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 earnest in 1728 with the publication of the first comprehensive book on dentistry by Fauchard. In it Fauchard 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 teeth move either because the orthodontic forces bend the alveolar bone, or because 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. Basic medical research then began evolving at an increasing pace, and newly developed research methods were being adapted by investigators in the various fields of dentistry, including orthodontics. At that time 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. Among the investigative tools were high quality light and electron microscopes, and a large array of instruments used in physiological and biochemical research. The main fields of research that have been plowed by these investigations include histochemistry, immunohistochemistry, immunology, cellular biology, molecular biology, and molecular genetics. A logical conclusion from this broad research effort is 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 dental velocity. The means used 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 well illuminated. It is a two-lane highway, consisting of a continuous stream of basic experiments aimed 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.

**Keywords:** Orthodontic tooth movement; Tissue, cellular, and molecular biology; Enhancement of tooth velocity; Effects of age on tooth movement

**Introduction**

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, on cathedral ceilings, 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 curved 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, for example Picasso, attracted attention by intentionally distorting well established facial features. Frequently, facial features in old as well as in 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 important role of teeth in determining the shape of the face goes back to Biblical times, where straight, shiny teeth were compared to “a flock of white sheep after emerging from a wash” (Song of Songs). Every artistic work that displays human faces displays only the facial surface, not any of the tissues located under the skin, including skeletal, muscular, and dental elements. However, we are keenly aware that these tissues are essential participants in the determination of facial form, as well as the shape of the dental arches. Naturally, therefore, orthodontic research has followed closely the scientific footprints imprinted by biologists and physicians. At first, the investigations focused on the microscopic appearance of the tissues, followed by a close examination of the involved cells, and most recently the emphasis has shifted toward the fields of molecular biology and genetics, and tissue engineering.

The enlightening findings about the intimate details of the organism’s response to mechanical loads have paved the way to searches for means to improve the efficiency of orthodontic treatment. For this purpose, investigators utilized pharmaceuticals, physical stimuli, and surgical procedures. Their results have demonstrated that, in most cases, the application of mechanical force to teeth, in the presence of another factor(s) known to affect the metabolism and function of various cell types in the involved areas in and around the teeth, may, predictably, increase or inhibit the velocity of tooth movement. These experiments are spearheading ongoing efforts to improve the quality of orthodontic care for all patients.

Orthodontic treatment in the ancient world, the Middle Ages, and through the Renaissance period: shear mechanics, but few biological considerations

Archeological evidence from all continents and many countries, including written documents, reveals that our forefathers were aware of the presence of teeth in the mouth, and of various associated health problems. Early civilizations confronted diseases such as 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, while 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 our ancestors’ awareness of 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), founder of Greek medicine, instituted for the first time a careful, systematic, and thorough examination of the
patient. In his writings is found 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 this, grow old with the person, unless disease destroys them.” He also commented that the teeth are important in processing nutrition and in 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 otorhea” (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), was apparently the first to recommend the use of mechanical force to evoke tooth movement. He wrote: “If a permanent tooth happens to grow in children before the deciduous one has fallen out, that which ought to be shed, is to be extracted and the new one daily pushed towards its place by means of the finger until it arrives at its proper position.” 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 was 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. Another exception was Vesalius (1514–1564), whose dissections produced the first illustrated and precise book on human anatomy.

**Orthodontic treatment during the Industrial Revolution: emergence of identification of biological factors**

Fauchard (1678–1761) was the first to advocate broader education for dentists, and gave dentistry its first scientific work. In the book he published in 1728, Fauchard described an orthodontic appliance that used silk or silver ligatures to move malposed teeth to new positions, and “pelican” pliers that were used for instant alignment of incisors, facilitated by bending of the alveolar bone. Hunter (1728–1793), in 1778, explained that teeth might be moved by applied force, because “bone moves out of the way of pressure.” In 1815, Delabarre reported that orthodontic forces cause pain and swelling of paradental tissues. Pain and swelling are two cardinal signs of inflammation. In 1888, Farrar hypothesized that orthodontic forces move teeth by bending of the alveolar bone, and/or by causing resorption of this bone. He therefore recommended the application of heavy forces to teeth in order to move them rapidly.

**Orthodontic tooth movement in the twentieth and twenty-first centuries: from light microscopy to tissue engineering**

**Histological studies of paradental tissues during tooth movement**

The results of the first histological examination of tissues surrounding orthodontically treated teeth were reported by Sandstedt (1904–1905) (Figure 1.3). He subjected teeth in a dog to orthodontic forces for increasing periods of time, and observed stretching of the periodontal ligament (PDL) in tension sites, and narrowing of this tissue in pressure sites. New alveolar bone formation was seen in the former locations, while necrosis (hyalinization) and bone resorption, direct and undermining, were noticed in the latter sites. Figure 1.4 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. In 1911–1912, Oppenheim reported that tooth movement in one pre-adolescent baboon resulted in complete transformation (remodeling) of the entire alveolar process, indicating that orthodontic force effects spread beyond the limits of the PDL. The effects of orthodontic force magnitude on dog paradental tissue responses were examined with light microscopy by Schwarz (1932). 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. This opinion was supported by Reitan (1957, 1958, 1961) and Reitan and Kvam (1971) (Figure 1.5), who conducted thorough histological examinations of paradental tissues incidental to tooth movement. Reitan’s studies (Reitan, 1957, 1958, 1961; Reitan and Kvam, 1971) were conducted on a variety of species, including rodents, canines, and primates including humans, and their results were published during the 1950s to the 1970s. Figure 1.6 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 cat maxillary canine that had been tipped distally for 28 days with an 80 g force (Figure 1.7) appear 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 had taken place. Figure 1.8 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 response to orthodontic loads, Reitan and Kvam (1971) favored the use of light intermittent forces, because they cause minimal amounts of tissue damage and cell death. They noted that the nature of tissue response differs from species to species, reducing the value of extrapolations. They also called attention to the role of factors such as gender, age, and type of the alveolar bone, in determining the nature of the clinical response to orthodontic forces.
Fig. 1.7 A 6 μm 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. ×180.

Fig. 1.8 The mesial (PDL tension) side of the tooth shown in Figure 1.7. Here, new trabeculae protrude from the alveolar bone surface, apparently growing towards the distal-moving root. H & E staining. ×180.

Experimenting in rodents, Storey (1973) used light microscopy to determine that these forces can be classified as bioelastic, bioplastic, and biodisruptive. The bioelastic force is a light force that mainly distorts the tissues, depending upon their degree of elasticity. The bioplastic force is greater, resulting in remodeling without tissue damage. The biodisruptive force, on the other hand, is large enough to cause extensive damage to teeth and their surrounding soft and hard tissues. Storey stated that a certain amount of damage may result even when bioelastic forces are employed, primarily because the alveolar bony socket is not entirely smooth. A common denominator for all these force categories was found to be inflammation. Storey observed migration of leukocytes out of PDL capillaries 20 min after orthodontic force application to incisors in rabbits. He concluded that inflammation is an integral part of the tissue response in orthodontics, a mechanism providing cells essential for both the resorptive and depository functions that facilitate tooth movement. 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), who used transmission electron microscopy in studies on rodents. They detected macrophages at the edge of the hyalinized zone during the early phases of treatment, invading the necrotic PDL and phagocytizing its cellular debris and strained matrix.

**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 studies aimed at elucidating enzymes that might participate in this remodeling process. In 1983, Lilja et al. 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. Davidovich et al. (1976, 1978, 1980a–c, 1992, 1996) used immunohistochemistry to identify a variety of first and second messengers in cats’ mechanically stressed paradental tissues. 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 1.9 shows a cat maxillary canine section, stained immunohistochemically for prostaglandin E2 (PGE2), a 20-carbon essential fatty acid produced by many cells that acts as a paracrine and autocrine regulator. This tooth was not treated orthodontically (control). The PDL and alveolar bone surface cells stain lightly for PGE2. In contrast, 24 h after the application of force to the other maxillary canine, the stretched cells (Figure 1.10) stain intensely for PGE2. The staining intensity is indicative of the cellular concentration of the antigen in question. In the case of PGE2, it is evident that orthodontic force stimulates the target cells to produce higher levels than usual of PGE2. Likewise, these forces increase significantly the cellular concentrations of cyclic AMP, an intracellular second messenger (Figures 1.11–1.13),
Cellular and molecular biology: major determinants of the outcome of orthodontic treatment

A review of bone cell biology as related to orthodontic tooth movement identified the osteoblasts as the cells that control both the resorptive and formative phases of the remodeling cycle (Sandy et al., 1993). 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 tooth movement have unveiled numerous components of the cell nucleus, cytoplasm, and plasma membrane that seem to impact the 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 mechanical loads. The receptor activator of nuclear factor kappa B ligand (RANKL) and its decoy receptor and osteoprotegerin (OPG) were found to play important roles in the regulation of bone metabolism. Essentially, RANKL promotes osteoclastogenesis whereas 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 D3, 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 D3 down-regulated the expression of OPG and up-regulated the expression of RANKL. These results suggest that these molecules play key roles in regulating bone metabolism. The effect of compressive force on RANKL expression in human PDL cells in vitro was reported by Nakao et al. (2007). The cells were subjected to compressive forces for either 8 or 24 h/day for 2–4 days. The cells exposed intermittently expressed higher levels of RANKL than cells treated continuously, and these increases were inhibited by adding an IL-1 receptor antagonist to the culture medium. Another related study, by Yamaguchi et al. (2006), was conducted on human PDL cells removed from teeth that had experienced severe root resorption during orthodontic treatment, or from teeth that were not damaged by such treatment. The increase in RANKL and the decrease of OPG were greater in the severe root resorption group than in the non-resorptive group.

In contrast, Kanzaki et al. (2004) tested the effect of cyclical tensile forces on human PDL cells in vitro. The tensile forces up-regulated mRNA expression for RANKL and OPG, as well as TGF-β in these cells. The conditioned media in which these cells were cultivated up-regulated OPG mRNA and inhibited osteoclastogenesis. Administration of neutralizing antibodies to TGF-β abolished the OPG up-regulation and the inhibitory effect of the conditioned media.

The presence of RANKL in vivo in compressed PDL was demonstrated by immunohistochemistry (Kim et al., 2007). In 55-day-old rats, maxillary molars were moved laterally for 1–7 days. This movement was accompanied by a finding of positive staining for RANKL in PDL cells in compression sites after 1 day of treatment, suggesting
a role for RANKL in bone resorption during tooth movement. Zuo et al. (2007) examined the PDL from rats undergoing orthodontic tooth movement, and detected sharp increases in the activation of nuclear factor κB (NFκB) by phosphorylation of the p65 component at amino acid 536 after 3 and 12 h of treatment. This reaction is apparently crucial in promoting osteoclast differentiation by RANKL. In cell culture the concentrations of p65 did not change in osteoclasts in response to RANKL, but rapid increases occurred after mechanical scraping. These results suggest that NFκB p65 may be important in bone remodeling during orthodontic treatment.

The discovery that RANKL expression is increased in compressed PDL cells, being an important regulator of osteoclast differentiation, has led to an attempt to inhibit this reaction (Kanzaki et al., 2004) in order to prevent teeth from moving. Such an accomplishment could be very helpful in preventing movement of anchor teeth during orthodontic treatment, and relapse during the post-treatment period. To achieve this goal, Kanzaki and coworkers (2004) constructed a mouse OPG expression plasmid for this purpose. An envelope of an inactivated virus (HVJ) containing the OPG plasmid was injected into the palatal PDL of the maxillary first molar of rats undergoing orthodontic tooth movement. This local gene transfer induced OPG production, inhibited osteoclastogenesis, and significantly reduced tooth movement. This finding demonstrates the potential value of employing a biological agent as an adjunct of orthodontic treatment. It is based on laboratory research, and can be applied judicially by the orthodontist whenever needed.

The above-mentioned studies illuminate information on the biological aspects of orthodontic tooth movement. As this picture continues to unfold, it is evident that the evolving image consists of many details that eventually interlock. But many gaps still exist. 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. These entities may differ significantly from patient to patient, and such differences may have profound effects on treatment outcome. 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, may be useful for the prediction of the duration and outcome of orthodontic treatment.

**Efforts to increase the velocity of orthodontic tooth movement**

**Effects of pharmacological agents on tooth velocity**

The existence of compelling evidence about the important role of biology in orthodontics has provided clinicians with an opportunity to repeat an old question: *Is it possible to enhance the rate of orthodontic tooth movement and shorten its duration?* The speed of tooth movement was found to be related to the force magnitude, the level of cytokines in the GCF, and the IL-1 gene predisposition (Iwasaki et al., 2006). The actual velocity of tooth movement may depend on the rate of bone turnover. The latter was modified pharmacologically, in rats undergoing maxillary molar mesial movement, by inducing either hypothyroidism or hyperthyroidism (Verna et al., 2000). In rats with high bone turnover, the rate of tooth movement was increased, while it was reduced in animals with a low turnover. Although all teeth had been moved in the same manner (controlled tipping), the location of the center of rotation differed, depending on the metabolic state of the bone. Examination of histological sections from the jaws of these rats (Verna et al., 2003) showed that root resorption had occurred in both groups, as well as in the control group, but that it was more pronounced in the low bone turnover group. However, bone metabolism normally demonstrates measurable diurnal fluctuations that may affect the rate of tooth movement.

The use of chemical agents in attempts to increase the pace of tissue remodeling and tooth movement has been tested in various laboratories and clinics. Yamasaki et al. (1980, 1984) injected prostaglandin E1 into the gingiva of moving teeth in rats and in human subjects, resulting in rapid movement. Systemic application of misoprostol, a PGE1 analog, to rats undergoing tooth movement for 2 weeks increased significantly the velocity of movement without enhancing root resorption (Sekhavat et al., 2002). Similar results were reported following intraperitoneal injections of PGE2 in rats (Seifi et al., 2003). Chumbley and Tuncay (1986) systemically administered the prostaglandin synthetase inhibitor indomethacin; Collins and Sinclair (1988) used local applications of vitamin D3, while Engstrom et al. (1988) moved teeth in hypocalcemic, vitamin D-deficient lactating rats. The bone matrix component osteocalcin was injected in rats into the palatal bifurcation of a tipping molar, causing rapid tooth movement due to the attraction of numerous osteoclasts to this site (Hashimoto et al., 2001).

The search for biological agents that would increase tooth velocity has led to the experimental application of the hormone relaxin to rats undergoing tooth movement (Madan et al., 2007). Relaxin is capable of reducing
the organizational level of connective tissues, facilitating rapid separation between adjoining bones, i.e. the pubic symphysis during pregnancy. Maxillary molars were moved for 2–9 days, with or without relaxin application. Tooth velocity was found to be similar in both groups. However, relaxin reduced the level of PDL organization and mechanical strength, leading to increased tooth mobility.

Acceleration of tooth velocity with physical stimuli

The realization that tissue remodeling in orthodontics is mediated by a variety of cells, including fibroblasts, root and bone surface lining cells, endothelial, epithelial, and nerve cells, as well as by different leukocytes, prompted clinical investigators to apply physical and chemical agents concomitant with orthodontic forces, in order to augment the effect of the mechanical forces. Tweedle (1965) used local application of heat to paradental tissues surrounding orthodontically treated teeth in dogs. In another experiment, rats were exposed to light for 24 or 12 h per day for 21 days while subjected to orthodontic force during the light periods. The teeth in the 24 h light group presented doubling of the rates of tooth movement and bone remodeling, as compared with animals that received the force during the 12 h of daily darkness (Miyoshi et al., 2001).

Minute electric currents were applied locally near moving teeth by Beeson et al. (1975), and by Davidovitch et al. (1980c, 1984). Blechman (1998), on the other hand, advocated the use of static magnetic fields for the purpose of generating optimal forces and for accelerating tooth movement. Beeson et al. reported that their electric device, which had been fabricated for use in cats, with electrodes placed at a noticeable distance from the tooth, failed to accelerate its movement. In contrast, Davidovitch et al. placed the electrodes much closer to the cat’s canine, resulting in a significant enhancement of movement. Blechman hypothesized that magnets generate mechanical forces, as well as magnetic fields, and that this combination acts synergistically causing the teeth to move faster. However, an experiment in rats (Tengku et al., 2000) revealed that magnets do not speed up the mesial movement of maxillary molars, and actually increase root resorption in the early phases of treatment. Application of static magnetic fields to rat calvarial osteoblasts in vitro for 20 days by Yamamoto et al. (2003) enhanced significantly the number and size of bone nodules, and their content of calcium, alkaline phosphatase, and osteocalcin.

When mechanical loads are applied to intact tissues in vivo or in vitro, the tissues usually become distorted (strained). In the case of the skeleton, loads such as gravity prompt cells to arrange the architecture of the bony structural features in a way that would resist redundant loads. This phenomenon is known as “Wolff’s Law,” outlined by Julius Wolff in 1892. However, when bone cells are subjected to non-redundant loads such as orthodontic forces, the cells are activated and remodeling of the alveolar process ensues, which facilitates tooth movement. In vivo applications of compressive loads to ulnae in turkeys and roosters by Lanyon and Rubin (1984), Rubin and Lanyon (1984, 1985, 1987) and Skerry et al. (1988, 1990) revealed that extensive osteogenesis can be evoked by short-term dynamic (intermittent) forces. In those experiments, the optimal load magnitude was 2000–4000 microstrain, and its daily duration was 10–20 min. These findings suggest that orthodontic forces would be most effective when applied for brief periods rather than continuously. This assumption was found to be correct in an experiment in rats by Gibson et al. (1992). In that experiment, maxillary molars were subjected to mesial-moving forces for 1 h, 1 day, or 14 days. Teeth exposed to only 1 h of force application continued to move mesially for 14 days and achieved 75% of the distance reached by the teeth that had been subjected to orthodontic forces continuously for 14 days.

Acceleration of tooth movement by surgical means

Surgery offers another powerful means to significantly increase the velocity of orthodontic tooth movement. Specifically, various alveolar corticotomies and selective alveolar decortication (SAD) are most effective in this regard. An experiment in young adult beagle dogs by Ren et al. (2007) revealed that surgical reduction of the osteonal resistance of tooth extraction socket walls enhances the rapidity of orthodontic movement of adjacent teeth into the sockets. In another experiment in adult beagles, by Ino et al. (2007), premolars were moved for 2 weeks after alveolar corticotomy. This movement was significantly greater than that recorded for teeth that were not treated by alveolar surgery. These authors also report more osteoclasts and less PDL hyalinization near teeth that had been operated than near non-surgically treated teeth. It is likely that these findings result, at least in part, from inflammation and wound healing processes that are evoked by the surgical trauma to the alveolar bone. Alveolar bone surgery may also stimulate a variety of cell types inside marrow cavities, including mesenchymal stem cells (MSC). These cells can function synergistically with neighboring PDL and alveolar bone cells that have been activated by the orthodontic forces, and model* and remodel the bone faster.

* Some authorities, e.g. W.E. Roberts of Indiana University, make a point of distinguishing the term “modeling” (bone reaction to exogenous stimulus) from “remodeling” the process of steady state equilibrium. This fine semantic point is often overlooked or ignored but it is probably important to use the word “modeling” when discussing changes in bone that derive from surgical perturbation or the application of orthodontic force.
Even where the bucco-lingual dimension of the alveolus is great, the decortication depth should not exceed the thickness of the cortex by more than 1–2 mm. Yet the degree of therapeutically induced reversible osteopenia is commensurate with the degree of surgical manipulation, given individual patient biodiversity in response. The pattern of punctate or linear decortication does not seem to be as critical to the therapeutic effect as the degree of surgical manipulation per se.

Understanding the role of osteoprogenitor cells is important because, as a tooth is moved through a surgical wound, healing recapitulates regional tissue ontogeny (Murphy, 2006) and, with the addition of a bone graft, can actually increase the total bone mass of the novel alveolus phenotype while enhancing long-term stability. The best technique consists of punctate and linear decortication in areas of the alveolus where accelerated and stable tooth movement is desired. Bone is added ad hoc where augmentation is needed (Figure 1.16). As teeth are moved through a healing wound, with or without a bone graft, the bone is stressed. The normal metabolic rate of inflammation and wound healing processes, investigated in depth and coined the “regional acceleratory phenomenon (RAP)” by the collaboration of Frost (1983, 1996, 2000) and Jee (1989), is accelerated. However, because the movement of teeth produces tensional stress in the bone, the maturation and eventual recalcification of the repaired tissue is delayed as long as the bone “senses” tooth movement. The reaction is similar to a bone fracture that requires immobilization to achieve full development of the healing callus but will be delayed in final calcification if subjected to tensional stress. The clinical orthodontist can exploit this natural phenomenon in dentoalveolar physiology to ensure faster tooth movement by engineering the...
regional healing metabolism to a more stable clinical outcome (Kelson et al., 2005; Sebaoun et al., 2006).

With simple orthodontic tooth movement there is no increase in bone volume, even 2–3 years later, as assessed by computerized tomography 3-D replicates (Fuhrmann, 2002). However, when the teeth are moved through a combination of decorticated alveolar bone and certain kinds of bone graft, new phenotypes may be engineered and a net increase of bone volume is evident. The degree of bone decalcification is commensurate with the amount of therapeutic trauma but penetration is rarely deeper than 1–2 mm beyond the labial alveolar cortex (Figure 1.17). Where minimal tooth movement is needed, simple segmental surgery can be performed on as few as three teeth or on either side of an extraction site and the pattern of decortication seems less important than the total surface area that is decorticated (Figure 1.18).

The usual rate of orthodontic tooth movement (OTM) by conventional biomechanical protocols is relatively slow (about 1 mm/month) compared with the 1 mm/week that is possible with surgical intervention, and movement approaching 1 mm/day has been reported in some cases (Iseri et al., 2005). This latter rate is significant because it approaches the optimal speed used by medical orthopedists as a guideline for surgical distraction osteogenesis of long bones (Paley, 2002).

Moreover, the entire “bone morphing” (Figure 1.19) possibilities promise to take dentofacial orthopedics to an entirely new level of science that has witnessed a volcanic eruption of scientific data over the last few decades under the rubric of “tissue engineering”. While most of the developments in this nascent science have been achieved merely in “bench-top science”, anecdotal evidence of in vivo achievements by forward-thinking orthodontists has given the specialty new visions of the role of the orthodontic clinician and educator for the twenty-first century. Clinical results can quite dramatically alter facial form without the risk and morbidity of hospital surgery (Figure 1.20).

The history of surgically facilitated OTM actually pre-dates the twentieth century but little was done in the United States until the late 1950s. This may have occurred
When the PAOO procedure is extended beyond the alveolus and coordinated with a specific protocol of orthodontic/orthopedic mechanotherapy, dramatic results can be achieved by a kind of “face morphing” that mimics the intraoral alveolar phenotype alteration. This patient presented with a skeletal class II malocclusion (left) but declined all options for orthognathic surgery. The right image demonstrates the final clinical outcome achieved without hospitalization or the risks and morbidity of orthognathic surgery.

The stability of the surgically facilitated orthodontic treatment derives from the alteration of bony phenotype as the bone morphogenetic protein (BMP) of human allograft guides regional wound healing to an engineered phenotype more compatible with the orthodontic treatment goal. Part (a) demonstrates inadequate bone for a non-extraction OTM, yet with a periodontally accelerated osteogenic orthodontic protocol (PAOO) the post-orthodontic treatment is engineered to a manifestly superior treatment outcome. The total treatment time in this case was 6 months. The stability of this kind of augmented alveolar form in (b) is in its third year post-retention without signs of regression to the original, inadequate phenotype. Images courtesy of Professor M. Thomas Wilcko, Case Western Reserve University School of Dental Medicine, Cleveland, Ohio, USA.

When the PAOO procedure is extended beyond the alveolus and coordinated with a specific protocol of orthodontic/orthopedic mechanotherapy, dramatic results can be achieved by a kind of “face morphing” that mimics the intraoral alveolar phenotype alteration. This patient presented with a skeletal class II malocclusion (left) but declined all options for orthognathic surgery. The right image demonstrates the final clinical outcome achieved without hospitalization or the risks and morbidity of orthognathic surgery.
because of the crude nature of rudimentary nineteenth-century surgical techniques and the dubious observation that “. . . a tooth in its normal position without vitality is more valuable than a vital tooth in an abnormal relationship”. Ironically this original presentation was made in Chicago in 1893 but would not be presented again in America for over half a century.

Its American revival appeared in a seminal work by Kole (1959), wherein he summarizes a decortication of the dentoalveolar process with some notable refinements. This is the basic technique that is employed today by those who promote the integration of orthodontic therapy and periodontal surgery. The Kole surgery was limited to the cortex of the dental alveolus but subapical decortication was embellished by extending buccal and lingual cortical plate incisions until they communicated through the subapical spongiosa.

The naiveté of the early surgeons is noted in early admonitions about the risk of periodontal pocket formation or alveolar necrosis with facilitative periodontic surgery. While the former is doubtful to those who understand the pathogenesis of periodontitis, the latter is perhaps a wise admonition indeed where overly aggressive osteotomies are combined with alveolar decortication, major flap reflection and especially any luxation (“mobilization”) of the dentoalveolar complex. Various investigators have given professional opinions on the merits and disadvantages of the procedure throughout the twentieth century (Bell and Levy, 1972; Düker, 1975; Merrill and Pedersen, 1976; Generson et al., 1978; Mostafa et al., 1985; Goldson and Reck, 1987), and slight variations of the procedure have also been studied (Nakanishi, 1982; Sasakura et al., 1987; Yoshikawa, 1987; Matsuda, 1989).

These contributions were essential to the ultimate development of modern selective alveolar decortication (SAD), but the foundation of Kole’s work lay generally undeveloped until Suya (1991) revived academic interest in “corticotomy-facilitated orthodontics” by reporting his experiences with hundreds of patients. Suya made a significant change in that he did not connect the buccal and labial incisions through the alveolus, simply relying on the effects of linear interproximal decortication. This refinement has essentially set the standard for decortication procedures that followed, because it suggested that the concept of “bony block” movement of bone–tooth might not be the most appropriate theory of efficacy.

Like Kole, Suya noted accelerated rates of tooth movement. Later, others also reported cases treated with the combined orthodontic–periodontal treatment, praising the procedure and stimulating contributions by Kawakami et al. (1996), and Liou and Huang (1998). Anholm et al. (1986) noted no significant attachment loss that might contraindicate the procedure. This was followed up by studies by Gantes et al. (1990), who confirmed accelerated tooth movement, noting a mild root resorption (probably a function of their biomechanics) but no loss of root vitality.

Wilcko et al. (2000, 2001) studied the sophisticated synthesis of periodontal regenerative techniques and the refinements of selective decortication of the alveolus. They not only confirmed the veracity of previous anecdotal data, but also discovered that adding periodontal regenerative surgery to the orthodontic protocol increased the quality of care in terms of clinical outcome and long-term stability (Nazarov et al., 2004). The effects on bone are apparent regardless of the biomechanical systems employed because Owen (2001) treated himself with a removable acrylic appliance without significant pain or other negative sequelae. His first-person account confirmed previous data of researchers and patients.

Academic studies in the twenty-first century have delivered a plethora of investigations that are confirming 100 years of testimonial data and explain, with hard data and creative theories, an exciting new area of surgical dentofacial orthopedics. This development in the orthodontic specialty has essentially marked a parallel path of Ilizarov’s work in medical distraction osteogenesis (Paley, 2002) and the basic sciences that define modern tissue engineering taught by Alberts et al. (2002) and Lanza et al. (2007).

The enthusiasm displayed by former patients has matched that in postdoctoral students who have confirmed that both decortication (SAD) and periodontally accelerated osteogenic orthodontics (PAOO) can predictably produce: increased labio-lingual width (Twaddle, 2001; Hajji, 2002), faster tooth movement (Fulk et al., 2002), less root resorption (Machado et al., 2002; Skountrianos et al., 2004), and equal or higher quality outcome than conventional orthodontic protocols (Skountrianos et al., 2004; Ashlawat et al., 2006; Dosanjh et al., 2006; Ferguson et al., 2006; Oliveira, 2006; Walker et al., 2006). Only time will reveal the full potential of surgical dentoalveolar applications. For now, as an evidence-based complement to conventional biomechanical protocols, these surgically accelerated modalities have achieved a standard of care and a pantheon of clinical alternatives that can be offered to patients to enable their fully informed consent to treatment.

**Shortening the duration of orthodontic treatment by using biomechanics properly, and avoiding unnecessary root movements**

The reports cited above suggest that the extent of tissue remodeling and the velocity of tooth movement can be significantly influenced by numerous factors capable of interacting with paradental cells. However, if our goal is to complete orthodontic treatment successfully and in the shortest possible time, then we should avoid moving dental roots into areas from which the roots would have to be retrieved later. As discussed in Chapter 9 of this
book, following this fundamental principle usually leads to treatment completion within 18–24 m, with virtually no signs of tissue damage. It may be concluded that the duration of orthodontic treatment can be reduced substantially in a number of ways: (a) by moving dental roots directly to their final positions, avoiding unnecessary movements that require corrections, and (b) by combining the mechanical load with another physical and/or chemical agent, and/or surgical procedure capable of evoking synergistic reactions by alveolar bone and PDL cells.

The age factor in tooth movement

Another question that may be asked on the basis of the understanding that in orthodontics, mechanics and biology are two parts of the same process is: what is the effect of age on the tissue response to orthodontic force? This question has occupied the minds of orthodontists since Hunter, in the eighteenth century and probably earlier. Hunter observed that orthodontic treatment takes longer in adults than in children. Studying histological sections of human teeth and their surrounding tissues, Reitan (1957, 1961) concluded that the PDL is less cellular in adults than in children. He therefore recommended that, when treating adults, their teeth should initially be subjected to light forces in order to stimulate cellular proliferation, and then the force magnitude should be increased in order to stimulate these cells to remodel the paradental tissues. This observation implies that, in essence, the nature of the biological response to orthodontic forces is similar in young and adult subjects.

This hypothesis was confirmed by Shimpo et al. (2003), who moved molars lingually in young (13 weeks old) and old (60 weeks old) rats, then studied their compensatory alveolar bone apposition under the lingual periosteum. They reported that in both age groups there had been vigorous compensatory alveolar bone growth. Thus, alveolar bone is successfully maintained, even in aged rats. Similar findings were reported by Ren et al. (2005), who moved maxillary molars in young (1.5 months old) and old (9–12 months old) rats with a force of 10 cN, for 1–12 weeks. A histological examination of the roots and their surrounding tissues revealed that, at PDL compression sites, osteoclast numbers increased in both age groups. In the young rats, a maximum number was reached after 2 weeks of treatment whereas in the adult animals this level was reached after 4 weeks. In the following weeks, the number of osteoclasts in the adult rats was twice as high as in the young rats, but the velocity of tooth movement was the same in both groups. It was concluded that osteoclasts in young animals are more efficient than in members of the older age group. It is also possible that bone matrix in young rats can be resorbed more readily than in old rats, due to structural and chemical differences such as the presence of high concentrations of inhibitors of metalloproteinases in bone of old animals.

Age can also refer to the duration of healing of a postoperative regenerate following distraction osteogenesis (Nakamoto et al., 2002). In an experiment on 15-month-old beagles, mandibular premolars were moved into a 2-weeks or a 12-weeks regenerate. The former consisted of immature, fibrous, and poorly mineralized bone, whereas the latter was composed of mature, well organized and mineralized bone. Tooth movement was significantly faster in the “young”, immature regenerate, but this movement was accompanied by extensive resorption that extended from the cemento-enamel junction to the root apex.

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. His assumption was correct, but had no scientific foundation and could not be proven. Sandstedt’s histological study, which was first published in an obscure Scandinavian dental journal in 1901 and later (1904–1905) in an international periodical, had opened the gates widely to scientific exploration of orthodontic biology. Sandstedt revealed that the main figures in the drama of tooth movement are cells, mainly those of the PDL and alveolar bone. This landmark discovery raised an immediate question about the mechanism whereby mechanical stress activates various types of dental and paradental cells, and what is the best way to obtain an optimal response by these cells. Histology was the first tool in this quest, followed by histochemistry, electron microscopy, immunohistochemistry, molecular biology, and molecular genetics. Much information on the behavior of cells involved in tooth movement has emerged from those investigations. Despite this progress, the final answer to the above question remains elusive. Many parts of the puzzle have been found, but the picture is still incomplete.

The increasing understanding of the nature of the biological effects of mechanical loading on tissues and cells has led to experiments aimed at finding means of enhancing velocity of tooth movement. These experiments were based on the finding that cells are capable of responding to a vast array of chemical and physical stimuli. Accordingly, various pharmaceutical agents were applied locally or systemically during the course of orthodontic treatment.
Physical entities, such as heat, magnetic fields, and electrical currents were utilized, and surgical procedures encompassing decortication of the alveolar bone were tried. Most of these experiments have yielded evidence supporting the hypothesis that combining mechanical force with another cell-stimulating agent(s) is capable of increasing the pace of tissue remodeling and tooth movement.

Adaptation of new biological investigative tools to orthodontic research is ongoing, and will continue to expose blank parts of the puzzle. At present, molecular biology and molecular genetics remain at the cutting edge of the advancing front of orthodontic research. Multiple genes that may be involved in the cellular response to mechanical loads have been identified (Reyna et al., 2006), as well as genes associated with orthodontically induced root resorption (Abass and Hartsfield, 2006). The role played by specific genes in tooth movement was revealed by Kanzaki et al. (2004). They reported that a transfer of an OPG gene into the PDL in rats inhibits orthodontic tooth movement by inhibiting RANKL-mediated osteoclastogenesis. According to Franceschi (2005), future efforts in dental research will include genetic engineering, focusing on bone regeneration. This evolving field may have a profound effect on orthodontics and dentofacial orthopedics, by facilitating regenerative processes of hard and soft orofacial tissues. It may be concluded that the way ahead will be paved with new investigations that will continue to unveil additional information on the biological mechanisms of tooth movement.

The body of knowledge that has evolved from multi-level 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.

References


