The Mechanobiology of Tooth Movement

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Biological Foundations of Orthodontics and Dentofacial Orthopaedics

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SAPERE AUDE
Te Whare Wānanga o Otāgo

Orthodontic tooth movement

- Much of the previous discussion regarding bone remodelling in Seminar 12 is applicable to tooth movement, some of which is repeated for continuity. However, orthodontic tooth movement is a more complicated process involving both the periodontal ligament and alveolar bone.
- Tooth movement is described today in terms of the pressure–tension hypothesis, which implies that when a force is applied to a tooth, resorption of bone occurs on the pressure or compression side of the root, and bone formation on the tension side. (In orthopaedic theory, compression is regarded as an osteogenic stimulus which can be confusing.)
- If the force is of sufficient magnitude to be transmitted beyond the periodontal ligament, bending of the supporting bone can occur, particularly in the anterior part of the mouth where the thinness of the alveolar plates makes deflection easier.

The periodontal ligament

- The periodontal ligament (PDL) is a specialized connective tissue that has evolved to provide attachment of teeth to the bones of the jaws. The PDL functions in a mechanically active environment, and in addition to its attachment role, serves as a shock absorber to protect the tooth-supporting alveolar bone from excessive occlusal loading.
- From a mechanical point of view, the PDL and alveolar bone represent two separate functional domains – an important distinction when it comes to understanding the remodelling dynamics of the tissues of the periodontium during tooth movement.
- An additional problem in understanding orthodontic tooth movement is that investigators have tended to focus on changes in the PDL at the expense of the bone – the pressure-tension hypothesis is a PDL-driven concept.

Laying the foundations: Carl Sandstedt

Originalartiklar.

Einige Beiträge zur Theorie der Zahnregulierung

von CARL SANDSTEDT.[1]

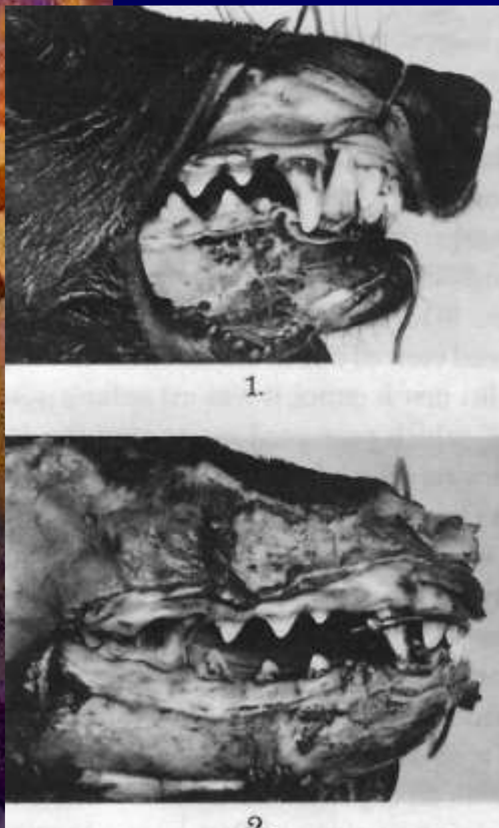
Einleitung.

Die Orthodontie, oder die Lehre von der Regulierung der Zähne, ist ein ziemlich neuer Zweig der Zahnheilkunde. Noch in der Mitte des 19:ten Jahrhunderts widmete die damals erscheinende odontologische Litteratur den Anomalien in der Zahnstellung, wie der Behandlung derselben keine oder wenig Aufmerksamkeit. Es ist auch ganz natürlich, dass man zu einer Zeit, wo die Tätigkeit des Zahnarztes sich im wesentlichen auf das Ausziehen schmerzender Zähne und auf Beschaffung eines mehr oder weniger zufriedenstellenden Ersatzes für dieselben beschränkte, einem

[1] Der Zahnarzt Carl Sandstedt starb als Lehrer am Zahnärztlichen Institut des Schwedischen Staates im Laufe dieses Jahres. Vorliegender Artikel beleuchtet ein besonders interessantes, wiewohl noch unerforschtes Gebiet innerhalb der Zahnheilkunde. Leider war es dem Verfasser nicht vergönnt, seine Arbeit über die Theorie der Zahnregulierung abzuschliessen. Was er hinterlassen hat, macht nämlich nur einen Teil der beabsichtigten Arbeit aus, ist aber nichtdestoweniger der grössten Aufmerksamkeit wert. *Die Red.*

- It is now more than 100 years since the article which forms the basis of our present knowledge of the mechanobiology of tooth movement was published by the Swedish dentist Carl Sandstedt.
- It appeared in three parts in 1904 and 1905 under the title *Einige Beiträge zur Theorie der Zahnregulierung* (Some contributions to the theory of the regulation of teeth) published in the Swedish dental journal *Nordisk Tandläkare Tidskrift* shortly after his death.

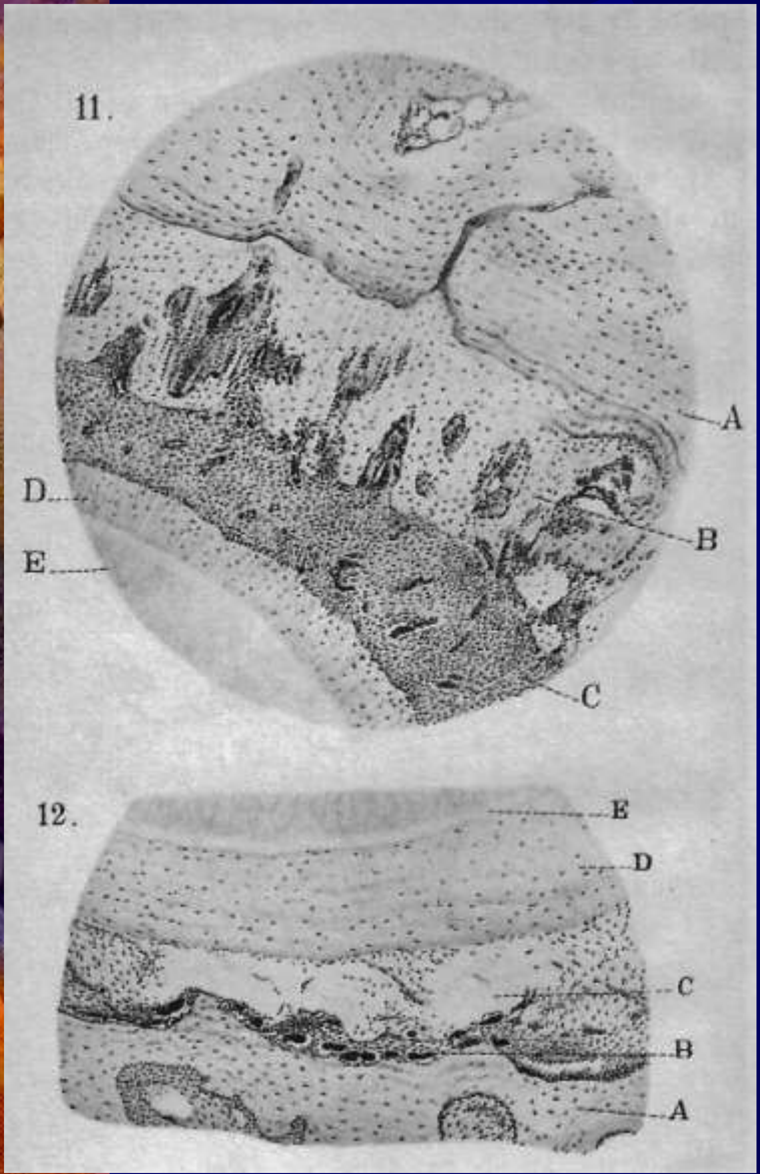
Sandstedt's experiments



- Sandstedt's experiments were carried out on dogs; a labial arch was bent to engage the six maxillary incisors and attached to bands on the canines.
- A screw mechanism was used to apply retraction to the incisors, and when activated the incisors moved lingually and the canines mesially. (Top images) The experiment lasted 3 weeks and during that time the incisors moved 3 mm.

Images from the review by Bister and Meikle (2013). Re-examination of 'Einige Beiträge zur Theorie der Zahnregulierung' (Some contributions to the theory of the regulation of teeth) published in 1904–1905 by Carl Sandstedt. *European Journal of Orthodontics* **35**,160–168. 5 plates with 16 figures were included in the three articles but were not accompanied by figure legends. These were added by the authors to the best of their ability!

Sandstedt's histological findings



- Fig. 11: Sandstedt found bone was deposited on the alveolar wall of the tension side of the tooth with both light and heavy forces; the newly formed bony trabeculae (B) on the original bone (A), followed the direction of the periodontal fibre bundles. (C) PDL; (D) cementum; (E) dentine.
- Fig. 12: On the compression side, with light forces the bone of the original alveolar wall (A) was resorbed directly by osteoclasts in Howship's lacunae (B). Localized cell-free areas he called hyalinization, owing to its resemblance to hyaline cartilage can be seen at (C). These resulted from vascular occlusion and cell-death of the PDL, and usually associated with resorption of the adjacent bone from adjacent marrow spaces; a process he called undermining resorption.
- All Sandstedt's microscopic images were drawn by hand.

Oppenheim and the law of bone transformation

- In 1911 the Viennese orthodontist Albin Oppenheim (1875–1945) published his famous article entitled ‘Tissue changes, particularly of the bone, incident to tooth movement’ in *Transactions of the European Orthodontic Society* 303–359. Reprinted (2007) in the *European Journal of Orthodontics* **29**, i2–i15.
- At the time, there were two competing theories regarding the biological basis for orthodontic tooth movement. The pressure-tension hypothesis dating back to Chapin Harris (1839), *The Dental Art. A Practical Treatise on Dental Surgery*, supported by the histological evidence of Carl Sandstedt; and the theory of bone bending advanced by Norman Kingsley (1880) in *A Treatise on Oral Deformities as a Branch of Mechanical Surgery,* based on the elastic properties of bone.
- Oppenheim rejected both and proposed an alternative – the law of bone transformation, in which a complete reorganization of the alveolar bone took place in accordance with Wolff’s Law (1892).

Oppenheim's experiments–I

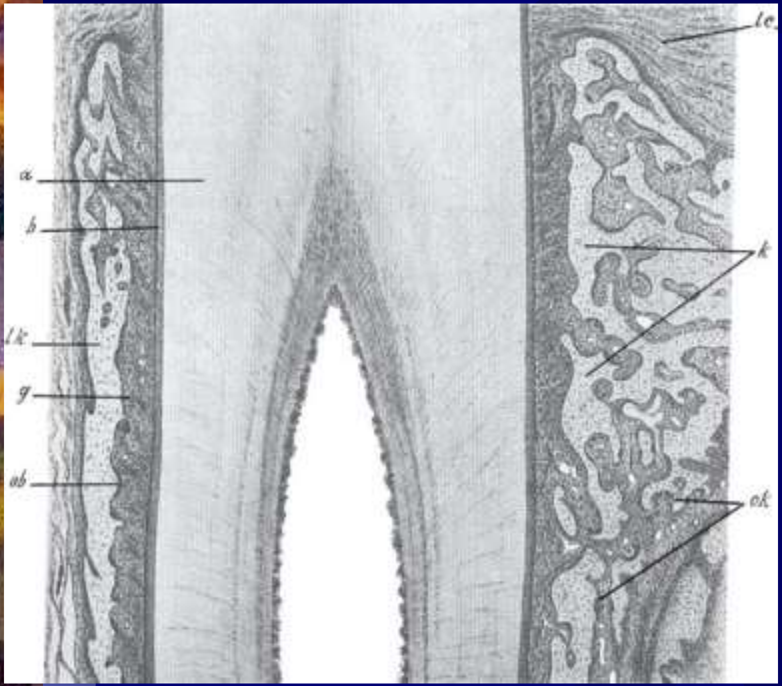
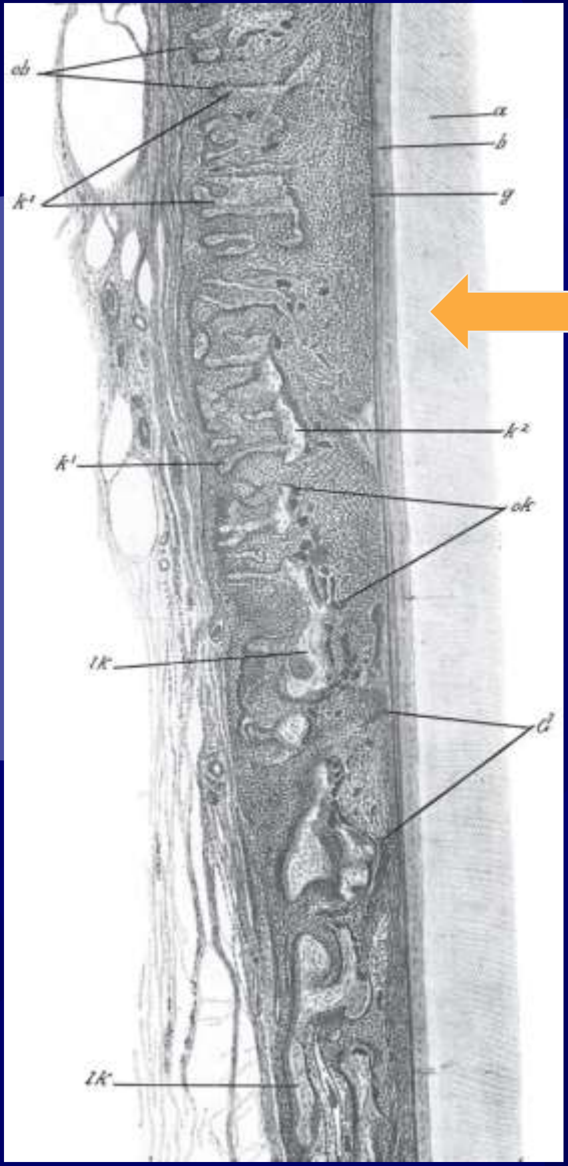


Figure 3. Section through a normal tooth. On the left labial side; a dentine; b cementum; g periodontal membrane; l,k. compact bone of lamellated structure; ob osteoblasts; l,c dental ligament; k spongy bone on the lingual side; ok osteoclasts. From Oppenheim (1911). *Transactions of the European Orthodontic Society* 303–359.

- Oppenheim's experiments were carried out on the lower deciduous incisors of baboons, although it is not clear how many animals were involved.
- The movements performed were labial, lingual, depression, elongation and rotation; one half of the jaw was operated on, the other served as a control. The paper fails to include a description or illustration of the appliance, the magnitude of the applied force, or how far the teeth were moved. The time-course was 40 days.
- The image is a sagittal section through a lower incisor, what is particularly noticeable is the thinness of the labial plate of bone.

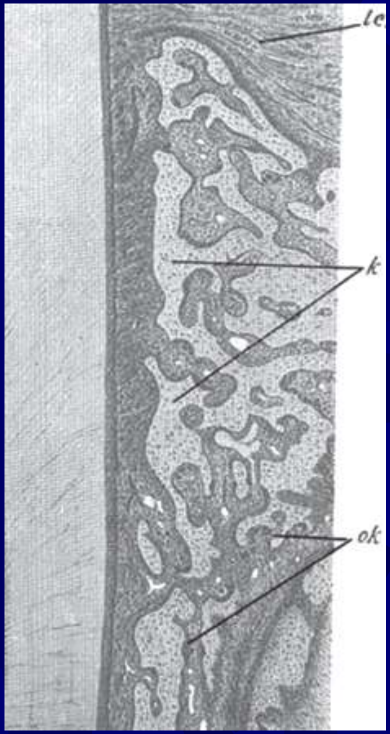
Oppenheim's experiments–II

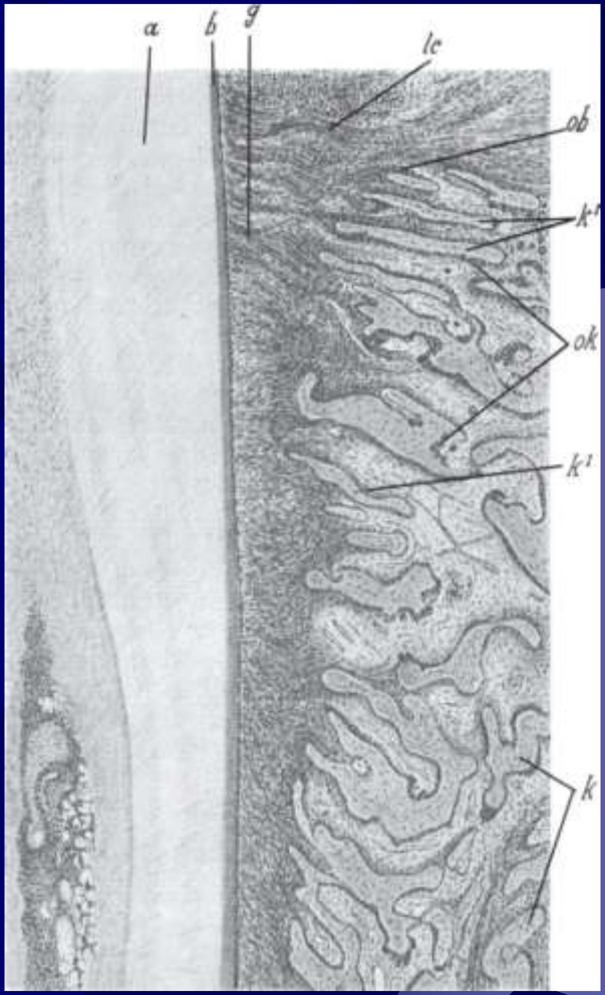


- Sagittal section through the labial bone near the alveolar border (top 2/3rds of the section) following labial movement of the tooth.
- There are no signs of bone resorption; but new bone has been laid down on the old bone, with the trabeculae orientated vertically to the long axis of the tooth.
- Although not realized at the time, the spicules of new bone resulted from the bending of the labial plate, and the deposition of bone on concave surfaces.
- *a* dentine; *b* cementum; *g* periodontal membrane; *lk* compact old bone; *ok* osteoclasts; *k1* new formed bony spicules with numerous osteoblasts ; *k2* is the remains of the original compact bone.
- Figure 4. From Oppenheim (1911).*Transactions of the European Orthodontic Society* 303–359.

Oppenheim's experiments–III

- Changes in the lingual alveolar bone following labial movement of the tooth; again, the response has been osteogenesis.
- In other words, tooth movement resulted in bone formation on both sides of the tooth with no evidence of resorption.
- Left: Lingual side of a normal tooth (Figure 3) composed of spongy bone arranged more or less in the longitudinal direction of the tooth. Right: (Figure 6) labial movement, lingual side. Newly formed bone is orientated vertically to the long axis densely populated with osteoblasts.



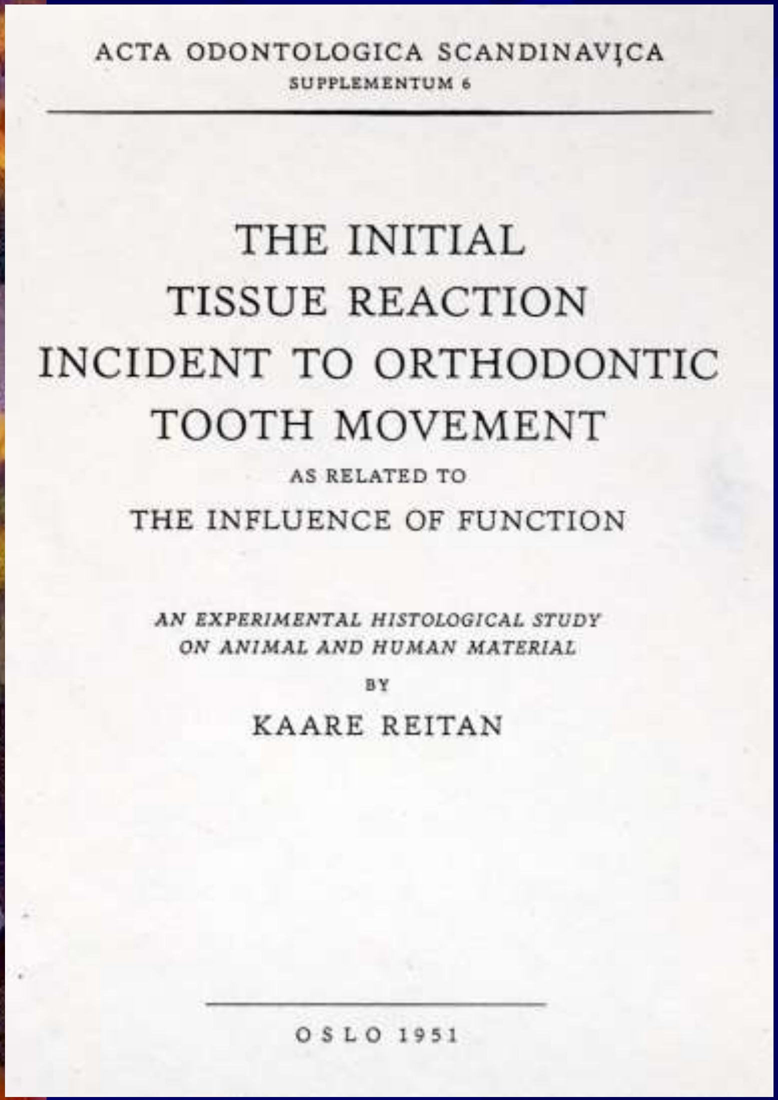


The theory of bone transformation

- Oppenheim believed that bone reacts to pressure by a transformation of its entire architecture – by resorption of the existing bone and its replacement by new bone, until finally deposition exceeds resorption. He emphasized bone transformation occurred only with very light forces, which in his hands must have been very light indeed, as he failed to observe any hyalinization of the PDL, shown by Reitan (1957) to occur with forces as light as 30 gm.
- Having found bone formation on both sides of the teeth, it is unclear how Oppenheim thought teeth were moved into a new position. In retrospect the theory made such little sense, it's surprising anyone believed it.
- Given that Sandstedt's descriptions of tooth movement are ones we recognize today, the Big Question is why his research languished in obscurity for so many years. His premature death and publishing in Swedish and German and not the Anglosphere didn't help, but are not the whole story. At this point Edward Hartley Angle (1855–1930) enters the narrative.

- Oppenheim’s research was brought to the attention of Angle who invited him to give a series of lectures at the Angle School of Orthodontia, then located in New London, Connecticut. Oppenheim and his theory of bone transformation were tailor-made for Angle and his acolytes – someone with proof that expanding the dental arches with an orthodontic appliance could stimulate the growth of bone – which became the cornerstone of Angle’s non-extraction philosophy.
- More importantly, Oppenheim remained active until his death in Los Angeles, having escaped from Austria in 1938 following the ‘Anschluss. He also had the support of many influential pupils of Angle including Frederick Noyes, Dean of Dentistry at Illinois, who in a posthumous tribute in 1945 was contemptuous of the findings of other workers.
- Sandstedt thus became the forgotten man of tooth movement research until rescued from obscurity by Schwarz in 1932. However, it was not until after WWII and the expansion of university training programmes that his work became mainstream – a salutary reminder of how ideologies or dogmas can become entrenched by powerful and dominant personalities.
- Schwarz AM (1932). Tissue changes incidental to orthodontic tooth movement. *International Journal of Orthodontia, Oral Surgery and Radiography* **18**, 331–352.

The initial tissue reaction - Reitan


ACTA ODONTOLOGICA SCANDINAVICA
SUPPLEMENTUM 6

THE INITIAL TISSUE REACTION INCIDENT TO ORTHODONTIC TOOTH MOVEMENT

AS RELATED TO

THE INFLUENCE OF FUNCTION

AN EXPERIMENTAL HISTOLOGICAL STUDY ON ANIMAL AND HUMAN MATERIAL

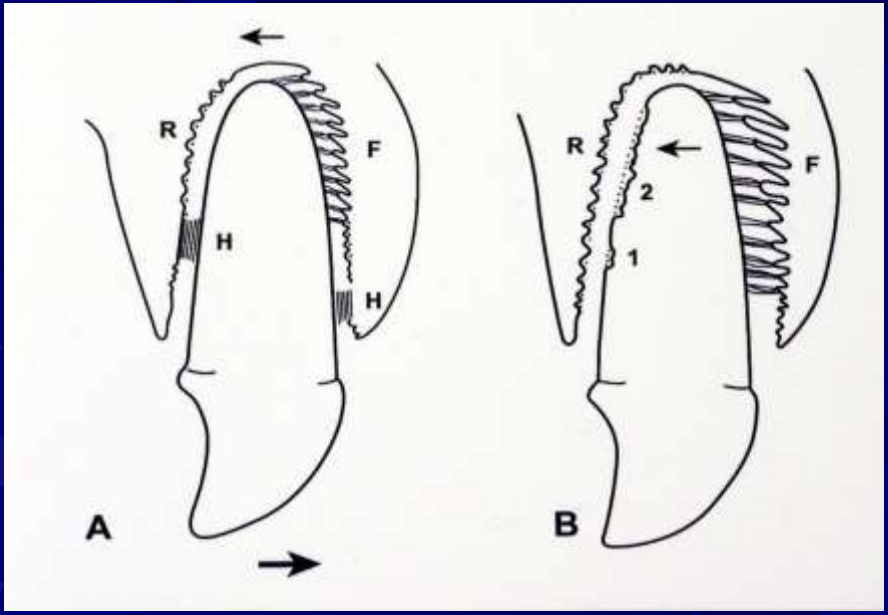
BY

KAARE REITAN

OSLO 1951

- It was not until the 1950s that tooth movement studies attracted wider attention. The leading histological investigator of the period was the Norwegian orthodontist Kaare Reitan, whose classic memoir was published in English in 1951.
- Reitan made extensive use of human material, particularly premolars destined for orthodontic extractions. His work highlighted the complexity of the tissue response, depending upon (1) the type (continuous v intermittant) and magnitude of the force applied, (2) the mechanics involved (tipping v bodily movement), and (3) the variation in tissue reaction between individuals.

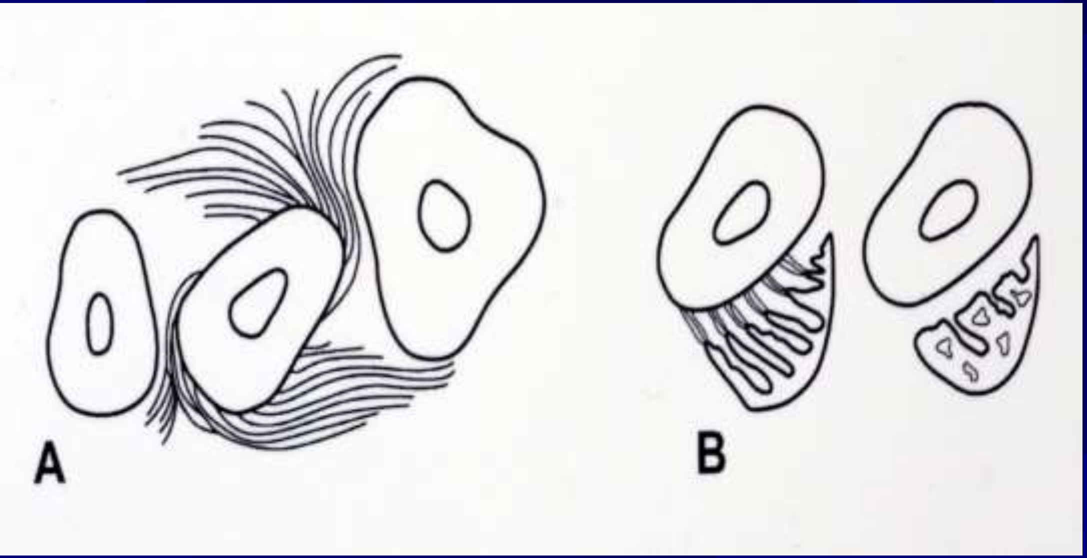
Tipping v bodily movement



Redrawn from Reitan (1964). *The Angle Orthodontist* **34**, 244–255.

- Reitan observed that during the initial stages of a tipping movement, cell-free or hyalinized areas were frequently created with continuous forces as low as 30 gm. The time taken to remove such tissue by undermining resorption varied from 2-4 weeks and was influenced by the length of the root.
- Cell-free areas were more common in tipping (A) than in bodily movements (B), presumably because in the latter the force was more evenly distributed along the root/bone interface.

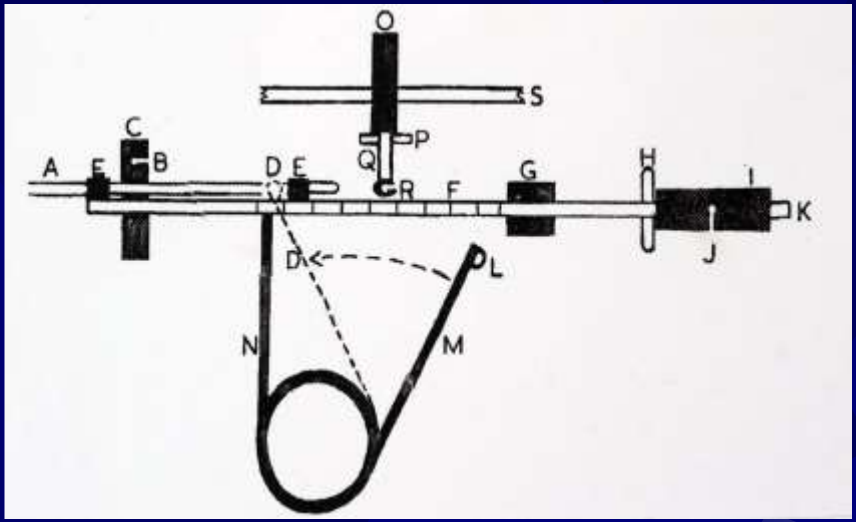
Rotational relapse



- Of Reitan’s many contributions to the literature, perhaps the most important was his study of rotated teeth in young dogs. He found that while the principle fibres of the periodontal ligament remodelled within 28 days, even after a retention period of 232 days some of the free gingival fibres remained displaced and stretched.
- He concluded rotational relapse was caused primarily by a contraction of the supra-gingival fibres (which contain elastic or oxytalin fibres), and advised over-rotation and/or pericision of these fibres to ensure tooth stability.
- From Reitan (1959). *The Angle Orthodontist* **29**, 105–113.

Force magnitude in orthodontic tooth movement

From Storey and Smith (1952). *Australian Journal of Dentistry* **56**, 11–18.



- Another key investigator from the post-war period was Elsdon Storey in Melbourne, who in a collaboration with R Smith a metallurgist, used canine retraction springs to determine optimal force levels in clinical practice.
- They found that movement of canines into premolar extraction sites occurred rapidly with forces of 150–250 gm (5–9 ounces); below 150 gm the canines did not move significantly.
- However, when springs were activated to apply forces in the range 400–600 gm (14–21 ounces), the so-called anchor teeth moved forward while the canines remained relatively stationary.

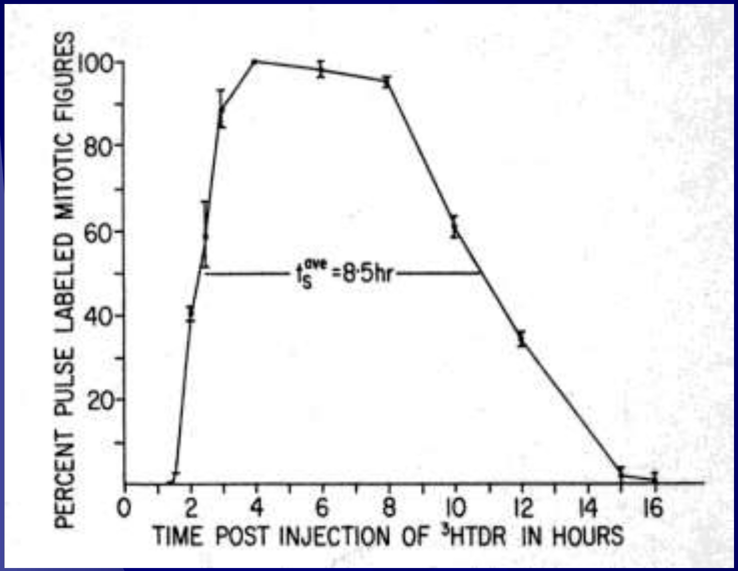
The differential force concept

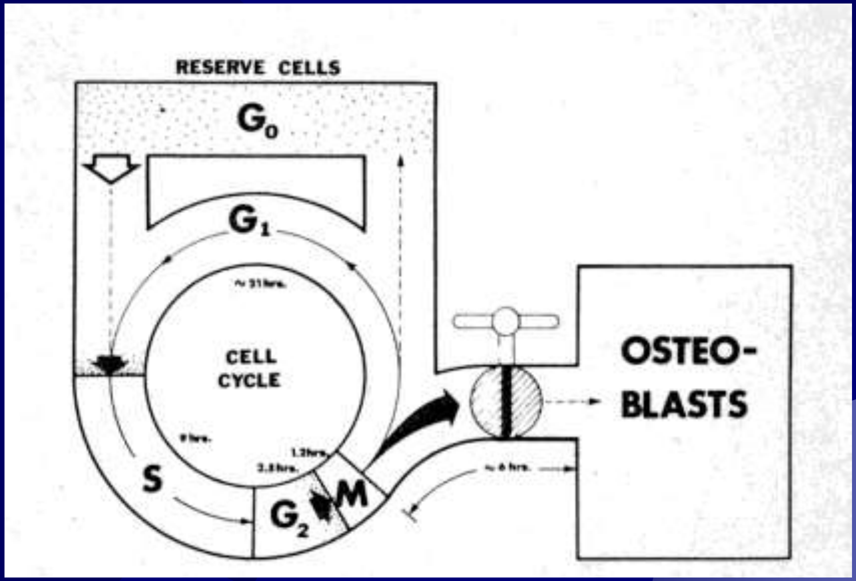
- Storey and Smith also emphasized the importance of root surface area. They estimated that the ratio of the surface areas of the bone adjoining the canine and anchor teeth was 3:8; the same as the ratio of the force required to bring about the maximum rate of movement of the canine.
- These experiments gave rise to the differential force concept, and the idea there is an optimum range of force values that will produce the maximum rate of tooth movement.
- Subsequent research, however, found that the rate of canine retraction to the forces recommended by Storey and Smith was highly variable between individual patients. This does not invalidate the concept as implied at the time, but indicates that the optimal force will be different for each patient. In any event, the magnitude of the applied force is just one of many variables affecting the rate of tooth movement.
- Another reminder of the fact that we treat individuals, not averages.

Autoradiographic studies of tooth movement

- One of the key technical developments in histology during the 1960s was the introduction of autoradiography. Tritium-labelled molecules in particular, enabled, for the first time, changes in cell proliferation and metabolic activity to be measured with reasonable accuracy.
- Using a rat molar tooth movement model, Baumrind (1969) and Baumrind and Buck (1970) reported that cell proliferation (measured by ^{3}H-thymidine incorporation) and metabolic activity (^{3}H-uridine incorporation) were increased, and protein synthesis (^{3}H-proline incorporation) was decreased, on both the 'tension' and 'pressure' sides of the PDL. This led them to question whether significant differences between the two sides actually existed.

Cell kinetics of initial response of rat PDL

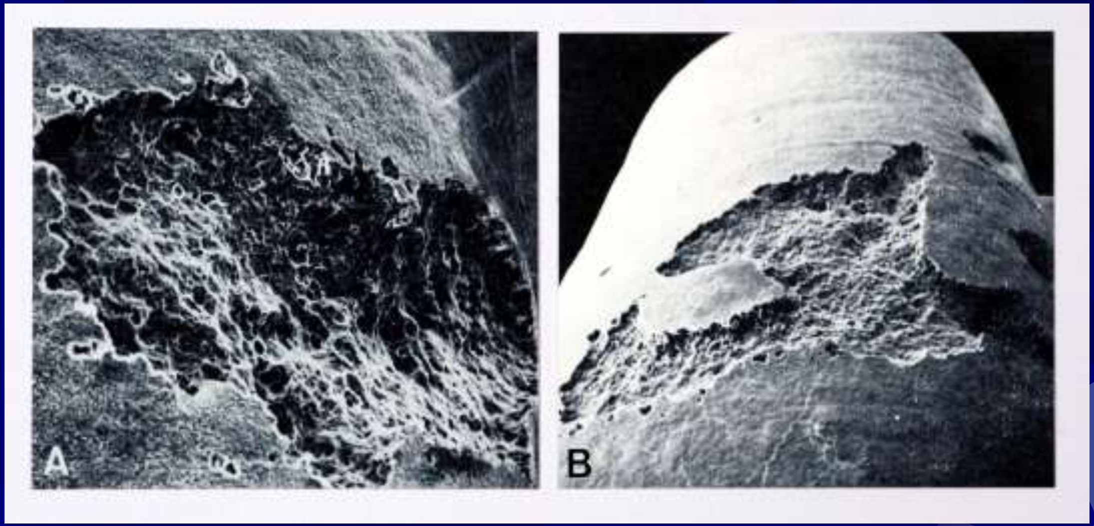




- Left. Percentage of pulse-labelled mitoses following injection of 0.5 µCi of ^{3}H-thymidine/gm body weight. The curve rose to a peak of 100% at 4 hours and dropped to basal levels at 16 hours. Duration of the DNA synthetic phase was 8.5 hours. From Roberts and Jee (1974), *Archives of Oral Biology* **19**, 17–20.
- Right. Cell cycle characteristics of rat PDL stimulated to form osteoblasts. Orthodontic stimulation releases G_1 and G_2 blocked cells and stimulates G_0 cells to enter the cell cycle. From Smith and Roberts (1980), *Calcified Tissue International* **30**, 51–56.

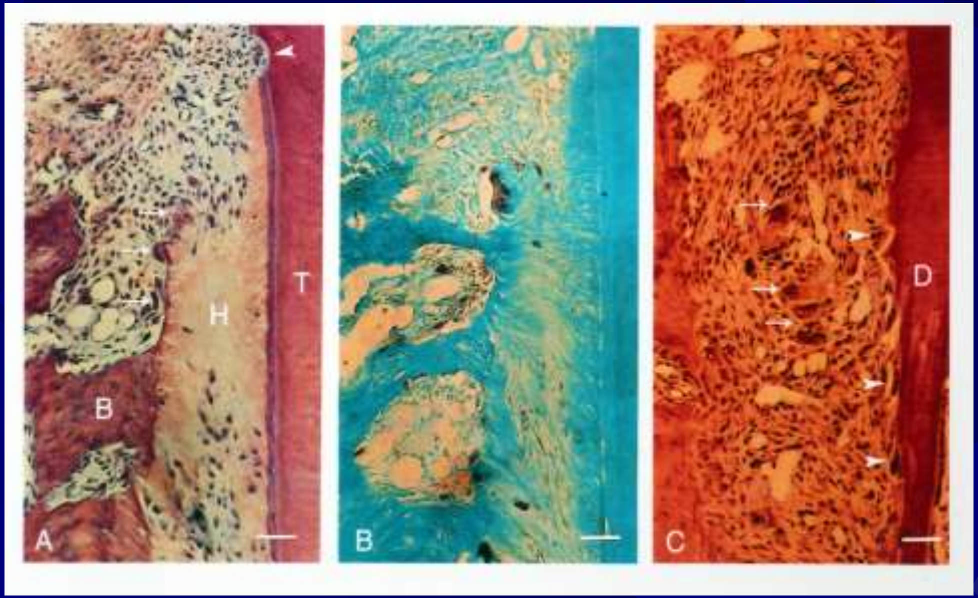
Hyalinization and root resorption

From Kvam (1972). *Scandinavian Journal of Dental Research* **80**, 357–368.



- The Scandinavian tradition of tooth movement research was continued by Kvam and Rygh, with emphasis on the cellular and tissue changes on the pressure side.
- It became clear that root resorption was a side-effect of the cellular activity associated with the removal of necrotic hyalinized tissue. Resorption defects in the dentine of human premolars occurred following the application of forces as low as 50 gm, as shown in these SEMs of teeth from patients aged 10–12 following experimental tooth movement.

The role of macrophages and giant cells



- Tartrate-resistant acid phosphatase (TRAP) staining has shown the involvement of TRAP-positive macrophages and multinucleate giant cells in the removal of hyalinized tissue and root resorption.
- In (A) the hyalinized zone (H) reveals an afibrillar structure. Resorption of bone occurs from the marrow spaces (arrows); there is also a resorption lacuna in the dentine (arrowhead). (B) Shows TRAP-positive cells. (C) The hyalinized tissue has almost been removed and multinucleate cells line the dentine surface.
- From Brudvik and Rygh (1994). *European Journal of Orthodontics* **16**, 249–263.

The propriety of the pressure-tension hypothesis

- The idea that pressure and tension sites are generated in the periodontal ligament during tooth movement is so firmly embedded in the orthodontic subconscious it is here to stay. In any event it continues to play a key role in organizing our ideas, as well as advancing our understanding of a complex biological process. However, there are two major conceptual problems associated with the hypothesis.
- First, does stretching of the principal fibre bundles of the periodontal ligament generate tension? And second, can differential pressures be developed within the tissues of the periodontium?

Does stretching the collagen fibres of the PDL generate tension?

- A persistent dogma of the orthodontic literature was that the collagen fibres of the PDL are stretched during tooth movement. Tension is thereby generated in the fibres which is responsible for the cellular response, particularly the stimulation of osteogenesis at the cortical bone surface into which the fibres are inserted. This seems to have originated from textbook images of vertical sections of teeth suspended in bone, which emphasize the role of collagen fibres in tooth support, at the expense of proteoglycans and other non-collagenous molecules not evident in conventional histology.
- To test the hypothesis that tension in the collagen fibres of the PDL provides the stimulus for osteogenesis, Heller and Nanda (1979) disrupted collagen metabolism in rats by the systemic administration of the lathyritic agent β-aminoproprionitrile (BAPN), which inhibits cross-linking of the collagen molecule. They found in lathyritic rats the histological response of the bone to tooth movement appeared normal, making it unlikely the principle fibres of the PDL undergo tensile strain, or transfer force directly to the alveolar bone via Sharpey's fibres.
- Heller IJ and Nanda R (1979). *American Journal of Orthodontics* **75**, 239–258.

Can differential pressures be generated within the PDL?

- Measurements of the experimental intrusion of teeth, suggest that when mechanically loaded the PDL behaves as a viscoelastic gel. These flow when subject to a steady force, but bounce when a load is applied briefly, and then removed. The damping of forces acting on a tooth were originally attributed to three distinct but interacting fluid systems: (1) the vascular system, (2) cells and PDL fibres, and (3) the interstitial fluid (Bien, 1966).
- While these fluid systems undoubtedly play a part, the shock-absorbing function of the PDL is more likely to result from the ability of hydrophilic proteoglycan molecules to form a strongly hydrated space-filling gel, while at the same time, their displacement is limited by the collagen fibre network, and the lamina dura of the alveolar bone.
- Momentary pressures created by mastication are therefore of different physiological significance to the prolonged pressures of orthodontic appliances, since biting forces in the neighbourhood of 1500 gm/cm^2 do not crush the periodontal membrane, and impact the tooth through bone.
- Bien SM (1966). *Journal of Dental Research* **45**, 907–914.

- Baumrind (1969) proposed that since the PDL appears to behave as a continuous hydrostatic system, any force delivered to it will in accordance with Pascal’s law, be transmitted equally to all regions of the ligament.
- But is the analogy appropriate? This depends on how one defines a fluid. To what extent can the supporting structures of a tooth (cells, collagen, proteoglycans, blood vessels, tissue fluids) be regarded as a fluid? And can the lamina dura of the tooth socket with its numerous vascular perforations be regarded as a closed vessel?
- Apart from minor adjustments following normal occlusal loading (and perhaps even then), the evidence from tooth movement experiments (localized vascular stasis, hyalinization, direct versus undermining bone resorption) would seem to support the hypothesis that differential pressures can be generated within the periodontium.
- Baumrind also observed that the crown of the first molar was displaced on average,10 times more than the average reduction in PDL width on the pressure side, suggesting that bone deforms more readily than the PDL.

- Baumrind S (1969). A reconsideration of the propriety of the “pressure-tension” hypothesis. *American Journal of Orthodontics* **55**, 12–22.

The role of bone bending in tooth movement

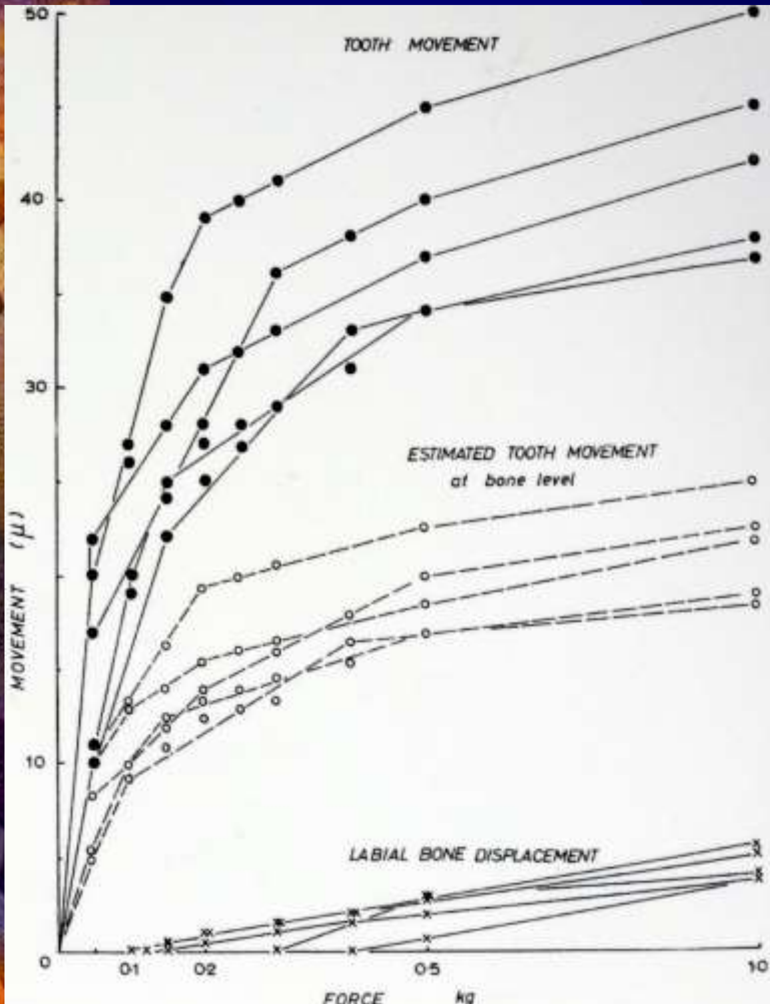
- Chapter 6 in Angle's Seventh Edition (1907, p. 132) entitled *Tissue Changes Incident to Tooth Movement* begins with the following paragraph:
- "When a force is exerted upon the teeth to be moved two principal changes take place in the alveolar process. First, a bending of the process; second, absorption of the process in advance of the moving teeth and deposition of bone behind it. These changes vary greatly: according to the age of the patient, in different patients of the same age, in the direction of movement and also in the rapidity of movement."
- The role of bone bending, and the resorption and deposition of bone in tooth movement was then ignored for the next 50 years, even by Angle himself.

- These comments by Angle in 1907 make interesting reading in the light of Oppenheim's subsequent research. Although Oppenheim rejected the pressure-tension hypothesis, he still refers to the side of pressure and the side of pull, and regarded his experiments as indubitable refutation (*sic*) of the pressure theory.

- There was also a certain amount of ambiguity in Oppenheim's attitude to bone bending, and like Angle, he recognized the elasticity of bone and the role the property might play in tooth movement, particularly in children and young adults. What neither Angle or Oppenheim realized or were prepared to ignore, was that the bone deposited on the labial bone surface of a tooth moved labially was the result of bending of the labial plate and the deposition of new bone on concave (compression) surfaces (see Slide 28).

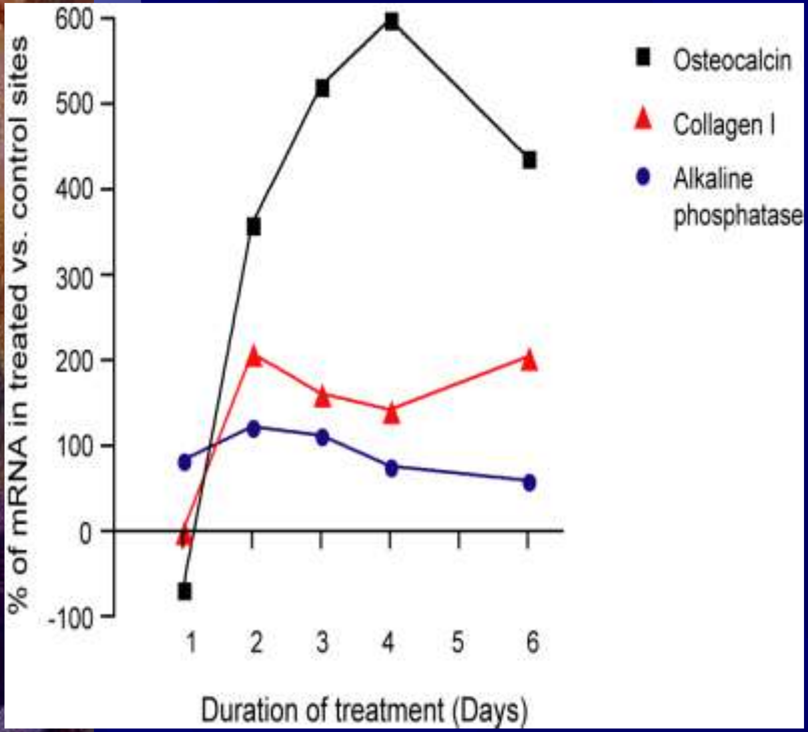
- During locomotion and other forms of physical activity, the skeleton is loaded intermittently. Alveolar bone is also loaded intermittently during mastication, but is subject to a continuous deformation or strain during tooth movement, and if the applied force is of sufficient magnitude and duration bending of the alveolus will occur.

Measurements of bone deflection



- The unequivocal demonstration that bone deflection accompanied tooth movement (Mühlemann, 1954; Picton, 1965) came not from orthodontics, but from physiological studies of tooth support.
- Using a transducer mechanism Picton measured the distortion of alveolar bone when horizontal and axial forces were applied to the maxillary incisors of adult monkeys. Bone displacement started in response to forces less than 100 gm and occurred in a linear manner up to 1 kg.
- In this figure tooth movement following a horizontal force was measured at the cervix of the tooth. Labial bone displacement was measured at the alveolar crest.
- Image from Picton DCA (1965). *Archives of Oral Biology* **10**, 945–955.

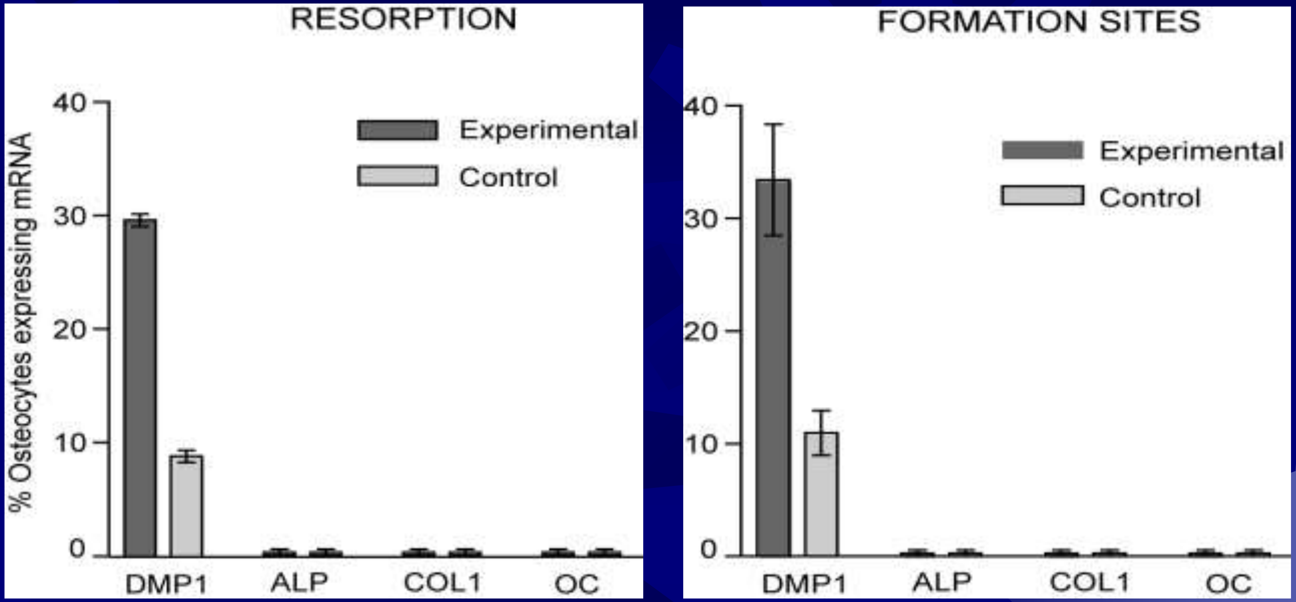
Changes in osteoblast-associated genes *in vivo*



- Pavlin *et al*.(2001) found a rapid response of osteoblast-associated genes in the layer of osteoblasts adjacent to the alveolar bone surface following mechanical loading of the bone in a mouse molar tooth movement model.
- Using *in situ* hybridization, *alkaline phosphatase* mRNA was detected after 24 h, followed by the stimulation of *type I collagen* and *osteocalcin* expression from 24–48 h.
- From Pavlin *et al*. (2001). *Connective Tissue Research* **42**, 135–148.

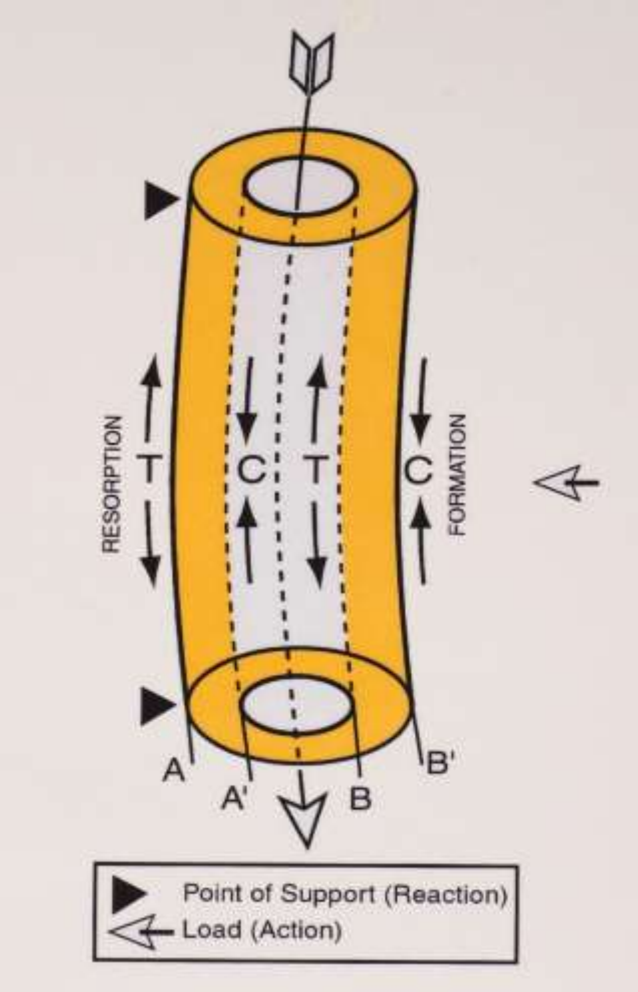
Changes in osteocyte gene expression *in vivo*

Effect of 4d loading on osteocytes expressing bone associated genes.



- Dentine matrix protein-1 (DMP-1) is also expressed in osteoblasts and osteocytes, and is a member of the family of matrix proteins that includes osteopontin, bone sialoprotein and dentine sialoprotein.
- In an *in vivo* mouse tooth movement model, the expression of *Dmp-1* mRNA in the osteocytes of alveolar bone was increased 2–fold within 6 h of loading, on both resorptive and formative sides of the tooth.
- From Gluhak-Heinrich *et al.* (2003). *Journal of Bone and Mineral Research* **18**, 807–817.

Stress-generated electrical effects in bone

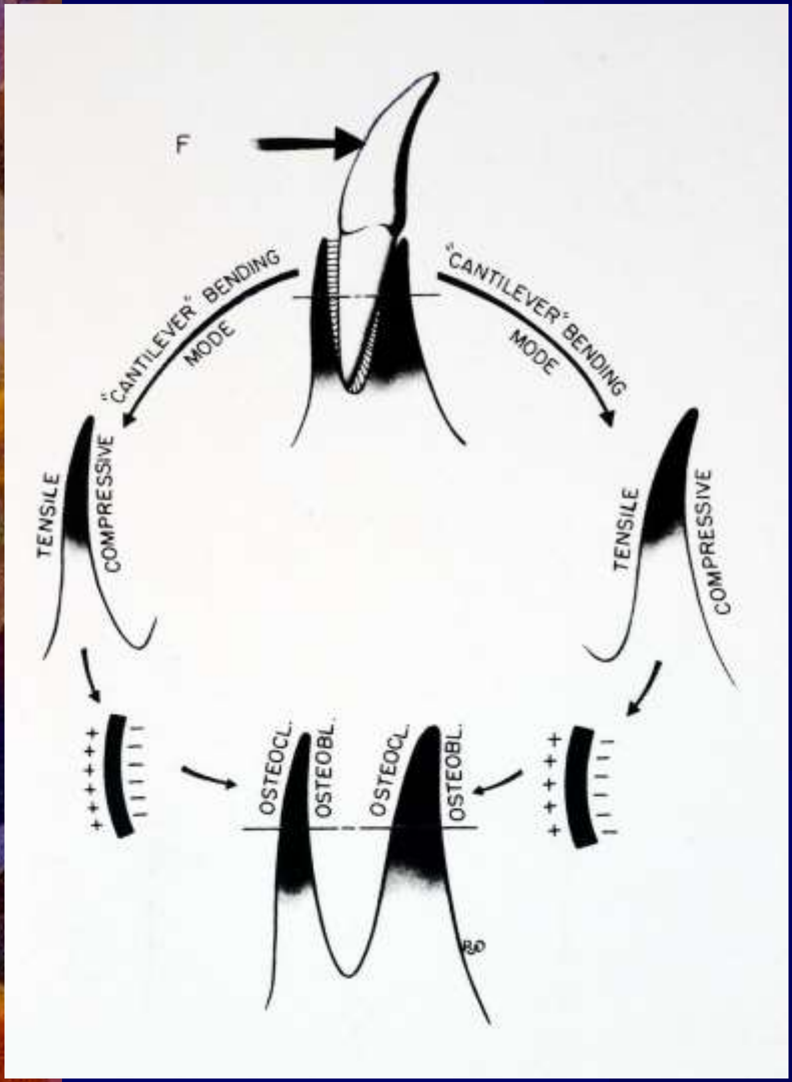


- When an external load is applied to a long bone deformation occurs producing stress-generated electrical potentials (piezoelectrical effects). The external surface of the left cortex elongates in tension, while the internal surface shortens in compression: opposite effects are produced on the right cortex.
- Increasing concavity has been shown to be associated with bone formation and electronegativity. In contrast, increasing convexity is consistently associated with bone resorption and electropositivity.
- Redrawn from Epker BN and Frost HM (1965). *Journal of Dental Research* **44**, 33–41.

Problems with the piezoelectrical theory of bone remodelling

- It is not sufficiently discriminatory to be able to regulate the action of cells as diverse as osteoblasts and osteoclasts which function in close proximity at bone surfaces.
- Piezoelectricity does not require the presence of living cells; dead bone displays the same effects, which appears to be generated by shearing forces acting on the collagen fibres of the bone matrix.
- It seems likely that stress-generated electrical potentials are an irrelevant by-product of bone deformation, physical phenomena that provided a plausible explanation for the regulation of bone remodelling prior to the discovery of cytokines, growth factors and other cell–cell signalling molecules in the 1980s.

Stress-generated electrical effects and tooth movement



- Hypothetical model of the role of stress-induced bioelectric potentials in regulating alveolar bone remodelling during orthodontic tooth movement. The force F applied to the labial surface displaces the tooth in its socket, deforming the alveolar bone convexly towards the root at the leading edge, and producing concavity towards the root at the trailing edge.
- During the 1960s and 70s the regulation of bone remodelling by piezoelectrical effects enjoyed considerable support within the orthopaedic and orthodontic communities.
- From Zengo AN *et al*. (1973). *American Journal of Orthodontics* **64**, 12–27.

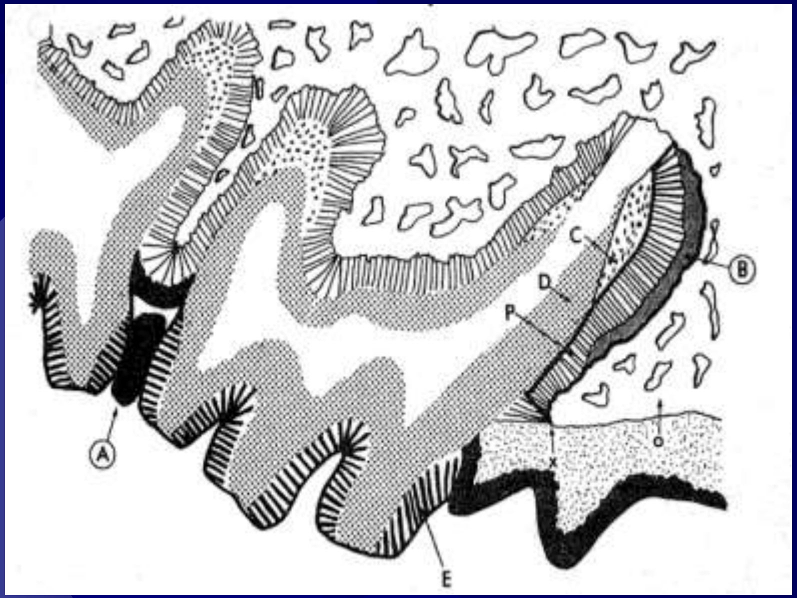
Rat models of tooth movement

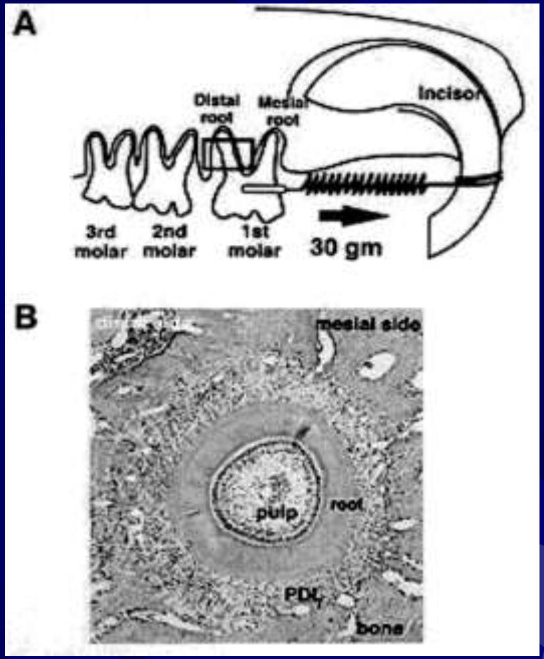
- *In vitro* models have been valuable in advancing our understanding of orthodontic tooth movement at the molecular level. To understand whether these molecules are involved in tooth movement at the holistic level requires *in vivo* animal models.

- A large variety of animal species including mice, rats, rabbits, guinea pigs, dogs, cats and monkeys have been used to investigate orthodontic tooth movement at the histological level. However, bearing in mind cost issues and the availability of cDNAs and antibodies to an increasingly wide range of rodent proteins, the rat has become the experimental animal of choice.

- Nevertheless, the rat does have some shortcomings. The bone is denser than in humans, lacking osteons and marrow spaces; osteoid is also less abundant. Calcium balance in rats seems to be controlled more by intestinal absorption than bone remodelling, and structural dissimilarities in the PDL and supporting structures have been reported.

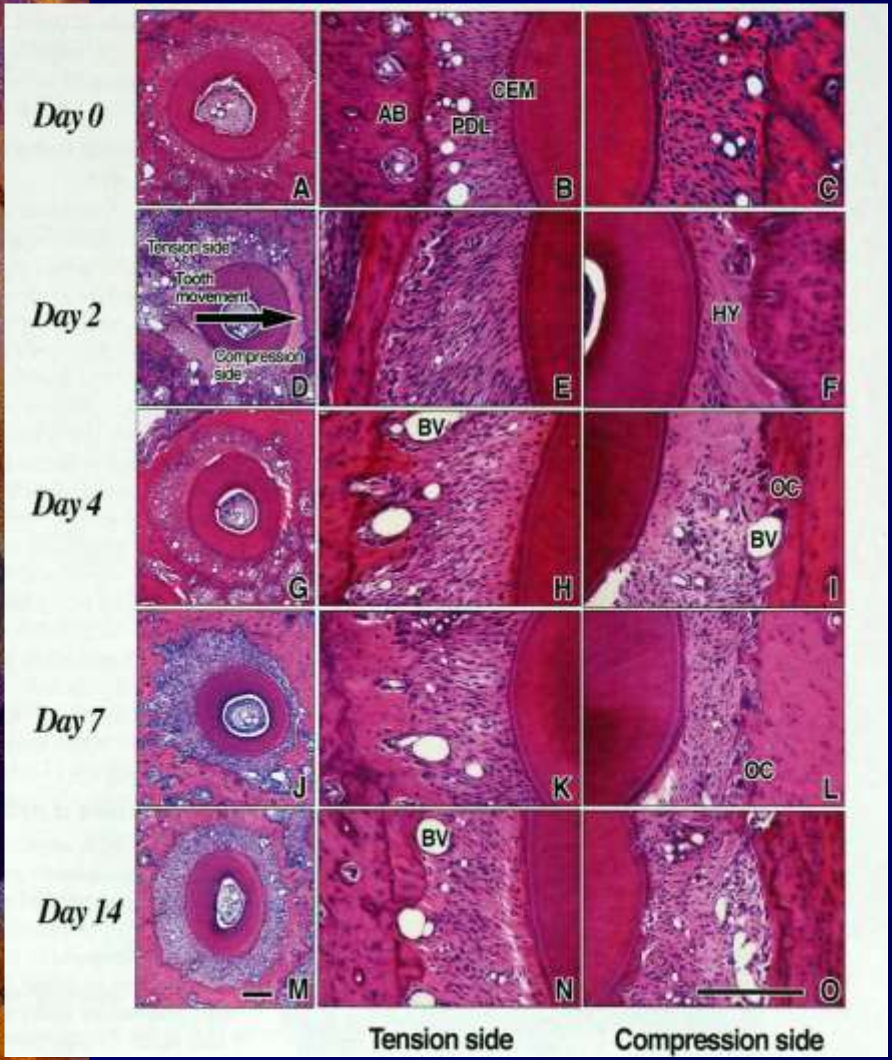
Rat models of tooth movement





- Two are commonly used. (1) The Waldo method in which an elastic is inserted between maxillary M1 and M2 molar teeth. The disadvantage is an acute inflammatory reaction in the tissues, and lack of information regarding the magnitude of the force.
- (2) A coil spring is attached to M1 and incisors to give a more definable controlled force that can be pre-tested in the laboratory.
- Waldo & Rothblatt (1954). *Journal of Dental Research* **33**, 481–486.

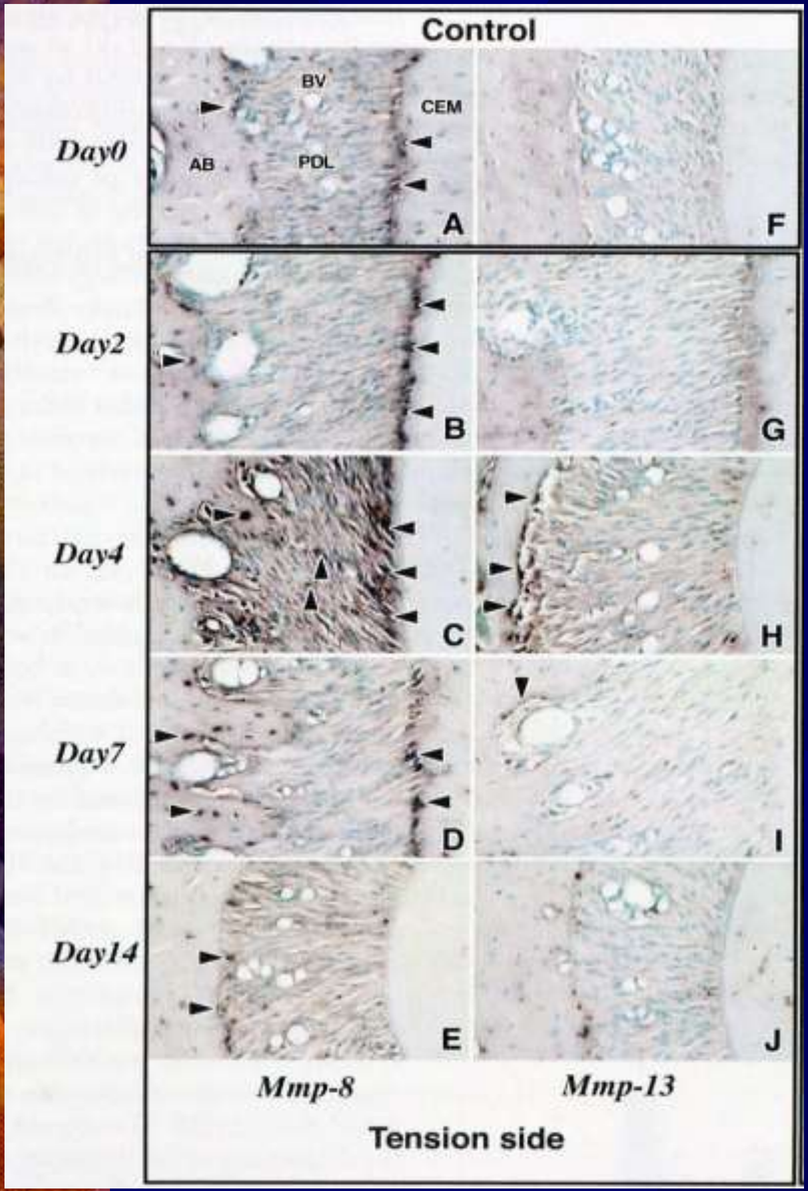
Histology of tooth movement in the rat



- Horizontal sections through six-week-old rat maxillary first molars. Teeth were moved buccally; collagen fibres were elongated on the tension side.
- On the pressure side the PDL was compressed at 2, 4 and 7 days, with foci of hyalinization (HY) evident by day 2: (OC) osteoclast; (BV) blood vessel.
- *In situ* hybridization and RT-PCR was used to study the expression of *Mmp8* (collagenase-2) and *Mmp13* (collagenase-3) mRNAs.

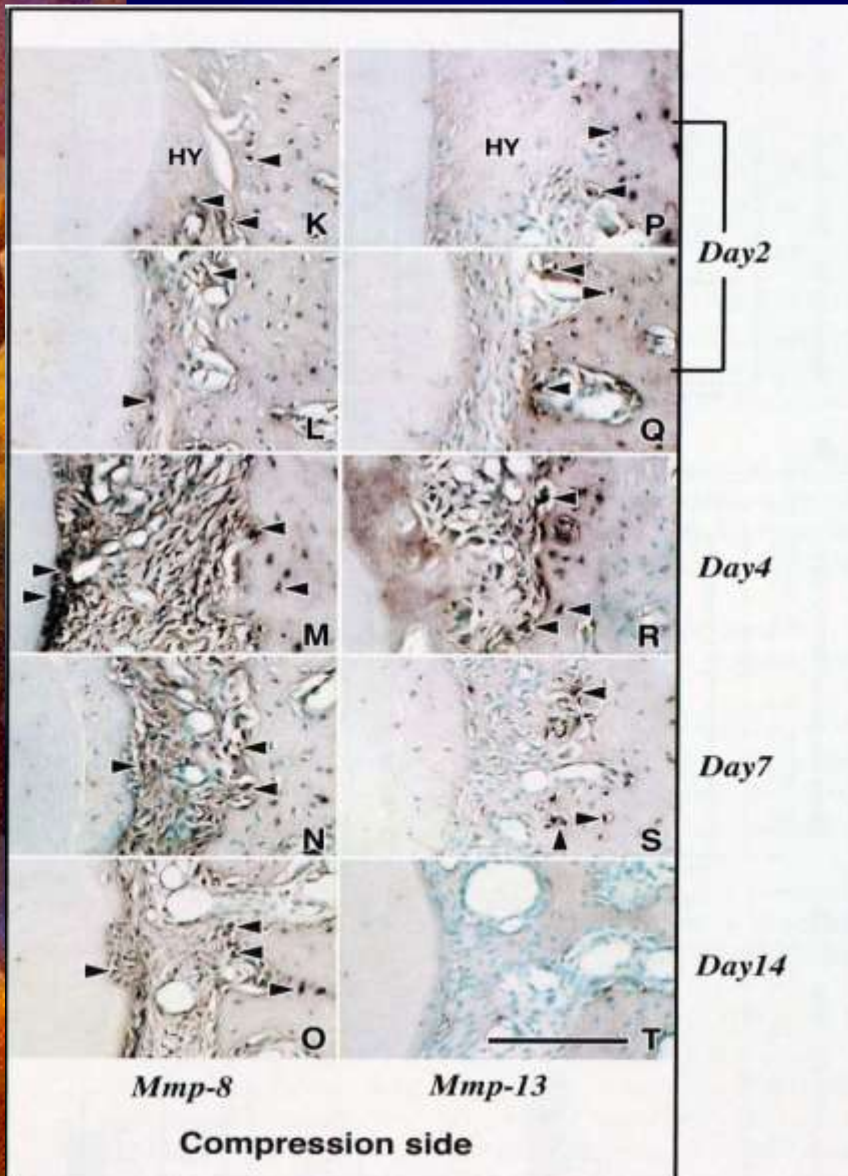
From Takahashi I *et al*. (2003). *Journal of Dental Research* **82**, 646–651.

MMP-8 and MMP-13: tension side



- *In situ* hybridization was used to detect the expression of the enzymes *Mmp8* (collagenase-2) and *Mmp13* (collagenase-3) in the PDL of a rat model (with a bilateral expansion spring).
- At day zero, *Mmp8* was expressed in cementoblasts and osteocytes in alveolar bone; *Mmp13* was not detected.
- Both were increased transiently in PDL cells and cells lining the alveolar bone surface at day 4.
- Osteocytes in alveolar bone expressed *Mmp8* at days 4 and 7. The expression pattern of both MMPs returned to normal at 14 days.
- From Takahashi *et al*. (2003). *Journal of Dental Research* **82**, 646–651**.**

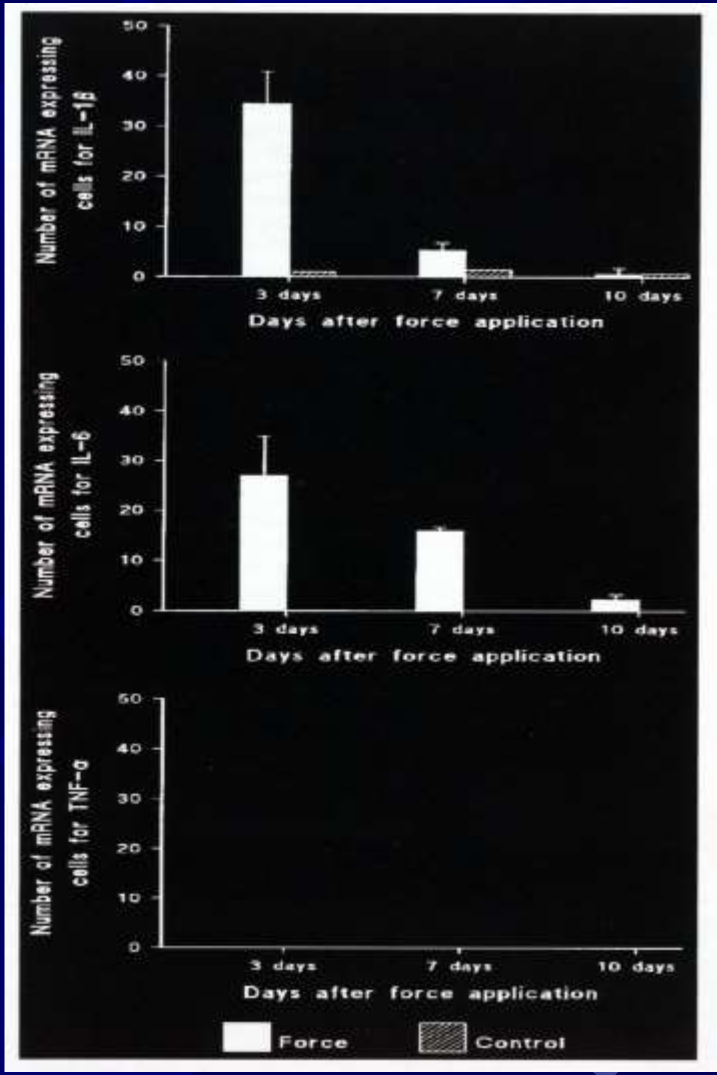
MMP-8 and MMP-13: compression side



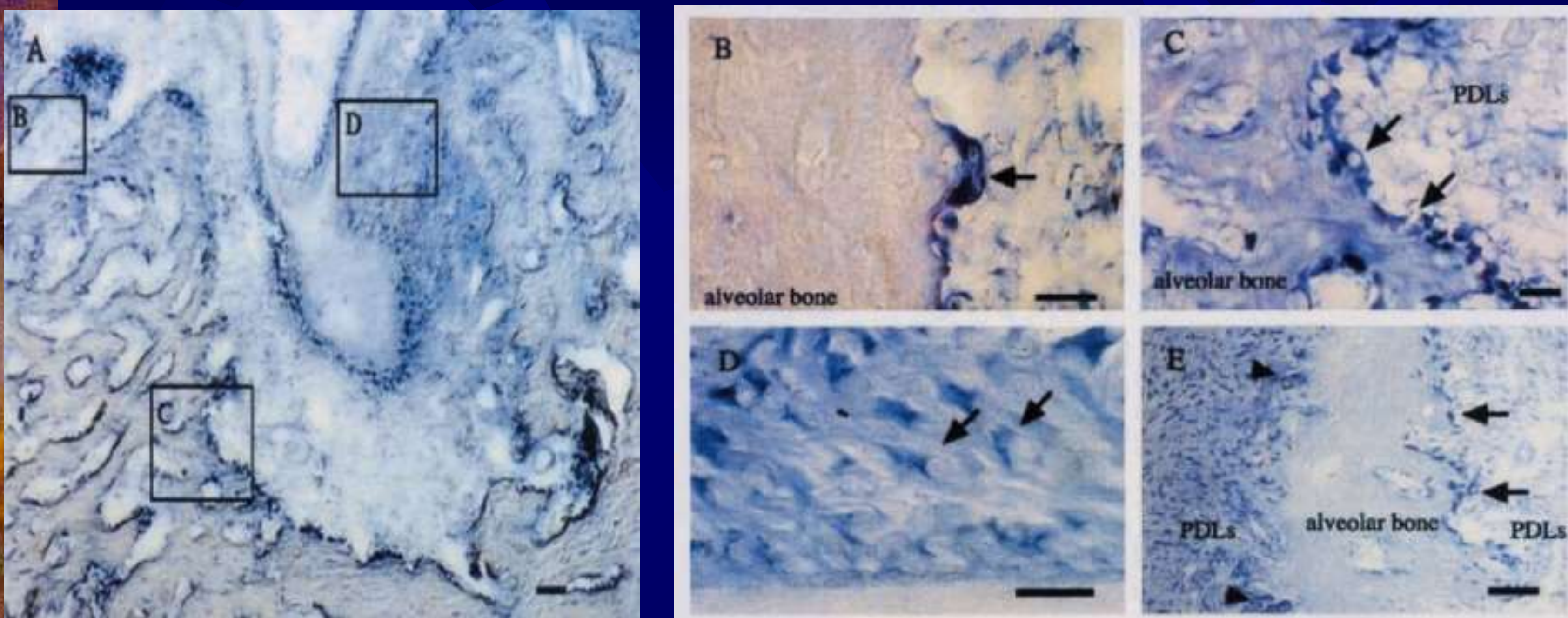
- *Mmp8* was transiently expressed in the cells around the hyalinized tissue (HY) and fibroblasts on the compression side from days 2 to 7.
- Osteocytes in the adjacent bone strongly expressed *Mmp13* at days 2 and 4.
- PDL cells and cells lining the resorbing bone surface expressed *Mmp13* at day 4.
- By day 14 expression levels of both enzymes had returned to control levels.
- From Takahashi *et al*. (2003). *Journal of Dental Research* **82**, 646–651**.**

IL-1β, IL-6 and TNF-α expression in the PDL

- In this study by Alhashimi *et al*. (2001), *in situ* hybridization with radiolabelled oligonucleotide probes was used to measure cytokine mRNA expression in a rat molar tooth movement model.
- *IL1β* and *IL6* positive cells, but not *TNFα* were up-regulated in the PDL, particularly on the compression side.
- Alhashimi *et al*. (2001). Orthodontic tooth movement and de novo synthesis of proinflammatory cytokines. *American Journal of Orthodontics and Dentofacial Orthopedics* **119** , 307–312 *.*

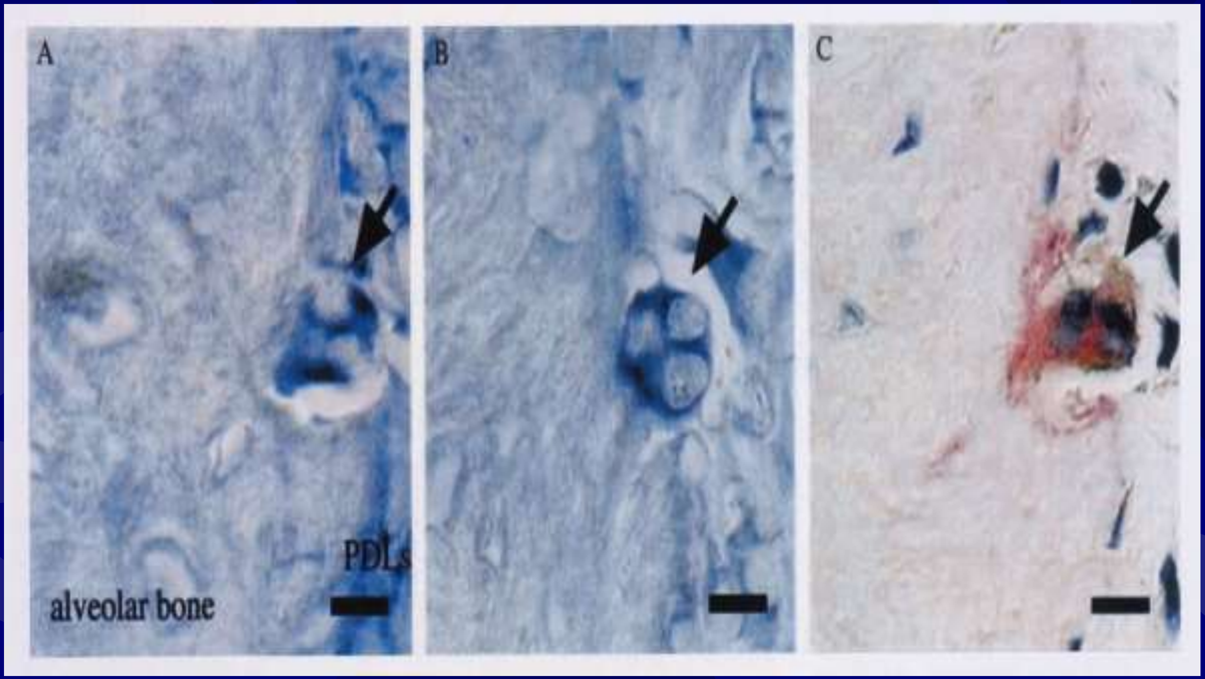


RANKL and OPG in the rat PDL



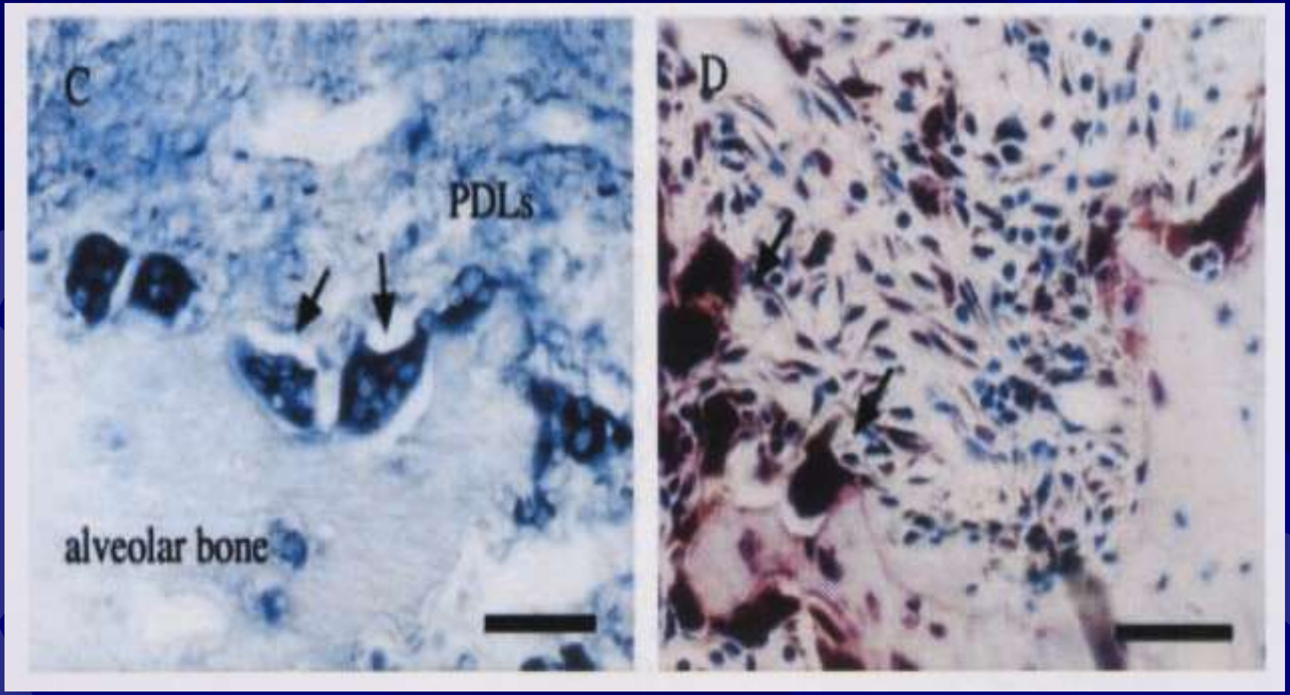
- A. *In situ* expression of *Rankl* mRNA in the rat periodontium; positive cells appear dark blue. Some osteoclasts (B), osteoblasts (C) and PDL cells (D) are clearly expressing *Rankl.*
- (D). *Opg* (osteoprotegerin) was expressed in osteoblasts, PDL cells and odontoblasts, but not osteoclasts or osteocytes.
- From Ogasawara *et al*. (2004). *Journal of Periodontal Research* **39**, 42–49.

RANK and RANKL in osteoclasts



- *Rankl* (A) and *Rank* (B) mRNA expression in the same osteoclast as shown by serial sections; this osteoclast is also TRAP-positive.
- Tooth movement up-regulated *Rankl* expression, as well as IL-1β and TNFα in some osteoclasts and PDL cells near sites of active bone resorption.
- From Ogasawara *et al*. (2004). *Journal of Periodontal Research* **39**, 42–49.

RANKL in tooth movement



- In a Waldo rat tooth movement model the number of *Rankl*- and TRAP-osteoclasts increased on the compression side as shown above. The number of *Rankl*-positive PDL fibroblasts also increased.
- No change in the number of *Opg*-positive osteoblasts, odontoblasts or PDL cells was observed following tooth movement.
- From Ogasawara *et al*. (2004). *Journal of Periodontal Research* **39**, 42–49.

Summary

- After more than 100 years we have reasonably good understanding of the sequence of events involved in orthodontic tooth movement at the tissue and cellular level on both the tensile and compression sides of the periodontium. At the molecular level, however, although significant progress has been made over the last 20 years our knowledge remains far from complete.

- Both *in vivo* and *in vitro* methods have been widely used to investigate the response of cells to mechanical deformation and it is important to stress that the two approaches are complementary; data from *in vitro* model systems in which the mechanical stimulus applied to the cells can be carefully regulated (tension versus compression; intermittent versus continuous) should be correlated with *in vivo* data obtained from animal models, and clinical data.

- It would appear Sandstedt and Oppenheim arrived at different conclusions regarding the tissue response to orthodontic tooth movement on the seemingly trivial difference of the plane of section. In Sandstedt’s figures the tissue blocks have been sectioned horizontally and in Oppenheim’s vertically.

- It is perhaps ironic that while Oppenheim was identified in many people’s minds as the key figure in tooth movement research, Sandstedt’s concepts dominate orthodontic theory today.

- The take home message for the contemporary investigator is that (1) a three-dimensional perspective is essential for a complete understanding of events, and (2) tooth movement involves two inter-related processes: the bending of alveolar bone and remodelling of the periodontal tissues.