

Seminar 13

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Mechanobiology of tooth movement

The idea that orthodontic tooth movement is dependent on the resorption and deposition of the bone of the socket dates back at least to 1839 with publication of *The Dental Art* by Chapin Harris MD, DDS (1806–1860). In Chapter V, *Irregularities of the Teeth – Their Treatment*, Harris writes: “If, previously to this time, there be any pressure against a tooth, it causes an absorption of the side of the alveolus against which its fang is pressed. But this does not necessarily destroy the socket, for as the internal paries (wall) is carried off by the absorbents, the external of the same side is thickened by a deposition of new bone; and the vacuum thus made on the opposite side, is also filled up” (p. 104).

Tissue reaction to orthodontic tooth movement

However, it was not until the turn of the twentieth century that the histological investigation that forms the foundation of our present knowledge of tooth movement, was carried out on dogs by the Swedish dentist Carl Sandstedt (1864–1904) (Reviewed by Bister and Meikle, 2013). His findings were first published in 1901 as a monograph in Swedish from the Anatomy Department of the Karolinska Institute in Stockholm entitled *Några bidrag till tendregleringens teori* (Some contributions to the theory of tooth movement; Sandstedt, 1901). Later three articles in German based on the same work *Einige Beiträge zur Theorie der Zahnregulierung* (Some contributions to the theory of the regulation of teeth) were published in the journal *Nordisk Tandläkare Tidskrift* (Sandstedt, 1904, 1905), shortly after his death (Persson, 2005). (Slide 4)

Much of the narrative is in the first person and one could not accuse Sandstedt of using one word when several would suffice, exhibiting a fondness for particularly lengthy sentences. (This may not have been entirely due to Sandstedt, as the articles were edited and published after his death.) Nevertheless, in spite of the often turgid prose and the tendency to repeat phrases, it does contain a good deal of what we understand today about the histology of tooth movement. Sandstedt was a man who was clearly ahead of his time, and has to be admired for applying the experimental method to what he regarded as a very important problem that ‘nobody had ever thought it worthwhile to investigate’ (pp 242). There seems little doubt that Sandstedt’s tragic death at the age of forty, not only impeded the progress of tooth movement research for almost 50 years, but also the establishment of clinical orthodontics based on sound biological principles.

Carl Sandstedt: Laying the foundations

In Sandstedt’s experimental model, a labial arch was bent to engage the six maxillary incisors of a dog and inserted into horizontal buccal tubes attached to bands on the canines. (Dogs have been popular experimental models in Scandinavia, but as “man’s best friend,” rarely used in the UK or USA.) The appliance was activated over a 3-week period by screws distal to the buccal tubes, and during that time the crowns of the incisors were moved lingually by 3 mm (Slide 5). Sandstedt found that bone was deposited on the alveolar wall on the tension side of the tooth with both heavy and light forces, and that the newly formed bone spicules followed the orientation of the periodontal fibre bundles. On the pressure side, with light forces, alveolar bone was resorbed directly by numerous multinucleate osteoclasts in Howship’s lacunae (Slide 6). With heavy forces, the periodontal tissues were compressed, leading to capillary thrombosis, cell death, and the production of localized cell-free areas of what he called hyalinization (owing to its glasslike appearance resembling hyaline cartilage). At these sites, osteoclastic resorption of the adjacent alveolar wall did not take place directly, but was initiated by a process referred to by Sandstedt as ‘undermining resorption’ from the neighbouring marrow spaces.

The enduring question, bearing in mind that both the illustrations and the descriptions of tooth movement quoted above are ones we would recognize today, is why Sandstedt's research languished in obscurity for so many years? His premature death and publishing in Swedish and German certainly played their part, but are not the whole story.

Albin Oppenheim and the Law of Bone Transformation

In 1911 the Viennese orthodontist Albin Josef Oppenheim (1875–1945), published an article entitled 'Tissue changes, particularly of the bone, incident to tooth movement' in the *Transactions of the European Orthodontic Society*, forerunner of the *European Journal of Orthodontics* (Oppenheim, 1911). Oppenheim experimented on the lower deciduous incisors of baboons, although it is not clear exactly how many animals were involved. The tooth movements reported were labial, lingual, depression, elongation and rotation – one half of the jaw being operated upon, the other serving as an internal control; the paper fails to include either a description or illustration of the orthodontic appliances used, the magnitude of the applied force, or how far the teeth were moved. The time-course of the experiments was 40 days at which point the animals were sacrificed (Slide 8).

His observations proved to be substantially different from those of Sandstedt as far as the response of the bone was concerned. He found that where a tooth had been tipped labially, the original bone disappeared completely from the labial surface and was replaced by new bone. He concluded that ... "bone tissue, be it compact or cancellated, reacts to pressure by a transformation of its entire architecture; this takes place by resorption of the bone present and deposition of new bone tissue; both processes occur simultaneously. Deposition finally preponderates over resorption." It seems what Oppenheim was describing was the response of the periosteal and endosteal bone surfaces to the bending of the labial alveolar plate. The labial alveolar bone is particularly thin in his illustrations and would have been easily deformed in a monkey in the primary dentition (Slide 9). When bones are subjected to continuous mechanical deformation, concave surfaces are characterized by osteogenesis, and convex surfaces by bone resorption (Seminar 12).

Interestingly, 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 is also a certain amount of ambiguity in his attitude to bone bending and it is apparent he recognized the elasticity of bone and the role that property might play in tooth movement, particularly in children and young adults. Finally, since he was of the opinion that the fulcrum of movement was at the apex of the tooth, and having found bone formation and bone resorption on *both* sides of the teeth, it is unclear precisely how Oppenheim thought teeth were moved into a new position. In retrospect, Oppenheim's theory of bone transformation made such little sense it's surprising that anyone believed it. At this point Edward Angle enters the narrative. (Slide 11)

Oppenheim had lectured at the Angle School of Orthodontia in New Haven, Connecticut, and his theory of bone transformation supported Angle's nonextraction philosophy, and the widespread belief that orthodontic appliances could 'grow bone.' More importantly Oppenheim remained research active and continued to publish in German and English language journals up until the time of his death in Los Angeles, having managed to escape from Austria in 1938 following the *Anschluss* (Atkinson, 1957). He also had the support of many influential pupils of Angle including Frederick Noyes, Professor of Histology and Orthodontics, and later Dean (1924–1940) of the College of Dentistry, University of Illinois Chicago. In a posthumous tribute to Oppenheim's research, Noyes (1945) was contemptuous of the findings of other workers, writing in a rather pejorative tone: 'One investigator thought that the bone was bent, and another that the tooth plowed (*sic*) through the substance of the bone by means of absorption on one side and deposit on the other.' The latter comment presumably a reference to Sandstedt.

One orthodontist who did recognize the significance of his work at the time and discussed it in Chapter 8 of his textbook *Atlas und Grundriss der Zahnärztlichen Orthopädie* was Emil Herbst (1910), but the lack of English translations and his premature death, meant Sandstedt became the

forgotten man of tooth movement research. It was not until the Austrian orthodontist Martin Schwarz attempted to reconcile the differences between the experimental findings of Sandstedt and Albin Oppenheim (not entirely successfully one might add), in what eventually became the *American Journal of Orthodontics* (Schwarz, 1932), that Sandstedt became partially rescued from obscurity and introduced to the English-speaking world.

With the centre of gravity of orthodontics firmly embedded in North America during the twentieth century, the outcome was that Oppenheim's research appeared in mainstream English language textbooks to the exclusion of all others (if any reference to the histology of tooth movement appeared at all), until after World War II, and the expansion of university-based orthodontic training programmes – a salutary reminder of how ideologies or dogmas can become entrenched by powerful and dominant personalities. The problem of course with ideologies is that they provide all the answers – lack of evidence or evidence to the contrary is completely irrelevant.

Kaare Reitan and the post-war period

Following the work of Sandstedt and Oppenheim, reports by other investigators appeared in the literature (Gottlieb and Orban, 1931; Schwarz, 1932; Breitner, 1940), but it was not until the 1950s that research into orthodontic tooth movement attracted wider attention. The leading histomorphological investigator of the period was the Norwegian orthodontist Kaare Reitan MSD, PhD (1903–2000), whose classic memoir *The Initial Tissue Reaction Incident to Orthodontic Tooth Movement as Related to the Influence of Function* was published in 1951 (Slide 13).

Reitan (1957, 1964) made extensive use of human material, particularly premolars destined for orthodontic extraction. His work highlighted the complexity of the tissue response to orthodontic treatment depending upon (1) the type (continuous versus intermittent) and magnitude of the force applied, (2) the mechanics involved (tipping versus bodily movement), and (3) variation in tissue reaction between individual patients. He observed that during the initial stages of a tipping movement, cell free or hyalinized areas were frequently created with a continuous force as low as 30 gm. The time taken to remove such tissue by undermining resorption varied from 2 to 4 weeks, and occasionally longer depending on the length of the root (Slide 14). Even with applied forces as low as this, some resorption craters in the root are virtually guaranteed.

His study of rotated teeth in young dogs was a particularly valuable contribution to understanding the physiological basis of rotational relapse (Reitan, 1959). He found that while the principal collagen fibre bundles of the PDL were rearranged or remodelled within 28 days, even after a retention period of 232 days, some free gingival fibres remained displaced and stretched. He concluded that rotational relapse was caused primarily by a contraction of the supra-alveolar gingival fibres (later shown to contain elastic or oxytalin fibres) and advised the over-rotation (often talked about but rarely performed), or transection (pericision) of these fibres at the completion of treatment to ensure tooth stability (Slide 15).

Elsdon Storey and the concept of differential force

Meanwhile, at the University of Melbourne in Australia, Elsdon Storey MDS, DSc, PhD (1924–1988), in addition to analysing the histological changes produced by torsion springs applied to rodent and largomorph incisors (Storey, 1955 a,b,c), also carried out a series of experiments with canine retraction springs to determine what force levels should be used in clinical practice (Storey and Smith, 1952; Smith and Storey, 1952). In an investigation involving nine patients, they found that movement of the canine teeth into premolar extraction sites occurred rapidly when the value of the applied force was in the range of 150–250 gm (5–9 ounces); however, below 150 gm, the canines did not move significantly. When the springs were activated to apply forces in the range of 400–600 gm (14–21 ounces), the anchor teeth (molars and second premolars) moved forward, with the canines remaining relatively stationary. These experiments gave rise to the differential force concept, and the idea that 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 using the force levels recommended by Storey and Smith (1952) and Smith and Storey (1952) were highly variable between patients (Hixon *et al.* 1970; Boester and

Johnston, 1974). 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 (Slides 16, 17).

Autoradiographic studies of tooth movement

A key technical development during the 1960s as far as histomorphometry was concerned was the introduction of autoradiography. Tritium-labelled molecules in particular, enabled changes in cell proliferation and metabolic activity to be measured with reasonable accuracy for the first time. Using a rat molar tooth movement model, Baumrind (1969) and Baumrind and Buck (1970) reported that cell proliferation (measured by ³H-thymidine incorporation) and metabolic activity (³H-uridine incorporation) were increased, and protein synthesis (³H-proline incorporation) decreased, on both the ' tension ' and ' pressure ' sides of the PDL. This unexpected finding led them to question whether significant differences existed between the two sides (Slide 18).

Roberts and co-workers used the same rat model to study the cellular kinetics of ³H-thymidine incorporation into PDL cells at tension sites. Smith and Roberts (1980) reported that over a time course of 20 hours, a continuous force produced a three-stage proliferative response. An interesting finding was a burst of mitotic activity within 2 hours, suggesting the initial effect of mechanical strain was to allow G2-blocked cells to enter the cell cycle and undergo mitosis, as well as stimulate G1-blocked cells to synthesize DNA (Slide 19). Application of mechanical stress to the rat model also suggested that under strained conditions the cells of the PDL were primarily osteogenic (Roberts and Chase, 1981). This observation was supported by subsequent *in vitro* studies discussed in Seminar 14. PDL fibroblasts are functionally heterogeneous and contain a subpopulation of cells able to produce the osteoblast-related matrix proteins osteopontin, alkaline phosphatase, and bone sialoprotein (Lekic *et al.* 2001; Murakami *et al.* 2003).

Hyalinization and root resorption

The Scandinavian tradition of tooth movement research was continued by Kvam (1972) and Rygh (1972 a,b), with particular emphasis on the cellular and tissue changes on the compression side. It had been realized by Sandstedt that hyalinization was related to changes in vasculature, and Gianelly (1969) had shown that bone resorption was dependent on the maintenance of vascular channels. Rygh (1972b) studied the ultrastructural changes in blood vessels in both human and rat material and found (1) packing of erythrocytes in dilated blood vessels within 30 minutes, (2) fragmentation of erythrocytes after 2–3 hours, and (3) disintegration of blood vessel walls and extravasation of their contents after 1–7 days. He also observed necrotic changes in PDL fibroblasts such as dilatation of the endoplasmic reticulum and mitochondrial swelling within 30 minutes, followed by rupture of the cell membrane and nuclear fragmentation after 2 hours; cellular and nuclear fragments remained within hyalinized zones for several days Rygh (1972a). There was no difference in the response of rat and human tissues apart from timing; changes observed after 2 days in humans were seen after 2 hours in rats.

Both Kvam and Rygh showed that root resorption is a side-effect of the cellular activity associated with the removal of the necrotic hyalinized tissue. Scanning electron microscopy of premolar root surfaces following the application of a 50 gm force to the crown in a lateral direction revealed resorption cavities extending into the dentine, but where the hyalinized tissue remained intact, the root surface was unaffected (Kvam, 1972). Tartrate-resistant acid phosphatase (TRAP) staining in a rat tooth movement model has highlighted the involvement of TRAP-positive macrophages and multinucleate giant cells in the removal of hyalinized tissue (Brudvik and Rygh, 1994), and clearly demonstrated that on reaching the root surface, TRAP-positive cells continue to remove the cementum and subjacent dentine producing resorption lacunae (Slides 20, 21).

Propriety of the pressure–tension hypothesis

The idea that pressure and tension sites are generated within the PDL is firmly embedded in the orthodontic subconscious; 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 generate tension and second, can differential pressures be developed within the tissues of the periodontium? (Slide 22)

Does stretching of the principle fibres of the PDL generate tension?

A persistent dogma of the orthodontic literature is that the collagen fibres of the PDL are stretched during tooth movement. Tension is thereby generated in the fibres responsible for the cellular response, particularly the stimulation of osteogenesis at the cortical bone surface into which the fibres are inserted. This belief seems to have arisen from traditional textbook representations of a tooth suspended in its socket by the PDL; this overemphasizes the role of collagen in tooth support, and obscures the structure and function of ligamental proteoglycans not visualized by conventional histological processing.

To test the hypothesis that tension generated in the collagen fibres of the PDL provides the stimulus for osteogenesis, Heller and Nanda (1979) disrupted collagen metabolism and function in rats by the systemic administration of the lathyritic agent β -aminopropionitrile; this inhibits the intermolecular cross-linking of the polypeptide chains of the collagen molecule. They found that in lathyritic rats the histological response of the bone to orthodontic tooth movement appeared to be normal. This suggests that when a tooth is loaded, it is unlikely the principal fibres of the PDL undergo significant tensile strain, or transfer forces directly to the alveolar bone via Sharpey's fibres. (Slide 23)

Can differential pressures be generated with the PDL?

Direct measurements of the experimental intrusion of teeth (Parfitt, 1960; Bien and Ayres, 1965; Picton, 1965) suggested that when mechanically loaded, the periodontal tissues behave as a viscoelastic gel which flows when subjected to a steady force but 'bounces' when a load is briefly applied and then removed. The damping of the mechanical forces acting on a tooth was originally attributed to three distinct but interacting fluid systems: (1) the vascular system, (2) cells and periodontal fibres, and (3) the interstitial fluid continuum (Bien, 1966). While these fluid systems undoubtedly play apart, 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, whose displacement is limited by the collagen fibre network and lamina dura of the alveolar bone. Momentary pressures created by the sudden forces of mastication are therefore of different physiological significance to the prolonged pressures of orthodontic appliances, since biting forces in the neighbourhood of 1500 g/cm² do not crush the periodontal membrane and impact the tooth through bone (Bien, 1966). (Slide 24)

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. (Slide 25)

The role of bone bending in tooth movement

Baumrind (1969) 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.

Chapter 6 in Angle's Seventh Edition (Angle, 1907, p. 132) 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 in orthodontic tooth movement was then ignored for the next 50 years, even by Angle himself (Slide 26).

Bone deflection studies

Laboratory investigations that demonstrated unequivocally that bone deflection accompanied tooth displacement (Mühlemann, 1954 ; Mühlemann and Zander, 1954 ; Picton, 1965) were not undertaken with orthodontics in mind, but were physiological studies of tooth support. The experiments of Mühlemann and Zander (1954) with *Macaca mulatta* (rhesus) monkeys found that forces of 50–100 gm were required to initiate labial or lingual displacement of a tooth from its physiological rest position; deformation of the alveolar bone started when forces greater than 100 gm were applied to the teeth. Picton (1965) measured the distortion of alveolar bone with horizontal and axial forces in adult monkeys and noted that bone displacement started in response to forces less than 100 gm and occurred in a linear manner up to 1 kg. Horizontal forces of more than 50 gm caused the labial and lingual plates to be displaced in the same direction as the applied force; however, intrusive forces of the same magnitude caused dilatation of the socket, making it difficult to explain tooth support in terms of a tensional mechanism (Slide 28).

Although most bone deflection studies have been carried out on laboratory animals, experiments in humans have shown that the interseptal bone can also be bent. Measurements of interseptal bone deformation adjacent to tooth extraction sites were undertaken in two 12-year-old patients by Grimm (1972). Apart from variations in the rate and magnitude of tooth movement, bending of the alveolar crest was detectable with forces of less than 50 gm and reached 35 µm with a load of 1.5 kg. Somewhat surprisingly, he recorded a 5 to 30 µm initial deflection of the crestal bone in the opposite direction to the tooth movement; this effect was transitory, however, and reversed to a slow positive trend after 1 minute.

The cellular and molecular response to bone deflection

Osteocytes are sensitive to mechanical deformation, and the idea that the cytoplasmic syncytium may detect changes in mechanical loading and therefore act as mechanoreceptors in bone has a long history (Pritchard, 1956). Experimental studies using both *in vitro* and *in vivo* models indicate that osteocytes are sensitive to stress applied to intact bone, and may indeed function as mechanoreceptors. Load-related increases in glucose-6-phosphate dehydrogenase, ³H-uridine, c-fos, and IGF-1 (insulin-like growth factor-I) expression have been detected in osteocytes within 6 hours (Skerry *et al.* 1989; El Haj *et al.* 1990; Lean *et al.* 1996), demonstrating that intermittent loading at physiological strain magnitude produces rapid changes in metabolic activity.

Pavlin *et al.* (2001), Pavlin & Gluhak-Heinrich (2001), and Gluhak-Heinrich *et al.* (2003) focussed on the temporal expression of osteoblast- and osteocyte-associated genes following the loading of alveolar bone in a mouse molar tooth movement model. They found the response of osteoblast-associated genes to deformation in cells at the PDL–bone interface to be 10- to 20-fold greater than the increase in their number, suggesting that differentiation and increased cell function were the initial responses to loading the bone. *Alp* (Alkaline phosphatase) and *Bsp* (bone sialoprotein/osteocalcin) gene expression were detected after 24 hours, followed by stimulation of osteocalcin and collagen type I expression from 24 to 48 hours (Slide 29). Most interesting, however, was the response of the osteocytes; the expression of *Dmp1* (dentine matrix protein-1) mRNA in the osteocytes of alveolar bone was increased twofold as early as 6 hours after loading, on both the formative and resorptive sides of the tooth (Slide 30).

Stress-generated electrical effects in bone

When an external load is applied to a long bone, deformation occurs, thus producing changes in the surface curvature (Slide 31). The external surface of the left cortex elongates in tension, while the internal surface shortens in compression; opposite effects are produced on the internal and external surfaces of the right cortex (Epker and Frost, 1965). Increasing concavity has consistently been shown to be associated with electronegativity and bone formation. In contrast,

increasing convexity is associated with electropositivity and bone resorption (Bassett and Becker, 1962).

Stress-generated electrical potentials have been recorded with surface electrodes in a dog mandible following the application of a mechanical force to the teeth (Gillooly *et al.* 1968), and Zengo *et al.* (1973) proposed that electrical potentials are responsible for regulating osteogenesis and bone resorption in the course of orthodontic tooth movement. During the 1960s and 1970s, the regulation of bone remodelling by piezoelectrical effects enjoyed considerable support within the orthopaedic and orthodontic communities. However, the problems from a biological point of view are whether electrical phenomena are sufficiently discriminatory to be able to regulate the metabolic activity of cell types as diverse as osteoblasts and osteoclasts, which function in close proximity; also the fact that piezoelectricity does not require the presence of living cells. Dead bone displays the same effects, which appear to be generated by shearing forces acting on the collagen fibres of the bone matrix. The more that is learnt about cell – cell and cell – matrix interactions, the more it is likely that stress-generated electrical potentials represent a by-product of deformation, a physical phenomenon that provided a plausible explanation for bone remodelling before the discovery of growth factors, cytokines, and other locally produced biochemical mediators (Slide 32). Nevertheless, while piezoelectricity as an explanation for the regulation of bone remodelling may have been incorrect, Slide 33 shows a theoretical model of the manner in which the alveolar plates are deformed when a tooth is loaded horizontally, and the sites where deposition and resorption bone takes place.

Rat models of tooth movement

In vitro models have been valuable in advancing our understanding of orthodontic tooth movement and dentoalveolar remodelling at the reductionist or molecular level. However, to understand the mechanisms involved at the holistic level requires an animal model. A large variety of animal species including mice, rats, rabbits, guinea pigs, dogs, and cats have been used to investigate tooth movement at the cellular level. However, bearing in mind ethical and cost issues, the availability of cDNAs and antibodies to an increasingly wide range of rat proteins has meant 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. (Slide 34).

Molecular studies of tooth movement in the rat

Connective tissue degradation and bone resorption involves the interaction of several differentiated cell types. *In vivo* methods are therefore essential if the cascade of molecular events responsible for the recruitment and activation of osteoclasts, as well as multinucleated giant cells, is to be fully understood. The application of *in situ* hybridization techniques to tooth movement studies in the rat has proven to be particularly useful in this respect. Two rat models have been commonly used: (1). The Waldo method in which an elastic ring is inserted between the maxillary M1 and M2 molars (Waldo and Rothblatt, 1954), and (2). A coil spring is attached between M1 and the incisors to give a more definable controlled force that can be pretested in the laboratory (Slide 35).

Takahashi *et al.* (2003) studied the expression of two key enzymes involved in matrix degradation, MMP-8 (collagenase-2) and MMP-13 (collagenase-3) by *in situ* hybridization during tooth movement in the rats (Slides 36–38). The expression of *IL1 β* and *IL6* mRNAs (but not *Tnfa*) has been shown to be upregulated in both PDL cells and osteoblasts on the compression side (Alhashimi *et al.* 2001; Slide 39). Both *Rankl* and *Opg* mRNAs are widely expressed in osteoblasts and PDL cells throughout the periodontal tissues (Ogasawara *et al.* 2004), and following tooth movement using the Waldo method positive signals for *Rankl* and *Rank* were detected in multinucleate osteoclasts at sites of active bone resorption (Slides 40-42).

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 that 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 thanks to Edward Angle, Oppenheim is identified in many people's minds as the key figure in tooth movement research, it is the research of Sandstedt that dominates 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.

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