CASE WESTERN RESERVE UNIVERSITY

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THE EFFECTS OF CONTINUOUS PASSIVE MOTION IN THE REGENERATION OF FULL-THICKNESS ARTICULAR CARTILAGE DEFECTS ON THE CONDYLE OF THE TMJ IN ADULT GUINEA PIGS

- A PILOT STUDY -

By

ROXANA MUSSA CONTRERAS

Submitted in partial fulfillment of the requirements

for the Degree of Master of Science

Department of Orthodontics

School of Dentistry

CASE WESTERN RESERVE UNIVERSITY

May 1990

THE EFFECT OF CONTINUOUS PASSIVE MOTION IN THE REGENERATION OF FULL-THICKNESS ARTICULAR CARTILAGE DEFECTS ON THE CONDYLE OF THE TMJ IN ADULT GUINEA PIGS

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Abstract

by

ROXANA MUSSA CONTRERAS

A full-thickness articular cartilage defect was surgically created on the right condyle of 11 adult Hartley guinea pigs. The left condyle served as control for each animal. The animals were divided into three groups: an experimental group, an immobilization, Valium-induced (IMM) control group, and an intermittent active motion (IAM) control group. A Continuous Passive Motion (CPM) device suitable for the guinea pig was developed. CPM was applied to the experimental animals during 7 hours per day, from the second to the 7th day following surgery. The IMM control group was restrained for the same period. Healing of the articular cartilage defects was assessed using three different parameters: range of motion, macroscopic appearance, and microscopic evaluation of histologic structures. Due to procedural difficulties it was not possible to obtain valid information from any of the experimental animals with regard to the effect of CPM on the

healing of the osteochondral defects created on the condyle of the TMJ. Nevertheless, the experimental results did indicate that CPM prevents joint stiffness, and the formation of fibrous or bony ankylosis. The results further suggest that CPM helps in maintaining and/or increasing the original range of motion. An important finding was that CPM protects articular cartilage from degeneration caused by infections. CPM did not seem to interfere with the soft tissue healing process of the operative incisions, and may actually stimulate surviving chondroblasts to synthesize the various components of the matrix. The present experimental investigation demostranted that it is possible to obtain repair of a full-thickness defect in the condyle of the TMJ with a cartilage-like tissue in an adult animal. The most significant finding was that CPM produced an increase in condylar cartilage thickness similar to that seen with hyperpropulsor-type appliances. This finding suggests that increasing mandibular function within the physiologic range of motion may be a valid method for stimulating mandibular growth.

DEDICATED TO

My wonderful parents, Alberto and Carmen Mussa to whom I owe everything, and whose sacrifices and unselfish love have provided us, their children, with the best education.

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INTRODUCTION

Temporomandibular joint disorders are becoming a cause of common concern among the general population. In addition to organic diseases, lifestyle stress and other psychologic factors have also been mentioned as a cause for the increasing number of people suffering from this condition. Patients present with signs and symptoms that include facial pain, joint noises and locking of the jaw. Non-invasive treatment with occlusal splints, muscle relaxants and physiotherapy provides adequate relief for most patients. However, for a small percentage of patients these methods fail to provide relief from pain and establish normal joint motion. For these patients, intracapsular joint surgery is sometimes indicated. Recovery of joint function after surgery is variable. Patients sometimes return post-operatively with the same complaints of stiffness, swelling, pain and limited range of motion. Therefore, there is a great deal of interest in the post-surgical management of patients who have undergone TMJ surgery.

The importance of preserving function after joint surgery has been well documented. However, appropiate guidelines to aid in the repair of articular tissues immediately after TMJ surgery remain poorly defined. Most rehabilitation programs after surgery of the TMJ include some form of Intermittent Active Motion (IAM). Continuous Passive Motion (CPM) is a recently developed concept of post surgical therapy. CPM consists of moving a synovial joint passively and constantly through its normal range of motion. This mode of therapy has been used to treat a variety of disorders

and injuries to other synovial joints. CPM has been shown to accelerate repair of defects in articular cartilages and has been used during the post-surgical management of total implant arthroplasty and intraarticular fractures. In addition CPM has been shown to help clear abnormal metabolites in pyarthrosis and hemarthrosis.

Clinical experience in the application of CPM to the TMJ has been limited and very few animal studies have been reported. The objectives of this study are twofold. First, to develop a methodology that will allow the application of CPM to the TMJ in an animal model. And second, to test the hypothesis that CPM has a beneficial effect on the healing of a surgically created full-thickness defect in the articular cartilage of the mandibular condyle.

A surgical defect that penetrates into the subchondral bone will be created in the articular cartilage of the condyle. Adult guinea pigs will be used, the experimental group will be subjected to CPM for 8 hours per day during the first week after surgery. Half of the control group will be restrained for 8 hours per day during the first week after surgery. These animals will be allowed normal cage activity for the following 5 weeks. The remaining control animals will be allowed normal cage activity right after surgery. The amount of maximum opening will be measured before surgery and before the animals are sacrificed 6 weeks after surgery. The condyles will be removed from the mandibular ramus and the repair tissue will be examined both macroscopically and microscopically.

LITERATURE REVIEW

DESCRIPTIVE ANATOMY:

Joints have been classified by structural features into three main types: fibrous, cartilaginous and synovial. The first two types frequently are termed synarthrosis. Both fibrous and cartilaginous joints are immovable or only slightly movable through an intervening deformable tissue. The fibrous joints are united without an intervening cavity. The participating bones are held together by dense fibrous connective tissue. Fibrous joints have been classified according to the physical characteristics and microscopic appearance of this connective tissue. If the union is extremely tight, the joint is termed a suture. When growth is complete and the connective tissue undergoes ossification, the suture becomes a synostosis. A fibrous joint is called a syndesmoses when the amount of fibrous tissue uniting the bones is considerably greater than that found in a suture. A gomphosis is another type of fibrous joint. It is a specialized articulation between the teeth and the maxilla and mandible. The teeth are attached by a unique fibrous tissue termed the periodontal membrane. Cartilaginous joints are divided into two types, primary and secondary. In these joints the surfaces of the bones are covered by hyaline cartilage. Primary cartilaginous joints are united by direct apposition of their hyaline cartilage while secondary cartilaginous joints have fibrous tissue interposed between the bones.[46, 99]

Synovial joints are different from cartilaginous and fibrous joints because they allow considerable freedom of movement.[11, 46, 99] For this reason they are also referred to as a diarthrosis.[15, 19, 46] Injuries to synovial joints represent one of the most common causes of disability. The bones are held together by an articular capsule[11, 19, 46, 99] This capsule consists of an outer fibrous layer which is continuation of the periostium.[11, 19, 46, 99] The inner layer is called the synovial membrane[11, 46, 79] The synovial membrane lines the non-articular surfaces of the joint cavity.[11, 46, 99] The articulating parts are connected by ligaments that strenghthen the joint, preserve its integrity and define the limits of joint movement.[19, 21,99]

The cavity in some synovial joints is subdivided partially or completely by intra-articular discs or menisci.[11, 19, 37, 46, 76, 95, 99] These discs are avascular and made up of fibrocartilage.[11, 19, 76] It is beleived that the meniscus improves the fit between the articulating bones, prevents wear on the articular surfaces and acts as a shock absorber.[11, 19, 46, 76, 94] Menisci are most common in joints where shearing forces are present.[46] Movement between the bones is possible because the gliding surfaces are lubricated by synovial fluid. This viscous and transparent fluid is produced by the synovial membrane.[11, 21, 46, 79, 99] Synovial fluid contributes to the nutrition of the disk and articular surfaces and facilitates removal of catabolic waste from the joint cavity.[11, 21, 46, 99]

The articulating ends of the bones are capped with highly resilient hyaline cartilage. Hyaline cartilage provides a smooth surface that helps to

minimize friction.[11, 21, 25, 80] Because articular cartilage is hyaline cartilage it is devoid of blood vessels, lymphatics and nerves.[11, 25, 46, 79] It is not covered by perichondrium and the surfaces in contact consist of naked uncalcified articular cartilage matrix.[11, 25, 46, 79] The principal constituents of the articular cartilage matrix are collagen type II fibrils and ground substance. Type II collagen determines and maintains tissue shape and resists tensile forces. Ground substance contains glycoproteins and proteoglycan aggregates which form a hydrated viscous gel that absorbs compressive forces. These two components account for the remarkable resilience of cartilage.[11, 21, 25, 46, 79]

The molecular organization of the extracellular matrix, with proteoglycan aggregates occupying the interstices of the fibrillar scaffolding of collagen, is ideally suited to its function on the weight bearing articular surfaces of bone.[11, 21, 25, 46, 79] Chondroblasts are embedded in the intercellular substance. These cells synthesize and secrete collagen and proteoglycans to make up the surrounding matrix.[11, 25, 46, 79]

All synovial joints follow this general structure, but each joint is adjusted to meet specific functional needs. The TMJ is an example of a specially adapted synovial joint. This articulation of the lower jaw with the cranium is distinguished from most other joints by its unique anatomic, functional, histologic and developmental characteristics. Anatomically and functionally it is distinctly different. Although it is a bilateral articulation, movement within the joint is limited to the mandible. The complex is actually one functioning joint.[19] The TMJ is also a combined hinge-glide

articulation with more translation and rotation than any other joint in the body.[19, 72] The mandible also articulates with the maxilla through the dental occlusion. This peculiar characteristic makes the TMJ the only joint with a rigid end-point of closure.[19, 21, 76] In addition, the shape and alignment of the dentition influences the direction and extent of joint movements.[19, 21, 60, 76, 99]

There are also histologic differences. The articular surfaces of the TMJ are not covered by the "classic" naked hyaline cartilage present in most other synovial joints.[11, 25, 46, 55, 79, 102] Much controversy exists regarding the nature of the cartilage covering the articulating surfaces of the condyle, the glenoid fossa and the articular eminence. Many authors have termed the covering tissue, fibrocartilage. They describe it as a dense, avascular, fibrous connective tissue that may contain a variable number of cells.[20, 25, 46, 79, 95, 102] Others have described the covering tissue as hyaline cartilage, but agree that fibrocartilage can occur on the condyle and articular eminence. An important feature that distinguishes the condylar cartilage from most of the other growth cartilages involved in endochondral bone formation is its histologic organization. The condylar cartilage has a special multidirectional capacity for growth and remodeling, unlike the epiphyseal plates which only have unidirectional growth capacity due to the linear orientation of the epiphyseal chondroblasts. In addition the condyle is always covered by a unique capsular layer of poorly vascularized connective tissue. This membrane is highly cellular and proliferative in the early periods of development, but becomes densely fibrous and non-proliferative

with age. This special fibrous covering is what differentiates the condylar cartilage from the rest of the articular cartilages.[21, 24, 48, 99]

Developmentally, there are also marked contrasts between the TMJ and the other synovial joints. Most articulating surfaces of the body are developed from primary cartilage. The condylar cartilage is a secondary cartilage developed from the dentary bone. It is a local modification of periostium in response to the functional demands that were imposed upon the condyle to efficiently articulate with the cranium.[13, 24, 56, 99] The mandible is essentially a membranous bone, and unlike the long bones, is not endochondral in origin.[13, 24, 55, 99]

PHYSIOLOGIC AND PATHOLOGIC CHANGES IN ARTICULAR CARTILAGE

One of the reasons why articular cartilage is of interest to researchers and clinicians is because sooner or later it undergoes changes that may deteriorate the integrity of the joint. This deterioration results in pain and/or functional disturbances.[11, 60] Various processes, such as remodeling, aging and osteoarthritis, can affect articular cartilage structure and morphology.[17] Remodeling is a biologic process that serves to maintain an equilibrium between joint form and function. It is a physiologic, non-pathologic response to mechanical stimuli.[17] Aging, is also a non-pathologic process. Senescence-related events are associated with chronologic age.[16] Calcification and subsequent nutritional difficulty, is one of the retrogressive changes related to the aging of cartilage.[46]

Osteoarthritis is a pathologic condition that is also associated with aging of cartilage. It is characterized by deterioration and abrasion of the articular cartilage and remodeling of the underlying bone.[16, 17, 60] Degenerative arthritis, degenerative joint disease, arthropathy, and arthrosis deformans are a few of the terms that have been used as synonyms for osteoarthritis.[16, 60] Osteoarthrosis has been used to describe lesions in the non-inflammatory phase.[36] Osteoarthritis generally affects the weight-bearing synovial joints of most people by the time they reach old age. Premature onset can be triggered by trauma,[11, 55, 60, 81] joint malalignment,[11, 81] or biomechanical overloading.[16, 17, 60, 77] In addition, normal loading forces can produce joint degeneration if the functional capacity of the joint is reduced idiopathically.[16, 81]

The process of osteoarthritis consists of a combination of degenerative and proliferative changes in the articular cartilage.[11] Degeneration occurs in the central part of the articular surface. It is characterized by desintegration of the collagen fiber network and depletion of the ground substance.[11, 16, 46, 77] In the absence of successful repair, the articular tissues are lost. This is postulated to be the result of a declining ability of the chondroblasts to replace proteoglycans and fibrous components at a rate sufficient to keep pace with the degenerative changes. Microscopically, these signs are described as fibrillation (increased roughness) of the articular surface.[11, 16, 60, 77, 100] Unfortunately, these initial changes are followed by fissuring, flaking and abrasion of the

cartilage. This ultimately leads to denudation of bone.[16, 17, 60, 77, 102] The proliferative bony response in osteoarthritis results in the formation of bony spurs known as osteophytes[11, 100, 102] These are seen around the periphery of the articular surface. The cartilage develops to excess and subsequently becomes replaced by bone.[11, 100] Fatty degeneration of the articular cartilage,[16, 17] increased cellular activity[16] and clustering of chondroblasts,[16, 17, 77] are also found in osteoarthritis. Because all of the adaptive mechanisms characteristic of remodeling play an active role in aging and in osteoarthritis, it is difficult to define the boundaries between a joint that can be regarded as "remodeled" or "aged", from a joint that has become pathologically involved.[17, 60]

HEALING OF ARTICULAR CARTILAGE

Under ordinary circumstances, the articular cartilage in long bones manifests a dissapointingly poor capacity for effective healing and regeneration.[11, 46, 53, 71, 80] There is little doubt that immature cartilage is capable of regeneration to a limited extent.[1, 18, 22, 49, 50] Numerous studies have shown that chondroblasts from immature cartilage are capable of cell replication,[22, 49, 53] along with synthesis of proteinpolysacharides and collagen.[11, 53] As articular cartilage reaches maturity, its potential for repair after injury decreases considerably.[1, 22, 27, 51, 52] The capacity for cell division is reduced and mitotic figures are rarely found in normal

mature tissue.[24, 51, 53] Nevertheless, cartilage cells remain capable of secreting the matrix constituents throughout life.[11] Therefore, renewed matrix production[11] and collagen turnover[12] seem to be the only mechanisms by which articular cartilage can compensate for everyday wear and tear.[11]

Experimental evidence now exists to support the concept that under circumstances of chronic injury and altered physical conditions, (such as seen in osteoarthritis,[12, 53] increased functioning of a joint,[80] varied oxygen tension[53] and mechanical injury,[9, 12]) chondroblasts from immature and adult animals are capable of increasing their rate of ground substance[53] and collagen synthesis.[12] In addition these chondroblasts can increase their DNA replication rate to form new cells.[9, 53] Unfortunately, sometimes this response is not effective in producing sufficient new tissue to repair a damaged cartilaginous surface.[9, 11, 53]

Partial-thickness defects are injuries confined to the substance of the cartilage without violating the junction of the calcified zone and the underlying osseous end-plate. Injuries of this type do not demonstrate a significant reparative response in either weight-bearing or non-weight bearing areas.[9, 18, 27, 28, 50, 53] These observations appear to be independent of the extent of the lesion[53] and are applicable to both skeletally mature and immature animals.[1, 2, 18, 53] Even after 18 to 24 months, the cartilage surface appears almost identical to the appearance immediately after injury.[18, 53] The cellular response is characterized by

abortive and disappointing attempts on the part of the cartilage to add cellular and matrix elements.[9, 18, 53] This poor capacity of articular cartilage for effective restoration is related to its avascular nature. The response to injury in well vascularized, nonarticular tissues is traditionally divided into three phases:[52, 96] The first phase, necrosis, begins immediately after injury. This phase is largely dependent upon the degree of injury and the interruption of oxygen tension. It is characterized by varying degrees of tissue necrosis. The second phase, inflammation, follows almost immediately and is mediated by the vascular system. During this phase, a fibrovascular mass forms and serves as a scaffold for the impending repair process. The third phase, repair, consists of cellular proliferation and differentiation along with the synthesis of cell products such as collagen. In considering the application of this repair process to injuries of articular cartilage, it is apparent that the response is likely to vary because of the avascular nature of cartilage. In cartilage, the traditional phases of repair are interrupted after the necrosis phase and the inflammation and repair phases are absent.

The response of articular cartilage to penetrating full-thickness injury produces a much different sequence of events. When the lesion penetrates into the subchondral bone, a vascularized sequence is initiated. Bleeding and secondary clot formation occur within the base of the defect. Later, proliferation of the capillary buds, allows a fibrovascular lattice-work to be established with secondary invasion of pluripotential mesenchymal cells. This process eventually results in resurfacing of the

articulation with some form of cartilage.[1, 7, 9, 27, 29, 41, 53, 96] The nature of the reparative process does not appear to be affected by the skeletal maturity of the animals.[1, 9, 18] However, the healing of these defects depend on their size. The repair tissue of small osteochondral defects is superior to that of larger defects. Defects that are less than 3 mm in diameter ussually show complete regeneration and the repair tissue resembles some form of hyaline cartilage. When the defects are too large (9mm to 21mm) the cartilaginous material does not fill the defect and is unable to restore the surface continuity. The repair tissue in large defects consists of a poorly differentiated fibrocartilage or fibrous tissue.[7, 9, 11, 29, 53, 71] The tendency for regeneration has also been found to be greater if the defects are localized within the weight-bearing part of the the articular surface.[1, 7, 18] The tissue reaction and cartilage formation occurs at a slower rate when the full-thickness defect is located in a non weight-bearing area. Moreover, the cartilaginous repair tissue has been noted to be more undifferenciated than that formed in the weight-bearing areas.[18]

When examining full-thickness defects, it has been dissapointing to find that the cartilaginous-like repair tissue never appears like normal hyaline articular cartilage. Various investigators have noticed that the process of spontaneous healing of osteochondral defects on an articular surface leads to restoration of this surface with a variable mixture of poorly differentiated cartilage, regenerating subchondral bone and loose connective or fibrous tissue.[1,7, 9, 11, 12, 27, 41, 53, 62, 93, 96] Such a heterogeneous and disorganized mass of repair tissues fails to provide the smooth gliding

surfaces needed for articular cartilage. It is poorly adapted to withstand the stresses that result from normal joint function.[11] Not surprisingly, it is repeatedly found that this hyaline-like chondroid tissue begins to show degenerative and fibrous changes with time.[18, 27, 41, 53, 62, 71, 93, 96] Therefore, it is necessary to revise the approach to damaged cartilage and attempt to provide the best conditions for repair in the hope that natural processes can be enhanced.

Immobilization, the traditional, time-honored practice following joint injury, has been demonstrated to have a harmful effect on all musculo-skeletal structures including tendons, ligaments and articular cartilages.[35, 39, 44, 63, 68, 80, 88, 93, 96] The ill-effects of immobilization such as cartilage degeneration, formation of tissue clefts, destruction of intercellular matrix, development of adhesions, muscle and bone atrophy, etc[75, 96] can be recognized even when it is applied for very short duration.[44, 81, 93] On the other hand, functional stress as created by early motion and weight bearing has a definitive stimulating effect on the process of cartilage regeneration.[1, 11, 18, 35, 41, 63, 67, 68, 71, 80, 93, 96, 98] Experimental investigations have clearly shown that retention of articular function is important for the differentiation of granulation tissue into cartilage. Undifferentiated mesenchymal cells are transformed into chondroblasts and the quality of the repair cartilage and joint function are markedly improved[1, 11, 18, 41, 67, 71, 80, 93, 96, 98].

Because Intermitent Active Motion was better than immobilization for the rehabilitation of joints, Robert Salter hypothesized that Continuous

Motion should be even better. However, because of the fatigability of skeletal muscle it was obvious that continuous motion of a joint would have to be passive rather than active. On this basis, he originated the concept of Continuous Passive Motion (CPM). CPM is a mechanical method of post-operative joint rehabilitation. Immediately after surgery, the synovial joint is passively and constantly moved through its normal range of motion. This motion is uninterrupted and does not require any voluntary effort.[11, 91, 96]

Before the development of the concept of CPM, no method had been successful in stimulating the tissues of a mature or even immature joint to replace lost or damaged articular cartilage with new hyaline cartilage. The repair tissue formed under the influence of CPM is almost indistinguishable from the original cartilage. The benefits of CPM have been demonstrated on different synovial joints in both experimental and clinical studies.[8, 26, 35, 63, 68, 69, 70, 71, 82, 83, 86, 91, 93, 96, 98, 110] One of the most important features of CPM is that it is not dependant on age. Although most of the experimental studies have been done on adolescent animals [69, 70, 71, 82, 93, 110] clinical studies have given the same successful results, regardless of the age of the patient.[8, 26, 35, 63, 68, 83] Futhermore, the superiority of the repair tissue produced by CPM is maintained after 6 to 12 months.[11, 39, 63, 78, 83, 86, 87]

Various authors have found that CPM must be applied immediately after surgery and should be continued for one week.[8, 82, 83, 93, 96] New collagen deposition occurs in wounds as early as the second post-operative

day and peaks around the 5th to 7th day.[96] It is important to implement the use of CPM during these periods in order to facilitate proper organization of the collagen-based scar tissue and stimulate undifferentiated pluripotential cells of the subchondral bone to differentiate into chondroblasts.[82, 96] It has been reported that one week of CPM achieves the same benefits as three weeks of CPM.[83] In terms of the dose-response characteristics of CPM, it was found that CPM for 8 hours/day is as effective for adequate cartilage repair as CPM for 24 hours/day.[93]

APPLICATION OF CPM TO SYNOVIAL JOINTS

Intraarticular fractures [11, 63, 75, 77, 83, 96]

Intraarticular fractures are usually managed by open reduction and stable internal fixation. When this procedure is followed by a course of CPM, healing of the fractures within the cartilage is remarkably good. The animals that received CPM showed fewer cartilage gaps, repair of the defects with hyaline cartilage, no adhesions and increased range of motion. Long term stability of the results has been reported. However, if the joint is immobilized or permitted only IAM, healing is slower and loose connective tissue grows into the fracture gap from below and fills it with fibrous tissue. These findings have been interpreted to mean that CPM promotes effective healing of articular cartilage by augmenting the secretion of organic matrix constituents. This in turn results in sufficient interstitial growth of

cartilage on both sides of the fracture line to close up the fracture gap. Another possible interpretation is that, under the influence of CPM, new chondroblasts might also arise from uncommitted mesenchymal cells associated with the subchondral bone tissue.

Repair of small to moderate full-thickness defects (1 to 3 mm)[11, 83, 93, 96,

In healing tissues, the metaplasia from undifferentiated mesenchymal tissue to hyaline articular cartilage is more rapid and complete with CPM than with either immobilization or IAM. Perhaps the most useful attribute of CPM is that it increases the chances that a full thickness articular cartilage defect will become replaced with hyaline cartilage.

Repair of major osteochondral defects (3.5 mm)[11, 39, 71, 83, 110

The repair of large defects is clinically more important than small defects.[93, 110] Recent experimental investigations have demonstrated the feasibility of "biologically resurfacing" major defects in articular surfaces. Even an entire surface of an arthritic joint can undergo neochondrogenesis with autogenous osteoperiosteal grafts when stimulated by post-operative CPM. In experimental animals, neochondrogenesis produced in the joints stimulated with CPM is superior to that in the joints treated with either cast immobilization or normal cage activity. Biological resurfacing of human joints may become an alternative to joint excision and prosthetic

replacement, especially for children, adolescents and young adults.[71, 110]

Periosteal grafts, with or without attached bone grafts, have been successful when placed into synovial joints either as free bodies or grafted into large full-thickness defects in articular cartilage. The application of CPM significantly enhances the chondrogenic capacity of the bipotential "osteochondrogenic" cells from the grafted periosteum. These grafts produce enough cartilage to bond the graft edges to the graft bed and restore the surface with biochemically and histologically normal articular cartilage.

Clearance of hemarthrosis [35, 69, 70, 83, 96]

To avoid cartilage destruction due to a secondary degenerative or rheumatoid-like arthritis, the removal of blood from the joint and synovium should be rapid and complete.[70] By enhancing the absorptive capacity of the synovial membrane CPM increases the rate of reabsorption of blood from the synovial fluid. This reduces the trapping of erythrocytes in the synovial membrane. The rate of clearance has been found to be more than twice as fast with CPM than with cast immobilization.[69, 70, 83, 96] Explanations include a raising and lowering of the intraarticular pressure in a sinusoidal fashion. This "pumping effect" presumably assists the synovium in clearing the synovial cavity of the blood and blood elements.[68, 69, 70, 96] It has also been suggested that the clearance of blood may be facilitated by an increase in blood flow to the joint during CPM.[70]

Management of acute septic arthritis [63, 82, 83, 96]

Acute septic arthritis, especially when caused by staphylococcus aureus, represents a potentially harmful disorder of synovial joints. Such infection is devastating to the articular cartilage. The damage is usually irreversible and progressive.[82] Acute septic arthritis should be diagnosed and treated early by adequate surgical drainage and appropiate antibiotic therapy. Subsequent application of CPM for two weeks has a statistically significant protective effect on preventing further degeneration of the articular cartilage when compared with the effects of immobilization or IAM. [82, 83, 96] This has been explained by the following sequence. CPM prevents the formation of synovial adhesions, including pannus formation. At the same time, this prevents the collagenolytic enzymes present in the synovial membrane from getting into direct contact with the underlying articular cartilage.[82, 83, 96] CPM increases the diffusion of the nutrients of the synovial fluid into the matrix of the articular cartilage[63, 82, 96] enhances the clearance of lysosomal enzymes as well as purulent exudates from the synovial cavity[63, 82, 96] and stimulates the viable chondroblasts to increase their synthesis of the various matrix components.[82, 96]

Recovery and rehabilitation of the total knee prosthesis recipient [8, 26, 96, 98]

Total and post-operative length of hospitalization and number of physical therapy treatments to achieve rehabilitation goals are significantly reduced in those patients having CPM immediately following total knee

arthroplasty.

Repair of tendons partial-thickness lacerations [83, 96]

It has been shown that CPM improves the quality of the repair response after tendon lacerations. It hastens the healing and increases their breaking strengh, the tendon callus has been found to be thicker and the alignment of the collagen fibers superior to that formed under immobilization or IAM.

Reconstruction of ligaments [68, 83, 96]

Similar studies have demonstrated that CPM significantly increases the maximum strengh of the repair[83, 96] and decreases the deleterious effects of immobilization such as stiffness.[96]

Summary of the characteristics of CPM:

Based on the clinical and experimental results of CPM, the following conclusions can be made:

1. CPM is well tolerated[8, 26, 83, 96]
2. CPM causes no harm to the intact normal living articular cartilage [8, 26, 83, 96]
3. CPM stimulates the healing and regeneration of articular tissues [8, 70, 83, 96, 98]

4. CPM decreases the quantity and the quality of intraarticular adhesions [8, 70, 91, 96]

5. CPM prevents joint stiffness[70, 83, 94]

6. CPM allows for normal wound healing [83]

7. CPM produces no complications [83]

8. CPM helps to maintain the range of motion gained at operation[83] or increases it [84, 98]

9. CPM protects articular cartilage from degenerative changes [70]

10. CPM eliminates the requirements for post-operative manipulation and deminishes the difficulty in accomplishing post-operative rehabilitation goals [35]

11. CPM helps in clearing abnormal and deleterious metabolites in joints where septic arthritis, hamarthrosis or abnormal fluids are present. [35, 61, 96]

12. CPM is more beneficial for adjacent musculo-skeletal tissues than either IMM or IAM.[75]

13 CPM enhances the flow of intraarticular fluids (blood and lymph).[63, 70, 75]

14. CPM enhances the transfer of nutrients to the articular cartilage.[82, 96]

Nevertheless, some disadvantages of the use of CPM have also been reported in the literature:

1. The patient is forced to remain supine, which makes it prone to

develop pressure areas, circulatory and pulmonary stasis, and other sequelae of limited mobility.[98]

2. The requirement for night time sedation is greater [8], basically due to the noise of the motor.[8, 98]

3. Patients treated with CPM manifest an increase in sanguineous drainage, [8, 26] requiring increased blood transfusions.[8]

4. It is still controversial whether CPM decreases the amount of post-operative pain. Some authors have reported a greater requirement for pain medication.[8, 26] Others found the amount of post-operative pain to be decreased.[96, 98] Meanwhile another study showed no statistical significance in the level of pain medication reqired for the patients under the influence of CPM.[68]

TMJ PATHOLOGY

The TMJ is subject to a wide range of pathologic and traumatic injuries. Some of which are usually described under the term Internal Derangement. Internal Derangements of the TMJ include any disturbance that compromises joint integrity. Several conditions such as ankylosis [4, 15, 37, 44, 76], intraarticular adhesions [65, 66, 76, 88, 107], synovitis [65, 66, 76, 88] and fibrosis of the articular capsule [65, 88] can develop within the joint and render it functionally deficient. In the last few years, Internal Derangement of the TMJ has commonly been used to refer to changes in the relationship of the disc to the condyle, fossa and articular eminence, when the teeth are together in the intercuspal position.[4, 17, 19, 88, 102, 107, 109] Most commonly the disc is displaced anteromedially.[4, 19, 102, 109] Displaced disks can mechanically interfere with jaw movement[19] and result in abnormal mandibular function.[17, 102] Recently, Internal disk derangement of the TMJ has been extensively studied due to the increasing awareness of TMJ disorders among the public.[4, 61] Most patients with TMJ problems have some form of disc displacement and/or disk degeneration.[40, 102, 109] However, anatomic derangements such as the one mentioned above are not the only abnormalities found in these patients. TMJ disorders constitute a complex set of medical orthopedic disorders which are closely related to congenital, developmental, and iatrogenic musculo-skeletal problems demonstrated by other joints. They also include painful symptoms that can be difficult to differentiate from other head and neck pain symptoms. In

addition and contrary to the general belief, TMJ disorders are not caused by poor occlusal or maxillomandibular relationships.[34]

Osteoarthritis and other abnormalities of the articular surface[102] are often found in joints with deformed and/or perforated disks. The incidence of abnormalities in the articular surface is not as common in joints with normal biconcave disks.[19, 60, 100, 107] Abnormalities have also been found to predominate in joints displaying anterior disk displacement without reduction.[19, 60, 100, 102, 107, 108] Structural changes in the hard tissues of the temporomandibular joints have been interpreted as signs of progression of the disease.[19, 55, 102, 107] Some authors have assumed a causal relationship between disk displacement and osteoarthritis.[16, 17, 60, 76, 90, 108] However, a cause and effect relationship between asymptomatic joints with disk displacement and/or disk derangement and subsequent osseous changes has not been shown.[102]

The subjective and clinical symptoms of patients with Internal Derangement of the TMJ in the form of disc displacement, are basically the same as those presented by patients with other forms of TMJ pain/dysfunction. They consist of limited jaw movement or hypomobility,[4, 15, 37, 44, 47, 65, 102, 109] inability to open the mouth, (described as locking or closed lock)[15, 37, 65, 66, 102, 107] pain,[4, 60, 65, 102, 107, 109] muscle tenderness [4, 60, 102, 107] trismus,[65] and joint noises (such as clicking and crepitus).[4, 53, 60, 102, 107, 109] In addition patients complain of headache, neckache, and earache.[4, 102, 109] However, these signs and

symptoms may exist in the absence of significant organic changes. On the contrary, symptoms may be absent in cases of joints with advanced osseous changes.[4, 60, 109] A high percentage of patients with internal derangement of the TMJ benefit from non-surgical therapy.[6, 40, 60, 66, 76, 109] These non-surgical treatment modalities include: counseling,[6, 20, 40, 44] pharmacologic agents[1, 6, 20, 36, 66, 76, 102] occlusal splints[6, 20, 36, 40, 44, 66, 88, 102] occlusal adjustments[6, 36, 40, 102, 109] physical therapy[1, 6, 20, 36, 40, 76] mandibular manipulation to unlock the jaw[66, 88] and injection of anaesthetics into the joint cavity.[66] For patients who do not respond satisfactorily to conservative methods and have pain and dysfunction that significantly alters their life style, surgical intervention may be indicated.[20, 44, 53, 102] Various surgical procedures have been advocated for internal derangement. These include disk repositioning and repair,[20, 61, 64, 88, 105] meniscectomy with or without implants,[32, 61, 78, 88] arthroscopic procedures,[6, 20, 64, 65, 66, 88] partial or total joint replacements[15, 44, 47, 64, 88] and articular recontouring.[61, 64]

Surgical treatment has some drawbacks. Middle ear infection and damage to the facial nerve may follow a surgical procedure in the area of the TMJ. However, the most bothersome complication is the development of either fibrous or bony ankylosis.[37, 38, 47, 61, 66, 100, 102] Ankylosis always produces a marked limitation of mandibular movement.[38, 45, 102] The response of the articular cartilage of the condyle to immobilization, to function, and to injury is similar to that seen in the other articular

cartilages.[38, 48, 56, 72, 97] Therefore a regimen of rehabilitation, based on physical therapy initiated early after surgery, has also been strongly recommended to achieve full range of motion.[44, 45, 54, 73, 76, 95, 97, 102] Some devices such as a mechanical mouth dilator[97] and a jaw exerciser[14] have been described as helpfull for the management of Internal Derangements of the TMJ. Although there is no biological reason to beleive that CPM would not be as beneficial for the TMJ as it has been for the other synovial joints, research studies in this field are necessary. In addition, CPM may be of greater value to the TMJ than to other synovial joints due to the high responsiveness of the condylar cartilage to local biomechanical factors.

MATERIALS AND METHODS

Description and Rationale

Eleven adult female retired breeder Hartley guinea pigs, about 20 months of age and weighing 0.800Kg. to 1.200 Kg. were utilized in this study. They were housed in the Animal Resource Center facilities at Case Western Reserve University.

The animals were arbitrarily divided into experimental and control groups. The control group was further subdivided into two groups: Intermittent Active Motion control group (IAM) and the Immobilization, Valium induced, control group (IMM) (Table Nº 1). Both the experimental and the IMM groups consisted of four animals each while the IAM group consisted of three animals. The experimental animals were placed in polycarbonate rodent shoe boxes 13 1/2 inches wide, 17 1/2 inches long and 8 inches tall. Aspen wood shavings were used as bedding material and the food was placed in plastic feeding dishes. These accomodations were necessary because the guinea pig, like other rodents, spends a considerable amount of time gnawing. This gnawing involves biting and chewing on drinking tubes, the edge of feeding dishes, wood particles and on metal cage bars.[101] In order to apply CPM to the TMJ it was necessary to cement crowns on the maxillary and mandibular incisors. It was very probable that, if metal bars or feeding dishes were used, once the crowns were cemented the gnawing behavior of the animals would result in fracture of the teeth. The control animals were

Table Nº 1: Initial Sample Distribution

Experimental Group	IMM Control Group	IAM Control Group
Nº 4	Nº 1	Nº 8
Nº 5	Nº 2	Nº 10
Nº 6	Nº 3	Nº 11
Nº 9	Nº 7	

Table Nº 1

placed in regular cages.

Guinea pigs have a very "finicky" feeding behavior. They appear to have definite taste preferences and alterations in the composition of their feed, and the introduction of a new feed may result in a sharp decline in feeding, to the point of starvation.[101] Guinea pigs purchased from vendors are usually fed a hard pelleted diet. Because this type of food is contraindicated after TMJ surgery, it was decided to start the animals on the soft-pelleted diet as soon as they arrived from the vendor. In this manner they could progressively get accostomed to the new food, and the risk of the animals refusing to eat after surgery would be reduced. The regular guinea pig chow was moistened with water for this purpose. These animals also have difficulty adapting to limited feeding times because they normally feed throughout the day. They generally feed during the daylight hours and especially around dawn and dusk.[101]

Because of their eating habits, guinea pigs are very susceptible to developing life-threatening dietary conditions such as scurvy and ketosis. Among the commonly used laboratory species, only guinea pigs and primates require a dietary source of Vitamin C. The known effects of ascorbic acid deficiency in guinea pig are related to defects in collagen synthesis. Ascorbic acid is essential in hydroxylase reactions in the formation of hydroxyproline and hydroxylisine in the collagen molecule. Impaired synthesis of these molecules would produce a definitive detrimental effect on cartilage regeneration and effect the results of the present study. Some of the early

clinical signs of hypovitaminosis C in the guinea pig are reduced food intake and weight loss. The symptoms progress to include weakness, muscle lassitude, anorexia (resulting in a decrease in body weight), anemia, and widespread spontaneous hemorrhages. Death of the animal either from starvation or from opportunistic secondary infections is the usual final consequence. The onset of scurvy in the guinea pig has been mentioned as depending on many factors including diet, age, sex, pregnancy or lactation, and stress. Ketosis is a disease that affects guinea pigs mainly during pregnancy. Nevertheless it has been found that an inadequate diet, obesity, lack of exercise, fasting and stress are key factors in the developing of this condition in the guinea pig. The clinical signs of ketosis are very similar to those of scurvy. The first signs of this illness are a sudden quietness, depression accompanied by adipsia, anorexia, weight loss and death within one to four days.[101]

For these reasons the experimental and the IMM, Valium Induced control group required thorough pre-experimental conditioning. The conditioning was done in a very slow and progressive manner to allow the animals to get used to the restraining device without eating for 8 hrs/day. At no time were the animals severily stressed or allowed any significant weight loss. Weight was monitored on a daily basis, and if beginning weight loss or changes in the animals behavior were noticed the conditioning was adjusted or "backed up" . The conditioning program was started on the third day after the guinea pigs were received. It has been found that inhibition of activity

occurs when guinea pigs are placed in unfamiliar surroundings, and an exposure period of one to two days is necessary in order for the animals to habituate to a new cage.[101]

Part I: Conditioning to the restraining box.

1st day	1/2 hr.	AM	1/2 hr.	PM
2nd day	1 hr.	AM	1 hr.	PM
3rd day	1 1/2 hr.	AM	1 1/2 hr.	PM
4th day	2 hrs.	AM	2 1/2 hrs.	PM
5th day	3 hrs.	AM	3 1/2 hrs.	PM
6th day	4 hrs.	AM		
7th day	5 hrs.			

Part II: Conditioning to the box with the neck restrained

8th day	6 hrs.
9th day	7 hrs.
10th day	through aproximately the 20th day, 8 hrs. day

The guinea pig was chosen as the animal model for this project because of its size and, especially, its tractable nature.[101] The application of CPM to the TMJ in a guinea pig demands cooperation on the part of the animal. Throughout the project the animals were treated as pets to make them more docile and responsive to the conditioning. Guinea pigs will voluntary

fast if they are overstressed, and the consequences of fasting and stress in terms of developing scurvy and /or ketosis can result in the animal's death. Only after the animals were satisfactorily acclimated to remain in the device with the neck restrained for 8hrs/day, could TMJ surgery be performed.

All the animals were subjected to the same surgical procedure. The surgery on the TMJ was performed under general anaesthesia induced by intramuscular injection with 0.5cc/0.800 Kg and 0.75cc/1.00 Kg of Ketamine 100mg/ml mixed with Acepromazine 10mg/ml in a 10cc to 1cc ratio. Local anaesthesia was also provided by injection of 2% xylocaine R at the surgery site. Ketamine with Acepromazine was chosen over pentobarbital because it was found that with pentobarbital, the animals remained anaesthesized for a longer period of time and tended to lose more weight than when ketamine was used. The recommended dose of ketamine is 0.5 cc/400 gms of body weight. A dose of 0.5cc/800 gms of body weight produces enough anaesthesia and lasts long enough for the type of surgery performed.

The range of motion was examined by measuring with manual manipulation the amount of maximun opening from the incisal edge of the upper incisor to the incisal edge of the lower incisor. The length of these teeth was also recorded. The measurement of the range of motion was done pre-surgery and before the animals were sacrificed.

The animals were shaved for an aseptic surgical field, and sterilized instruments were prepared. The right TMJ of each animal was subjected to

the following operative procedure. After the surgical area had been prepared with providine iodine, a 10 mm skin incision was made in the preauricular region (Figure 1). The joint was exposed, and the assistant surgeon then manipulated the mandible anteriorly and inferiorly to dislocate the condyle. A hand drill with a dental bur was used to create a defect that penetrated into the subchondral bone, aproximately 1.5 mm in diameter and 0.5 mm deep, in the "pressure-bearing" region of the condyle. During this procedure the joint was irrigated with normal saline solution. The previously dislocated condyle was then reduced and the skin wound closed with sutures.

It was found that when the animals were anaesthesized they could loose about 30 gms. of weight during that day, and without compensation they tended to lose even more weight after the TMJ surgery. It was very important not to let the animals loose weight, especially those animals that were going to be restrained after surgery and those to which CPM was going to be applied. Once awakened from the anaesthesia, the animals were given 3cc of a high caloric nutrient, Nutrical R and returned to their cages. After two to three hours they were fed about 9 cc of baby cereal food and/or baby apple sauce with a syringe (Figure 2). This was done two more times during the rest of the day and the following day. A period of two to three hours was allowed between each feeding time. The guinea pigs accepted the apple sauce very easily and can be used as a "treat" to positively reinforce them for remaining in the restraining device. It should not be used as the sole element

FIGURE 1: TMJ surgical incision and joint exposure

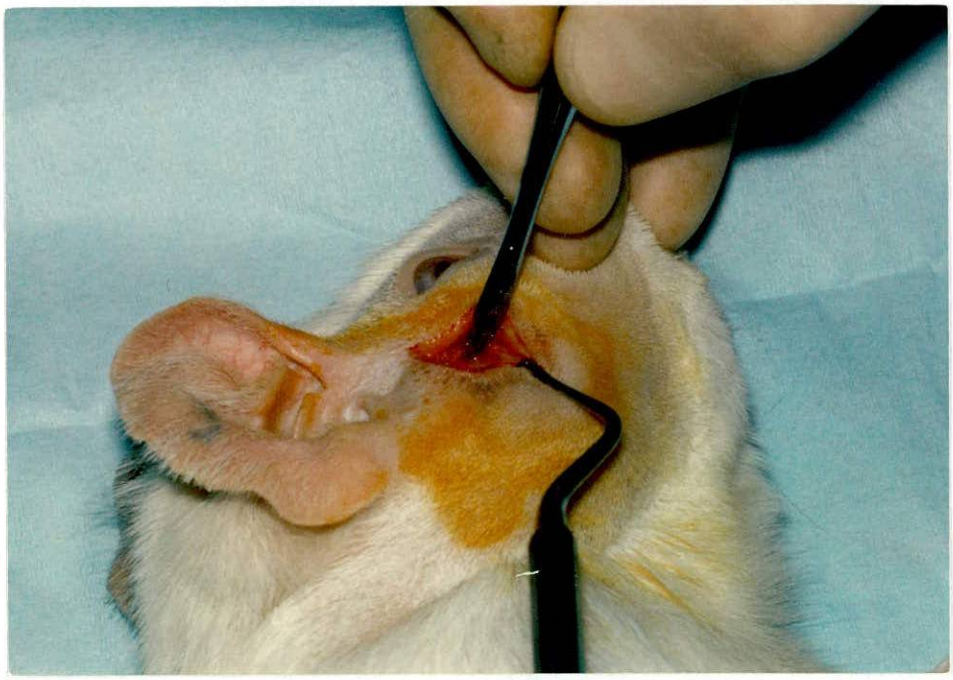


FIGURE 1

FIGURE 2: Feeding guinea pig apple sauce with a syringe



FIGURE 2

of diet because the animals tend to develop diarrhea. In those cases when the animals fail to eat and it is necessary to feed them with a syringe, baby cereal (Gerber rice, etc.) mixed with water was used.

On the second day after surgery and for a period of 5 days, the experimental animals were subjected to CPM for 7hours/day and permitted normal cage activity for the rest of the time. Even though it has been reported that CPM should be applied for a minimum of 8 hours/day during one week starting immediately after surgery, it was decided to apply CPM for only 7 hours/day. The rationale behind this was to allow the animals two hours of light at dawn and dusk to encourage eating. The light period in the animal facilities is set from 6:00 am to 6:00 pm. It usually took more than one hour from the time the animals were taken out of their cages to the time that they were actually under CPM. The animals had to be weighed, transfered to the laboratory and injected with the valium. A period of about 30 minutes was required before the valium produced the level of sedation required, then the wires were put on and the animal was placed in the CPM device. The animals were placed on the CPM devices under sedation induced by an Intraperitoneal injection of Valium R 5 mg/ml. An initial dose of 3 cc was used and repeated as necessary during the 7 hours of CPM. It usually required extra doses of 3 cc each to put the wires on and to attach the animal to the CPM device. Some animals required up to 20 cc of Valium in one day. It is better to start with heavy doses and wait until the animal is deeply sedated rather than give small doses (1 to 2 cc) repeatedlly.

Approximately 15cc of Valium was required to keep the animal calmed in the CPM device for a period of 7 hours.

After 7 hours of CPM the animals were still under the effects of the drug and were not able to eat or drink on their own. On a daily basis they were given 3cc of Nutrical R orally before and after the period of CPM. The animals were also fed about 15cc of baby cereal food and apple sauce, two or three times during the night and in the morning. It was also necessary to supplement the animals with fluids (lactated ringers solution) subcutaneously and with Vitamin C orally. For the animals that developed diarrhea, lactobacillus cultures were given orally to help to reestablish natural gastrointestinal flora. Usually one dose of 1/2 cc is enough but can be repeated for two or three days. The feeding regimen and supplementation were continued for as long as the animals required it. However, we tried to reduce it to encourage the animal to eat on its own. It is very helpful to mark the level of water on the bottles and check the amount of food in the feeding dishes to determine how much the guinea pig is eating and drinking.

The immobilization, Valium induced, control group, was restrained for the same period of time the experimental group remained in the CPM apparatus. This group was given about the same amount of Valium that the experimental animals required to tolerate the application of CPM. They also were allowed normal cage activity for the remainder of the day. The intermmittent active motion group was allowed normal cage activity for the entire post surgical period. Of the seven control animals only one did not

require the same type of supplementation provided to the experimental group. This animal was from the IAM group.

Impressions of the incisors were taken during the first days of the conditioning program. The animals were anaesthesized, as previously described, and the teeth were trimmed to a length of approximately 7 mm for the upper and 8 mm for the lower (Figures 3 and 4). It is very hard to obtain a good impression if the teeth are too long and the model tends to fracture because the "incisal third" is usually extremely thin. It also has to be remembered that the teeth will not wear down after the crowns are cemented and it becomes easier for the guinea pig to fracture them. Custom made trays in the shape of a cylinder 7 mm in diameter and 20 mm in lenght were fabricated with base plate wax. No conditioning was done during that day. Caulk Dentsply, Hydrosil R (regular set) impression material was used (Figure 5). The trays were filled with the use of a syringe and the teeth were also covered with the impresion material prior to the taking of the impression (Figures 6, 7 and 8). The impressions were poured with Whip-Mix, Silky Rock dental stone plaster (Figure 9). The crowns were cemented three days before surgery. After the animals were anaesthesized, the teeth were trimmed again and throughly cleaned with a prophylaxis cup and pumice. Once the teeth had been washed and dried, the crowns were cemented with Teledyne Getz, Lee Smith zinc phosphate. It is recommended to cement the crowns a few days before surgery so the animal has time to recover from the anaesthesia and can get used to the crowns. However, they should not be

FIGURE 3: Maxillary and Mandibular incisor teeth: Before trimming

FIGURE 4: Maxillary and Mandibular incisor teeth: After trimming

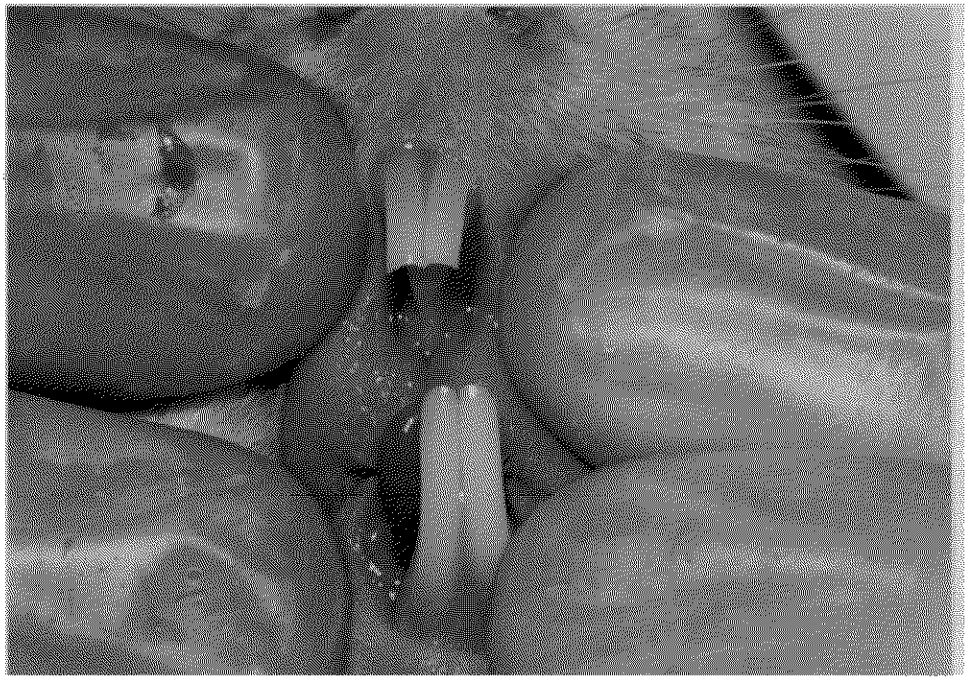


FIGURE 3

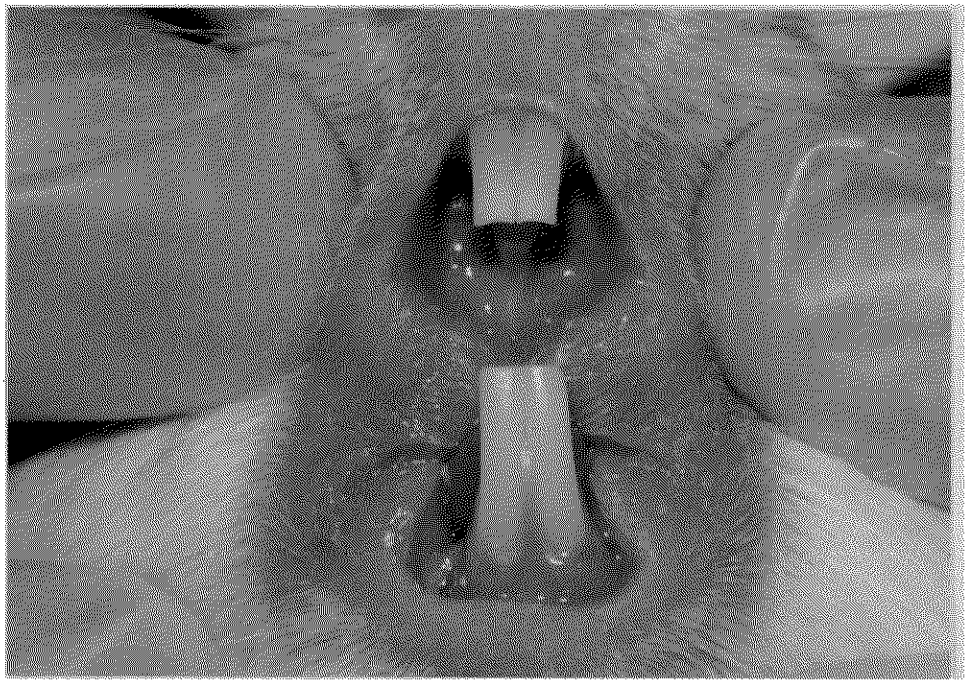


FIGURE 4

FIGURE 5: Set up for impression: note custom tray

FIGURE 6: Maxillary incisors covered with Hydrosil

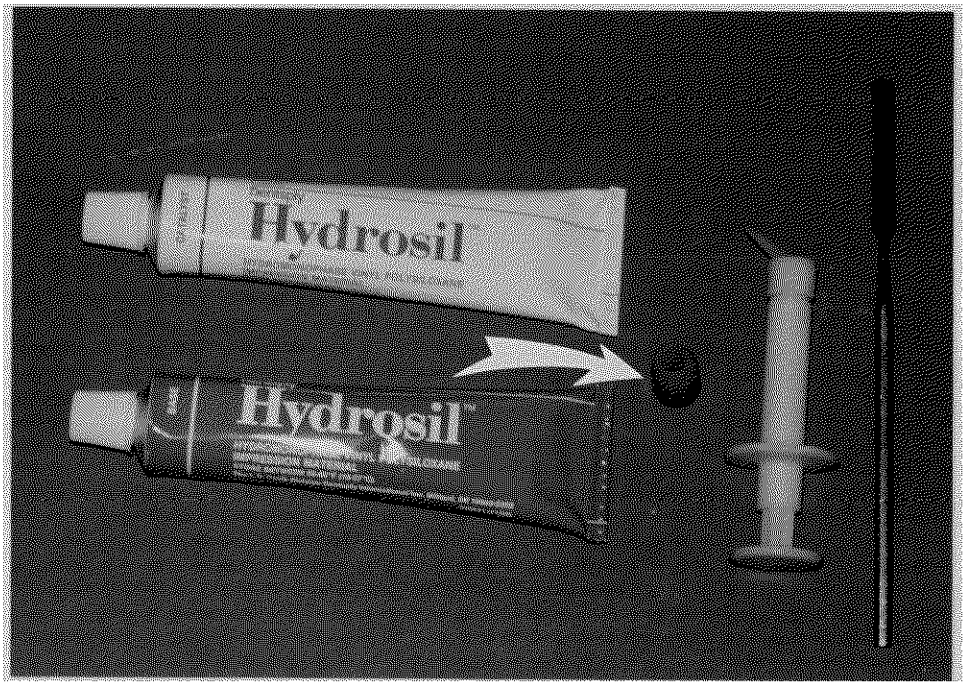


FIGURE 5

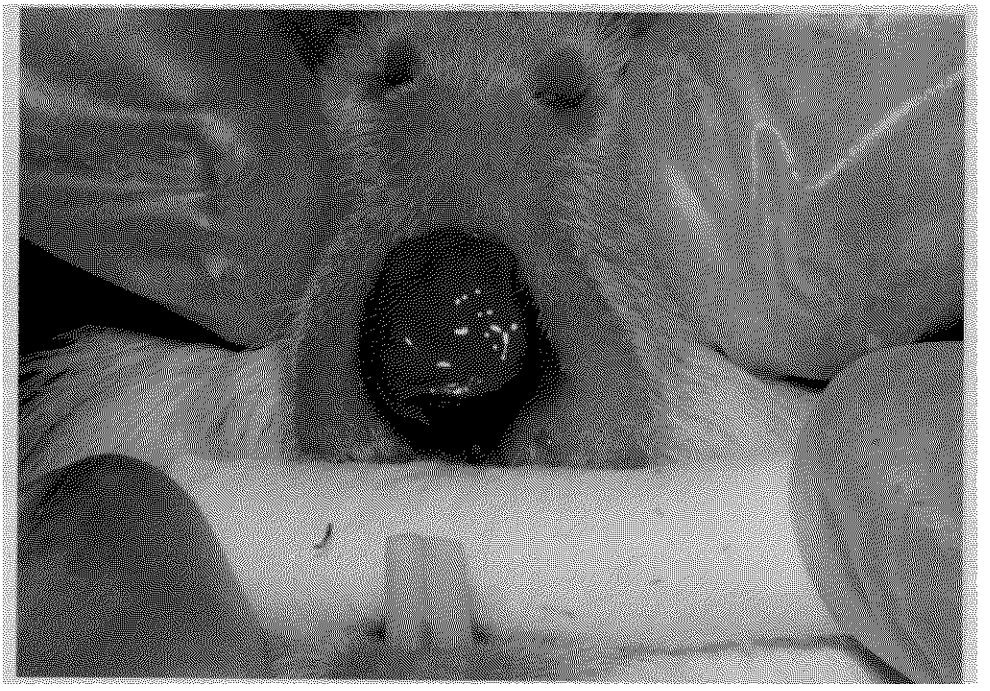


FIGURE 6

FIGURE 7: Taking of the impression: Maxillary incisors

FIGURE 8: Taking of the impression: Mandibular incisors



FIGURE 7



FIGURE 8

FIGURE 9: Models of the Maxillary and Mandibular incisors



FIGURE 9

cemented more than three days in advance. Guinea pigs have continuously erupting teeth, and after the crowns are cemented normal wear of the incisal edge is not possible. Needless delay between crown cementation and the application of CPM result in the teeth becoming excessively long. This factor added to their gnawing habits, could easily result in breakage of the teeth. The animals were allowed to rest for the remainder of the day.

CPM was applied to the TMJ by opening and closing the mouth, using the upper and lower incisors as anchorage. The method of attachment of the teeth to the CPM device was through a rectangular stainless steel wire 0.215 x 0.28 tied with ligature wires to an edgewise brackett that had been soldered to a gold crown (Mr. John Lavicka, Dental Ceramics INC) (Figures 10 and 11). In both arches, the right and left incisors served as one unit. Therefore only two crowns were cemented in each animal (Figure 12). The CPM device consisted of a restraining plastic box (24 cms. long, 9 cms. wide and 11 cms. tall) and an electric motor (Figure 13). The anterior wall of the box consisted of two parts: the inferior one was fixed to the box and the superior one was adjustable. Each one of them presented a reciprocal notch so when both parts were in place they formed an opening of 4.5 cms in diameter. The box also had a double posterior wall (Figure 14). The interior wall was adjustable anteroposteriorly. After the animal was placed in the box the animal was pushed anteriorly by this posterior wall. The head of the animal was positioned so that the neck rested on the notch of the fixed inferior part of the anterior wal. The superior part was placed to secure the

FIGURE 10: Maxillary and Mandibular crowns: Buccal Surface

FIGURE 11: Maxillary and Mandibular Crowns: Lingual Surface

FIGURE 12: Guinea Pig with Maxillary and Mandibular crowns cemented



FIGURE 12

FIGURE 13: Schematic drawing of the CPM device

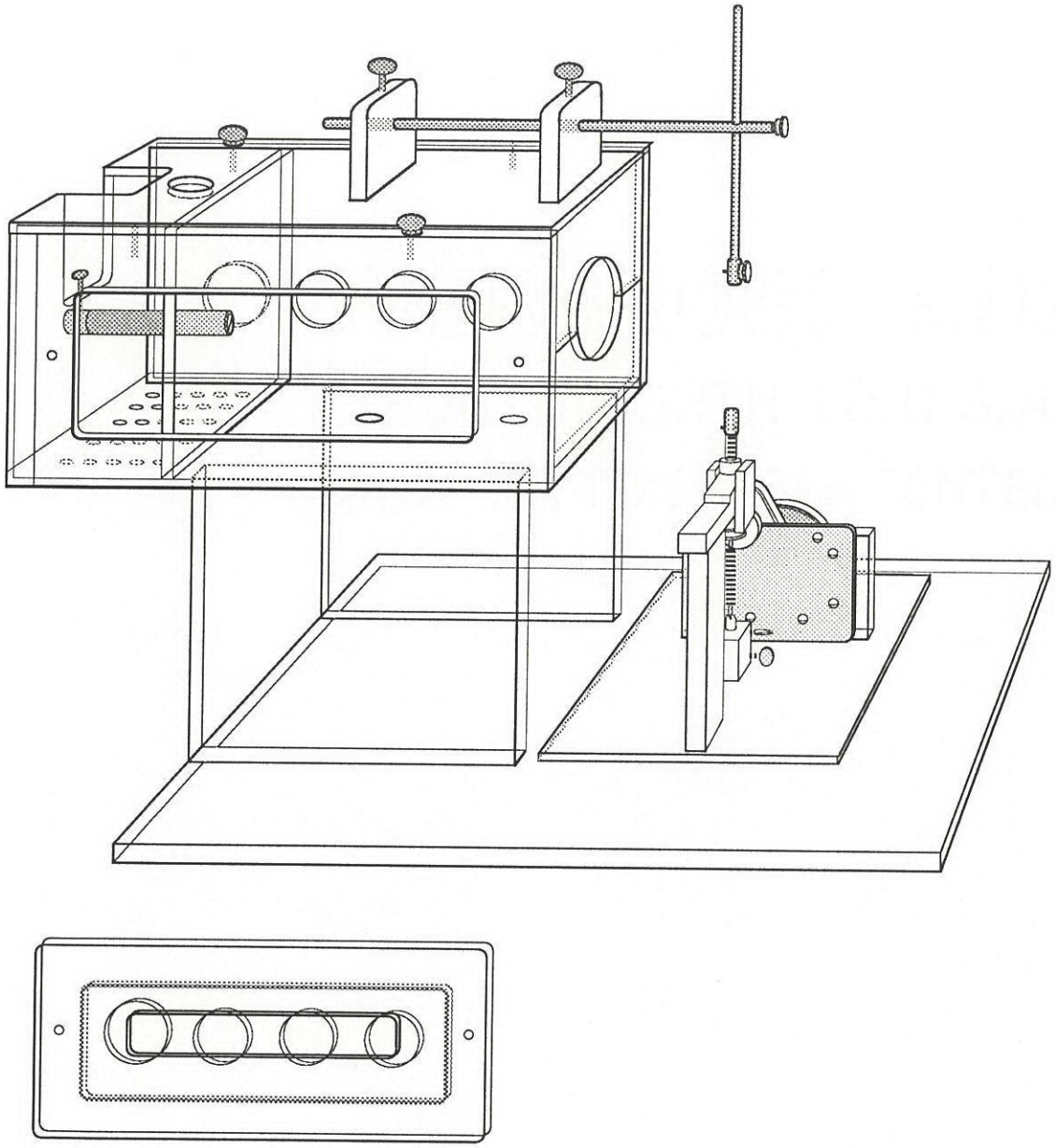


FIGURE 13

FIGURE 14: Restraining box showing the adjustable posterior wall

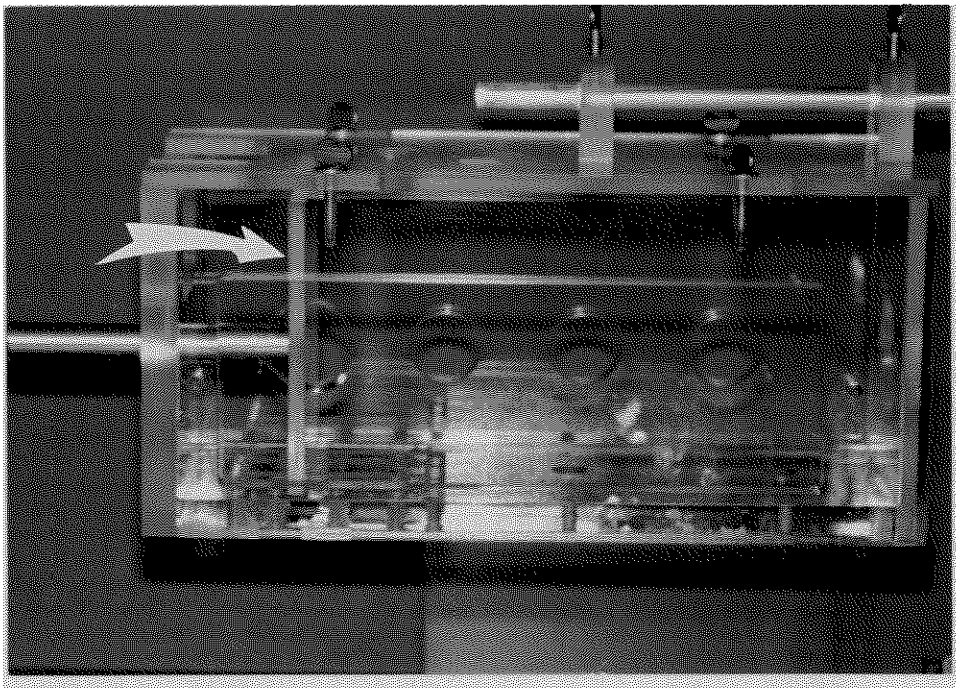


FIGURE 14

animal's head. Therefore, the body of the animal was kept restrained within the box, while the head was left free outside the box (Figures 15 and 16). The lid of the box had a horizontal post from which a vertical post descended. Both posts were adjustable in all directions. The head was stabilized by attaching the wire of the upper crown to this vertical post, which was adjusted in front of the face of the animal in order to provide the guinea pig with the most comfortable position both antero-posteriorly and vertically. The CPM device, in the narrowest sense of the word, consisted of another vertical post moved up and down by an electric motor (Figures 17 and 18). Continuous passive motion was applied by attaching the wire of the lower crown to the vertical post of the CPM device. Since the head was kept in a fixed position, the vertical movement of the post attached to the lower incisor moved the mandible up and down (Figure 19 and 20). The passive motion machine was arbritarily designed to complete one cycle every two minutes, with a motion range of 12 mm. Therefore, the mouth was opened to a maximum of 12 mm and one cycle of opening and closing the mouth was completed in two minutes. This range of motion eliminated the risk of skeletal-muscle fatigue and excessive loading, factors that need to be avoided during the application of CPM.[75, 87] However, it would be better if the range of motion could be adjusted to acommodate each animal's incisal opening. The level of noise produced by the appliance was almost negligible. One of the lateral walls of the box was not permanently fixed. Being kept in place by screws, this design facilitated the readministration of Valium R to the

FIGURE 15: Guinea pig in restraining box: Lateral view

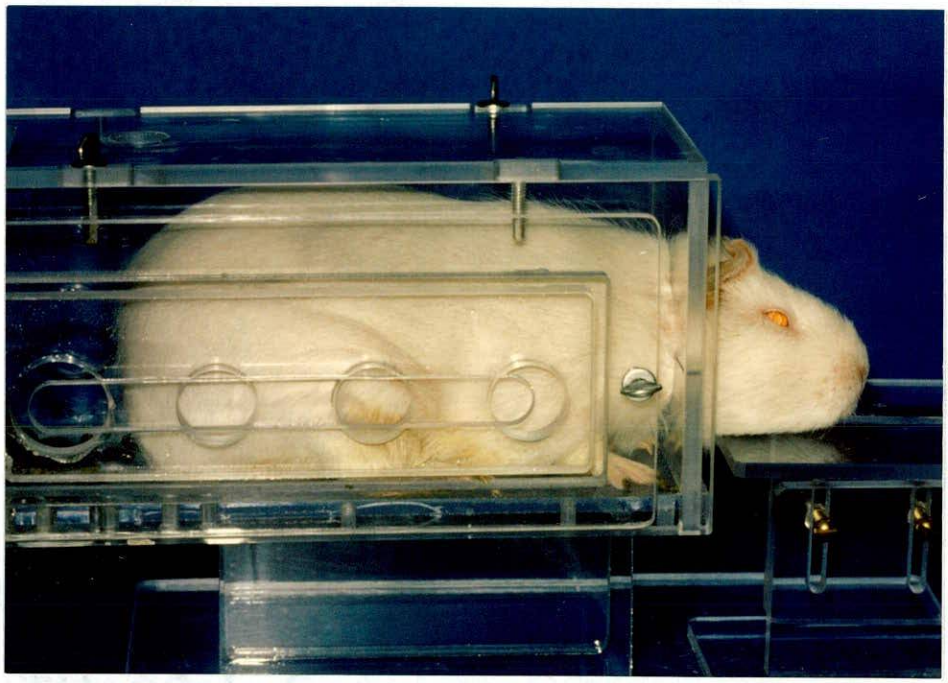


FIGURE 15

FIGURE 16: Guinea pig in restraining box: Frontal view

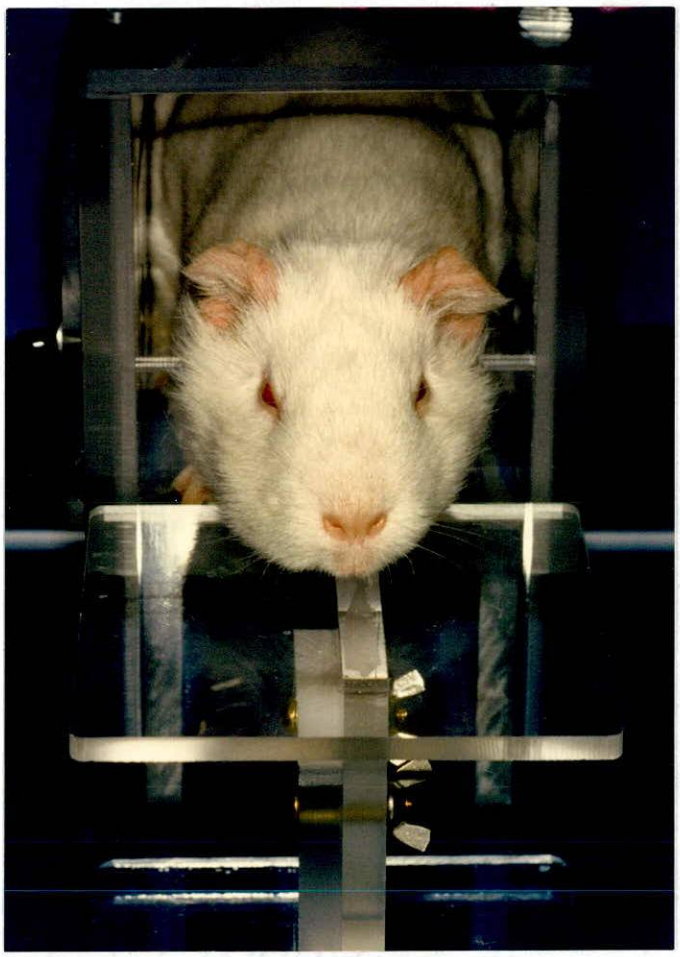


FIGURE 16

FIGURE 17: CPM electric motor: Vertical post at the highest point

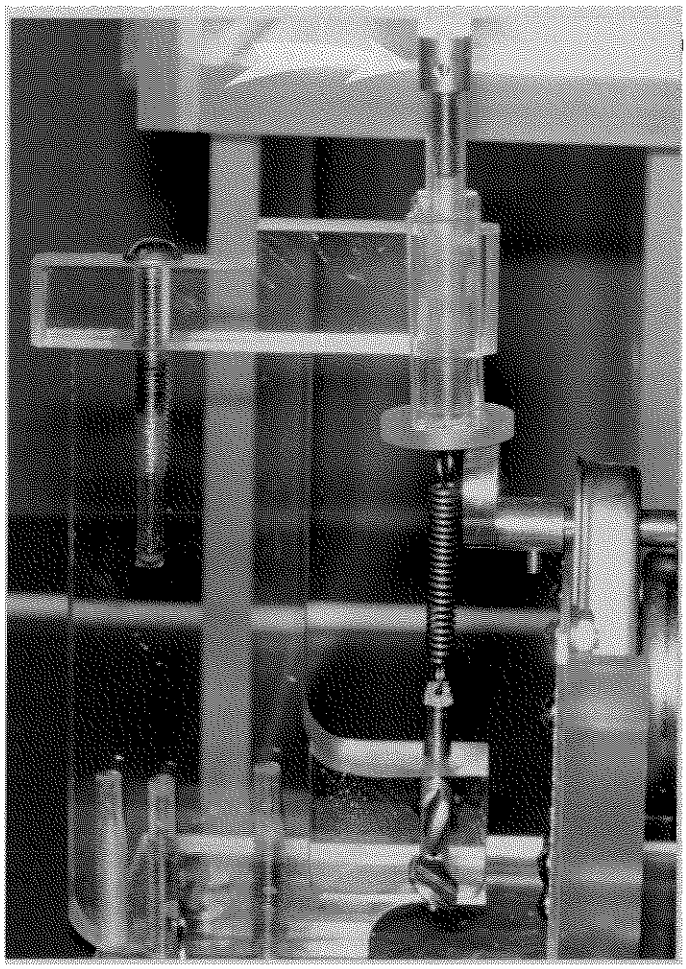


FIGURE 17

FIGURE 18: CPM electric motor: Vertical post at the lowest point

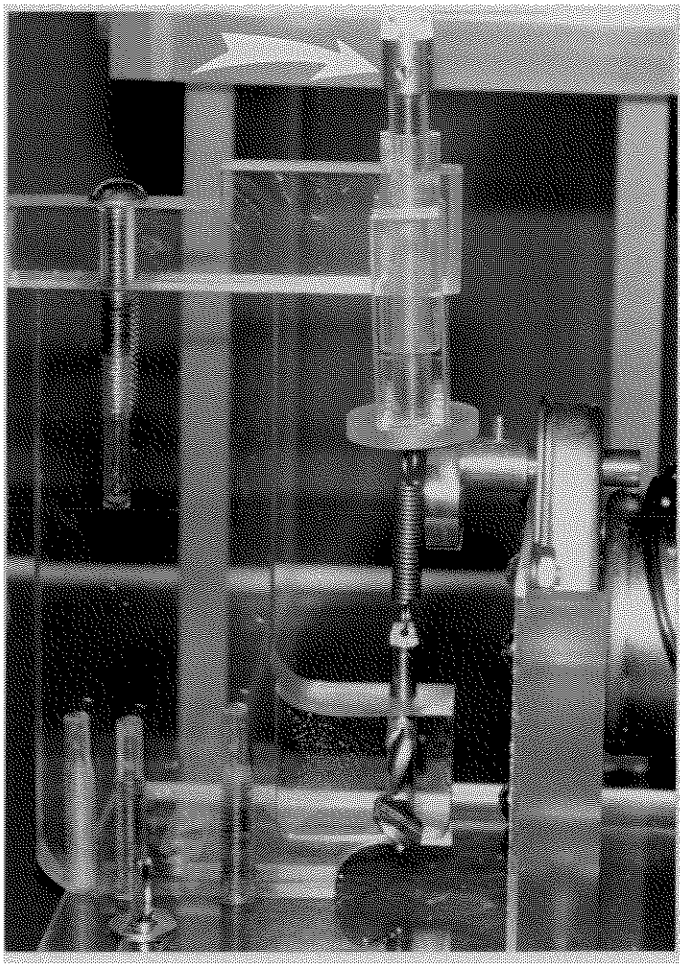


FIGURE 18

FIGURE 19: Guinea pig attached to the CPM device: Maximum opening

FIGURE 20: Guinea pig attached to the CPM device: At closure

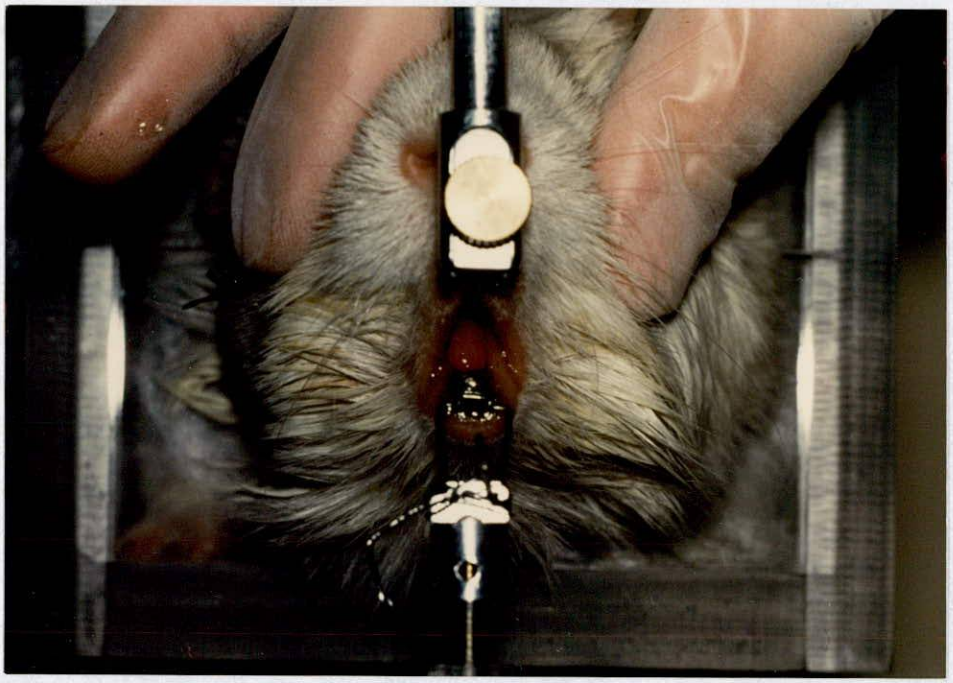


FIGURE 19

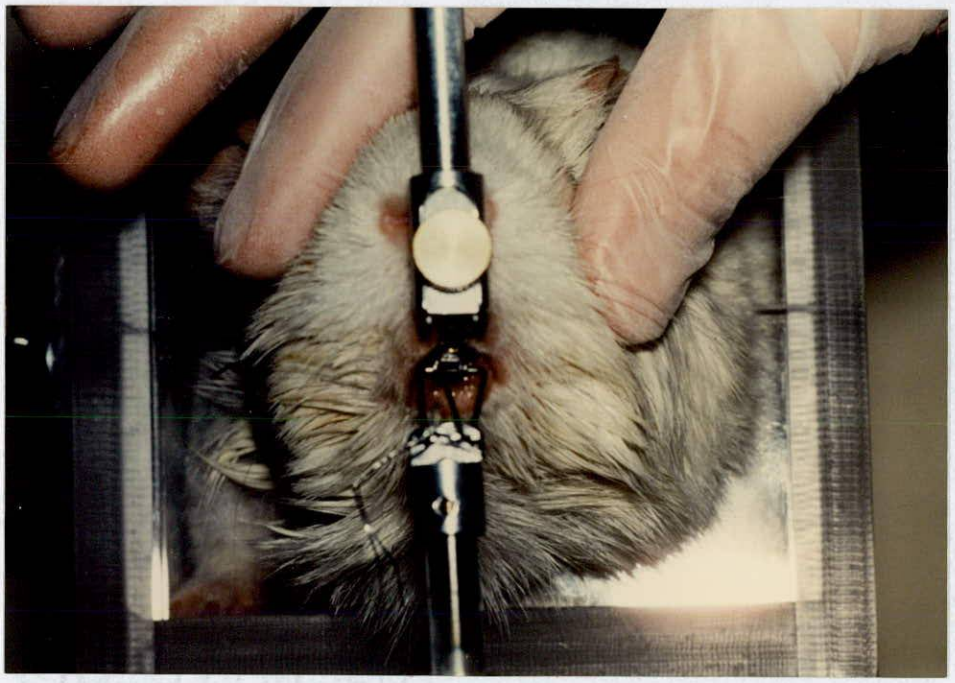


FIGURE 20

experimental animal after it was attached to the upper post and to the CPM device (Figure 21). The posterior part of the floor of the box had some small openings to allow drainage of excrements (Figure 22). Therefore, it was easy to keep the animal dry and avoid developing of skin lesions. The animals were constantly monitored during both the conditioning period and during the application of CPM. This was necessary to prevent them from injury caused by sudden movements of the head or mandible.

The animals were sacrificed by an overdose of Ketamine 100mg/ml mixed with Rompun R 5mg/Kg intramuscularly. In this case Rompun was used instead of Acepromazine because it provided deeper relaxation. The range of motion was measured again along with the maxillary and mandibular incisor lengths. The thoracic cage was then opened for vascular fixation. The vena cava was sectioned for drainage, and 10% buffered formalin fixative then injected into the left ventricule. The animals were decapitated, the heads skinned and the mandible disarticulated. The condyles were studied macroscopically. The evaluation of the gross appearance was done qualitatively. The total appearance of the right condyle (surgical side) was compared with the appearance of the left condyle (unoperated or control side). The cartilage repair area was examined for surface irregularities, flatness, roughness, color and continuity in the boundary area between the repair tissue and the original cartilage. The heads and mandibles were placed in fixative for two days after which the condyles were removed along with the subjacent portion of the ramus. The specimens were decalcified and paraffin

FIGURE 21: Guinea pig in restraining box:
Lateral window removed

FIGURE 22: Restraining box showing the openings on the floor

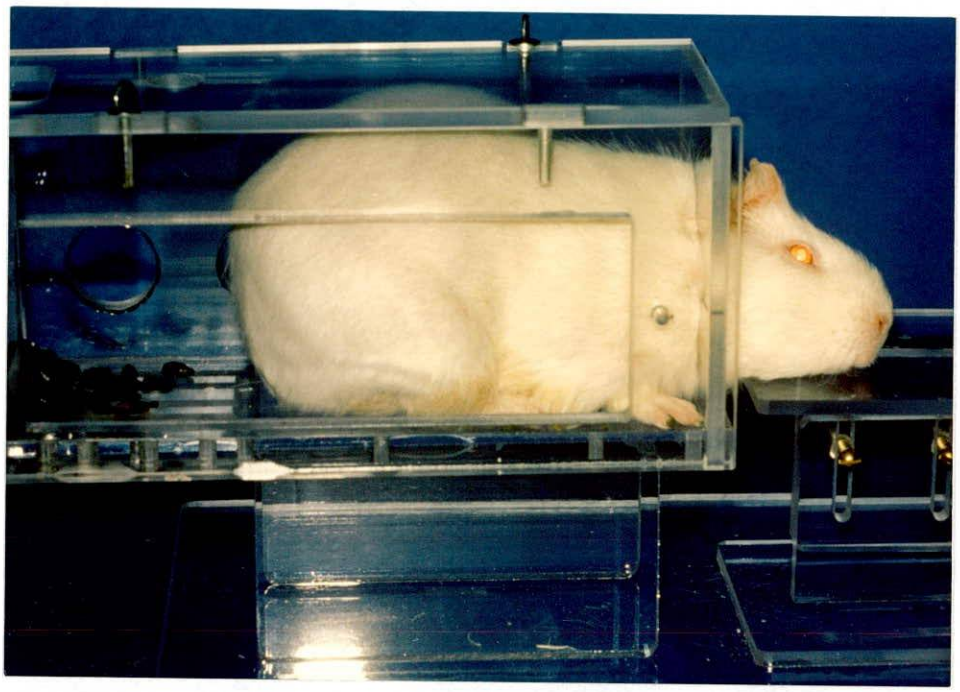


FIGURE 21

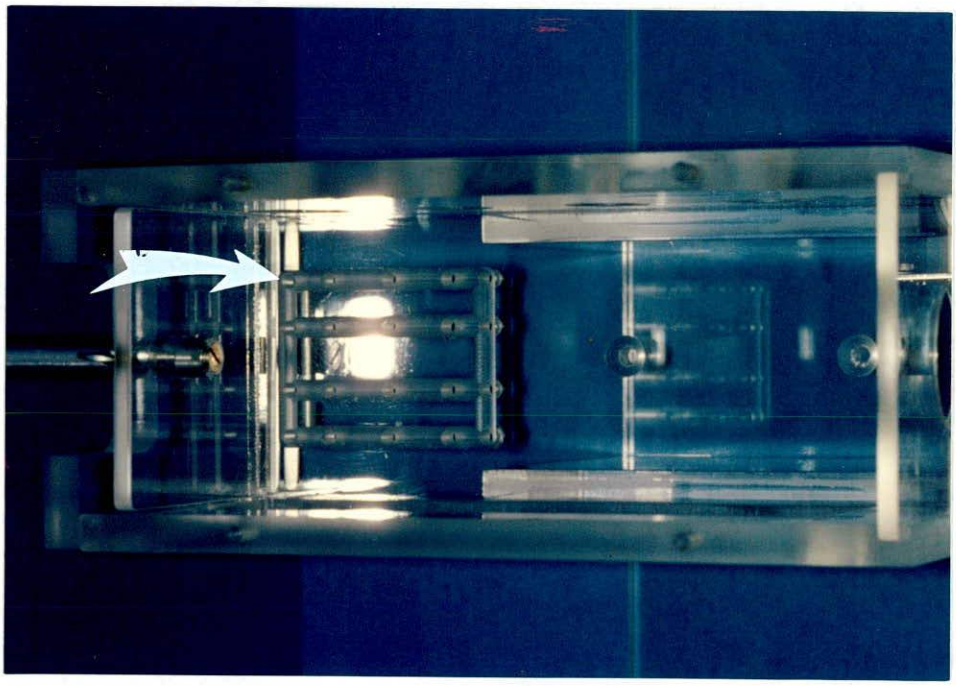


FIGURE 22

embedded. A solution of formic acid 90% and sodium citrate 20% in equal portions was used for decalcification. The specimens required about four weeks to decalcify fully with the solutions changed every two days. The samples were washed in running tap water overnight and processed in a tissue processor (Autotechnicon R) for a cycle of 12 hours. The samples were then soaked in the vacuum infiltrator for one hour and embedded in paraffin blocks. The sections were sliced with stainless steel disposable blades mounted on a conventional microtome adjusted to 6 microns. The mounted sections were stained with hematoxylin-eosin and microscopically examined under ordinary light.

RESULTS

The original experimental disign included four experimental and 7 control animals. During the course of the experiment 5 animals were lost or prematurly sacrificed (Table Nº 2). Two experimentals and three controls (one from the IAM group and two from the IMM group). One experimental animal died immediately after surgery, and the other experimental animal and the animal from the IAM group suffered infection of the surgical side. The IAM control animal had to be sacrificed three days after surgery and the experimental was sacrificed two weeks following surgery. Two animals from the IMM control group also had to be sacrificed two weeks after surgery due to extreme weakness and complete loss of appetite. The remaining two animals in the IAM control group will be referred to as the sham operated control group since the defect was misdirected and was not on the condyle. One of the objectives of this study was to examine the effect of CPM on a surgically created fullthickness defect on the articular cartilage of the mandibular condyle. Unfortunately, none of the three animals to which CPM was applied during the first week after surgery can provide us with a definitive answer to this question. As was mentioned above, one of the experimental animals was involuntarily infected during the surgical procedure, in a second animal the defect was not on the articular cartilage of the condyle. In the remaining experimental animal most of the articular cartilage was damaged during surgery. This animal moved at the instant when the defect was being created, resulting in

Table Nº 2: Final Sample Distribution

	Number of animals per group		
	CPM	IMM	IAM
Initial Sample	4	4	3
Surgical Death	1		
Death due to Weakness		2	
Death due to Infection	1		1
Final Sample	2		2 (Sham)

Table Nº 2

extensive damage to the cartilage. While congnizant of these experimental limitations, worthwhile observations were still possible.

The results of the present study will be presented in three sections: I. Macroscopic Examination, II. Microscopic Examination, and III. Range of Motion Evaluation.

Macroscopic Examination

This evaluation was done qualitatively. In the two animals from the IMM group sacrificed at two weeks, the defects were easily identifiable. There was very little tissue filling the defect. The surface of the defect area looked concave, rough and brownish. The overlying skin wound had healed partially. In the other two animals from the IMM control group sacrificed 6 weeks after surgery the defect area could be identified as well, but in these animals the surface of the newly formed tissue had almost reached the level of the original cartilage, and the contour of the condyle was nearly restored. However, the repair tissue still had a rough and brownish appearance. In one of these animals the repair area had a better macroscopic appearance and appeared to be covered with a translucent tissue. In the sham operated control animals, there was no apparent change in the articular cartilage of the right condyle, and it resembled the left or non-operated condyle. In the experimental animal sacrificed two weeks after surgery the skin wound had partially healed. There was a marked concavity in the center of the condyle and the defect looked completely empty. Of the two experimental animals

sacrificed after 6 weeks, in the one that the defect was done behind the condyle, the repair tissue had incompletely filled the defect and looked brownish and rough.

With regard to the cartilage surrounding the defect, this was intact in all of the previously described animals. In the experimental animal that moved during surgery, the condyle itself appeared greatly changed, and the portion of the mandibular ramus behind the condyle had increased in size and could not be distinguished from the condyle itself. The surface was very rough and irregular. This was the only animal in which the operated (right) side had a totally different appearance from that of the non-operated (left) side. The right condyle looked brownish and about three times bigger than the left condyle. There was no similarity between the right and the left condyles. This experimental specimen demonstrated the poorest macroscopic appearance associated with a very irregular surface with subsided and elevated areas and loss of the original surface. In all the animals sacrificed at 6 weeks, the skin wounds were well healed.

Microscopic Examination

The histologic appearance was also evaluated qualitatively. In the IMM control animals sacrificed two weeks after surgery, the defects were only partially filled with new tissue. The histologic appearance was very similar in both animals. The regenerated tissue was depressed in relation to the adjacent cartilage. The repair consisted of some form of scar comprising

a dense fibrous connective tissue. It was not completely attached to the surface of the bone, but showed proliferation of bundles of collagenous fibers at the periphery of the defect which actually extended into the former medullary cancellous area of the condyle having continuity with the stroma of the bone marrow. Scar tissue attachment was thereby made. The repair tissue was attached as well to the original cartilage around the lateral edges of the defect (Figure 23). In the two IMM control animals sacrificed 6 weeks after surgery, the defects were almost completely filled but each had a different histologic appearance. In one of the two animals, the repair resembled scar, fibrous connective tissue, which appeared to be attached to both the underlying osseous plate by the collagenous fibers of the scar tissue extending into the precollagenous fibers of the bone marrow, and to the original cartilage by dense fibrous connective tissue. In this animal, endochondral bone formation was found to the right side of the defect (Figures 24, 25 and 26). In the other animal, it was of surprise to find new mature cartilage, almost indistinguishable from the original cartilage, filling the defect. There was also regeneration of the capsular layer. Although the repair tissue was not entirely attached to the bone, there were some attempts of bonding between the newly formed cartilage and the base of the defect (Figures 27 and 28). In both animals there was proliferation of precollagenous fibers in the marrow spaces around the defect. With respect to the sham operated control group there was no evidence of damage or change in the articular cartilage. The condyles were considered normal. In the experimental animal sacrificed at two weeks after surgery, the histologic

FIGURE 23: Histologic section from the right condyle of one of the animals of the IMM control group: two weeks after surgery. Defect partially regenerated with dense fibrous connective tissue.

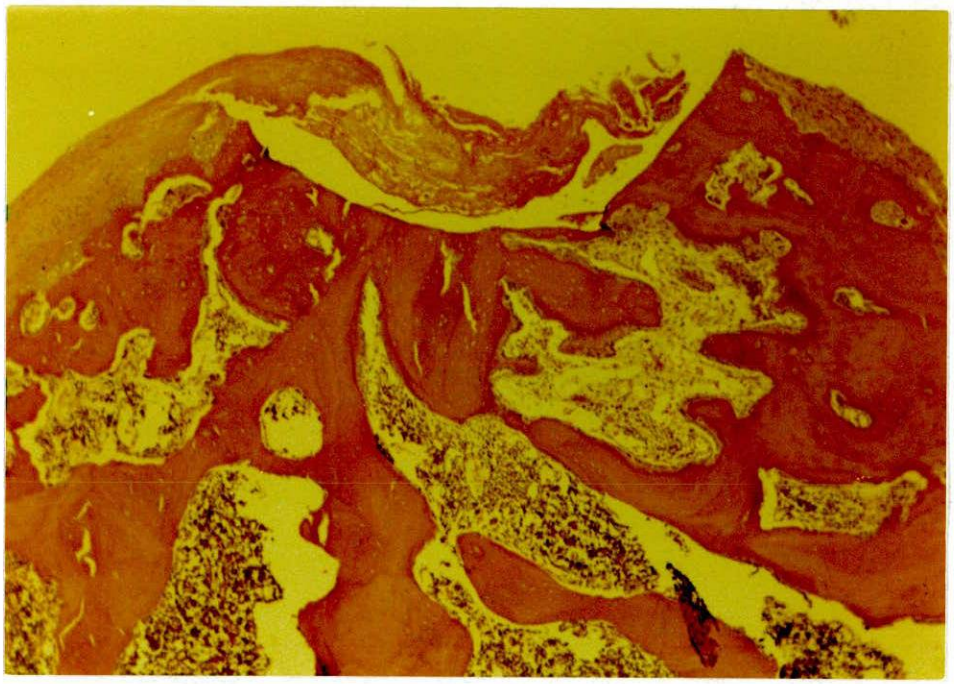


FIGURE 23

FIGURE 24: Histologic section from one of the animals of the IMM control group: six weeks after surgery. Defect completely regenerated with dense fibrous connective tissue.

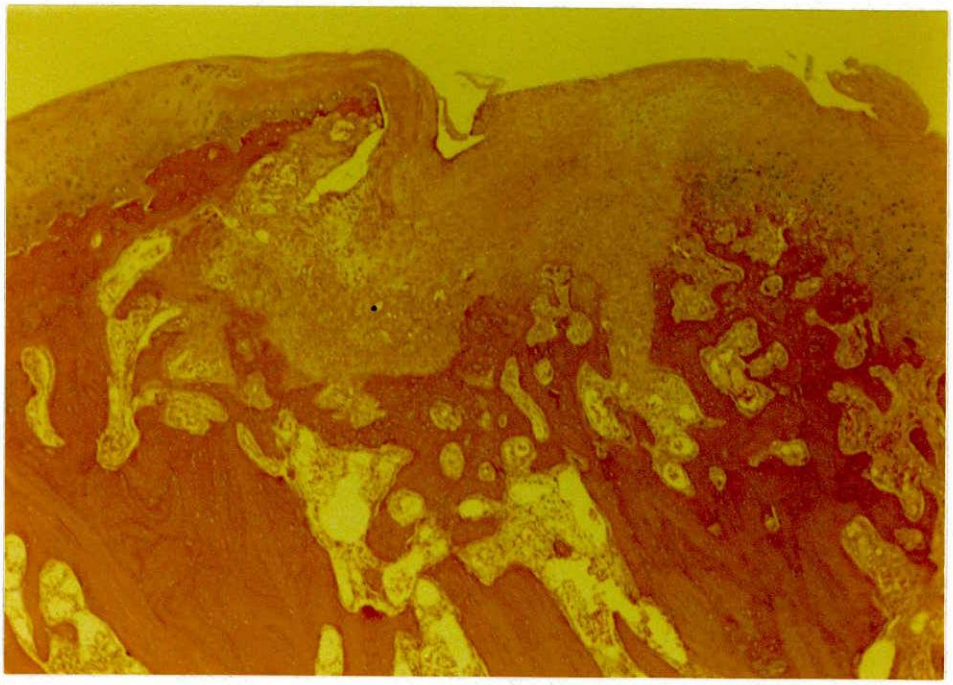


FIGURE 24

FIGURE 25: Histologic section from the right condyle of one of the animals of the IMM control group (6 weeks after surgery). Higher magnification of the articular cartilage to the right side of the defect. Note the loss of the normal delimitation between cartilage and bone.

FIGURE 26: Histologic section from the right condyle of one of the animals of the IMM control group. Higher magnification of the articular cartilage to the left side of the defect. Note the distinctive interphase between the articular cartilage and the underlying bone.

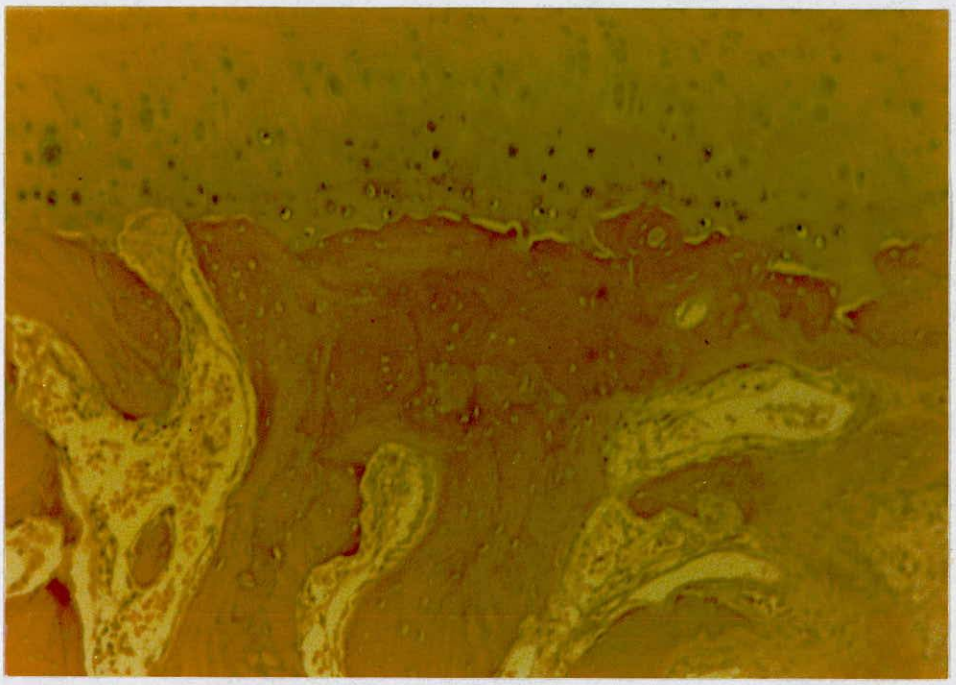


FIGURE 25

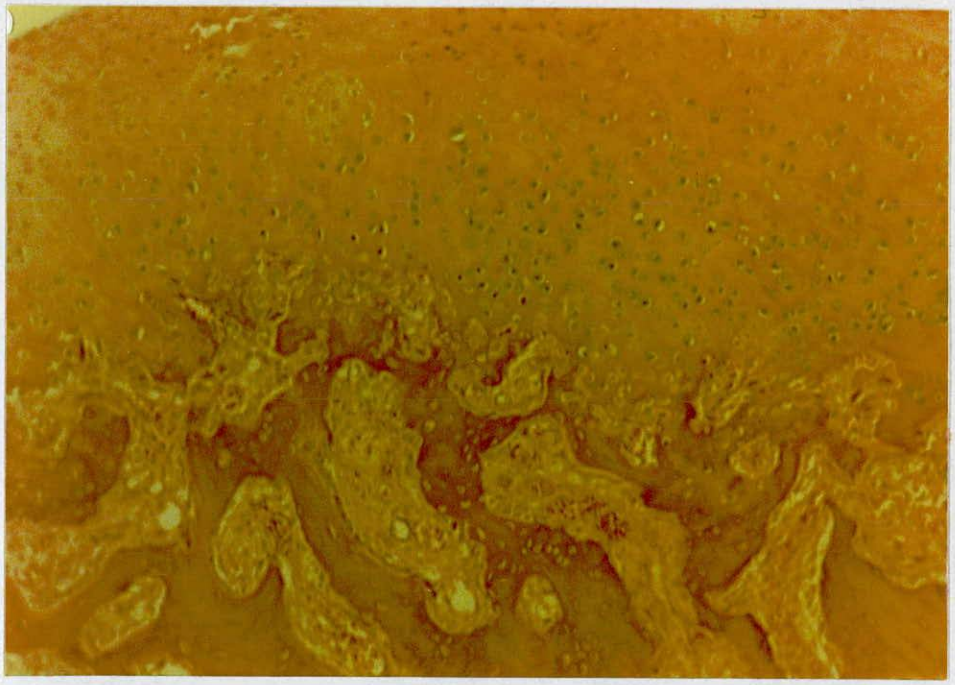


FIGURE 26

FIGURE 27: Histologic section from the right condyle of one of the animals of the IMM control group: six weeks after surgery. Defect completely regenerated with a cartilage-like tissue.

FIGURE 28: Histologic section from the right condyle of one of the animals of the IMM control group: six weeks after surgery. Defect completely regenerated with a cartilage-like tissue. Higher magnification.

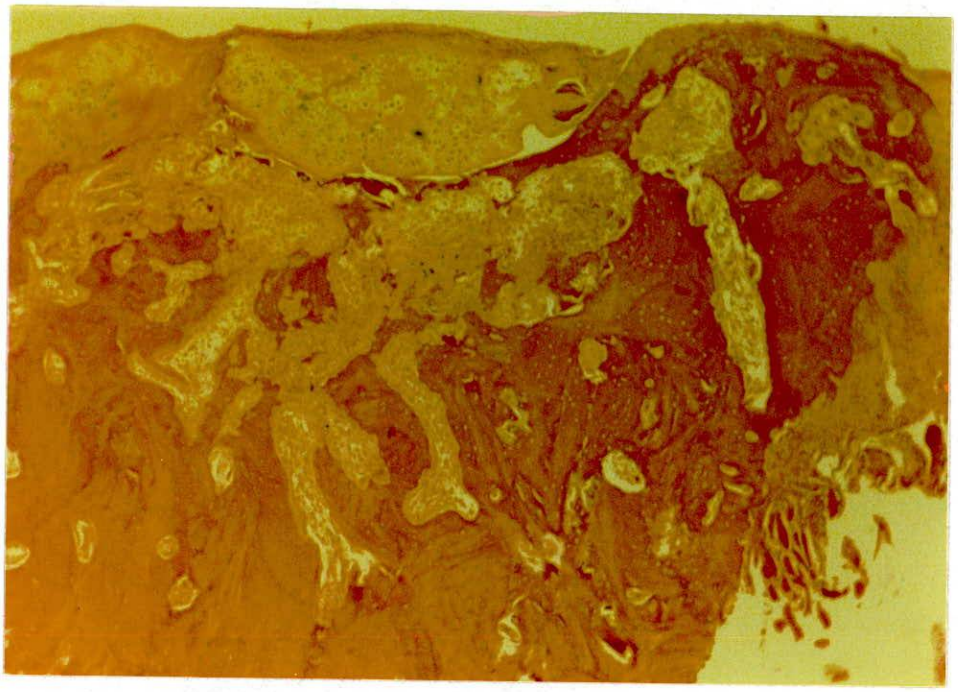


FIGURE 27

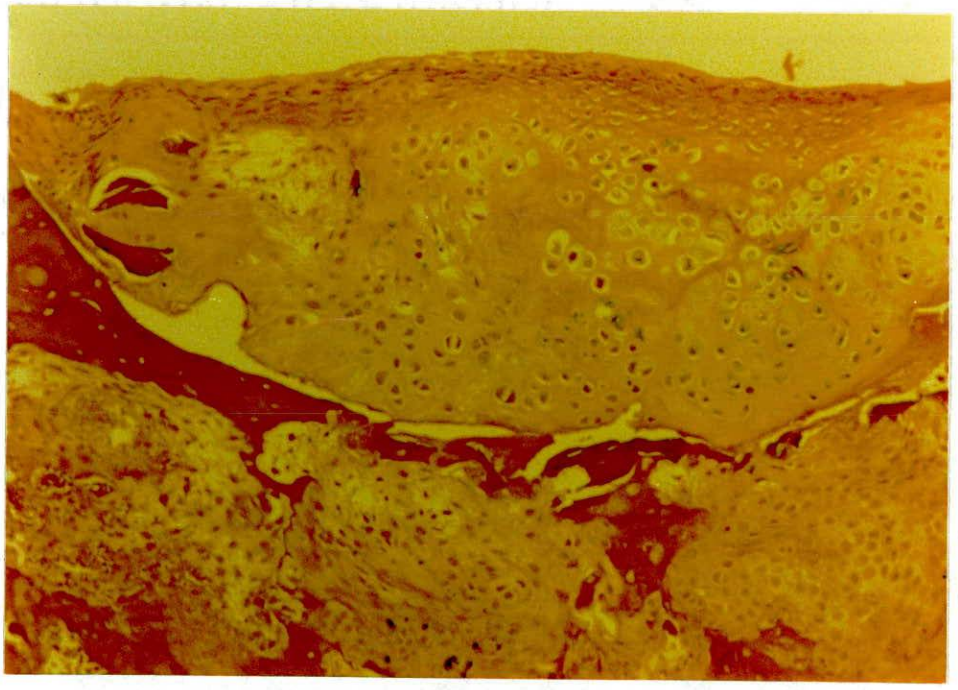


FIGURE 28

appearance confirmed the macroscopic findings. The defect was empty with no apparent attempt for regeneration. There was very little proliferation of new precollagenous fibers in the marrow spaces surrounding the defect. The original cartilage surrounding the defect appeared intact, despite the fact that this animal suffered infection of the surgical side (Figure 29). In the experimental animal sacrificed at 6 weeks after surgery in which the defect was behind the condyle, the regenerated tissue consisted of immature dense fibrous connective tissue. It showed partial adherence to the preexisting bone and was not filling the defect entirely. The other experimental animal sacrificed six weeks after surgery was the one that moved during surgery. As a consequence, the articular cartilage along with the capsular layer were lost. New cartilage did not regenerate. The response of the condyle to this type of injury consisted of bone callus formation and osteophytes. Very active intramembranous bone formation was observed. The articulating surface of the condyle as well as the most superior portion of the ramus behind the condyle were replaced by an exuberant amount of new fine cancellous bone (Figures 30 and 31). It was also noted that the most active or intense endochondral bone replacement was found around the only, and very small, remanent of articular cartilage present on the condyle (Figures 32 and 33).

Rest lines analogous to the growth rings of a tree were observed in the dense areas of compact bone present in the specimens. It is suggested that these lines be used as natural markers (Figure 34).

Osteophyte proliferation of a different nature was also observed in

FIGURE 29: Histologic section from the right condyle of the experimental animal sacrificed two weeks after surgery. Defect empty.

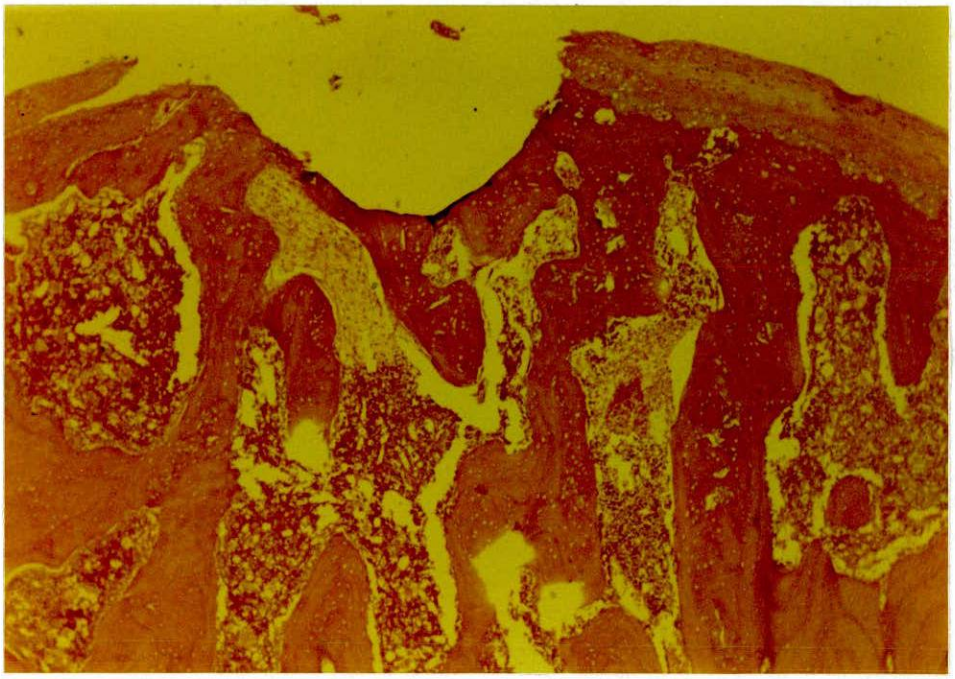


FIGURE 29

FIGURE 30: Histologic section from the right condyle of the experimental animal that showed intense bony proliferative response. Superficial layer: newly formed bone.

FIGURE 31: Histologic section from the right condyle of the experimental animal that showed intense bony proliferative response. Deeper layer: original bone.

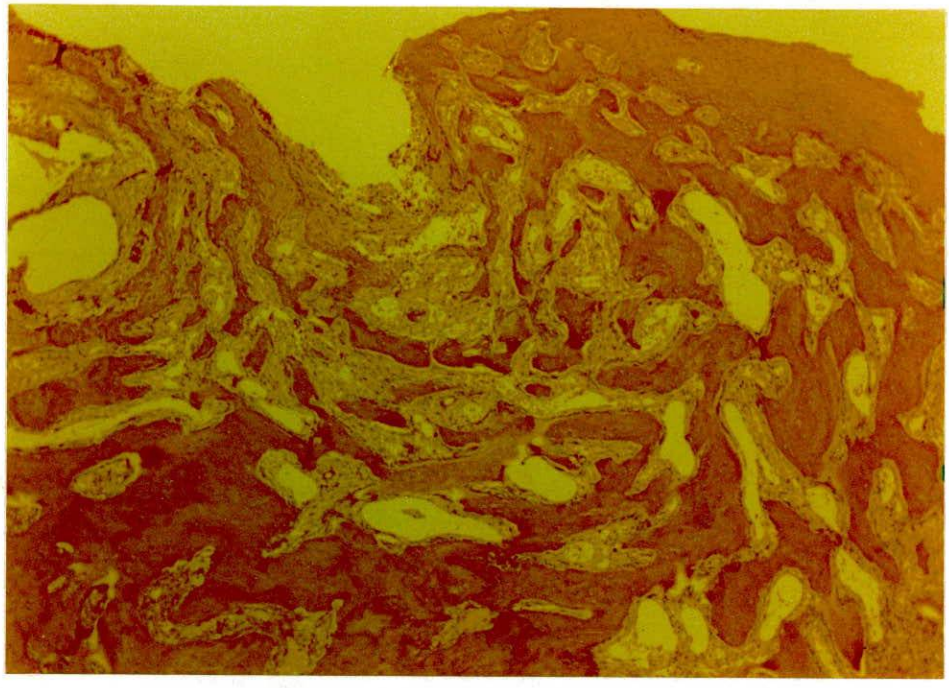


FIGURE 30

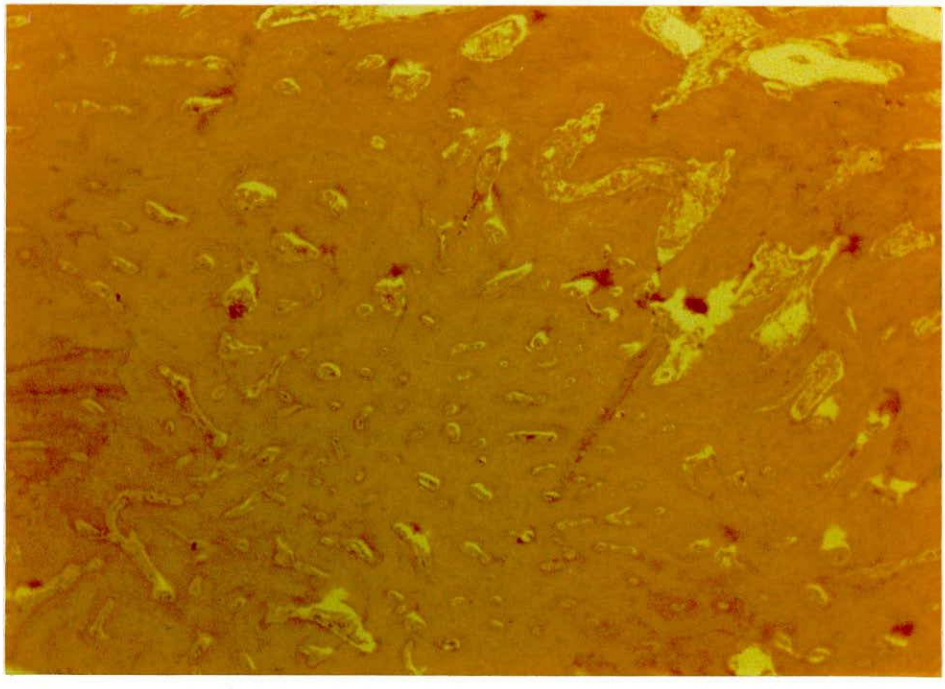


FIGURE 31

FIGURE 32: Histologic section from the right condyle of the experimental animal that showed the intense bony proliferative response. Superficial layer: newly formed bone underneath the only remanent of cartilage.

FIGURE 33: Histologic section from the right condyle of the experimental animal that showed the intense bony proliferative response. Deeper layer: original bone.

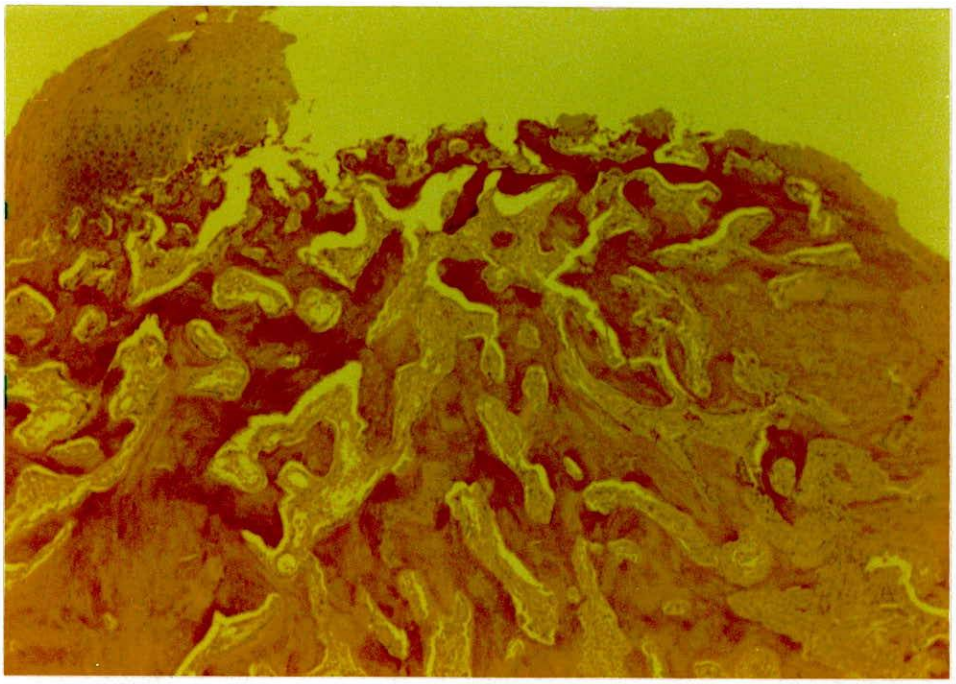


FIGURE 32

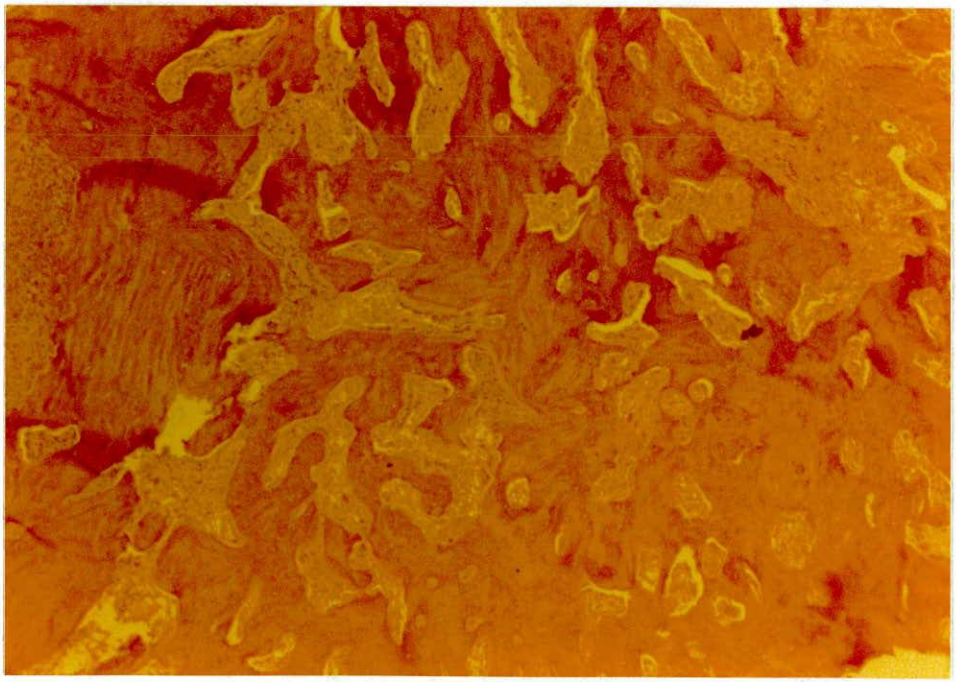


FIGURE 33

FIGURE 34: Histologic section showing the rest lines.

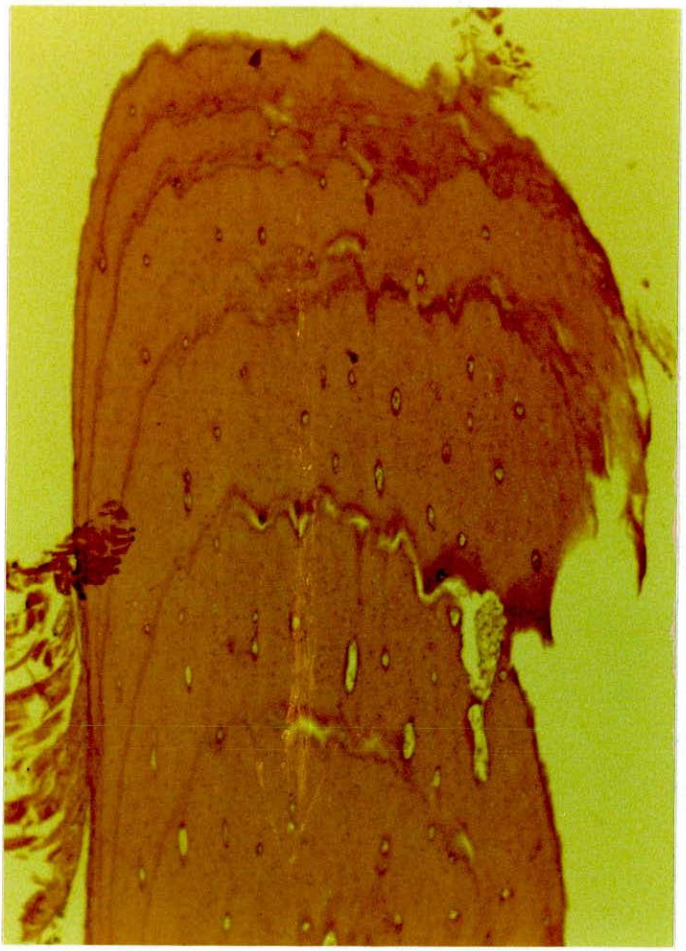


FIGURE 34

some of the specimens. In the guinea pig, the condyle is seated atop a very thin mandibular ramus. In antero-posterior view the condyle appears to be supported by this thin mandibular ramus only in its lateral portion. Thus, the medial half of the condyle lacks bony support from the ramus. Interestingly, the osteophytes were found on this side of the condyle, opposite to the articulating surface. They were seen in the right condyles (operated side) only (figures 35 and 36).

When comparing the thickness of the articular cartilage of the non-operated sides (left condyles) among the animals of both control groups and the experimental animals, it was found that on average the articular cartilage of the experimental group was 320 microns whereas the control group averaged 205 microns (Table Nº 3). This difference represented an increase of 64% in articular cartilage thickness among the experimental animals (Figures 37 and 38).

Range of Motion Evaluation

The changes in the amount of maximun opening are shown in tables Nº4 and Nº 5. Teeth length accounts for the sum of the maxillary and mandibular incisor lengths at the time of the maximum incisal opening measurements. Three of the seven control animals showed a decrease in the amount of maximun opening, whereas none of the three experimental animals had a decrease in their range of motion. In the control groups the

final range of motion was between -3 mm and +5 mm, compared to the presurgical maximum incisal opening, while in the experimental group was between +2 mm and +11 mm. Of the two animals involuntarily infected, the control animal showed -5 mm, while the experimental animal had +2 mm in range of motion. In general, the experimental group showed an average increase in maximun opening of 5.7 mm whereas the control group showed an average of 2.8 mm increase in range of motion.

FIGURE 35: Histologic section showing the osteophyte proliferation in the right condyles (operated sides).

FIGURE 36: Histologic section showing the absence of osteophytes in the left condyles (non-operated sides).

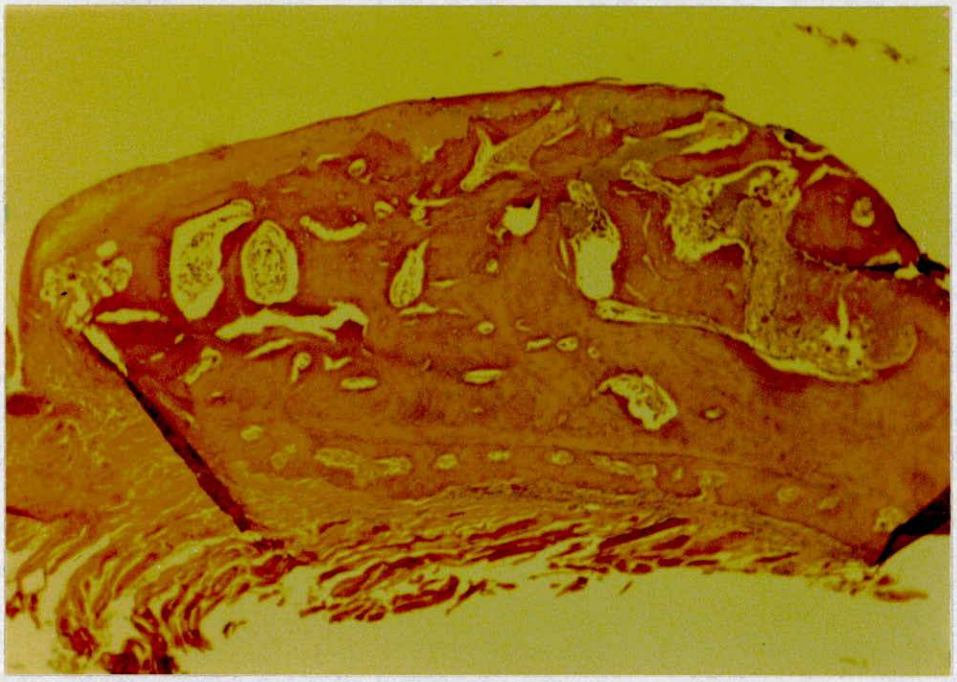


FIGURE 35

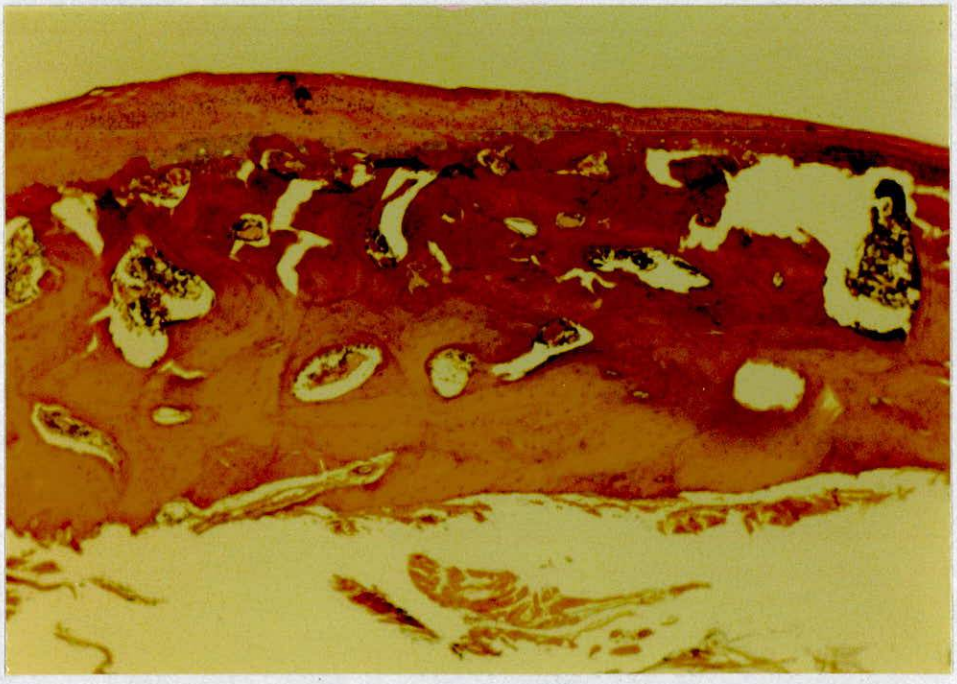


FIGURE 36

Table Nº 3: Thickness of the Articular Cartilage in the Non-operated Condyles (Control Side).

Group	Specimen	Articular Cartilage Thickness
IMM	Nº 1	240 microns
IMM	Nº 2	90 microns
IMM	Nº 3	270 microns
IMM	Nº 7	210 microns
IAM	Nº 10	150 microns
IAM	Nº 11	270 microns
EXPERIMENTAI	Nº 4	270 microns
EXPERIMENTAL	Nº 5	360 microns
EXPERIMENTAL	Nº 9	330 microns

Table Nº 3

FIGURE 37: Histologic section from the left condyle of one of the experimental animals. Average thickness in articular cartilage found within the experimental animals.

FIGURE 38: Histologic section from the left condyle of one of the control animals. Average thickness in articular cartilage found within the control animals.

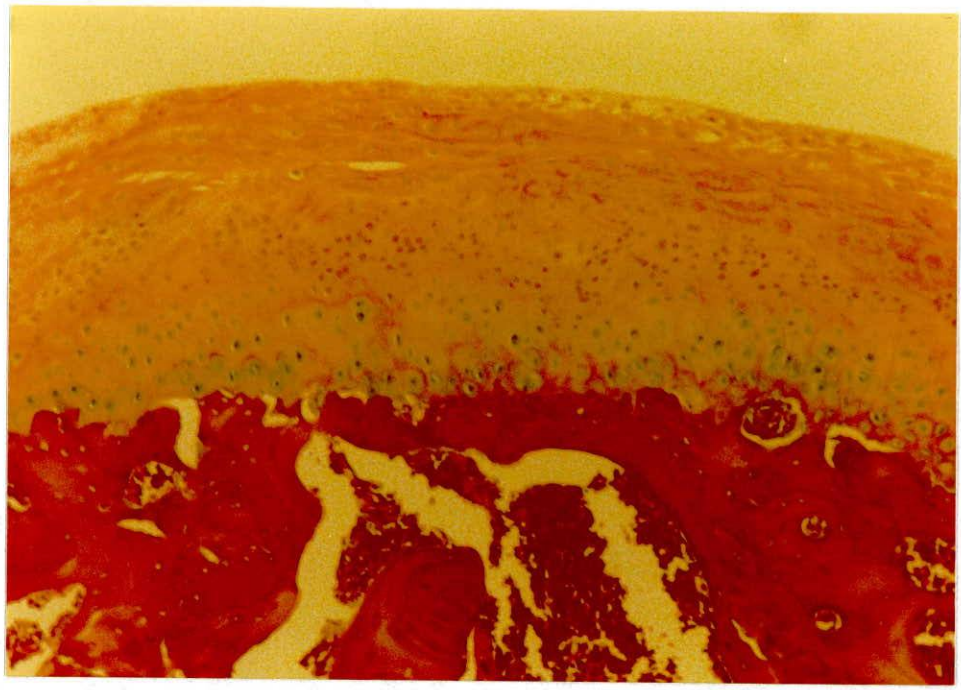


FIGURE 37

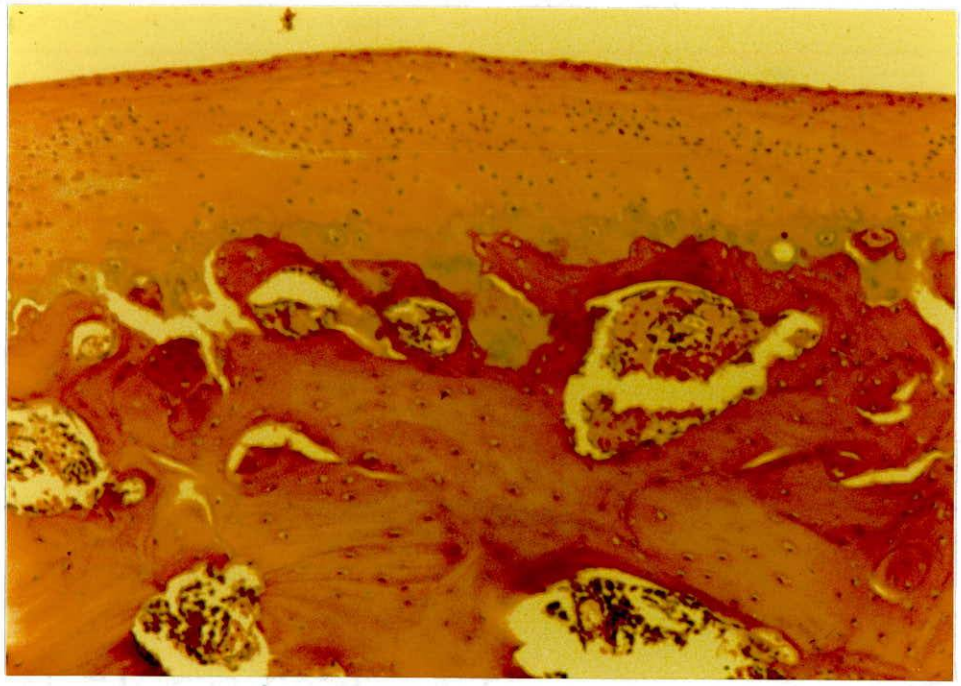


FIGURE 38

Table Nº 4: Numerical Data Recorded to evaluate the Range of Motion.

Group	Specimen Number	Time after surgery at which the animal was sacrificed	Maximun Opening		Teeth Length	
			Pre-surgical	Before sacrificed	Pre-surgical	Before sacrificed
IMM	Nº 2	2 weeks	17 mm	11 mm	16 mm	19 mm
IMM	Nº 7	2 weeks	17 mm	15 mm	16 mm	17 mm
IMM	Nº 1	6 weeks	20 mm	24 mm	16 mm	17 mm
IMM	Nº 3	6 weeks	18 mm	17 mm	17 mm	21 mm
IAM	Nº 8	3 days	22 mm	17 mm	15 mm	15 mm
Sham-Operated	Nº 10	6 weeks	14 mm	15 mm	18 mm	19 mm
Sham-Operated	Nº 11	6 weeks	18 mm	19 mm	18 mm	18 mm
Experimental	Nº 4	2 weeks	16 mm	17 mm	15 mm	16 mm
Experimental	Nº 5	6 weeks	17 mm	22 mm	15 mm	14 mm
Experimental	Nº 9	6 weeks	23 mm	29 mm	15 mm	20 mm

Table Nº 4

Table Nº 5: Summary of the actual increase or decrease occurred in the maximum opening, teeth length, and range of motion at the end of the experiment.

Group	Specimen number	Suplementation provided	Net change in Maximum opening	Net change in teeth length	Final range of Motion
IMM	Nº 2	Yes	-6 mm	+3 mm	-3 mm
IMM	Nº 7	Yes	-2 mm	+1 mm	-1 mm
IMM	Nº 1	Yes	+4 mm	+1 mm	+5 mm
IMM	Nº 3	Yes	-1 mm	+4 mm	+3 mm
IAM	Nº 8	Yes	-5 mm	0 mm	-5 mm
Sham-operated	Nº10	None	+1 mm	+1 mm	+2 mm
Sham-operated	Nº11	Yes	+1 mm	0 mm	+1 mm
Experimental	Nº 4	Yes	+1 mm	+1 mm	+2 mm
Experimental	Nº 5	Yes	+5 mm	-1 mm	+4 mm
Experimental	Nº 9	Yes	+6 mm	+5 mm	+11 mm

Table Nº 5

DISCUSSION

The use of different various parameters for joint evaluation, including range of motion, gross appearance and histological examination, has been demonstrated to be adequate to asses the repair of articular cartilage defects. The macroscopic surface congruity is one of the important factors affecting the repair tissue and the surrounding normal articular cartilage. Macroscopic appearance has been regarded as clinically important. The other two parameters represent important additional evidence of the healing characteristics of the repair tissue and of the integrity within the joint.[93]

In previous investigations, it has been observed that there are no apparent differences between an immature and a mature animal with regard to the effect of CPM on articular cartilage repair. Internal Derangements of the TMJ are more common among the adult human population. For this reason and to insure uniformity in the present study, adult guinea pigs of about 20 months of age were chosen as the animal model for this project. The utilization of guinea pigs as the experimental animal model also appeared to have resembled some aspects of the clinical situation. Guinea pigs are easily stressed and stress has been mentioned as one of the main causes for developing internal derangements of the TMJ in humans. In addition, patients suffering from TMJ disorders are usually prescribed some form of tranquilizers and this study involved the administration of Valium. The experimental animals required large amounts of this drug to remain in the

CPM apparatus for up to 7 hours per day. This repeated tranquilization had a strong effect on both their behaviour and physical conditions. As it was mentioned before, guinea pigs do not adapt easily to changes, and are likely to become overstressed by them. This project involved major variations in some of their basic life style habits, the food was different and they were not allowed to eat or drink during an 8 hour period each day. The application of CPM demanded physical restriction of the animal during most of the daylight hours. In order to evaluate the effects of long periods of restraining and the Valium injections might have had on the natural healing process, two types of control groups were necessary. One control group was restrained for the same period of time that the experimental animals remained in the CPM device and was administered the same amount of Valium R that was given to the experimental group. These animals also served as an immobilization control group. The other control (IAM) group was allowed normal cage activity from the first day after surgery, and no Valium R was administered to this group. It was expected to find better repair in the IAM group than in the Valium induced immobilization group. Unfortunately one of the animals in the IAM group suffered infection of the surgical side and had to be prematurily sacrificed three days after surgery. To further complicate analysis of the results the other two animals could not be used for comparison with regard to cartilage regeneration because the defects were not made on the condyles. These last two animals are referred to as the sham-operated control group, although it is understood that they can not be strictly considered as so, since the post-surgical management was different from the

other two groups.

The first animal to which CPM was applied was not supplemented in any way. Although a continuous weight loss was observed, it was not realized at the time that the animal had completely stopped eating and drinking. It was very difficult to keep the animal on CPM during the first two days, but then it progressively became much easier, and the animal required less Valium R (never more than 15 cc). However, after the 5 days of CPM this animal was very weak, and it was very difficult to save its life. For the other two animals it was decided to supplement their total fluid requirement (20 cc twice a day given before and after the hours of CPM), and they were continuously fed during the night and early in the morning. This time the five days of CPM were a "nightmare". The animals were very "wild", and seemed never to have enough Valium. (These animals required up to 20 cc of Valium R). However, they recovered much easier than the first one. A possible alternative feeding schedule would be to supplement the animals with 20 cc of fluids daily given only after the CPM hours. The animals could then be fed with 3 cc of Nutrical and some of the cereal food and apple sauce twice in the afternoon. This method would make it easier to apply the CPM and at the same time the animals would not become nutritionally debilitated. CPM was applied for only 5 days because the animals were extremely weak and were developing ulcers on their lips due to the sling divice. The latter device was improvised after they broke the upper attachment.

It is apparent that, in all, this study was found to be procedurally difficult, with many problems encountered with regard to animal behavior

and physical reactions. Subsequent studies will need to take these into account, as explained in the previous paragraphs.

It was intended to sacrifice all the animals 6 weeks after surgery to allow for appropiate cartilage repair. However, as previously mentioned, some of the animals were sacrificed before that time due to extreme weight loss or illness. It seems that the guinea pigs have a very weak instinct for survival, and their response to stressful situations appears reduced to complete loss of appetite. This makes the animal more susceptible to depression, which subsequently places it in a vicious cycle from which it can't recover. At autopsy the most striking gross lesions in these guinea pigs were fatty livers, an empty stomach and abundant fat depots. These are common findings in guinea pigs which have died of ketosis.[101]

Although many changes occur following injury to articular cartilage, this investigation was purposely simplified and narrowed to probe two questions: 1) Will CPM positively influence the repair of a full-thickness defect in the articular cartilage in the condyle of the TMJ ? And 2) Will the range of motion achieved by the CPM group be better than that of the control groups? Previous studies have demonstrated the beneficial effects of CPM in the regeneration of articular cartilage defects in the rabbit's knee.[87, 93] It is not possible in this study to evaluate the effects of CPM in the healing of osteochondral defects in the condyle of the TMJ. Nevertheless, some worthwhile results were obtained, and the methodology that was developed will serve as start for future research in this field. It has been reported that the normal function of the synovial membrane is impaired by

immobilization.[53] Some investigators have shown the protective effect of CPM on living articular cartilage in cases of infected joints.[63, 82] It was not the primary intention of this project to test the influence of CPM on infections of the TMJ. However, the protective effects of CPM in the articular cartilage against the harmful effects of infection were observed when two of the animals, one from the CPM group and one from the IAM group were involuntarily infected. Motion is known to enhance complete and continuing drainage of a joint. It increases the diffusion of the nutrients of the synovial fluid into the matrix of the articular cartilage and enhances the clearance of lysosomal enzymes as well as purulent exudate from the synovial cavity. Septic arthritis is usually devastatingly destructive to the articular cartilage. Lysosomal enzymes are capable of both collagenolytic activity and proteoglycan degradation. It has been found that septic arthritis can cause complete loss of the articular cartilage in three weeks. Although there was no sign of regeneration in the defect of the experimental animal, there was no detectable damage or abnormality in the original cartilage (Figure 29). Futhermore, the control animal had to be sacrificed three days after surgery due to an extreme swelling in the retrobulbar area, corneal edema and ulceration. On the other hand, the acute phase of infection of the experimental animal was mild in comparison to that experienced by the control and by the time the animal was sacrificed two weeks after surgery the infection had already subsided.

More residual motion has also been reported as a characteristic benefit of the implementation of CPM in cases of septic arthritis because it

prevents the formation of synovial adhesions. At the time the animals were sacrificed the control showed a decrease of 5 mm in its maximum incisal opening while the experimental showed an increase of 2 mm in its motion range. In general, CPM appeared to be more effective in producing better joint mobility. The experimental animals showed a trend toward better range of motion. The two animals from the IMM (Valium induced) control group sacrificed two weeks after surgery where the ones most strongly affected by the Valium and even with small doses they would remain completely sedated, therefore immobilized for 7 hours or more. These animals showed the worst range of motion among all the non-infected animals. These results parallel other studies in that subjects (animals or patients) who are immobilized develop more synovial adhesions and consequently manifest more difficulties in achieving their initial range of motion. It should also be noted that in the experimental animal that suffered loss of articular cartilage and exhibited the intense bony proliferative response, some form of ankylosis, either bony or fibrous, should have been expected. Ankylosis would have produced some limitation in the amount of maximum opening. Instead, this animal had an increase of 4 mm in its range of motion. These results suggest that continuous passive motion is more effective in helping the animals regain motion than are intermittent active motion or immobilization (Tables Nº 4 and Nº 5).

In addition the regulatory mechanism of the condylar cartilage upon the growth of the subjacent bone in the condyle was observed in the experimental animal that lost its articular cartilage. Once the condyle loses

its condylar cartilage it appears that there is no control in the amount of bone formed, and it can develop to an unexpected extent (Figures 30, 31, 32 and 33). In one of the control animals from the IMM group sacrificed 6 weeks after surgery there was more endochondral bone formation to the right side of the defect, this served to demonstrate that there was active condylar growth in that part of the condyle. Interestingly, microscopic examination revealed that the normal delimitation found between the articular cartilage and the underlying bone was lost in that side of the condyle. There appears to be no distinctive interphase betweeen the two layers. The new endochondral bone forming was intermixed with the condylar cartilage and resembled endochondral bone growth characteristic of long bones (Figures 24, 25 and 26).

The microscopic findings of the present experimental investigation demonstrated that it is possible to obtain repair of a full-thickness defect in the condyle of the TMJ with a cartilage-like tissue in an adult animal (Figure 27 and 28). Whether or not post-operative CPM can improve the quality of the regeneration requires further investigation. The fact that fibrous connective tissue was found filling the defects in the other animals is consistent with the findings of a previous investigation.[41] It was reported in this study that hyaline cartilage was filling the defects in only a third of the animals operated, whereas the defect area of the remainder had regenerated with fibrous connective tissue. On the other hand, other studies described total restoration of the defects with hyaline-like cartilage in all animals.[18, 62] It has been demonstrated that an adult articular cartilage

does react to increased functioning of the joint by increasing the amount of matrix production and the number of chondroblasts.[80] Thicker articular cartilage found in the unoperated side of the experimental animals suggests that post-surgical management with CPM increases chondroblast activity (Figures 37 and 38). The possibility that the animals would have used the left side as the preferred side of mastication and consequently may have increased function on the left side was considered. However, since the right TMJ was operated in all animals this variable was rejected as the cause for the increase in condylar cartilage thickness in the left side of the experimental animals. It has also been reported that animals treated with CPM show more new bone formation than those immobilized.[93] The large amount of intramembranous bone formed in one of the experimental animals in the present study could also have been triggered by the implementation of CPM after surgery (Figures 30, 31, 32 and 33). Osteophyte formation was observed in some of the specimens and can be interpreted as part of the response of the condyle to injury, since it was only found on the operated condyles (right side) (Figures 35 and 36). The present investigation also demonstrated that it is possible to provide the TMJ with the benefits of early motion after surgery without the threat of interference to the healing connective tissues. In all the animals sacrificed at 6 weeks, the skin wounds were well healed. Thus, intermittent active motion, induced immobilization or continuous passive motion did not interfere with soft tissue healing of the operative incisions.

Previous studies have focused on the effect of continuous passive

motion on articular cartilages which are primary cartilages in embryonic origin and which have very limited contribution to bone growth. Post-natal growth of long bones occurs as a result of interstitial growth of the cartilage of the epiphyseal growth plate and not by growth of articular cartilage.[11] The main concern in previous studies has been the restoration of the joint surface and ultimately to establish normal joint function.

The present study provides new information concerning the response of the mandibular condyle to a physiologic increase in functioning. The condylar cartilage has its embryologic origin as a secondary cartilage.[13, 24, 56, 57, 97] The mandibular condylar cartilage is also unique because it has a dual function. It serves as an articular surface and has an important role in the growth of the condyle and in the normal mandibular development. It is generally accepted that intrinsic mechanisms are primarily responsible for controlling growth of primary cartilages such as the epiphysis,[58] although it is accepted that they also appear to be subject to the influence of general extrinsic factors.[33] Long bone growth is achieved by cell division of differentiated chondroblasts within the epiphyseal plate.[11,33] When long bones are transplanted in vivo into a nonfunctional environment they can achive growth levels comparable to that of the bone in situ.[58] On the other hand, when the mandibular condyle is transplanted into a nonfunctional environment the amount of growth does not approach that of the condyle in situ.[58] Most researchers agree that the condylar cartilage lacks the independent growth potential manifested by epiphyseal cartilages.[33, 58]

Biologically, secondary cartilages such as the condylar cartilage behave completely different from primary cartilages like the epiphysis.[33] The condylar cartilage responds to local biomechanical stimuli to a much greater degree than epiphyseal cartilages.[3, 33] Condylar growth results from division of undifferentiated cells.[33] These cells differentiate into either chondroblasts or osteoblasts in response to local extrinsic factors.[33] For example, in growing rats, functional appliances such as the postural hyperpropulsor, Frankel, L.S.U. Activator, Bionator, and even Class II elastics have been shown to have an effect on the mandibular condyle.[33] It has been reported that these appliances produce significant decrease of intracellular Ca++ concentration in skeletoblasts and prechondroblasts as well as significant increases of intracellular Na+ concentration in condylar cartilage prechondroblasts.[33] These factors are associated with an increase in cell division, chondroblast differentiation and cartilage growth rate.[33] This type of biomechanically induced ability for modification appears to be totally absent in primary cartilages.[33] Tensile forces of similar or higher magnitude do not produce detectable changes of intracellular Na+ concentration in epiphyseal plate chondroblasts.[33] In further studies secondary cartilage was developed in a number of articulations in the skull of embryonic chicks.[58] Interestingly, the cartilage was always developed in membranous bones and only at articulations that were mobile or at articulations in which the anatomy of the musculature produced conditions of strain during the developmental stages.[58] Meanwhile, in the embryos that

were grafted and paralized there was no cartilage formation and multipotential cells which normally form cartilage instead produced bone.[58] The embryologic origin of the condylar cartilage can be used to understand its high dependence on local factors. The articular and proliferative zones of the condyle have been regarded as being derived from periosteum.[24, 57, 58] The change from the normal osteogenic function of periosteum to one of chondrogenesis has been explained as a result of the evolutionary development of an articular condylar process in the mandible of mammals along with the altered functional requirements of the periosteum covering the articular joint surface.[24, 58] The dependence of the condylar cartilage on functional activity of the mandibular joint has been demonstrated in various studies. Within 24 hours of transplantation of the condyle into a non-functional environment the cells of the proliferative zone cease to divide and no longer differentiate into chondroblasts. Three to four days later, the transplants become revascularized and proliferative activity is re-established. Although cell division is restored, the multipotential cells of the proliferative zone differentiate into osteoblasts and not into chondroblasts as in situ.[57] Similar results were obtained by other investigators. After five weeks of intratesticular or intraocular transplantation, the mitotic compartment of the condyle consisted only of skeletoblasts. These skeletoblasts later differentiated exclusively into preosteoblasts and osteoblasts.[33] The condyle also manifests these histologic modifications after resection of the lateral pterygoid muscle.[33] When in a growing rat the condylar cartilage, the superior head of the lateral pterygoid muscle, the

articular disc, and the retrodiscal pad are all resected, and the condylar bone is maintained intact, skeletoblasts originating from the subperiosteal layer multiply, migrate and finally completely cover the resected surface. Following this initial response, if no inflammation has ocurred and if mandibular mobility has been maintained the newly formed skeletoblasts differentiate locally into chondroblasts and form secondary cartilage in the head of the condyle.[33] It is clear then that the influence of the extrinsic mechanical stresses associated with functional activity is on cellular differentiation rather than on proliferative activity.[57, 58] Cell division within the proliferative zone may be linked to some intrinsic genetic program and although it is under the influence of hormonal and humoral factors cell division can operate independently of local regulation including regional biomechanical factors. This ability of the mandibular condyle to respond to variations in the local environment has been utilized to regulate (stimulate or restrain) condylar growth rate and amount. There are innumerable functional and orthopedic appliances capable of modifying condylar cartilage growth.[33] Condylar cartilage growth rate and amount can be increased by using functional appliances that adequately place the mandible in a forward position.[33] In addition, the growth rate and amount of the condylar cartilage can be stimulated as well by the use of intermaxillary intraoral elastics (Class II) placed daily for 14 hours and by appliances such as the Herren-type and L.S.U. Type activator when they are worn for 12 or 18 hours daily and if the molar bite height is 0.4mm or 0.8mm.[33] On the other hand, appliances that produce active retropulsion of

the mandible such as the chin cup, Class III activator and the Frankel III, induce a dramatic decrease in the number of dividing cells in the mandibular condylar cartilage.[33] But, to what extend does some increase or decrease in the growth of the condylar cartilage affect the growth of the whole mandible? Although the condyle does not have total control on the growth of the entire mandible, it is nevertheless necessary for normal mandibular growth.[58] The growth of the mandible at the condylar cartilage is important during the vertical growth of the lower face and enlargement of the ramus.[24, 33, 58, 89] The posterior border of the ramus and the condylar cartilage are two separate regional growth cites. However, their growth is correlated and growth at the posterior border of the ramus keeps pace with any given amount of condylar growth.[24] Condylar growth is not directly responsible for the increase in length of the mandibular body but it does contribute to the overall length of the mandible.[89] The mandibular condyle rests against the articular fossa of the temporal bone at the cranial base, upward and backward growth at the condyle causes a downward and forward shift of the entire mandible.[24, 89, 106] Secondarily, an increase occurs in the subperiosteal ossification rate at the posterior border of the ramus and as a result of these two factors the mandible becomes longer. Downward and forward displacement of the mandible enables the upper and lower teeth and alveolar processes to grow at their free borders.[24, 89] When an increase in ramus height is inhibited, increases in maxillary and mandibular body height are also inhibited.[89]

Mandibular growth does not stop if the condylar cartilage is destroyed.[89] The mandible continues to grow and attains a characteristic

shape. However, it never reaches normal size.[89] Functional appliances influence condylar cartilage growth as well as the growth of the rest of the mandible. Those appliances that increase condylar cartilage growth also produce a supplementary lengthening of the mandible. Those appliances that restrict growth in the condyle also produce a marked decrease in the overall length of the mandible. Close review of the literature indicates that it is not the simple increase or decrease in condylar cartilage thickness or growth that produces the change in the rest of the mandible. It is the increase in the functional demands that are placed upon the whole mandible that produces the increase in its size.

The following are some of the explanations that have been given as the modus operandi of functional appliances. "When a young rat is fitted with a postural hyperpropulsor or similar functional appliances for 10 to 12 hours daily, everything occurs as if the upper dental arch were in a more anterior position than is actually the case. The confrontation between the dental arches gives rise to a deviation signal, which is reduced by an appropiate forward positioning of the lower dental arch through the propulsion of the mandible". It is beleived that the increase in contractile activity of the lateral pterygoid muscle (detectable electromyographically) produces a supplementary lengthening of the mandible. "With time, this supplementary lengthening reduces the anatomic retropositioning of the mandible and, thus, the intensity of the deviation signal". It is beleived that subsequent decreases in the activity of the lateral pterygoid causes a reduction in the supplementary growth of the condylar cartilage and

mandible.[33] With respect to the stimulating action of Class II elastics on the length of the condyle and mandibular growth it has been suggested that it is mediated by the meniscotemporocondylar frenum (retrodiscal pad). Class II elastics do not give rise to a significant increase in the contractile activity of the lateral pterygoid muscle. This type of elastics are able to produce an earlier start of the chondroblast hypertrophy only in the presence of the retrodiscal pad.[33] According to previous investigations this structure also at least partly mediates the stimulating effect of the increased contractile activity of the lateral pterygoid muscle on condylar cartilage growth.[33] The intensification of the retrodiscal pad activity during the wear of Class II elastics has been associated with the increased growth rate of the condylar cartilage.[33] However it has been noted that extraoral Class II elastics designed to effect active hyperpropulsion of the mandible do not significantly stimulate the growth of the condylar cartilage and the lengthening of the mandible.[33] When postural hyperpropulsor appliances or intraoral Class II elastics are used, the whole mandible is forced to function in a forward position. In other words the mandible is submitted to an increase in functional demands. After some compensatory growth occurs, the mandible achieves a new balanced position and the functional demands decrease. Extraoral Class II elastics do not promote mandibular growth because they are not causing an increase in the functional demands. Extraoral Class II elastics act by immobilizing the mandible in a forward position while intraoral Class II elastics allow mandibular function.[33]

The retardation of condylar growth which results from the distal

displacement of the mandible by the chin cup or similar appliances has been explained by a different mechanism. The breaking action observed in the prechondroblastic proliferation during Class III force application is attributed to the suppression of functional movements and by pressure of the condyle against the posterior wall of the glenoid fossa.[33] It is admitted that the role of the lateral pterygoid muscle and retrodiscal pad is of great importance in regulating the growth of the condylar cartilage and that of the condyle as some authors have proposed.[33] Nevertheless, the study of mandibular growth should consider as well the influence of the rest of the supra and inframandibular muscles. All muscles that are attached to the mandible influence its movements and postural positions[21] and many studies have shown how these muscles exert a strong influence on craniofacial morphology.[43, 101] The function of the masticatory muscles influences bone remodelling in local areas by direct muscle action.[43] Experimental investigations have shown that low muscle function, induced by feeding with soft diets produces a decrease in the size of the mandible and a decrease in the transverse width of the maxilla.[43] Lower bone appositional rate in the animals fed a soft diet was found also in the gonial angle and in the lateral cortical region near the nasopremaxillary suture.[23, 43] The influence of reduced loading or reduced functional demands placed upon the masticatory muscles have been implicated as a cause for the craniofacial growth changes observed in the soft-diet group.[23, 43] In further studies it was found that reduced masticatory function may also influence suture closure.[23] It was

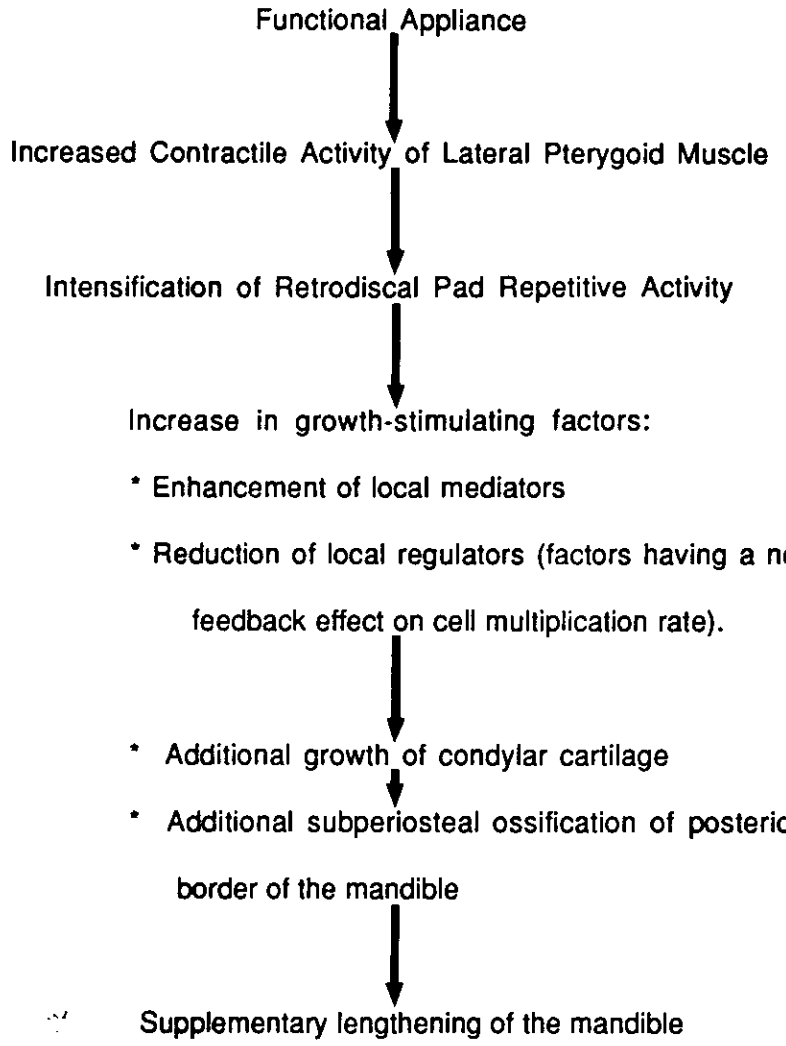
observed that obliterative osteogenesis occurred in the internasal suture in the group fed with a soft diet.[23] Other researchers have shown that when all the teeth on the right side of the mandible and the upper right incisor are ground down, the mandible and the bones of the skull develop asymmetrically.[101] Greater bony development was found in the side of the mandible under the influence of masticatory function. Evenmore, there was lack of development of the condyle on the side without function.[101] While the inherent genetic factors concerned in the development of bones are important, the influence of masticatory function on growth and development of the jaws appears to be very significant.[101] In fact, these bones need the stimulus of masticatory function to develop to their fullest extent.[101] In a study in which the mandible of a rat was transplanted into the leg muscle of a young female rat, the transplanted mandible grew and attained a shape similar to that of a regular mandible, however, it was only about half of the normal size.[101] In addition, it is a common clinical finding that young patients in which muscular function is limited or absent due to ankylosis of the TMJ usually manifest a pronounced underdevelopment of the mandible.[44, 101]

It is established then that in order to produce a favorable growth response in the mandible it is necessary to produce an increase in the functional demands. However, it is important that the functional stimulus of mastication be within the physiologic tolerance of the individual. This avoids muscular fatigue and excessive loading. "Variations in local mechanical

conditions must be similar to those encountered during normal activities. That is, the nature of the loading regimen should continue to be intermittent and the loads should not be abnormal in either direction or magnitude."[5] It has been observed that the best procedure to obtain an orthopedic increase in mandibular length consists of functional maxipropulsion involving periodic forward repositioning of the mandible.[33] If the vertical dimension in the Herren-type and L.S.U.-type activators is increased to 1.8 mm, there is no further stimulation in the growth of the condylar cartilage and mandibular length.[33] Also when these activators are worn for 22 1/2 hours daily or almost fulltime, although the length of the lateral pterygoid muscle is decreased, a stimulating effect on condylar cartilage growth rate has not been detected.[33] Experimental studies in young rats showed that if the vertical dimension in those activators is opened to 1.8 mm, the length of the mandible is not stimulated.[33] When young rats were submitted to continuous forward and inferior desplacement of the mandible (24 hours per day) for 24 days it was found that the treated animals had thinner condylar cartilages than the controls. However they also found that the resting and proliferative zones expressed in percentages of total thickness were larger in the experimental animals than in the controls, and that the area of the hypertrophic zone relative to the total cartilaginous area was smaller in the experimentals than in the controls. It was beleived that an initial increase in cartilage formation did occur but this was later neutralized by a simultaneous increase in the rate of erosion of the hypertrophic cartilage.[30] This implies an accelerated ossification of the hypertrophic zone. If this is true, there

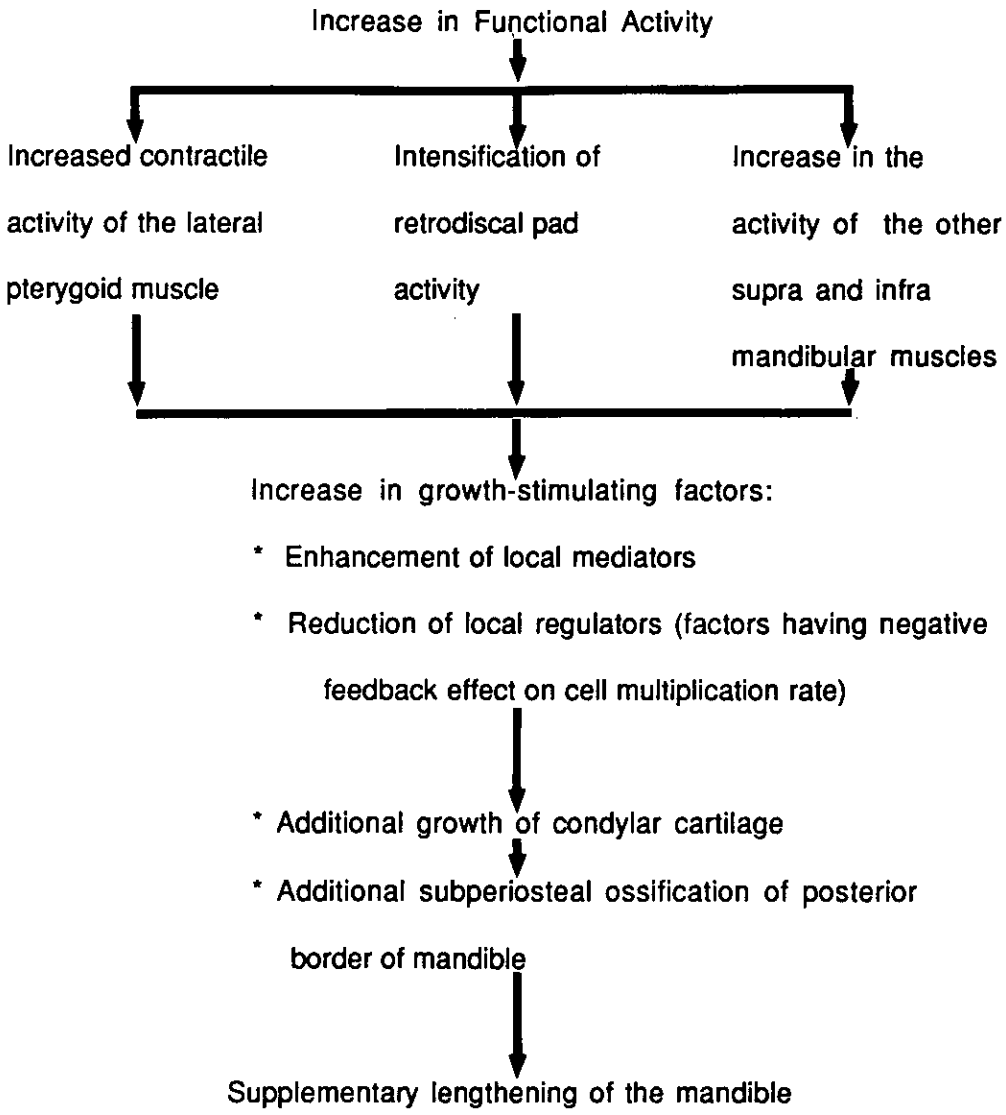
should have been either an increase in the size of the condyle, height of the ramus or lengthening of the mandible, but no information was given in this aspect. Several key questions remain unanswered. How does an increase in functional activity stimulate mandibular growth? What are the mechanisms involved? The basic relationship between muscular function and bone growth has not been completely elucidated.[57] Muscular function is associated with an increased in blood supply.[101] In fact, one of the major factors that has been advocated for the marked decrease in condylar cartilage growth rate after resection of the lateral pterygoid muscle is the interruption of the circulatory (i.e. nutritional) dependence on the blood supply provided by this muscle both directly and indirectly through the retrodiscal pad.[33] It has been suggested that the supplementary growth of the condylar cartilage caused by functional appliances is closely related with an increase in retrodiscal pad activity. It is beleived that the intensification of the retrodiscal pad activity produces an increase in blood and lymph flow and a decrease in cell catabolite concentration and negative feedback factors.[33] Also mechanical stresses may stimulate chondrogenesis by producing localized ischemia and anoxia.[24,58] It has been established that chondrogenesis is enhanced by anoxia and osteogenesis is enhanced by hypoxia.[58] However, these are not but some of the factors involved in growth. A multitude of factors are involved in growth control and the control mechanisms of craniofacial growth are related to local and regional extrinsic factors (as represented by tissue contacts, muscles, blood supply, nerve signals, etc) as well as to general factors (growth hormone [STH], and

somatomedin, thyroxine, and sex hormones).[33] The following causal chain was proposed to explain the mode of action of the various functional appliances.[33]



However, because the growth of the whole mandible is influenced by various regional forces,[24] including the function of all mandibular muscles

and not only by the lateral pterygoid muscle and retrodiscal pad, I would suggest the following modifications of the causal chain.



In this study it was found that the condylar cartilage in the unoperated side was thicker in the experimental animals than in the controls. It was suggested that CPM may have stimulated the viable chondroblasts to

increase their synthesis of the various matrix components since it is unlikely that the proliferative activity could have been enhanced due to the age of the animals. However, what would it be the effect of CPM if it is applied during the growth period? CPM is beleived to increase the diffusion of nutrients of the synovial fluid into the matrix of the articular cartilage, produces an increase in blood flow to the joint and enhances the clearance of abnormal and deleterious metabolites in joints where septic arthritis, hamarthrosis or abnormal fluids are present. All of these factors have been associated with condylar growth. CPM also appears to fullfill some of the "requirements" for stimulating mandibular growth. CPM produces an increase in the functional activity of the mandible, the mandible is moved within the physiologic range of the individual and the motion does not require any voluntary effort, therefore muscle and skeletal fatigue are avoided. Evenmore, since the application of CPM significantly enhances the chondrogenic capacity of the bipotential osteochondrogenic cells from osteoperiosteal grafts, it is reasonable to think that it could increase cell division, chondroblast differentiation and condylar growth when applied during the proliferative stage of the capsular layer of the condyle.

Some procedural aspects of the application of CPM to the guinea pig should be changed if this project is to be repeated. The stabilization of the head by using the upper incisor as anchorage was inadequate. The strength of the animals was greatly underestimated and all of the animals broke the upper attachment off. It would have been much easier, less time consuming, less stresfull for the investigator, and the animals would have

required smaller doses of Valium, if the head had been stabilized more securely. Perhaps, some type of sling device that could hold the head firmly would give better results. There were no problems associated with the lower attachment. In addition, the animals should be housed in the same building were the experiment is carried out. The transportation of the animals from one building to another only represents more stress for the animals and more time spent out of their cages.

SUMMARY AND CONCLUSIONS

It is well understood that the proper conditions for the maturation and differentiation of repair tissues are necessary to obtain the best possible tissue regeneration. Although the TMJ has been described as a synovial joint, its unique characteristics make it a very special type of diarthrosis. In broad terms, the TMJ is affected by lesions, and undergoes degenerative changes similar to those seen in other synovial joints. However, internal derangements of the TMJ not only can disrupt tissue integrity within the joint but can also produce adverse sequelae on adjacent musculo-skeletal tissues and other neighboring structures. Non-surgical therapy has been advocated as the primary treatment of choice. Nevertheless, as in other synovial joints, when non-invasive modalities are unsuccesfull in reestablishing normal joint function, surgery can be necessary. Experimental and clinical studies have pointed to the beneficial effects of continuous passive motion (CPM) on the post-surgical healing process of articular and periarticular tissues in different synovial joints, and in a variety of joint disorders. The first objective of this study was to develop a methodology that would allow the application of CPM to the TMJ in an animal model. The second objective was to determine if CPM could produce the same beneficial effects reported for other synovial joints with regard to regeneration of surgically created full-thickness articular cartilage defects. The guinea pig sample was divided in three groups: a experimental group, an immobilization, Valium induced (IMM) control group and an intermittent

active motion (IAM) control group. The IMM control group allowed determination of the influence of long restraining periods and repeated tranquilization on the repair of full-thickness articular cartilage defects. The IAM control group would have allowed appraisal of the natural healing process, and the experimental group would have permitted the study of the regeneration of condylar osteochondral defects under the influence of CPM. However, due to procedural difficulties that were encountered, it was not possible to fullfil all the objectives of this project. Nonetheless, some of the beneficial effects of implementing CPM early following surgery were observed, and the results obtained provided helpful information for an understanding of the response of the condyle to injury and to altered physical conditions. The following conclusions were made:

1. Proliferation of precollagenous fibrils in the marrow spaces around the surgically created full-thickness articular cartilage defects were consistantly found.
2. It is possible to provide the TMJ with the benefits of early motion after surgery without the threat of damaging the healing of connective tissues.
3. In cases of infected joints, CPM prevented articular cartilage degeneration.
4. CPM contributed to the prevention of joint stiffness and the formation of fibrous or bony ankylosis.
5. CPM helped to maintain and/or increase the original range of motion.
6. CPM may enhance the amount of new bone formed, either

endochondral or intramembranous in origin.

7. No adverse effects were found with respect to the application of CPM itself, and no damage was done to normal articular cartilage by CPM.

8. CPM may stimulate living chondroblasts to increase their rate of synthesis of the matrix constituents even in adult animals. This, in turn, could provide an aged or degenerated joint with a cartilage more suitable for withstanding the demands of normal function, therefore preventing the need for surgical procedures. Or in those cases of advanced pathology (i.e. severe osteoarthritis) in which conservative treatments have failed, the implementation of CPM as the post-surgical mode of therapy could be of great value for the repair or totally resurfacing of these joints.

9. The articular cartilage of a joint appears to contribute to a regulatory function in the differentiation of mesenchymal-like cells in the repair tissue fillling a full-thickness defect.

10. The condylar cartilage appears to exert a regulatory influence on the growth of the subjacent medullary bone of the condylar head.

11. It is suggested that prominent rest lines found in the bone of the growing condyle can be utilized as natural markers in research studies.

12. The trauma caused by the creation of a full-thickness articular cartilage defect may have induced a loss in the histologic stratification typical of the condyle.

13. The increase in condylar cartilage thickness is similar to that seen

with hyperpropulsor type appliances. This finding suggests that increasing mandibular function within the physiologic range of motion may be a valid method for stimulating mandibular growth.

The introduction of CPM as a mode of treatment, has represented a great improvement in the care of injured synovial joints. Because of the unique characteristics that differentiate the TMJ from most of the synovial joints, and the difference among the surgical procedures performed on the TMJ, a great deal of experimental studies will be necessary to determine the appropiate utilization of this concept in the temporomandibular joint.

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