, Simion et al. 1998). Although the use of HA can eliminate donor site morbidity, the tendency for granular migration and incomplete resorption has become a long-term problem (Rosen & McFarland 1990, Byrd et al. 1993, Mercier 1996, Prousaefs et al. 2002).

Apart from HA, there are three other types of ceramics: tricalcium phosphate (TCP), bioglasses, and calcium sulphate (Peltier 1961, Shafer & App 1971, Metsger et al. 1982, Hollinger & Batristone 1986, Kim et al. 1998). TCP is a similar to HA being a calcium phosphate with a different stoichiometric profile (Mors & Kaminski 1975, Hollinger et al. 1989). TCP has been formulated into pastes, particles or blocks, which have demonstrated an ability to be biocompatible and biodegradable (Naghara et al. 1992). Clinically the one disadvantage with TCP is its unpredictable rate of bioresorption. Its degradation has not always been associated with concomitant deposition of bone (Ogushi et al. 1991, Buser et al. 1998). Two products (Norian SRS®, Norian Corporation, Cupertino, California, USA and Bone Source®, Leibinger, Dallas, Texas, USA) have been used for the repair of cranial vault defects. Calcium salts are mixed with water to form a paste having an isothermic setting reaction and placed into the defect. Early versions of these materials tended to be easily washed out of the wound by haemorrhage. The materials tend to fracture and are resorbed unevenly in cranial vault defect studies (Clokie et al. 2002).

Bioactive glasses are silico-phosphate chains that have been used in dentistry as restorative materials such as glass ionomer cement. These materials have the ability to chemically bond with bone and are supposed to function as small bone regenerative chambers (Ziffé et al. 1991, Merkx et al. 2003). Bioactive glasses may have osteoconductive properties and have been tested in animal trials (Turunen et al. 1997). Bioactive glasses have been used in the treatment of periodontal bony defects (Nasr et al. 2000, Yukna et al. 2001). In order to preserve the form of the alveolar ridge after tooth-loss, bioactive glass root replicates have been introduced (Ylimaz et al. 1998). While these are able to preserve the crestal width and height of the alveolus, they may impair the later placement of dental implants due to incomplete resorption.
Polymers by their nature can be fashioned in seemingly endless configurations (Barrows 1986, Shalaby 1988, Haas et al. 1998a). Combinations of polyglycolic acid (PGA) and polylactic acid (PLA) have been successfully used in the form of bioresorbable sutures for many years (Aderriotis & Sándor 1999) and more recently as bioresorbable fixation materials (Suuronen et al. 1999, 2000). Giant cell reactions presented as a problem with earlier combinations of this material (Brekke 1995). As with bioglasses, root replicates have been introduced to preserve the form of the alveolar ridge after tooth-loss. These are made of PLA (Suhonen & Meyer 1996). The ability of PLA implants to preserve the crestal width and height is an advantage. Unfortunately because of incomplete resorption they may impair the later placement of dental implants (Suhonen & Meyer 1996). The future of bone regeneration could lie with this class of synthetic materials (Clokie & Sándor 2001). These materials could be better utilized once their ability to resorb at variable rates, over set periods of time is better understood and an appreciation for their compatibility with the emerging bioactive agents is developed. The ideal would be a completely synthetic bioimplant, which is predictably degradable and is innately osteocompetent (Clokie & Sándor 2001). Such synthetic materials could also play a very important role in tissue engineering (Vesala et al. 2002), serving as bioactive scaffolds.

One important advantage related to all xenogenic and allogenic materials is that they could potentially be used as bone graft expanders by mixing them with autogenous bone chips. This mixing could decrease the volume of autogenous bone graft needed, which in turn could convert an extra-oral harvesting procedure to an intra-oral harvesting procedure, potentially reducing donor site morbidity (Hallman et al. 2001a, Kainulainen et al. 2002a). However, data from clinical histology indicates that not all xenogenic and allogenic materials will be resorbed and replaced by autogenous bone with time (Hallman et al. 2001b, Merkx et al. 2003). This may leave the augmented bone with a composite rather than a homogenous structure, which could influence future dental implant survival (Merkx et al. 2003).

In fact Merkx et al. found after an extensive review of clinical reports, that autogenous bone without anorganic additives seemed to result in the greatest amount of bone in sinus floor augmentation after a four to six month healing period. Bovine bone material and HA seemed to result in the lowest amount of bone formed (Merkx et al. 2003).

2.4.7 Osteoactive agents

An osteoactive agent is any material which has the ability to stimulate the deposition of bone (Clokie & Sándor 2001). The phenomenon of osteoinduction was first described in the works of Urist and co-workers in (Urist & McLean 1952, Urist 1965, Kale & Di Cesare 1995). Bone matrix was shown to induce bone formation when implanted within muscle pouches of a number of different species of animals. Urist’s group identified a specific extract from bone, a protein now referred to as Bone Morphogenetic Protein (BMP), as that factor which caused the phenomenon (Urist et al. 1977, 1979, Mizutani &
Urist 1982). Since then, many other entities have been found with a variety of effects on bone (Goldring & Goldring 1996). These may be classified as osteoinducers, osteopromotors or bioactive peptides (Hauschka et al. 1988).

The compounds in the first two categories are growth factors, a group of complex proteins of approximately 6 to 45 kilo Daltons which function to regulate normal physiological processes and biological activities such as receptor signalling, DNA synthesis, and cell proliferation (Wozney et al. 1988, Schliefhake 2002). Growth factors that are referred to as cytokines have a lymphocytic origin, being nonantibody proteins released by one cell population on contact with a specific antigen and act as intracellular mediators. Other growth factors are described as morphogens. These are diffusible substances in embryonic tissues that influence the evolution and development of form, shape or growth. Still other growth factors are mitogens. They induce blast transformation by regulating DNA, RNA and protein synthesis (Kawamura & Urist 1988).

An example of the importance of such factors in cranial growth is the effect of fibroblast growth factors (FGF) and their receptors. Normal growth and morphogenesis of the cranial vault reflect a delicate balance between cell proliferation in the sutures of membranous bones and osteogenesis of the cranial bones (Moore et al. 2002). The discovery that mutations in FGF receptors cause the major craniosynostosis syndromes implicates FGF-mediated signalling in the skeletogenic differentiation of the cranial neural crest (Sarkar et al. 2001, Sándor et al. 2001). In fact blocking of endogenous FGF-2 activity prevents cranial vault osteogenesis (Moore et al. 2002), whereas mutant FGF receptors can induce chondrogenesis in neural crest cells, potentially perturbing this complex process of skeletogenesis (Petiot et al. 2002).

2.4.7.1 Bone morphogenetic protein

Bone morphogenetic protein (BMP) has been shown to have osteoinductive properties (Wozney 1989, Wozney et al. 1990). BMP is recognized to be part of a larger family of growth factors referred to as the TGF-β superfamily (Sampath et al. 1990) with a 30–40% homology in amino acid sequence with other members in the family. BMP acts as an extracellular molecule that can be classified as a morphogen as its action recapitulates embryonic bone formation. The identifying pattern of the BMP subfamily is their seven conserved cysteine residues in the carboxy-terminal portion of the protein and this is where the unique activity of BMP’s is thought to reside (Sampath et al. 1990).

Bovine & porcine sources were used in much of the original work attempting to purify the BMP molecule, a protein less than 50 kilo Daltons in size (Sampath & Reddi 1981, Besho et al. 1989, Rosen et al. 1989, Ko et al. 1990, Wang et al. 1990) and a number of recombinant human forms of BMP (rhBMP) have been derived. Interestingly the amount of human rhBMP necessary to produce bone induction in vivo is more than ten times higher than that of highly purified native bone extracted BMP (Tuominen 2001). This difference was also demonstrated between human BMP derived from human bone matrix and human rhBMP (Bessho et al. 1999), suggesting that native BMP is a combination of different BMP’s or represents a synergy between them (Wang et al. 1990). This has revived interest in xenogenic derived native BMP’s (Viljanen et al. 1997). Although
concern regarding the immunogenicity of interspecies BMP has been raised in the literature, moose-derived BMP showed strong osteoinductive capacity and weak immunogenicity in a sheep study (Viljanen et al. 1996).

Large and small animals have been used to study the influence of BMP on bone regeneration (Nilsson et al. 1986, Yamazaki et al. 1988, Johnson et al. 1989, Nakahara et al. 1989). Critical sized osseous defects are defined as bony defects of a specific size, which will not heal spontaneously with bone tissue alone but with fibrous scar (Lindholm et al. 1988, Hollinger & Kleinschmidt 1990, Lindholm 1995). Bone lesions above a critical size become scarred rather than regenerated, leading to nonunion (Petite et al. 2000). BMP has demonstrated the ability to heal many different varieties of critical sized defects including cranial vault defects, long bone defects and mandibular continuity defects (Lindholm et al. 1988, Covey & Albright 1989, Johnson et al. 1990, Lindholm 1995) without the addition of a bone graft.

One of the challenges in the use of BMP is in its delivery to a site of action. As a morphogen BMP is rapidly absorbed into the surrounding tissues dissipating its effectiveness. Many different carrier vehicles have been used to deliver BMP including other noncollagenous proteins, DBM, collagen, HA, PLA and or PGA combinations, calcium carbonate, calcium sulphates and fibrin glue (Harakas 1984, Urist et al. 1984, Damien et al. 1993, Urist 1995, Ono et al. 1995, Davis & Sàndor 1998, McCallister et al. 1998, Si et al. 1998, Lindholm 2002b). More recently biodegradable gels, collagen sponges impregnated with BMP and silica glass have been used as carriers (Boyne 1996, Howell et al. 1997a, Bostrom & Camacho 1998, Johnson & Urist 1998, Lindholm 2002a). DBM has been shown to contain BMP and may be used as a bone graft substitute with predictable healing in critical sized rabbit calvarial defects (Clokie et al. 2002) and has been used successfully in a human mandibular defect in vivo with native human BMP, a poloxamer carrier and bank bone (Moghadam et al. 2001).

### 2.4.7.2 Transforming growth factor β

The proteins in the family of transforming growth factor β (TGF-β) should be considered as osteopromotors, agents, which enhance bone healing. TGF-β is found in the same supergene family as BMP. TGF-β has been shown to participate in all phases of bone healing (Celeste et al. 1990). During the initial inflammatory phase TGF-β is released from platelets and stimulates mesenchymal cell proliferation. It is chemotactic for bone forming cells, stimulating angiogenesis and limiting osteoclastic activity at the revascularization phase. Once bone healing enters osteogenesis then TGF-β increases osteoblast mitoses, regulating osteoblast function and increasing bone matrix synthesis, inhibiting type II collagen but promoting type I collagen. Finally, during remodelling it assists in bone cell turn-over (Mohan & Baylink 1991, Roberts & Sporn 1993, Miyazono et al. 1994, Cunningham et al. 1995). TGF-β has a biphasic effect, which suppresses proliferation and osteoblastic differentiation at high concentrations (Schliephake 2002).

While less work has been undertaken to explore the applications of TGF-β than with BMP’s as an adjunct to bone healing, TGF-β may be more effective than BMP in those situations where enhanced bone healing is preferred to bone induction (Clokie & Sàndor...
Moreover, combinations of BMP and TGF-β, may enhance the osteoinductivity of an implant while, at the same time, making it osteopromotive. As with BMP, carrier vehicles for the delivery of TGF-β are under development.

2.4.7.3 Platelet-derived growth factor

Platelet-derived growth factor (PDGF) is angiogenic and is known to stimulate the reproduction and chemotaxis of connective tissue cells, matrix deposition (Singh et al. 1982, Antonaides & Williams 1983, Bowen-Pope et al. 1984, Ross et al. 1986). These properties are all crucial to bone healing.

Insulin-like growth factor (IGF) has demonstrated a capacity to increase bone cell mitoses and increase the deposition of matrix. PDGF and IGF have shown an ability to work together during the reparative stages of bone healing. PGDF-IGF impregnated devices have proven to increase bone healing in defects associated with dental implants and teeth (Giannobile et al. 1996, 1997, Howell et al. 1997b).

Platelets are known to contain a number of different growth factors of which TGF-β, and PDGF are two. As platelets degranulate they release these factors which may play a role in initiating graft healing. Platelet rich plasma (PRP) is one potential source of concentrated platelets that could be used in bone regeneration (Landesberg et al. 1998, Marx et al. 1998, Whitman & Berry 1998). A single unit of freshly harvested autologous blood is centrifuged at 5,600 rpm to separate the platelet poor plasma from the erythrocytes and theuffy coat (platelets and leukocytes). Once platelet poor plasma is removed, the specimen is further centrifuged at 2,400 rpm to separate the packed red blood cells from the PRP. The remaining PRP contains 500,000 to 1,000,000 platelets, which are mixed with a thrombin/calcium chloride (1,000 units/10%) solution to form a gel (Marx et al. 1998). This gel can then be used in conjunction with bone regeneration materials such as HA or DBM as a source of autogeneic growth factors (Landesberg et al. 1998). When used in combination with autogenous bone, PRP is reported to increase the maturation rate of a bone graft up to 2 fold and also increase the bone density of the graft (Marx et al. 1998, 2002).

2.4.7.4 Bioactive polypeptides

The last category of bioactive molecules is the polypeptide group. They may act as osteoinducers or osteoenhancers. Two short amino acids chain peptides that have demonstrated a bone activity are known as P-15 and OSA-117MV. The P-15 polypeptide was designed to take advantage of a conformational arrangement known as the "beta bend", which was found to have an influence on bone induction and growth when utilized in some in vitro studies (Qian & Bhatnager 1996, Yukna et al. 1998). The OSA molecule is even smaller than P-15 and was discovered in relation to the treatment of osteoporosis
where OSA’s effect is concentrated in areas of high stress. Researches have started to explore the local effects of this peptide and initial reports (Clokie & Sándor 2001) suggest that it may enhance the osteoinductive effect of demineralized bone matrix.

2.4.7.5 Stem cells

The area of tissue engineering has brought to the forefront, the possibilities of hybrids of biomaterials seeded with osteocompetent cells to be used as an implant. The “hybrid graft” could consist of a porous matrix, on which bone marrow cells could grow (Petite et al. 1995).

The use of bone marrow as the source of cells is logical as bone marrow contains stem cells which have the potential to differentiate along various pathways and lines, including the direction of bone producing osteocompetent cells (Friedenstein 1976, Owen 1985, Triffitt 1987, Beresford 1989, Friedenstein et al. 1996). Seeding a porous matrix with bone marrow cells could enhance the osteogenic potential of the matrix as a hybrid. Another possibility is the tissue culturing of bone marrow cells to further expand their numbers (Petite et al. 1995). Bone marrow derived cells are responsive to the influence of dexamethasone and 1, 25 dihydroxycholecalciferol (Leboy et al. 1991, Petite et al. 1995) and can be influenced to differentiate in the direction of bone cells. Human bone marrow cells have been reported to adhere to porous coral matrices (Petite et al. 1995, 2000) and to matrices made of HA and TCP (Ohgushi et al. 1989a,b, 1991, Bernard & Picha 1991). A coral scaffold together, with in vitro-expanded marrow stromal cells have been used as tissue-engineered artificial bone. This artificial bone has been used to treat a large segmental long bone defects in the murine model with morphogenesis leading to complete recorticalization and the formation of a medullary canal (Petite et al. 2000). Osseous cells could also be combined with such matrices, making hybrid grafts. The source of bone cells could be suction trap harvested bone (Kainulainen et al. 2002c, Lindholm et al. 2002). In the case of suction trap harvested bone cells, future hybrid grafts for the same individual could be made at the time of harvesting, or from the same harvested, but stored frozen cells, at a later date (Lindholm et al. 2002). The development of such hybrids, the culturing of bone cells and improvements in cell storage methods may be the way of the future and could also diminish donor site morbidity by the elimination of the donor site.
2.5 Harvesting autografts

2.5.1 Vascularized versus non-vascularized bone grafts

Autogenous bone grafts are usually classified as either vascularized or nonvascularized (Marx 1993). The difference is that vascularized grafts retain their existing network of nutrient vessels which, when anastamosed with the recipient blood vessels at the site of reconstruction will make the graft immediately viable by providing an instant and intact blood supply (Shpitzer et al. 1997b). Therefore these types of bone grafts are particularly well suited in poorly vascularized recipient beds, such as those exposed to radiation therapy (Schmelziesen & Schon 1998, Shpitzer et al. 1999).

Possible donor sites for osseous cranio-maxillofacial reconstruction include radial forearm, scapula, anterior iliac crest, fibula and metatarsal. A major drawback to this form of transplant is that the surgical harvesting and reanastamosing of this type of graft is very time consuming, extremely invasive and creates significant morbidity, with unsightly donor site defects, which in some cases may cause longstanding functional impairment (Tang et al. 1998, Shpitzer et al. 1997a).

2.5.2 Potential non-vascularized donor sites

Both intra-oral and extra-oral bony donor sites have been used successfully as sources of non-vascularized autogenous bone for grafting of maxillofacial defects (Marx 1993). The volume of bone graft required determines the choice of the donor site.

If the defect is small, often local, intra-oral sources can be used (Sindet-Pederson & Enemark 1990). Intra-oral sites are often preferred since they allow harvesting of bone from the area adjacent to the reconstruction. A second distant surgical site and the extra-oral scar can be avoided. Intra-oral harvesting can mostly be performed on an outpatient basis under local anaesthesia. These intra-oral sites can include mandibular symphysis, mandibular ramus and retromolar area, coronoid process, maxillary tuberosity, maxillary torus palatinus or mandibular tori, if they are present, and the zygomatic bone. These sites can be harvested using a specially designed bone collector or suction trap (Oikarinen et al. 1997, Kainulainen et al. 2002c). However the volume of bone available in intra-oral sites may be insufficient for moderate to large defects (Kainulainen et al. 2002a).

When a greater volume of bone is required, extra-oral sources are usually employed. These may include the anterior or posterior iliac crest, the calvarium, the rib and the proximal tibia (O’Keefe et al. 1991, Boyne 1997, Kainulainen et al. 2002b).
2.6 Bone graft harvesting methods at the iliac crest

The iliac crest is a favoured extra-oral donor site because of its accessibility and the large quantity of bone available (Dingman 1950, Converse & Campbell 1954, Flint 1964, Levy & Siffert 1969, Crockford & Converse 1972, Mrazik et al. 1980, Hall & Smith 1981). Within the ilium, grafts may be harvested from either its anterior or posterior crest.

The anterior ilium provides an adequate volume of bone for many maxillofacial reconstructive procedures requiring grafting. A variety of techniques have been devised to reduce morbidity associated with harvesting bone from the anterior ilium (Wolfe & Kawamoto 1978, Mrazik et al. 1980, Grillon et al. 1984, Tilley & Davis 1984, van der Wal et al. 1986). The most commonly employed and least complex technique is to harvest a corticocancellous block through either a medial or lateral approach to the anterior ilium. No significant difference in morbidity has been found when comparing the medial and lateral approaches (Tayapongsak et al. 1994).

When a larger volume of bone is required, the posterior iliac crest should be considered (Bloomquist & Feldman 1980, Leyder et al. 1985). The posterior ilium provides a greater quantity of both cortical and cancellous bone with less morbidity than the lateral approach to the anterior ilium (Marx & Morales 1988). However, a major disadvantage of the posterior approach is the need to turn the patient intra-operatively from the prone to the supine position, thus leading to increased operating time plus the risk of injury to the patient during the change of operating position.

Utilizing the anterior ilium allows the graft harvest to be performed simultaneously with the preparation of the recipient site, thereby reducing operative and anaesthetic time. However, standard approaches to the ilium can still produce significant morbidity for the patient (Cocklin 1971, Marx & Morales 1988, Tayapongsak et al. 1994). Thus, there is an advantage to developing a method for obtaining bone from the anterior ilium, which is less invasive than the traditional method.


2.6.1 Minimally invasive surgery

The current trend in most surgical specialties is the development of minimally invasive techniques, which are designed to minimize post-operative morbidity. Sophisticated instrumentation and miniaturized endoscopes have been developed to facilitate such surgery. These techniques include endoscopic cholecystectomy (Bradley & Dempsey 2002, Conlon & McMahon 2002), endoscopic face lifts and forehead lifts (Freeman
2001), endoscopic rhinoplasty (Tasca 2002), endoscopic sinus surgery (Venkatchelam & Jain 2002), temporomandibular joint arthroscopy (Liesenhoff & Funk 1994), and more recently endoscopic paediatric cardiac surgery (Tiete et al. 2002).

2.6.2 Trephines and the iliac crest

Traditionally, autogenous bone from the iliac crest has been harvested as corticocancellous blocks using an open approach, which requires significant dissection of soft tissues. Elevation of musculoperiosteal flaps to gain access to the iliac crest may result in significant post-operative morbidity, including pain, haematoma, delayed ambulation, and increased length of hospital stay. This is true whether an antero-medial, antero-lateral, or the posterior approach is used (Laurie et al. 1984, Marx & Morales 1988).

The philosophy of minimally invasive surgery can be extended to the procurement of autogenous bone by means of a trephine. Various techniques, which attempt to minimize morbidity have been reported (Dragoo & Irwin 1972, Schwartz & Leake 1979, Tilley & Davis 1984, Caddy & Reid 1985, Abubaker & Sotereanos 1989, Wagner & Moore 1991, McGurk et al. 1993, Altman & Blenquisopp 1994, Billmire & Rotatori 1994). In the past, trephines have been used to harvest bone biopsy specimens (Waldman & Kleinfeld 1970, Smirnov & Baranov 1971, Braun 1974, Schuyt et al. 1979, Johnson et al. 1997, Minns & Sher 1983). Initially, these trephines were small hand held instruments that were used with a twisting motion (Smirnov & Baranov 1971, Minn & Sher 1983, McGurk et al. 1993, Altman & Blenquisopp 1994) and later power driven ones were developed (Johnson et al. 1997, Faugere & Malluche 1983, Billmire & Rotatori 1994, Kreibich et al. 1994). While the safety and yield of trephines has been reported with respect to their use as a biopsy tool, their use in procuring bone grafts has not been thoroughly evaluated (Habal 1995).

The safety and benefit of trephines has been demonstrated by Kreibich who showed that the percutaneous sampling of bone when compared to open procedures resulted in significantly reduced pain, less pain on walking, less sensory disturbance and less local tenderness (Kreibich et al. 1994). Evaluation of the safety of biopsy trephines has shown a low incidence of complications (Duncan et al. 1980).

Trephines have a long history of application in bone biopsy harvesting for the diagnosis of metabolic bone diseases and for research purposes (Malluche & Faugere 1986). These biopsy techniques demand proper sampling without destruction of bone, thereby producing viable bone for grafting purposes.

Trephines are either hand powered or electrically driven drills. Previous studies (Smirnov & Baranov 1971, Faugere & Malluche 1983, Caddy & Reid 1985, McGurk et al. 1993, Altman & Blenquisopp 1994) have demonstrated the possibility of obtaining bone with hand powered trephines, although the samples were not quantified. The Craig Bone Biopsy Set® (George Tiemann, Hauppauge, New York, USA) has been studied for iliac crest harvesting for patients requiring a maxillary bone graft to reconstruct cleft palate defects (Caddy & Reid 1985). A small skin incision was made over the iliac crest and the cortex was breached only once as the angle of the trephine was changed for
multiple passes. Quantification of the bone volume from one cadaver hip was estimated to be 4.15 cc of bone. No complications were reported with the 10 patients in the report (Caddy & Reid 1985).

McGurk reported on the use of a hand powered trephine that penetrated up to 8 cm in length. Although the diameter was not specified it was suggested that up to 6 cc of bone could be obtained. The results on 11 patients indicated no complications and reduced post-operative pain (McGurk et al. 1993). Care was suggested at depths greater than 80 mm.

The Zimmer Power Driven Trephine Drill® (Zimmer/Hall, Warsaw, Indiana, USA), which removes iliac bone of 7.5 mm in diameter has also been described as a harvesting technique (Johnson et al. 1997) This drill is used mostly for percutaneous bone biopsy of the iliac crest. In a 48 patient retrospective study morbidity was assessed in terms of post-operative pain, deep or superficial infection, and patient satisfaction. Based on these criteria, the reported morbidity rate was extremely low. Unfortunately there was no quantification of bone yield using this technique. This power driven trephine was aimed at right angles to the lateral surface of the ilium and although the reported complication rate is low, the medial cortex is always intentionally perforated in this technique, creating a potential risk of peritoneal disruption.

The Corb Needle Biopsy Set® (Zimmer/Hall, Warsaw, Indiana, USA), which obtains cores of up to 30 mm long with a variable diameter has also been evaluated (Billmire & Rotatori 1994). This set of instruments was described by these authors as being capable of harvesting 5 – 10 ml of cancellous bone from the anterior iliac crest. Morbidity was assessed as a function of donor site pain lasting greater than two weeks, post-operative dysesthesias, soft tissue haematoma or infection. This retrospective study of 20 donor cancellous bone graft sites reported that the morbidity rate was zero based on the above parameters (Billmire & Rotatori 1994). This report does not indicate the frequency or occurrence of perforations. Apparently, a resistance is felt before the needle punctures through the medial cortex ensuring minimal incidence of perforations. A comparison between a power driven trephine and the Jamshidi Needle® (Allegence Healthcare Corporation, Chicago, Illinois, USA) for the purposes of biopsy evaluation revealed no differences in qualitative aspects but significantly larger bone volumes were harvested with the power driven trephine (Faugere & Malluche 1983).

A number of researchers have evaluated the post-operative morbidity associated with the use of trephines (Duncan et al. 1980, Williams & Ford 1986, Billmire & Rotatori 1994). They have been shown to leave minimal scaring, decrease morbidity and produce less dysesthesia than open procedures (Billmire & Rotatori 1994). A retrospective study of complications following 14,810 iliac crest biopsies from 14 centres (Duncan et al. 1980) reported local haematomas, lateral cutaneous nerve neuropathies and pain in excess of 7 days duration, following 0.63% of trephinations. When the vertical approach was used the complication rate decreased to 0.36%. The use of the 8 mm diameter trephine drill had the highest rate of associated complications and only one major complication was reported being a fracture of the ilium in a patient with severe osteomalacia (Duncan et al. 1980). A case of a pneumoperitoneum has been reported and attributed to air entry into the pararenal space as a result of the direct penetration of the trephine; however, the trephine in this case was used at a 90° angle to the ilium (Williams & Ford 1986). A single case of avulsion of the anterior iliac spine in a post menopausal woman following a
transiliac bone biopsy has been reported (Stellon et al. 1985). Several authors (Duncan et al. 1980, Faugere & Malluche 1983) believe that the likelihood of complications increase when heavy pressure is applied, rather than gently allowing the instrument to do its work. Compared to the complications published with respect to open iliac crest grafting (Wolfe & Kawamoto 1978, Cowley & Anderson 1983, Laurie et al. 1984, Keller & Triplett 1987, Cohn & Krakow 1988, Marx & Morales 1988, Tayapongsak et al. 1994, Arrington et al. 1996, Hill et al. 1999) the trephine technique seems both simple and attractive and may help to reduced donor site morbidity.

2.7 Coral-derived granules

An ideal bone graft substitute should be biologically inert, readily available, and easily adaptable to the recipient site in terms of size and shape. It should be biodegradable and replaceable by host bone (Bajpai 1983). Coral-derived granules (CDG) exhibit a number of these properties.

CDG are xenograft coral exoskeletons harvested from the French part of the Great Barrier Reef in New Caledonia (Guillemin et al. 1987). The organisms used, are all part of the Madreporian group belonging to the genera Acropora. Corals of this group are formed by a colony of individual coral organisms, each consisting of a soft part, the polyp and its hard exoskeleton. The coral exoskeleton consists of 99% calcium carbonate (CaCO₃) in the form of aragonite crystals, the high pressure form of calcite. The crystal is 100µm long and is prismatic in shape (Guillemin et al. 1981, 1995). The remaining 1% is composed of simple amino acids (Issahakian et al. 1987a, Ouhayoun et al. 1992) and has osteoconductive properties (Sautier et al. 1990).

The porosity of coral has been shown to be an important physical property for its behaviour as an implant. Coral skeletons present with different size porosities. The volume of porosity affects the rates of alloplast resorption and bone formation. Two genera of coral Acropora and Porites differ in the architecture of their exoskeletons. They both exhibit an open porosity, as all the pores communicate with each other. The Porites porosity volume is 49 ± 2% and their mean pore diameter is 250 µm (range 150–400 µm) while Acropora porosity volume is 12 ± 4% with a mean pore diameter of 500 µm (range 200–800 µm). The smaller the porosity of the coral exoskeleton is, the greater the density per volume unit and the greater the compressive strength and modulus of elasticity become. The rate of coral resorption and bone deposition is faster with larger porosity volumes and smaller pore diameters both in pig and in sheep models (Guillemin et al. 1989). Coral skeletons of higher porosity volume allow larger cellular infiltrate and ion exchange promoting a faster resorption and bone apposition (Guillemin et al. 1989, Jammet et al. 1994).

CDG are thought to be resorbed through the enzymatic action of carbonic anhydrase (CA) (Chétail & Fournie 1969, 1970). CA is known to catalyze the reversible reaction:

\[ \text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{HCO}_3^- + \text{H}^+ \]
CA has been shown to be present in the actively resorptive part of the osteoclast in its ruffled border (Simanski & Yagi 1960, Gay & Muller 1974). If the specific inhibitor of CA, acetazolamide is given to dogs implanted with coral exoskeleton grafts, the resorption of the coral is delayed and fractures treated with coral-derived grafts fail to heal (Guillemin et al. 1981, 1987, 1995).

Fig. 1. Photomicrographs showing the gradual incorporation of coral exoskeleton into mammalian bone. 1 Fibrovascular ingrowth. 2 Bony apposition onto coral exoskeleton. 3 Osteoclast resorbing coral skeleton. 4. Woven bone replacing coral exoskeleton.

Implanted coral is well tolerated in a variety of animal models (Issahakian et al. 1987b, Ouhayoun et al. 1991, Shababana et al. 1991), and also in humans (Souyris et al. 1985, Issahakian & Ouhayoun 1988, Ouhayoun et al. 1991). In orthopaedic indications coral-derived xenografts have been used to treat spinal fusions in children and for cervical fusions in adults, for femoral lengthening and for acetabular reconstruction (Patel et al. 1980, Pouliquen et al. 1989, Kehr et al. 1991).

CDG have been used as a bone graft substitute in the cranio-maxillofacial skeleton for situations ranging from small periodontal lesions to large cranio-maxillofacial defects and forehead recontouring (Issahakian et al. 1987b, Issahakian & Ouhayoun 1988, Roux et al. 1988a,b, Yukna & Yukna 1998). They are completely resorbable and replaceable by host

The use of a bone graft substitute like CDG avoids the need to create a second surgical site for harvesting a bone graft, along with the morbidity associated with this additional procedure. These granules could be useful both in the osseous reconstruction of the cranio-maxillofacial skeleton and could also serve potentially, as a safe and effective means to preserve the dimensions of the alveolar process, until such time as an implant can be placed. The time for total replacement of this implant by bone in the human craniofacial skeleton is approximately 18 months (Roux et al. 1988a). This could make CDG particularly useful in the paediatric population as an alveolar sparing material, where one would have to delay implant reconstruction until growth is complete.
3 Aims of the study

The purpose of this study was to expand the body of knowledge and to develop safe methods to reduce the morbidity associated with the osseous reconstruction of the cranio-maxillofacial skeleton, particularly from the harvesting of donor site defects. This reduction in morbidity could possibly have come from two approaches. The initial approach would be to reduce morbidity from bone graft harvesting sites by the development of less invasive more conservative surgical techniques. The second approach was to eliminate altogether, the need for a donor site by using a bone graft substitute. Therefore the specific aims of the study were:

1. To determine the safety of a minimally invasive surgical approach to the anterior iliac crest using a motorized trephine, quantify the amount of bone available for harvesting with a standardized approach and determine the anatomic limitations of this technique in the unique setting permitted by the cadaver model.

2. To test the suitability and use of a minimally invasive surgical approach to the anterior iliac crest using a motorized trephine in patients requiring bone graft reconstruction in the cranio-maxillofacial skeleton particularly as an outpatient procedure.

3. To compare the morbidity associated with the use of a motorized trephine to harvest cores of bone from the anterior iliac crest with the traditional open medial approach.

4. To study the safety and applicability of coral-derived granules as a bone graft substitute in the cranio-maxillofacial skeleton.

5. To evaluate the efficacy of coral-derived granules in the reconstruction of maxillomandibular, especially dento-alveolar defects in the growing patient.
4 Materials and methods

4.1 Subjects and grafts

This research project was performed involving a total of 253 subjects in whom either bone was harvested or bony reconstruction was necessary in the cranio-maxillofacial skeleton. The work was divided into two main areas, which together combined five studies. The subject of bone graft harvesting comprised three studies (studies I, II and III) and the subject of coral-derived bone graft substitutes comprised two studies (studies IV and V). The number of subjects and their demographic data, are listed in Table 1.

<table>
<thead>
<tr>
<th>Study</th>
<th>N (Female/Male)</th>
<th>Age X (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (Cadavers)</td>
<td>25 (10/15)</td>
<td>70.5 (58–86)</td>
</tr>
<tr>
<td>I (Patients)</td>
<td>11 (5/6)</td>
<td>25.4 (16–45)</td>
</tr>
<tr>
<td>II</td>
<td>84 (43/41)</td>
<td>27.2 (8–77)</td>
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<tr>
<td>III</td>
<td>76 (43/33)</td>
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<td>IV</td>
<td>36 (23/13)</td>
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<tr>
<td>V</td>
<td>21 (12/9)</td>
<td>13.6 (7–20)</td>
</tr>
</tbody>
</table>

The protocols were within the guidelines of the research ethics committees at the Hospital for Sick Children and University of Toronto, and the Department of Anatomy, University of Toronto, Toronto, Canada, that were in place prior to the commencement of the studies.

In study I, in order to assess the safety of the minimally invasive power driven trephine technique, a total of 25 adult cadavers were used to determine the volume and weight of bone that could be harvested using a motorized trephine (Osteocore®, Straumann, A.G., Waldenburg, Switzerland). A total of 50 anterior iliac crests were sampled. Core samples of cancellous bone were measured, weighed, and their volumes were determined. The harvested sites were then dissected and evaluated for perforations of the medial and
lateral walls of the ilium. These data were compared with the measurement of the first 40 consecutive in vivo cores trephined from 11 patients requiring bone grafts. The cadaver iliac sites were then intentionally perforated on the medial aspect of the ilium, towards the peritoneal cavity, to analyze the safety of the technique.

In study II, in order to assess the suitability of the minimally invasive technique in a clinical environment, a retrospective study analyzed 84 consecutively treated patients, requiring autogenous bone harvested using a motorized trephine (Osteocore®, Straumann, A.G., Waldenburg, Switzerland) over a three-year period, from 86 trephined iliac crest sites. A total of 333 cancellous cores were harvested. The inclusion criteria were all patients who required elective cranio-maxillofacial surgery, those who were admitted on the same day of their procedure, a follow-up of at least six months, and completion of a telephone survey.

For each patient a chart review was performed and a survey questionnaire was completed. Intra-operative information regarding the number of trephined cores of bone harvested per iliac crest, as well as the bone volume obtained was recorded. Additionally, intra-operative complications including bleeding, perforation of the medial and lateral walls of the ilium, and quantity of bone were recorded. Post-operative reports of pain, bleeding, possible paresthesia and suitability for discharge were also recorded. All patients were followed one week post-operatively and examined for ambulatory gait deficits, wound complications including incision breakdown, infection, paresthesia, and pain.

All patients were then surveyed by a questionnaire examining their short-term (1–14 days), and long-term (greater than 6 months post-operative) deficits, pain or remarks.

In study III, in order to compare the morbidity of the minimally invasive power driven trephine with traditional open iliac crest bone graft harvesting, a total of 76 consecutive patients, requiring less than 30 ml of bone for maxillofacial grafting, were placed into two treatment groups. A prospective case-control format was applied. Group One consisted of the first 22 consecutive patients. These patients underwent corticocancellous block graft (CCBG) harvest in the traditional open medial approach to the anterior ilium. Group Two consisted of the next 54 consecutive patients. These patients had cancellous cores (CC) harvested in a closed fashion through a 0.5–1.0 cm incision with a motor-driven trephine (Osteocore®, Straumann, A.G., Waldenburg, Switzerland).

ANOVA revealed no significant differences between Groups One and Two based on age: \( F(1,74) = 0.429 \) or gender: \( F(1,74) = .051, p>.05 \). The morbidity of the two groups was analyzed and compared. The following parameters were used to evaluate patient morbidity: number of days to unassisted ambulation, length of hospital stay, and pain scores for both the recipient and the donor sites. A visual analogue scale was used to grade the subjective hip and maxillofacial pain scores daily for the first three days following surgery.

In study IV, in order to assess the safety and applicability of coral-derived granules as a bone graft substitute in the cranio-maxillofacial skeleton, 36 patients with 54 craniofacial osseous contour defects received subperiosteal augmentations with natural coral-derived granules (CDG) made chiefly of calcium carbonate (Biocoral® Granules, Société Inoteb, St. Gonnorey, France). The distribution of the location of these sites is depicted in Table 2.
Table 2. Distribution by location, of patients requiring augmentation of cranio-maxillofacial osseous contour defects using coral-derived granules in study IV.

<table>
<thead>
<tr>
<th>Location</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td>17</td>
<td>(31.4)</td>
</tr>
<tr>
<td>Temporal</td>
<td>15</td>
<td>(27.7)</td>
</tr>
<tr>
<td>Malar</td>
<td>10</td>
<td>(18.5)</td>
</tr>
<tr>
<td>Maxilla</td>
<td>9</td>
<td>(16.6)</td>
</tr>
<tr>
<td>Infraorbital rim</td>
<td>2</td>
<td>(3.7)</td>
</tr>
<tr>
<td>Mandible</td>
<td>1</td>
<td>(1.9)</td>
</tr>
</tbody>
</table>

The patients were followed for 12 to 36 months to describe post-operative complication rates and to develop a sense of post-operative morbidity from the use of this resorbable xenogenic bone graft substitute. Technical notes pertinent to the use of this material were also recorded and analyzed.

In study V, in order to assess the efficacy of coral-derived granules in the reconstruction of maxillomandibular, especially dento-alveolar defects in the growing patient, CDG (Biocoral® Granules, Société Inoteb, St. Gonnorey, France) were used in alveolar ridge preservation procedures in a growing population of 21 patients with a mean age of 13.8 years and with 48 dento-alveolar defects. These patients are detailed in Table 3.

Table 3. Distribution of 48 sites of coral granule augmentations in 21 patients in study V.

<table>
<thead>
<tr>
<th>Gender</th>
<th>N</th>
<th>Age range</th>
<th>Mean age</th>
<th>Number of sites</th>
<th>Anterior maxilla</th>
<th>Posterior maxilla</th>
<th>Posterior mandible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>12</td>
<td>7–19</td>
<td>13.4</td>
<td>25</td>
<td>4</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>10–20</td>
<td>13.8</td>
<td>23</td>
<td>13</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

Patients were grouped according to the aetiology of alveolar ridge defect. Group One comprised 17 alveolar ridge defects in the anterior maxilla resulting from trauma. The causes of tooth-loss in this group included complete avulsion, subluxation, root fracture and root resorption. In all 17 cases the labial and palatal plates of bone were present at the time of coral granule placement. Group Two comprised 31 alveolar ridge defects resulting from the careful conservative removal of ankylosed retained primary molars without succedaneous permanent premolars. ANOVA revealed no significant differences between Groups One and Two based on age: F(1,24) = 0.78 or gender: F(1,74) = .158, p>.05. In all 31 cases, the buccal and lingual plates of alveolar bone were intact at the time of coral granule placement. The aetiology of the tooth-loss and location of the augmented alveolar ridge sites are listed in Table 4.
Table 4. Aetiology of tooth-loss and location of augmented alveolar ridge sites in study V.

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Group one</th>
<th>Group two</th>
<th>Group two</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>anterior maxilla</td>
<td>posterior maxilla</td>
<td>posterior mandible</td>
</tr>
<tr>
<td>Trauma</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankylosis of primary molars without succedaneous permanent tooth</td>
<td>10</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

Sites were augmented with 1 to 2 mls of Biocoral™ granules (Société Inoteb, Saint Gonnorey, France) placed into the otherwise intact avulsion or extraction sockets as inlay grafts. In all cases coral granules were placed the same day that the tooth was lost, either on the day of tooth avulsion or immediately following elective tooth removal.

4.2 Methods and techniques

4.2.1 Surgery

The research project employed four different surgical methods to study morbidity resulting from harvesting bone from the iliac crest, and the success of osseous reconstruction using coral-derived granules as xenograft bone graft substitutes. The initial goal was to test the applicability and safety of a minimally invasive motorized trephine harvest procedure on the iliac crest. The surgery was performed on a group of 25 cadavers using both open and closed harvesting techniques. Iliac crest harvests were then performed on patients, as part of their planned bony reconstruction. Then an attempt was made to avoid donor site morbidity by using coral-derived granules as a bone graft substitute in the reconstruction of bony contour defects of the cranio-maxillofacial skeleton and finally in dento-alveolar sites.

4.2.1.1 Cadaver iliac crest harvest

In study I, bone was trephined from the right and left iliac crests of twenty five freshly-preserved adult cadavers. An open technique was used on the left iliac crest. The overlying soft tissue was dissected free from the bone exposing the entire anterior iliac crest and the medial and lateral cortical walls. This permitted direct visualization of the bone being harvested by the trephine in the cadaver subjects. On the right side, the iliac crest was approached in a closed fashion. A one centimetre stab incision was made through the skin down to periosteum, through which the trephine could access the entire crest by displacing the soft tissues with a funnel shaped retractor. Five consecutive cores of cancellous bone were harvested from each of the open and closed sides using the percutaneous power driven trephine (Osteocore®, Straumann AG, Waldenbg, Switzerland) (Fig. 2).
Fig. 2. The osteocore with the pre-cutter and trephine drill bit.

The trephine consisted of a pre-cutter used to cut through the periosteum and to score the cortex of the iliac crest. The core drill or actual trephine then drilled and separated a cancellous core from the surrounding bone. The internal diameter of the trephine was 4.0mm and its length was 38mm. It engaged the original recess made by the pre-cutter and was drilled into the bone (Fig. 3).

A hand-held funnel-shaped winged positioner controlled by an assistant was used to stabilize the trephine (Fig. 4). Within the trephine, an internal forceps fractured the core of bone graft away from the iliac crest. An internal plunger was used to push out the core of bone from the trephine (Fig. 5).
Fig. 3. The trephine totally engaged within bone.

Fig. 4. The pre-cutter bit on the drill supported by a funnel-shaped winged positioner, which aids in obtaining proper axial inclination and stability.
Fig. 5. Bone being expressed by the plunger from the drill mechanism.

The medial and lateral aspects of the right and left iliac crests were dissected and examined for perforations through the cortical plates of the ilium (Fig. 6). The cores were then weighed and their volumes measured.

Fig. 6. View of the crest of the ilium with 5 cores drilled out. More bone can be obtained by entering the holes at different angles or simply removing the interseptal bone with Rongeurs.
The safety of the procedure was tested after acquiring the cadaver cancellous cores. Twenty additional sites in 10 cadavers were drilled in such a way as to intentionally perforate the medial cortex of the ilium. These perforations were made with the trephine pushed down maximally into the iliac crest to its length of 38 mm. The area medial to the ilium was then explored and dissected to check for the depth of soft tissue penetration past the medial cortical plate of the ilium. In particular, involvement of the iliacus muscle, peritoneum or peritoneal contents were checked.

4.2.1.2 Patient iliac crest harvest

Following the cadaver study, the trephine was used to harvest bone in a total of 149 patients requiring autologous free grafts for various augmentation procedures: 11 patients in study I, 84 patients in study II, and 54 patients in study III. All the patients underwent bone harvest from an essentially closed anterior approach, using the same motor-driven trephine (Osteocore®, Straumann, A.G., Waldenburg, Switzerland) used in the cadaver subjects from study I. A 0.5 to 1.0 cm stab incision was made through skin and subcutaneous tissue overlying the area between the anterior superior iliac spine (ASIS) and the iliac tubercle (Fig 7).

Fig. 7. Small stab incision used in the minimally invasive approach to bone graft harvesting to access iliac crest with motorized trephine.
Limited blunt dissection was directed down to the level of the fascia and periosteum. Tissue overlying the anterior ilium was incised. Care was taken to remain medial to the tensor fascia lata and gluteus medius muscles, and lateral to the iliacus and external abdominal oblique muscles. The same specialized trocar used in the cadaver study, with a serrated edge designed to engage the periosteum, was introduced through the stab incision (Fig 8).

Fig. 8. Funnel-shaped trocar retractor in position protecting the surrounding soft tissues and ensuring a pathway to the cortex of the iliac crest.

The cancellous core (CC) harvest involved the use of a pre-cutter drill which was inserted through the trocar and used to score the overlying periosteum and cortical crestal bone. Next, a 4 mm diameter core cutter was used to define and withdraw the core of cancellous bone. Up to 8 cores per patient were obtained through the same stab incision. The length of each CC was measured and recorded. The intervening bony septum between each core harvest defect was removed with rongeurs, and the cancellous component of the ilium was further curetted through the stab incision to maximize the harvest (Fig 9). Following irrigation with sterile saline, gelfoam was placed into the core defects and closure proceeded in a layered fashion. No drains were used, but a pressure dressing was applied for 48 hours.
In study III, the first 22 patients were assigned to a corticocancellous block graft cohort (CCBG) and underwent harvesting of corticocancellous block grafts through an anterior medial approach to the ilium. This involved a 6 cm incision beginning 1 cm posterior to the ASIS and 1 cm lateral to the bony prominence. Subcutaneous tissue dissection proceeded with electrocautery through Scarpa’s fascia without progressing through any adjacent muscles. Once the anterior crest was visualized, a midcrestal periosteal incision was made 1 cm posterior to the ASIS and the medial musculature was reflected in a subperiosteal plane. The external oblique abdominal and iliacus muscles were reflected and bone was removed from the area between the tubercle and 1 cm posterior to the ASIS. A 2.5 to 4.5 cm$^2$ (mean 3.8 cm$^2$) rectangular subcrestal cortical window was created with a reciprocating saw and cancellous bone was removed with chisels, curettes and gouges (Fig. 10). The surgical site was thoroughly irrigated with sterile saline solution. Gelfoam was placed into the bony defect, and closure was accomplished in layers from deep to superficial, including the musculoperiosteal flap, subcutaneous tissues, dermal layer and skin. A drain was not used in any of the 22 subjects.
4.2.1.3 Cranio-maxillofacial coral-derived granule reconstruction

In study IV, 36 patients requiring augmentation of osseous defects in various parts of the cranio-maxillofacial skeleton were treated with coral granules. The contour defect was identified and outlined at surgery. A solution containing 2 percent lidocaine with epinephrine in a concentration of 1:100,000 was injected subdermally, but not subperiosteally, in the area of the defect, until the contour defect was completely eliminated by the local anesthetic solution. The volume of the injected solution was measured and recorded. This was assumed to be the volume necessary to produce the desired correction of the osseous defect.

A distant skin incision, placed in a relatively inconspicuous location, was used as an entry to dissect a subperiosteal pocket large enough to eliminate the defect. The size of the periosteal pocket was always dissected so that its borders would precisely correspond to the borders of the contour defect. Inadvertent overextension of the pocket was avoided as this could lead to the spillage of coral granules into areas outside the defect.

The same volume of coral granules as measured with the local anesthetic solution was then introduced into the subperiosteal pocket using a preloaded syringe. The most distant portion of the subperiosteal pocket from the incision was always filled first. Once the pockets were filled external pressure and molding was used to attain the final desired contours, avoiding any edge effects that are commonly found with solid blocks of implanted materials and bone grafts (Fig 11).
Fig. 11. A. Pre-operative view of a defect in frontal bone in the right forehead region. B. Incision made above the hairline with syringe containing coral granules inserted into the wound to deliver granules into a subperiosteal pocket, distant from the incision. C. Soft mallet used to gently flatten granules deposited transcutaneously in the subperiosteal location to eliminate any edge effects. D. Post-operative appearance of patient’s forehead.

4.2.1.4 Dento-alveolar coral-derived granule reconstruction

In study V, a total of 48 single recently edentulated sites in 21 healthy patients were grafted with CDG using a so-called “alveolar preserving technique”. After the injection of 2 ml of 2 percent lidocaine with epinephrine local anaesthetic solution, traumatized or ankylosed teeth were removed from the anterior maxillary or posterior maxillary and or mandibular alveoli. Mucosal advancement flaps, using releasing incisions, were fashioned to cover the extraction socket defects in a tension free closure. Periosteal scoring was used to achieve this in all cases. Care was taken to deposit the CDG into the intact tooth sockets in the alveoli as an inlay graft. Care was taken to try to avoid the spillage of CDG into a subperiosteal location. The wounds were all sutured with 4–0 Vicryl-Rapide® (Ethicon, Peterborough, Ontario Canada). All patients were instructed to rinse their oral wounds twice daily with a 0.12% chlorhexidine gluconate containing mouth rinse until mucosal healing occurred (Fig 12).
Fig. 12. Coral granules deposited into an alveolar extraction socket defect in as an inlay graft.

Patients were reassessed post-operatively and seen at 2, 4, 6, 12 weeks, then at 6, 12, 18, 24 months and annually until osseointegrated implant placement. Clinical and radiographic examinations were performed at follow-up visits to check for complications including infection, inflammation, wound dehiscence and resorption. In all cases of maxillary anterior tooth-loss, a maxillary removable appliance was provided to the patients and was inserted at the 4-week post-operative visit. This prosthesis consisted of an acrylic tooth suspended from an acrylic resin occlusal splint and trimmed so that the acrylic was out of contact with the mucosa. The design of this prosthesis avoided any loading of the maxillary anterior edentulous site. No orthodontic retainers or partial dentures were placed in any of the posterior maxillary or mandibular edentulous sites. Space maintenance, when deemed necessary, was accomplished with fixed orthodontic appliances.

Success of the alveolar sparing procedure was defined as the ability to successfully place an osseointegrated dental implant into the xenograft reconstructed site without the need for a revisional bone graft.

Once the cessation of skeletal growth had been identified using serial cephalometric analysis, threaded, machined titanium Brånemark dental implants (Nobel Biocare AB, Göteborg, Sweden) were placed into the reconstructed sites, either into the coral granule-augmented sites, or into subsequently bone graft-augmented sites if the coral granules did not provide enough bone for the placement of a dental implant. The implants were followed annually after their restoration.

4.2.2 Evaluation of the surgical outcomes

In study I, procurement of cores from cadavers was performed by two investigators (GKBS & MFC). All weight and volumetric measurements were performed by one examiner (MFC) immediately after the harvesting procedure.

In studies I, II, III, all surgical procedures were either performed by or supervised by the same single investigator (GKBS). In study II, all the questionnaires were administered by one investigator (BNR) 14 days and 6 months postoperatively. In study III, because of
the realities of surgical practice and investigator availabilities, the post-operative clinical evaluations were all performed by one of two investigators (IAN & GKBS) daily while the patients remained in hospital and on post-operative day 3 if the patient had been discharged.

In study IV, all of the surgical procedures were performed by one investigator (DM) and all of the clinical evaluations were done by the second investigator (GKBS). In study V, all of the surgical procedures and clinical examinations were done by one investigator (GKBS).

4.2.2.1 Cancellous core dimensions

In the cadaver model in study I, the percutaneous power driven trephine was used to obtain 5 cores of corticocancellous bone per cadaver site. The medial and lateral aspects of the right and left iliac crests were surgically explored, dissected and examined for perforations. The cores were then measured and weighed and their volumes were determined.

Another 10 cadavers were then drilled with the trephine in an open approach on one side and a closed approach on the other producing 20 additional sites. An intentional perforation was created at each of the sites by drilling with the motorized trephine to the depth of maximal penetration into the bone of the ilium allowed by the trephine and retractor combination. The medial and lateral aspects of these iliac crests were then explored surgically to check for soft tissue and specifically for peritoneal involvement.

Following this cadaver study, the trephine was used in patients requiring autologous free grafts for various augmentation procedures. The first 40 CC’s were weighed, measured and their volumes were determined for comparative purposes with respect to the cadaveric model.

4.2.2.2 Questionnaire

In study II each subject participated in a follow-up telephone interview in which questions regarding morbidity and patient satisfaction with respect to the anterior iliac crest bone harvest were asked. Morbidity was defined as post-operative pain and/or gait disturbance noted by the patient. To assess overall satisfaction, patients were asked if they would undergo the same procedure again. Post-operative pain and gait disturbance were assessed as both short term (1–14 days post-op), and long term (greater than 6 months post-op) variables.
4.2.2.3 Post-operative clinical examination, gait and discharge criteria

In study III, the following parameters were used to evaluate patient morbidity: number of days to unassisted ambulation, length of hospital stay, and pain scores for both the recipient and the donor sites. Unassisted ambulation was defined as the ability of the patient to get up from bed and walk to the bathroom and hallway outside of their hospital room, without any assistance. Gait was noted to be normal or abnormal if on observation during ambulation, the patient had an obvious disturbance in the rhythm of gait post-operatively. Patients were discharged from hospital once they were clinically stable and able to care for themselves at home. A visual analogue scale was used to grade the subjective hip and maxillofacial pain scores.

4.2.2.4 Visual analogue scale

In study III a 10 cm visual analogue scale was constructed with 1 cm graduations. The label “no pain” was used as an anchor on the left side of the scale at position zero, with the “most severe pain” label used as an anchor on the right side at position 10. The visual analogue scale was used to grade the subjective hip and maxillofacial pain scores daily until the patients were discharged and on day 3 if the patients had been already discharged from hospital.

4.2.3 Statistics

In study I the first 40 cancellous core samples harvested from living patients were weighed and measured for comparison with the cores obtained from the cadaveric model. The student t-test was used to test for significant differences between the two groups.

In study II the clinical observations and the results of the questionnaire were tabulated with means and standard deviations.

In study III, to ensure comparability of the two study groups, ANOVA was performed. The means were calculated and the student t-test was used to compare the means between the two experimental groups.

In study IV descriptive statistics were used for analysis and presentation of data.

In study V, to ensure comparability of the two study groups, ANOVA was performed. The Chi-square test was used to test differences between Groups One and Two.

The statistical analysis was performed using the SPSS for Windows statistical package (SPSS Incorporated, version 10.1). Values of p<0.05 were considered statistically significant. A specialist was consulted regarding the planning of the statistical analysis.
Table 5. Summary of study design, data handling and study periods of studies I to V.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of study</td>
<td>Experimental cadaver surgery</td>
<td>Clinical retrospective</td>
<td>Clinical prospective</td>
<td>Clinical prospective</td>
<td>Clinical prospective</td>
</tr>
<tr>
<td>Study material</td>
<td>50 cadaver iliac crests</td>
<td>86 patient iliac crests</td>
<td>76 patient iliac crests</td>
<td>36 patients</td>
<td>21 patients</td>
</tr>
<tr>
<td>Data sources</td>
<td>250 trephined cadaver bone cores</td>
<td>333 trephined bone cores</td>
<td>22 corticocancellous blocks</td>
<td>54 craniofacial sites</td>
<td>48 dento-alveolar sites</td>
</tr>
<tr>
<td>Evaluation methods</td>
<td>Weight, volume, length, perforations</td>
<td>Chart review and questionnaire</td>
<td>Clinical data and visual analogue scale</td>
<td>Clinical data</td>
<td>Clinical data Ability to place dental implant without bone graft</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>Student t-test</td>
<td>Means and standard deviations</td>
<td>ANOVA, Student t-test</td>
<td>Descriptive statistics</td>
<td>ANOVA, Chi-square test</td>
</tr>
</tbody>
</table>
5 Results

5.1 Cadaveric and patient cancellous core dimensions and perforations of the medial iliac cortical plate

The first three studies produced a total of 849 cancellous cores that were harvested as shown in Table 6.

Table 6. Total number of cancellous cores harvested in studies I, II and III.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of cancellous cores harvested</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>250 from cadavers</td>
</tr>
<tr>
<td></td>
<td>40 from living patients</td>
</tr>
<tr>
<td>II</td>
<td>333</td>
</tr>
<tr>
<td>III</td>
<td>226</td>
</tr>
<tr>
<td>Total</td>
<td>849</td>
</tr>
</tbody>
</table>

In study I the bone harvested by the trephine took the form of a discrete and compact core of corticocancellous bone (Figs 5 & 13). The average core length was shorter than the core cutter, evidence of the core being compacted. In the cadaver (n=250 cores), the average core length was 33.5 mm (range 28 to 38 mm, S.D. =13.9). Each core had a diameter of 4 mm. The shortest cores were also the least compact and came from the most atrophic cadavers. The average weight of each core was 0.44 grams (range 0.37 to 0.49 grams, SD=0.001). Each core occupied an average volume of 0.42 ml (range 0.35 to 0.48, SD=0.002).

Perforations of the cortex of the iliac crest occurred in 11 out of 250 core samples (4.4% of cores). Four perforations occurred on the medial aspect and 7 occurred on the lateral aspect. Six perforations occurred on the closed side and 5 on the open side, which had the periosteum reflected. All perforations occurred with cores greater than 30mm in depth. The perforations consisted of a fraying or removal of cortical bone without periosteal disruption in 4 of the 6 closed sites.
All 20 of the intentional perforations involved the periosteum of the medial aspect of the ilium and the iliacus muscle. None involved the peritoneum or peritoneal contents as the instrument used in conjunction with its funnel-shaped retractor was not long enough to permit this.

The samples obtained from the patients (n=40 cores) had an average length of 34.1 mm (range 28 to 38 mm, SD=12.4) and an average weight of 0.46 g (range 0.4 to 0.5 g, SD=0.001) and an average volume of 0.46 ml (range 0.39 to 0.5, SD=0.002). The patient group was not statistically different from the cadaveric group.

**Fig. 13.** Histological section of a cancellous core with haematoxylin and eosin stain at 20x magnification. Note the largely cancellous structure of the core with minimal cortical bone on the superior-most aspect on the left side. The cancellous core is laden with endosteal cells.

### 5.2 Clinical course of anterior iliac crest harvesting methods

In study II a total of 84 patients had bone harvested using a power driven trephine from a total of 86 anterior iliac crest sites for a total of 333 cores (3.96 cores per patient). Forty-one patients were discharged on the same day as the operation. The volume of bone obtained ranged from 3 ml to 21 ml per harvest site (1–7 cores of 4 mm by 30–38 mm). The bone volume obtained was dependent on the size of the defect to be filled. Intra-operatively, one complication occurred [1 of 333 cores (0.3%)], namely, breakage of an instrument without perforation of the medial or lateral walls of the ilium, or excessive bleeding. There were no reports of paresthesias in the distribution of the lateral femoral cutaneous nerve. The complications rate was 3/84 (3.6%). No complication produced any long-term effects. The complications included the broken instrument mentioned above, 1 case with a gait disturbance of greater than 3 days duration and 1 case with pain related to the cancellous core harvest procedure of greater than 3 days duration. Patients surveyed up to 6 months post-operatively showed positive results, as they were content with the harvesting procedure (Table 7).
Table 7. Post-operative morbidity following trephined cancellous core harvesting procedure. (Results of a telephone interview) in study II.

<table>
<thead>
<tr>
<th>Variable Assessed</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-operative Gait Disturbance (&gt;3 days duration)</td>
<td>1/84 (1.2%)</td>
</tr>
<tr>
<td>Pain Related to the Trephined Cancellous Core Bone</td>
<td>1/84 (1.2%)</td>
</tr>
<tr>
<td>Procedure (&gt;3 days duration)</td>
<td></td>
</tr>
<tr>
<td>Patient Satisfaction with the Trephined Cancellous Core</td>
<td>83/84 (98.8%)</td>
</tr>
<tr>
<td>Bone Harvest Procedure</td>
<td></td>
</tr>
</tbody>
</table>

In study III the mean time to unassisted ambulation in patients following a cancellous core harvest was 0.8 days (Table 8). All of these patients ambulated on the first post-operative day. The majority of patients (96%) ambulated unassisted. The mean time to unassisted ambulation in patients following a corticocancellous block graft was significantly longer at 2.8 days (Table 8).

Table 8. Time to unassisted ambulation and length of hospital stay following harvest of corticocancellous block grafts and cancellous cores from the anterior ilium in study III.

<table>
<thead>
<tr>
<th>Morbidity Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Unassisted Ambulation</td>
<td>2.8 (2–4)</td>
<td>0.8 (0–1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Length of Hospital Stay</td>
<td>4.1 (3–5)</td>
<td>2.2 (0–4)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Group 1 (corticocancellous block grafts), n=22; Group 2 (cancellous cores), n=54; Means and Ranges in days.

The mean length of hospital stay following a cancellous core graft was 2.2 days. The mean length of hospital stay following a corticocancellous block graft was significantly longer at 4.1 days (Table 8).

The mean contemporaneous maxillofacial pain scores following procurement of cancellous core grafts (day 1: 5.6; day 3: 4.2) and procurement of corticocancellous block grafts (day 1: 5.8; day 3: 4.5) were not significantly different. The mean hip pain score was significantly greater (p<0.05) on day 1 in patients having undergone a corticocancellous block graft (pain score: 6.2) than in patients having undergone a cancellous core graft (pain score: 3.0) (Table 9).

Table 9. Maxillofacial and pelvic pain scores following harvest of corticocancellous block grafts and cancellous cores from the anterior ilium in study III.

<table>
<thead>
<tr>
<th>Site</th>
<th>Day</th>
<th>Pain Group 1</th>
<th>Pain Group 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxillofacial</td>
<td>1</td>
<td>5.8</td>
<td>5.6</td>
<td>NS</td>
</tr>
<tr>
<td>Maxillofacial</td>
<td>3</td>
<td>4.5</td>
<td>4.2</td>
<td>NS</td>
</tr>
<tr>
<td>Iliac</td>
<td>1</td>
<td>6.2*</td>
<td>3.0*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Iliac</td>
<td>3</td>
<td>5.8*</td>
<td>1.6*</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Group 1 (corticocancellous block grafts), n=22; Group 2 (cancellous cores), n=54; Means; NS (no significant difference). Asterisk denotes a significant difference between values.
The mean pelvic pain did not decrease by the third post-operative day in patients having undergone a corticocancellous block graft (pain score: 5.8), but did decrease in patients having undergone a cancellous core graft (pain score: 1.6). The difference in mean pain score between the two graft groups at day 3 was even more highly significant (p<0.01) than at day 1 (p<0.05).

All but two of the patients who underwent a cancellous core graft harvest technique were discharged from hospital by the second post-operative day. Post-operative assessment at 1 week identified gait disturbance in 15 of 22 patients (68%) who underwent a corticocancellous block graft. By contrast, only 1 of the 54 patients (1.9%) who underwent a cancellous core graft harvest exhibited an abnormal gait. No other complications were noted.

5.3 Cranio-maxillofacial reconstruction with coral-derived granules

In study IV of the 36 patients the majority of the 54 augmentation sites involved the frontotemporal region (32 sites, 59.1%). Most of these patients had been treated for pre-existing craniofacial problems, such as craniosynostosis. They therefore required touch-up procedures to treat residual minor bony defects in order to improve on the aesthetics of their surgical outcomes. All the sites in the upper facial skeleton were approached using distant transcutaneous incisions. In the malar region two of the ten sites were treated using an intra-oral approach. All nine maxillary sites and one mandibular site were approached intra-orally.

Table 10 lists the average volume of coral injected at each site. The amounts ranged from 1.0 to 6.0 ml. Small volumes were used because the majority of the corrections were touch-ups in children.

<table>
<thead>
<tr>
<th>Location</th>
<th>Average Volume (ml)</th>
<th>(Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td>4.5</td>
<td>(2.0–6.0)</td>
</tr>
<tr>
<td>Temporal</td>
<td>3.75</td>
<td>(2.0–4.0)</td>
</tr>
<tr>
<td>Malar</td>
<td>1.9</td>
<td>(1.5–4.0)</td>
</tr>
<tr>
<td>Maxilla</td>
<td>2.75</td>
<td>(2.0–4.0)</td>
</tr>
<tr>
<td>Infraorbital rim</td>
<td>3.0</td>
<td>–</td>
</tr>
<tr>
<td>Mandible</td>
<td>3.0</td>
<td>–</td>
</tr>
</tbody>
</table>

Three types of complications were observed in this series. Prolonged wound inflammation was noted in two patients (3.8% of sites) where coral granules were left inadvertently in the superficial layers of the wound. Inflammation was noted to subside once the granules were removed.
In one case of frank suppuration occurred in a patient who had a frontal bony irregularity resulting from previous trauma. The origin of the infection was a pre-existing perforation of the anterior wall of the frontal sinus, which necessitated removal of all the granules. This was followed by a resolution of the infection.

Resorption was clinically evident in five sites during the one to three-year follow-up period. Two occurred in the same patient who was afflicted with hemifacial atrophy or Rhomberg’s Disease. Three other sites of noticeable resorption occurred in areas where the bony contact with the implanted material was not very good, such as along the thin infraorbital rim. The remaining patients did not show any clinical or radiographic signs of resorption during the follow-up period.

### 5.4 Dento-alveolar reconstruction with coral-derived granules

In study V the 48 augmentation sites of coral granules in alveolar sockets healed well with few significant complications. In Group One, where tooth-loss was secondary to trauma in the anterior maxilla, the coral granules restored the dimensions of the alveolar ridges temporarily. However, over the course of follow-up only 3 of 17 sites (17.6%) grafted with coral granules yielded sufficient bony support for the placement of an osseointegrated dental implant without using a revisional bone graft. In the 14 sites where the coral had failed to maintain the volume of the alveolar process, a revisional bone graft provided enough osseous support for the successful future placement of an osseointegrated dental implant in all the failed cases. In Group Two, in the posterior maxilla and mandible, where tooth-loss was due to the elective removal of ankylosed primary molars, 29 of 31 (93.5%) of sites were able to support the successful placement of an osseointegrated dental implant without the use of a bone graft (Table 11). This difference between Groups One and Two was found to be statistically significant using a Chi-square test (p<0.001).

One case of infection with abscess and fistula formation, and radiographic signs of resorption of coral granules was observed in the anterior maxilla. The infection originated from a fractured root tip, and necessitated removal of the coral granules. No other complications as seen in previous studies, such as wound dehiscence due to inflammation from coral granules inadvertently left in the superficial layers of the wound were observed during the 3 to 8 year follow-up period in this study.

<table>
<thead>
<tr>
<th>Location</th>
<th>Anterior maxilla</th>
<th>Posterior maxilla and mandible</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Bone Graft Necessary</td>
<td>3</td>
<td>29</td>
<td>32</td>
</tr>
<tr>
<td>Bone Graft Necessary</td>
<td>14</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>31</td>
<td>48</td>
</tr>
</tbody>
</table>
A total of 32 dental implants were placed into coral granule-derived bone, which appeared to be of sufficient quantity to support an osseointegrated implant. Two implant fixtures failed to osseointegrate, one in the anterior maxilla and one in the posterior mandible. The 2 failed sites (6.3%) were subsequently grafted with autologous bone, which in both cases, resulted in successful osseointegration. All the other 30 dental implants (93.7%), placed in coral granule-generated bone are still currently in function from 3 to 7 years after their placement. They are followed annually on an ongoing basis. In those alveoli where the coral granules failed to provide sufficient bone to place an osseointegrated dental implant, a secondary or revisional bone graft was placed which resulted in later successful placement of dental implants at all the grafted sites.
6 Discussion

6.1 General comments

Both techniques of harvesting autogenous bone in the form of cancellous cores (CC) from the iliac crest, and the treatment of cranio-maxillofacial or dento-alveolar bony defects with coral-derived granules (CDG) as a bone graft substitute, are safe and successful techniques. They present opportunities for the reduction of morbidity in the osseous reconstruction of the cranio-maxillofacial skeleton. The harvesting of CC reduces potential morbidity by using a minimally invasive surgical technique. The use of CDG eliminates the need for a donor site totally and the accompanying morbidity. The results of the five studies support these two observations.

In study I, the well-documented morbidity associated with open iliac crest bone graft harvesting was the driving force to find a less invasive harvesting technique (Cocklin 1971, Marx & Morales 1988, Tayapongsak et al. 1994, de la Torre et al. 1999, Seiler & Johnson 2000). Trephines have a long history of application in bone biopsy harvesting for the diagnosis of metabolic bone diseases and for research purposes (Malluche & Fauguere 1986). These biopsy techniques require atraumatic sampling without the destruction of bone. The potentially gentle nature of this method makes such a technique attractive for bone graft harvesting as the harvested bone is viable for grafting purposes. Ultimately, if successful, such a method could change an in-hospital procedure requiring admission to a technique used on an outpatient basis.

The initial goal of this series of studies was to establish the safety of these techniques. A graduated method was chosen, beginning in study I with cadaver observations. Despite the fact that perforations are possible with any trephination technique, the nature of these perforations had not been previously documented in other studies (Smirnov & Baranov 1971, Johnson et al. 1997, Faugere & Malluche 1983, Caddy & Reid 1985, McGurk et al. 1993, Altman & Blenisopp 1994, Billmire & Rotatori 1994).

Once the safety of the technique had been determined, the technique was applied in vivo in the form of a retrospective study to determine complication rates and patient satisfaction in study II. Finally the technique was compared with an existing routine method of bone harvesting, the open approach to the iliac crest. A prospective format

With respect to CDG, the material was successful in reducing donor site morbidity within the strictly defined applications used in studies IV and V. Previous experience with this material in the cranio-maxillofacial skeleton and dento-alveolar region was scant with no reports on outcome measures of morbidity and few meaningful insights on whether this type of treatment was successful (Chiroff et al. 1975, Levet & Jost 1983, Guillemin et al. 1987, Issahakian et al. 1987b, Robier et al. 1987, Besins & Philipe 1988, Brasnu et al. 1988, Issahakian & Ouhayoun 1988, Levet et al. 1988, Roux et al. 1988a,b, Ouhayoun et al. 1991, Yukna & Yukna 1998). Therefore a strict definition of a successful outcome was developed for a narrow but well defined clinical scenario in the dento-alveolar region, in study V.

These studies I through V examine a large number of independent variables with a relatively small population. There were a total of 253 subjects of whom 196 participated in anterior iliac crest bone graft harvesting. A total of 849 CC’s of autogenous bone were harvested from these subjects. Using CDG, a total of 57 patients received augmentations to parts of their cranio-maxillofacial skeletons. The advantage of these studies is that the entry criteria were narrow and that the same surgeon-investigator supervised the majority of surgical procedures and follow-up visits.

None-the-less there exists with the trephine harvesting technique, the risk of perforation of the medial or lateral cortices of the ilium with the possibility of increased morbidity due to intramuscular haematoma. The other more major risk involves the possibility of peritoneal involvement. The results of intentional perforation of the medial cortex of the ilium in the cadaver subjects, perforating the medial cortex, to the fullest depth allowed by the instrumentation used in the study, showed that it was impossible to engage any of the peritoneal contents. When the donor sites were surgically explored after the intentional perforations, only the periosteum of the ilium or the iliacus muscle was noted to be involved in these intentional maximal perforations. The experience \textit{in vivo} with living patients confirmed this, as there were no clinically evident peritoneum-related complications following harvesting post-operatively. This is in contradistinction to other studies, which used different approaches and instrumentation than used in the present study. There were previous reports of fracture of the ilium (Duncan et al. 1980), avulsion of the anterior superior iliac spine (Stellon et al. 1985) and a case of pneumoperitoneum (Williams & Ford 1986). None of these major complications were observed in the study population using the current trephining technique.

Morbidity is consistently lower with CC trephine harvesting than with open CCBG harvesting at the anterior iliac crest. Patients with CC harvests ambulate sooner, are discharged from hospital more quickly and have lower pain scores at the donor site than do patients who undergo open CCBG harvests.

CDG seem to result in stable augmentation with few complications attributable to the use of this xenograft. The issue of material migration and ectopic placement of the material into more superficial layers of the wound must be addressed surgically at the time of placement of the material.
6.2 Methodological aspects

The findings in these five studies were based on a variety of observations and sampling methods. In study I the harvested cores were measured so that their dimensions, weights and volumes could be determined. The fact that the two investigators performed all of the surgical procedures together and that one investigator made all the measurements, helped to minimize the problems of interexaminer variability. There was good agreement between the measurements of the CC obtained from cadaver subjects and from actual patients with no statistical differences between the two.

Intra-operative observations, a chart review and survey questionnaire were used as the 3 components of study II. There was good agreement with study I with respect to CC dimensions, although the actual total volume of bone ultimately harvested in study II was determined by the reconstructive requirements of the patient. There was a 98.8% patient satisfaction rate with this procedure and generally the patients were quite happy to complete the survey questionnaire as evidenced by a 100% completion rate. The questionnaire was modelled after the well known SF-36 Health Survey (Ware & Sherbourne 1992). This type of questionnaire was designed to be administered in person by an individual trained in interviewing techniques or by telephone (Ware & Sherbourne 1992). The SF-36 has been tested in over 1700 patients with evidence of the responsiveness of the questionnaire to changes in perceived clinical status (Ware 1993, Garratt et al. 1994, 1995).

A prospective case-control format was used in study III with closely matched for age and sex treatment groups or cohorts. Analysis of variance (ANOVA) failed to show any statistically significant differences between the two groups. Scheduling issues required the participation of two investigators in data collection and interexaminer variability may remain an unknown entity in this study. However variables such as time to first ambulation and length of hospital stay are precisely defined objective outcome measures that have no subjective component and should not be affected by interexaminer variability. The main survey tool to measure pain was a visual analogue scale, which was self-administered. The visual analogue scale is an established, validated, self-report measure usually consisting of a 10 cm line on paper with verbal anchors clearly labelling the ends (Gracely & Kwilosz 1988, Gracely 1990, 1999, Eliav & Gracely 1988, Jamison et al. 2002). There are a number of variations on the use of the scale such as with palm top computers or personal digital appliances instead of paper, but the concept of a measurable line which connects two clearly defined anchors at either end is its major feature. This recording method has been validated using a multivariate analysis (Jamison et al. 2002). Such a scale can be quite useful in measuring pain experiences in the post surgical patient. Since the visual analogue scale was self-administered, it too should be minimally affected by interexaminer variability.

The format of study IV is that of a case series with no control group, in which there was excellent compliance by patients in terms of follow-up attendance. The short follow-up period of 1 to 3 years could have been extended and this may have revealed further problems with the resorption of the CDG material. Although only 5 of 54 (9.3%) of sites showed clinically or radiographically apparent resorption of the xenograft, it is possible that serial volumetric CT scans may have shown otherwise.
In study V closely matched for age and sex treatment groups were used and analysis of variance (ANOVA) failed to show any statistically significant differences between the two groups. While an attempt was made in study V to choose two very similar wound types to test the behaviour of CDG in the dento-alveolar region, the fact is that the biology of traumatically induced wounds may be quite different from elective surgical wounds. This could account for the dramatic difference in success of the CDG in the elective surgical wounds when compared to the traumatized wounds. The small sample size of 21 patients with 48 surgical sites may also have failed to disclose other differences or possible complications, which may occur with the xenograft. Finally this study was purposely carried out in a young population, but growth itself may also be a confounding variable in this study.

6.3 Reduction of morbidity

Although at the present time autogenous bone grafts continue to be the gold standard for reconstruction of traumatic, ablative or congenital defects, the source of autograft is not limitless in any particular patient. A point may be reached in reconstruction where the donor site morbidity may exceed the discomfort of the presenting complaint. The increased success and predictability associated with the use of autogenous bone has provided the impetus to examine alternative methods to harvest this bone. Parameters that must be assessed when evaluating various harvesting techniques include; bone yield versus the size of the defect to be grafted, technique difficulty and patient morbidity. Compared to the complications published with respect to open iliac crest graft harvesting (Laurie et al. 1984, Marx & Morales 1988, Tayapongsak et al. 1994) the trephine technique is both simple and attractive. CDG strive to eliminate donor site morbidity altogether. The overall results of this study correspond well with those previously reported, both with respect to bone harvesting techniques and in the use of bone graft substitutes. Both of these techniques allow the reduction of morbidity in osseous cranio-maxillofacial reconstruction.

6.3.1 Safety of trephine harvesting of the anterior iliac crest

Although previous reports have looked at the technique of trephining bone to avoid open procedures (Schwartz & Leake 1979, Altman & Blenisoppp 1994, Habal 1995) the bone harvest was not well quantified and the sites were not thoroughly evaluated for perforations. The use of a hand-held driven trephine with an unspecified diameter, that can penetrate the iliac crest up to 8 cm, was suggested for harvesting up to 6 ml of bone from the anterior iliac crest (McGurk et al. 1993). These authors suggest that care be taken at depths greater than 80 mm, a depth that is impossible with the system evaluated here, as demonstrated with the 20 intentional perforations performed on the cadavers. No peritoneal involvement was found on exploration of the intentionally perforated sites. In the 50 cadaveric sites where bone cores were harvested in a more routine fashion, the
perforation rate was 4.4% of cores and occurred in the most atrophic of cadavers with core lengths of greater than 30 mm. The perforations appeared as breaches of the cortex without periosteal disruption or with fraying of the innermost aspect of the iliacus muscle. The perforations never encroached upon the peritoneum or peritoneal contents.

The instrument used in this study derives its simplicity from the cutting core drill which engages the bone as the drill is turned on. The trephine advances on its own, with minimal force or pressure and practically using only its own weight. As the cutting core advances, it is bounded by the cortex on the medial and lateral sides of the ilium. The perforations seen in the cadavers occurred at depths greater than 30 mm which corresponded to areas where the ilium is narrow and has minimal cancellous marrow. The use of the hand held guide limits the penetration of the core cutter to 38 mm and thereby reduces the likelihood of perforations laterally or medially. Despite purposeful perforation, the peritoneum was untouched.

The cadaveric study quantifies the amount of bone that can be easily harvested using the power driven trephine evaluated in this study. Adequate amounts of bone can be harvested for use in many cranio-maxillofacial procedures. Harvesting 5 to 7 cores per iliac crest site can produce 2.3–3.2 ml of bone, which can adequately augment the maxillary sinus floor for dental implant placement, treat alveolar clefts, and fill bony defects. Clinically, almost all the cores are greater than 30 mm in length and it is easy to obtain 5 to 6 cores per hip. One can further increase the yield of harvested bone by changing the core direction even through the same opening.

The cadaveric bone in this study is a good estimation of the quantity of bone obtainable. The cadavers were under 30 days old but from an elderly population, which may have been slightly atrophic with some degree of degeneration even with formalin preservation. A previous attempt at this study resulted in grossly underestimated values of bone volumes due to the poor quality of bone taken from 8 month old cadavers.

**6.3.2 Morbidity with trephine harvesting**

In study II, a total of 333 corticocancellous bone cores were harvested from 86 iliac crests. These cores appeared as compact cylinders of bone that could be easily morcellized for packing or moulded into desired shapes. Generally four to six cores ranging in length from 32 to 38 mm could be easily obtained from a single 1 cm incision. Typically, the first 3 to 4 mm of the core was composed of cortical bone, the remainder was cancellous bone. The amount of bone obtained was related to the number of cores taken. The use of a curette introduced through the stab incision and placed through the osseous holes created by the trephine served to increase the yield of bone substantially. Using the cores alone, the mean volume obtained per site ranged from 3 to 21 ml of compacted bone.

The results of this study show a reduction in morbidity with the use of a power driven trephine to obtain anterior iliac crest cancellous cores and correspond well with previous reports (Duncan *et al.* 1980, Minns & Sher 1983, Caddy & Reid 1985, Williams & Ford 1986, McGurk & Barker 1993, Altman & Blenisopp 1994, Billmire & Rotatori 1994). In a retrospective study of complications following 14,810 iliac crest biopsies from 14
centres, trephines were reported to leave minimal scars, decrease morbidity and produce
different types of complications including:

1. Local haematomas
2. Lateral cutaneous nerve neuropathies
3. Pain in excess of 7 days duration

If the vertical approach was used, the rate of complications decreased to 0.36%.

Study II assessed the morbidity rate associated with the technique of using a power
driven trephine in a minimally invasive fashion from the anterior iliac crest. Intraoperatively, the complication rate was 0.3% and involved a single broken instrument.

Postoperatively, the complication rate was 3.6%. Short and long-term complications including:

1. Pain
2. Paresthesia
3. Post-operative gait disturbance
4. Patient satisfaction

Only one patient described having pain for more than 3 days. That same patient was the

only one to describe having a gait disturbance in excess of 3 days. With respect to patient

satisfaction, 98.8% of the patients stated that they would undergo the procedure a second
time if necessary. There were no reports of pain or gait disturbance that persisted longer
than 3 weeks post-operatively.

In comparison to the above results, a study of open anterior iliac crest harvesting in

100 patients was associated with a 2% incidence of major thromboembolic events and a

2% incidence of permanent sensory disturbance in the distribution of the lateral femoral
cutaneous nerve (van der Wal et al. 1986). As far as the patients’ expectations after

surgery were concerned, at the anterior ilium it was worse than expected for 18% of

patients, better for 81% and 1% had no opinion (van der Wal et al. 1986).

Study II showed that harvesting CC’s from the anterior iliac crest is a procedure that
can be carried out predictably in an outpatient or ambulatory surgery environment. In the

41 cases that were booked as outpatient procedures, all 41 patients were discharged
immediately after recovering from general anaesthesia, as planned. However, the ability
to use this technique on an outpatient basis is almost completely dependent on the extent
of the reconstructive procedure being performed, as well as the overall health of the

patient. The procedure can be regarded as a cost saving measure as it can avoid the

admission and hospital stay for the patient.

The results of study III demonstrated significantly less morbidity following

procurement of CC grafts from the anterior ilium using a power-driven trephine than
following the open harvest of a CCBG. Use of the trephine resulted in fewer days to first
unassisted ambulation, shorter overall length of hospital stay, and significantly less donor
site pain than following harvest of CCBG. The reduced morbidity associated with the use
of the power-driven trephine was likely a result of the minimization of muscle reflection
and exposure of the anterior ilium.

The concave-convex anatomy of the anterior ilium limits bone harvest to the superior
3–4 cm between the ASIS and the iliac tubercle. In the middle one-third, the medial and
lateral cortices come together with little or no intervening marrow. Because of this
osseous anatomy, all traditional approaches to the ilium involve the reflection of regional
muscle groups. A lateral approach involves reflection of tensor fascia lata, gluteus
medius, and gluteus minimus, while a medial approach involves the iliacus muscle.
Tensor fascia lata acts to lift, flex and stabilize the thigh during walking, and any injury
from reflection, retraction or inaccurate re-approximation can lead to marked post-

operative pain and gait disturbance. The iliacus, a postural muscle, inserts into the lateral
side of the psoas major muscle tendon. Trauma or haematoma formation can result in psoas muscle inflammation and may also contribute to post-operative pain and gait disturbance.

The reflection and retraction of the iliacus muscle used in the anterior medial approach to the ilium may play a significant role in patient morbidity. In addition, bleeding from the exposed cancellous marrow can lead to haematoma formation. While these effects can be minimized with clean subperiosteal reflection of the medial tissue, careful control of marrow bleeding, and precise muscle re-approximation, they cannot be abolished.

Bone procurement using a trephine can proceed without muscle reflection. The instrument described in this report is designed specifically to minimize dissection. The serrated edge of the trocar is used to engage the fascia and periosteum, and allows the procedure to be carried out through a stab incision. The pre-cutter drill is used to score the fascia, periosteum and crestal bone. The core cutter engages the recess in the cortical crestal bone made by the pre-cutter drill and advances through the cancellous marrow with minimal operator assistance. A series of clutches reverses the core from the ilium, and a built-in internal plunger is then used to eject the core from the trephine.

Due to the laxity of the overlying skin and subcutaneous tissues, the incision can be “walked” up and down along the crest of the anterior ilium to fresh harvest sites. Careful superficial dissection should allow the operator to remain directly over the iliac crest between the medial (external oblique, iliacus) and lateral (tensor fascia lata, gluteus minimus, gluteus medius) muscle groups. Minimal bony exposure is required to harvest the CC’s themselves, and the bony septae between them, even when the ilium is curetted. Bleeding from core donor sites can be controlled with the use of gelfoam. The spread of any residual bleeding is limited by the integrity of the cortical walls of the ilium and the musculoperiosteal attachments. Without the medial or lateral subperiosteal reflection typical of the standard approach, haematoma formation is minimized.

Although not formally evaluated in this study, procurement of cancellous cores with the motorized trephine approach was always faster than harvesting CCBG’s. Minimal surgical trauma and shorter operating time resulting from the use of the motorized trephine likely contribute to the reduction in overall patient morbidity.

Trephining the anterior iliac crest for the purpose of harvesting autogenous bone is reliable, safe and predictable. It is associated with minimal intra-operative and post-operative morbidity. An advantage of this technique is that it can predictably be used on an outpatient basis eliminating the need for admission to hospital and the expenses associated with it.

### 6.3.3 Morbidity with coral-derived granules in the cranio-maxillofacial skeleton

In study IV, the results with CDG subperiosteal implantation in the cranio-maxillofacial skeleton were quite encouraging. With the exception of five sites of clinically evident resorption of the material, the remaining patients enjoyed a seemingly stable augmentation. Also the resorption in the five sites was not complete so that there was an
improvement of the clinical situation, when compared to the premorbid condition. Even if the material required removal, as necessitated by infection, the nature of the procedure, with a small distant incision is such that the patient was not compromised aesthetically.

However, a follow-up period of 12 to 36 months may not be long enough to allow one to be conclusive with regards to the long term behaviour of xenograft derived bone in the cranio-maxillofacial skeleton. The results of study IV are in general agreement with previous reports of CDG placed into the cranio-maxillofacial skeleton (Levet & Jost 1983, Robier et al. 1987, Besins & Philipe 1988, Brasnu et al. 1988, Levet et al. 1988, Roux et al. 1988a,b), although none of these previous studies reported any long term follow-up.

As an addendum, this study initially considered only those patients operated on before June 1991. Since that time, a further 12 sites of augmentation with coral-derived granules have been performed in nine patients. Two of these nine patients developed infected sites post-operatively. The first was a 16-year-old girl who had three sites injected on the forehead, to treat sequelae of craniosynostosis surgery. All three sites developed postsurgical swelling with aseptic pus. This particular patient had an underlying case of severe acne vulgaris and required the total removal of the coral granules in order to allow resolution of the infection. The second patient had a post-traumatic asymmetry of the forehead and was treated with CDG augmentation. Two months later he was noted to have an otherwise asymptomatic fluctuant area on palpation of the forehead. A total of 1.5 ml of aseptic pus was evacuated and the infection subsided, although the CDG were not removed.

The procedure seems relatively easy to perform, but caution must be exercised. Dissection of the subperiosteal pocket must be precise to avoid deposition of granules in unintended locations. CDG must be placed in an appropriately prepared non-infected bed. The granules must be placed in a subperiosteal location with good bony contact if proper bony in-growth and replacement-resorption of this osteoconductive xenograft scaffold is to occur.

Aseptic technique is of paramount importance. The granules become implanted in a wound surrounded by blood and fibrin and present a potentially favourable environment for microbial proliferation.

It is important to differentiate between coral granular wound irritation and frank infection. In the two cases of wound irritation described in the study, one was in a subciliary wound used for a malar deposition, the other was in a scalp wound. In these cases an inflammatory reaction develops in response to the coral granules mistakenly left in a supraperiosteal location, in the superficial layers of the wound. Care must be taken to avoid leaving granules in an ectopic subcutaneous location.

In the case of frank infection, total evacuation of the coral granules may be the only recourse. The distant small incision used to introduce the granules, may pose a technical problem for complete curettage of the subperiosteal pocket.

The long term stability of coral augmentation remains an unknown. A prospective randomized trial would help to answer this question. Additionally serial computerized tomography scans with volumetric analysis may help determine the nature of the changes in the augmented volume of coral granules over time.
Coral granules seem to be well tolerated in the cranio-maxillofacial skeleton when introduced into a well vascularized, aseptic, subperiosteal pocket. Complications seem to be few in number and the result is an improvement over the pre-treatment situation in most cases. There however, is no direct evidence that coral granules actually become totally resorbed and transformed into bone in these cranio-maxillofacial sites. Future serial histological studies would be necessary to show this.

6.3.4 Morbidity with coral-derived granules in the dento-alveolar area

The results of study V show that CDG are well tolerated in the dento-alveolar region where placement of the material relies on an intra-oral approach and a wound in the oral cavity. Other studies are in agreement with this observation (Issahakian et al. 1987b, Issahakian & Ouhayoun 1988, Yukna & Yukna 1998).

However previous studies did not look at the prevention of alveolar ridge resorption in the paediatric dentition. In the deciduous paediatric dentition, loss of retained second deciduous molar, which has no succedaneous permanent replacement tooth, is associated with bone loss. This is manifested as a decrease in the width of the alveolar ridge of 25% within 3 years after extraction of the retained primary molars, and this continues to diminish a further 4% over the next 3 years (Ostler & Kokich, 1994).

This study demonstrates that CDG have been useful in the preservation of alveolar ridge dimensions following the elective removal of ankylosed primary molars lacking succedaneous premolars. This ridge preservation allowed the placement of dental implants into these sites without a bone graft in 93.5% of sites. Conversely, grafting coral granules into defects created in the anterior maxilla following post-traumatic loss of incisors failed to preserve ridge dimensions sufficiently to permit the placement of dental implants without revisionary bone grafting. Implants were possible in these traumatized sites in 17.6% of sites without the use of a revisional autogenous bone graft. The starkly dissimilar results between post-traumatic maxillary incisor sites and post-extraction primary molar sites might be accounted for by the distinctly different nature of the insult incurred by the tissues prior to grafting. A violent trauma to the front of the mouth may result in tooth avulsion, and also in fractures of the alveolar bone, and detachment and laceration of the mucoperiosteum. All of these injuries may lead to scarring and compromise of the local blood supply and consequently impair healing, even though the labial and buccal plates of bone were noted to be intact for all sites in the study.

In the healing of traumatized teeth a number of complications may follow that may further corrupt healing, potentially through the effects of inflammatory root resorption and replacement, ankylosis, interference with local alveolar bone growth, submergence of the ankylosed tooth and distortion of the occlusion, and surgical removal of the residual root. In contrast, the relatively atraumatic, elective removal of an ankylosed deciduous molar produces a wound with very much less collateral damage, less scarring, and fewer implications for healing and wound repair.

One other possible explanation for the different results with CDG at the two areas of the alveolus may be due to differences inherent to the two sites. The bucco-lingual width of the alveolar crest is greater in the posterior parts of the maxilla and mandible than in
the anterior maxilla. In addition the rate of alveolar resorption may be higher in the anterior maxilla than in the posterior maxilla and mandible. A great deal of resorption is known to occur in the first four months following tooth-loss in the anterior maxilla (Lam 1960). This anatomical difference and possibly different rates of alveolar resorption may place the maxillary anterior alveolus at a potential disadvantage when compared to at least a theoretically more favourable posterior maxillary or mandibular alveolar site (Ostler & Kokich, 1994).

Although controlled for in this study, the wearing of a routine acrylic mucosal-borne prosthetic replacement is thought to hasten the resorative process. The patients who had lost anterior teeth were all given prosthesis which loaded the neighbouring dentition with a bite plane, thereby removing the load from the ridge and the xenograft.

Based upon the results of this study, coral granules may be used to preserve the dimensions of the alveolar ridge following extraction of retained primary molars lacking succedaneous premolars, thereby sparing the patient the potential morbidity associated with a bone graft harvest.

6.4 Clinical implications and recommendations

The results of studies I, II, and III clearly show that it is possible to safely harvest CC’s of autogenous bone from the anterior iliac crest with a hand held power driven trephine, using a minimally invasive surgical technique. The technique is both rapid and simple in application. It is well-tolerated, acceptable to patients and creates less morbidity than open anterior iliac crest harvest based on the outcome measures examined in this study. Use of the trephine resulted in fewer days to first unassisted ambulation, shorter overall length of hospital stay, and significantly less donor site pain than following harvest of CCBG’s.

The cadaver study has shown that the technique is meant to be practiced in a gentle manner, in order to avoid perforation of the medial cortex of the ilium. The trephine cutting core guides itself, almost by its own weight through the soft cancellous bone between the medial and lateral cortices of the ilium. Not pushing too hard on the trephine will lessen the chances of perforation. Additionally respecting the funnel-shaped retractor, which will not allow harvested core lengths of greater than 38 mm will also lessen the chances of perforation. These two maneuvers will increase the safety of the technique.

The minimal morbidity and rare complications using this method have allowed the procurement of these grafts on an outpatient basis. This procedure can be carried out predictably in an outpatient or ambulatory surgery environment. However, the ability to use this technique on an outpatient basis is almost completely dependent on the extent of the reconstructive procedure being performed, as well as the overall health of the patient. The operative field in an obese person is far more difficult to manage surgically. It might be prudent to admit such a patient to hospital. Never-the-less modest graft harvests to treat local defects in the cranio-maxillofacial skeleton such as repair of a cleft alveolus, for sinus floor augmentation procedures, for alveolar augmentation and augmentation
rhinoplasty are routinely possible without admission to hospital for most patients. This decreased utilization of institutional facilities represents at least a financial savings to any health care system.

Coral granules seem to be well tolerated in the cranio-maxillofacial skeleton when introduced into a well-vascularized, aseptic, subperiosteal pocket. Complications seem to be few in number and the result is an improvement over the pre-treatment situation in most cases. All of the problems encountered with CDG were of two types, wounds of a questionable nature and in ectopic placement of the granules. CDG must never be placed into an infected bed or into beds with poor vascularity. To do otherwise almost guarantees loss of the xenograft. The granules must also be placed and retained in a subperiosteal location. The granules can cause an inflammatory reaction when placed into a subcutaneous location.

In the dento-alveolar skeleton the CDG placed into the 48 augmentation sites in alveolar sockets healed well with few significant complications and only one overt infection. In the anterior maxilla, the coral granules restored the dimensions of the alveolar ridges only temporarily. Here the CDG did not provide sufficient bony support for the placement of a dental implant without using a revisional bone graft in the vast majority of cases. In the posterior maxilla and mandible, where tooth-loss was due to the elective removal of ankylosed primary molars, almost all the sites were able to support the successful placement of an osseointegrated dental implant without the use of a bone graft. The published results of others (Ostler & Kokich 1994) and clinical experience suggest that the removal of retained ankylosed primary molars often triggers a pattern of resorption which compromises the suitability of these sites for restoration with dental implants. Based upon these results, the routine augmentation of extraction defects with CDG in an effort to preserve alveolar bone volume, until such time as it is safe to proceed with placement of a dental implant following the cessation of skeletal growth is recommended in the posterior maxilla and mandible but not in the traumatized anterior maxilla. Other treatment alternatives to preserve alveolar bone in the traumatized anterior maxilla, without the use of bone grafts including autotransplantation of teeth, orthodontic space closure and decoronation, could be considered.

### 6.5 Future prospects

This paper has demonstrated that trephining the anterior iliac crest for the purpose of harvesting autogenous bone is reliable, safe and predictable. It is associated with minimal intra-operative and post-operative morbidity. An advantage of this technique is that it can predictably be used on an outpatient basis eliminating the need for admission to hospital and the expenses associated with it. Future studies comparing this technique to other existing minimally invasive techniques, proximal tibia and bone marrow aspiration should also be performed to determine the best approach for patients requiring autogenous bone grafts. Additionally the future development of even less invasive intra-oral donor sites such as the zygomatic bone should be considered. In the future more
sophisticated instrumentation for bone graft harvesting such as suction traps, which can harvest viable bone cells, and bone cell storage methods should be developed and investigated.

CDG can be used as a bone graft substitute. They seem to be well tolerated in the cranio-maxillofacial skeleton when introduced into a well vascularized, aseptic, subperiosteal pocket. Complications seem to be few in number and the result is an improvement over the pre-treatment situation in most cases. There however, is no direct evidence that coral granules actually become totally resorbed and transformed into bone in these cranio-maxillofacial sites. Future serial histological studies and serial volumetric CT scans could be used to investigate this question.

CDG may be used to preserve the dimensions of the alveolar ridge following extraction of retained primary molars lacking succedaneous premolars, thereby sparing the patient the potential morbidity associated with a future autogenous bone graft harvest. Future studies in this area could examine the use of CDG in combination with osteoactive agents.

However the future of the minimization of morbidity in reconstruction lies in the total elimination of the autogenous bone donor site, whether intra-oral or extra-oral. The further understanding of the complex interplay between osteocompetent cells and osteoactive agents along with their delivery is a pre-requisite for any major future development in bone regeneration.
7 Summary and conclusions

The following main conclusions can be drawn from the results obtained in the present studies:

1. The minimally invasive surgical approach utilizing the motorized trephine used in these studies was found to be safe in harvesting bone from the anterior iliac crest in the cadaver model. Adequate quantities of bone for reconstruction of modest defects of the cranio-maxillofacial skeleton can be safely harvested using this technique. The injury of peritoneal structures is made impossible by the design of the apparatus used in this study.

2. Patients accept, tolerate and are satisfied with this minimally invasive surgical approach, which can routinely be performed on healthy patients in an outpatient setting.

3. Patients experience significantly less morbidity using a minimally invasive anterior iliac crest harvest using a motorized trephine than that experienced with a traditional open medial approach. This is characterized by lower overall pain scores, more rapid ambulation and fewer days of hospital stay with the motorized trephine group, when compared to the open iliac crest group.

4. Coral-derived granules are safe as a bone graft substitute in the cranio-maxillofacial skeleton, as long as they are placed in a subperiosteal pocket and in a well vascularized non infected graft bed. They can be used in many sites in the cranio-maxillofacial skeleton.

5. In the growing patient, coral-derived granules are most efficacious in reconstructing dento-alveolar defects for dental implant placement in the posterior maxilla or mandible. Coral-derived granules were less efficacious in the anterior maxilla, where tooth-loss was a result of trauma. There may be a difference in the nature of the wounds in these two areas that may account for this variation in treatment outcomes.
8 References


