

Seminar 11

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Remodelling the dentofacial skeleton

The bones and articulations of the craniofacial skeleton grow and function in an environment of mechanical forces. These forces which include muscle activity, the expansile growth of the brain, gravity and man-made orthodontic appliances, influence the shape and relative position of each bone in the complex through the process of biological adaptation termed remodelling (Moffett, 1971, 1973). Understanding the cellular and molecular mechanisms that enable the bones and other connective tissues of the dentofacial skeleton to adapt to changes in their mechanical environment, is fundamental to the practice of orthodontics and dentofacial orthopaedics based on sound biological principles.

With the exception of the cranial base synchondroses and the temporomandibular joints (TMJ), all the articulations between the bones of the skull are fibrous joints. Such articulations are responsive to changes in their functional environment; indeed, orthodontic tooth movement is dependent upon the ease with which the periodontal ligament (PDL) can be remodelled by mechanical means. The forces that orthodontic appliances apply to the teeth are transmitted through the PDL to the supporting alveolar bone. Changes in the metabolic and proliferative activity of the cellular constituents of the joint are initiated, leading eventually to the deposition or resorption of bone depending upon whether the bone surfaces are exposed to a tensile or compressive mechanical strain. Numerous well-documented primate studies have also shown that craniofacial sutures and the TMJ are amenable to mechanically induced remodelling activity, thereby providing the experimental basis for the practice of dentofacial orthopaedics. In this Seminar we will discuss the experimental evidence.

Facial sutures

Sutures are found only in the skull and have two main functions; (1) as a site of active bone growth, and (2) to provide a firm union between adjacent bones, while at the same time permitting slight movement in response to mechanical stress. The fibrous and cellular organization of sutures is not uniform and will vary depending on site, age and within the same suture over time (Persson, 1973), but as a generalization each is formed by a continuation of the fibrous and cellular periosteum around the margins of adjacent bones, united by of fibrous tissue and blood vessels with a central layer of fibroblastic stem cells (Pritchard *et al.*, 1956). The cellular layer provides the cells required for osteogenesis at the sutural margins; the intermediate layer allows for continued growth of the sutural connective tissue and permits small adjustments of the bones relative to each other.

Morphology of craniofacial sutures

Suture morphology is determined by the site and mechanical stresses to which they are exposed. In general midline sutures are butt-end while others are of the overlapping bevelled type (Kokich, 1976). During the growth period sutures have a predominantly linear configuration but with age, more complex bevelled and interdigitating sutures develop through functional modification. Where strong bonds are required, interdigitating sutures develop to enhance surface contact and resist separation. All sutures eventually undergo varying degrees of fusion by osseous union or synostosis. Sutural synostosis begins at different ages in the various sutures of the skull and proceeds at the endocranial slightly earlier than at the ectocranial surface (Todd and Lyon, 1924). In contrast to cranial sutures, facial sutures can remain patent quite late into adult life (Slide 3).

Patency of craniofacial sutures

There are two plausible explanations as to why cranial and facial sutures differ in their time of closure, one molecular the other mechanical. Much of what is known about suture biology at the molecular level comes from human studies of premature fusion or craniosynostosis. Despite differing phenotypes, accelerated closure in several autosomal-dominant craniosynostoses – Crouzon, Apert, Jackson–Weiss and Pfeiffer syndromes – have been shown to be due to gain-of-function mutations in the *FGFR-2* (fibroblast growth factor receptor-2) gene. The extent to which facial sutures are affected is less clear, although many of these syndromes are characterized by maxillary hypoplasia. In addition to causing achondroplasia, mutations in the *FGFR-3* gene are also responsible for the phenotypes of Crouzon syndrome with acanthosis nigricans, and Muenke-type craniosynostosis. (For further discussion and references see Meikle, 2002.)

Evidence from animal models suggests specific roles for growth factors as well as the BMP (bone morphogenetic protein), Shh (sonic hedgehog) and FGF signalling pathways. Nevertheless, where each of these factors fit into a complex morphogenetic cascade is poorly understood. Studies of the molecular mechanisms involved in suture morphogenesis and fusion suggest important roles for polypeptide growth factors. IGFs, TGF- β isoforms and FGF-2 have all been immunolocalized in the cells and matrix of the dura mater, and their expression is increased during synostosis (Opperman *et al.*, 1998; Bradley *et al.*, 1999), suggesting a paracrine signalling role for these factors. Facial sutures differ from cranial sutures in the absence of dura and that may partly explain why facial sutures remain open longer.

The other reason is related to the intermittent mechanical loading of the circum-maxillary suture system that occurs during mastication (Behrents *et al.*, 1978; Wagemans *et al.*, 1988; Jaslow, 1990; Herring and Mucci, 1991). Some idea of the loading to which craniofacial sutures are exposed has come from measurements of mechanical strain in cranial and facial sutures during mastication in animal models. These indicate that the various sutures are under distinct and dissimilar strain regimes (Rafferty and Herring, 1999). Experiments conducted on the miniature pig have shown that for the sutures of the calvaria (interparietal, interfrontal, coronal) peak strains are mainly tensile, and for those of the snout (internasal and nasofrontal) mainly compressive (Slide 4). Nevertheless, sutural strain is a very dynamic parameter and many sutures show temporal and regional variations in strain polarity; some sutures even show a small compressive strain before or after the tensile peak (Herring and Mucci, 1991).

Slide 4. Dorsal view of a miniature pig skull (*Sus scrofa*) showing average peak strains during mastication. Solid arrows directed towards sutures indicate compressive strains; open arrows indicate tensile strains. The sutures of the braincase are predominantly tensed, while those of the snout are compressed. (Redrawn from Rafferty and Herring (1999), *Journal of Morphology*.)

The strains to which facial sutures are exposed (tensile, compressive, shear) by masticatory muscle function will determine their morphology. In comparison to the zygomaticofrontal suture, for example, which has a relatively simple configuration, the frontomaxillary suture in the rhesus monkey is characterized by numerous interdigitations and reversal lines indicative of extensive remodelling activity (Slides 5, 6). Both tensile and compressive strains can be found in a suture, but for most it is likely that either tension or compression predominates. Sutures that are exposed to a predominantly compressive strain will continue to grow however, and it seems likely that in sutures with complex interdigitations, the oblique arrangement of the fibres of the sutural ligament may convert what was initially a compressive load into a tensile strain (Herring and Rafferty, 2000). For these reasons, trying to establish the loading pattern of a suture from the histological appearance is prone to a good deal of subjective interpretation.

Slide 5. A. Photomicrograph of the zygomaticofrontal suture from a *Macaca mulatta* monkey; oxytetracycline (50 mgm/kg body weight) had been injected intramuscularly on 2 occasions with an interval of 2 months. Unstained ground section viewed under ultraviolet light. Original magnification $\times 30$. The uptake of tetracycline suggests an asymmetrical pattern of sutural remodelling depending upon the surface strain. B. Photomicrograph of the frontomaxillary suture from the same animal. Haematoxylin and eosin stain $\times 75$. This suture has a more complex morphology characterized by numerous interdigitations and reversal lines with cellular evidence of current remodelling activity. H & E stain $\times 75$.

Slide 6. As a generalization each suture is formed by a continuation of the fibrous and cellular periosteum around the margins of adjacent bones, united by fibrous connective tissue with a central zone of fibroblastic cells. A is a section through the zygomaticofrontal suture with numerous reversal lines (arrowheads) in the adjacent bones indicative of remodelling activity. B shows signs of recent remodelling activity with new highly cellular woven bone (red) laid down on older compact bone (blue). Mallory stain x 120.

Remodelling the maxilla in non-human primates

The first evidence that anteroposterior changes in maxillary position could be achieved clinically came from cephalometric studies of patients who had worn extraoral traction (headgear) during treatment (Moore, 1959; Ricketts, 1960). Prior to these reports it was widely thought that the effects of headgear (HG) treatment (and orthodontic treatment in general) were confined to the dentoalveolar process producing tooth movement alone. These landmark clinical investigations demonstrated that headgear treatment could restrain the forward growth of the maxillary complex, and in some cases move it distally in relation to the anterior cranial base (Slide 7). They also provided the impetus for a research programme in the Department of Orthodontics and the Regional Primate Research Center, University of Washington, Seattle, into the effects of externally induced mechanical force on the craniofacial skeleton of the *Macaca mulatta* monkey. Under the direction of Dr Benjamin Moffett, the aim was to better understand the changes in the dentofacial skeleton at the cellular and tissue levels brought about by orthodontic treatment (Moffett, 1971).

Effect of distal movement

Experiments involving both adolescent and adult monkeys have shown that forces applied to the dentomaxillary complex can produce remodelling of facial sutures. Most of the early studies involved the use of HG to apply a posterior force, and a combination of metallic implants, radiography, *in vivo* bone markers and histology to analyze the outcome. All showed it is possible to alter the positional relationships of the bones of the facial skeleton (for review see Meikle, 2007). In growing monkeys, following appliance removal the maxilla resumes its normal forward growth pattern, which is to be expected in an animal still actively growing (Tuenge and Elder, 1974). A surprising finding was that HG wear compressed the external auditory meatus and induced resorptive remodelling of the articular surface of the condylar head (Brandt *et al.*, 1979; Slide 8), suggesting a transmission of occlusal forces from the upper to the lower jaw with posterior displacement of the mandible.

Slide 8. Left Pair. Top: TMJ in a control animal. The anterior surface of the postglenoid tubercle is flat to concave and the posterior surface is convex. The articular eminence is larger than in the experimental animal and the external auditory meatus circular in outline. Dry skull preparation x7. Bottom: TMJ after 10 months headgear treatment. The posterior surface of the postglenoid tubercle is concave and the articular eminence is flattened. The external auditory meatus has been compressed anteroposteriorly and shows increased remodelling activity. Dry skull preparation x7. (From Tuenge and Elder, (1974), *American Journal of Orthodontics*.)

Right Pair. (A). Articular surface of the left condyle viewed posteriorly in a control monkey. The articular surface in this area is smooth. Dry skull preparation x4. (B). Corresponding surface in an experimental animal. Resorptive remodelling of the articular surface has resulted in the appearance of crater-like voids. X4. (From Brandt *et al.* (1979), *American Journal of Orthodontics*.)

For my first venture into the world of research as an orthodontic resident, intermaxillary forces were delivered by Class II elastics to the jaws of three adult female *Macaca mulatta* monkeys. The radiographic evidence suggested significant dentofacial change with distal displacement and rotation of the maxilla; comparing the maxillary and mandibular superimpositions with the overall superimposition, suggested that 50 percent of the movement was due to changes in tooth position, and 50 percent to maxillary displacement (Slide 9). The histological evidence revealed resorptive remodelling of the pterygomaxillary (PTM) and zygomaticomaxillary sutures, and increased bone deposition at the frontomaxillary suture with distal displacement and rotation of the maxilla. Compression of the PTM resulted in resorption of the bony surfaces abutting the suture, accompanied by compensatory deposition (as shown by tetracycline labelling) on the endosteal bony surfaces of the scaphoid fossa and maxillary tuberosity (Slide 10).

Slide 9. Superimposition of pre-(solid) and post-treatment headfilms on the outlines of the anterior cranial base and maxillary and mandibular implants. Adult *Macaca mulatta* monkey in which Class II elastics (200 gm force) had been applied for 84 days to splints wired to the upper and lower teeth. (From Meikle (1970), *American Journal of Orthodontics*.)

Slide 10. A. Response of the PTM to compression. Unstained ground section viewed under UV light. Resorptive remodelling at the bony interface was compensated for by diffuse tetracycline labelling of the endosteal bone formation in the tuberosity of the maxilla (T) and by 3-clearly demarcated labels in the scaphoid fossa (S). Original magnification $\times 16$.

B. Distobuccal root of the third molar; where the roots had been moved through the buccal plate, the periosteum had responded by the deposition of woven bone (W) stained with tetracycline. Original magnification $\times 30$. C. PTM suture from a control monkey. The smooth edges of the bone and low cellularity of the sutural ligament are in marked contrast to the PTM suture in D from an experimental animal. Both stained with haematoxylin and eosin. Original magnification $\times 75$.

Maxillary orthopaedic change can be produced clinically by extra-oral traction using a headgear, where it is desirable to move the maxilla distally, typically in those patients with a Class II division 1 malocclusion characterized by maxillary prognathism. The optimal conditions for achieving orthopaedic change are fulfilled when heavy forces (1000 gm) are applied to a maxillary arch in which as many teeth as possible have been incorporated so the induced force can be transmitted beyond the teeth (Slide 11). This treatment plan was based on my earlier research experience with the plasticity of the monkey maxilla; ten years later with the benefit of hindsight I would have started this patient's treatment with a Twin-block, yet to be popularized by Bill Clarke (Clark, 1982, 1988).

Slide 11. Patient in the mixed dentition with a Class II division 1 malocclusion treated with a combination of a cervical traction (with the face-bow inserted into the first molars) and an anterior high-pull headgear (attached to hooks on the archwire between the central and lateral incisors). Comparing overall and maxillary superimpositions, since mandibular growth was limited, a major contribution to overjet reduction must have come from remodelling the facial sutures and repositioning the maxilla distally. (From Meikle (1980), *American Journal of Orthodontics*.)

Protraction of the maxillary complex

One of the drawbacks of trying to remodel facial sutures in Class III patients with maxillary retrognathia by applying forces directly to the teeth is their tendency to move, thereby reducing any orthopaedic effect. In another series of primate experiments, skeletal anchorage was used to apply force directly to the maxillary complex by means of endosseous implants (Turley *et al.*, 1980; Smalley *et al.*, 1988). In the Smalley *et al.* investigation involving four pigtail monkeys, titanium implants were placed surgically in the maxillary and zygomatic bones and allowed to osseointegrate for four months. Extraoral forward traction was then applied to the implant abutments. Cephalometric and dry skull analyses showed the amount of skeletal protraction was significant compared to conventional force application to the dentition (Slide 12). The clinical management of cleft lip and palate patients and others with maxillary retrognathia would benefit from the use of intraosseous mini-screws inserted into the tuberosity region, and applying forward traction directly to the bone.

Slide 12. A. Maxillary protraction when the force was applied directly to the teeth; these have tipped in a mesial direction. B. The protraction force was applied to osseointegrated titanium implants inserted into the zygomatic bones. The maxilla has moved anteriorly disarticulating the zygomaticotemporal pterygomaxillary sutures with no apparent movement of the teeth. Dry skull preparations. (From Smalley *et al.* (1988), *American Journal of Orthodontics and Dentofacial Orthopedics*.)

Rapid Maxillary expansion

The most dramatic example of sutural remodelling used clinically, is the result of rapid maxillary expansion in patients with maxillary hypoplasia, where separation of the two halves of the maxilla produces a large diastema between the central incisor teeth (Slide 13). For this well-established technique to be effective, the magnitude of the applied force must be of sufficient magnitude to be transmitted beyond the periodontal joints, otherwise the stresses will be absorbed within the alveolar processes resulting in tooth movement alone. Although not usually

recognized by orthodontists as such, rapid maxillary expansion can be regarded as a form of distraction osteogenesis. Given the aim of RME is to loosen up the articulations between the maxillary complex and the rest of the skull, the next logical step is to combine RME with intraosseous mini-screws to apply distraction directly to the maxilla to minimize tooth movement as suggested above (Slide 14).

Slide 13. In this patient a heavy orthopaedic force (applied by a Minne expander) has separated the two halves of the maxilla along the palatal suture. This creates a defect that will be restored by bone including a reconstituted suture, provided the expansion is retained long enough—usually 3-4 months. Rapid maxillary expansion in addition to increasing arch width will also increase arch length in the premaxillary region.

It is a common belief that the midpalatal suture fuses around the age of 15 years. However, there is anatomical and clinical evidence to suggest this is not necessarily the case. In a histological study of 60 human autopsy specimens aged 0–18 years, Melsen (1975) found that growth of the midpalatal suture continued up to the age of 16 in girls and 18 in boys. Furthermore, Persson and Thilander (1977) reported in an older age group (15–35 years), that although palatal sutures may show evidence of obliteration during the juvenile period, a marked degree of closure was rarely found until the third decade *i.e.* 20–30 years of age. The key issue is not whether osseous union has begun, but the overall percentage of the suture that has actually fused. Persson and Thilander speculated that if osseous bridging of 5 percent represented the upper limit for splitting the mid palatal suture, this would not be reached in most people before the age of 25 years. In a combined radiographic-histological investigation, Wehrbein and Yildizhan (2001) concluded that if this were true, RME would have been successful in nine of the ten individuals (ages 18–38 years) in their study sample. They also showed that a radiologically invisible suture does not mean the suture is fused histologically. In any event, undue focus on the palate rather obscures the fact that the greatest resistance to RME comes not from the midpalatal suture but from the circum-maxillary suture network (Isaacson and Ingram, 1964; Wertz, 1970) that attaches the maxilla to the rest of the skull (Slide 13).

Remodelling the temporomandibular joint

The condyle and cartilage of the mammalian mandible are different in several ways from the articular cartilage of long bones, and have always held a certain mystique for the dental profession. The presence of cartilage indicates that the joint surfaces of the TMJ are morphologically adapted to protect the subchondral bone from mechanical loading during mastication, and as might be expected from its structure and function, the articular surfaces are more resistant to mechanical loading than craniofacial sutures.

The major aim of dentofacial orthopaedic treatment in Class II patients with mandibular retrognathia (approximately 70 percent) is to enhance or optimize the growth of the condyle by functional anterior displacement of the mandible. The extent to which this can be achieved, however, and whether it has clinical significance are topics of long-standing controversy. Both rat and monkey models have been used to study adaptation to protrusive function, but the question remains. Can changes in the TMJ produced by so-called 'functional appliances' that alter jaw position, represent an actual increase in condylar growth of clinical utility, or simply local condylar remodelling? (Slide 15).

Condylar cartilage is derived from the cellular periosteum

Central to an understanding of condylar growth is the question why cartilage is present in a membrane bone in the first place (Slide 16). Of the many examples of connective tissues adapting to changing mechanical circumstances, the one most relevant to the condyle comes from the work of Murray (1963), who described the development of adventitious (secondary) cartilage in several articulations in the skull of the embryonic chick. He found that secondary cartilage always developed in membrane bones, but only at articulations that were mobile, or where the musculature set up conditions of strain. In subsequent experiments with grafted and paralyzed embryos (Murray and Smiles, 1965), cartilage did not form, and cells that normally formed cartilage produced bone instead (Slide 17).

Studies in which mandibular condyles have been transplanted into a nonfunctional environment have also shown that the progenitor cells of the proliferative zone (PZ) differentiate into osteoblasts, and not chondroblasts as *in situ* (Duterloo, 1967; Meikle, 1973a,b). The cells are therefore multipotential and can form either cartilage or bone depending on the environmental circumstances. Simple microscopic observation makes it obvious that the articular and proliferative zones of the condyle are no more than a continuation of the fibrous and cellular layers of the periosteum. The change from osteogenesis to chondrogenesis resulted from the evolutionary development of an articular condylar process on the mandible (dentary) of mammals, and as a consequence, the altered functional demands of the periosteum covering the articular joint surfaces (Meikle, 1973a,b).

Slide 16. Photomicrograph of a sagittal section through the head of the mandibular condyle (human, aged 10–12 years, the age when functional appliance treatment is usually started). There is some evidence of endochonral ossification, but chondrogenesis itself does not appear particularly active. (From Meikle (2007). *Journal of Dental Research* 86, 12–24.)

Only by recognizing that condylar cartilage is a product of the periosteum can the difference in cellular kinetics, structure, and growth that exist between condylar and epiphyseal cartilage be understood. These include failure of the chondrocytes to divide (growth is appositional as in bone), and as a result the cells are not organized into parallel vertical columns. In addition, it is worth being aware that functional activity also plays a role in the growth of epiphyseal cartilage. In the absence of function, the growth plates of rat metacarpals fail to maintain a satisfactory increase in transverse diameter, and the cells of the perichondrium at the perimeter differentiate into osteoblasts, not chondrocytes (Meikle, 1975).

TMJ remodelling in non-human primates

Studies of mandibular displacement in the rhesus (*Macaca mulatta*) monkey have a long history, and been shown to consistently produce significant morphological changes in the TMJ (Breitner, 1940, 1941; Baume and Derichsweiler, 1961; Meikle, 1970; Stockli and Willert, 1971; Adams *et al.*, 1972). Prior to the work of Carl Breitner, investigations into the effects of orthodontic treatment at the histological level in animal models had been confined to changes in the PDL and alveolar bone associated with tooth movement. Breitner was the first to look beyond the teeth and study tissue changes induced in the TMJ and other sites in the mandible (Slide 18). His findings were first published in the German literature during the 1930s and later in English in two classic papers entitled *Bone changes resulting from experimental orthodontic treatment* (Breitner, 1940, 1941). These provided convincing histological evidence that the influence of orthodontic treatment in experimental animals was not limited to the alveolar processes, but extended to other parts of the mandible causing bone transformations (bone remodelling in contemporary terminology), particularly of the glenoid fossa and condyle (Slide 19).

Slide 19. Sagittal sections through the TMJs of two young Rhesus monkeys. Left: Section (1) through the TMJ following raising of the bite in the incisal region by an inclined plane, showing deposition along the anterior (post-glenoid tubercle (A)). (From Breitner (1941), *American Journal of Orthodontics and Oral Surgery*.) Middle and Right: Sections (2) and (3) 46 days after a bite-jumping appliance cemented to the maxillary and mandibular canine and molar teeth. Shows bone deposition along the anterior wall of the postglenoid tubercle (A); deposition on the posterior surface of the condyle (B). Right: Resorption of bone along the anterior surface of the condyle at the insertion of the lateral pterygoid muscle (C). (From Breitner (1940), *American Journal of Orthodontics and Oral Surgery*.)

Breitner's papers have been criticized for containing only one animal in each experimental group and little if any evidence of control material. Nevertheless, despite the introduction of vital staining, improved histology, metallic bone implants and cephalometric radiography, subsequent investigations (Baume and Derichsweiler, 1961; Meikle, 1970; Stockli and Willert, 1971; Elgoyhen *et al.*, 1972; Woodside *et al.*, 1987), have added comparatively little new information to Breitner's original findings (Slide 20). This is graphically evident in Slide 21 in a monkey whose skeleton was labelled with tetracycline while undergoing posterior mandibular displacement, resulting in resorptive remodelling of the head of the condyle and anterior surface

of the postglenoid tubercle, with concomitant deposition along the posterior border. The remodelling response of the tubercle is likely to have resulted from bending of the bone.

Slide 22. These slides are sagittal sections through the insertion of the lateral pterygoid muscle into the condylar head in (1). A control monkey; a decalcified section stained with H & E, magnification x 75. (2). An unstained ground section viewed under UV light, magnification x 30; mineralizing tissues have been labelled with tetracycline. They show that the muscle insertion is normally a resorptive surface. (3). Following anterior mandibular displacement, the insertion of the lateral pterygoid muscle into the neck of the condyle is characterized by increased resorptive remodelling.

Slide 23. 6A. Sagittal section through the TMJ of an adolescent rhesus monkey after six weeks anterior mandibular displacement. Note bone formation along the anterior border of the postglenoid tubercle (arrows). The response of the condylar cartilage seems to be within normal limits. H & E stain x 8. 6B. Under higher magnification the new woven bone (nb, arrows) is clearly distinguished from the mature compact bone (mb) with its Haversian systems. R shows an area of bone resorption. H & E stain viewed with polarized light x 42. (From Woodside *et al.* (1987), *American Journal of Orthodontics and Dentofacial Orthopedics*.)

In a long-term histological study of mandibular adaptation to protrusive function in young rhesus monkeys, McNamara and Carlson (1979) reported significant morphological changes at the condyle. This took the form of increased thickness of the condylar cartilage, as well as increased bone deposition along the posterior border of the ramus (Slide 24). The changes were observed within 2 weeks, reached a maximum at 4–6 weeks and declined thereafter.

Slide 24. Condylar adaptation to protrusive function in the growing *Macaca mulatta* monkey; sagittal sections through the condylar head of a control (left) and an experimental (right) monkey after 2 weeks showing differences in the thickness of the condylar cartilage. (From McNamara and Carlson (1979), *American Journal of Orthodontics*.)

In a subsequent cephalometric study, McNamara and Bryan (1987) found that at the end of an experimental period of 144 weeks, the mandibles of treated animals were 5–6 mm longer than those of controls. Mandibular length was measured by the linear distance between infradentale and condylion (Slide 25). Changes in condylar position were measured by an angle termed the condylar–ramus–occlusal or CRO angle (Slide 37). This showed that rhesus monkeys undergo a forward mandibular growth rotation on average of 8.8°; in the experimental group the CRO angle opened an average of 2.8° (Slide 26). In other words, the forward growth rotation of the condyle that occurs in growing monkeys was neutralized by remodelling of the condylar head and brings into question once again the validity of measurements of mandibular growth that do not take into account condylar growth rotation. A similar opening of the gonial angle has been reported in rhesus monkeys wearing bite-opening appliances (Rowe and Carlson, 1990). However, they found that once normal mandibular posture was restored, this process was reversed with remodelling along the ramus and body of the mandible in a similar pattern to that observed in control animals.

Slide 25. Superimpositions of the mandible were made on metallic implants. Measurements of mandibular length were made between infradentale and condylion. After 48 weeks protrusive function, significant differences in mandibular length were recorded between the control (n=12) and experimental (n=11) animals. At the end of 144 weeks Co-Id was 5–6 mm longer in the experimental group. (From McNamara and Bryan (1987), *American Journal of Orthodontics and Dentofacial Orthopedics*.)

Slide 26. Changes in condylar position were measured by changes in the CRO angle. This showed that during normal growth the condyle of the rhesus monkey undergoes a forward growth rotation, closing on average by 8.8°. In the experimental group the CRO angle was shown to increase by 2.8° on average. The animal shown in the right figure had a 48-week control period during which the CRO angle decreased by 8.5°. During the subsequent 144-week experimental period the angle opened by 6.0°. (From McNamara and Bryan (1987), *American Journal of Orthodontics and Dentofacial Orthopedics*.)

It is clear that functional mandibular displacement in primate models can alter the surface contours of the condyle, glenoid fossa and post-glenoid tubercle. In this respect the TMJ is no different from any other joint. It has been known at least from the time of Alexander Ogston that

the articular surfaces of bones can be remodelled. There is also evidence from young growing monkeys that condylar growth can be directed in a more posterior direction. This would account for the increase in the length of the mandible using linear parameters, and provides an indication as to what might happen in growing children treated with 'bite-jumping' appliances such as the Twin Block and Herbst (Slide 27).

Functional mandibular protrusion in rats

Setting aside the ethics of carrying out experiments on one of our primate cousins – *mea culpa* – not to mention the expense of housing and maintaining a primate facility, few orthodontic departments had access to primates and had to make do with rats. It was Petrovic and the Strasbourg group that championed the idea that functional mandibular protrusion in the rat can stimulate the growth of the condyle by increasing cell division within the proliferative zone (Charlier *et al.*, 1969; Petrovic *et al.*, 1975; Petrovic and Stutzmann, 1977). This view has been embraced by many orthodontists as positive evidence for the clinical use of functional appliances in the treatment of Class II malocclusions (Slide 28). Attempts to replicate these results, however, using biochemical, histomorphometric and autoradiographic methods have proved elusive (Tonge *et al.*, 1982; Ghafari and Degroote, 1986; Tewson *et al.*, 1988).

Evidence in support of condylar growth stimulation

In the first English language publication of the Strasbourg group in the *American Journal of Orthodontics* (Charlier *et al.*, 1969), four-week-old rats were anaesthetized for 4 hours/day during which time they wore an anterior mandibular displacement device; this was continued for four weeks. The results section consisted of twenty lines of narrative and two figures containing a single histological section from a control and an experimental rat condyle (Slide 29). Even by the publishing standards of the leading orthodontic journal of the day this was clearly inadequate. After eyeballing the slides, they concluded because the proliferative zone (PZ) appeared wider in the experimental group, mandibular hyperpropulsion (their term for anterior functional displacement) had brought about the additional growth of condylar cartilage by stimulating PZ cells to undergo mitosis, followed by their differentiation into chondrocytes. No histomorphometric or statistical analyses were provided.

Slide 29. Sagittal sections through the condyles from control and experimental rats treated for a four-week period with anterior mandibular displacement (mandibular hyperpropulsion). The legend states that a comparison of the two figures shows that the prechondroblastic Zone in the treated rat is significantly increased. (From Charlier *et al.* (1969), *American Journal of Orthodontics*.)

Petrovic then presented two papers at the University of Michigan Craniofacial Growth Symposia in Ann Arbor in 1975 and 1977. Mandibular protrusion of varying amounts was produced in four-week-old rats for 8–12 hours/day for periods of 1–4 weeks. One hour prior to sacrifice each received an intraperitoneal injection of ³H-thymidine to label cells synthesizing DNA. They found a decline in the number of labelled PZ cells over the first 7 days but by 14 days the number had increased significantly. Significant differences were also detected in the number of labelled cells with additional 1.0 and 2 mm displacement (Slide 30).

Slide 30. The left figure shows the displacement device used and mode of action. The right figure represents variations in condylar growth rate (as measured by ³H-thymidine incorporation), as a function of the amount of longitudinal deviation produced by the displacement device. (Redrawn from Petrovic and Stutzmann (1977), *The Biology of Occlusal Development*.)

The publications from the Strasbourg group continue to be cited in the literature as scientific proof that growth of the condyle can be stimulated. But how reliable is the data? How well does it stand up to scientific scrutiny? In planning a research project destined for submission to an academic journal (even orthodontic journals are being more rigorously vetted), it is important the experimental design and research methods, or lack of them, do not compromise the validity of the results and hence the conclusions. As a guide, given the laboratory and animal house facilities available, the following should be observed.

(1). Provide adequate control data. In Petrovic *et al* (1977) a control group of 12 animals was measured at the beginning of the experiment, but not thereafter over a time-scale of 28 days. Zero-day controls are adequate for experiments lasting a matter of days, but biological systems do not remain stationary. Not measuring controls at corresponding points over a time-scale of 28 days is unacceptable; the error bars are also very small.

(2). Avoid subjective bias by counting the item of interest in histological sections 'blind'. Failure to do this makes any attempt at quantitation unsafe.

(3). The data should be normalized. Relate the number of labelled cells to the total number of cells in a representative field(s) to establish a labelling index (Slide 32). (What this means is that 3 labelled cells out of a total of 30, is the same as 30 out of 300). This is a fundamental principle of histomorphometry to compensate for the variation inherent in all biological systems. Quantitative histomorphometry may be mind numbingly dull, but can be made easier by analyzing digitized images on image analysis systems such as Image-Pro-Plus 2D Image Analysis Software (Media Cybernetics).

Slide 31. Autoradiograph of a coronal section through the condyle of a four-week-old rat labelled with ³H-thymidine 24 hours prior to sacrifice. Most of the labelled cells can be seen within the proliferative zone. To establish a labelling index, both the number of labelled and unlabelled cells in a given field(s) must be counted and preferably 'blind' to avoid subjective bias.

(4). Anyone who has practical experience of handling laboratory rats and observed the amount of anteroposterior mandibular movement they can achieve, will find it hard to believe it possible to accurately regulate mandibular advancement by 0.5–1.0 mm with an incisal bite plane (Slide 32).

Slide 32. Unlike monkeys and humans, the craniomandibular articulation of the rat does not have a post-glenoid tubercle or an anterior articular eminance. This provides the rat mandible with considerable anteroposterior mobility. Not something that can be controlled by adding 1 mm at a time to an anterior bite plate.

The sceptic's view

In the 1980s, two MSc research projects carried out at the Eastman Dental Institute, University of London, designed to confirm the findings of the Strasbourg group were published. In the first study (Tonge *et al.*, 1982), anterior mandibular displacement was produced in four-week-old rats by cast-gold splints cemented to the upper incisor teeth. At the end of an experimental period of 1–4 weeks the condyles were removed and pulsed labelled *in vitro* for 6 hours on stainless steel grids in culture medium containing ³H-thymidine. No statistically significant differences in the incorporation of ³H-thymidine into PZ cells between experimental and control condyles could be detected at any point in the time scale. Perhaps the most interesting finding was that after 4 weeks of constant mechanical loading, resorption of the subchondral bone and interarticular disc of the condylar head at the point of maximum compression produced changes in the joints characteristic of osteoarthritis (Slide 33).

Slide 33. Four weeks anterior mandibular displacement with a fixed appliance resulted in remodelling of the CMJ. The appearance of an area of hyalinization at the point of maximum compression was a consistent finding, and at its most extreme form involved resorption of the subchondral bone and signs of disc perforation. (From Tonge *et al.*, (1982), *American Journal of Orthodontics*.)

One of the problems of using a fixed appliance, apart from resorptive remodelling to the head of the condyle, was the experimental rats failed to gain weight at comparable rates as controls. In the next series of experiments therefore, a removable monobloc device was used and worn 10 hours/day (Tewson *et al.*, 1988). (This paper was first submitted to the *American Journal of Orthodontics*. The editor of the day sent it back with the comment that since functional appliances stimulated mandibular growth and the appliance did not, there must be something wrong with the appliance – a syllogism that Aristotle himself would have been proud!)

At the end of the experimental period the condyles were again removed and pulsed *in vitro* for 6 hours in culture media containing ^3H -thymidine, ^3H -proline or $^{35}\text{SO}_4^{2-}$ (Slide 34); proline and sulphate labelling were carried out to detect changes in matrix synthesis (protein and sulphated glycosaminoglycans). The explants were then digested, and the radioactivity counted in a scintillation counter. Mandibular displacement did not result in a significant increase in the incorporation of ^3H -thymidine into explant DNA. This was confirmed by quantitative autoradiography; a statistically significant increase in the labelling index of the PZ after 14 days in any of the three sites chosen for analysis could not be detected (The data in this histogram were counted blind by the principal investigator; it is interesting to compare the error bars with those in Slide 30) A significant increase in the incorporation of ^3H -proline into total protein, or $^{35}\text{SO}_4^{2-}$ into total glycosaminoglycans, could not be detected either.

Slide 34. In this series of experiments a removable monobloc device was worn 10 hours/day. At the end of the experimental period the condyles were removed and pulse-labelled *in vitro* on stainless steel grids for 6 hours. The histogram shows the radioactive or labelling index expressed as number of ^3H -thymidine labelled cells/1000 cells in each of the three fields (anterior, middle and posterior) counted. The counting was carried out 'blind' by the principal investigator. (Redrawn from Tewson *et al.* (1988), *Archives of Oral Biology*.)

One disadvantage of *in vivo/in vitro* methodology is that the experimental and control condyles are pulse labelled in a non-functional environment for 6 hours. It does have a distinct advantage, however, in that the tissue of interest can be labelled directly with a carefully controlled concentration of isotope, which is also economical where large numbers of animals are involved. A not unworthy consideration for cash-strapped academic clinical departments. For critics of such methodology it is worth mentioning the doctoral dissertation of Carl Degroote (1984) who also carried out mandibular displacement experiments in rats, but labelled the tissues with ^3H -thymidine *in vivo*. He failed to detect any increase in the number of labelled PZ cells in one-month-old rats subjected to full or part-time displacement for 28 days. Surprisingly, Degroote came to the conclusion that anterior displacement enhanced mandibular growth; an example, perhaps, of not having one's preconceived ideas spoiled by the experimental data.

It has been suggested (Degroote, 1984; Ghafari and Degroote, 1986; Tsolakis and Spyropoulos 1997; Tsolakis *et al.*, 1997), that the discrepancies reported in the literature could be due to differences in appliance construction, and such factors as the degree of opening, continuous versus intermittent displacement, and the extent to which a definite forward shift of the mandible might be achieved. To address this problem Tsolakis *et al.* (1997) designed a new appliance to produce a controlled, stable and reproducible anterior advancement of the mandible in rats by rubber elastics rather than by functional displacement. Following the application of a force of 25 gm for 12 hours/day for 30 days, they found that growth of the lower jaw was affected to some extent with the development of an anterior cross-bite and a class III molar relationship. However, although mandibular measurements indicated that mandibles forced into hyperpropulsion were longer than controls (the perils of measuring mandibular length have been discussed already), they were unable to conclude whether this was due to an increase in the growth of condylar cartilage.

Alterations in gene expression following protrusive function in rats

Whether functional appliance therapy can accelerate or enhance the growth of the condyle in rats was revived by Rabie and associates at the University of Hong Kong, who applied molecular methods to the problem (Rabie *et al.*, 2002, 2003, 2004; Tang *et al.*, 2004). These have shown that the transcription factor Sox-9 and its target gene type II collagen (Slide 36), are up-regulated in the glenoid fossa and PZ of the condyle following forward mandibular positioning in five-week-old female rats. Over an experimental period of 17 days, this reached a maximum on day 3 but declined thereafter (Rabie *et al.*, 2003).

Slide 36. Photomicrograph showing the expression of type II collagen at 38 days of natural growth in the anterior (A), middle (M) and posterior (P) regions of the glenoid fossa (G), as well as the mandibular condyle (C) of a rat. (From Rabie *et al.* (2003), *Journal of Dental Research*.)

Mandibular advancement also triggered an increase in the expression of the cell–cell signalling molecule Indian hedgehog (Ihh) in the cells of the PZ and the adjacent chondroblasts of condylar cartilage (Tang *et al.*, 2004). This coincided with an increase in cell proliferation within the PZ (Slides 37, 38). Both these increases proved to be transient, however, reaching a peak after 7 days and returning to control levels by day 14. (For a discussion of the role of PTH/PTH-rP and Ihh in the genetic control of growth plate chondrogenesis see Meikle, 2002, pp 110–113.)

Slide 37. Immunostaining for Ihh in the proliferative zone (arrowheads) and adjacent chondroblast layer (arrows) in the mandibular condyle of (C) 42-day-old rats and (D) 7 days after mandibular advancement. Bars measure 50 μm . (From Tang *et al.* (2004), *Journal of Dental Research*.)

Slide 38. (A). The temporal pattern of Ihh expression ($n = 10$) in the mandibular condyle following mandibular advancement. (B). Labelling index ($n = 5$) obtained by counting labelled cells following an intraperitoneal injection of iododeoxyuridine (IdU), followed one hour later by an injection of bromodeoxyuridine (BrdU). Values are mean \pm SD. (From Tang *et al.* (2004), *Journal of Dental Research*.)

Rabie and associates have interpreted these findings as proof that functional appliances enhance condylar growth by stimulating the differentiation of PZ cells into chondroblasts. Elegant though these experiments may be, the temporary nature of the reported changes does present a problem. Given the response of cells and tissues to mechanically induced strain, it is not surprising to find cells of the craniomandibular articulation respond in a similar manner, both in terms of changes in metabolic activity and cell proliferation. Bearing in mind the stimulatory effect of mechanical stress on cell proliferation and DNA synthesis in other model systems (Roberts and Jee, 1974; Meikle *et al.*, 1979), the transient burst in mitotic activity reported by Rabie and associates is likely to result from the release of G₂-blocked cells allowing them to undergo mitosis, as well as enabling G₁-blocked cells to enter the S phase. Ihh has been shown to be an essential component of mechanical force transduction in chondrocyte proliferation (Wu *et al.*, 2001), and to up-regulate the expression of cyclin D1, a kinase required for the transition of cells from G₁ to the S phase of the cell cycle (Long *et al.*, 2001).

Summary of animal experimentation

- Facial sutures attaching the dentomaxillary complex to the rest of the skull can readily be remodelled by mechanical forces of appropriate force, direction and duration.
- Function plays an important role in the differentiation and maintenance of condylar cartilage and is necessary for the differentiation of PZ cells (cellular periosteum) into chondroblasts – to put it simply – no function, no cartilage.
- However, the extent to which functional activity regulates the proliferative activity of PZ cells remains unclear. Do the transient changes in cell proliferation and metabolism reported by some groups simply represent a localized adjustment to altered mechanical strain – they may look impressive down a microscope, but do they represent an increase that might be translated into an enlargement of the condyle?
- Given the ambiguity of the experimental and anatomical evidence from rat models, the hypothesis that functional mandibular displacement stimulates the mitotic activity of PZ cells, and hence growth of the condyle in humans should remain in the category labelled ‘uncertain’.
- It would certainly seem to be a weak basis on which to make such statements as ... ‘this indicates that functional appliance therapy can truly enhance condylar growth’ (Rabie *et al.*, 2003). It would be nice to think so, but clinical experience suggests otherwise.
- Experiments performed on rhesus monkeys suggest that while anterior mandibular displacement does not stimulate condylar growth, it might alter mandibular growth

direction. There is some clinical evidence to support this hypothesis and may have clinical utility – particularly in an actively growing child.

- With this background information from animal models, let us now turn to the findings of clinical trials designed to evaluate the effect of various functional orthodontic appliances on dentofacial growth.

Dentofacial orthopaedics and growth modification

At the same time that fixed appliance systems were being developed in the United States, a parallel philosophy of treatment – dentofacial orthopaedics was evolving in Europe. This method was based on removable appliances, intended as the name implies to move bones as well as teeth. The earliest functional appliance the Monobloc, was introduced by the French stomatologist Pierre Robin (1867–1949) in the early 1900s, and was designed to increase the airway in patients with the syndrome he had described in infants with mandibular retrognathia and glossoptosis (the triad was completed by addition of clefting of the secondary palate in the 1960s). However, the first functional appliance to gain widespread clinical use was the Activator (the name was derived from activation of the musculature by the appliance), designed by Viggo Andresen (1870–1950) and developed in collaboration with Karl Häupl (1893–1960) into the Norwegian system of functional jaw orthopaedics. Their book *Funktions-Kieferorthopädie* (Andresen and Häupl, 1936) quickly became a standard reference work, particularly in Europe running to six editions up until 1957.

After World War II with Europe in ruins, functional appliances provided the means to treat large numbers of patients in socialized healthcare systems, in countries with limited manpower and financial resources. During this post-war period, functional appliances underwent numerous eponymous modifications, particularly in Germany by Häupl, Bimler, Balters, Fränkel, Korkhaus and others (Wahl, 2006). Andresen correctly believed the Activator was a tooth-moving appliance; the proposal that Class II malocclusions were corrected by stimulating condylar growth seems to have arisen about this time, and became an article of faith for many.

For most of the twentieth century with a few exceptions, functional jaw orthopaedics was studiously ignored by mainstream orthodontics in North America. It was seen as the preserve of eccentric *émigrés* from Europe, paediatric dentists, and others lacking recognized specialist orthodontic training. During my time as an orthodontic resident in Seattle (1967–69), I never once came across a functional appliance. Nevertheless, whatever the more fanciful claims made on their behalf, it was clear that for many patients, functional appliances could produce dramatic changes in jaw relationships not possible with fixed appliances, a technology that had largely stopped evolving. In the 1980s there was a synthesis of North American fixed appliance systems with European functional appliances, and the term growth modification replaced growth stimulation to describe the objectives of dentofacial orthopaedics. Rationalism it seemed had finally prevailed.

The Andresen Activator/Monobloc and its variants such as the Bionator and Harvold Appliance are essentially passive in action. Increasingly popular are the more active appliances such as the Herbst and Twin-block based on the principle of ‘jumping the bite’ originally proposed by Norman Kingsley. Although Emil Herbst (1872–1940) a German orthodontist in Bremen had developed his fixed-functional system in the early 1900s (Herbst, 1910), little was known about the appliance until it was rescued from obscurity by Hans Pancherz (1979). The Twin-block technique developed by William Clark (1982), uses inclined occlusal planes to displace the mandible forwards, a principle similar to an appliance illustrated in Herbst’s textbook (Slide 43). According to the website of the British Orthodontic Society (2020), Clark’s twin-block technique is now the most commonly used functional appliance worldwide.

Can the TMJ be remodelled clinically?

It is clear that functional displacement of the mandible in primate models alters the surface contours of the condyle, glenoid fossa and post-glenoid tubercle. In that respect it is no different from any other joint. There is also evidence to suggest that condylar growth can be directed in a

more posterior direction. Remodelling the TMJ in monkeys is one thing; remodelling it clinically quite another. Nevertheless, there is evidence from those treated with the Herbst appliance suggesting it might be possible. In a systematic review of the literature regarding the effects of Herbst treatment on TMJ morphology, Popowich *et al.* (2003) identified 80 studies related to the topic. Publications that used transpharyngeal radiographs to document morphological change were excluded, which eliminated the major report of Paulsen (1997) on 100 consecutive Class II patients (Slides 45, 46).

That left five publications meeting the selection criteria and of those four were from Giessen, Germany. In one of these, Ruf and Panzerz (1998) used magnetic resonance imaging (MRI) to analyse TMJ growth adaptation in 15 consecutive Class II patients treated for a period of 7 months. After 6–12 weeks of treatment, MRI signs of condylar remodelling were seen at the posterosuperior border in 29 of the 30 condyles while glenoid fossa remodelling was noted in 22 joints. In another study, Croft *et al.* (1999) used cephalometry and TMJ tomograms to evaluate treatment changes. They did not examine the effects of treatment on condylar morphology and found little evidence of glenoid fossa remodelling. They did conclude, however, that Herbst treatment in the mixed dentition produces significant long-term improvements in dental and skeletal relationships as a result of dentoalveolar changes and orthopaedic effects in both jaws.

These findings suggest that with 'bite-jumping' appliances such as the Herbst and Twin-block, growth modification can be regarded as a possibility. It is important, however, to regard these changes as a remodelling adaptation to the altered functional activity and mechanical loading of the joint (as in any other joint) and not a stimulation of normal condylar growth. Despite claims to the contrary, there is no convincing experimental proof for condylar growth stimulation in either rodent or primate models. Whether or not the changes demonstrable in animal models can be regarded as clinically significant will depend upon the educational background and clinical practice of the individual practitioner.

Randomized clinical trials

The first randomized clinical trial (RCT) was carried out by Sir Austin Bradford Hill (1897–1991) in 1946, when he was asked by the Medical Research Council to test the effectiveness of streptomycin in the treatment of pulmonary tuberculosis. Apart from the fact Hill wanted to test randomization as a method, there was insufficient streptomycin available at the end of the War to give it to all the patients that needed it; a good example of making a virtue out of a necessity. Hill was Professor of Medical Statistics at the London School of Hygiene and Tropical Medicine, a statistician who avoided almost all mathematical formulae, and cautioned against confusing statistical precision with validity. Worth remembering when next reading an article claiming to show statistically significant differences in some parameter at the 0.01 level, based on anatomical landmarks with measurement errors of up to 1.00 mm or more (Slide 47).

Today the RCT is seen to be the 'gold standard' for analysing treatment outcome, and for many the only valid source of clinical data. The scientific worth of the retrospective study, the traditional method used to evaluate orthodontic treatment has been criticized for several reasons; selection bias, inadequate sample size, lack of contemporaneous controls, and poor research design. Perfectly valid criticisms, but they do not confer on us the freedom to ignore the knowledge we already have. In the Brave New World of evidence-based practice, before administering the last rites over retrospective studies, one is bound to ask – just how good is the evidence from the prospective randomized clinical trials of orthodontic treatment? Over the past decade, having listened to several talks on the findings of RCTs designed to test the ability of various appliances to modify dentofacial growth, one is struck by the often quite marked difference between the conclusions of the presentation, and one's own clinical experience (Slide 48).

Randomized clinical trials in orthodontics

RCTs in orthodontics have been limited in number, most being concerned with evaluating the effect of various appliances on dentofacial growth, particularly the mandible (Slide 49). The first

by Jakobsson (1967), a man clearly ahead of his time, randomly assigned sixty subjects aged 8–9 years with a Class II division 1 malocclusion from triads of children to either an Andresen Activator, headgear (HG), or control. Both HG and activator treatments were found to have a distalizing effect on the maxilla, but did not support the hypothesis that Activator treatment altered condylar growth. A similar methodology was used by Nelson *et al.* (1993) in 42 children aged 10–13 years, the subjects in each triad being assigned to a Fränkel FR-2, Harvold Activator, or control group. Neither appliance was found to alter mandibular growth.

Slide 49: (1) Small but statistically significant differences in mandibular length were produced in the majority of these studies; (2) The Herbst and Twin-block based on ‘jumping the bite’ were more effective at modifying mandibular growth than the Activator and its variants. Apart from questions of patient compliance and operator effect, outcome measurements will be influenced by (1) Failing to take into account sexual dimorphism between males and females averaging two years; (2) The inaccuracy of cephalometric methodology and potential subjective bias; (3) Validity of the measurements of mandibular length/growth; and (4) The age of the patients and the timing of the pubertal growth spurt and PHV.

The most widely publicized RCTs have been the North Carolina and Florida studies testing the effectiveness of HG and Bionator in stage I of a two-stage treatment protocol for Class II division 1 malocclusions (Tulloch *et al.*, 1997; Keeling *et al.*, 1998), and the multicentre Herbst and Twin-block trials carried out in the United Kingdom (O’Brien *et al.*, 2003a, b). The general conclusion seems to be that a two-stage treatment started in the mixed dentition is no more clinically effective than one-stage treatment started in the early permanent dentition, and has been interpreted by some to indicate that functional appliances have no place in the management of Class II malocclusions. A Cochrane review of two-stage treatment has also concluded there are no advantages in providing orthodontic treatment in two stages, over one stage in early adolescence (Harrison *et al.*, 2007). One gets the impression RCTs, which originally set out to test the ability of various orthodontic appliances to modify dentofacial growth, seem to have turned into a debate about the merits of two-stage treatment in the management of Class II malocclusions; these are separate issues (Meikle, 2008).

We treat individuals, not averages

Orthodontic RCTs suffer from two major defects. The cross-sectional nature of the data, and the tendency to focus on mean or average changes; this encourages a Procrustean ‘one size fits all’ mentality and the concept of uniformity. The mean is a statistical artefact, designed to produce order from large amounts of population data such as height; given the small size of most orthodontic RCTs, very few patients are likely to show the mean change. My favorite example, given my antipodean origins, is the photograph of the 1924–25 New Zealand Rugby Team, aka ‘The All Blacks.’ (Slide 50) It was recognized long ago by Boas (1892), that treating growth values cross-sectionally and simply taking the average, flattens out individual variation; the reason why he insisted that longitudinal growth studies were needed to understand the dynamics of human growth. The subject is discussed at some length by Tanner (1962), particularly in relation to growth velocity curves. Clinicians treat individuals, and individuals need to be studied longitudinally.

Although the statistical analyses do include standard deviations, these data occupy an inferior status in deciding the effectiveness of treatment; in fact, if one accepts the abundant experimental and clinical evidence demonstrating that functional appliances cannot significantly increase the growth of the mandibular condyle, differences in the amount, direction and timing of inherent growth become important determinants of treatment outcome.

If one adds to the above: (1) Variability in the timing, magnitude, direction and duration of pubertal dentofacial growth; (2) Mixed study samples of male and female patients, characterized by sexual dimorphism in the onset of the pubertal growth spurt of up to two years; (3) The inherent inaccuracy of the cephalometric method; (4) Failure to measure cephalometric radiographs ‘blind,’ to eliminate subjective bias; and (5) The questionable validity of measurements used to quantitate change, particularly of the mandible discussed earlier, it is hardly surprising the conclusions of RCTs have not been as clear-cut as might have been hoped. Unlike a laboratory experiment where the difference between experimental and control groups

can be reduced to the single factor being investigated, in a clinical trial an orthodontic appliance is just one of severable variables affecting the outcome (Meikle, 2005).

Unfortunately, two of the cornerstones of RCTs – randomization and double-blinding are not feasible in orthodontics. Randomization to experimental and control groups minimizes allocation bias, but the optimal time for obtaining maximal therapeutic benefit from a functional appliance is around the pubertal growth spurt; randomly depriving some participants of treatment in this age group is ethically unacceptable, and blinding is clearly not possible except in data analysis (surprisingly ignored in all published orthodontic RCTs to my knowledge). It seems to me that orthodontic RCTs have been asking the wrong question. As anyone with clinical experience in treating patients with Class II malocclusions will appreciate, *the question is not whether functional appliances are effective in producing dentofacial change, but why are they effective in some patients and not in others?* Failure has usually been attributed to poor patient compliance, which is likely to have been unfair.

Conclusions

It is perhaps a fanciful notion, but given the variation in the amount and timing of mandibular growth in our patients, I'm tempted to think of a functional appliance as a form of artificial selection – a device acting to 'select' out those patients best able to respond to the treatment; in Darwinian terms it implies the appliance allows the intrinsic growth of the mandible to be optimally expressed. By focussing on individual variation we are in good company; genetic variation was the starting point for Charles Darwin and the most revolutionary and iconoclastic book of the nineteenth century – *On the Origin of Species by Means of Natural Selection* (1859).

Modern *Homo sapiens* are not genetically homoogeneous, we are characterized by endless anatomical and physiological variation; the greater the variation between individuals, the harder it is to demonstrate that a difference in treatment effect is significant, or does in fact exist. The key to understanding how patients respond to treatment in all branches of medicine is variation, variation, variation (Slide 51).

Slide 51: This slide illustrates the wide variation in condylar growth between individuals, The images will be familiar from the Seminar 10 on craniofacial growth: It shows: (1) The wide variability in the amount and direction of condylar growth in 12 boys and 9 girls over a 6-year period; the direction of growth was found to strongly correlate with rotational movements of the mandible (From Björk, 1963). (2) Expressing data as mean \pm SD may be statistically *de rigueur*, but does not have the same visual impact as this figure in which the subjects are ranked in order of forward movement of gnathion (From Lande, 1952). (3) Growth velocity curves for the mandibular condyle based on changes in condylion on serial mandibular tracings superimposed on Björk's structures. For a male on the 90th percentile, condylar growth will average 5 mm/year, while for another on the 25th the annual increment will be as little as 1–2 mm (Redrawn from Buschang *et al.*, 1999). These will have a significant impact on treatment outcome.

Optimal conditions for achieving growth modification with a functional appliance occur when treatment overlaps the pubertal growth spurt and peak height velocity (PHV); it is clear from Slide 46 that the ages of many of the participants in these orthodontic RCTs were were some distance from reaching these milestones. Also muddying the water is the fact that two-stage treatment means different things to different people. If two-stage means starting appliance therapy at age 7–9, followed by a break before starting a second stage in the permanent dentition with fixed appliances, this is clearly an inefficient way to provide a service. On the other hand to many clinicians including the present author, two stage means a Class II treatment protocol involving preliminary functional appliance treatment in the late mixed dentition, followed seamlessly in tandem by fixed appliances over a period of 24 months. Like many things in life, it's a matter of timing.

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