Remodelling the Dentofacial Skeleton

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Biological Foundations of Orthodontics and Dentofacial Orthopaedics

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UNIVERSITY of OTAGO
SAPERE AUDE
Te Whare Wānanga o Otāgo

Introduction

- With the exception of the cranial base synchondroses and temporomandibular joints (TMJs), the articulations between the bones of the skull (and teeth) are fibrous joints. These are responsive to alterations in mechanical loading; indeed, orthodontic treatment is dependent upon the ease with which the periodontal ligament (PDL) and supporting alveolar bone can be remodelled by mechanical means.

- Animal experimentation enables informed decisions to be made regarding the effects of treatment on the dentofacial skeleton at the tissue, cellular and molecular levels. Several rat and monkey studies have shown that facial sutures and the TMJs can be remodelled by externally applied mechanical strain, thereby providing an evidence base for dentofacial orthopaedics.

- The aim of this seminar is to discuss the significance of these findings, and the extent to which they can be utilized clinically in the correction of malocclusion; in particular, the amount and direction of growth of the maxillary complex and mandible.

- See Meikle MC (2007). Remodeling the dentofacial skeleton: the biological basis of orthodontics and dentofacial orthopedics. *Journal of Dental Research* **86**, 12–24.

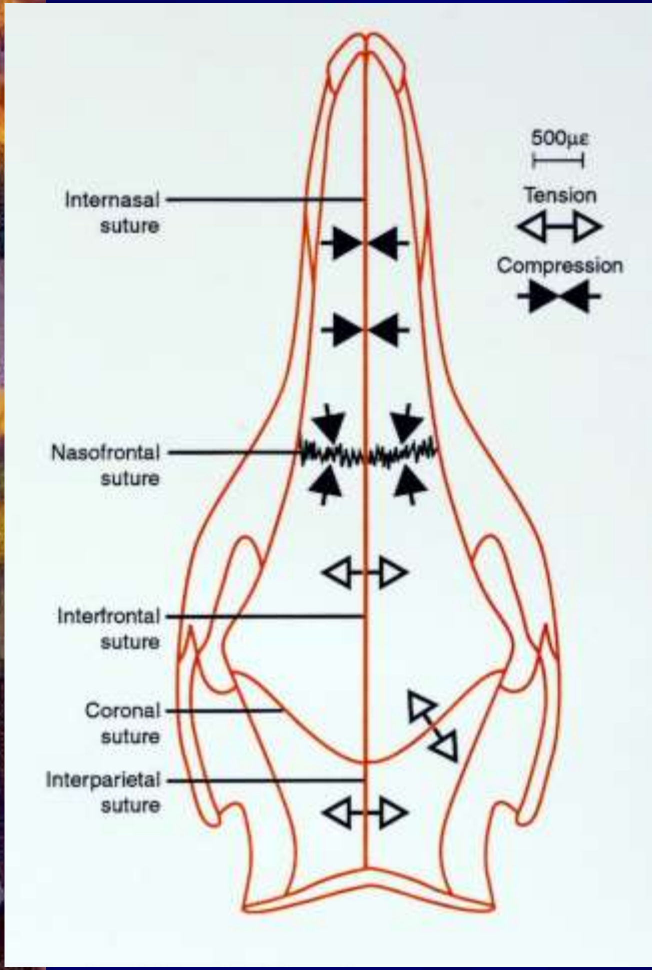
Patency of craniofacial sutures

Cranial Suture	Closure begins (years)	Facial suture	Closure begins (years)
Interfrontal (metopic)	2	Intermaxillary (palatal)	30 – 35
Interparietal (sagittal)	22	Frontomaxillary	68 – 71
Frontoparietal (coronal)	24	Frontonasal	68
Occipitoparietal (lambdoid)	26	Nasomaxillary Frontozygomatic	68 72
Temporoparietal (squamosal)	35–39	Zygomaticomaxillary	70–72

Data derived from Todd and Lyon (1924, 1925); Kokich (1976, 1986); Persson and Thilander (1977).

- Sutures have two main functions. (1) as a site of bone growth, and (2) to provide a firm union between adjacent bones, while permitting slight movement in response to mechanical loading, particularly during mastication.
- Suture morphology is determined by the site and mechanical stresses to which they are exposed. All sutures eventually undergo varying degrees of fusion by osseous union or synostosis. Synostosis begins at different ages in the various sutures of the skull (see above), and starts earlier at the endocranial than the ectocranial surface.

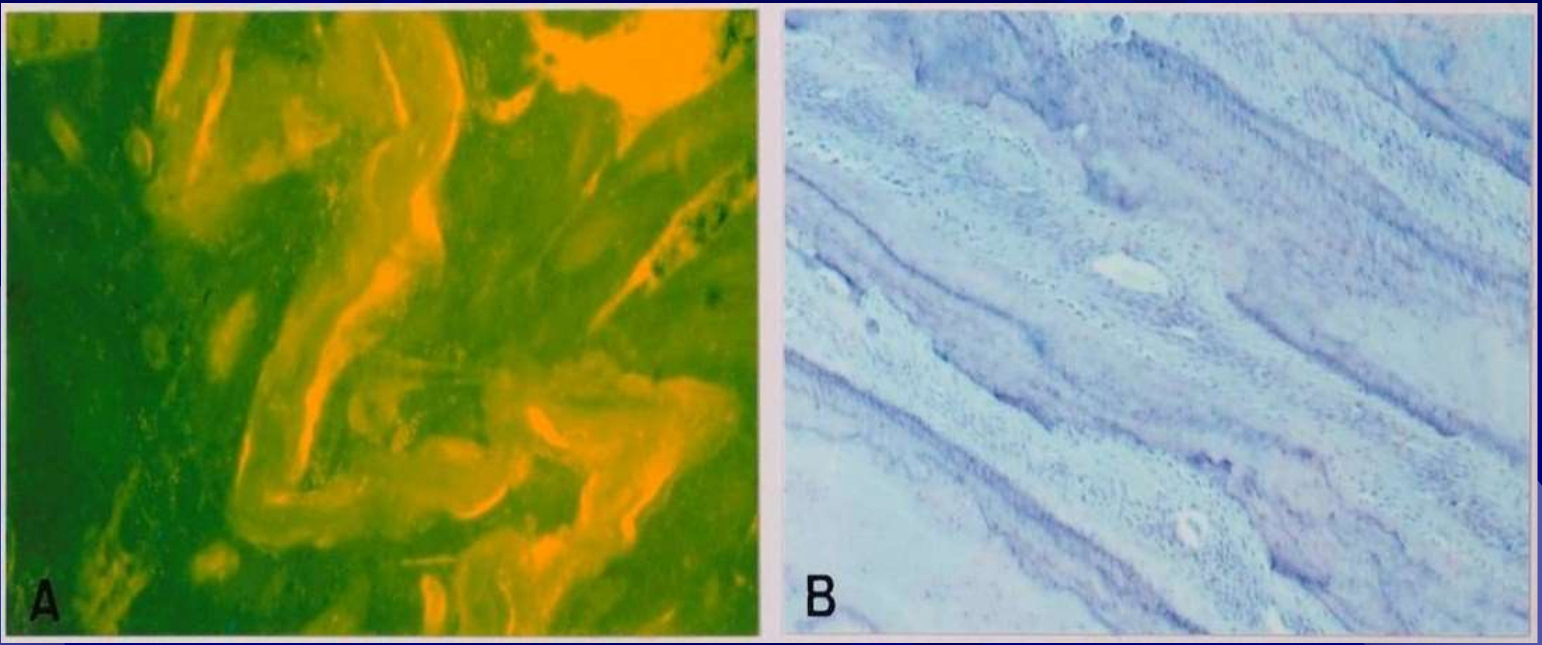
Loading of craniofacial sutures



Redrawn from Rafferty and Herring (1999). *Journal of Morphology* **242**, 167–179.

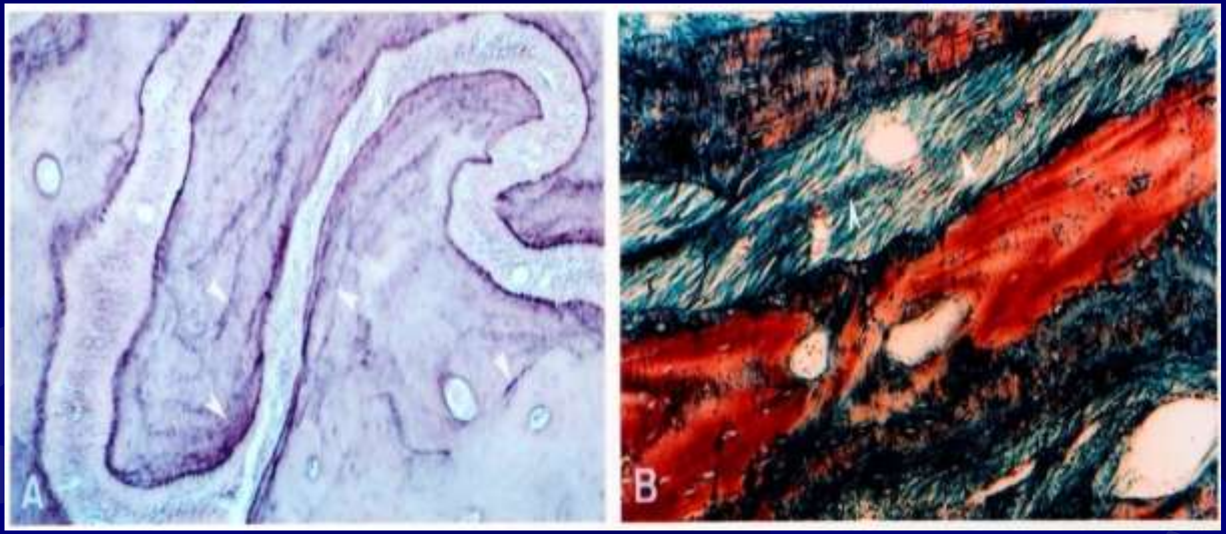
- Intermittent mechanical loading of the facial sutures during mastication as shown from measurements of mechanical strain in the miniature pig. Sutural strain is a dynamic parameter and sutures show temporal and regional variations in strain polarity; some sutures even show a small compressive strain before or after a tensile peak.
- Sutures of the braincase are predominantly tensed, while those of the snout are compressed. 500με = 500 microstrains.
- Growth factors such as IGFs, TGF-β isoforms and FGF-2 have all been immunolocalized in the dura mater and their expression increased during closure, suggesting a paracrine signalling role.

Facial suture morphology



- Zygomaticofrontal suture (A) from a *Macaca mulatta* (Rhesus) monkey. The uptake of tetracycline suggests an asymmetrical pattern of sutural remodelling depending on the surface strain. Ground section viewed under UV light. x30.
- Frontomaxillary suture (B) from the same animal. This suture is characterized by numerous osseous reversal lines and cellular evidence of extensive remodelling activity. H&E stain. x75.

Patterns of sutural remodelling

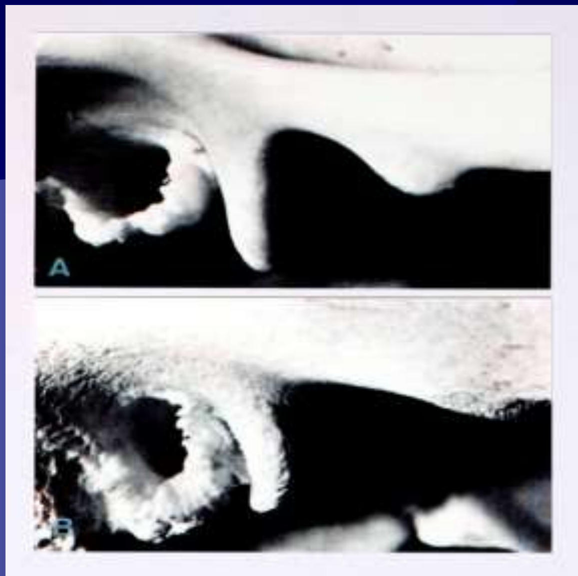


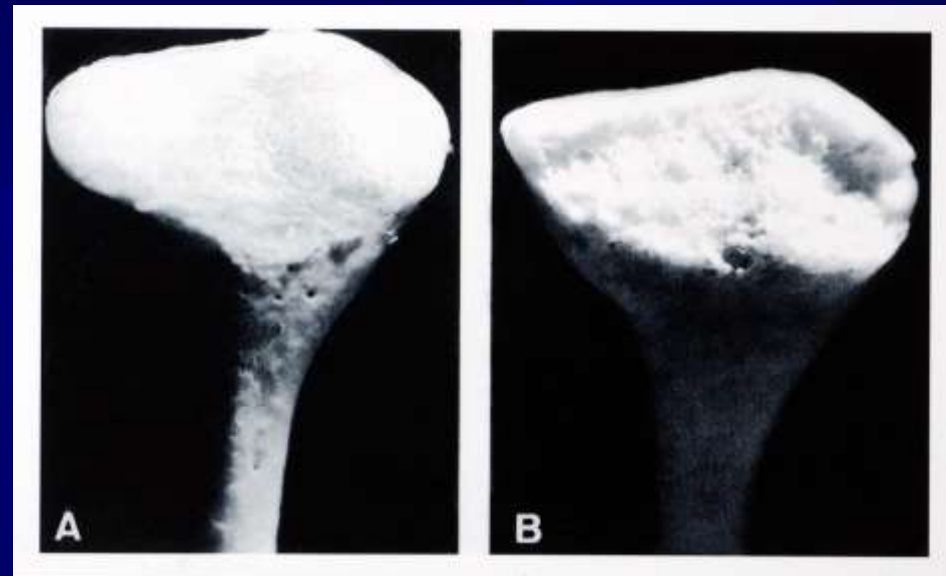
- As a generalization each suture is formed by a continuation of the fibrous and cellular periosteum around the margins of adjacent bones, united by fibrous connective tissue with a central layer of fibroblastic precursor cells.
- A. Section through the zygomaticofrontal suture of an adult *Macaca mulatta* monkey, with numerous reversal lines (arrowheads) in the bone indicative of past remodelling. Decalcified section, Haematoxylin & eosin stain x75.
- B. Frontomaxillary suture; experimental animal showing recent remodelling activity with highly cellular new bone (blue) deposited on old bone (red). Arrowheads indicate activated central cell layer. Decalcified section, Mallory stain x120.

Remodelling the maxilla

- The first clinical evidence that changes in the anteroposterior position of the maxilla could be achieved by the application of external load, emerged from cephalometric studies of patients who had worn extra-oral traction or headgear (HG) during orthodontic treatment (Moore, 1959; Ricketts, 1960).
- These landmark investigations provided the impetus for research into the effects of externally applied mechanical force on the craniofacial skeleton of the macaque monkey. During the 1960s and 70s the outcome this research from the University of Washington and other centres with primate facilities, most notably Michigan and Toronto, established many of the biological principles underlying contemporary dentofacial orthopaedics.
- This research involving both adolescent and adult monkeys has shown that controlled external force applied to the dentomaxillary complex can alter the positional relationships of the bones of the facial skeleton.

Changes in the TMJ



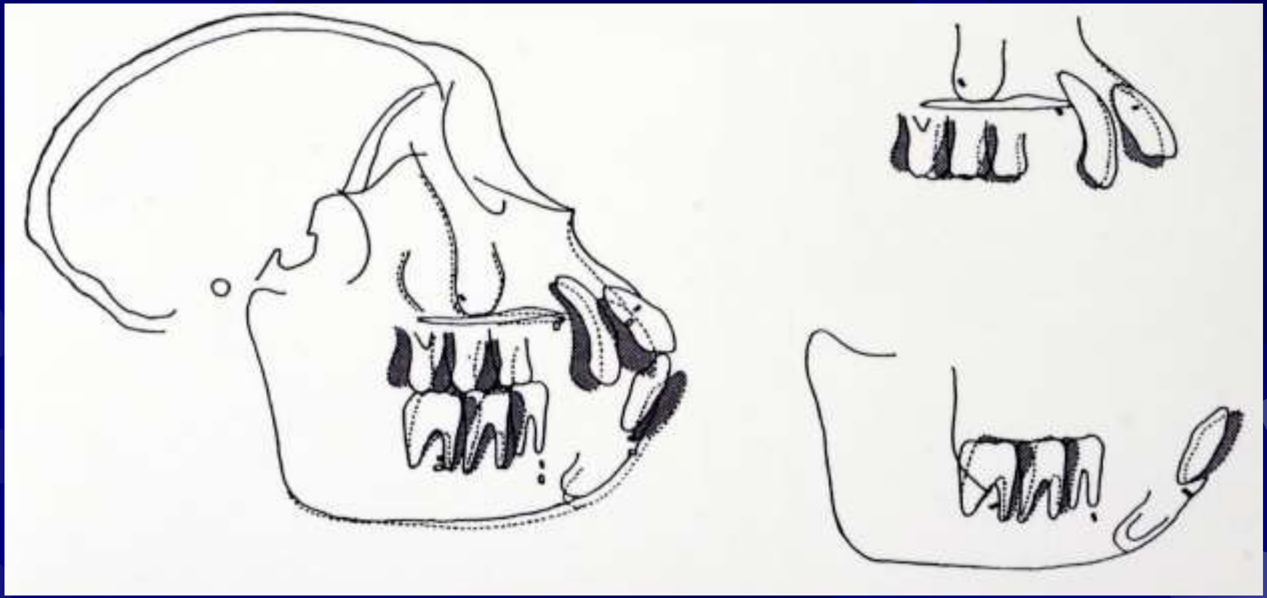


- Alterations in the bony surfaces of the TMJ and adjacent osseous structures produced by headgear, which suggest transmission of occlusal forces from one jaw to the other and distal displacement of the mandible. Left pair show the effects on the temporal bone. From Tuenge RH, Elder JR (1974). *American Journal of Orthodontics* **66**, 618–644.

- Right: A. Control. B. Crater-like voids in the condylar head of an experimental monkey.

- From Brandt *et al.* (1979). *American Journal of Orthodontics* **75**, 301–317.

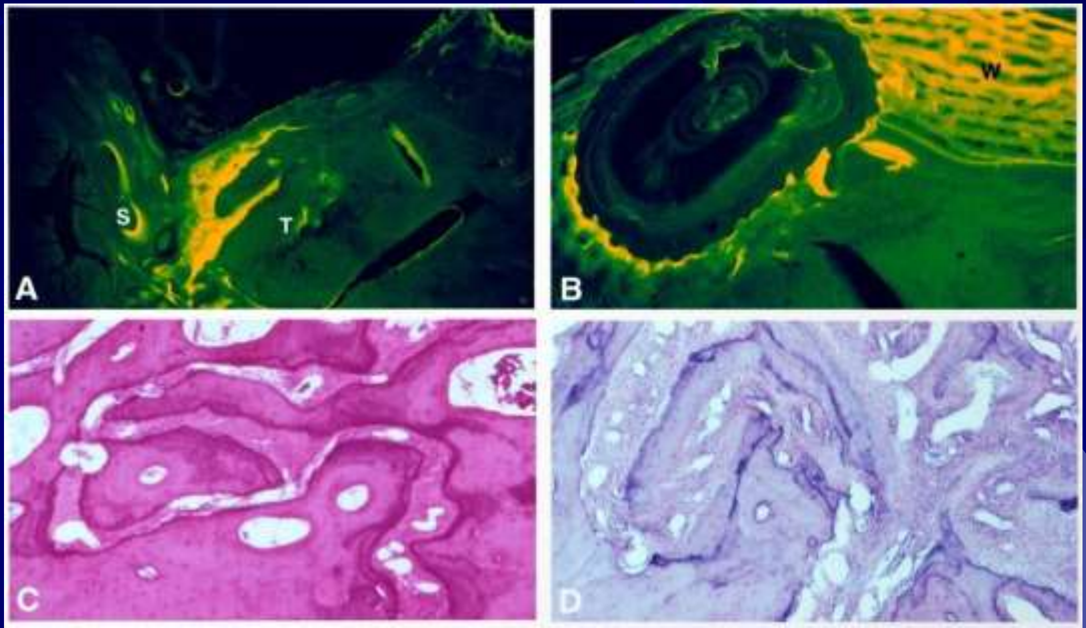
Experimental alteration of the maxilla



- Class II elastics (200 gm) were applied for 84 days to splints wired to the jaws of an adult *Macaca mulatta* monkey. Pre- and post-treatment tracings have been superimposed on the anterior cranial base and on implants.
- The outcome was remodelling of the sutures of the maxillary complex with distal displacement and rotation of the maxilla; 50% of the movement was due to changes in tooth position, and 50% to maxillary displacement.
- From Meikle (1970). *American Journal of Orthodontics* **58**, 323–340.

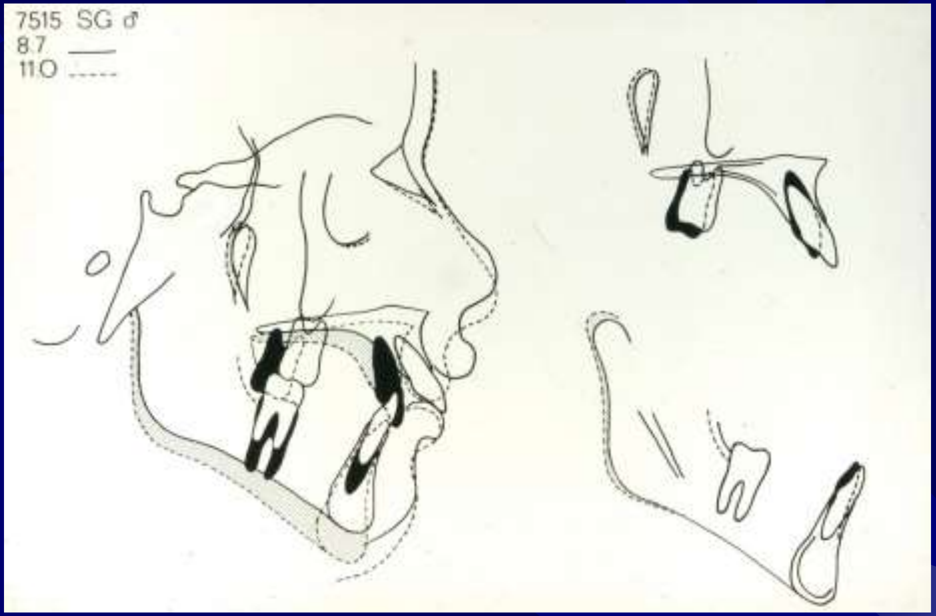
Compression of the pterygomaxillary fissure

A,B: Ground sections viewed with UV light.
C,D: H & E.



- Response of the pterygomaxillary fissure to compression. In slide A, resorptive remodelling at the bony interface has been compensated by diffuse endosteal deposition in the tuberosity (T) and scaphoid fossa (S).
- In slide B, where the distobuccal root of the third molar has been moved through the buccal plate, the periosteum has responded by the deposition of woven bone (W). This was not observed at other non-growing sites where the roots penetrated the buccal plate.

Effect of headgear on the dentofacial skeleton

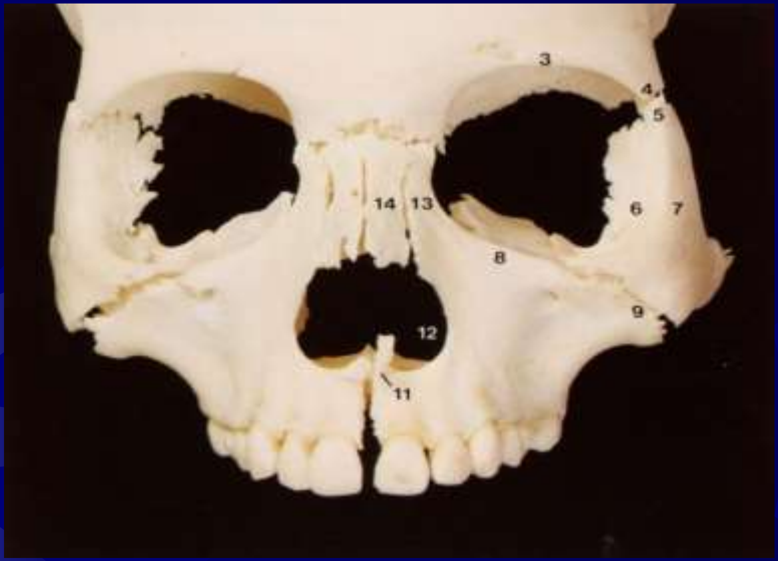


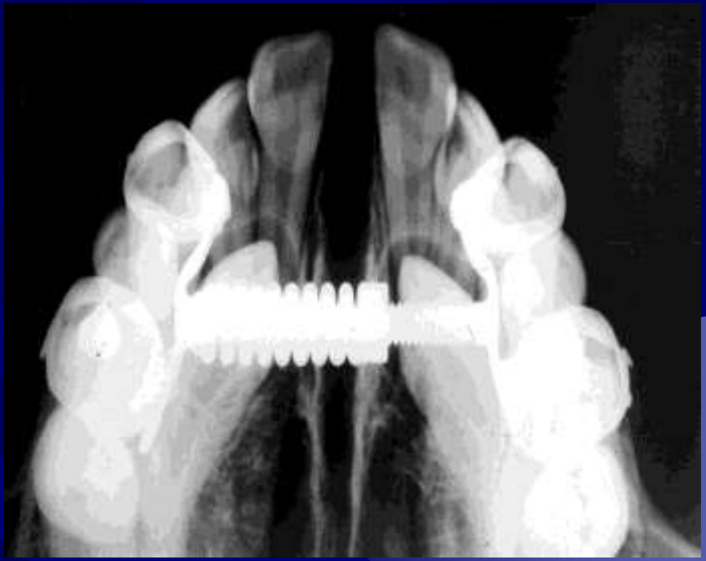
- Patient with a Class II division 1 malocclusion, treated with a combination of cervical traction and anterior high-pull headgear engaging fixed appliances. Ten years later, with the benefit of hindsight, I would have treated this patient with a Clark Twin-block, followed by fixed appliances.
- Comparing maxillary and overall superimpositions; as condylar growth was limited, a major contribution to overjet correction came from remodelling the sutures of the facial skeleton, and moving the maxilla distally.
- Meikle (1980). *American Journal of Orthodontics* **77**, 184–197.

Distracting the maxillary complex

- In this experiment, to avoid undesirable tooth movement in Class III patients treated with a facemask, and traction applied to the teeth, titanium implants were placed in the maxillary and zygomatic bones of pigtail monkeys and allowed to osseointegrate. Extraoral forward traction was applied directly to the implant abutments.
- In (A) maxillary protraction was applied via the teeth. In (B) traction was applied to osseointegrated implants. CL/P patients would benefit from having mini-screws inserted to facilitate application of forward traction.
- From Smalley *et al*. (1988). *American Journal of Orthodontics and Dentofacial Orthopedics* **94**, 285–295.

Rapid maxillary expansion





- The most dramatic example of maxillary suture remodelling comes from RME. It is a common belief the mid-palatal suture fuses around 15 years. Anatomical and clinical evidence, however, suggests otherwise. Melsen (1975) and Persson and Thilander (1977) found a marked degree of closure was rare before the third decade, *i.e.* 20–30 years of age.
- The key issue is not whether osseous union has begun, but the overall percentage of the suture that has actually fused. The greatest resistance to RME comes from the circum-maxillary suture network.

From McMinn *et al*. (1981). *A Colour Atlas of Head and Neck Anatomy.*

Maxillary protrusion and RME

- Maxillary protrusion in the treatment of Class III malocclusion increased in popularity due to the work of Delaire with the orthopaedic face mask (Delaire, 1971; Delaire *et al*. 1972).
- Several studies have reported the skeletal and dental effects of maxillary protraction in the correction of skeletal Class III malocclusions, both with RME (Ngan *et al*., 1996; Kapust *et al*. 1998; Franchi *et al*. 2004) and without (Wisth *et al*. 1987; Takada *et al.* 1993). Together with the findings of a meta-analysis, these showed that maxillary protraction is more effective if (1) undertaken in the mixed dentition, and (2) combined with RME.
- Given the aim of RME is to loosen the articulations of the maxillary complex this is not surprising. The next logical step is to combine RME with the use of intraosseous mini-screws to apply forward distraction directly to the bones of the maxilla itself, and minimize tooth movement.
- For references see Meikle (2007). *Journal of Dental Research* **86**, 12–24.

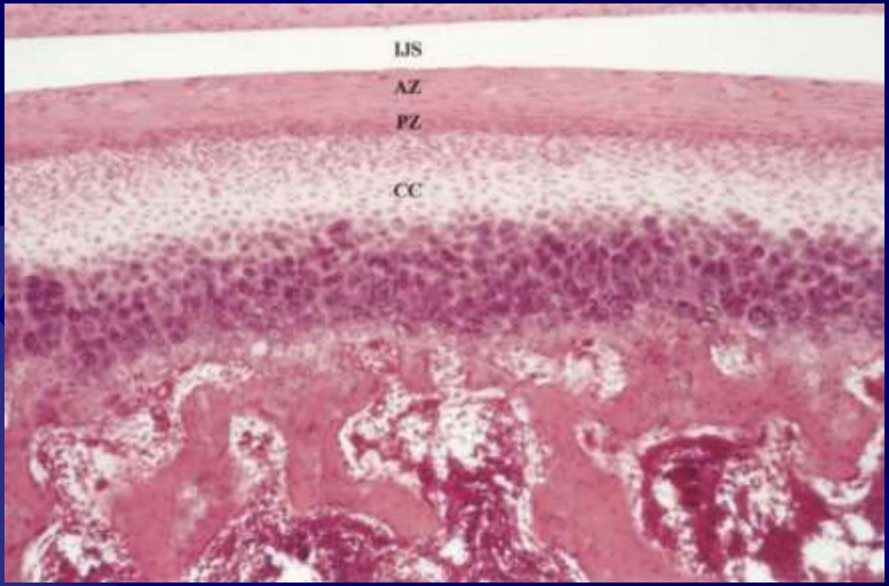
Remodelling the TMJ

- The condyle and the cartilage of the mammalian mandible are different in several ways from the articular cartilage of long bones, and seem to have held a certain ‘mystique’ for the dental profession. Central to an understanding of condylar growth and its modification is the question – what is a secondary cartilage, and what is it doing in a membrane bone in the first place?

- The presence of cartilage indicates that the joint surfaces are adapted to protect the subchondral bone from the effects of mechanical loading during mastication and other functional activity – and as one might suppose from its structure and mobility, the TMJ is more resistant to altered mechanical loading than a facial suture.

- Whether functional anterior mandibular displacement can significantly alter condylar growth is controversial. The question remains – Can changes in the TMJ produced by so-called functional appliances that alter jaw position, represent an actual increase in condylar growth of clinical utility – or more simply localized articular remodelling?

Structure of the mandibular condyle



IJS, inferior joint space
AZ, articular zone
PZ, proliferative zone
CC, condylar cartilage

- Sagittal section through the head of the condyle (human aged 10–12 years) when functional appliance treatment is usually carried out. There is some evidence of endochondral ossification, but chondrogenesis itself does not appear particularly active.
- The proliferative zone is composed of mesenchymal stem cells that differentiate into cartilage cells. The surface articular zone is composed of fibrous connective tissue; cartilage cells gradually appear in response to functional loading by the age of 20 converting it to fibrocartilage.

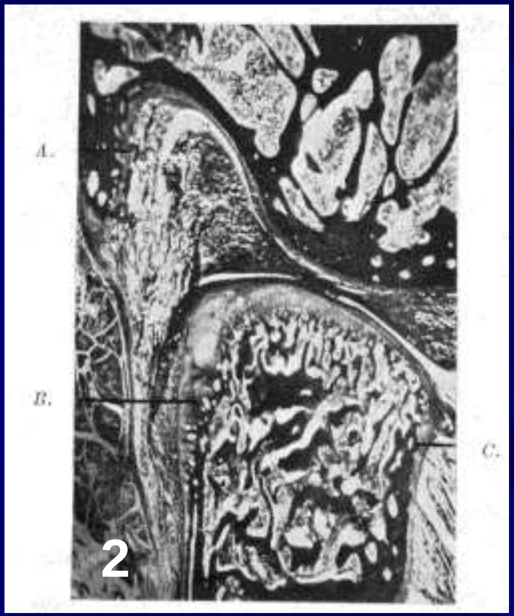
Condylar cartilage is derived from the periosteum

- Central to understanding condylar growth is to remember the cartilage is not a remnant of the primary cartilaginous skeleton, but an example of how connective tissues adapted to changes in their biomechanical environment during evolution. PDF Murray (1963) described the development of secondary (adventitious) cartilages in membrane bones of the chick, but only at articulations that were mobile. In grafted or paralyzed embryos (Murray and Smiles, 1963) cartilage did not form, and cells that normally formed cartilage produced bone instead.
- Studies in which the mandibular condyles of rats were transplanted into a non-functional environment, have also shown that PZ cells differentiate into osteoblasts, not chondroblasts as *in situ* (Duterloo,1967; Meikle, 1973).
- Condylar cartilage is thus the product of periosteal chondrogenesis and resulted from the development of an articular condylar process in the mandible (dentary) of mammals, and consequently, the altered functional demands placed upon the periosteum covering the articular joint surfaces.

Remodelling the TMJ in non-human primates

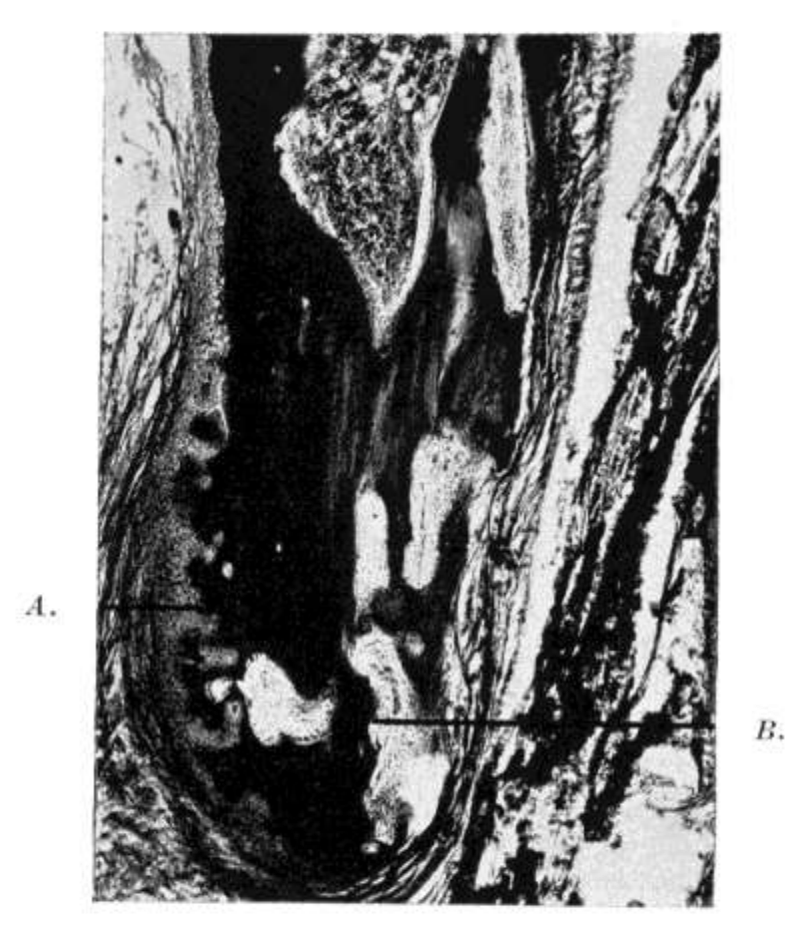
- Experimental forward displacement of the mandible in the rhesus (*Macaca mulatta*) monkey has a long history, and been shown to produce significant histological changes in the TMJ.
- First used by Carl Breitner MD, DDS, to investigate the effects of mandibular displacement on the TMJ, the rhesus monkey proved to be a valuable experimental model in numerous subsequent investigations (Baume and Derichsweiler, 1961; Meikle, 1970; Stockli and Willert, 1971; Adams *et al.*, 1972).
- Breitner's findings were first published in the German literature in the 1930s, and in two classic papers in the *American Journal of Orthodontics and Oral Surgery* (1940, 1941), after he had escaped to the USA to avoid the pogrom being waged against the Jewish people in Hitler's Germany and Austria.

Carl Breitner's experiments



- Breitner was the first to look beyond the teeth and study tissue changes in other sites of the mandible. (1) TMJ showing deposition along the anterior surface of the post-glenoid tubercle (A) after 'raising the bite'.
- (2 and 3) Changes following 'jumping the bite' showing deposition along the anterior surface of the postglenoid tubercle (A); posterior surface of condyle (B), with resorption at the insertion of the lateral pterygoid muscle (C).
- Breitner (1940). *American Journal of Orthodontics and Oral Surgery* **26**, 521–547. Breitner (1941). *American Journal of Orthodontics and Oral Surgery* **27**, 605–632.

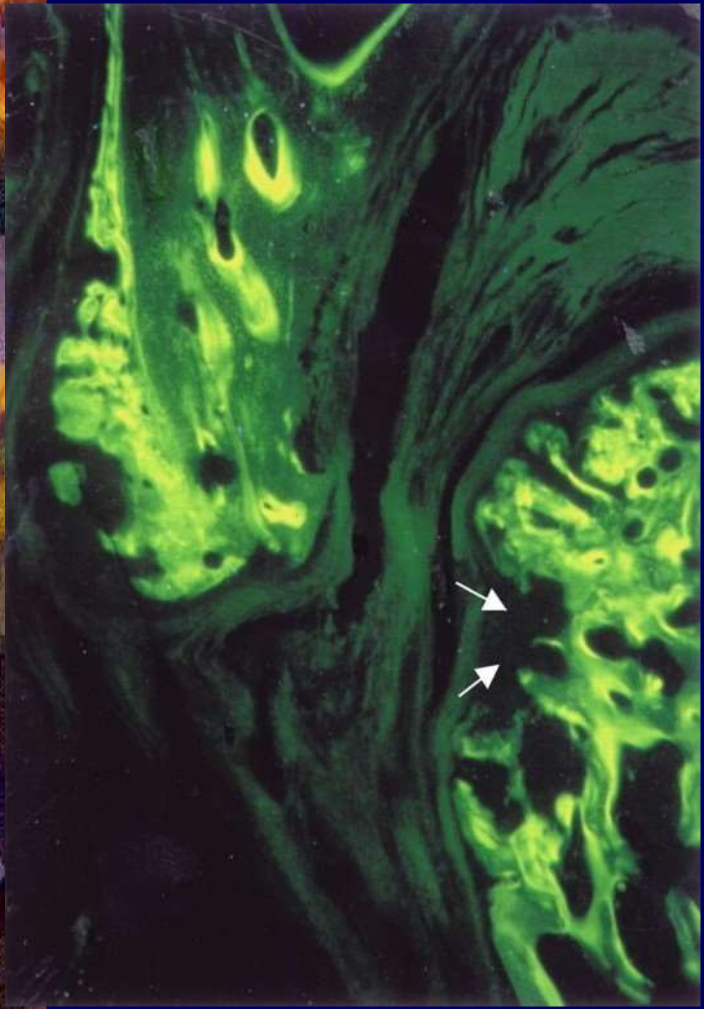
Breitner's results



From Breitner (1940). *American Journal of Orthodontics and Oral Surgery* **26**, 521–547

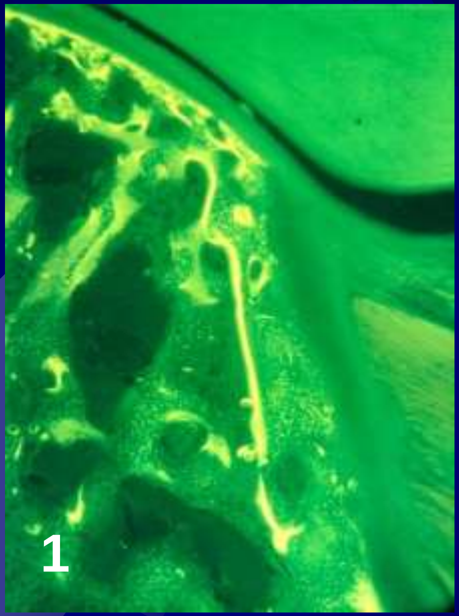
- Breitner provided convincing histological evidence that the influence of orthodontic treatment was not limited to the teeth.
- After distal displacement of the mandible in a monkey by Class III elastics for 72 days. Bone deposition (A), bone resorption (B).
- His papers were criticized by having limited numbers and little if any controls. Nevertheless, (as the three following slides demonstrate), despite vital staining, improved histological techniques, metallic bone implants and cephalometric radiography, subsequent investigations added little new information to Breitner's original findings, although the slides looked nicer!

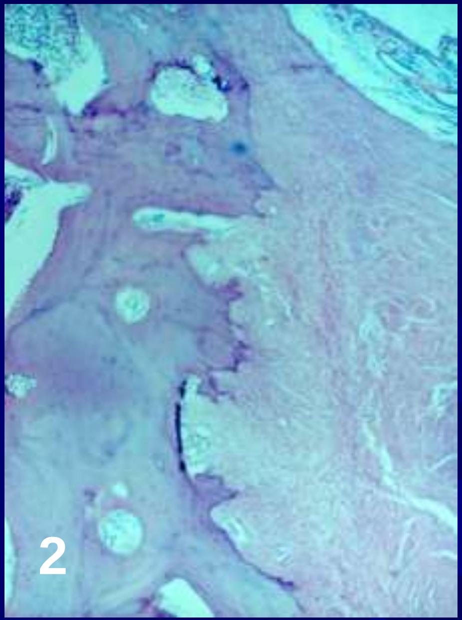
Distal mandibular displacement

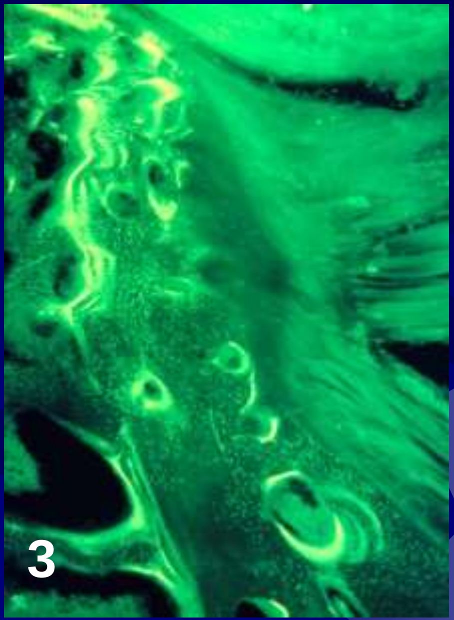


- Posterior mandibular displacement in this *Macaca mulatta* monkey labelled with tetracycline, has resulted in resorptive remodelling of the condyle (arrows) at the point of maximal compression and anterior surface of the tubercle, with concomitant deposition along the posterior border.
- The remodelling response of the post-glenoid tubercle, is likely to have been a consequence of the bending of bone. Unstained ground section, viewed with UV light. x15.
- Image from Meikle (1970). *American Journal of Orthodontics* **58**, 323–340.

Remodelling the condyle





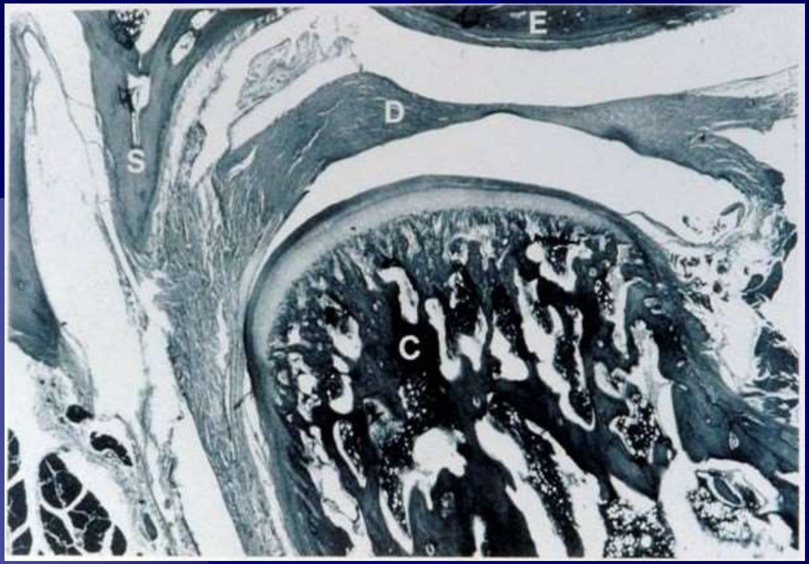


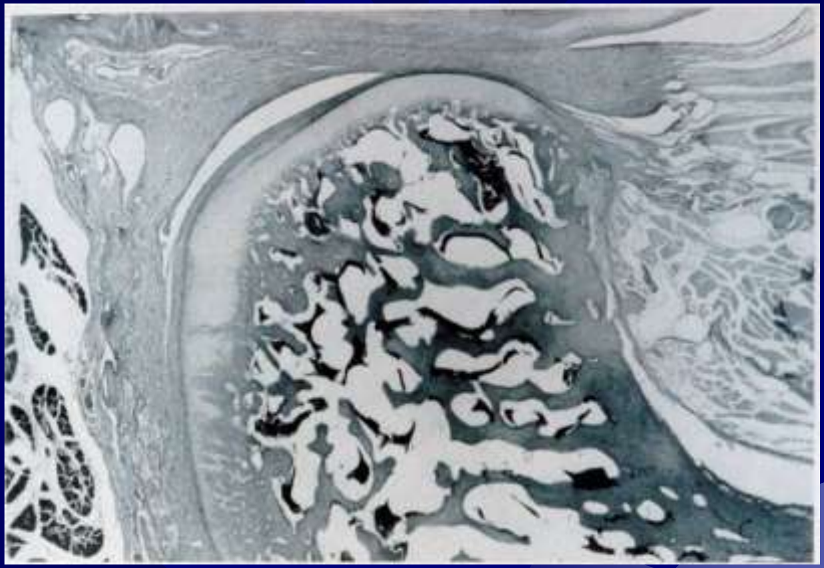
- Sagittal sections through the condyle showing insertion of the lateral pterygoid muscle in two rhesus monkeys labelled with tetracycline.
  (1). Control. The insertion of the muscle is normally a resorptive surface.
- (2). Following anterior mandibular displacement for six weeks, resorptive activity along the anterior surface has increased. H&E stain. (3). Labelling indicates this induced compensatory deposition on the endosteal surfaces of the cortical bone in both a control (1); and an experimental animal (3) that received three tetracycline injections.

Glenoid fossa remodelling

- In a study from Toronto, forward displacement of the condyle has resulted in the deposition of bone along the anterior border of the postglenoid tubercle (arrows), suggesting forward repositioning of the glenoid fossa.
- New woven bone (nb) is clearly distinguished from the pre-experimental mature compact bone (mb); R shows areas of bone resorption at the posterior border.
- Image from: Woodside *et al.* (1987). *American Journal of Orthodontics and Dentofacial Orthopedics* **92**, 181–198.

TMJ adaptation to protrusive function





- In a long-term study of protrusive function in *Macaca mulatta*, McNamara and Carlson (1979) reported significant morphological changes at the condyle.
- This took the form of increased thickness of the condylar cartilage, as well as increased bone deposition along the posterior border of the ramus. The changes occurred within 2 weeks, reached a maximum at 4–6 weeks and declined thereafter. Left, control. Right, 2-week experimental.
- Images from McNamara and Carlson (1979). *American Journal of Orthodontics* **76**, 593–611.

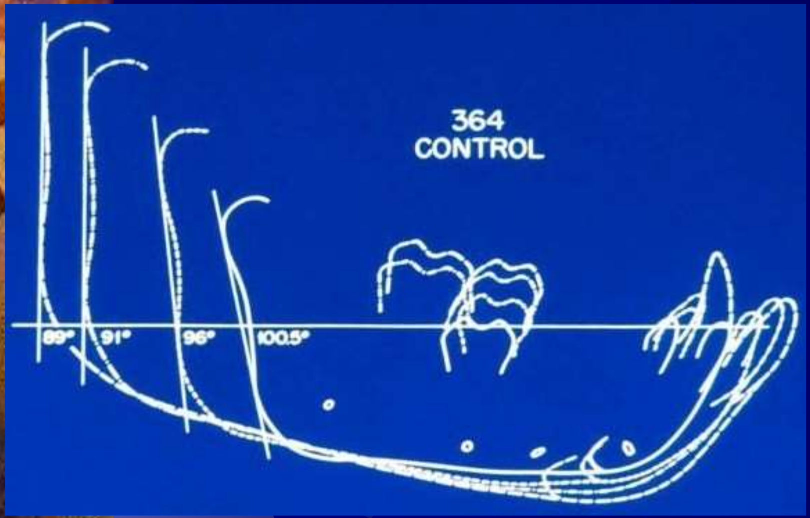
Mandibular adaptation to protrusive function

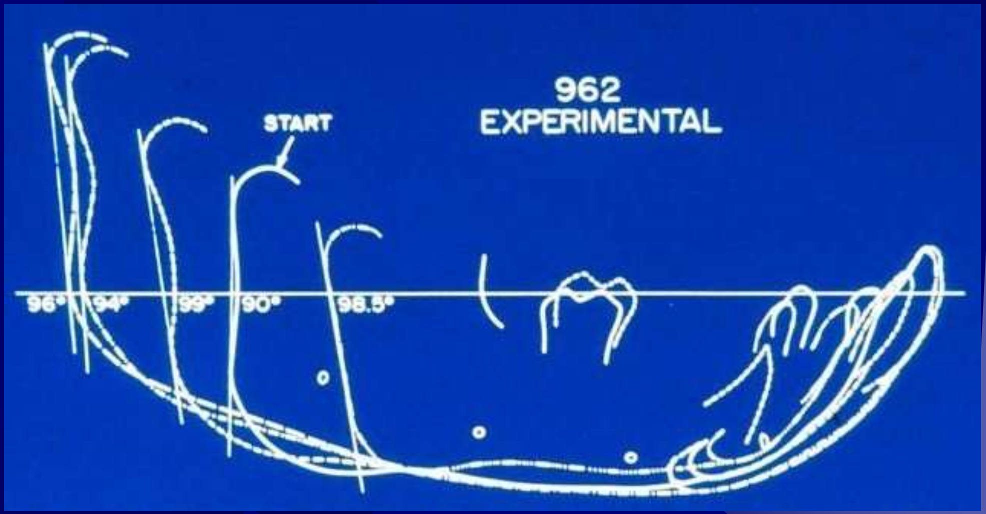
- Breitner believed that forward displacement of the mandible could enhance condylar growth. This received support from McNamara and Bryan (1987) in a cephalometric study of 23 juvenile *Macaca mulatta* monkeys (12 control; 11 experimental) at Michigan.

- Mandibular length was measured from infradentale to condylion. After 144 weeks the mandibles of treated animals were 5–6 mm longer than controls. However, this measurement contains a fundamental flaw in an angular bone, illustrated in the next slide.

- McNamara and Bryan (1987). *American Journal of Orthodontics and Dentofacial Orthopedics* **92**, 98–108.

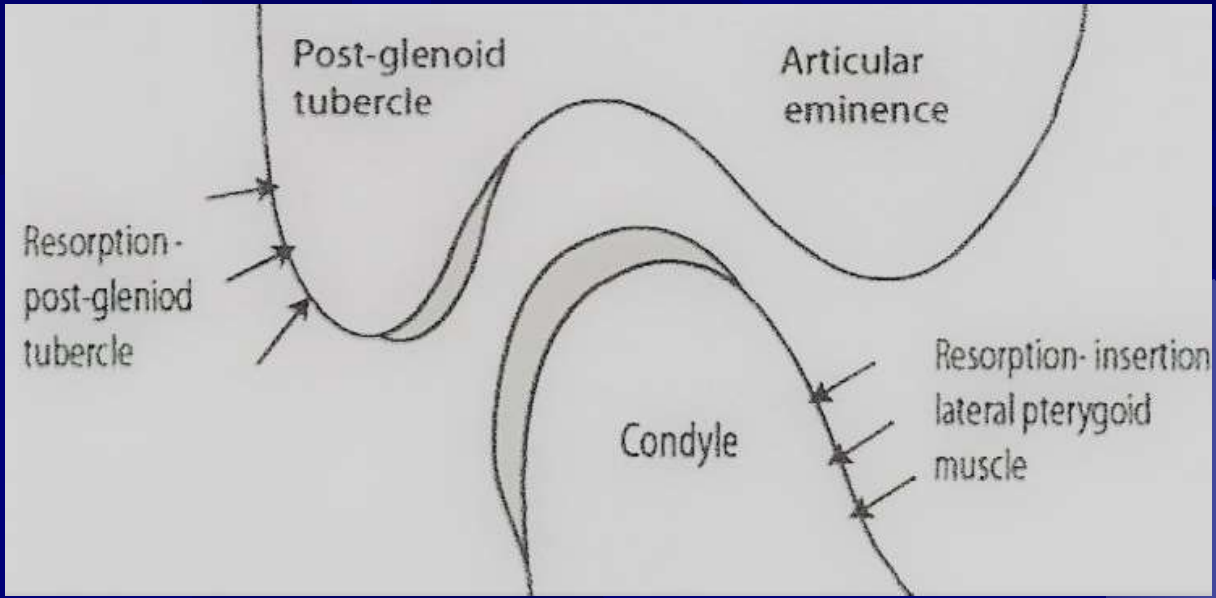
The CRO angle and condylar growth rotation





- Changes between the ramus and body were measured by the condylar-ramus-occlusal (CRO) angle. As in humans, the condyle undergoes an age-dependent change in growth direction – In controls, closure of the CRO (gonial) angle averaged 8.8º, while opening by 2.8º in the experimental group.
- In other words, the forward growth rotation of the condyle in growing monkeys wearing bite-protrusive appliances, appeared to be neutralized by remodelling of the condylar head. From McNamara and Bryan (1987).

Summary of TMJ remodelling in rhesus monkeys



- Anterior displacement of the mandible in primate models alters the surface contours of the condyle, glenoid fossa and post-glenoid tubercle.
- Experiments on young monkeys suggest that condylar growth might be directed in a more posterior direction. This would account for the increased length of the mandible in experiments using linear parameters – and provides an indication as to what might be happening in growing children treated with 'bite-jumping' appliances such as the Twin-block and Herbst.

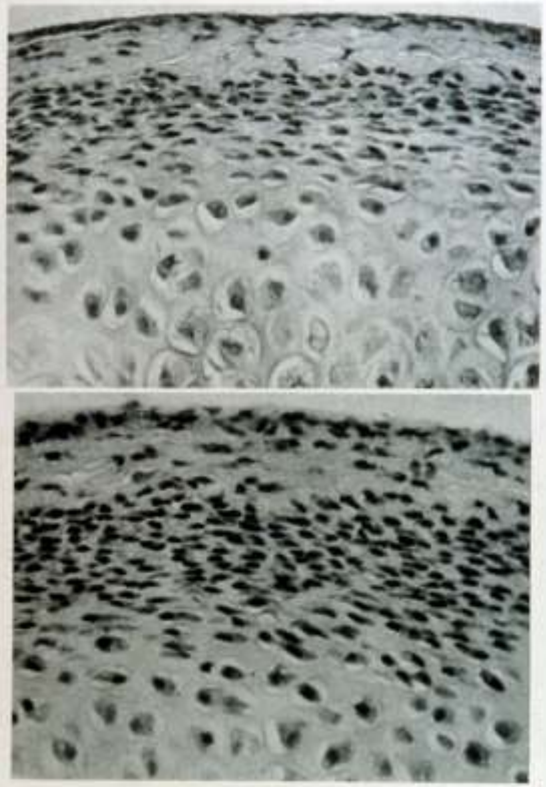
Protrusive function in rats

- Setting aside the ethics of carrying out experiments on one of our primate cousins – *mea culpa* – not to mention the considerable expense of housing and maintaining a regional primate centre, few orthodontic departments had access to monkeys, and had to make do with rats.

- It was Petrovic and the Strasbourg group in the 1960s that championed the idea that functional mandibular protrusion in the rat can stimulate growth of the condyle by increasing cell division within the proliferative zone. A view that became widely embraced by many orthodontists as an evidence base for the use of functional appliances.

- In their first English language article (Charlier *et al*., 1969) they described an experiment in which 4-week-old rats wore an anterior mandibular displacement device 4h/day for 4 weeks.

Effect on the proliferative zone

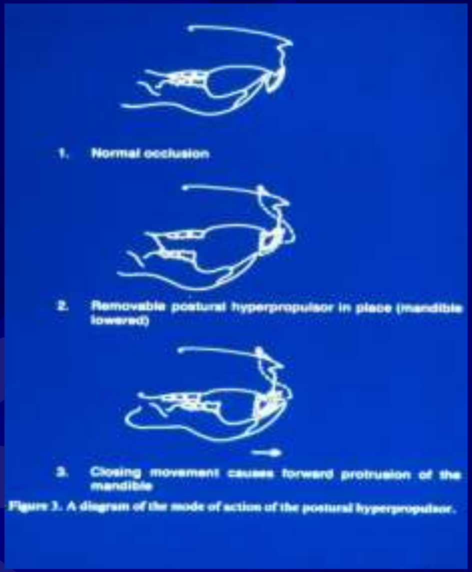


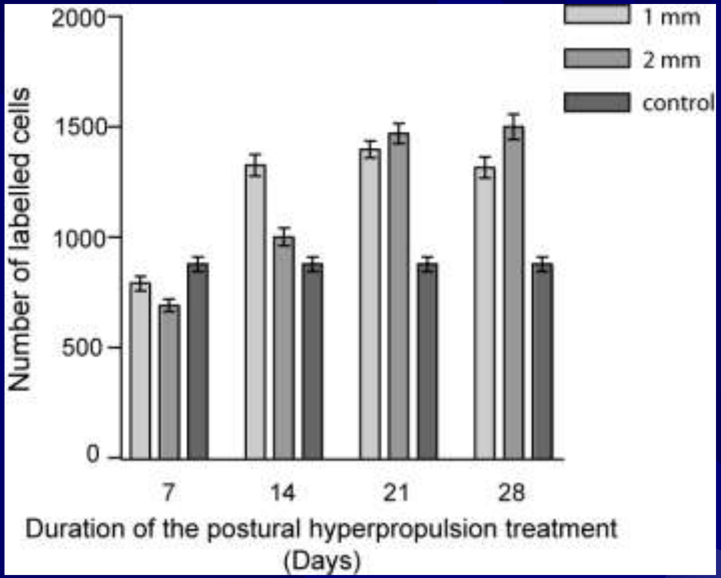
Figs. 1 and 2. Condyles of control and treated rats. These rats came from the same litter, one (**Fig. 1**) as a control and the other (**Fig. 2**) being put for a 4 week period under mandibular hyperpropulsion. The above figures show sagittal sections through the condyles. A comparison of the two figures shows that the prechondroblastic zone in the treated rat is significantly increased in length.

- The results section consisted of 19 lines of narrative and the figures shown here; parsimonious even by the standards of the time. No quantitation was attempted, eyeballed data being apparently acceptable by the editor of the leading orthodontic journal of the day.
- Attempts to confirm these data using biochemical, histomorphometric and autoradiographic methods have been equivocal (Tonge *et al*., 1982; Degroote, 1984; Ghafari and Degroote,1986; Tewson *et al*. 1988).

Image from: Charlier J-P, Petrovic AG, Herrmann-Stutzmann J (1969). Effects of mandibular hyperpropulsion on the prechondroblastic zone of the young rat condyle. *American Journal of Orthodontics* **55,** 72–74.

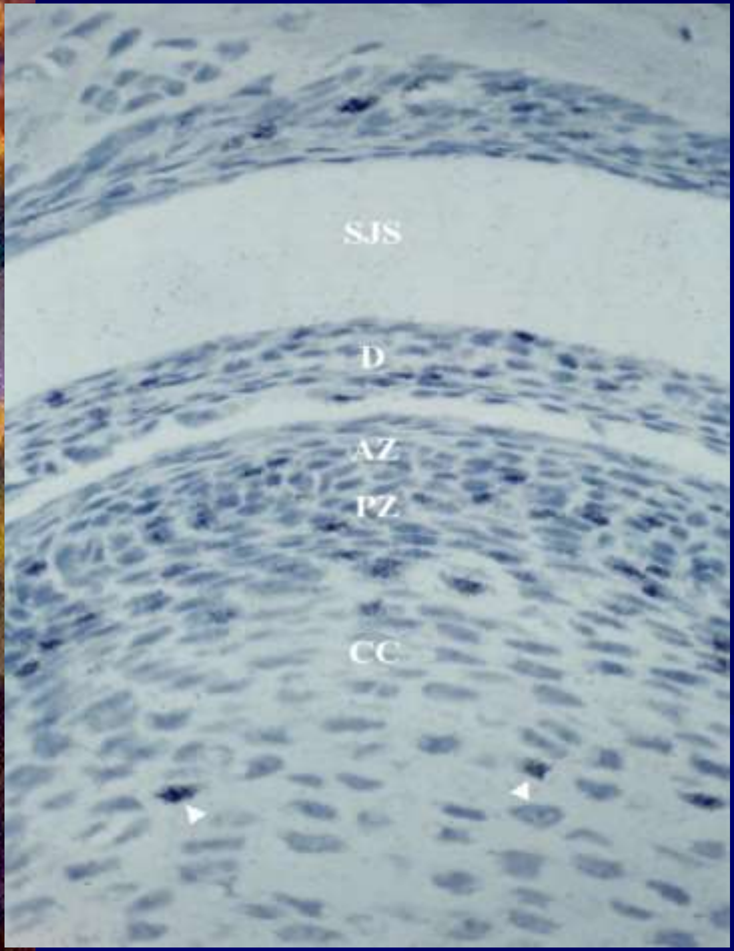
Ann Arbor symposium





- At the Craniofacial Growth Symposia held at Ann Arbor, Michigan in 1975 and 1977, Petrovic presented further data on mandibular protrusion for 8–12 hrs/day in 4-week-old rats; this time ^{3}H-thymidine had been injected 1 h prior to sacrifice and the tissue processed for autoradiography.
- They reported an increase in the number of labelled cells, and further claimed stepwise advancement by 1mm and 2mm could increase the number of labelled cells. This seemed unlikely given the anatomy of the rat craniomandibular joint, and the A–P mobility of the mandible.
- Data from Petrovic *et al*. (1977). In: *The Biology of Occlusal Development.*

Significance of a labelling index



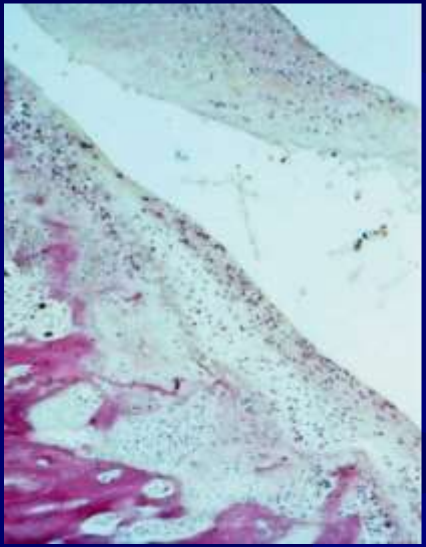
Autoradiograph of a rat craniomandibular joint sectioned coronally and labelled with ^{3}H-thymidine 24 h prior to sacrifice.

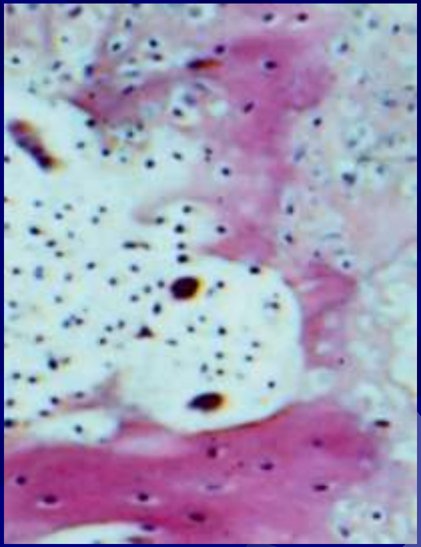
- It is important to present autoradiographic data in the form of a labelling index. *i.e*. the number of labelled cells related to the total number of cells counted in a standardized field to normalize the data. Just counting the labelled cells alone is not acceptable.
- This is a fundamental principle in any system of quantitation to compensate for the variation inherent in all biological systems (3 labelled cells out of 30 is the same as 30 out of 300). Sections for analysis should also be counted ‘blind’ to eliminate potential subjective bias.
- In Slide 30, the same control group was used over the 4-week time-course – an unacceptably long time.

Anatomy of the rat skull

- The craniomandubular articulation of the rat does not have a post-glenoid tubercle, or an anterior articular eminence as in monkeys and humans.
- This provides the rat mandible with a considerable degree of anteroposterior mobility, as we found out through hard experience with a fixed bite plate (Slide 33). It is not something that can be regulated by the addition of just 1 mm or even 2 mm to the incisal edge of an anterior bite plane.

Effect of a fixed bite plate

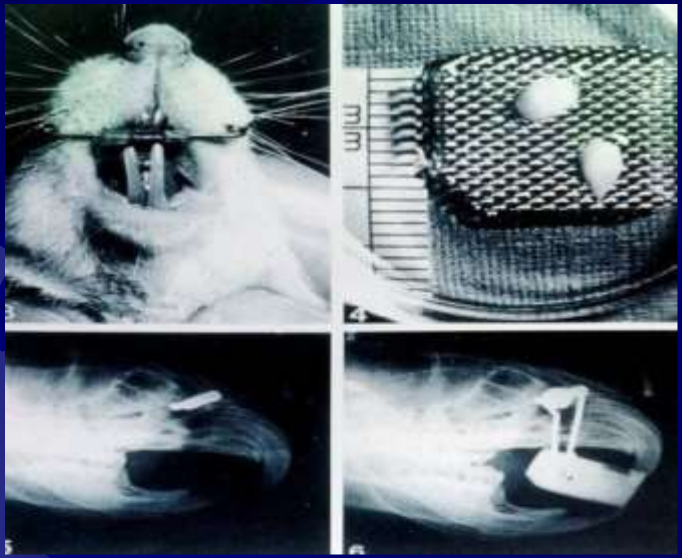


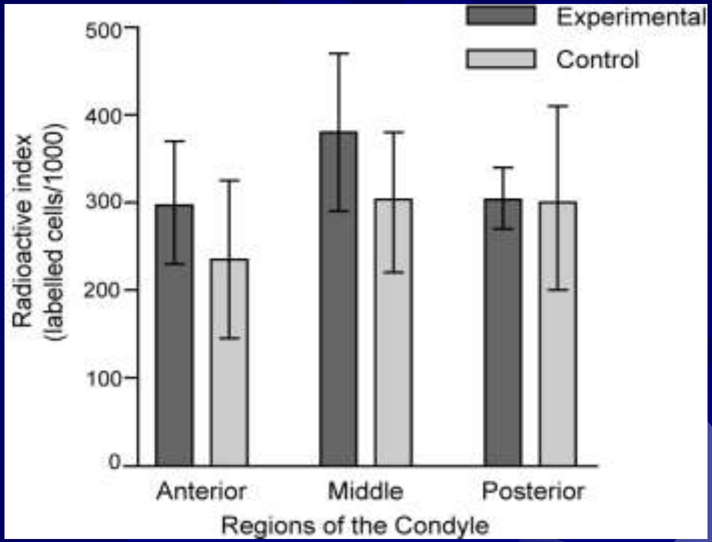


- In a University of London MSc research project, anterior displacement of the mandible in 4-week-old rats was produced by (1) cast-gold splints cemented to the upper incisors, and (2) a removable stainless steel mesh appliance worn 6 h each day.
- The most striking effect in the fixed-appliance group was to induce resorptive remodelling of the condylar head, with thinning of the adjacent disc; this took the form of hyalinization of soft tissues, or in more extreme forms, resorption of the subchondral bone and induction of osteoarthritic-like lesions.

From Tonge *et al*. (1982). *American Journal of Orthodontics* **82**, 277–287.

An *in vivo/in vitro* rat model



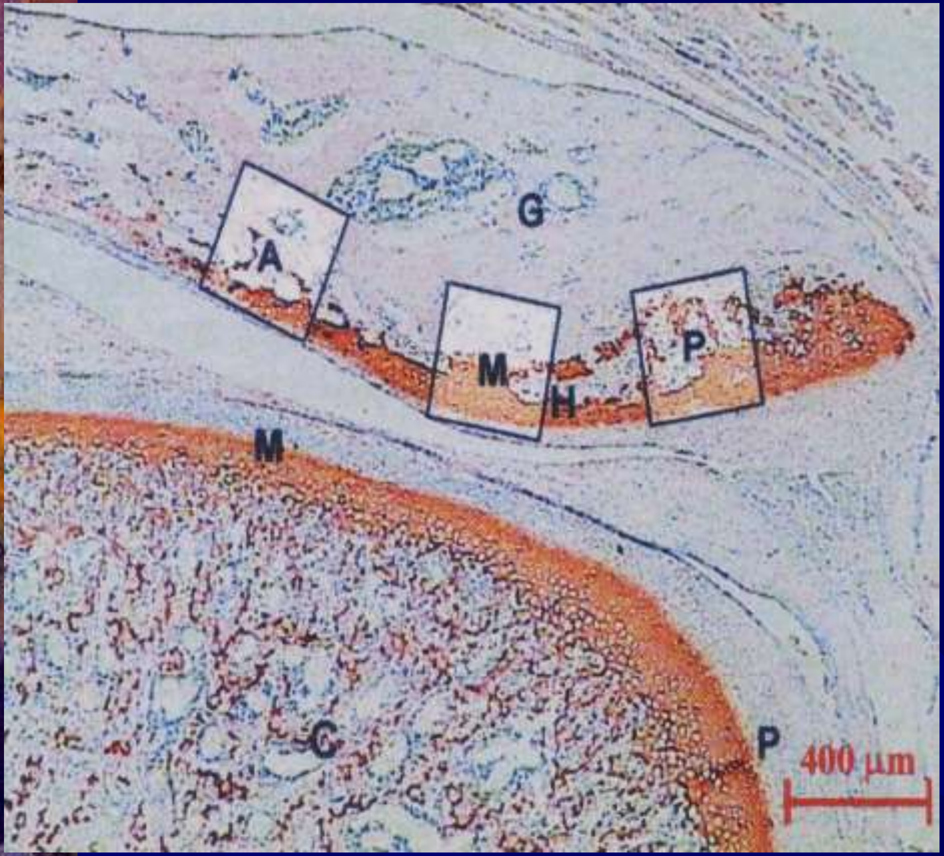


- In another London MSc research project, a removable mandibular displacement appliance was worn 10 h/day for 2 weeks; after sacrifice condylar explants were pulsed *in vitro* for 6 h with either ^{3}H-proline for matrix formation, or ^{3}H-thymidine and processed for autoradiography. The labelling index was expressed as labelled cells/1000.
- No significant increase in matrix formation or cell proliferation could be detected in the experimental group at any point in the time scale. The sections were counted 'blind' which accounts for the size of the error bars.
- From Tewson *et al*. (1988). *Archives of Oral Biology* **33**, 99–107.

Alterations in gene expression in rats

- More recently attention has been focussed on the molecular mechanisms involved in adaptation of the craniomandibular joint of the rat to protrusive function, both with fixed and removable displacement devices.
- The effect of mandibular advancement on the expression of growth factors (IGFs, VEGF, TGF-β), structural proteins (collagen types II and X), transcription factors (Sox-9, Cbfa-1) and hedgehog (Hh) genes have been reported, most notably from the University of Hong Kong.

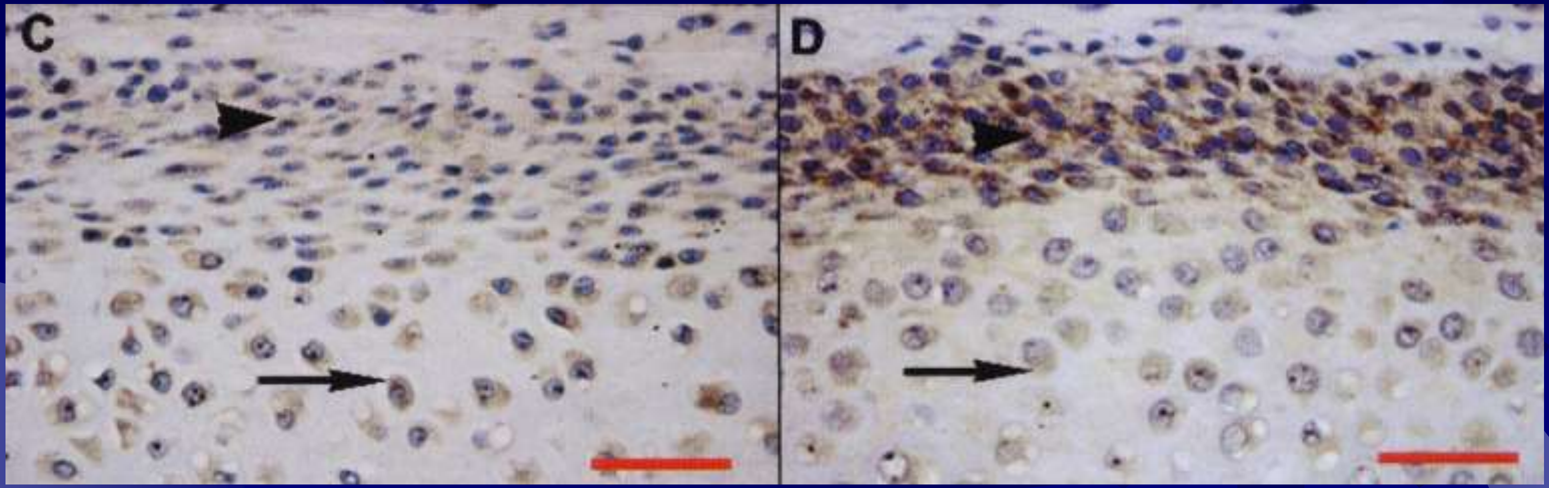
Sox9 and type II collagen expression



- Sox9 is a transcription factor that controls the differentiation of mesenchymal stem cells into chondroblasts, while type II collagen is the principal collagen in cartilage.
- Both these markers were found to be up-regulated in the glenoid fossa (the Fig. shows type II collagen expression) and Sox9 in the proliferative zone following forward mandibular positioning, suggesting enhancement of chondrogenesis.

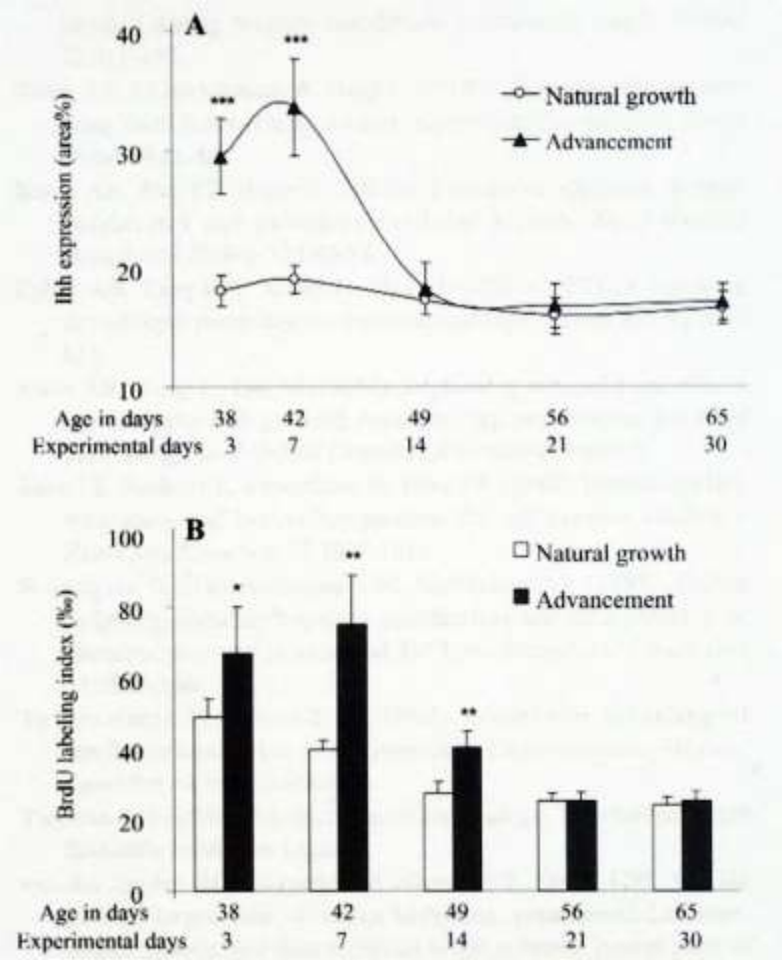
From Rabie *et al.* (2003). Forward mandibular positioning up-regulates Sox9 and type II collagen expression in the glenoid fossa. *Journal of Dental Research* **82**, 725–730.

Indian hedgehog expression



- Indian hedgehog (Ihh) is a member of the Hh family of signalling molecules which play key roles as morphogens in skeletal development.
- Ihh regulates the differentiation of chondrocytes in the growth plate of long bones in a negative feedback loop with PTH-RP (parathyroid hormone-related protein) produced in the perichondrium.
- The figure shows the immunolocalization of Ihh in the proliferative zone in control (C) and (D) experimental condyles after 7 days mandibular displacement.
- From Tang *et al.* (2004). Indian hedgehog: a mechanotransduction mediator in condylar cartilage. *Journal of Dental Research* **83**, 434–438.

Temporal pattern of Ihh expression



- This figure shows the temporal expression of Ihh (A) and the proliferation of undifferentiated mesenchymal cells in the proliferative zone of the condyle using BrdU labelling (B), during natural growth and following mandibular advancement.
- Both these increases proved to be transient, however, reaching a peak after 7 days and returning to control levels by day 14 for Ihh, and day 21 for BrdU.
- From Tang *et al*. (2004). *Journal of Dental Research.* **83**, 434–438.

Interpretation of these findings

- These findings have been interpreted by some as proof that functional appliances enhance condylar growth by stimulating the proliferation and differentiation of PZ cells into chondroblasts.
- Elegant thought these experiments may be, the temporary nature of the reported changes presents a problem – furthermore, the ability of cells and connective tissues to respond to mechanically induced strain is well-established in other model systems, including tooth movement in the rat (Smith and Roberts (1980) *Calcified Tissue International* **30**, 51–56).
- It is perhaps not surprising therefore, to find that cells in the craniomandibular joint of the rat respond to mechanical deformation in a similar manner, in terms of both changes in proliferation and metabolic activity.

Summary of the findings of animal experimentation

- Facial sutures attaching the dentomaxillary complex to the rest of the skull can be readily be remodelled by mechanical forces of appropriate force, direction and duration.

- Function plays an important role in the differentiation and maintenance of condylar cartilage and is necessary for the differentiation of PZ cells into chondroblasts – to put it simply – no function, no cartilage.

- However, the extent to which functional activity regulates the proliferative activity of PZ cells remains unclear. Do the transient changes in cell proliferation and metabolism reported by some groups simply represent a localized adjustment to altered mechanical strain – or an increase that might be translated into an enlargement of the size of the condyle?

- Given the ambiguity of the experimental and anatomical evidence from rat models, the hypothesis that functional mandibular displacement stimulates the mitotic activity of PZ cells, and hence the growth of the condyle in humans, should remain firmly in the category labelled ‘unproven’.

- It would certainly seem to be a weak basis on which to make statements such as ... ‘this indicates that functional appliance therapy can truly enhance condylar growth’ (Rabie *et al*., 2003). It would be nice to think so, but clinical experience suggests otherwise.

- Experiments performed on rhesus monkeys suggest that while anterior mandibular displacement may not increase condylar growth (addition of a few layers of cells, impressive though it make look down a microscope, is unlikely to make much difference to a 10 mm overjet), it may alter mandibular growth direction. This hypothesis may have clinical utility in an actively growing child.

- With this background information from animal models, let us now turn to the evidence of clinical investigations undertaken to evaluate the effect of various functional orthodontic appliances on dentofacial growth.

Dentofacial orthopaedics and growth modification

- While fixed appliance systems were being developed in the United States, a parallel philosophy of treatment – dentofacial orthopaedics was evolving in Europe. This method was based on removable appliances, intended as the name implies to move bones as well as teeth.
- The earliest functional appliance the Monobloc, was introduced by the French stomatologist Pierre Robin (1867–1949) in the early 1900s and was designed to correct jaw relationships in infants with Pierre Robin Syndrome – mandibular retrognathia and glossoptosis (clefting of the secondary palate was added in the 1960s).
- The first functional appliance to gain widespread clinical use was the Activator (the name was derived from activation of the musculature by the appliance), designed by Viggo Andresen (1870–1950) and developed in collaboration with Karl Häupl (1893–1960) into the Norwegian system of functional jaw orthopaedics.

Herbst and Twin-block appliances

- Appliances designed to treat Class II malocclusions. The original Herbst appliance consisted of a telescopic hinge attached to bands on the upper first molars and lower canines, rescued from obscurity by Hans Pancherz in the 1970s. The Twin-block developed by Scottish orthodontist William Clark, uses simple bite blocks with inclined occlusal planes to displace the mandible forwards, a principle similar to the appliance illustrated above in Herbst's textbook of 1910.
- According to the British Orthodontic Society website (2020), Clark's Twin-block is now the most commonly used functional appliance worldwide. Easy to make,, well-tolerated by patients and usually worn full-time, it is the author's functional appliance of choice.

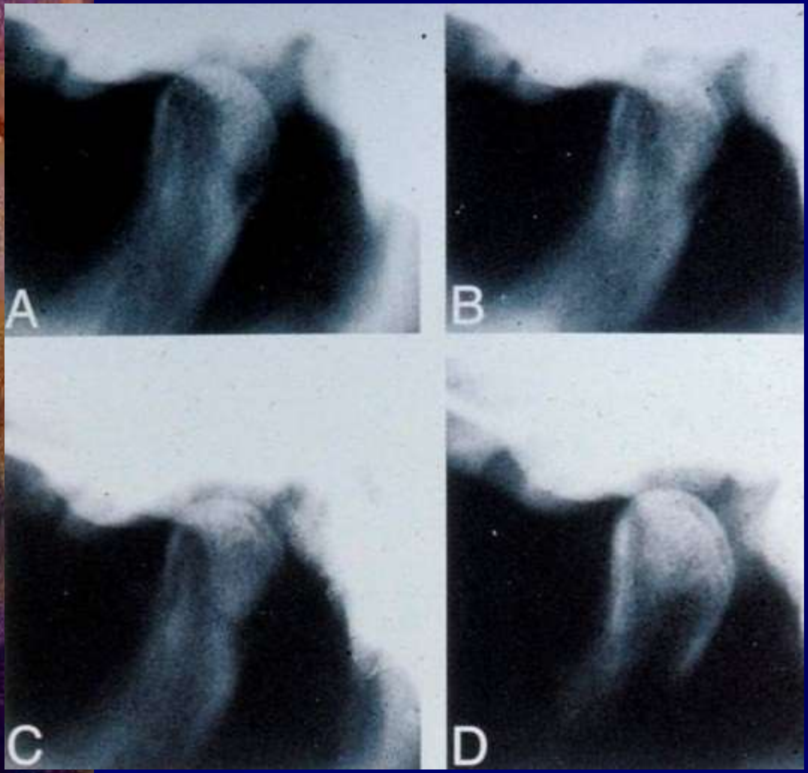
Can the TMJ be remodelled clinically?

- It is clear that functional displacement of the mandible in primate models alters the surface contours of the condyle, glenoid fossa and post-glenoid tubercle. In this respect the TMJ is no different from any other joint. It has been known at least from the time of Alexander Ogston in the mid-19th century, that the articular surfaces of bones can be remodelled.

- There is also evidence from experiments on young rhesus monkeys to suggest that condylar growth might be directed in a more posterior direction. This would account for the increased length of the mandible in experiments on monkeys using linear parameters – and provides a valuable indicator as to what might be happening in growing children treated with 'bite-jumping' appliances.

- Remodelling the TMJ in monkeys is one thing, remodelling it clinically another. Nevertheless, there is some evidence from patients treated with the Herbst appliance to suggest that it might be possible.

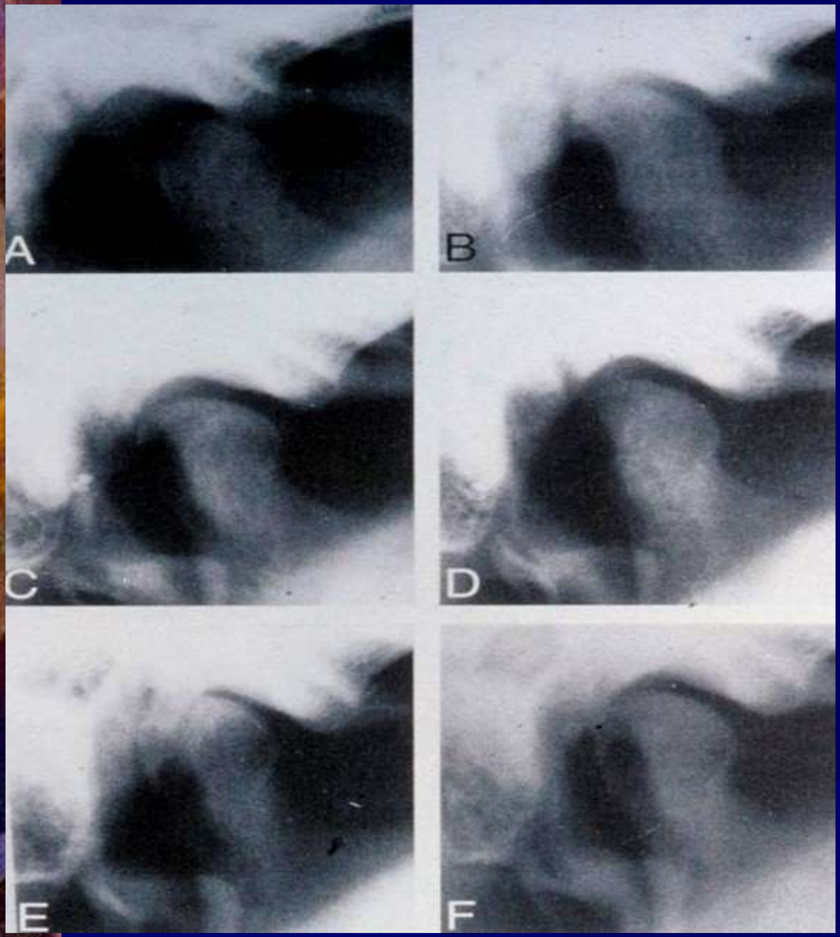
Changes in TMJ morphology



- The TMJs of 100 patients consecutively treated with the Herbst appliance were analyzed by OPG and transpharyngeal radiographs.
- The orthopaedic effect was in most cases visible as a change in the morphology of the condyle, represented by a double contour of the condylar head and in some cases, the distal border of the ramus - and persisted for a few months to several years.
- Female treated with a Herbst appliance in adulthood. (A), pre-treatment; (B), 8 months active treatment; (C), after 1 year (D) 2 yrs.

Images from: Paulsen HU (1997). Morphological changes in the TMJ condyles of 100 patients treated with the Herbst appliance in the period of puberty to adulthood: a longitudinal radiographic study. *European Journal of Orthodontics **19**, 657–688.*

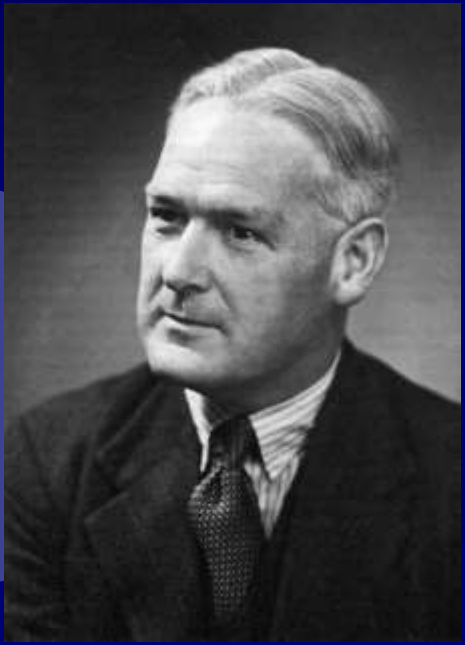
TMJ remodelling at pubertal peak



(A) pre-treatment; (B) 6 mo; (C) 9 mo; (D) 1yr 6 mo; (E) 3 years; (F) 4 years.

- Girl treated with Herbst at pubertal peak. The newly formed bone appeared to be stable and no TMJ problems were reported.
- The changes in contour were interpreted as representing remodelling activity at the condylar head. In other words, an adaptive response to the continual forward displacement of the mandible.
- However, the ability to induce remodelling in late puberty in some girls was minimal with the condyles seemingly unchanged.
- From Paulsen (1997). *European Journal of Orthodontics* **19**, 657–688.

Sir Austin Bradford Hill and the randomized clinical trial



- The first randomized clinical trial (RCT) was carried out by Sir Austin Bradford Hill in 1946, when he was asked by the Medical Research Council to test the effectiveness of streptomycin in the treatment of pulmonary tuberculosis. Apart from the fact that Hill wanted to use randomization as a method, there was insufficient streptomycin available at the end of the War to give it to all the patients that needed it, thereby making a virtue out of a necessity.

Bradford Hill (1897–1991) was Professor of Medical Statistics at the London School of Hygiene and Tropical Medicine, a statistician who avoided almost all mathematical formulae, and cautioned against confusing statistical precision with validity. Worth remembering when next reading an article claiming to show statistically significant differences in some parameter at the 0.01 level, based on anatomical landmarks with measurement errors up to 1.00 mm or more.

Randomized clinical trials

- The prospective RCT is seen to be the ‘gold standard’ for analysing treatment outcome, and for many the only valid source of clinical data. The scientific worth of the retrospective study, the traditional method used to evaluate the effects of orthodontic treatment has been criticized for a number of reasons.
- These include selection bias, inadequate sample size, lack of contemporaneous controls, poor research design; and as a consequence have fallen out of favour. These are perfectly valid criticisms, but do not confer on us the freedom to ignore the knowledge we already have.
- In the Brave New World of evidence-based practice, before administering the last rites over retrospective clinical studies, one is bound to ask – just how good is the evidence obtained by prospective randomized clinical trials of orthodontic treatment?
- Over the past decade, having listened to many talks on the findings of RCTs designed to test the hypothesis that certain orthodontic appliances can modify dentofacial growth, one is struck by the often quite marked difference between the conclusions, and one’s own clinical experience.

RCTs of Class II treatment

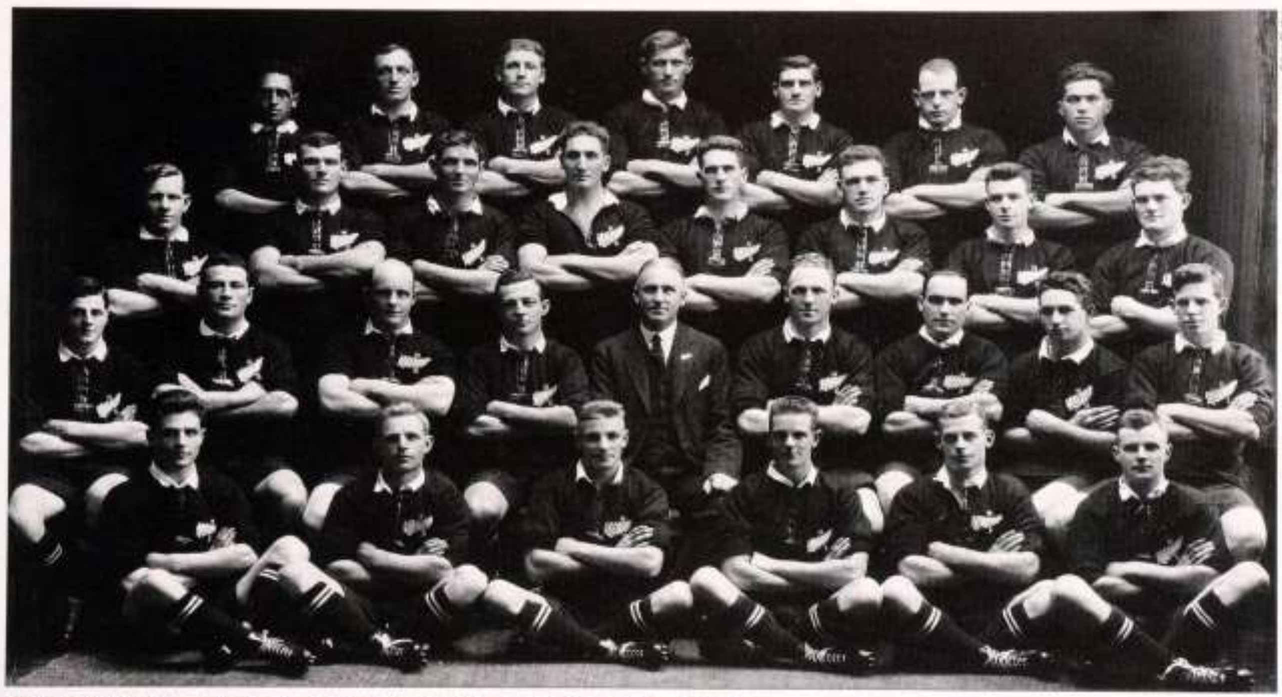
Table 1 Randomized clinical trials of class II treatment: effect on mandibular growth. Reproduced from Meikle.[21]

Study and analysis	Appliance	Number treated/control	Age	Change* (mm)
Jakobsson (1967)[73] Change in Pog	Andresen activator	17/19	8.5 (mean)	NS
Nelson *et al.* (1993)[74]	Fränkel FFR	13/17	11.6 (mean)	NS
Co–Pog	Harvold activator	12/17		
Tulloch *et al.* (1997)[75] Co–Pog	Bionator	53/61	1 year pre-PHV	1.33†
Keeling *et al.* (1998)[76] Johnston analysis	Bionator	78/78	9.6±0.8	0.8†
Pancherz (1982) Pancherz analysis	Herbst	22/20	12.1±0.11	2.2
Lund and Sandler (1998) Ar–Pog	Twinblock	36/27	12.4 (mean)	2.4
O'Brien *et al.* (2003)[77] Pancherz analysis	Twin block	73/74	8–10 (range) 9.7 (mean)	1.55

*Mean differences between experimental and control groups.
†Mean annualized change (mm/year). In the Pancherz (1982) study, the treatment time was 6 months.
NS: not significant; all other differences are small but statistically significant. PHV: peak height velocity.

- (1) Small but statistically significant differences in mandibular length were detected in the majority of these studies; (2) The Herbst and Twin-block based on 'jumping the bite' were more effective at modifying mandibular growth than the Activator and its variants.
- Outcome measurements will be influenced by (1) Failing to take into account sexual dimorphism amongst the participants; (2) Inaccuracy of cephalometric methodology; (3) Validity of the measurements of mandibular growth; (4) Age of the patients, and the timing of the pubertal growth spurt and PHV.

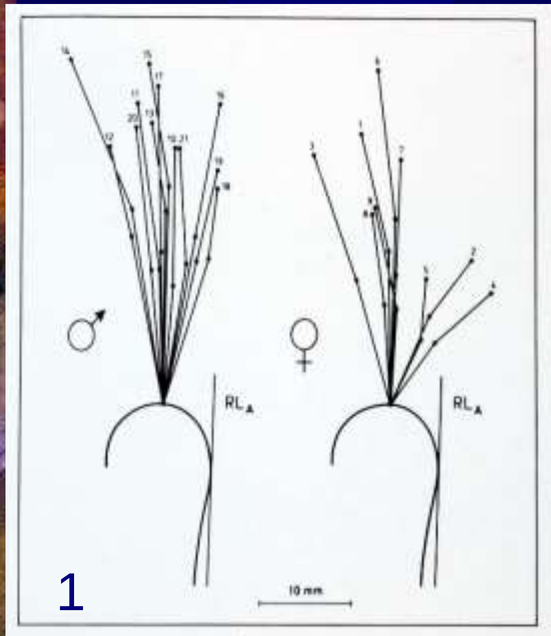
We treat individuals not averages

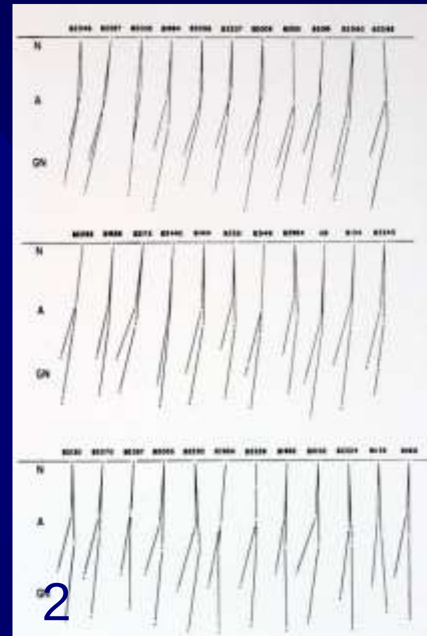


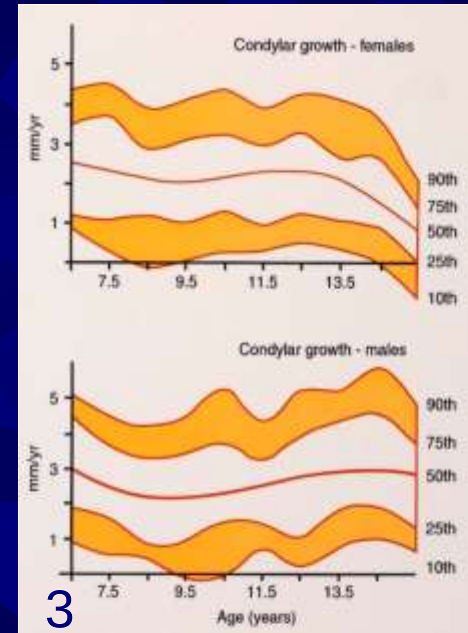
THIRD ROW: L.M. Paewai, J.H. Parker, M.J. Brownlie, C.J. Brownlie, A. White, Q. Donald, G. Nepia.
SECOND ROW: W.R. Irvine, I. H. Harvey, A.H. West, L.F. Cupples, R.T. Stewart, R.R. Masters, A.C. Robilliard, J. Steel.
FRONT ROW: A.H. Hart, B. McCleary, H.G. Munro, C. Badeley, S.S. Dean (manager), J. Richardson (vice-captain), C.J. Porter (captain), J. Mill, M.F. Nicholls.
IN FRONT: N.P. McGregor, W.C. Dalley, A.E. Cooke, F.W. Lucas, K.S. Svenson, H.W. Brown.

- New Zealand Rugby Team, aka ‘The All Blacks’ that toured the United Kingdom, Ireland, France and Canada 1924–25 – nicknamed ‘The Invincibles’ after winning all 32 of their games.
- The average height of the 29 players was 5 feet 8 inches (1.77 metres), and the average weight 12.2 stone (77.5 kg). Two were the average height; none were the average weight.

Variability in condylar growth







- (1) The wide variability in the amount and direction of condylar growth in 12 boys and 9 girls over a 6-year period. (From Björk, 1963).
- (2) Thirty-four subjects from 3–18 years in the Bolton Study ranked in order of forward movement of gnathion. Change in Gn ranged from –3.7 mm (B2049) to +12.75 mm (B1168). (From Lande, 1952).
- (3) Growth velocity curves for the mandibular condyle based on changes in condylion. (Redrawn from Buschang *et al*., 1999).
- These differences/variations will have a significant effect on treatment outcome.

Conclusions

- I'm tempted to think of a functional appliance as a form of artificial selection – being used by the clinician to 'select' out those patients with sufficient growth potential to respond to a particular type of treatment. In Darwinian terminology, the appliance enables the intrinsic growth of the mandible to be optimally expressed.

- By focussing on individual variation, we are in good company; genetic variation was the starting point for Charles Darwin and the most revolutionary and iconoclastic book of the nineteenth century – *On the Origin of Species by Means of Natural Selection* (1859).

- Modern *Homo sapiens* are not genetically homogeneous, we are characterized by endless anatomical and physiological variation; the greater the variation between individuals, the harder it is to demonstrate that a difference in treatment effect is significant or does in fact exist. The key to understanding how patients respond to treatment in all branches of medicine is variation, variation, variation.

- Optimal conditions for achieving growth modification occur when treatment coincides with the pubertal growth spurt and ideally peak height velocity (PHV); it is clear from Slide 49 that the ages of many of the participants in these orthodontic RCTs were some distance from reaching these milestones.

- Also muddying the water is the fact that two-stage treatment means different things to different people. If two-stage means starting appliance therapy at age 7–9 years, followed by a break before starting a second stage in the permanent dentition with fixed appliances, this is clearly an inefficient way to provide a service.

- On the other hand, to many clinicians including the present author, two stage means a Class II treatment protocol involving preliminary functional appliance treatment in the late mixed dentition, followed seamlessly in tandem by fixed appliances, and a total active treatment time of 24 months. Like many things in life, it’s a matter of timing.