

Brackets, epitopes and flash memory cards: a futuristic view of clinical orthodontics

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Orthodontics continues to be a profession anchored in traditional technology using appliances that cause inflammatory periodontal ligament (PDL) responses. Existing concepts of biological tooth movement based largely on histological tissue observations and the application of physical principles require major reassessment. In the next millennium, the genome revolution and knowledge of protein production and control could lead to the genetic correction of dentofacial anomalies and pain-free, biomolecular methods of malocclusion correction and long-term stability. A fundamental change is likely to be the abolition of bracket systems and their replacement with preprogrammed microchips driven by computers, and the control of PDL blood vessels and cells by pharmacological targeting. Future survival of the profession will depend on a radically different specialist who will be educated with a postgraduate curriculum based on molecular biology and computer engineering. *Aust J Orthod* 1999; 15: 260–8.

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Introduction

Much of current orthodontic practice, thinking and education remains enmeshed in the traditions of yesteryear. In the United States, and elsewhere, the veneration of Dr E.H. Angle, as well as the generalised application of his non-extraction concepts and the Edgewise slot, remain strongly entrenched as a mode of delivering clinical treatment. Nowadays, any new and seemingly radical orthodontic methodology is viewed with considerable suspicion, particularly if it is perceived to challenge the established concepts of teaching institutions or threaten the sale of a popular attachment. Nevertheless, major computer technology and cell biology changes are already knocking at the profession's door and we can only ignore them at our future peril and to the detriment of our patients.

Edgewise brackets were made at the Angle School by Dr P.R. Begg and Fred Ishi in 1924. Dr Begg claimed to be the first student to use them on a patient under Dr Angle's direction. Moreover, Dr Begg stated that Dr Angle even devised an angulated slot for the Edgewise bracket, but considered it to be impractical. Although the Edgewise bracket is now more than 70 years old, mechanically it remains largely unaltered, despite being adjusted with angulated slots, variable bases and external shape modifications. A major bracket change has been the adaptation of the Sved Edgewise pattern to form the Tip-Edge bracket design, which allows not only Begg principles of treatment but also provides uprighting with simultaneous torque without the need for auxiliary wires. Another Edgewise variation has been the Speed attachment with its inbuilt locking system.

Archwire configuration has always been an integral part of bracket development. In more recent times the combination of prescription attachments with preformed archwires has been an attempt to overcome the bracket/archwire nexus. Some current appliances, while relatively aesthetic for the patient and less demanding on the wire bending expertise of the specialist, are amenable to exploitation of the patient by being used and serviced by auxiliary

personnel. Nevertheless, the concepts of absolute mechanical and physiological control over multi-dimensional tooth movement remain the theoretical ideal for today's clinician.

It is rare nowadays for an orthodontic journal not to contain the word "force". Orthodontists practise in a world of mechanical gadgetry justified by such biological platitudes and anachronisms as "physiology", "biomechanics", "gentle forces" and even "energy". A key question that remains to be answered unequivocally in the affirmative is, "Do you use a biological technique that ensures that your patients do not experience any pain"? Blechman¹ has challenged this unresolved issue by asserting that the clinical use of magnetic force fields, albeit by rather cumbersome appliances, currently provides pain-free and mobility-free orthodontic treatment.

Since fixed appliance tooth movement was first employed, the clinical approach has been to mechanically operate from outside the tooth inwards. That is, via the external bracket attachment to bring about the internal periodontal ligament (PDL) tissue changes necessary for tooth movement. If we are to establish systems that provide quanta of physiological tooth movement, it will be essential for orthodontists to dramatically reorientate their present thinking of bracket attachments and archwire interactions. Current scientific research offers a number of real possibilities for the biomolecular alternative of internal PDL orthodontic control.

The rapid advancements in medical research and their clinical application during the past decade have not seen parallel progress in orthodontic knowledge and treatment. This situation will undoubtedly change, since much of the dramatic new genome science in medicine has direct relevance and application to orthodontic treatment. Assuming that a major new clinical orthodontic appliance has a life cycle of some 20 years, there is time for only one more technically-innovative bracket system to be established in the next five to ten years before the new sciences of the twenty-first century begin to revolutionise orthodontic education and practice.

Current research concepts

In the new millennium, genetics and molecular and cell biology will be the determinants of the provision of orthodontic services to support the needs and demands of the public. The knowledge for some of these biological systems has been available for a considerable time. Four examples of the multitude of new concepts are as follows.

Elastic biomolecular machines² are synthetic chains of amino acids, patterned after those in the PDL connective tissue, that can efficiently transform heat, light, pressure and chemical energy into motion by the folding and unfolding of proteins.

Every living organism represents the successful integration of many biomolecular machines. Biomolecular machines could portend a new kind of servo-mechanism. They can deliver drugs and prevent the formation of scar tissue. These bioelastic, amino-acid chains can sense almost any change in the environment around them and they can produce chemical, electrical or physical responses. Bioelastic materials are constituents of the PDL.

Power medicine³ utilises transdermal patches for the delivery of drugs. The question will be, "How do we best deliver substances that target selected structures in the PDL and alveolar bone"? It could be by way of an ingested tablet, or via a transdermal patch using a computerised type of "wrist-watch" as a drug delivery device driving a precise dose of ionised peptide that targets bone resorption/deposition. Another method may be the use of a radio-controlled computer system to drive a subdermal implant, acting as a preprogrammed transmitter to deliver a prescribed spectrum of target drugs.

There are molecular machines available⁴ that control and tightly regulate the activity of our protein-coding genes. These genetic systems offer a means to regulate the PDL by means of transcription factors to control the rate at which the enzyme ribonucleic acid (RNA) polymerase begins to carry out a central step in protein synthesis that is the transcription, or copying, of deoxyribonucleic acid (DNA) into messenger RNA. These genetic systems offer a means to regulate the PDL structures with transcription factors.

Targeted gene replacement⁵ is a commonly employed laboratory technique. More than 98 per cent of the genes in mice and humans are the same and serve quite similar purposes. Researchers can now create transgenic mice bearing any chosen mutations in any known gene. This technology is now revolutionising the study of mammalian biology and may become applicable to balance potential tooth and jaw size discrepancies. Thus, many skeletal malocclusions could well be eliminated in the future.

These and many other new technological systems of biological input and pharmacological therapy could mean that, within the next 25 years, orthodontic attachments as we know them today will have passed into history. Our current attachments will be totally re-engineered to accommodate biological principles. Future bracket alternatives will be the programmed mediators of data, providing the link between microelectronics and molecular biology.

A clinical perspective of maxillary bicuspid extraction space closure helps to place our limited knowledge of the role of the PDL and its microvascular bed (MVB) into a more realistic biological context. During the simultaneous

retraction of six maxillary anterior teeth, a first premolar extraction space of 8 mm can be routinely closed within 24 weeks. This distance of tooth repositioning means that the canine and MVB investing its root must be translocated over a distance of 8 mm. Under these circumstances, tooth movement must occur at a rate of approximately 0.3mm/week, or twice the width of the PDL every seven days. As yet, we do not really understand how the complicated vascular system continually readapts to such changes.

In daily clinical practice it tends to be overlooked that orthodontic tooth loading produces an inflammatory tissue response in the PDL.⁶ Moreover, without the presence of a MVB in the PDL, orthodontic tooth movement and tissue repair would not be possible and, therefore, there would be no need for orthodontists.

Much of our knowledge of the tissue changes associated with orthodontic tooth relocation is largely based on histological findings.⁷ More recently, in some of the animal experiments reported, the applied loading has sometimes been excessive; in fact, pathological, particularly in relation to the root size. For example, a 50 gm load applied to a small rat molar, while useful for experimental studies,^{8,9} if extrapolated to the size of a molar in man would be a very heavy load indeed. Even data gained from transmission electron microscopy of PDL morphology has inherent limitations in its interpretation of laboratory-processed tissue.

The comprehensive immunological cellular studies of Davidovitch⁶ have shed much knowledge on the PDL cellular components. During the past decade ongoing immunohistochemistry (IHC) research^{10,11,12,13,14,15} has superseded histological studies in enhancing our understanding of PDL cellular reactions to tooth loading and movement. Yet, endothelial cells that line the blood vessels represent one of the largest organ systems and have been designated to be of the highest research priority.¹⁶

Nevertheless, the role of the PDL blood vessels has been largely ignored. Anatomically, we continue to live with the erroneous view of a traditional arterio-venous vascular system based largely on the latex cast models of the rat PDL as described by Kindlova and Matena.¹⁷ It tends to be ignored that, in reality, this MVB, and those in rats, mice, marsupials, primates and man^{18,19,20,21,22,23} are predominantly venous structures.

Each MVB consists of a small number of large conduit vessels, the collecting venules that provide convective transport, and a large number of small vessels, the venous capillaries and postcapillary-sized venules, which permit diffusive exchange between the blood and tissues.²⁴ Blood vessels should be recognised as the significant and active regulatory structures in the PDL tissue. Their

influence is exerted through the anatomical and functional properties of the endothelial wall, which is traversed by all the fluids, substances and cells that enter and leave the ligament.^{25,26}

Mammalian circulations must comply with physical design principles to operate efficiently.²⁷ These principles may also parallel those operating in the PDL vasculature. Vessels form hierarchical branching networks whose architecture continually adapts to functional demands and tissue-growth needs. This adaptive ability is prescribed by genetic information, and by local action in response to biochemical and mechanical stimuli, and influences the tissue remodelling process.²⁴

The application of physiological principles established for the MVB elsewhere could also apply in the PDL vasculature. As in other tissues, local haemodynamics such as vessel-wall shear stress, luminal pressure and circumferential stress generated by routine blood flow, could provide sufficient stimulus to initiate major biomolecular alterations within the wall and the surrounding ligament and so determine the characteristics of the normal PDL.²⁸ Physiological vessel stresses are tension and compression perpendicular to the endothelial surface, or shear stresses with a tangential orientation to the surface elements.²⁶ Shear stress generated by routine blood flow is thus sufficient to initiate major biomolecular alterations within the wall and the surrounding ligament. However, rapid tooth movement through the alveolar process causes continual PDL remodelling. The resulting reorganisation produces structural modifications to the existing vascular system, including the growth of new vessels and the regression of existing vessels.²⁶ This process of angiogenesis involves the sprouting and budding of endothelial cells from pre-existing vessels, particularly the postcapillary venules and small terminal venules.²⁹

Important MVB attributes also include spatial differences in vessel and cell functions among input arterioles, smaller arterioles, capillaries, small venules and large draining venules. Moreover, larger arteries are more sensitive to shear stress than smaller arterioles.²⁶ To further complicate any research agenda, it is known that endothelial cell heterogeneity exists among different vascular endothelial cell beds and within any particular MVB.^{30,31}

In the MVB remodelling of non-dental tissues, current research interest is in shear stresses due to blood viscosity on the endothelial walls and circumferential wall stress due to vessel inflation by the blood pressure. Blood vessel, strain-dependent, responses include endothelial cell proliferation, protein synthesis, F-actin stress fibre alignment, increased inositol triphosphate levels and endothelial nitric oxide synthase activation.²⁶

To date, little research has been devoted to immunological studies of MVB response to tooth loading of the PDL. Vascular endothelium plays a pivotal role in controlling blood vessel function through the generation of vasoactive dilator and constrictor mediators. These include the dilator molecules nitric oxide and prostacyclin, as well as the constrictor substances endothelin-1 (ET-1) and angiotensin II.¹⁶

The use of immunohistochemistry (IHC) antigen-antibody reactions as probes to explore gene expression is one of the most specific methods for determining biomolecular events in cells. A cell molecule may contain several antigenic determinants called epitopes. These epitopes can be detected in tissues by the introduction of a specific antibody that has a fluorescent dye conjugated to it. Excitation of the fluorochrome under a microscope produces a visible fluorescence that enables the sites where these biomolecular substances are formed to be pin-pointed with the antigen-antibody reaction and recorded. When cells are stimulated by physiological and inflammatory events, they produce countless numbers of different biomolecular substances that have a time-dependent diversity of effects upon each other.

Investigations of the MVB in the PDL can be undertaken with IHC and confocal laser scanning microscopy (CLSM) to map the spatial geometry of the vascular system by detecting the endothelium and the vascular smooth-muscle actin and myosin elements. One method of defining the endothelial lining of arterial, venous capillary, postcapillary-sized venule and collecting venule segments of the PDL is to employ IHC techniques using the antibody RECA-1. This is a rat endothelial cell monoclonal antibody that recognises the endothelial cell epitope.³⁰ Recent studies reveal that RECA-1 shows that the vascular endothelial cells share cell-specific molecules that react to tooth loading by upregulation of the antibody within 10 minutes.³² The application of IHC to the PDL blood vessel endothelium and vascular smooth muscle is demonstrated in the accompanying CLSM images (Figures 1, 2 and 3).

Orthodontic intervention with the PDL causes the activation of cytokines such as ET-1.³³ Cytokines are secreted regulatory proteins that control the survival, growth, differentiation and effector function of tissue cells. The cytokines include families of regulators known as growth factors, colony stimulating factors, interleukins and interferons. Cytokine-producer cells are the biological sensors, the cytokine the means of signal transduction, and the receptor cells produce the biological response.³⁴

Synergistic and antagonistic interactions occur

between the different cytokines and other molecules; for example, ET-1, nitric oxide, prostacyclin, angiotensin II and noradrenaline.¹⁶ The cytokines have varying life spans, exhibit time-dependent, interacting cascade effects and are also able to alter filamentous actin and cell shape, which produce changes in vascular tone and cell permeability.

Cytokine activity is especially associated with inflammation³⁵ and wound-healing angiogenesis³⁶ as would occur during orthodontic PDL tissue remodelling. When mechanical stress is applied *in vitro* to cultured venous endothelial cells, it alters cytoskeletal elements and cell morphology and releases cytokines in the endothelium. These cytokine profiles are significantly altered by tension changes dependent on time, magnitude and direction.³⁷

ET-1 is a particularly interesting example of one of the cascade of cytokines released by PDL endothelial cells during a mechanically-induced inflammatory response, such as experimental loading.³³ This biologically active, multifunctional, vaso-peptide has been shown to play a pivotal role in controlling blood vessel function and may be of dental relevance. It is the most potent and sustained vasoconstrictor known, and is significant in the regulation of blood pressure and responsible for the maintenance of vascular tone.³¹ Furthermore, ET-1 plays an important role in vascular modelling, the regulation of cell proliferation, matrix synthesis, growth factor and adhesion molecule release^{31,38} and dentofacial developmental anomalies.¹⁶

Endothelins exist as a family of three isoforms: ET-1, ET-2 and ET-3. Each one is derived from a separate gene and, as with many peptides, initially synthesised as a large precursor preproET-1 of 212 amino acids. This peptide is cleaved intracellularly to big ET-1 and, as the last step in the synthesis, further cleaving occurs by a metalloprotease endothelin-converting enzyme to the active ET-1 of 21 amino acids. For each of these isoforms there are receptor subtypes mediating different vascular responses in the endothelium and vascular smooth muscle.^{31,39} However, the receptor mediated vasoconstriction varies with the species, vessel type and vessel size.⁴⁰

Normal blood flow produces endothelium shear stress, a physical factor that can activate the transcription gene for preproET-1 to produce ET-1, which passes across the abluminal endothelial cell boundary, to act on the underlying smooth muscle and cause its contraction. The synthesis and release of ET-1 is thought to occur *de novo* as a response to stimulation of the endothelial cell. Shear and compression factors have different effects on different types of blood vessels.²⁴

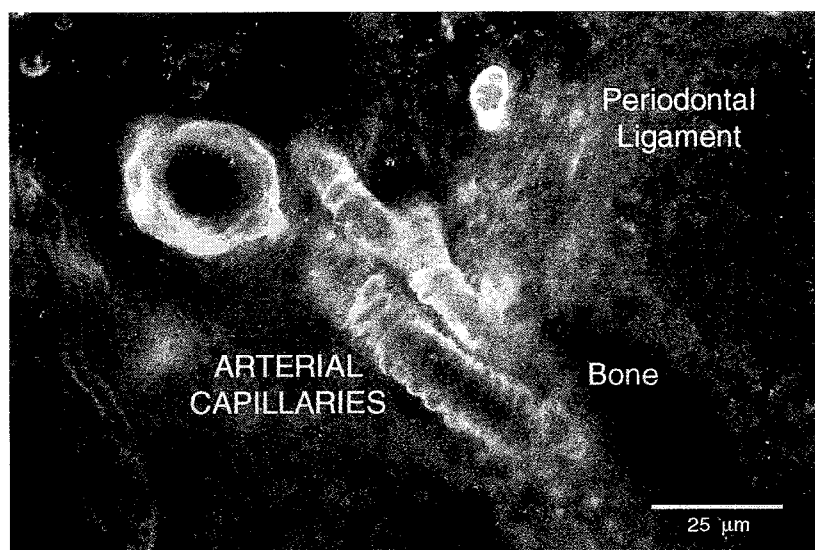


Figure 1. Identification of arterial capillaries and their encircling smooth-muscle profiles with the application of α -smooth muscle myosin. Junction of the apical PDL and bone below a rat mandibular first molar.

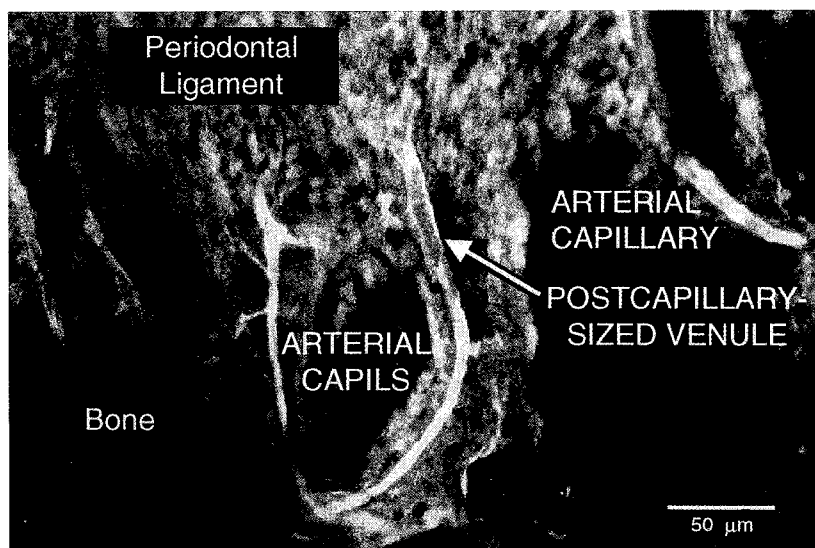


Figure 2. RECA-1 primary antibody and CY3 conjugated secondary antibody used to reveal the endothelium of a single arterial capillary and an arterial capillary loop which extends from the alveolar bone into the apical PDL and venules. On entering the PDL the capillary loops suddenly form a distribution system of thin-walled postcapillary-sized venules.

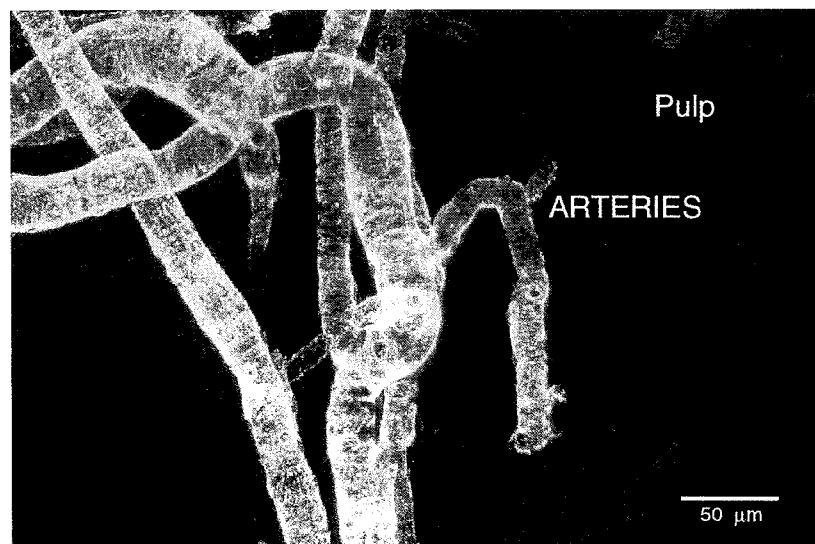


Figure 3. A merged confocal laser scanning microscope IHC image of a portion of the complex intercommunicating blood system in the rat molar pulp. The vessel musculature is demonstrated with α -smooth muscle actin and CY3. Seventy five slices with a total depth of 220 μ m.

Therapeutic considerations

Skalak and Price²⁶ in their extensive review of mechanical stress and vascular remodelling state that blood vessel adaptation and remodelling play a central role in wound healing and tissue homeostasis. Similarly, in the PDL the MVB can also be considered a prime mediator of the inflammatory reaction and tissue remodelling in response to orthodontic tooth loading. Recent research demonstrates that there are already therapeutic molecule systems available for the direct control of blood vessel function by way of pharmacological treatments. Ojeifo *et al.*⁴¹ report that the intravenous injection of genetically-modified endothelial cells could be directed to sites of active angiogenesis. Thus, it is likely that activation markers will be developed to allow the site-specific uptake of genetically-modified cells in other microvessels as well.

Clearly, the alteration of vascular structure will become an important therapeutic goal in the future.^{16,26,31,42,43,44,45} Furthermore, Ziegler and Naren⁴⁶ propose that the use of tissue engineering to regulate vascular biology by mechanical stresses is a realistic objective. Therefore, the ability to manipulate orthodontic tooth movement by the administration of pharmacological molecules to target the PDL blood vessels is a real possibility.

Relevance to Orthodontic Treatment

In the light of recent microvascular research, it is clearly necessary for the orthodontist to develop a rational perspective of some of the functional features of the normal MVB. Under normal metabolic conditions, blood-flow viscosity produces endothelium shear stresses, which generate the biomolecular signals that maintain vascular and connective tissue homeostasis.

Physiological maintenance of the normal MVB involves wall shear stresses^{24,26} in the order of 10–100 dynes/cm². This level of physiological cell activation is far removed from the advocated orthodontic activation, which ranges from 25–100 gm of “force”; the word “force” being the current pseudonym implying physiological activation. Such heavy pathological forces transmitted through the PDL may well contribute to common patient complaints of pain and the current dilemma of root resorption. Future tooth moving methods utilising “stimulation” systems operating at, or near, the physiological threshold of endothelial cell wall response²⁶ will eliminate pain, increase the rate of tooth movement⁷ and offer the potential for vastly improved post-treatment stability.

The ongoing use of the word “force” in the orthodontic literature has bedevilled our clinical thinking over the years. It is time we began to put our pathological, PDL-inflammatory house in order and moved to appliances that apply

techniques of very light stimulation to reposition teeth. In the future, it is this type of system that can produce an optimal biomolecular orthodontic response.

The future role of microchips and computers in orthodontic treatment

With this very brief reference to IHC detection systems, and the genes with their role in the biomolecular control of cell function, it is now possible to suggest a future scenario for Orthodontics on the basis of current knowledge and research. This century has seen the ongoing industrial revolution, the physics and chemistry ages, and the information technology revolution. During the new millennium, genome research will provide the information superhighway for the era of cell biology.

The last 20 years have seen great strides in digital technology. Computers have diminished in size quite remarkably and processors continue to double in speed every twelve months. Nevertheless, the days of the silicon chip are numbered. Currently, there are parallel computers in service, and under development are quantum computers with potentially awesome power based on random computing at the sub-atomic level. Other emerging designs include neural network computers and the creation of protein-structured computers where DNA strands will replace silicon and provide thinking machines. Within the lifetime of many orthodontists, artificial intelligence will become capable of reproducing itself without human intervention and a new species will be born. This intelligence will be created from non-organic materials rather than the genes of another species. These are just a few examples of the multitude of new events looming around the corner in the new millennium.⁴⁷

According to Rivkin⁴⁸ the microchip has the power to transform virtually every aspect of our lives. He insists that, “the marriage of computers and genetic science will change our world more radically than any other technological revolution in history, leading to economies based on genetic commerce. In the future, tiny computers will be embedded in everything, including our bodies”.

With genetic medicine, it will be possible to cure disease with the use of designer drugs that activate and deactivate selected genes using gene switching. We will also be able to control genes to help human tissues to repair themselves and grow replacement body parts and organs. The whole focus of health care will be on prevention rather than the current emphasis on cure.

Clearly, future orthodontic appliances must limit the level of inflammatory response generated by their use. Currently, there are many new developments in orthodontic bracket design. Some

of these prototypes bear no resemblance to either current Edgewise or Ribbon Arch attachments. In the next decade the delivery of orthodontic treatment will begin to take on a totally new dimension. The correction of malocclusions will be achieved with appliances completely unlike any mechanism currently in vogue. Present methods will be replaced by the application of internal biomolecular therapy. The application of light stimulatory loads, with individually designed microchip sets controlled by radio, or infra red, output from personal computer systems, will be the treatment methods of the twenty-first century.

Minimal stimulatory loads will produce transduction effects that generate biomolecular signals, by activating the promotor genes in designated cell fields, to produce a temporal cascade of vasoactive and other substances with functionally distinct roles. These mediators will regulate the metabolism of individual cell "types" within a broad spectrum of cellular control. Many factors, including those affecting angiogenesis, basement membrane formation, neural reconstitution and bone metabolism will be programmed to produce pharmacologically-induced tooth movement.

Conclusions

Because the new millennium will usher in the era of the genome associated with biologically-based computers, the profession must be willing to look into the future and prepare to adapt itself for the revolutionary changes that will be dictated by new biological and technological advances. In order to stimulate some thinking on the "future shock" of professional practice, the following hypotheses are put forward suggesting that Orthodontics could be practised along the following lines within the next 20 years.

The patient's head may be scanned by a system of non-ionising radiation, such as optical or positron emission tomography, to produce a three-dimensional image that is viewable and measurable from any aspect of the dental and osseous tissues.

A saliva sample will provide a genetic-code readout and a physiological analysis of the patient's tissue properties.

A concurrent scan of the MVB in the gingivae and PDL, plus the retina vascular bed, could determine orthodontic loading rates based upon blood vessel configuration and flow rates.

The total information package will be fed into the orthodontist's configurable quantum or protein-based computer server and the software analysis systems will produce an individual diagnosis and treatment system based on the analysed biological data.

Using the treatment system data, the orthodontist's computer will design and control the manufacture of a minute flash memory card as a microchip

holding the treatment plan, routine patient monitoring program, and guidance system for tooth movement. A "what if" program will be included to compensate for unexpected, or undetected, biological variations encountered during treatment.

The orthodontist's computer will also formulate a designer-drug protocol and dosage based on individual patient genetic and cell functional characteristics.

At the orthodontist's office, the patient may have minute flash memory microchips, which can retain controlling tooth-movement data without a power supply, attached to the lingual surface of the teeth. That is, individually monitored patients with custom-preprogrammed tooth chips.

The patient's course of treatment could be controlled from the flash-memory chip by the home computer, which will interface with a computerised "wrist-watch" worn by the patient.

The "wrist-watch" will deliver a regulated drug dose released via a dermal patch.

Alternatively, a subdermally-implanted pre-programmed flash memory microchip could be monitored continually by a wearable computer to provide the non-ionising electromagnetic field, and possibly also a pharmacological cocktail drug release system, to control sequenced three-dimensional tooth movement via the tooth lingual microchips.

At the completion of treatment, the application of a "stabilising" biochemical prescription could maintain the occlusion in permanent and "stable" functional retention.

Such a system will have the great advantage of readily lending itself to adaptation for the treatment of patients in near, and all outback, regions of Australia via telemedicine.

Despite these prognostications, there remain some significant clouds on the horizon associated with the development and management of certain aspects of this forecast treatment mode.

Genetic patenting will raise many new ethical issues on the future of orthodontic practice.

Advanced computer systems and methods of robotic treatment may well threaten the future of the orthodontic profession as we know it today. Orthodontists will need to be trained to become computer-literate programmers, diagnosticians, geneticists, designer pharmacologists and cell biologists if they are to maintain their specialty status. Otherwise, they could well find their role usurped by government paramedical personnel providing packaged treatment systems, based on state- or federal-designed politically-expedient computer models, to the general population.

These imperative professional education changes will bring a further dichotomy in views between academics and specialists as to the best postgraduate teaching curriculum and clinical training objectives.

And a final question. Is the specialty preparing to respond to the organisation known as "bands.com" that will offer patients orthodontic diagnosis, treatment planning and appliances on the Internet?

On a positive note, Orthodontics requires to be rapidly restructured to become a high-profile proactive and innovative profession to lead the specialty into a new and exciting millennium.

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References

1. Blechman AM. Pain-free and mobility-free Orthodontics? *Am J Orthod Dentofac Orthop* 1998; 113: 379–83.
2. Urry DW. Elastic biomolecular machines. *Sci Am* 1995; 272: 44–9.
3. Stix G. Power medicine. *Sci Am* 1994; 271: 87.
4. Tjian R. Molecular machines that control genes. *Sci Am* 1995; 272: 38–45.
5. Capecchi MR. Targeted gene replacement. *Sci Am* 1994; 270: 34–41.
6. Davidovitch Z. Cell biology associated with orthodontic tooth movement. In: Berkovitz BKB, Moxham B, Newman HN, eds. *The periodontal ligament in health and disease*. 2nd edition. London: Mosby-Wolfe, 1995; 259–78.
7. Reitan K, Rygh P. Biomechanical principles and reactions. In: Graber TM, Vanarsdall jnr RL, eds. *Current orthodontic concepts and techniques*. St Louis: Mosby, 1994; 96–112.
8. Brudvik P, Rygh P. The initial phase of orthodontic root resorption incident to local compression of the periodontal ligament. *Eur J Orthod* 1993; 15: 249–63.
9. Vandevska-Radunovic V, Kristiansen AB, Heyeraas K J, Kvinnsland S. Changes in blood circulation in teeth and supporting tissues incident to experimental tooth movement. *Eur J Orthod* 1994; 16: 361–9.
10. Davidovitch Z, Nicolay OF, Ngan PW, Shanfield JL. Neurotransmitters, cytokines and the control of alveolar bone remodelling in Orthodontics. *Dent Clin North Am* 1988; 32: 411–35.
11. Davidovitch Z, Gogan MH, Okamoto Y, Slivka MW, Shanfield JL. Inflammatory mediators in the mechanically stressed periodontal ligament in vivo. In: Davidovitch Z, ed. *The biological mechanisms of tooth movement and craniofacial adaptation*. Columbus: The Ohio State University College of Dentistry, 1992; 391–400.
12. Saito S, Kurabayashi H, Yamasaki K, Shibasaki Y. Effects of centrifugal forces on bone resorption and osteoclast-like cell formation in vitro. In: Davidovitch Z, Norton LA, eds. *The biological mechanisms of tooth movement and craniofacial adaptation*. Birmingham: EBSCO, 1996; 137–52.
13. Greenfield EM. The role of interleukin-6 in stimulation of osteoclast differentiation and activity by neuropeptides and other bone resorptive agents. In: Davidovitch Z, Norton LA, eds. *The biological mechanisms of tooth movement and craniofacial adaptation*. Birmingham: EBSCO, 1996; 301–8.
14. Sinha PK, Nanda RS. The relationship between orthodontic tooth movement and root resorption in PGE2 and non-PGE2 treated sides in a rat model. In: Davidovitch Z, Norton LA eds. *The biological mechanisms of tooth movement and craniofacial adaptation*. Birmingham: EBSCO, 1996; 337–48.
15. Vandevska-Radunovic V, Kvinnsland S, Kvinnsland IH. Effect of experimental tooth movement on nerve fibres immunoreactive to calcitonin gene-related peptide, protein gene product 9.5, and blood vessel density and distribution in rats. *Eur J Orthod* 1997; 19: 517–29.
16. Webb DJ. Endothelin: from molecule to man. *Br J Clin Pharmacol* 1997; 44: 9–20.
17. Kindlova M, Matena V. Blood vessels of the rat molar. *J Dent Res* 1962; 41: 650–60.
18. Weekes WT, Sims MR. The vasculature of the rat molar periodontal ligament. *J Periodontal Res* 1986; 21: 186–94.
19. Wong RST, Sims MR. A scanning electron-microscopic, stereo-pair study of methacrylate corrosion casts of the mouse palatal and molar periodontal micro-vasculatures. *Archs oral Biol* 1987; 32: 557–66.
20. Freezer SR, Sims MR. A transmission electron-microscope stereological study of the blood vessels, oxytalan fibres and nerves of mouse-molar periodontal ligament. *Archs oral Biol* 1987; 37: 407–12.
21. Sampson WJ, Sims MR. Oxytalan fibre organisation in marsupial mandibular periodontal tissues. *J Morphol* 1977; 154: 115–31.

22. Parlangue LM, Sims MR. A TEM stereological analysis of blood vessels and nerves in marmoset periodontal ligament following endodontics and magnetic incisor extrusion. *Eur J Orthod* 1993; 15: 33-44.
23. Foong KWC, Sims MR. Blood volume in human bicuspid periodontal ligament determined by electron microscopy. *Archs Oral Biol* 1999; 44: 465-74.
24. Pries AR, Secomb TW, Gaetgens P. Design principles of vascular beds. *Circ Res* 1995; 77: 1017-23.
25. Collin-Osdoby P. Role of vascular endothelial cells in bone biology. *J Cell Biochem* 1994; 55: 304-9.
26. Skalak TC, Price RJ. The role of mechanical stresses in microvascular remodeling. *Microvasc Res* 1996; 3: 143-65.
27. LaBarbera M. Principles of design of fluid transport systems in zoology. *Science* 1990; 249: 992-1000.
28. Price RJ, Skalak TC. A circumferential stress-growth role predicts arcade arteriole formation in a network model. *Microcirculation* 1995; 2: 41-51.
29. Polverini PJ. The pathophysiology of angiogenesis. *Crit Rev Oral Biol Med* 1995; 6: 230-47.
30. Duijvestijn AM, van Goor H, Klatter F, Majoor GD, van Bussell E, van Breda Vriesman PCJ. Antibodies defining rat endothelial cells: RECA-1, A pan-endothelial cell-specific monoclonal antibody. *Lab Invest* 1992; 66: 459-66.
31. Haynes WG. Endothelins as regulators of vascular tone in man. *Clin Sc* 1995; 88: 509-17.
32. Sims MR. Blood vessel response to pan-endothelium (RECA-1) antibody in normal and tooth loaded rat periodontal ligament. *Eur J Orthod* 1999: In press.
33. Shiohama Y, Sasaki T, Shibasaki Y. Histological and immunohistochemical study of endothelin-1 localisation in periodontal ligament during experimental tooth movement. *Dent Jap* 1995; 32: 75-8.
34. Nicola NA, ed. Guidebook to cytokines and their receptors. Oxford: Sambrook & Toole, Oxford University Press, 1994: 1-16, 237-240.
35. Gerritsen ME, Bloor CM. Endothelial cell gene expression in response to injury. *FASEB J* 1993; 7: 523-32.
36. Roesel JF, Nancy LB. Assessment of differential cytokine effects on angiogenesis using an in-vivo model of cutaneous wound repair. *J Wound Rep* 1995; 58: 449-597.
37. Lewis PJ. A model for the response of blood vessels to tensile forces. 1996. Masters Thesis. The University of Sydney.
38. Wang X, Douglas SA, Loudon C, Vickery-Clark LM, Feurstein GF, Ohlstein EH. Expression of endothelin-1, endothelin-3, endothelin-converting enzyme-1, and endothelin-A and endothelin-B receptor mRNA after angioplasty-induced neointimal formation in the rat. *Circ Res* 1996; 78: 322-8.
39. Turner AJ, Murphy LJ. Molecular pharmacology of endothelin converting enzymes. *Biochem Pharmacol* 1996; 51: 91-102.
40. Davenport AP, Maguire JJ. Is endothelin vasoconstriction mediated only by ETA receptors in humans? *Trends Pharmacol Sci* 1994; 15: 9-11.
41. Ojefo JO, Forough R, Paik S, Macaig T, Zwiebel JA. Angiogenesis-directed implantation of genetically modified endothelial cells in mice. *Cancer Res* 1995; 55: 2240-4.
42. Fan TP, Jaggar R, Bicknell R. Controlling the vasculature; angiogenesis, anti-angiogenesis and vascular targeting of gene therapy. *Trends Pharmacol Sci* 1995; 16: 57-66.
43. Folkman J. Clinical applications of research on angiogenesis. *N Engl J Med* 1995; 333: 1757-63.
44. Mulvany MJ. Determinants of vascular structure. *J Cardiovasc Pharm* 1992; 19: S7-S11.
45. Thybo NK, Stephens N, Cooper A, Aalkjaer C, Heagerty AM, Mulvany MJ. Effect of antihypertensive treatment on small arteries of patients with previously untreated essential hypertension. *Hypertension* 1995; 25: 471-81.
46. Ziegler T, and Nerem RM. Tissue engineering a blood vessel: regulation of vascular biology by mechanical stresses. *J Cell Biochem* 1994; 56: 204-9.
47. Kaku M. Visions: How science will revolutionise the 21st century. Oxford University Press, 1998.
48. Rivkin J. The Biotech century. Penguin Putnam, 1998.