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Guided tissue regeneration - Rationale and Factors affecting its outcome.

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Abstract: *The ultimate goal of periodontal therapy is to restore the tissues that have been lost as a result of periodontal diseases. The objective of regenerative procedures is to form a new connective tissue attachment to a root surface that has been infected by plaque and calculus. This review focuses on GTR, its biologic rationale and factors affecting its outcome.*

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I. Introduction

- The ultimate goal of periodontal therapy has been the regeneration of the supporting tissues lost as a consequence of inflammatory periodontal disease.
- **Periodontal regeneration**: is defined as a reproduction or reconstruction of a lost or injured part in such a way that the architecture and function of the lost or injured tissues are completely restored**. (Glossary of periodontal term 1992).**
- During the last two decades, significant research and clinical advances in the area of periodontal therapy have led the therapist closer to achieving a predictable regeneration of the periodontium via the principle of guided tissue regeneration
- Barriers are employed in the hope of excluding epithelium and connective tissue from the root surface in the belief that they interfere with regeneration.
- This method is derived from the classic studies of Nyman(1982), Lindhe(1984), Karring(1986) and Gottlow(1986) and is based on the assumption that only the PDL cells have the potential for regeneration of the attachment apparatus of the tooth.
- This review focuses on biologic rationale of GTR and factors affecting its outcome.

Guided tissue regeneration
The 1996 World Workshop in Periodontics defined GTR as "procedures attempting to regenerate lost periodontal structures through differential tissue responses''.
The AAP(1992) has defined GTR as "the procedure wherein regeneration of lost periodontal ligament structures is sought via selective cell and tissue repopulation of periodontal ligament tissue wound.

Rationale
- The guided tissue regeneration is based on the concept of selective growth of cells derived from periodontal ligament by placing a physical barrier which prevents the apical migration of epithelium and gingival connective tissue cells along the root surface.
- Along with this the physical barrier is also thought to provide protection to blood clot during early phases of wound healing and ensures space maintenance for ingrowth of newly formed periodontal apparatus.
- **MELCHER'S CONCEPT/TISSUE COMPARTMENT HYPOTHESIS**
- In **1976, Melcher** proposed that the type of cell which repopulates the root surface after periodontal surgery determines the nature of the attachment that will form.[1]
- After flap surgery curetted root surfaces may be repopulated by four different types of cells (fig 1), fig 2

:
- 1.Epithelial cells.

- 2.Cells derived from the gingival connective tissue
- 3.Cells derived from the bone
- 4.Cells derived from the periodontal ligament

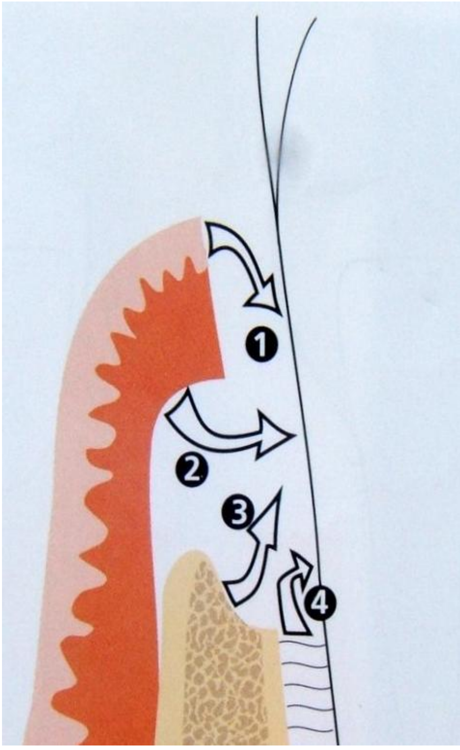
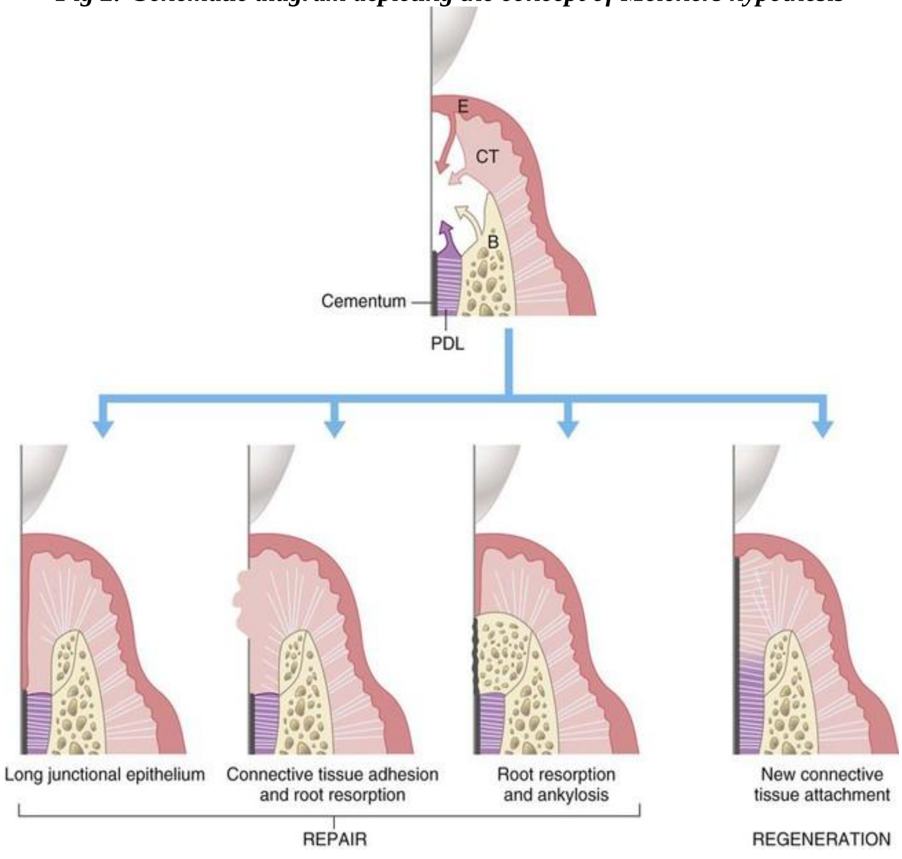


Fig 1

Fig 2. Schematic diagram depicting the concept of Melchers hypothesis



Possible healing patterns for a periodontal wound, which are dependent on the four possible cell types that predominate that wound site. The downgrowth of epithelial cells (E) results in a long junctional epithelium. The proliferation of connective tissue (CT) may result in connective tissue adhesion ± root resorption. With the predominance of bone cells (B), there may be root resorption, ankylosis (although this is relatively uncommon in humans when compared with animal models), or both. With the ingress of periodontal ligament (PDL) and perivascular cells from the bone, a regenerated periodontium with new cementum develops.

Although the rationale for GTR is relatively new, the application of tissue exclusion during healing has been reported much earlier.

The use of a barrier has first been reported by Younger in the Dental Cosmos of 1904, of which a japanese paper saturated with liquid celluloid was used to form a protecting wall over the roots and the edge of the gingiva. “The covering hardens and forms a protective shield to the granulation tissue which grow up and fill the space between the roots.

Prichard in 1957 further stated that cells that are necessary for the genesis of periodntal ligament, cementum, and alveolar bone are available in the area that border the bony deformity

Further investigations in the 1970’s and 80’s supported Melcher’s concept

Bjorn et al in 1961, 1965 realized that epithelium must first be excluded from root surface before new attachment could be produced. Therefore they cut off the crowns of endodontically treated teeth so that the roots could be completely covered by mucosal tissue flap.

Because the healing epithelial margin was distant from the tooth, no epithelial migration along the root was found.

Ellegard et al in 1976 developed another technique to exclude the epithelium from healing process but without resecting the crown of treated teeth. Since it was known that surface epithelium of free gingival graft would completely degenerate and needed to be regenerated prior to epithelial down growth, it was postulated that epithelial proliferation along the root could be delayed for 10 to 12 days if flap margin could be replaced by free gingival graft. Therefore FGG were placed over the areas with infrabony pockets in hope of preventing early epithelial migration into the lesion and to allow new attachment formation.

Regenerative capacity of bone cells

Karring et al. in (1980)[2]conducted a study in beagle dogs that led to concept of GTR. Roots of periodontitis-affected teeth were extracted and placed in surgically created sockets in edentulous areas of dogs (fig 3).

The implanted roots were covered with tissue flaps (submerged) and the results of healing were examined histologically after 3 months (**fig4**).

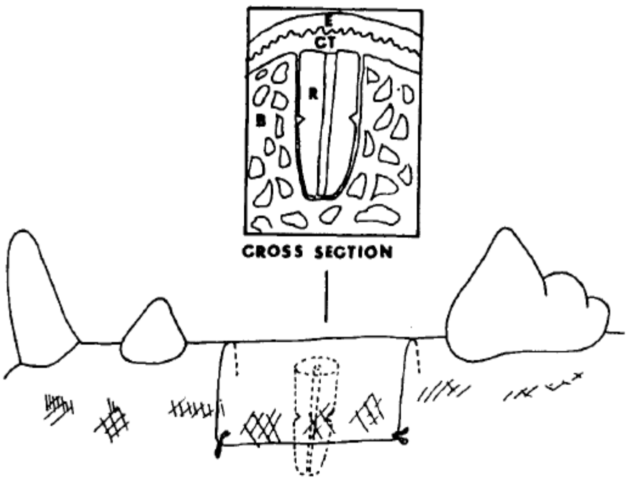


Fig 3. Schematic drawing illustrating the implantation of roots (R) into bone tissue (B).The roots were completely covered by a soft tissue flap, i.e., epithelium (E) and connective tissue *(ct*

A periodontal ligament was re-established in the apical portion of the re-implanted roots where, at the time of implantation, remnants of periodontal ligament tissue were preserved.

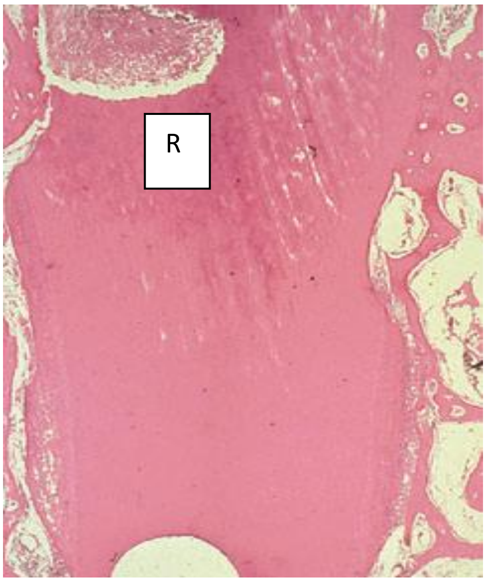


Fig 4 Microphotograph of a re-implanted root after 3 months ofhealing. A periodontal ligament (PL)has become re-established in the apicalportion of the root whereas ankylosis(A) and root resorption (R) is the predominant feature in the coronal portion.

In the coronal portion of the roots which were previously exposed to periodontitis and then scaled and planed, healing had consistently resulted in ankylosis and root resorption. On the basis of this finding, it was concluded that tissue derived from bone lacks cells with the potential to produce a new connective tissue attachment

Regenerative capacity of gingival connective tissue

A slightly modified experiment was performed by **Nyman et al in 1980** in dogs and monkeys to find out whether gingival connective tissue is capable of inducing the formation of a new connective tissue attachment.[3] In this study, the roots were prepared in the same way as in the experiment described above, but the teeth were now transplanted and placed in such a way that only half of Stheir circumference was located in contact with bone, and the other half was in contact with the gingival connective tissue of the covering soft tissue flap (fig5)

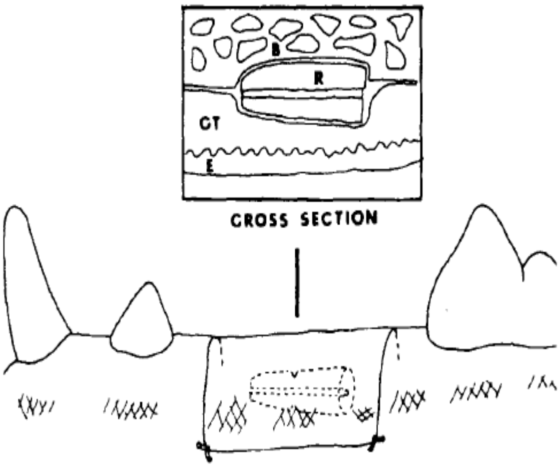


Fig 5.**Schematic drawing illustrating the position of the implanted root. The root (R) is embedded to half its circumference into bone tissue (B). The remaining part is covered by a soft tissue flap, i.e., connective tissue (CT) and epithelium (E).**

Histological analysis, performed after 3months of healing, showed that the part of the root surfaces facing the gingival connective tissue exhibited as much root resorption as the part facing bone tissue(fig 6)**.**

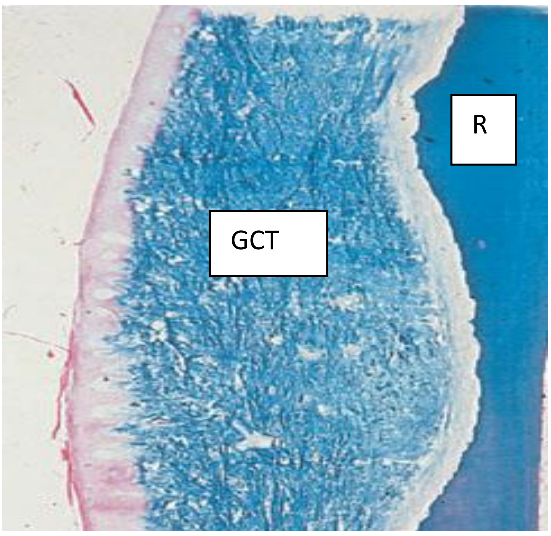


Fig 6. Microphotograph of root (R) which has been reimplanted with its surface facing the gingival connective tissue (GCT). The surface exhibits extensive resorption.

Based on this finding, it was concluded that gingival connective tissue lacks the potential to induce the formation of new connective tissue attachment to a root surface that has been deprived of its original periodontal ligament.

Regenerative capacity of periodontal ligament cells

Karring *et al. in 1985* *conducted a study, where periodontitis*-involved roots were retained in their sockets and subsequently submerged, significant amounts of new connective tissue attachment formed on the coronal portion of the roots

- The finding of new attachment only on the roots with a non-impaired periodontal ligament (fig 7)., but never on the extracted and re-implanted roots with an impaired ligament, indicates that periodontal ligament tissue contains cells with the potential to form a new connective tissue attachment on a detached root surface.[4]

Fig 7. Microphotograph showing new attachment formation (between the arrows) on a submerged root with a non-impaired periodontal ligament. Coronal to the cementum, root resorption is the predominant feature.

Role of epithelium in periodontal wound healing

Some of the roots in the experiment described above (Karring *et al. 1985) penetrated the mucosa* at early stages of healing, thereby allowing the epithelium to grow apically along the root surface.[4]

The amount of new connective tissue attachment on these roots was considerably smaller than that formed on the roots which remained submerged throughout the study.

This finding and those of other investigators (Moscow 1964; Kon *et al. 1969; Proye & Polson 1982)* indicate that the apical migration of epithelium reduces the coronal gain of attachment, evidently by preventing periodontal ligament cells from repopulating the root surface (fig 8).

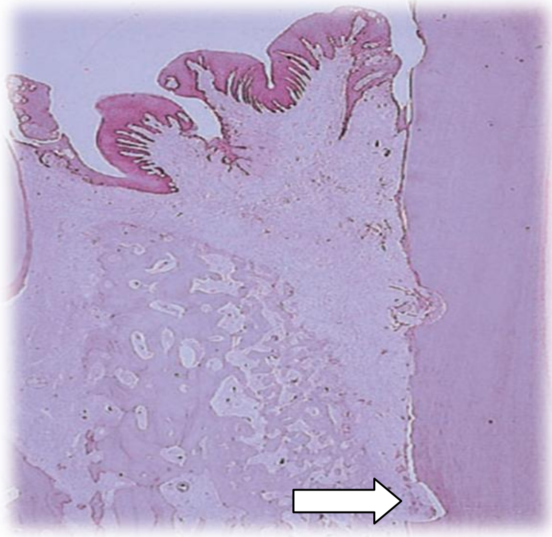


Fig 8. Microphotograph illustrating an intrabony defect after regenerative treatment. New bone (NB) has formed in the defect but epithelium has migrated apically along the root surface to the notch (arrow) in the root surface indicating the bottom of the defect before treatment.

Based on the findings **of the experiments described** above, the treatment modality **GTR was developed** and **designed**.

All periodontal tissue components that are incapable of inducing the formation of new connective tissue attachment must be prevented from making contact with the root surface during healing, thereby promoting the proliferation of periodontal ligament cells along the surface.

The first studies that demonstrated the formation of a new connective tissue attachment as a result of GTR treatment were presented by Nyman et al. and Gottlow et al.

Gottlow *et al. 1984* conducted study in monkeys using barrier membrane. After reduction of the supporting tissues around selected experimental teeth, the root surfaces were exposed to plaque accumulation for 6 months.[5]

Soft tissue flaps were then raised and the exposed root surfaces were curetted. The crowns of the teeth were resected and the roots were submerged.

However, prior to complete closure of the wound, **a membrane was placed over** the curetted root surfaces on one side of the jaws in order to prevent gingival connective tissue contacting the root surface during healing, and to provide a space for in-growth of periodontal ligament tissue. No membranes were placed over the contralateral roots.

The histologic analysis after 3 months of healing demonstrated that the roots covered with membranes exhibited considerably more new attachment than the non-covered roots (fig 9).

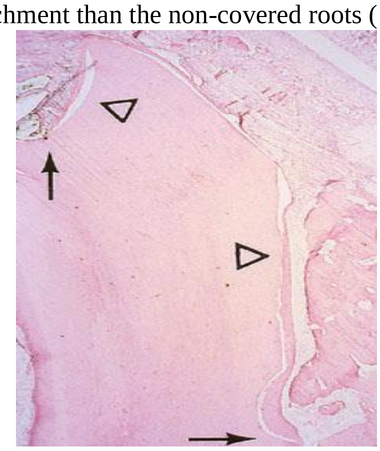


Fig 9. Microphotograph of membrane (M) covered root. Newly formed cementum is visible on the entire length of the buccal root surface coronal to the notch (N) and also on part of the coronal cut surface (arrow)

This observation provided the basis for the clinical application of the treatment principle termed "**guided tissue regeneration" (GTR).** Thus. GTR treatment involves the placement of a physical barrier to ensure that the previous periodontitis-affected root surface becomes repopulated with cells from the periodontal ligament

Nyman et al. (1982) presented the first report of a human tooth treated according to the principle of GTR. The tooth was assigned for extraction due to severely advanced periodontal breakdown which, in turn, enabled histological documentation of the treatment result.[6]

At the surgical procedure, a periodontal defect was diagnosed that measured 11 mm from the cementoenamel junction to the bottom of the defect

Three months following GTR treatment (fig 10), the tooth was removed as a whole together with its buccal periodontium. The histological analysis demonstrated **new connective tissue attachment** extending 7 mm coronally, as measured from the bottom of the previous defect (fig 11).

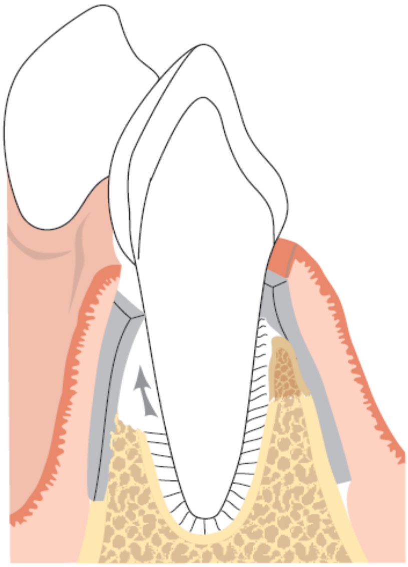


Fig 10.Drawing illustrating the placement of the physical barrier which prevents the epithelium and gingival connective tissue from contacting the root surface during healing. At the same time the membrane allows cells from the periodontal ligament (arrow) to repopulate the previously periodontitis-involved root surface.

Fig 11.Microphotograph of a human tooth 3 months following GTR treatment using a Millipore filter (F) New cementum with inserting collagen fibers (about 5 mm) has formed from the notch (N) to the level of the arrow.

Later, case reports of 12 patients were presented by Gottlow et al. in which the regeneration of connective tissue attachment was evaluated clinically and in ***5 of them also histologically.***

Indications of GTR

✓ *2 to 3 walled intrabony defects with at least 4mm of attachment loss and a 4mm infrabony component.*

GTR has been studied in a number of clinical trials for the treatment of various periodontal defects such as intrabony defects (Cortellini & Bowers 1995),[7] furcation involvements (Machtei & Schallhorn1995; Karring & Cortellini 1999), and localized gingival recession defects (Pini-Prato et al. 1996)(Fig 12).

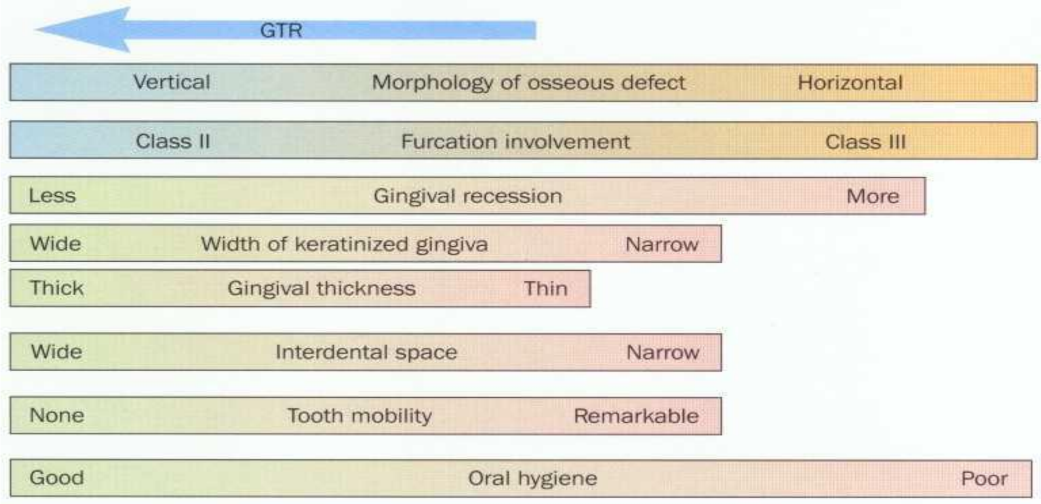


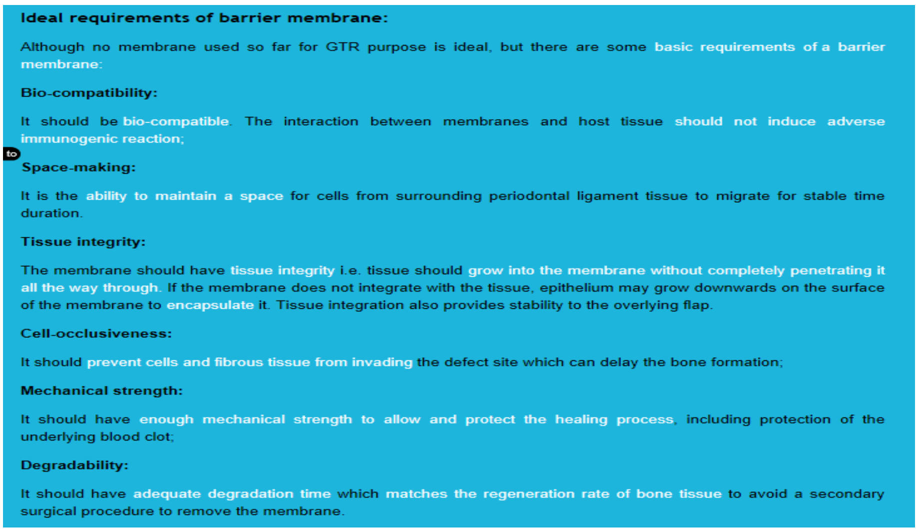
Fig12

- ✓ Circumferential defects
- ✓ Alveolar ridge augmentation.
- ✓ Repair of apicoectomy defect.
- ✓ Osseous fill around immediate implant placement sites.
- ✓ Repair of osseous defect associated with failing implants.

Contraindications

- ✓ Class II furcations on mesial and distal of maxillary molars.
- ✓ Class III furcations
- ✓ Premolar furcations
- ✓ Horizontal bone loss
- ✓ One walled intrabony defects
- ✓ Multiple adjacent defects
- ✓ Inadequate zone of attached gingiva

Ideal requirements of barrier membrane design criteria *Scantlebury, Gottlow and Hardwilk (1982)*



Ideal requirements of barrier membrane:

Although no membrane used so far for GTR purpose is ideal, but there are some basic requirements of a barrier membrane:

Bio-compatibility:

It should be bio-compatible. The interaction between membranes and host tissue should not induce adverse immunogenic reaction;

Space-making:

It is the ability to maintain a space for cells from surrounding periodontal ligament tissue to migrate for stable time duration.

Tissue integrity:

The membrane should have tissue integrity i.e. tissue should grow into the membrane without completely penetrating it all the way through. If the membrane does not integrate with the tissue, epithelium may grow downwards on the surface of the membrane to encapsulate it. Tissue integration also provides stability to the overlying flap.

Cell-occlusiveness:

It should prevent cells and fibrous tissue from invading the defect site which can delay the bone formation;

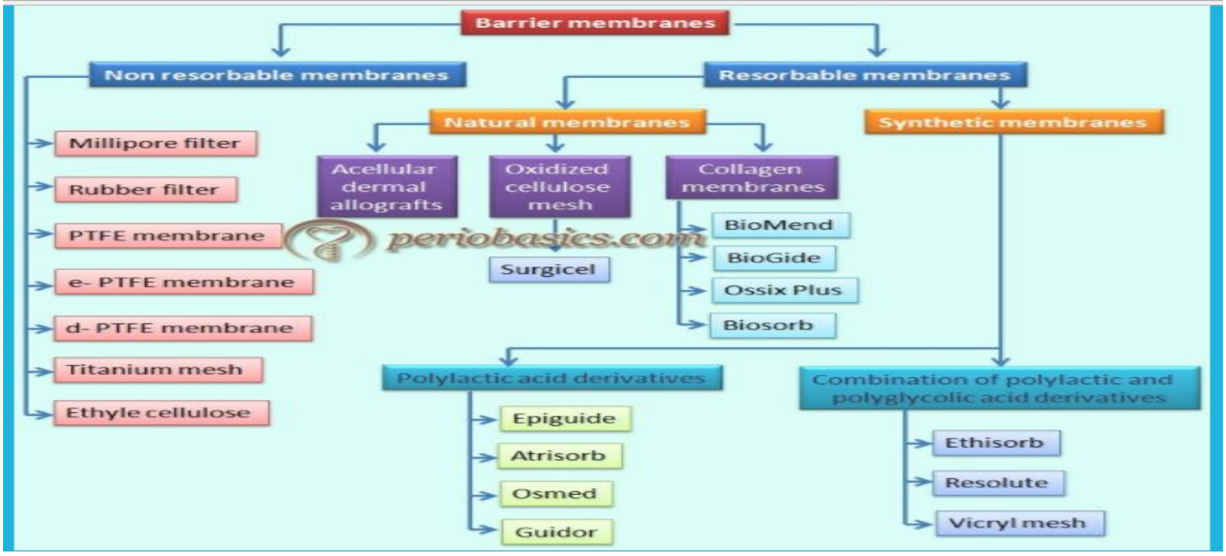
Mechanical strength:

It should have enough mechanical strength to allow and protect the healing process, including protection of the underlying blood clot;

Degradability:

It should have adequate degradation time which matches the regeneration rate of bone tissue to avoid a secondary surgical procedure to remove the membrane.

CLASSIFICATION



Factors affecting treatment outcome of intrabony defects.

- 1. The patient
- 2. Defect morphology
- 3. Tooth mobility
- 4. Surgical technique
- 5. Infection prevention
- 6. Post surgical care
- 7. Treatment evaluation

1. The patient

- To qualify for GTR therapy the patient should be well motivated and should have gone through the hygienic phase of therapy. This would first give an assessment of patient's willingness and ability to perform good oral hygiene as this is a critical factor(fig 13).
- Secondly, this will solve inflammation in the gingival tissue to convert into a collagen dense tissue endurable to surgery and that will not shrink after surgery.

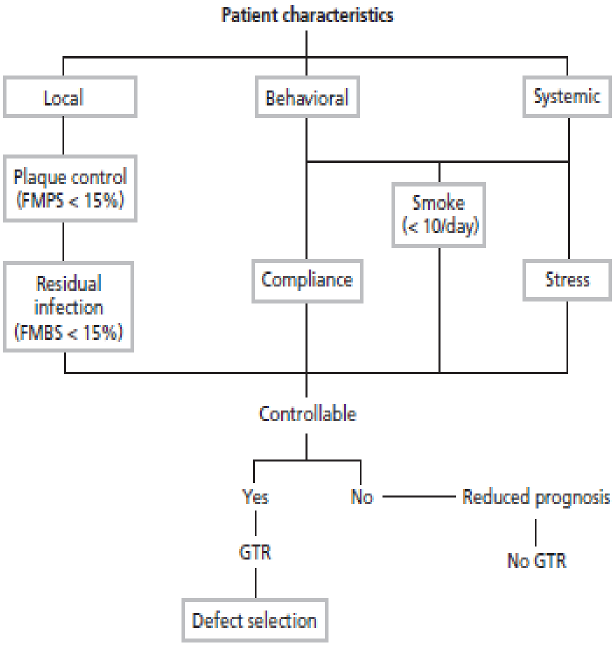


Fig 13

2. Defect morphology

- Predictibility of GTR depends on morphology of osseus defects.
- Cortellini et at measured osseous defects before surgery and on re-entry and reported the relation between the amount of new tissue, attachment gain, and defect morphology
- The results revealed that the amount of new tissue and attachment gain depended on the numbers of walls composing the osseous defects. Three-wall defects were filled to 95% of their initial depth, two-wall defects were filled to 82%, and one-wall defects 39%, suggesting that the predictability of bone regeneration is extremely high in areas surrounded by bone walls (fig 14).[8]

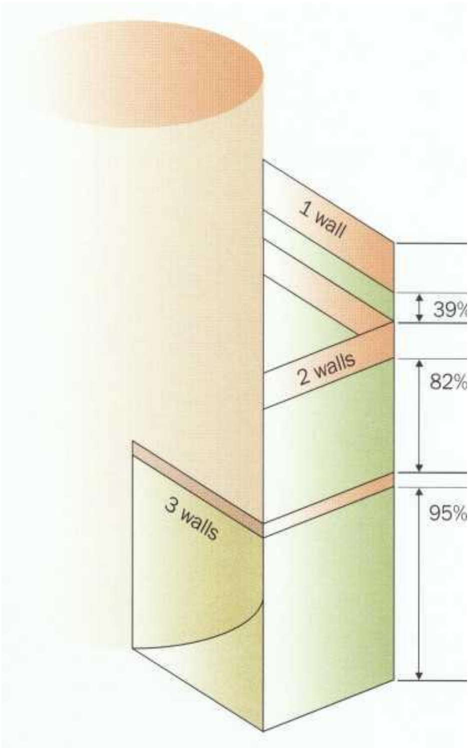
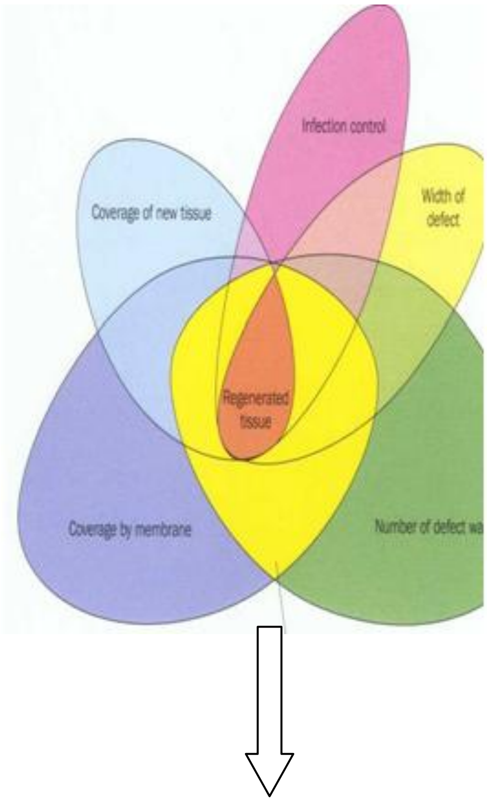


Fig 14

Tonetti et al described the factors that influence the predictability of regeneration of deep intrabony defects treated by GTR as follows[9] (fig 15)

- The amount of regenerated tissue under the membrane is dependent on the baseline depth of the intrabony component
- The width of the intrabony defect-the greater the distance between the root and bone wall, the less regeneration achieved.
- Infection control, measured as full-mouth bleeding scores, significantly affects the maturation process.
- The regenerated tissue obtained at membrane removal should be protected during the maturation phase. Lack of good coverage of the regenerated tissue results in a decrease of attachment gain and bone fill.



New tissue formed

Fig 15

3. Tooth mobility

- Hypermobile teeth ought to be splinted at least temporarily for several reasons;
- Hyper mobility may momentarily increase following surgery with discomfort to the patient
- hypermobility may jeopardise clot stabilisation in the defect,
- when the tooth 'rocks' the barrier, which is attached to the tooth, moves with it and this may compromise flap healing with maintained closure.

4. **Surgical technique**

GTR procedures are technique sensitive, requiring excellent surgical skills and considerable experience before predictability is obtained.

- **Surgical technique includes**
- flap management (incision,flap elevation, flap positioning), defect debridement,
- root surface preparation (scaling, root planing, and chemical root surface preparation) and barrier placement and flap suturing.
- *Incision and flap management*
- These have to be designed so as to enable later complete closure of the defect and coverage of the membrane.
- The flap design for GTR consists of sulcular incisions and interproximal incisions connecting the sulcular incisions.
- The interdental papilla should be preserved as much as possible in interproximal incisions.
- An interproximal incision for maximum preservation of the interdental papilla has variations, depending on whether there is sufficient or insufficient interdental space.fig 16

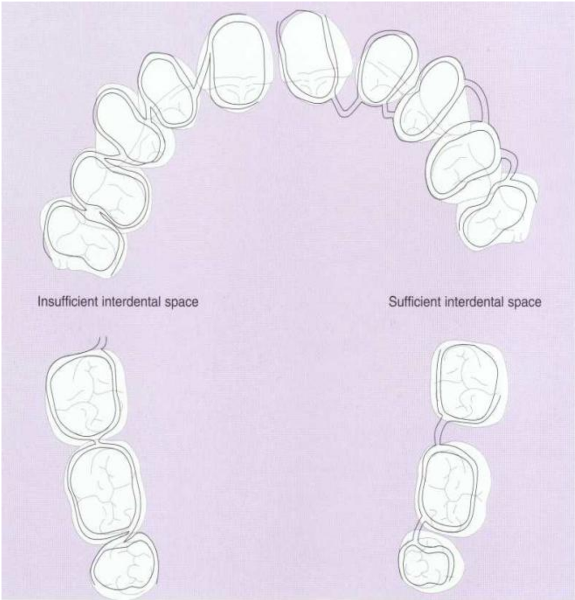


Fig 16

- **A combined** full thickness and partial thickness buccal flap is recommendable as this enables coronal advancement of the flap and allows for some elongation of the interproximal papillae.
- A mobile flap also facilitates suturing without apical tension in the flap
- *Defect debridement*
- The defect should be carefully debrided to remove all granulation tissue and expose the bony walls.
- Hand instruments, ultrasonic instruments and various types of rotating instruments may be used fig 17

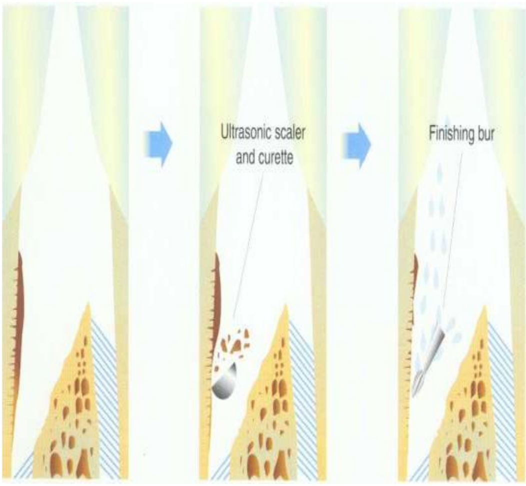


Fig 17

- Once the root surface preparation is completed the bony walls may be decorticated to enhance new bone formation. Although not proven beneficial for periodontal defects, but for bone augmentation, the biological rational is to facilitate ingrowth of vessels and bone forming cells from the underlying bone marrow (fig18).

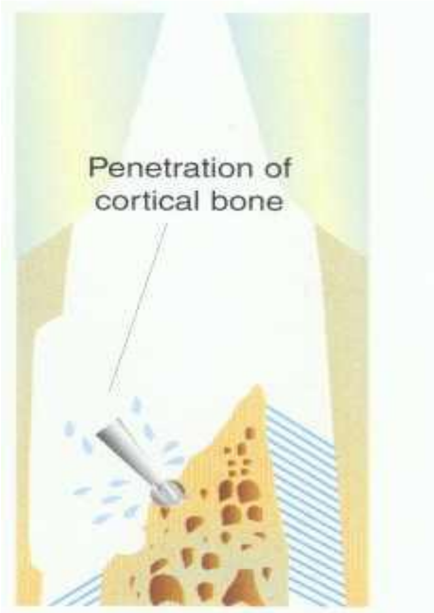
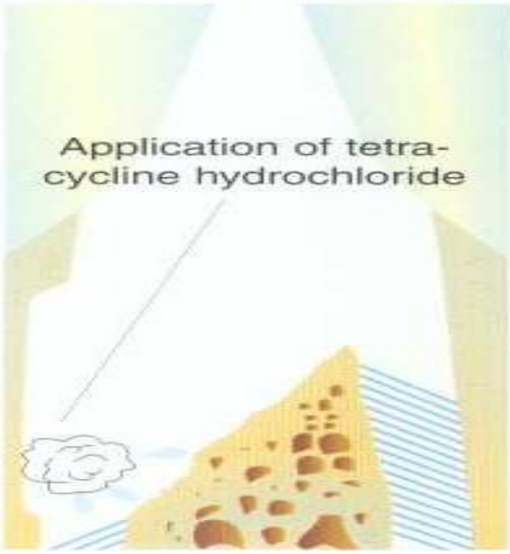


Fig 18

- *Root surface preparation*
- Following mechanical instrumentation, chemical etching agents are widely used with the goal is to remove smear layer from the mechanical instrumentation, detoxify the root surface from bacterial toxins and demineralise the root surface to expose dentine-collagen matrix. Citric acid or tetracycline hydrochloride (fig 19).



- *Barrier placement*
- The barrier is adjusted to cover the defect and 3-4mm of the surrounding bone and then firmly attached to the tooth.
- This extension is needed to accomplish peripheral sealing and prevent the barrier from collapsing into the defect.

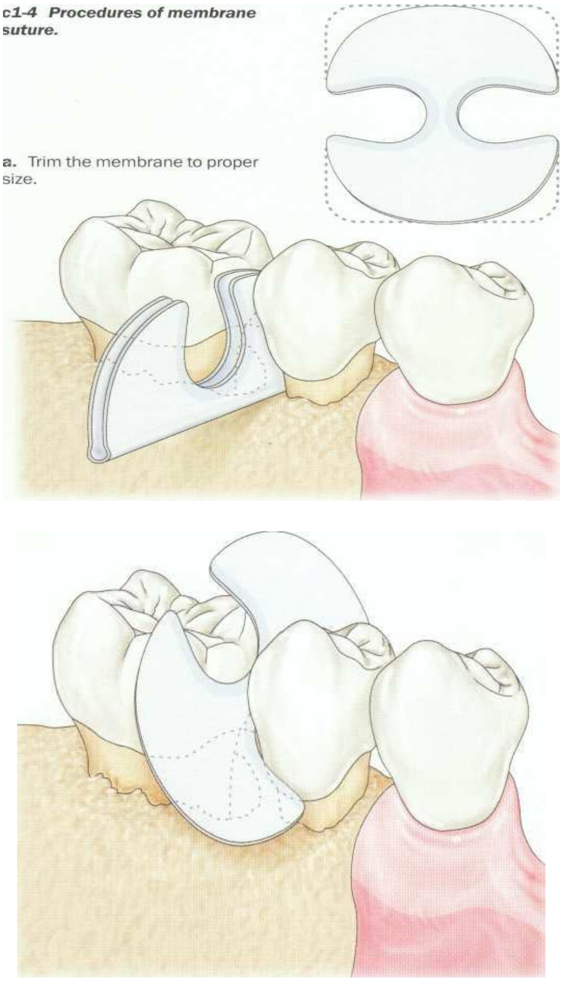
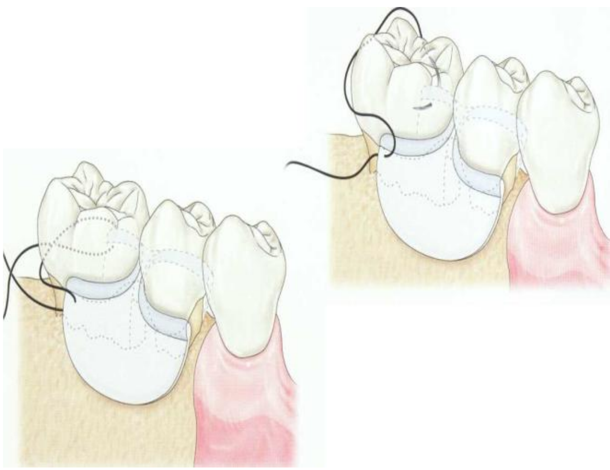


Fig 20

- **Considerations for membrane suture**
- 1. If the contact point is tight, insert the folded membrane interproximally,
- 2. Curve the membrane to follow the bone morphology.
- 3. Start the suture from the tooth in the defect area.
- 4. Make a suspensory sling suture and tie three times to avoid loosening and to bring the knot to the line angle area (fig 21).



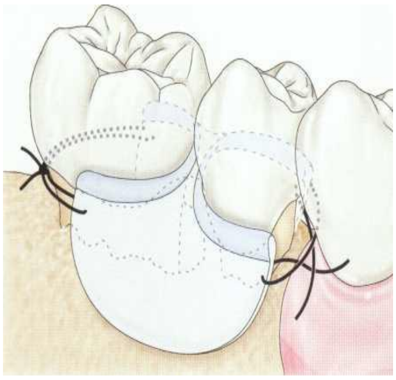
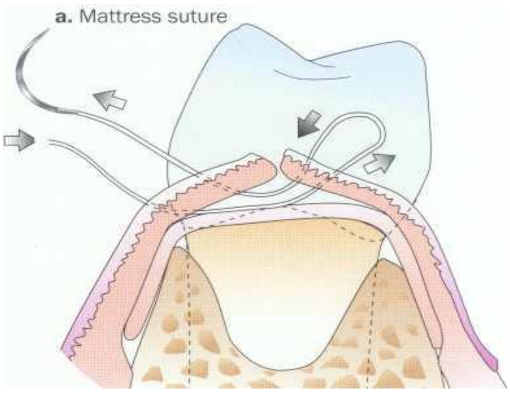


Fig 21

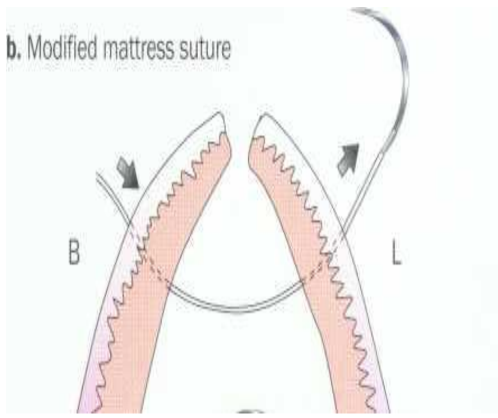
- *Grafting(combination therapy*
- GTR has been performed both with or without graft use of graft materials. The benefit of this combined treatment can be questioned. In fact, the *consensus report from the World Work Shop in Periodontology* 1996 stated that for *intrabony defects bone* grafts or bone substitutes add nothing to barrier alone.
- If graft is used ,it is frequently best to presuture the barrier over the defect, then retract the barrier to permit placement of graft. The barrier is then replaced and flap sutured.
- One may place the graft and then barrier but sometimes the graft is lost or displaced before the barrier can be positioned and secured. Therefore placement of non resorbable barriers are recomended if a bone replacement graft is used.

Suturing of flap

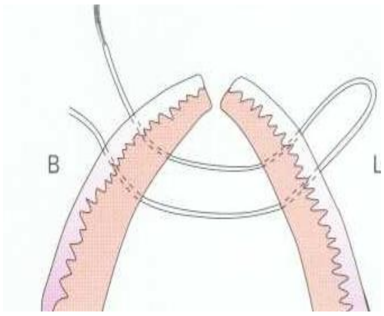
The flaps in the interdental papilla covering the osseous defect area are sutured by a modified mattress suture (fig 22)(vertical mattress). The area is closed completely. The flaps in the osseous defect area are sutured first, then the vertical incised area is sutured and closed.



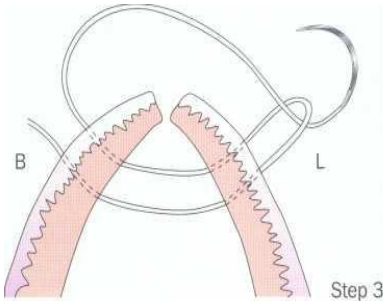
Modified mattress suture.

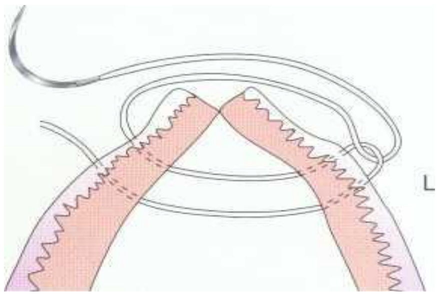


Step 1

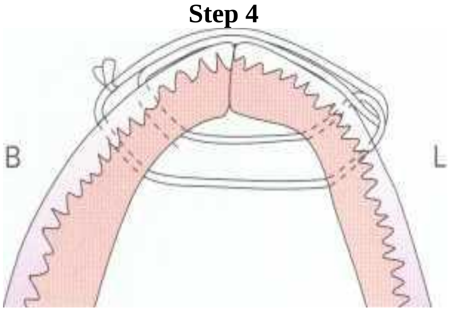


Step 2





Step 4



Step 5
Fig 22

5. Infection prevention

- Preventing post surgical infection is another key parameter to success in GTR therapy.
- As the patient has to refrain from mechanical tooth cleaning in the treated area during early healing (4-6 weeks) plaque control is achieved by rinsing with, or local application of, an antiseptic solution during this time.
- chlorhexidine (0.2or 0.12 per cent solutions) applied twice or three times daily until tooth brushing is resumed.
- In addition patients are frequently put on antibiotics, usually tetracycline or tetracycline derivates.

6. Postoperative care

- Postoperative care is critical to success of GTR procedures. it is desirable to see the patient frequently while barrier is in place. weekly visits are desirable. The purpose of these sessions is to remove gently any debris accumulated and reinforce oral hygiene.

7. Evaluation of results

- For the patient the expectation, of the performed treatment is to save a severely diseased tooth for a significant time with maintained function and aesthetics
- For the periodontist, treatment success is usually expressed as reduced probing depth and shallow residual pockets, minimal gingival recession, gain of clinical attachment and bone fill.

The extent of these changes, however, has to be evaluated with reference to the morphology of the defect at the time of treatment for both remaining versus lost PDL area and number of bony walls.

Class II furcation defects

The primary objective for the treatment of class II furcations is to achieve horizontal fill of the defect to complete closure or improvement to class i defects which can be successively maintained by normal oral hygiene measures. Study by Hugoson et al allowed for some conclusion on predictive factors apart from the general factors as discussed for intrabony defects[10] (fig 23)

1.Defect morphology Defects with a horizontal depth of 3-5mm seemingly heal better than deeper defects. Defects with an intrabony defect, that is, a minor buccal bone crest resorption, heal better than defects without an intrabony component which become more like a 1-wall intrabony defect.

2. Root trunk A short root trunk, the distance from CEJ to furcation entrance, also makes placement of the barrier and the flap coronal to the furcation entrance difficult. Thus, even a minor flap recession during early healing may expose the furcation and jeopardise regeneration.

3. Interproximal bone crest level To facilitate placement and maintenance of the barrier and the flap coronal to the furcation the interproximal bone crest should be at a level coronal to the furcation entrance.

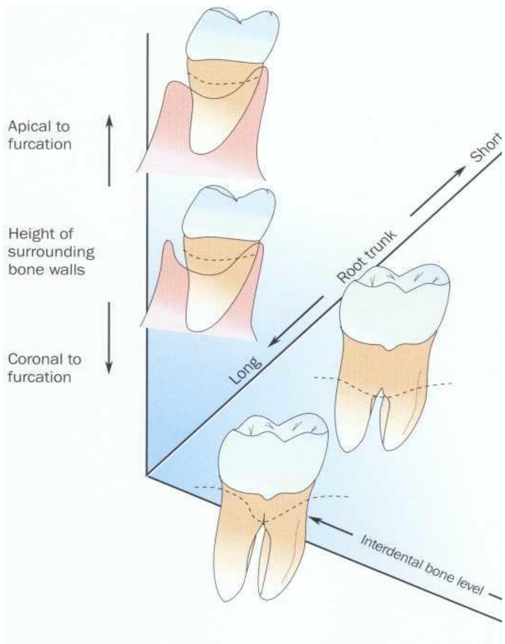


Fig 23

Healing

- Wound healing is commonly divided into three sequential phases;
  - Inflammation(early and late)
  - Granulation and
  - Matrix formation and remodelling
- At wound closure, blood clot fills the space between the tooth and flap. Within seconds plasma proteins primarily fibrinogen precipitate onto the wound surfaces and provides initial basis for adherence of fibrin clot.
- Within an hour, early inflammatory phase of healing is initiated by neutrophils infiltrating the clot from the mucogingival flap.
- Within 6 hours the root surfaces become lined by neutrophils, which decontaminate the wound by phagocytising injured and necrotic tissue.
- Within three days inflammatory sreaction moves into its late phase as neutrophil infiltrate gradually decreases while influx of macrophages increase.

- Within seven days the phase of granulation tissue formation gradually enters into third phase of healing in which newly formed cell-rich tissue undergoes maturation and remodelling to meet functional demands.
- In guided tissue regeneration, our main focus is to find out the regeneration of new periodontal apparatus.
- Studies have demonstrated lack of mechanical stability of the wound and lack of root surface adhering fibrin clot as main factors in the formation of long junctional epithelium instead of new attachment formation.
- To systematically study the periodontal regeneration following additive procedures like GTR, **Koo et al** developed a preclinical model, designated as the 'critical size supraalveolar periodontal defect model'.[11]
- In this animal model the periodontal defect was made in such a way that regeneration could not take place without adjunctive methods.
- They surgically removed alveolar bone and periodontal attachment including cementum, circumferentially around premolar teeth to a level 5-6mm from CEJ.
- This model was then subjected to various clinical investigations
- In their first study, they investigated the importance of fibrin clot absorption, adhesion and maturation to the root surface.
- They coated test root surfaces with heparin (anticoagulant) and control sites were treated with normal saline before flap closure.
- They found that at control sites the epithelial migration stopped immediately apical to CEJ whereas in test sites epithelial attachment (long junctional epithelium) was formed. Thus fibrin clot adherence to root surface was major factor affecting regeneration.
- In subsequent studies they covered heparin treated root surfaces with polylactic acid or ePTFE membranes. Connective tissues rather than long junctional epithelium was demonstrated in areas showing importance of wound stability and space maintenance.

II. Conclusion

- The principle of GTR lies in the establishment of the cells of periodontal ligament to selectively repopulated the root surface.
- Clot establishment and stabilization, site selection, epithelial cell exclusion, space provision, neovascularization, and complete gingival coverage are favourable characteristics in any GTR procedure.
- The use of GTR membranes can lead to significant periodontal regeneration and formation of cementum with inserting fibers, although complete regeneration has never been reported.
- It has considerable value as a regenerative procedure, particularly in intrabony, furcation and gingival recession defects.
- In the future, GTR can be combined with the use of biological growth factors that allowed for selectively control the type of cells proliferated from the fibroblast precursor.

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