

Third Edition

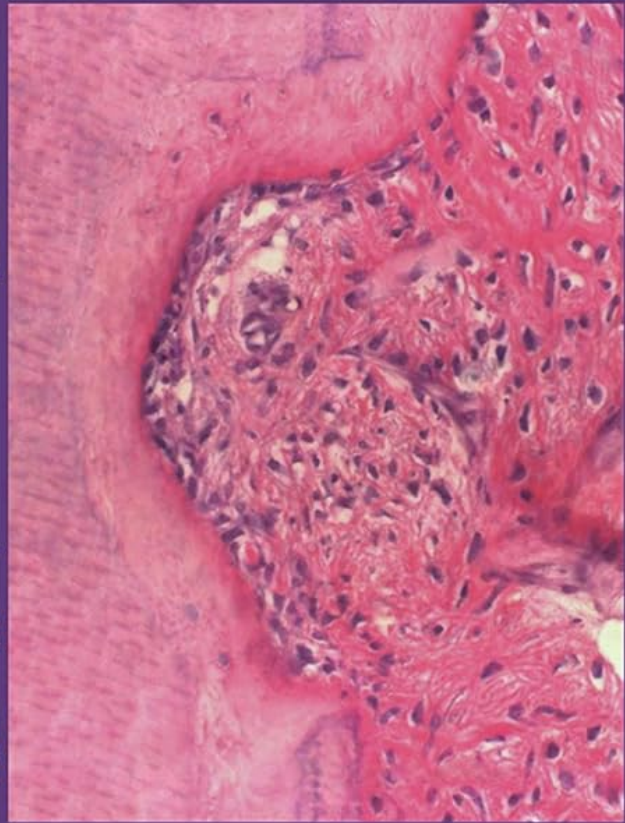
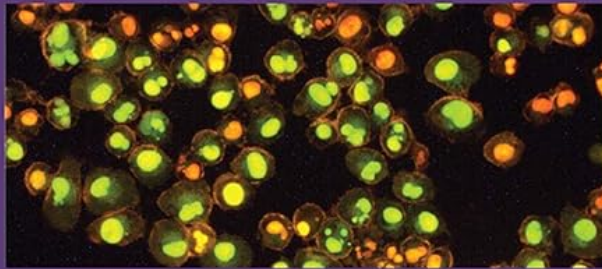
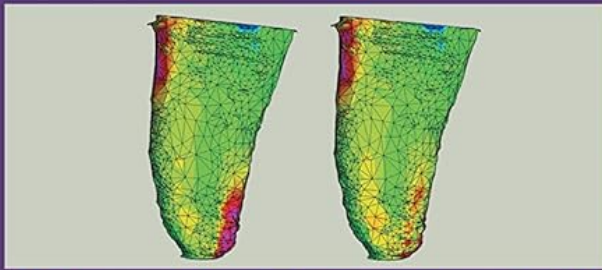
# Biological Mechanisms of Tooth Movement

Edited by

**Vinod Krishnan**

**Anne Marie Kuijpers-Jagtman**

**Ze'ev Davidovitch**



**WILEY** Blackwell

## **Biological Mechanisms of Tooth Movement**

# Biological Mechanisms of Tooth Movement

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My ever inspiring family, especially my parents, brother, wife, and kids (Jithu and Malu) who supported me throughout this project.

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Vinod Krishnan

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Zeev Davidovitch

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# Preface to the First Edition

The first international conference on the biology of tooth movement was held in November 1986 at the University of Connecticut, under the leadership of Louis A. Norton and Charles J. Burstone. In the Foreword to the book that emanated from that conference, Coenraad F.A. Moorrees, to whom the first edition of this book is dedicated, wrote:

Notwithstanding continued progress from numerous histologic and biochemical studies describing tissue behavior after force application, the key question on the biology of tooth movement remains unresolved: namely, how force application evokes molecular response in the cells of the periodontal membrane. Only when this fundamental question in bone physiology is better understood can appliances for optimal tooth movement in orthodontics be achieved.

In the two decades that have passed since that conclusion, scientists worldwide seem to have followed the direction pointed out by Professor Moorrees. Basic research pertaining to the response of tissues and cells to mechanical loading has grown broader and deeper. The emphasis at the end of the first decade of the twenty-first century is on molecular biology and molecular genetics. Genes are being identified which seem to play important roles in the response of parodontal cells and tissues to orthodontic forces, and a growing number of signal molecules that modulate this process have been elucidated. These findings now enable clinicians to utilize

some of these molecules as markers of processes associated with tooth movement, such as inflammation and root resorption.

This unrelenting increase of knowledge in basic science has not yet resulted in the development of orthodontic appliances that can be tailored to fit the biological peculiarities of individual patients. But with the growing understanding of the nature of various common diseases, such as diabetes, asthma, arthritis, obesity, and various cardiovascular diseases, it is now possible to assess their potential effects on orthodontic tooth movement, clinically and molecularly. The time seems to be approaching when the nature of optimal orthodontics will be fully exposed as a consequence of the increasing widening of the highway connecting clinical and basic sciences.

The goal of this book is to inform orthodontic students as well as practitioners on the known details of the biological aspects of tooth movement. We hope that this information will enhance their ability to render excellent treatment to all of their patients, young and old. Moreover, we hope that this compendium will convince readers that the dentofacial complex is an integral part of the complete human body, and as such, and like any other region of the body, is prone to be influenced by many factors, genetic or environmental.

*Vinod Krishnan  
Zëv Davidovitch  
Editors*

# Preface to the Second Edition

Basic biologic research in orthodontics has witnessed rapid growth since the publication of the first edition of *Biological Mechanisms of Tooth Movement*. This research not only identified biologic factors associated with tooth movement and its iatrogenic reactions but has expanded even deeper into exploration at the molecular and genomic levels, to generate new knowledge that can be used in clinical settings.

The concept of personalized or individualized medicine is rapidly gaining a hold in medicine as may be seen from the global annual conferences on this subject. In medicine, at this time, the focus is on the personal determinants of cancer and diabetes. Efforts to adapt this concept to all of medicine are gaining momentum. Dentistry is no exception, and orthodontics is potentially the pioneer in this regard. Orthodontists have long been customizing their diagnoses and treatment plans according to the physical characteristics of their patients but now we are entering a period when it would be possible to evaluate the biological features of each patient, by measuring specific tissue markers in fluids, such as saliva and gingival crevicular fluid. The task of establishing reliable tests for the identification of the sought-for markers may not be imminent because of the complexity and variability of the individual genomics but investigations of this pathway have already begun.

The role of basic biologic research has frequently been portrayed as the identification of factors and processes that participate in clinical functions, and test the validity of any hypothesis regarding the efficacy and safety of new and old clinical methods. The specialty of orthodontics has benefitted from this relentless flow of new information, derived from a plethora of publications in numerous scientific periodicals, which focused on mechanism of mechanotransduction, the birth, life and death of the osteoclast, the molecular genetics of bone modeling and remodeling, and the effects of hormones and drugs on soft and mineralized connective tissues. This ongoing growth in information is already affecting clinical orthodontics. One major concept gaining support is the proven ability of bone and periodontal fibroblastic cells to respond simultaneously to more than one signaling factor. Evidence in support of this principle has already led to the application, in addition to orthodontic force, of surgical procedures, vibrations, laser radiation, electricity, and vitamin D3. All of these factors have displayed an ability

to enhance the velocity and reduce the duration of tooth movement. The orthodontist now has at his/her disposal a choice of methods, invasive and noninvasive, local and systemic, that can augment the pace of tissue changes that facilitate tooth movement. These mechanisms act on the tissue and cellular levels, and can be manipulated based on increasing knowledge derived from worldwide laboratory experiments and clinical trials, all of which elevate the clinical potential of orthodontics to attain positive results, with a long-range stability, and with a low risk for undesirable side effects.

We are pleased to present this second edition of *Biological Mechanisms of Tooth Movement*, in which we have assembled chapters about topics closely related to the *basic biologic aspects of orthodontics*, which affect the movement of teeth during orthodontic treatment. It updates most of the subjects addressed in the first edition, and includes new topics, such as the search for efficient methods to accelerate tooth movement.

We would like to thank all our contributors who have demonstrated dedication to this project. We would also like to express our sincere appreciation to the book reviewers, who critically analyzed the first edition of the book and let us know its shortcomings so that the second edition is made much stronger. We express our gratitude to our publisher, Wiley-Blackwell, especially Sophia Joyce, Hayley Wood, Jessica Evans, Sara Crowley-Vigneau, and Katrina Hulme-Cross, who helped us complete the project successfully. We would also like to thank the support staff, Jayavel Radhakrishnan, David Michael and all others, who worked tirelessly to facilitate this publication.

As we have stated in the preface to the first edition of this book, “we really hope that this compendium will convince the readers that the dentofacial complex is an integral part of the complete human body, and as such, is prone to be influenced by any factor, genetic or environmental, like any other region of the body.” Orthodontic academicians and clinicians increasingly recognize this principle and try to treat patients as humans, not merely as typodonts. We hope that this book will assist all orthodontists in this effort.

Vinod Krishnan  
Zeev Davidovitch  
Editors

# Preface to the Third Edition

Oral health, as defined by the FDI World Dental Federation, is multifaceted and includes the ability to speak, smile, smell, taste, touch, chew, swallow, and convey a range of emotions through facial expressions with confidence and without pain, discomfort, or disease of the craniofacial complex. Oral health has a close relationship with the general health of an individual and dental treatment contributes to the overall wellbeing of the individual, which is a well-established fact that remains undiminished. The definition from the FDI implicates that malocclusion is not only an aesthetic problem, and states that orthodontic treatment can prevent and intercept further oral diseases and improve quality of life. To effect this, and to reach the stated goal together with our patients, we need to have a broad knowledge ranging from basic science to psychology, or stated in another way, from molecule to man.

Orthodontic tooth movement is the outcome of subjecting teeth to a wide variety of mechanical forces, for long periods of time. This movement is totally dependent upon stimulation and activity of cells near the affected dental roots. Investigations of these cellular responses focus on molecular events on the nuclear, cytoplasmic, and plasma membrane levels. We are very pleased to discover that our initial effort to organize all research related to tooth movement ‘under one roof’ and the subsequent second edition of *Biological Mechanisms of Tooth Movement* has made its mark among researchers, academicians, residents, and clinicians, equally. It stimulated basic science research in orthodontics, leading to the creation of a strong scientific foundation for the specialty. A sizeable body of new information related to the biology of orthodontic tooth movement has emerged since the publication of the second edition of this book by Wiley-Blackwell in 2015. Since then, reports on studies about the molecular biology of bone metabolism, root resorption, and relapse of orthodontic treatment outcomes have appeared in orthodontic literature. With Professor Anne Marie Kuijpers-Jagtman joining the team, who has contributed extensively to tooth movement research and its clinical translation, we are sure that the third edition will be a ‘reading and learning treat’ to all those who embrace it.

We have made the utmost effort updating the contents of this third edition and organizing it into specific areas, with the aim of highlighting the recent findings emanating from basic research, and

bring them to the attention of clinicians specializing in moving teeth to new positions, effectively and comfortably. This edition presents four new chapters (tissue reactions, periodontal microbiology, surgically assisted tooth movement, as well as micro-osteoperforations) and extensive revision of existing ones, especially the third chapter on mechanisms of tooth movement with orthodontic force application.

We would like to thank all our contributors, who are experts in their research area and have demonstrated dedication to this project. We would also like to express our sincere appreciation to the book reviewers, who analyzed critically the first and second editions of the book, which helped us to improve this edition. We express our gratitude to our publisher, John Wiley & Sons, especially Loan Nguyen, Tanya McMullin, Susan Engelken, Jayadivya Saiprasad, Bhavya Boopathi and to our copy-editor Jane Grisdale who helped us complete the project successfully. We would also like to thank the supporting staff who worked hard to facilitate this publication.

The third edition of the book is aimed at the same audience as the first and second edition – clinicians, academicians, and researchers in the field of orthodontics and allied specialties such as periodontists, bone biologists, and also basic science researchers. The book is also indispensable for postgraduates in orthodontics, not only to understand *how* but also *why* teeth can be moved. Our main goal is to decipher the minute details of the investigations on cellular responses, focusing on molecular events on the nuclear, cytoplasmic, and plasma membrane levels, and its cross-interactions leading to tissue level changes. We attempt to provide clinically plausible translational data which lead to practising a better, biologically oriented orthodontic treatment. We really hope that the educated clinicians who follow these developments can collect pieces of the unfolding puzzle, and relate them to individual patients, leading to a ‘biologic-friendly orthodontics.’

Vinod Krishnan  
Anne Marie Kuijpers-Jagtman  
Zëv Davidovitch  
Editors

**PART 1**

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# **Evolution of Biological Concepts**



## CHAPTER 1

# Biological Basis of Orthodontic Tooth Movement: A Historical Perspective

Vinod Krishnan and Ze'ev Davidovitch

### Summary

For millennia, we were unable to understand why teeth can be moved by finger pressure, as advocated by Celsus around the dawn of the Common Era, but it was working. Indeed, our ancestors were keenly aware of malocclusions, and the ability to push teeth around by mechanical force. The modern era in dentistry began in 1728 with the publication of the first comprehensive book on dentistry by Fauchard. He described a procedure of “instant orthodontics,” whereby he aligned ectopically erupted incisors by bending the alveolar bone. A century-and-a-half later, in 1888, Farrar tried to explain why teeth might be moved when subjected to mechanical loads. His explanation was that the teeth move either because the orthodontic forces bend the alveolar bone, or they resorb it. The bone resorption idea of Farrar was proven by Sandstedt in 1901 and 1904, with the publication of the first report on the histology of orthodontic tooth movement. Histology remained the main orthodontic research tool until and beyond the middle of the twentieth century. At that time medical basic research began evolving at an increasing pace, and newly developed research methods were being adapted by investigators in the various fields of dentistry, including orthodontics; Farrar’s assumption that orthodontic forces bend the alveolar bone was proven to be correct, and the race was on to unravel the mystery of the biology of tooth movement. During the second half of the twentieth century, tissues and cells were challenged and studied *in vitro* and *in vivo* following exposure to mechanical loads. The main fields of research that have been plowed by these investigations include histochemistry, immunohistochemistry, immunology, cellular biology, molecular

biology, and molecular genetics. From this broad research effort it has been concluded that teeth can be moved because cells around their roots are enticed by the mechanical force to remodel the tissues around them. This conclusion has opened the door for quests aimed at discovering means to recruit the involved paradental cells to function in a manner that would result in increased tooth movement velocity. The means tried in these investigations have been pharmaceutical, physical, and surgical. In all these categories, experimental outcomes proved that the common denominator, the cell, is indeed very sensitive to most stimuli, physical and chemical. Hence, the way ahead for orthodontic biological researchers is clear. It is a two-lane highway, consisting of a continuous stream of basic experiments aiming at uncovering additional secrets of tissue and cellular biology, alongside a lane of trials exploring means to improve the quality of orthodontic care. Gazing toward the horizon, these two lanes seem to merge.

Biological research has exposed differences between individuals based on molecular outlines and entities. In people who possess similar facial features and malocclusions, this variability, which should be reflected in the diagnosis, may require the crafting of treatment plans that address the individual molecular peculiarities. These differences may be due to genetic and/or environmental factors and should be addressed by a personalized orthodontic treatment plan, adapted to the biological profile and needs of each individual patient.

### Introduction

Orthodontics, the first specialty of dentistry, has evolved and progressed from its inception to the present time, and the credits for this evolution belong to pioneers, who aimed at improving their clinical capabilities. The evolution of clinical orthodontics is rooted in strong foundations, based on scientific studies and mechanical principles. However, as the specialty began prospering, interest in its association with biological facts began to decline. For a while, orthodontics was taught predominantly as a mechanical endeavor. It can be taught in a short course lasting a few days, usually without

any associated clinical exposure. However, recent advancements in medicine have provided orthodontic researchers with investigative tools that enable them to pave new roads toward the target of personalized orthodontics, adapted to the biological profile and needs of each individual patient.

The unfolding of science behind the biology of orthodontic tooth movement (OTM) has been slow and tedious. Our ancestors, as far back as the dawn of history, in all civilizations, cultures, and nations, were interested in images of bodies and faces, covered or exposed. Their artists painted these images on cave walls, cathedral ceilings,



**Figure 1.1** Ancient Greek marble statue of a man's head. (Source: National Museum of Greece, Athens.)

and on canvas pieces that were hung in private homes. They also created a huge array of sculptures as monuments, religious fixtures, or outdoor decorations. These works of art reflected images of faces that were carved and crafted along guidelines unique for each tribal, ethnic, and cultural group. Figure 1.1 presents a profile view of a marble statue of a man's head, found in an archeological dig in Greece. Typically, the facial profile is divided into three equal parts (upper, middle, and lower), and the outline of the nose is continuous with the forehead. Figure 1.2 shows a contemporary sculpture of a shrine guardian in Korea. The features are exaggerated, but the facial proportions are similar to those of the ancient Greek statue. Some artists, like Picasso, attracted attention by intentionally distorting well established facial features. Frequently, facial features in old and contemporary paintings and sculptures express a variety of emotions, ranging from love to fear, and a wide array of shapes, from the ideal to the grotesque.

The importance of possessing a full complement of teeth was very evident in ancient times as evidenced by the complimentary words of Solomon to the queen of Sheba "Thy teeth are like a flock of sheep that are even shorn, which came up from the washing" (Song of Solomon 4:2). Even the first code of Roman law, written in 450 BCE, specifies the importance of teeth by incorporating penalties for the master or his agent if they dare to pull out the teeth of slaves or freemen. If this happens, the law stated that the slave is eligible for immediate freedom. The prose and poetry of the Greek and Roman era portrays numerous references to teeth, smiling faces, and the importance of having a regular arrangement of teeth,



**Figure 1.2** Contemporary bust sculpture of a shrine guardian, Seoul, Korea.

indicating a desire to correct dental irregularities. There was an emphasis on a correct relationship between the dental arches, and its importance in defining female beauty, and a correct enunciation in oratory. With attention focusing on correction of dental irregularities, orthodontia in that era was already divided into biological and mechanical fields, and it was assumed that a successful practitioner should have clear idea of both. The first orthodontic investigators adopted the biological knowledge of the day and concluded that success or failure in the treatment of malocclusions depends on these fields. The superstructure of orthodontics is built upon this fundamental relationship.

Naturally, therefore, orthodontic research has followed closely the scientific footsteps imprinted by biologists and physicians. Present day orthodontists are aware of scientific advances in material and biological sciences, that gradually move us all closer to an era of personalized medicine and dentistry, in which a high degree of diagnostic accuracy and therapeutic excellence is required.

### **Orthodontic treatment in the ancient world, the Middle Ages, and through the Renaissance period: Mechanics, but few biological considerations**

Archeological evidence from all continents and many countries, including written documents, reveal that our forefathers were aware of the presence of teeth in the mouth, and of various associated health problems. These early Earth dwellers confronted diseases

like caries and periodontitis with a variety of medications, ranging from prayers to extractions, and fabrication of dentifrice pastes. Gold inlays and incisor decorations were discovered in South America, and gold crowns and bridges, still attached to the teeth, were discovered in pre-Roman era Etruscan graves (Weinberger, 1926). All these findings bear witness to the awareness of our ancestors to oral health issues.

Recognition of malocclusions and individual variability in facial morphology and function were first noted in Ancient Greece. Hippocrates of Cos (460–377 BCE), who is the founder of Greek medicine, instituted for the first time a careful, systematic, and thorough examination of the patient. His writings are the first known literature pertaining to the teeth. He discussed the timing of shedding of primary teeth and stated that “teeth that come forth after these grow old with the person, unless disease destroys them.” He also commented that the teeth are important in processing nutrition, and the production of sound. Hippocrates, like other well-educated people of his time, was keenly aware of the variability in the shapes of the human craniofacial complex. He stated that “among those individuals whose heads are long-shaped, some have thick necks, strong limbs and bones; others have highly arched palates, their teeth are disposed irregularly, crowding one on the other, and they are afflicted by headaches and otorrhea” (Weinberger, 1926). This statement is apparently the first written description of a human malocclusion. Interestingly, Hippocrates saw here a direct connection between the malocclusion and other craniofacial pathologies.

A prominent Roman physician, Celsus (25 BCE–50 CE; Figure 1.3), was apparently the first to recommend the use of mechanical force to evoke tooth movement. In his Book VII,



**Figure 1.3** Aulus Cornelius Celsus (25 BCE–50 CE). (Picture courtesy: <http://www.general-anaesthesia.com/>.)

Chapter XII entitled “Operations requisite in the mouth,” he wrote: “If a permanent tooth happens to grow in children before the deciduous one has fallen out, that which should have dropped must be scrapped round and pulled out; that which is growing in place of former must be pushed into its proper place with the finger every day, till it comes to its own size.” Celsus was also the first to recommend the use of a file in the mouth, mainly for the treatment of carious teeth (Weinberger, 1926). Another Roman dentist, Plinius Secundus (23–79), expressed opposition to the extraction of teeth for the correction of malocclusions, and advocated filing elongated teeth “to bring them into proper alignment.” Plinius was evidently the first to recommend using files to address the vertical dimension of malocclusion, and this method had been widely used until the nineteenth century (Weinberger, 1926).

There were few, if any, known advances in the fields of medicine, dentistry, and orthodontics from the first to the eighteenth centuries, with the exception of Galen (131–201), who established experimental medicine, and defined anatomy as the basis of medicine. He devoted chapters to teeth, and, like Celsus, a century earlier, advocated the use of finger pressure to align malposed teeth. Galen advocated the same method to that of Celsus through his writings in 180 CE, which stated that a tooth that projects beyond its neighbors should be filed off to reduce the irregularity (Caster, 1934). Another exception was Vesalius (1514–1564), whose dissections produced the first illustrated and precise book on human anatomy.

For reasons connected with the church, Galen and his writings monopolized medicine for more than a thousand years. However, there were minor advancements in European medicine during that protracted era and advancements evidenced by writings of Muslim physicians from Arabia, Spain, Egypt, and Persia.

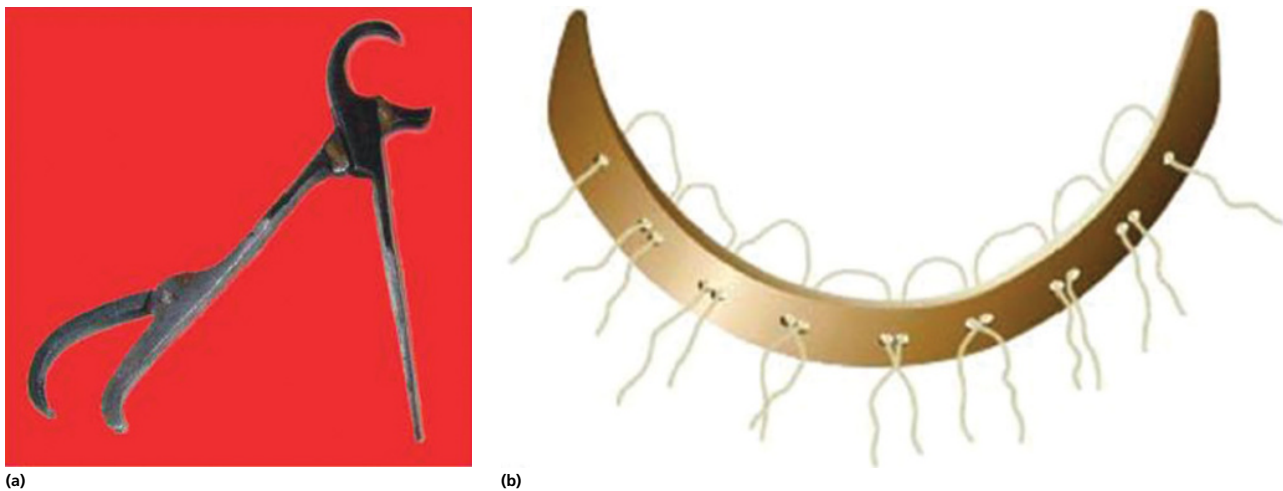
### Orthodontic treatment during the Industrial Revolution: Emergence of identification of biological factors

The writings of authors in the Middle Ages were mainly repetitions of what already existed, and there were no new references to mechanical principles for correcting dental irregularities. It was Pierre Fauchard (1678–1761), the father of dentistry and orthodontics (Figure 1.4), who organized previous knowledge and opinions, and provided an extensive discussion on the rationale for numerous clinical procedures (Wahl, 2005a). His book titled *Le chirurgien dentiste* (*The Surgeon-Dentist*) was published in two editions, the first in 1728 and the second in 1746. The second edition described a few orthodontic cases (Volume II, Chapter VIII) along with an extensive description of appliances and mechanical principles. This book is considered to be dentistry’s first scientific publication. Fauchard also advocated keeping young patients under observation and removing long-retained deciduous teeth to prevent irregularity in the permanent dentition. He also stated that blows and violent efforts may increase the chances of developing an irregular tooth arrangement and reported that the greatest incidence of these mishaps occur in the incisor and canine regions. Most of the appliances he fabricated were made of gold or silver and were designed according to the patient’s needs, marking the beginning of “customized orthodontic appliances” (Figure 1.5). The orthodontic appliance described by Fauchard used silk or silver ligatures to move malposed teeth to new positions, and “pelican” pliers for instant alignment of incisors, facilitated by bending of the alveolar bone. After placing teeth in position with pelican forceps, he retained them with silver ligatures or lead plates adjusted on either side, over





**Figure 1.4** (a) Pierre Fauchard (1678–1761), the father of dentistry and orthodontics. (Source: Vasconcellos Vilella, 2007.) (b) His book titled *Le chirurgien dentiste* (*The Surgeon-Dentist*). (Source: Picture courtesy: Andrew I. Spielman.)

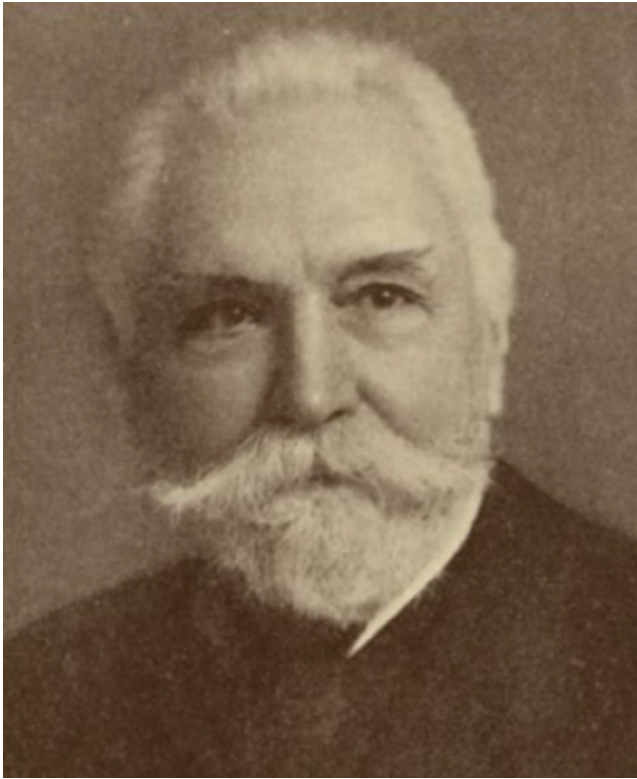


**Figure 1.5** (a) Dental pelican forceps (resembling a pelican's beak). (Source: Courtesy of Alex Peck Medical Antiques.) (b) Bandeau—the appliance devised by Pierre Fauchard. (Source: Vasconcellos Vilella, 2007.)

which linen was placed and sewed into position with needle and thread, between interproximal spaces and over the occlusal surfaces of the teeth. This device, named *bandeau*, marked the beginning of the era of modern orthodontic appliances and their utilization in treating malocclusions (Asbell, 1990).

John Hunter (1728–1793), in 1778, in his book titled *A Practical Treatise on the Diseases of the Teeth*, stated that teeth might be moved by applied force, because “bone moves out of the way of pressure.” This book, along with his previously published book, titled *The Natural History of Human Teeth*, marked the beginning of a new era in the practice of dentistry in England (Wahl, 2005a). Hunter recognized the best time to carry out orthodontic treatment to be the youthful period, in which the jaws have an adaptive disposition. In 1815, Delabarre reported that orthodontic forces cause pain and swelling of paradental tissues, two cardinal signs of inflammation.

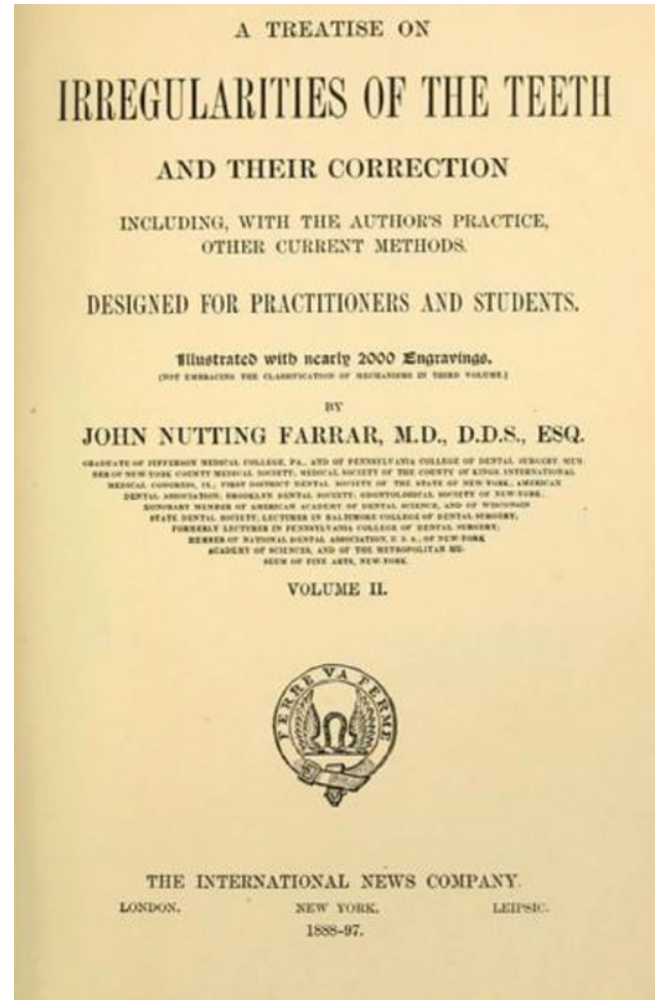
Up to 1841, about a century after Fauchard had written a chapter about orthodontics, there was no single book devoted entirely to orthodontics alone, but in 1841, Schangé published a book solely confined to orthodontics (Wahl, 2005a), which served as a stimulus for conducting investigations in this defined clinical field. Moreover, this book initiated the notion that orthodontics is a unique dental specialty. Schangé described the tooth-eruption process, causes of irregularities, their prevention, and classified defects of conformation. In treating irregularities, Schangé took a different view from Fauchard, who had advocated the use of radical procedures. He warned practitioners of the attendant danger to the tooth when these procedures were performed and favored application of delicate forces in a continuous manner, hence being the first to favor light orthodontic forces. He recommended silk ligatures to apply light forces, and gold for constructing bands and plates, and recognized the importance of retaining teeth after OTM.



**Figure 1.6** Norman William Kingsley (1829–1913). (Source: Dr Sheldon Peck, University of North Carolina at Chapel Hill. Reproduced with permission of Dr Sheldon Peck.)

Samuel Fitch's book titled *A System of Dental Surgery*, published in 1835, marked the beginning of a new era in the practice of dentistry in America. He drew attention to the mobility of teeth within the alveolar process during OTM and characterized the growth period as the time for attaining best results of treatment. Norman Kingsley's treatise on "oral deformities" (1880) had an immediate impact, by placing orthodontics as a specialty, which requires more than general information to solve many of the problems its practitioners face. The book emphasized the importance of basic biology and mechanical principles while studying orthodontia as a science. While describing structural changes due to tooth-moving forces, Kingsley (Figure 1.6) stated that "the physiological fact being that bone will yield or become absorbed under some influences, and also be reproduced ... and in moving teeth, the power used creates a pressure which produces absorption." He also stated that "the function of absorption and reproduction may or may not go coincidentally, simultaneously and with equal rapidity."

The article published in *Dental Cosmos* by John Nutting Farrar in 1887 titled "An enquiry into physiological and pathological changes in animal tissues in regulating teeth" stated that "in regulating teeth, the traction must be intermittent and must not exceed certain limits." He also stated that the system of moving teeth with rubber elastic is unscientific, leads to pain and inflammation, and is dangerous to future usefulness of the teeth. He tried to describe optimal rate of tooth movement as 1/240 inch twice daily, in the morning and the evening, and stated that at this rate, tooth movement will not produce any pain or nervous exhaustion. He stated further that the tissue changes with this procedure are physiological, but if the rate exceeds this range, the tissue reactions will become pathological.



**Figure 1.7** The front page of the book *A Treatise on the Irregularities of the Teeth and their Correction* by John Nutting Farrar. (Source: Picture courtesy: <https://openlibrary.org>.)

His work, which appeared as a series of articles in *Dental Cosmos* from 1876 to 1887, was summed up in his book titled *A Treatise on Irregularities of The Teeth and Thier Correction* published in 1888 (Figure 1.7). In this book he devoted a large section to fundamental principles behind orthodontic mechanics and to the use of various mechanical devices (Asbell, 1998). Farrar, the "Father of American Orthodontics," was credited with developing the hypothesis that rated intermittent forces as best for carrying out OTM which led to the introduction of a screw device for controlled delivery of such forces. A remarkable statement by Farrar was that OTM is facilitated by bending or resorption of the alveolar bone, or both. His publications endowed him as the founder of "scientific orthodontics" (Wahl, 2005b).

Eugene Talbot, in his book titled *Irregularities of Teeth and their Treatment* (1888) rightly mentioned that "without the knowledge of etiology, no one can successfully correct the deformities as is evident in the many failures by men who profess to make this a specialty." He argued that every case of malocclusion is different, making it difficult to classify, and proposed customizing appliances suited for each patient. He was the first to use X rays as a diagnostic aid in orthodontics, to identify abnormal and broken roots, locate third molars, and expose absorption of roots and alveolar process due to OTM.

## Orthodontic tooth movement in the twentieth and twenty-first centuries: From light microscopy to tissue engineering and stem cells

### Histological studies of parodontal tissues during tooth movement

Chappin Harris, in 1839, published a book titled *The Dental Art*, which stated that OTM in the socket depends on resorption and deposition of bone, but it took more than 60 years to have the first histological picture of this phenomenon, which was provided by Carl Sandstedt (Figure 1.8). Sandstedt's experimental studies of tooth movements in dogs were first published in German in 1901, and later in English (Sandstedt, 1904, 1905). His systematic way of conducting experiments was evident from the incorporation of a control group from the same litter as his two experimental dogs. A sectional fixed appliance was inserted in the upper jaw, which was subjected to repeated activations for palatal tipping of the upper incisors over a three-week period. Histological sections of the incisor areas were prepared to assess tissue changes. In order to document positional changes of the teeth, plaster casts and radiographs were obtained. With these experiments, he could observe stretching of the periodontal ligament (PDL) in tension sites and narrowing of this tissue in pressure sites. He demonstrated new bone formation in areas of tension, while resorption was observed in areas of compression. In the compressed periodontium, he initially saw signs of necrosis (hyalinization), and described it as "an obviously degenerated product, a hyaline transformation of the connective tissue, in which regenerative processes take place ... the old mortified tissue is resorbed and substituted by granulation tissue." He further noted that "at the limit of the hyaline zone, the alveolar wall presents a deep, undermining notch filled by proliferating cells as in resorptive areas." Furthermore, "the intensive resorptive process even attacked the incisor itself deeply into the dentine," and he assumed that this process is a common secondary effect of OTM. Figure 1.9 is a photograph of a cross section of a premolar root, showing areas of necrosis in the PDL, as well as multiple osteoclasts in Howship's lacunae at the PDL-alveolar bone interface. These cells were, in Sandstedt's opinion, the main cells responsible for force-induced tooth movement (Persson, 2005; Bister and Meikle, 2013).

He ended his landmark article by proposing a role for bone bending in the tooth movement process in line with the thinking provided by Kingsley and Farrar.

In 1911/1912, Oppenheim reported that tooth-moving forces caused complete transformation (remodeling) of the entire alveolar process, indicating that orthodontic force effects spread beyond the limits of the PDL. E.H. Angle, the father of modern orthodontics, invited Oppenheim to lecture to his students, who accepted Oppenheim's hypothesis enthusiastically. Oppenheim, the proponent of "the law of bone transformation," rejected both the pressure/tension hypothesis supported by the histological evidence of Sandstedt, and the theory of bone bending hypothesis advanced by Kingsley and Farrar, based on the elastic properties of bone. Oppenheim's experiments were conducted on mandibular deciduous incisors of baboons (the number of animals he used and the appliances he used remain ambiguous) and suggested that only very light forces evoke the required tissue responses. He stated that an increase in the force levels will produce occlusion of the vascular supply, as well as damage to the PDL and the other supporting tissues, and that the tooth will act as a one-armed lever when light forces were applied, and like a two-armed lever during the



**Figure 1.8** Carl Sandstedt (1860–1904), the father of biology of orthodontic tooth movement.



**Figure 1.9** A figure from Carl Sandstedt's historical article in 1904, presenting a histological picture of a dog premolar in cross section, showing the site of PDL compression, including an osteoclastic front and necrotic (hyalinized) areas.

application of heavy forces. He also demonstrated how alveolar bone is restored structurally and functionally during the retention period (Noyes, 1945). As a proponent of bone transformation and Wolff's law, Oppenheim received acceptance from Angle, as it supported his thoughts in the matter. Oppenheim was also supported by Noyes, one of Angle's followers and an established histologist.

Oppenheim's research highlighted common concepts, shared by orthodontists and orthopedists, who were convinced that both specialties should be based upon a thorough knowledge of bone biology, particularly in relation to mechanical forces and their cellular reactions. However, it became evident that in orthodontics the PDL, in addition to bone, is a key tissue with regards to OTM.

Working on *Macacus rhesus* monkeys in 1926, Johnson, Appleton, and Rittershofer reported the first experiment where they recorded the relationship between the magnitude of the applied force and the distance in which it was active. In 1930, Grubrich reported surface



**Figure 1.10** Albert Ketcham (1870–1935), who presented the first radiographic evidence of root resorption. He was also instrumental in forming the American Board of Orthodontics. (Source: Siersma, 2015. Reproduced with permission of Elsevier.)

resorptions in teeth subjected to orthodontic forces, a finding confirmed by Gruber in 1931. Even before these histological observations of surface changes were reported, Ketcham (Figure 1.10) (1927, 1929) presented, radiographic evidence that root resorption may result from the application of faulty mechanics and the existence of some unknown systemic factors. Schwarz (1932) conducted extensive experiments on premolars in dogs, using known force levels for each tooth. The effects of orthodontic force magnitude on the dog's paradental tissue responses were examined with light microscopy. Schwarz classified orthodontic forces into four degrees of biological efficiency:

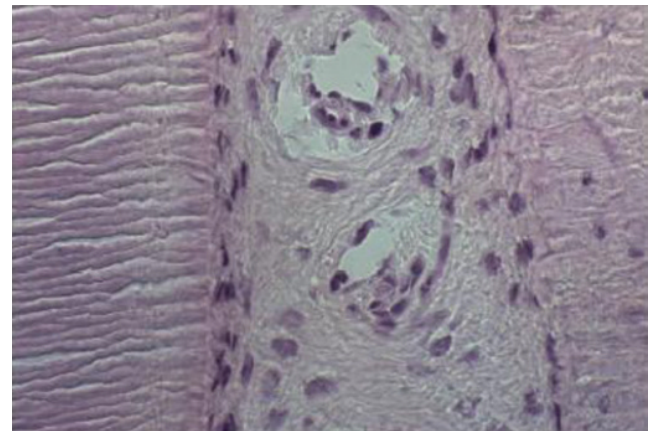
- below threshold stimulus;
- most favorable – about 20 g/cm<sup>2</sup> of root surface, where no injury to the PDL is observed;
- medium strength, which stops the PDL blood flow, but with no crushing of tissues;
- very high forces, capable of crushing the tissues, causing irreparable damage.

He concluded that an optimal force is smaller in magnitude than that capable of occluding PDL capillaries. Occlusion of these blood vessels, he reasoned, would lead to necrosis of surrounding tissues, which would be harmful, and would slow down the velocity of tooth movement.

The proposed optimal orthodontic force concept by Schwartz was supported by Reitan (Figure 1.11), who conducted thorough histological examinations of paradental tissues incidental to tooth movement. Reitan's studies were conducted on a variety of species, including rodents, canines, primates, and humans, and the results

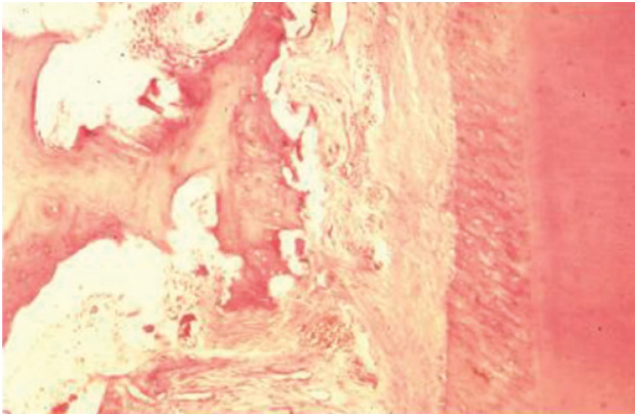


**Figure 1.11** Kaare Reitan (1903–2000), who conducted thorough histological examinations of paradental tissues.



**Figure 1.12** A 6  $\mu$ m sagittal section of a frozen, unfixed, nondemineralized cat maxillary canine, stained with hematoxylin and eosin. This canine was not treated orthodontically (control). The PDL is situated between the canine root (left) and the alveolar bone (right). Most cells appear to have an ovoid shape.

were published during the period from the 1940s to the 1970s. Figure 1.12 displays the appearance of an unstressed PDL of a cat maxillary canine. The cells are equally distributed along the ligament, surrounding small blood vessels. Both the alveolar bone and the canine appear intact. In contrast, the compressed PDL of a



**Figure 1.13** A 6  $\mu\text{m}$  sagittal section of a cat maxillary canine, after 28 days of application of 80 g force. The maxilla was fixed and demineralized. The canine root (right) appears to be intact, but the adjacent alveolar bone is undergoing extensive resorption, and the compressed, hyalinized PDL is being invaded by cells from neighboring viable tissues (fibroblasts and immune cells). H & E staining.



**Figure 1.14** The mesial (PDL tension) side of the tooth shown in Figure 1.13. Here, new trabeculae protrude from the alveolar bone surface, apparently growing towards the distal-moving root. H & E staining.

cat maxillary canine that had been tipped distally for 28 days, with an 80 g force (Figure 1.13), appears very stormy. The PDL near the root is necrotic, but the alveolar bone and PDL at the edge of the hyalinized zone are being invaded by cells that appear to remove the necrotic tissue, as evidenced by a large area where undermining resorption has taken place. Figure 1.14 shows the mesial side of the same root, where tension prevails in the PDL. Here the cells appear busy producing new trabeculae arising from the alveolar bone surface, in an effort to keep pace with the moving root. To achieve this type of tissue and cellular responses to orthodontic loads, Reitan favored the use of light intermittent forces, because they cause minimal amounts of tissue damage and cell death. He noted that the nature of tissue response differs from species to species, reducing the value of extrapolations.

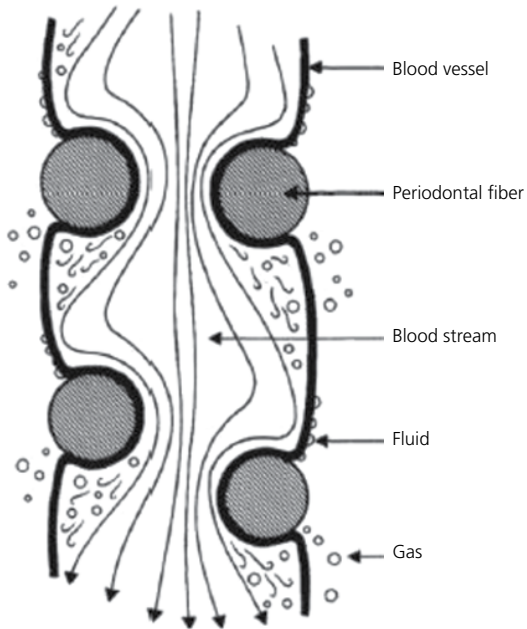
With experiments on human teeth, Reitan observed that tissue reactions can vary, depending upon the type of force application, the nature of the mechanical design, and the physiological constraints of the individual patient. He observed the appearance of hyalinized areas in the compressed PDL almost immediately after continuous force application and the removal of those hyalinized areas after

2–4 weeks. Furthermore, Reitan reported that in dogs, the PDL of rotated incisors assumes a normal appearance after 28 days of retention, while the supracrestal collagen fibers remain stretched even after a retention period of 232 days. Consequently, he recommended severing the latter fibers surgically. He also called attention to the role of factors such as gender, age, and type of alveolar bone, in determining the nature of the clinical response to orthodontic forces. He also reported that 50 g of force is ideal for movement of human premolars, resulting from direct resorption of the alveolar bone.

Another outlook on differential orthodontic forces was proposed by Storey (1973). Based upon experiments in rodents, he classified orthodontic forces as being bioelastic, bioplastic, and biodisruptive, moving from light to heavy. He also reported that in all categories, some tissue damage must occur in order to promote a cellular response, and that inflammation starts in paradental tissues right after the application of orthodontic forces.

Continuing the legacy of Sandstedt, Kvam and Rygh studied cellular reactions in the compression side of the PDL. Rygh (1974, 1976) reported on ultrastructural changes in blood vessels in both human and rat material as packing of erythrocytes in dilated blood vessels within 30 minutes, fragmentation of erythrocytes after 2–3 hours, and disintegration of blood vessel walls and extravasation of their contents after 1–7 days. He also observed necrotic changes in PDL fibroblasts, including 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. Root resorption associated with the removal of the hyalinized tissue was reported by Kvam and Rygh. This occurrence was confirmed by a scanning electron microscopic study of premolar root surfaces after application of a 50 g force in a lateral direction (Kvam, 1972). Using transmission electron microscopy (TEM), the participation of blood-borne cells in the remodeling of the mechanically stressed PDL was confirmed by Rygh and Selvig (1973), and Rygh (1974, 1976). In rodents, they detected macrophages at the edge of the hyalinized zone, invading the necrotic PDL, phagocytizing its cellular debris and strained matrix.

After direct measurements of teeth subjected to intrusive forces, Bien (1966) hypothesized that there are three distinct but interacting fluid systems involved in the response of the PDL to mechanical loading: the fluids in the vascular network, in the cells and fibers, and the interstitial fluid. Mechanical loading moves fluids into the vascular reservoir of the marrow space through the many minute perforations in the tooth alveolar wall. The hydrodynamic damping coefficient (Figure 1.15) is time dependent, and therefore the damping rate is determined by the size and number of these perforations. As a momentary effect, the fluid that is trapped between the tooth and the socket tends to move to the boundaries of the film at the neck of the tooth and the apex, while acting to cushion the load and is referred to as the “squeeze film effect”. As the squeeze film is depleted, the second damping effect occurs after exhaustion of the extracellular fluid, and the ordinarily slack fibers tighten. When a tooth is intruded, the randomly oriented periodontal fibers, which crisscross the blood vessels, tighten, then compress and constrict the vessels that run between them, causing stenosis and ballooning of the blood vessels, creating a back pressure. Thus, high hydrodynamic pressure heads can be created suddenly in the vessels above the stenosis. At the stenosis, a drop of pressure would occur in the vessel in accordance with Bernoulli’s principle that the pressure in the region of the constriction will be less than elsewhere in the system. Bien also differentiated the varied responses obtained



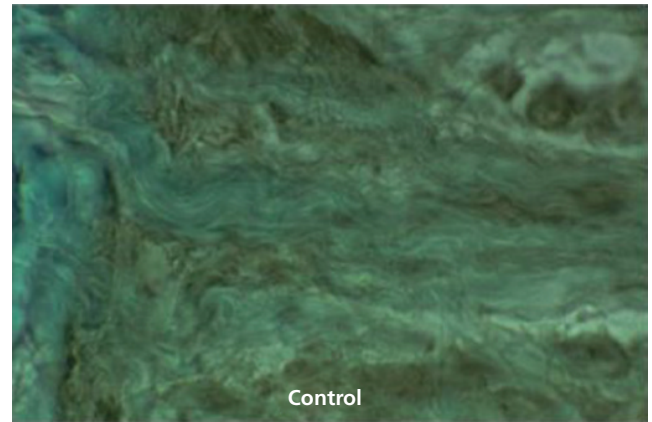
**Figure 1.15** The constriction of a blood vessel by the periodontal fibers. The flow of blood in the vessels is occluded by the entwining periodontal fibers. Below the stenosis, the pressure drop gives rise to the formation of minute gas bubbles, which can diffuse through the vessel walls. Above the stenosis, fluid diffuses through the walls of the cirroid aneurysms formed by the build-up of pressure. (Source: Bien, 1966. Reproduced with permission of SAGE Publications.)

from momentary forces of mastication from that of prolonged forces applied in orthodontic mechanics and suggested that biting forces in the range of 1500 g/cm<sup>2</sup> will not crush the PDL or produce bone responses.

Pointing out a conceptual flaw in the pressure tension hypothesis proposed by Schwarz (1932), Baumrind (1969) concluded from an experiment on rodents that the PDL is a continuous hydrodynamic system, and any force applied to it will be transmitted equally to all regions, in accordance with Pascal's law. He stated that OTM cannot be considered as a PDL phenomenon alone, but that bending of the alveolar bone, PDL, and tooth is also essential. This report renewed interest in the role of bone bending in OTM, as reflected by Picton (1965) and Grimm (1972). The measurement of stress-generated electrical signals from dog mandibles after mechanical force application by Gillooly *et al.* (1968), and measurements of electrical potentials, revealed that increasing bone concavity is associated with electronegativity and bone formation, whereas increasing convexity is associated with electropositivity and bone resorption (Bassett and Becker, 1962). These findings led Zengo *et al.* (1973) to suggest that electrical potentials are responsible for bone formation as well as resorption after orthodontic force application. This hypothesis gained initial wide attention but its importance diminished subsequently, along with the expansion of new knowledge about cell-cell and cell-matrix interactions, and the role of a variety of molecules, such as cytokines and growth factors in the cellular response to physical stimuli, like mechanical forces, heat, light, and electrical currents.

### Histochemical evaluation of the tissue response to applied mechanical loads

Identification of cellular and matrix changes in paradental tissues following the application of orthodontic forces led to histochemical

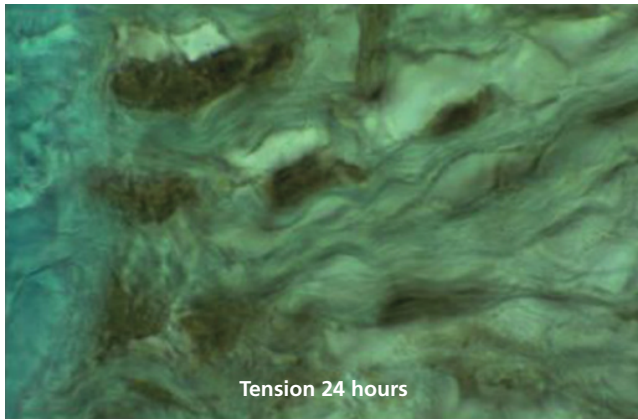


**Figure 1.16** A 6 μm sagittal section of a cat maxilla, unfixed and nondemineralized, stained immunohistochemically for PGE<sub>2</sub>. This section shows the PDL-alveolar bone interface near one canine that received no orthodontic force (control). PDL and alveolar bone surface cells are stained lightly for PGE<sub>2</sub>.

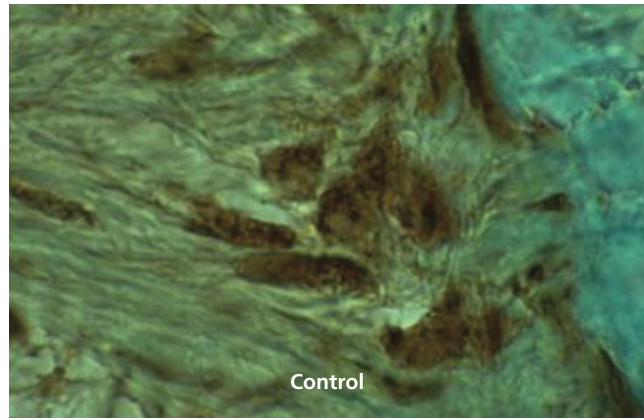
studies aimed at elucidating enzymes that might participate in this remodeling process. In 1983, Lilja, Lindskog, and Hammarström reported on the detection of various enzymes in mechanically strained paradental tissues of rodents, including acid and alkaline phosphatases, β-galactosidase, aryl transferase, and prostaglandin synthetase. Meikle *et al.* (1989) stretched rabbit coronal sutures *in vitro*, and recorded increases in the tissue concentrations of metalloproteinases, such as collagenase and elastase, and a concomitant decrease in the levels of tissue inhibitors of this class of enzymes. Davidovitch *et al.* (1976, 1978, 1980a, b, c, 1992, 1996) used immunohistochemistry to identify a variety of first and second messengers in cats' mechanically stressed paradental tissues *in vivo*. These molecules included cyclic nucleotides, prostaglandins, neurotransmitters, cytokines, and growth factors. Computer-aided measurements of cellular staining intensities revealed that paradental cells are very sensitive to the application of orthodontic forces, that this cellular response begins as soon as the tissues develop strain, and that these reactions encompass cells of the dental pulp, PDL, and alveolar bone marrow cavities. Figure 1.16 shows a cat maxillary canine section, stained immunohistochemically for prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), a 20-carbon essential fatty acid, produced by many cell types and acting as a paracrine and autocrine. This canine was not treated orthodontically (control). The PDL and alveolar bone surface cells are stained lightly for PGE<sub>2</sub>. In contrast, 24 hours after the application of force to the other maxillary canine, the stretched cells (Figure 1.17) stain intensely for PGE<sub>2</sub>. The staining intensity is indicative of the cellular concentration of the antigen in question. In the case of PGE<sub>2</sub>, it is evident that orthodontic force stimulates the target cells to produce higher levels than usual of PGE<sub>2</sub>. Likewise, these forces increase significantly the cellular concentrations of cyclic AMP, an intracellular second messenger (Figures 1.18–1.20), and of the cytokine interleukin-1β (IL-1β), an inflammatory mediator, and a potent stimulator of bone resorption (Figures 1.21 and 1.22).

### The era of cellular and molecular biology as major determinants of orthodontic treatment

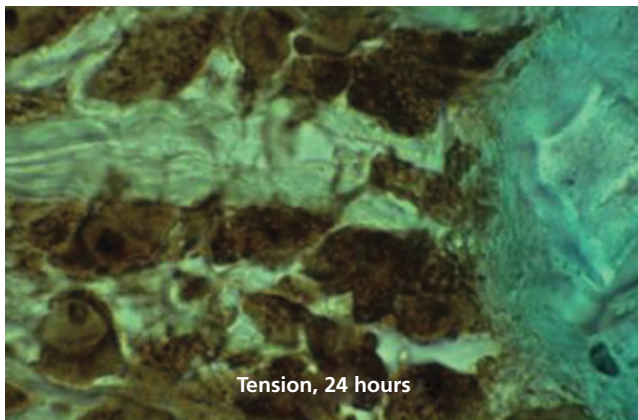
A review of bone cell biology as related to OTM identified the osteoblasts as the cells that control both the resorptive and formative phases of the remodeling cycle (Sandy *et al.* 1993). A decade after this publication, Pavlin *et al.* (2001) and Gluhak-Heinrich *et al.* (2003)



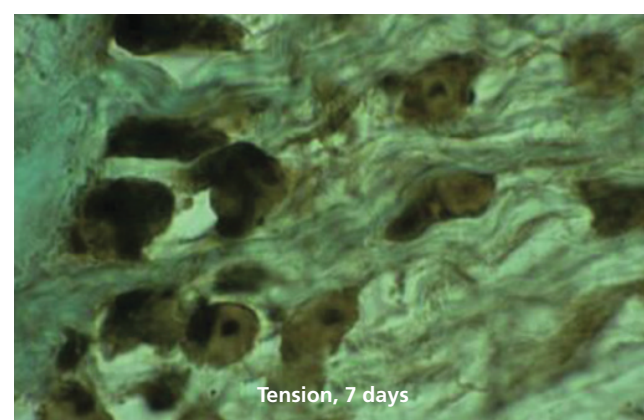
**Figure 1.17** A 6µm sagittal section of the same maxilla shown in Figure 1.16, but derived from the other canine that had been tipped distally for 24 hours by a coil spring generating 80 g of force. The PDL and alveolar bone-surface cell in the site of PDL tension are stained intensely for PGE<sub>2</sub>.



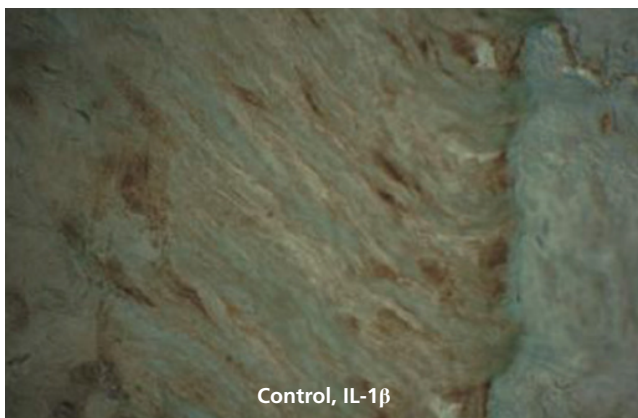
**Figure 1.18** Immunohistochemical staining for cyclic AMP in a 6µm sagittal section of a cat maxillary canine untreated by orthodontic forces (control). The PDL and alveolar bone surface cells stain mildly for this cyclic nucleotide.



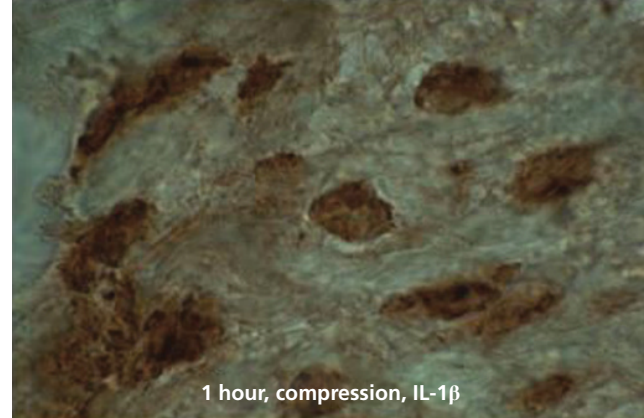
**Figure 1.19** Staining for cyclic AMP in a 6µm sagittal section of a cat maxillary canine subjected for 24 hours to a distalizing force of 80 g. This section, which shows the PDL tension zone, was obtained from the antimer of the control tooth shown in Figure 1.18. The PDL and bone surface cells are stained intensely for cyclic AMP, particularly the nucleoli.



**Figure 1.20** Staining for cyclic AMP in the tension zone of the PDL after 7 days of treatment. The active osteoblasts are predominantly round, while the adjacent PDL cells are elongated. All cells are intensely stained for cAMP.



**Figure 1.21** Immunohistochemical staining for IL-1β in PDL and alveolar bone cells near a cat maxillary canine untreated by orthodontic forces (control). The PDL and alveolar bone surface cells are stained lightly for IL-1β.



**Figure 1.22** Staining for IL-1β in PDL and alveolar bone surface cells after 1 hour of compression resulting from the application of an 80 g distalizing force to the antimer of the tooth shown in Figure 1.21. The cells stain intensely for IL-1β in the PDL compression zone, and some have a round shape, perhaps signifying detachment from the extracellular matrix. × 840.

highlighted the importance of osteocytes in the bone remodeling process. They showed that the expression of dentine matrix protein-1 mRNA in osteocytes of the alveolar bone increased twofold as early as 6 hours after loading, at both sites of formation and resorption. Receptor studies have proven that these cells are targets for resorptive agents in bone, as well as for mechanical loads. Their response is reflected in fluctuations of prostaglandins, cyclic nucleotides, and inositol phosphates. It was, therefore, postulated that mechanically induced changes in cell shape produce a range of effects, mediated by adhesion molecules (integrins) and the cytoskeleton. In this fashion, mechanical forces can reach the cell nucleus directly, circumventing the dependence on enzymatic cascades in the cell membrane and the cytoplasm.

Efforts to identify specific molecules involved in tissue remodeling during OTM have unveiled numerous components of the cell nucleus, cytoplasm, and plasma membrane that seem to affect stimulus-cell interactions. These interactions, as well as those between adjacent cells, seem to determine the nature and the extent of the cellular response to applied mechanical forces. The receptor activator of nuclear factor kappa B ligand (RANKL) and its decoy receptor, osteoprotegerin (OPG) were found to play important roles in the regulation of bone metabolism. Essentially, RANKL promotes osteoclastogenesis, while OPG inhibits this effect. The expression of RANKL and OPG in human PDL cells was measured by Zhang *et al.* (2004). The cells were cultured for 6 days in the presence or absence of vitamin D<sub>3</sub>, a hormone that evokes bone resorption. The expression of mRNA for both molecules was assessed by RT-PCR, while the level of secreted OPG in the culture medium was measured by ELISA. It was found that both molecules were expressed in PDL cells, and that vitamin D<sub>3</sub> downregulated the expression of OPG and upregulated the expression of RANKL. These results suggest that these molecules play key roles in regulating bone metabolism. The response of human PDL and osteoblast-like cells to incubation for 48 hours with PGE<sub>2</sub> revealed that both cell types were stimulated to express RANKL, but that the bone cells were significantly more productive in this respect. When the cells were co-cultured with osteoclast-like cells, the osteoblasts evoked osteoclastogenesis significantly greater than the PDL cells (Mayahara *et al.*, 2012). Recent studies in this regard have confirmed the same in human volunteers (Otero *et al.*, 2016) and were even able to establish a clear role between RANKL production and the root resorption process associated with OTM (Yamaguchi, 2009).

The abovementioned studies illuminate information on the biological aspects of OTM but many gaps still remain. Tooth movement is primarily a process dependent upon the reaction of cells to applied mechanical loads. It is by no means a simple response, but rather a complex reaction. Components of this reaction have been identified in experiments on isolated cells *in vitro*. However, in this environment the explanted cells are detached from the rest of the organism and are not exposed to signals prevailing in intact animals. In contrast, in orthodontic patients the same cell types are exposed to a plethora of signal molecules derived from endocrine glands, migratory immune cells, and ingested food and drugs. A review of pertinent literature published between 1953 and 2007 by Bartzela *et al.* (2010) revealed details on the effects and side-effects of commonly used medications on tooth movement. Nonsteroidal anti-inflammatory drugs and estrogen were found to decrease OTM, whereas corticosteroids, PTH, and thyroxin seem to accelerate it. However, the individual responses to these medications may differ significantly from patient to patient, and such differences may have profound effects on treatment duration and outcomes.

This fact implies that an orthodontic diagnosis should include information about the overall biological status of each patient, not merely a description of the malocclusion and the adjacent craniofacial hard and soft tissues. Moreover, periodic assessments of specific biological signal molecules in body fluids, especially in the gingival crevicular fluid and saliva, may be useful for the prediction of the duration and outcome of orthodontic treatment. The ever-growing flow of basic information into the orthodontic domain promotes the adoption of the concept of “personalized medicine” (Kornman and Duff, 2012). The main investigative tool in this regard is molecular genetics, which has been used successfully in oncology in the search for faulty genes, responsible for the initiation, growth, and dissemination of a variety of tumors. This approach is growing in significance in medicine and is beginning to occur in dentistry. Orthodontics, where genetics plays a major role in determining the morphology and physiology of the orofacial region, is a natural candidate to use this rapidly expanding body of basic information in order to formulate treatment plans that fit closely the biological features of each individual patient.

### Conclusions and the road ahead

Orthodontics started with the use of a finger or a piece of wood to apply pressure to crowns of malposed teeth. The success of those manipulations proved convincingly that mechanical force is an effective means to correct malocclusions. Until the early years of the twentieth century, understanding the reasons why teeth move when subjected to mechanical forces was only a guess, based on reason and empirical clinical observations. Farrar hypothesized in 1888 that teeth are moved orthodontically due to resorption of the dental alveolar socket and/or bending of the alveolar bone. Both hypotheses were proven to be correct during the twentieth century, as orthodontic research has spread into increasingly fundamental levels of biological basic research. The rationale for these basic investigations was the wish to unveil the mechanism of translation of mechanical signals into biological/clinical responses; the etiology of iatrogenic effects resulting from OTM; and to discover efficient means to shorten significantly the duration of OTM. Many details on the behavior of cells involved in OTM have emerged from those investigations but, despite this progress, the final answer to the above issues remains elusive.

At present, molecular biology and molecular genetics remain at the cutting edge of orthodontic research. Multiple genes that may be involved in the cellular response to mechanical loads have been identified (Reyna *et al.*, 2006), and genes associated with orthodontic-induced root resorption (Abass and Hartsfield, 2006). The role played by specific genes in OTM was revealed by Kanzaki *et al.* (2004), who reported that a transfer of an OPG gene into the PDL in rats inhibits OTM by inhibiting RANKL-mediated osteoclastogenesis. According to Franceschi (2005), future efforts in dental research will include genetic engineering, focusing on bone regeneration. Recently, Zhao *et al.* (2012), through experiments in male Wistar rats, reported inhibition of relapse with local OPG gene transfer through the inhibition of osteoclastogenesis.

The body of knowledge that has evolved from multilevel orthodontic research supports the notion that the patient's biology is an integral part of orthodontic diagnosis, treatment planning, and treatment. Therefore, orthodontic appliances and procedures should be designed to address the patient's malocclusion in light of his/her biological profile, in much the same fashion as is done by medical specialists in other fields of medicine. As outlined by Jheon *et al.* (2017),



analyses of genetic and molecular factors may soon uncover indicators predicting slow tooth movement, increased predisposition to root resorption, and accelerated late stage skeletal growth. Patients will be provided with customized appliances printed through the treatment stages, as per the devised virtual plan. In addition, specific biologic/pharmacologic agents based on patients' molecular and genetic background will be delivered to enhance treatment efficiency and outcomes.

Orthodontics started in ancient times by pushing malposed teeth with a finger for a few minutes a day, but today we know that the reason teeth can be moved is because cells respond to changes in their physical and chemical environment. Research will continue to unravel new details of this process, and the beneficiaries will be all people seeking and receiving orthodontic care.

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