Coincidence of the Cranial Base Facial and Upper Cervical Midlines and Soft Tissue Markers of the Face and their Correlation with Cranial Base and Facial Asymmetry

Dr Karen McCloy B.D.Sc.

Thesis submitted in partial fulfillment of the requirement for the degree of Master of Science

Tufts University School of Dental Medicine

Masters Committee Members

Principal Advisor

Dr Steven J Scrivani, Professor, D.D.S., D.Med.Sc., General Dentistry – TMD, Tufts University School of Dental Medicine

Thesis Committee

Dr Noshir Mehta, B.D.S., D.M.D., M.D.S., M.S., Professor & Chair, General Dentistry – Dental, The Craniofacial Pain, Headache and Sleep Center Tufts University School of Dental Medicine

Dr Aruna Ramesh, B.D.S., D.M.D., M.S., Dip. A.B.OM.R., Associate Professor, General Dentistry – Dental, Tufts University School of Dental Medicine

Dr Matthew Finkelman, Ph.D., Assistant Professor, Research Administration Dental, Tufts University School of Dental Medicine

Abstract

Introduction and Purpose: This longitudinal study uses cone beam computerized tomography (CBCT) to investigate midline, facial, cranial base, cervical, and rotational asymmetry to the cranial base midline (CBML) in 120 patients in a general dental population in Australia. Many dental patients require alterations to the habitual midline mandibular position during treatment. Little is known about facial midline asymmetry in the general population.

Materials and Methods: A 0.4voxel, 20 second CBCT scan was taken with soft tissue midline points marked. The CBML was drawn from foramen cecum to basion, and extended onto the coronal scan. Measurements were made from soft tissue, skeletal midline points, and various cranial base, cervical, and facial skeletal points to the CBML. Midline coincidence was accepted if points fell within 0.5mm of the left or right of the cranial base midline. Correlations were made using the Pearson correlation coefficient (r) between midline, facial, cervical, cranial base, and rotational asymmetry.

Results: The frontonasal suture (0.22mm) was the most reliable skeletal indicator of the CBML. There were no soft tissue facial points that were reliable midline markers of the CBML. The maxillary midline frenum (0.87mm) was not coincident with the CBML, but was coincident with the buccal maxillary midline suture (0.49mm). The mandibular midline frenum was not a reliable midline marker of the mandible at the genial foramen (0.84mm). The spinous process of C2 was angled an average of 4.44% from the CBML in 91.7% of cases,. There was generally positive

correlation between midline facial structures. The cervical midline points, tip of dens and tip of the spinous process of C2 showed no correlation with any midline facial structures.

Conclusions: Frontonasal suture and Posterior nasal spine are reliable skeletal midline markers. There are no clinically reliable soft tissue markers of the cranial base midline. The maxillary frenum is a reliable midline marker of the maxilla, but the mandibular midline frenum is not a reliable midline marker of the mandible. Rotational asymmetry is common in C2, and is not correlated to any other midline structure. The cervical midline points had no correlations with any facial skeletal or soft tissue midline point. There was no correlation between the medial or lateral pterygoid plates and GF or any soft tissue midline points. The distance from the medial surface of the condyle to the CBML had mild correlation with the distal pterygoid plate, and moderate correlation with the medial pteryrgoid plate distance to the CBML.

Table of Contents

List of Tables and Figures

Review of Literature

Craniofacial midline development consists of a complex sequence of interactions between genetic, epigenetic, ontogenetic and teratogenic factors[1,2,3]. Individuals inherit their genotype from their parents. The phenotype is the eventual level of expression of those genes, and is affected by epigenetic and teratogenic modifiers[3]. Signaling factors interact with embryonic tissues to control the shape and position of the craniofacial and cervical structures. For craniofacial development to proceed in a normal fashion, both the timing and quantities of the signaling factors must be precisely regulated[4, 5]. An error or change in the timing or quantity of the above signaling factors may alter the midline relationships of the cranial base and face.

Identifying and using the correct craniofacial midline is integral in providing esthetic dental treatment for complex restorative, orthodontic, and surgical therapy. Alignment of the maxillary and mandibular midlines may be needed to resolve the pain caused by temporomandibular disorder (TMD) [6]. The maxillary midline frenum (MMF) and the mandibular midline frenum (MaMF) are commonly used as markers of the facial midline[6-10], but little is known about their relationship with the underlying skeletal midline. Little is known about whether other soft tissue facial midline markers such as soft tissue nasion (STN), and the superor (SMP) and inferior midlines of the philtrum (IMP) are more accurate midline markers than the midline frena.

Cone beam computerized tomography (CBCT) is now available, and allows investigation of the relationships of anatomical structures that have not been visible on conventional lateral and frontal cephalometric radiographs. This study uses CBCT radiographs in a general dental population to investigate the relationships between soft tissue midline structures of the face, and midline skeletal structures, and their relationship with generalized facial asymmetry.

1. Development of the Facial Midline.

The facial midline is important structurally[11] and esthetically[12-15] . The facial midline grows more slowly in utero than the lateral areas of the face[16]. Asymmetry of the facial midline may occur due to changes in the growth process which may are initiated in either the pre- or post- natal period initiated by a number of different factors, which will be discussed.

A. Craniofacial Embryology

The fetal primordia start from a lateral position, and grow centrally before fusing in the midline [2, 11] . Midface skeletal points are in the position of this fusion. If the amount of growth on the left and right sides before fusion differs, the midline points may not be placed in the middle of the face [17-20]. Midline asymmetry may result due to asymmetric growth of other facial structures prior to fusion.

The requirements for midline symmetry begin in utero. Although there is a topographic organization of embryonic precursors in all species that is mediated by the Hox genes[21,11], the specifics of this organization in the formation of the craniofacial region may differ in different species[19, 22, 23, 23,24,25] . In humans, ossification of the cranial base begins at the frontal bone[26], moves to the occipital bone, and travels forwards along the embryonic cranial base. The ossification of the cranial base, maxilla, mandible, vomer and pterygoid plates is coordinated temporally as well as spatially[26] . Intramembranous ossification begins at sites of pre-existing neural structures [27, 28, 29] and proceeds into mesenchyme, which is undergoing shearing or tensile force[30] . The first and second cervical vertebrae, C1 and C2, are formed from embryologic structures which also form the occipital area of the skull base[11, 31-33]. Midline structures that share a common embryological origin are expected to have a common midline, and to exhibit symmetry around that midline. It would be expected that the midline positioning of C1 and C2 would be related to the midline positioning of the skull and cranial base.

Closure of the lateral facial processes results in the formation of the midline skeletal points. The closure of the shelves of the secondary palate at 60 days[34] results in the formation of midline structures, which include the anterior nasal spine, the posterior nasal spine, and the mid-palatal suture [35-37]. The nasopalatine foramen is in the midline of the hard palate, although it may be contained anatomically within the primary maxilla[38]. The fusion of the mandibular processes at the mandibular symphysis results in the absence of a radiographically identifiable midline suture

[39]. The genial/ lingual foramen (GF) is a midline structure of the mandible. Its presence has been reported at 81-98% of the general population [40,41-43], and multiple canals were present in 29% of subjects [40].

The midline soft tissue and muscles of the craniofacial region develop in conjunction with, and along the vectors of growth of, the underlying skeletal structures [30, 30]. Many craniofacial muscles undergo large movements from their origins to their final positions [44]. The upper lip forms at 35- 48 days in utero [45] by fusion of the maxillary, median nasal, and lateral nasal processes. The intermaxillary part of the median nasal process forms the midline part of the upper lip [45]. Lip formation is a complex process, which may be affected by many different factors, including the amount and timing of growth of each of the constituent processes [46,45,2]. Cleft lip with or without accompanying cleft palate may be subepithelial [47,46], or may occur in the midline or lateral positions, and may involve other areas of the facial skeleton [48]. It may be related to an accompanying syndrome [45], the ingestion of various teratogens [49, 50, 45, 51-53], hypoxia [54], or a restrictive pressure in the area of the cleft [48].

B. Functional Matrices

The fusion of the fetal primordia results in the formation of a functional matrix.[11]. The contents of each functional matrix interact with the surrounding environment. Epigenetic signaling regulates the growth of the functional matrix and of the surrounding area[55,3,56,57,58, 59]. The

resultant growth vectors are controlled not only by the activity in each individual functional matrix, but by the overall pattern of growth and change for the whole organism[57,60,61]. The same alteration of a functional matrix in one species may have a different outcome in another species[62,63, 60].

Functional matrices are either capsular or periosteal[60,55]. Capsular matrices in the craniofacial area include the neurocranium and its contents, the orbital cavity, the respiratory tract[64,62,55], the oral cavity[65], and the periodontal membrane/ tooth complex sutures[60, 66, 67]. The attachments of muscle to bone are periosteal matrices[60]. The factors acting on functional matrices to stimulate growth of the cranial base and skull in utero are different to those acting on the face after birth.

In utero the major determinant of the growth of the neurocranium and cranial base is the growth of the neural tissue of the brain [68]. The brain itself exhibits differing rates of growth of its midline structures [69]. Asymmetric neural and facial growth has been associated with autistic spectrum disorders[70]. The midface area establishes a stable pattern of growth by 9 weeks in utero, with the midline area being the most stable [71]. The growth of the cranial base and of the face interact with each other[72, 73], but the lateral areas of the basicranium may be more relevant to facial shape than the midline of the cranial base[74-76].

Most of the growth of the skull base is completed by 5 years of age [68, 77]. Bone growth continues at the sutures, the paranasal sinuses, the nasal septal cartilage, the condylar cartilage, the periosteum, and the synchondroses[78]. The spheno-occipital synchondrosis, and to a lesser extent, the sphenethmoidal synchondrosis make the major contributions to the continued growth of the cranial base after the age of 5[79]. Growth at the synchondroses occurs under tension [80,81-84]. The spheno-occipital synchondroses can remain patent up to the age of 12-15 years, and is usually fused by around 20 years of age[85,77,68]. It has been theorized that growth of the paranasal sinuses[86, 87] and the spheno-occipital synchondrosis are mechanisms for adjustment of cranial base and facial growth patterns[88,89,79].

During childhood and adolescence, the rate of facial growth and the growth of the airway take precedence over the earlier precocious growth of the calvaria and tongue[34]. The environmental influences which modify the expression of phenotype are very different to those that were operating in utero. It is thought that these are influenced heavily by airway and myofunctional issues[55, 60, 62, 64, 90-97] . Changes in breathing and myofunctional patterns may alter the growth and development of the craniofacial region especially up until late adolescence and early adulthood, but during adulthood, craniofacial growth continues at a reduced rate[98,99,100].

C.Genetic Signaling Factors

Genetic signaling factors are proteins which may act singly or in combination with other factors to regulate different aspects of facial growth. Fibroblast Growth Factor 8 (FGF8) has been implicated in the outwards growth of the facial processes [101,35], and Sonic Hedgehog (Shh) in the process of fusion [102,103,20,104, 22,105]. Variations in the spatial and temporal signaling of Shh lead to a variety of disorders ranging from loss of midfacial and midline neural elements, to differences in the left versus right side growth processes[17,18,20, 19, 106]. The net result may be alterations in the amount or direction of the left right growth patterns, or localized alterations to signaling in specific areas. Midline structures may be absent, malformed, or not placed in the true midline.

Signaling factors such as FGF8, Shh, Indian Hedghog (Ihh), the distalless gene and Sprouty 2 are a few of the many factors that work in combination to control endochondral ossification of the cranial base[107,107,108], the development of the frontal processes[109,101], and the growth of the pterygoid plates[5]. An imbalance in Shh has been implicated in the development of holoprosencephaly[110]. Tumor Growth Factor α (TGFα) has been implicated in the failure of fusion of the shelves of the hard palate[5,111]. Many of these signaling factors continue to affect gene expression throughout life.

There are many other signaling factors involved in craniofacial development, and a complete discussion of their interactions is beyond the scope of this project. It is evident that the

orchestration of normal facial growth is an undertaking of massive complexity. Any small misstep or lack of timing may have serious consequences for the final relationships of the bones, muscles, and ligaments of the facial region.

D.Epigenetic Factors

Epigenetic signaling is the process by which the organism adapts to a changing environment. The adaptations include stable, reversible, and local alterations to the DNA in the form of methylation[112, 113,3,114] and chromatin compaction [115, 116]. Epigenetic methylation of imprinted genes is transferred through the gene line[115, 116]. Epigenetic factors are stimuli which result in genetically mediated changes to localized growth patterns without altering the gene sequence. Prenatal and postnatal nutrition and teratogens are known to cause epigenetic changes [117-119]. A study of 40 pairs of monozygotic in 2005 [120] has shown that epigenetic modifications are responsible for phenotypic differences between twins, with older twins having a larger range of epigenetic modifications than younger pairs. Boughner et al[121] have shown that a gene that causes a change in the size of the brain in mice will affect the shape of the face in a way which does not correspond with what would be expected if the shape change was purely allometric. They hypothesized that this is an example of an epigenetic process affecting the interaction between the size of the brain and the face. Little is known about the corresponding mechanisms in humans. More work is needed to elucidate the exact environmental/ gene interactions that are responsible for phenotypic variations in craniofacial growth patterns.

E.Teratogenic Factors.

A teratogen is a substance that will cause birth defects if introduced into the fetal environment[2]. Many dietary factors such as retinoic acid [2,129], alcohol [124,125,126, 127,128], and alkaloids[122, 123] will alter the normal sequence of craniofacial growth.

Retinoic acid, alcohol, and dietary alkaloids induce symptoms of holoprosencephaly. Administration of antioxidants may reverse the effects of dietary alkaloids[122], while vitamin B12, alpha napthoflavone, and resveratol have been shown to prevent palatal clefts in the presence of a known teratogen [51, 53, 130]. Cleft repair is an example of the ability of the body to normalize growth in favorable conditions.

F.Craniofacial Syndromes or Disorders Leading to Facial Asymmetry or Loss of Midline Structures.

There are many disorders that alter craniofacial growth and result in alterations of facial symmetry or midline structures. This study involves a nonsyndromic population. Subjects with disorders such as occulo-auricular- vertebral spectrum, (a disorder of structures of the first and second branchial arch) [131]or Cannistra[132, 133](hemifacial microsomia or mandibulofacial dysostosis) would be excluded, and so various syndromic disorders will not be discussed.

Articular disorders of the temporomandibular joint may result in a decrease in growth of the condyle[134, 135], ramus, and cranial base on the affected side [136], and a deviation in the mandibular midline[137, 138,139,140]. It is uncommon for disc displacement to occur before the age of 5 [141], but disc displacement with or without reduction has a prevalence of 40-70% in the adult American population [142,143,140], and an incidence of 50% - 70 % in a pediatric pre-orthodontic population[144], rising to 97% in a symptomatic pediatric population[145]. None of these studies were conducted on a general population. Instead they focused either on symptomatic or asymptomatic populations, often a preorthodontic population. The differing study populations may account for the large spread in incidence of disc displacement. Never the less, the prevalence data suggest that some form of asymmetry resulting from an articular disorder is likely to be encountered in a non-syndromic general population.

Holoprosencephaly is a disorder involving the loss or alteration of midline facial and cerebral structures [146,1, 22, 147,102,110]. In a severe form, it has an incidence of 1/16,000 live births[122, 102]. The term holoprosencephaly is a descriptor for the results of interruption of Shh signaling, and applies to disorders with a variety of etiologies, ranging from a mutation of the Shh gene[148], to teratogenic factors such as the fetal alcohol syndrome [149,125,104], and prenatal exposure to dietary alkaloids[122, 123]. In its more severe forms, it will result in preterm abortion of an alobar fetus, cyclopia[102], or unilateral clefting of the lip or palate[104]. Many individuals with holoprosencephaly suffer from cognitive impairment, while others may only be missing a central incisor [150, 103, 151], or exhibit maxillary midface retrognathia with normal cognitive development. The differing

expression of the symptoms may be related to temporal aspects of interruptions in Shh expression[105]. The wide variation in expression of external midline defects in holoprosencephaly have led to a recommendation for a more extensive radiographic evaluation of any individuals who present with congenital loss of any midline structure[103,152,153]. It is conceivable that a patient with a mild form of holoprosencephaly may be included in this study.

Plagiocephaly is a deformation of the shape of the cranium. It may be syndromic or nonsyndromic. Nonsyndromic plagiocephaly is either deformational or synostotic. Deformational plagiocephaly is an alteration of the normal shape of the skull caused by repeated localized force. The force may be induced by repeated positioning of an infant in one position[154, 22, 147], infant head binding as practiced by some Peruvian tribes[155], or subsequent to a restricted intrauterine position [156], as in the case of multiple births. Deformational plagiocephaly will resolve without treatment [154], although it resolves more quickly with a combination of repositioning and headgear.

Synostotic plagiocephaly relates to the early fusion of one or more cranial sutures [154]. Early synostosis of a cranial suture will result in deformation of the cranial vault, cranial base, maxilla, and mandible [155, 157,158,154, 159]. Early release of a synostosed suture is recommended to limit the amount of permanent deformation during growth[157, 154, 160]. The syndromic forms of plagiocephaly are associated with other syndromic conditions such as Saethre-Chotzen

syndrome, Crouzon syndrome, Apert syndrome, Pfeiffer syndrome, and Muenke syndrome [131]. These are not conditions associated with a normal population of dental patients, and will not be discussed. Both deformational and non-syndromic synostotic plagiocephaly may occur in a normal population

2. Craniomandibular and Cervical Relationships.

The maintenance of normal spatial relationships of the elements of the craniofacial and cervical regions is a delicate balancing act. Many factors may affect the midline placement of the various elements of the craniofacial and cervical systems in a normal population not affected by syndromic craniofacial abnormalities. These may include

A. Divergence in the growth pattern of the cranial base and facial processes.
B. Asymmetry in the size and position of the attachments and insertions of the muscles of mastication and the cervical musculature.
C. Abnormalities in the formation of the cranial base and the position of the glenoid fossa.
D. Articular disorders of the temporomandibular joint.

E. Alterations of mandibular position caused by dental malocclusion, and changes in the orthopedic positioning of the craniofacial structures.

F. Injuries or abnormalities of the cervical structures.

A. Divergence in the Growth Patterns of the Cranial Base and Facial Processes

The maxilla and upper face can be considered as one connected block. The maxilla is fixed to the cranial base via the palatine bone, vomer, sphenoid bone, lacrimal, ethmoid, frontal, zygoma, and nasal bones[161]. The frontonasal processes form separately to the cranial base[1, 23]. The nasal connection to the maxilla in the midface makes that area especially prone to influences from airway disorders, which may cause differences in the direction of growth between the cranial base and face as previously discussed [162].

A diet consisting of predominantly soft rather than hard food, may decrease craniofacial growth, especially of the maxilla and mandible[61,163, 164,165-169, 169,170]. Myofunctional issues, such as tongue thrust, open mouth breathing posture, and abnormally high or low muscle tonus can act as further growth modifiers [171,95, 172-174,175-178,62, 179-183 ,184, 185,174], and impact the development of the maxilla and the surrounding musculature.

B. Asymmetry in the Size and Position of the Attachments and Insertions of the Muscles of Mastication and the Cervical Structures

The boney structures of the craniomandibular system and their muscles are closely inter-related. The position of the mandible is reliant on the relationship between the supporting ligaments, the size of the muscles of mastication, and the positions of their origins and insertions. Hyper- and hypotonic musculature will also affect the growth patterns of the craniofacial and cervical skeleton[186,171,178, 187,188]. Asymmetry of the masticatory muscles results in changes in the anatomy of the insertion of the muscles, and an alteration in the growth pattern of the surrounding bone[183,175, 176], but does not necessarily induce obvious midline asymmetry, due to compensatory growth in other areas[189].

It is likely that changes in masticatory muscle volume are usually preceded by the underlying boney changes [136, 175, 190].

The lateral and medial pterygoid muscles form a direct connection between the mandible and the cranial base. They arise in the cranial base, insert into the mandible, and are responsible for the midline positioning of the mandible[191, 192]. The superior head of the lateral pterygoid muscle arises from the infratemporal fossa, and inserts into the disc- capsule complex, and sometimes the neck of the condyle. The inferior head arises from the lateral aspect of the lateral pterygoid plate and inserts into the fovea of the condyle. The traditional concept of lateral pterygoid

anatomy is that it consists of two distinct muscles with two[193, 194,195] or three heads [193] however recent studies have thrown doubt on this concept. It is now thought that the lateral pterygoid is one muscle, with a fibre system that exerts different directions of force because of the differing positions of the superior attachments of its components [196-199]. Any functional or anatomical discrepancies of the lateral and medial pterygoids may be related to a change in midline positioning of the mandible.

Hyperactivity of the superior head of the lateral pterygoid at its insertion into the condyle may be related to disc displacement of the temporomandibular joint [193, 200-202], although this is not a universally accepted concept [199, 203]. Bakke et al.[202] were able to resolve severe temporomandibular joint clicking by magnetic resonance imaging-guided botox injections into the lateral pterygoid muscles. Taskaya- Yilmaz et al. [200, 200, 201] found that lateral pterygoid muscles attached to temporomandibular joint discs that were displaced without reduction suffered from significantly more atrophy than those attached to discs in a normal superior position. It was not clear whether the atrophy of the lateral pterygoid muscle had a causal relation to the disc displacement; and there may be insufficient attachment of the lateral pterygoid muscle into the disc to cause displacement[204, 205].

The lateral pterygoid muscle is active in many mandibular movements, including horizontal, protrusive, retrusive, and opening and closing movements of the mandible [197, 206]. A change in

the relationship between the pterygoid plates of the sphenoid bone and the mandibular condyle may affect the function of the condyle- lateral pterygoid complex [207]. A symmetrical midline relationship between the maxilla and mandible is required for the correct positioning of the condyle and disc within its fossa. The lateral pterygoids will be silent in the correct neuromuscular midlined position [191, 192], and so will limit the possibility of hyperactivity of the lateral pterygoid muscle contributing to disc displacement within the temporomandibular joint [200-202], and the possible sequelae of pain and asymmetry that occur in disc displacement with and without reduction[143 140].

The midline position of the mandible is often altered during complex restorative procedures, affecting the function of the lateral and medial pterygoid muscles. Both the lateral and medial pterygoid muscles are most active in horizontal chewing motions [208, 209] . The correct mandibular midline position is needed to decrease the amount of lateral force exerted by these muscles. The lateral pterygoid muscle cannot be palpated, and is not visible intraorally, so an easily seen soft tissue marker of the skeletal midline for mandibular placement is needed to provide the treating practitioner with a clinical indication of the functional position of the lateral pterygoid muscle, and of the relationship of the skeletal structures of the mandible to the cranial base.

Changes to the dorsal arch of the first cervical vertebra caused by muscular forces are well investigated[176]. Changes in head posture alter the shape of the dorsal arch due to changes in

muscle tension at the attachment areas [210,211,91,212]. Muscle tension affects the growth and shape of the bony attachments [66, 67, 183] . Underlying bony asymmetries affect muscle attachment positions. The final shape and position of the hard and soft tissues of the craniofacial and cervical complex are the result of this interaction.

C. Abnormalities in the Formation of the Cranial Base and Position of the Glenoid Fossa.

The mandible connects to the cranial base and maxilla via muscles and ligaments, and through its articulation with the temporal bone at the glenoid fossa[194]. The position of the glenoid fossa and the length of the cranial base and maxilla affect the sagittal position of the mandible[213, 214, 215, 215, 216, 217]. The position and shape of the glenoid fossa will change in response to alterations of the growth and function of the mandibular condyle, especially in response to retrusive and midline shifts of the mandible[139, 138, 140, 218,189, 219, 220,180, 221, 222,203].

Therapeutic changes in mandibular position, such as those that occur during oral appliance therapy for TMD will also induce permanent boney changes in the shape of the condyle and the glenoid fossa if maintained for extended time periods[223, 224, 225-227,228,229] . It is imperative that the correct mandibular midline position be established early during treatment, as this may lead to an earlier resolution of symptoms [6], and limit permanent and undesirable boney changes to the condyle and fossa.

D. Articular Disorders of the Temporomandibular Joint

Articular disorders of the temporomandibular joint affect the midline position and shape of the mandible. Articular disorders encompass a wide range of conditions, including congenital disorders, disc derangements, subluxation, and inflammatory disorders such as the arthritides, synovitis, capsulitis, and noninflammatory disorders such as osteoarthritis, ankylosis and fractures[230]. Of these, the disc derangement disorders are the most commonly seen in general practice. Disc displacement without reduction is associated with changes to the shape, symmetry, midline position and closing trajectory of the mandible[137-139,140], and changes in the shape and position of the glenoid fossa[221, 231, 232]. The extent of the structural changes is related to the stage of growth of the patient at the time of the articular disorder[140,137].

E. Alterations of Mandibular Position Caused by Dental Malocclusion/ Crowding, and Changes in the Orthopedic Positioning of the Craniofacial Structures.

Class II and Class III Angle's malocclusions may be the result of combinations of differences in glenoid fossa position, changes in midfacial growth, changes in the sagittal relationship of the cranial base, maxilla and mandible[213,214, 215,215, 216, 217], or functional alterations of the mandibular path of closure caused by dental interferences. Functional shifts in the mandibular path of closure

result in complex alterations to the three dimensional maxillomandibular relationships, and a change from a neuromuscular closure pattern to a tooth guided closure of the mandible [233].

While there is little evidence to support a link between the development of TMD and occlusal schemes in the general population[234, 235], there is some evidence that occlusal interferences can lead to the onset of the symptoms of TMD in patients who have a prior history of TMD[236, 237].

Lateral interferences during closure can increase the amount and asymmetry of the forces placed on the lateral pterygoid muscles [238]. Rottner et al. [239] found that the angle and force of occlusion on anterior interferences may combine to either loosen the front teeth, or contribute to TMD. This concept has been coined the Weak Link Theory when applied to patients who suffer from nocturnal parafunction [240]. Alterations to the closing trajectory of the mandible caused by intermittent anterior retrusive interferences, such as in many Class II division (ii) malocclusions, have resulted in structural changes to the posterior surface of the condyle, and nerve injury in the retrodiscal area of the glenoid fossa[241]. A lateral functional shift of the mandibular condyles permanently alters the condylar mechanoreceptors especially on the side opposite to the shift[242] and may permanently alter function al patterns of mastication.

A unilateral crossbite occurring at a young age causes compensatory changes in the shape of the mandibular condyles and ramus [189, 219,203,243, 244]. There have been many studies which report a link between unilateral crossbites, and orthopaedic disturbances, including asymmetry of the spine in both the frontal and sagittal planes[245-247, 248, 249].

By bonding a 0.5mm composite resin pad to the right upper molar of rats for one week, D'Atillio [250] induced a lateral shift of the mandible, a posterior cross bite, and scoliotic changes in the vertebral column of rats. The scoliotic changes were reversed by leveling the interference with another 0.5mm composite resin pad on the left upper molar, eliminating the functional shift, and allowing closure in a midline position. It is unlikely that this type of study will ever be replicated with a human population. There has been no definite causation shown as yet between midline asymmetry of the mandible and kyphotic and scoliotic spinal changes in humans[246 245]. Nevertheless, it would seem prudent to establish a reliable method for determining the midline positioning of the mandible, especially when undertaking orthodontic or TMD therapy for young children. The possibility of a midline shift inducing scoliotic or kyphotic changes is an unacceptable treatment outcome for what is usually discretionary treatment. The identification of soft tissue midline markers of the face which correspond with the underlying skeletal structures would eliminate the introduction of a midline shift of the mandible as part of the etiology of any orthopedic disturbances.

F. Injuries or Abnormalities of the Cervical Structures.

It is becoming evident that the cranial and cervical elements function harmoniously in normal health and function. It would be expected that there must first be a coincidence of the midline elements of the craniofacial and cervical systems, for harmonious function to occur. Little is known about either the functional or static relationships between the craniofacial and cervical systems in the normal population.

The muscles of mastication orient the mandible around the maxilla and cranial base. The mandible is linked to the clavicle and sternum via the supra and infrahyoid musculature. The hyoid region forms a fulcrum between the boney elements of the stomatognathic system and cervical area via its styloid, clavicular, and mandibular connections [251,252,253]. There is coincidence of motion of the hyoid bone and the mandible during deglutition and speech[254, 255,256]. Because the infrahyoid and supra hyoid muscles form the counter balances to the posterior cervical musculature, midline asymmetry may affect the function of both the stomatognathic and cervical systems.

There is simultaneous involvement of the head and neck musculature during chewing movements[257-259]. Whiplash associated disorders involve a comorbidity between the cervical spine and the TMJ that results in pain and disturbance of function of the stomatognathic and cervical stsructures[260-264, 265]. Elements of the stomatognathic system, such as the vertical

dimension of occlusion, affect the strength of the cervical musculature[266-268]. Changing the mandibular position will alter cervical, as well as orofacial, surface electromyography readings [8, 269-271]. Horizontal changes in mandibular position affect gait and postural control [7,9,272,273], and these effects may be magnified during function[274].

Most research on the anatomic relationship of the first and second cervical vertebrae, C1 and C2, has been done for the purposes of diagnosing changes in position, following trauma [275-279] and rheumatoid arthritis [280, 281]. CT imaging is considered the gold standard for measurements of cervical and cranial relationships in the atlanto-axial and atlanto-occipital joints [278, 279, 281,277]. It provides excellent visibility of the anatomical features of the condylar and odontoid regions, as well as the ability to accurately measure structural relationships. Radiographic diagnosis of the cervical spine suffers from inaccuracy with increasing laxity of cervical ligaments [279]. The inaccuracy is increased if the positioning of the subject has caused movement of the segments [275], or if the images are reconstituted using incorrect sagittal and coronal planes [282]. Imaging of functional movements of the cervical structures is more diagnostic of pathology than a static image [275, 283, 284].

Rocabado [251, 285] has postulated a connection between mandibular and cervical elements in function. Rotational instability has been associated with cervical pain [277, 286,278]. In a study utilizing CT to measure atlanto-occipital dislocation, Pang et al.[287] concluded that up until 18 years of age, there was a symmetrical arrangement of the atlanto-occipital joint, corresponding to

tightness of the ligamental connection. Rotational instability may occur in childhood, as the result of either trauma, or an upper pharyngeal infection[277]. More work needs to be done with CBCT to determine if there are correlations between cervical rotations in the upper cervical spine and aberrant midline positioning of the mandible in static occlusion .

3. Soft Tissue Markers of the Facial Midline.

There is convincing evidence that most members of a normal population have various degrees of facial soft tissue asymmetry [288-290]. Soft tissue landmarks have often been used with varying success in both removable and fixed prosthodontics as a means of calculating sizes and positions of teeth in relation to other facial structures during occlusal rehabilitation[291, 292, 293]. It has been reported that there is no correlation between the facial midline and the bisector to the interpupillary line [15]. There is no accepted facial soft tissue marker of the facial midline plane. The location of the facial midline is usually left to the judgment of the operator[13]. It would be an advantage clinically if a reliable soft tissue marker of the skeletal midline could be found.

To avoid errors in a clinical situation, if a soft tissue point is used as a marker of the facial midline, it must be easily visualized by the clinician while taking a maxillomandibular registration. The maxillary and mandibular midline frena are soft tissue markers which fulfill the

ease of use criterion. The frena have been proposed most frequently as possible markers of the maxillary and mandibular skeletal midlines. STN, and the superior and inferior midlines of the philtrum of the nose will also be investigated as possible soft tissue midline markers of the face.

A. Maxillary and Mandibular Midline Frena

The midline frenum is a fold of tissue extending from the midline area of the gingival attachment to the vestibule and central area of the lip of the maxilla or mandible [294]. It is usually located between the central incisors, is easily seen, and has been used as an indicator of the dental midline, especially in the absence of teeth [10, 291]. Dental crowding may make it difficult to interpret the exact nature of the midline relationship of the frenum and teeth to the facial midline in dentate subjects.

The maxillary and mandibular midline frena are easily seen by dentists each time they examine a patient. The attention of the clinician is fixed mainly on the MMF because of its close association with the occurrence of a midline diastema between the central incisor teeth[295, 296]. The MaMF attracts less attention, but is occasionally implicated in the origin of periodontal problems around the lower central incisors [297].

The attachment of the MMF has a variety of positions and shapes. The attachment can occur at the mucogingival junction, at the attached gingiva, or on the interdental papilla[298, 299]. The MMF is of medial nasal process origin, and is often missing in various syndromic and nonsyndromic conditions, such as Ehlers-Danlos syndrome, holoprosencephally, infantile hypertrophic pyloric stenosis, Ellis-von Creveld syndrome, oral-facial digital syndrome, Opitz and opitz C syndrome, Pallister-Hall syndrome, and W syndrome[300-302,151].

The histology of the MMF is variable. The epithelium ranges from being non-keratinized in the superior portion, to being para-keratinized over the alveolar mucosa[303]. The frenum may interrupt trans-septal fibers running between the two central incisors[299]. In 35% of cases there may be striated muscle in the MMF[295].

The MMF has been used in cases of edentulousness as a facial midline marker[304]. Others have used the maxillary and mandibular midline frena as markers of the skeletal midline, and aligned them during treatment and investigations of TMD[8, 171,7,6,9]. Fu et al [6] constructed a non-positioned stabilization splint for a group of symptomatic patients, and found that the frena moved towards midline alignment during treatment. The mandibular movement towards a midlined position was associated with resolution of the symptoms of craniomandibular disorder when the frena were within 0.5mm of each other. There is little information on the relationship of the midline frena to the skeletal mandibular, maxillary, facial, cervical, or cranial base midlines.

B.The Philtrum.

The philtrum is a soft tissue midline structure connecting the nose and the lips, which receives its vascular supply from the internal carotid artery[11] via the ascending, accessory, and central philtral arteries [305]. The philtrum has midline markers in the cupid's bow of the upper vermillion border, and the base of the nose. Both of these structures are easily visualized while working in the oral cavity. The superior surface of the philtrum and the midline of the maxillary vermillion border mark its superior and inferior extension. This study will investigate whether the superior and inferior midlines of the philtrum may be useful soft tissue midline markers of the skeletal facial midline plane.

There has been research on lip asymmetry[306, 307] which indicates that lip asymmetry exists in patients with a unilateral crossbite, and that the lower lip is not a reliable marker of skeletal midline, because of the deviation of the mandible, and because of the reliance of the lip contour on support from the dentition. Little is known about lip midline symmetry [306, 307].

C.Other Potential Soft Tissue Markers of the Facial Midline

Soft tissue nasion overlays the location of the first ossification centres in the face [28]. The bisector of the interpupillary line is close to soft tissue nasion, but is not in the facial midline [15]. CBCT will be used to determine if soft tissue nasion is close to the cranial base midline.

4. The Use of CBCT as an Analytic Tool.

The orthodontic and maxillofacial surgery disciplines have traditionally relied on frontal and lateral cephalograms to help determine if asymmetry and midline symmetry are present. With the ready availabiity of the new CBCT machines, some of the obvious drawbacks of traditional cephalometric analysis can be overcome.

One obvious inaccuracy of conventional cephalometrics is that the points and lines obtained from the x-rays do not represent anatomical reality, but are the result of superimposition of many boney layers into a two-dimensional representation. The inaccuracy of two-dimensional radiographs is most obvious when using a posteroanterior cephalogram to diagnose frontal midline symmetry[308]. The points and lines of conventional cephalometrics do not represent craniofacial growth fields[68, 309], or expected growth trends [310].

Many authors have described various analyses using three-dimesional points for the investigation of craniofacial asymmetry and surgical planning[171, 311-321,322]. These analyses are of relevance to surgeons and orthodontists treating syndromic patients and patients presenting with gross asymmetry requiring a multidisciplinary approach to treatment. Their population base does not reflect the kind of asymmetry that would be encountered on a daily basis by practitioners treating

a normal population base of patients. Surgical based analyses deal with gross measurements of asymmetry, and not with asymmetry of the midlines of the cranial base, face, and cervical structures. Although there is a growing realization of the interdependence of the cranial and cervical complex, there is little research using three dimensional CBCT technologies on the relationship between the two.

As yet there is no single three-dimensional radiographic analysis which has gained universal approval for use in the orthodontic field. New analyses will need to be developed, because it is difficult to find anatomic points which correspond to the traditional cephalometric points [323]. The counterpoint analysis of Enlow has been developed for quantification of three dimensional growth[68]. New cephalometric analyses will be developed specifically for use with the CBCT data, but it is not certain how long it will take for those analyses to gain acceptance.

Kyrkanides[324] used conventional cephalometrics to compare the coincidence of the midlines of facial and cranial base points in a normal population, versus a population with cleft lip and palate. Baek[325, 325]used CBCT and found that mandibular factors had the greatest influence on chin point deviation in Class III malocclusion in females with chin asymmetry. Sonneson[326, 326], using lateral cephalograms, found an association among condylar hypoplasia, changes in head posture, and cervical column morphology.

The use of three-dimensional CBCT technologies will yield more accurate information about midline discrepancy in the cranio- cervical region than conventional cephalometrics. Although the accuracy of linear measurements obtained from volumetric three dimensional renderings has been called into question[327], most authors accept the accuracy of linear measurements made using the coronal, axial, and sagittal sections[328-333].

This study will use linear and angular measurements made on the axial and coronal planes of a standard CBCT machine to investigate the coincidence of skeletal midline structures of the face and upper cervical structures with the cranial base midline in a general population. It will be determined if the maxillary and mandibular midline frena, STN, and midline of the superior and inferior boundaries of the philtrum are accurate markers of the CBML, and the maxillary and mandibular midlines. We will investigate whether correlations exist among asymmetry of the cranial base, upper cervical and facial structures.

Research Design and Methods

Research Design

This cross-sectional study was approved by the Bellberry Human Research Ethics Committee in Australia (Appendix 1), and involved 120 subjects. Participants signed a consent form (Appendix 2), and a photographic release form (Appendix 3) agreeing to allow their records to be used for the purposes of research.

Subjects who were eligible to be part of this study met the inclusion and exclusion criteria (below), gave informed consent, and required CBCT as part of their dental treatment plan. The types of treatment that required CBCT included oral surgery, multiple extractions, complex treatment plans, orthodontic treatment, and treatment for craniofacial pain in agreement with the Consensus Guidelines of the European Academy of Dental and Maxillofacial Radiology [334] . The CBCT (i-CAT ® Cone Beam 3D Dental Imaging System Version 3.0.34. Imaging Sciences International Inc, Hatfield Pennsylvania, United States of America) scans were taken at no cost for study participants, and every CBCT scan was screened for pathology by a qualified oral and maxillofacial radiologist.

Inclusion Criteria

Subjects were included in the study if they met certain inclusion criteria. Participants must have been at least 20 years of age. A CBCT scan must have been prescribed by their dentist to facilitate their treatment. To make this possible, it was necessary for them to be able to sit without moving in the i-CAT® chair for 20 seconds. It was also necessary that all of the radiographic points required for measurement in the study were able to be clearly visualized in the radiographic scan.

To ensure that the bite obtained for the purposes of the study was taken in the correct habitual occlusion of each subject, each participant was required to have at least 3 posterior teeth in each quadrant, and to be able to bite on those teeth in a repeatable position. As the documents for the study were written in English, it was necessary that all participants be familiar with English, and be able to understand the wording of the consent form.

Exclusion Criteria

Subjects were excluded from the study if they had a prior history of orthognathic surgery; or orthodontic or orthopedic therapy, as those procedures may alter both midline and lateral asymmetry of the face, and change the original midline relationships of the maxilla and

mandible. The use of an oral appliance which prevents or alters the normal tooth to tooth position was also a basis for exclusion from the study.

As the study involved a general nonsyndromic dental population, participants with a diagnosis of a congenital or acquired craniofacial syndrome or condition were excluded. Subjects with a medical history that was positive for a neurologic disorder which could cause an alteration to the normal soft tissue symmetry of their face, such as Bells palsy or stroke, were also excluded.

The soft tissue midline structures were marked with Tetric®EvoFlow opaque composite resin from Ivoclar Vivadent. Each participant had alginate impressions using Integra™ alginate from Kerr Corporation. Allergy to any component of either of these materials was a reason for exclusion form the study.

Subjects who wore a piece of metallic jewellery, or had a surgical plate which covered any of the radiological points needed for measurements were excluded from the study. Metallic dental restorations such as implants, amalgam fillings, and crowns caused radiographic scatter which at times obscured key areas of the CBCT scan, and were reasons for exclusion from the study.

Outcomes

The primary outcome was coincidence of facial and upper cervical skeletal midline points and soft tissue midline points of the face with the CBML. The distance form the CBML was measured to 2 decimal points in millimeters.

Secondary outcomes were:

-The coincidence of the maxillary and mandibular midline frena with the skeletal midline structures of the maxilla and mandible in millimeters;

-The amount of cranial base, facial, and upper cervical skeletal asymmetry, and its correlation with midline skeletal and soft tissue asymmetry in millimeters;

-The amount of rotational asymmetry and its correlation with midline skeletal and soft tissue asymmetry, measured in degrees;

-The correlation of facial and cervical asymmetry with cranial base asymmetry.

Methods

Subjects who were screened as eligible for this study and consented to participate could have study records taken when they were accepted into the study, or at another more convenient appointment. All clinical data was recorded by a research assistant who was trained in the standardized administration and collection of all clinical data as outlined in the section 'records' below. . The CBCT scan was obtained using the i-CAT® unit (Imaging Sciences International Inc, Hatfield Pennsylvania, United States of America) by a single general dental practitioner who was not the primary investigator.

Prior to starting the study the intraoperator reliability was calibrated by measuring points on a CBCT scan of a skull with the InVivoDental Application Version 4.0.78.0 (Anatomge Inc, San Jose California, United States of America) measuring tool, and directly with digital calipers. The average difference in measurement accuracy was 0.28mm (Appendix 4). After completion of the initial measurements, 50% of the measurements in the study were repeated to ensure measurement accuracy and minimize intraobserver variability.

Data Collected

All participants in the study were required to complete a set of standardized paperwork. Each subject filled out a Visual Analogue Scale detailing subjective symptom levels from 0-10 in various areas on the left and right sides of the body (Appendix 5).

Each subject completed the Research Diagnostic Criteria for Temporomandibular Disorder (Appendix 6). The requirements for this included questions on their history of symptoms of orofacial pain, a graded chronic pain questionnaire, a disability questionnaire, a depression and a nonspecific physical symptoms questionnaire. A clinical examination was performed on each subject by a trained research assistant who included a muscle palpation test scored form 1-3, pain quality questions, an examination of the direction and range of motion of the mandible, and the presence and functional position of joint noises.

A sleep evaluation form was required. This included the Epworth Scale of Daytime Tiredness, and a sleep hygiene evaluation (Appendix 7).

Soft Tissue Markings

Soft tissue midline structures were marked with a 1mm diameter dot of Tetric® EvoFlow low viscosity opaque flowable resin (Ivoclar Vivadent Inc.). The resin was cured with a diode light for 10 seconds (Appendix 8).

The tissues marked were the STN(Figure 1), the SMP (Figure 2), the IMP at the vermillion border (Figure 2), and the maxillary and mandibular midline frena (Figure 3).

Photographic Records

Intra- and extra-oral facial and postural photographs were recorded for each patient.The intra-oral photography (Appendix 9) included full arch and occlusal views. The extra-oral photography included facial and postural views (Appendix 10).The intra- and extra- oral photography was used as a means of patient identification, as verification that the soft tissue markers were accurate, and as an indication of the accuracy of the natural head posture and level of asymmetry found on the radiographs.

Study Models

Integra™ alginate impressions from Kerr Corporation (Appendix 11), and dental study models were taken. The impressions were poured in Yellowstone extra hard dental stone from Ainsworth Dental Company, and mixed in the VPM2 vacuum mixing unit (Appendix 12).

CBCT Scan Procedure

A 20-second CBCT scan was taken on an i- Cat ® Version 3.0.34 (Imaging Sciences International Inc, Hatfield, Pennsylvania, United States of America) with a 13cm field of view and 0.3 mm voxels (Appendix 13). The patients were seated and asked to look straight ahead at their reflection in the viewing window. Their head position was stabilized lightly in the head rest with the head strap so that the radiograph could be taken as close as possible to natural head posture. A chin cup was not used.

For each scan we measured (Appendix 16):

1. The coincidence of skeletal midline facial and cervical structures with the CBML;
2. The coincidence of soft tissue facial midline structures with the CBML;
3. The level and position of cranial base asymmetry;
4. The level and position of any facial asymmetry;

5. The level and position of upper cervical asymmetry and rotations.

CBCT Scan Analysis

A research assistant exported each scan to InVivoDental Application Version 4.0.78.0 (Anatomage Inc,, San Jose California, United States of America) as dicom multi-units (Appendix 14). Patients were entered into the InVivo program as anonymous files, and were allocated an ID number provided by the random number generator from Microsoft Office Excel 2003. The record of the names and ID numbers of each participant were kept in a separate locked draw accessible only to the research assistant and the principal investigator.

Each scan was aligned in the sagittal, coronal and axial windows using InVivoDental Application Version 4.0.78.0 dental imaging software from Anatomage Inc. (Appendix 15). All measurements were made using the InVivo Dental Application Version 4.0.78.0 dental imaging software measuring tool from Anatomage Inc. Measurements were made in millimeters to two decimal points. Distances to the left of the CBML were recorded as negative values. Distances to the right of the CBML were given positive values.

Sample Size Justification

NQuery Advisor Version 7® (Statistical Solutions, Saugus, Massachusetts, United States of America) was used to assess the amount of precision that was attained for our primary analysis. A sample size of 120 provided a half-width of 0.089 for the 95% CI of each percentage of coincidence. This calculation assumes the most conservative percentage of coincidence (50%). Data were analyzed with SPSS software package 17.0. (IBM Corporation, Somers, New York, United States of America).

Statistical Analysis

To account for the possibility of measurement uncertainty, we allowed 0.5mm as measurement uncertainty for both the hard and soft tissue points. The 0.5mm measurement relates to uncertainty in locating and measuring from the same point on the radiograph for each hard tissue point, and for a 0.5mm of uncertainty in measurement of the soft tissue points, as the soft tissue markers are 1mm in diameter. Coincidence with the midline will be accepted if the measurement falls within 0.5mm to the left or right side of the CBML. Raw values give an indication of whether the measurement was to the left or right of the CBML, with negative values falling on the left of the CBML and positive values on the right.

Coincidence of Facial and Upper Cervical Skeletal Midline Points, and Soft Tissue Midline Points of the Face with the Cranial Base Midline.

At each hard and soft tissue midline point, we measured the distance from the midline point to the CBML, and established whether or not midline coincidence existed. We calculated the percentage of cases that were coincident with the CBML, and the percentage that were positioned to the left or right of the CBML.

We calculated the mean and standard deviation of the distance and absolute value of the distance from the CBML in millimeters, and a 95% CI. for the percentage of cases to the left or right of the CBML in millimeters, the mean and absolute distance form the CBML in millimeters, and the percentage of points that were coincident with the CBML.

From these values we determined whether the facial and upper cervical soft tissue midline markers were coincident with the CBML. Any soft tissue markers coincident with the CBML were accepted as clinical markers of the facial midline.

Coincidence of the Maxillary and Mandibular Midline Frena with the Skeletal Midline Structures of the Maxilla and Mandible

To determine whether the midline frena were reliable indicators of the midline of the maxilla and mandible, we calculated whether or not the maxillary and mandibular frenal markers were coincident with the skeletal midline structures of the maxilla and mandible.

We also calculated the percentage of cases with coincidence and non-coincidence of the frenal markers to the midline structures of the maxilla and mandible, the.percentage of cases for which the frenal markers were to the left or to the right of the midline structures of the maxilla and mandible, and the mean and standard deviation of the distance and absolute value of the distance of the frenal markers from the midline structures of the maxilla and mandible in millimeters.

A 95% confidence interval (CI) was calculated for the percentage of cases for which the frenal markers were to the left or to the right of the midline of the maxilla and the mandible, the mean distance of the frenal markers from the midline structures of the palate and mandible, and the mean absolute distance of the frenal markers from the maxillary and mandibular midline structures.

The Amount of Cranial Base, Facial, and Upper Cervical Asymmetry, and its Correlation with Midline Asymmetry.

To determine whether there was a correlation between midline asymmetry and facial, cervical, and cranial base symmetry, we recorded measurements at each facial, cervical, and cranial base point (Appendix 16).

We then calculated for each measurment the mean, standard deviations, and 95% CI for base points in millimeters; and the difference and absolute difference between the measurements the distance from the cranial base and facial skeletal midline points to facial, cervical and cranial of peripheral facial markers to the CBML on the left and right sides.

We calculated a 95% CI for the average difference between the left and right sides; and the percentage of times the distance was to the left or the right of the CBML.

We computed the Pearson Correlation Coefficient (r) for the relationship between midline asymmetry and facial, cervical, and cranial base asymmetry, to determine whether there was an overall correlation between different asymmetries, or if there is a

specific correlation to midline asymmetry and asymmetry in particular points or areas of the face.

The Amount of Rotational Asymmetry and its Correlation with Midline Asymmetry.

The angular measurements of the mandibular and occipital condyles were assumed to be the same on each side. We were interested in differences between the left and right sides, and not the absolute value of the measurements; except for the rotation of the spinous process of C2 and the transverse process of C1, which were unpaired. Rotational asymmetry across the transverse processes of C1 and the spinous process of C2 was assigned a value of 0 degrees. Rotation to the right was assigned a positive value. Rotation to the left was assigned a negative value.

We calculated the differences from the expected outcomes for C1 and C2 (0 degrees rotation), and the mean and standard deviation for the amount of rotational difference, and whether the difference is more often to the left or right

We calculated a 95% CI for the percentage of cases with no rotational asymmetry, the percentage of times that the rotation was to the left or to the right of the CBML, and the average amount of rotation from normal in degrees.

Correlation of Facial and Cervical Asymmetry with Cranial Base Asymmetry

Using the Pearson correlation coefficient (r), we computed the correlation between asymmetry of the cranial base, facial and cervical structures, both in general, and to determine if there are particular structures which were most often asymmetric, or were asymmetric at the same time. We wanted to determine if measured asymmetry in the cranial base was related to measured asymmetry in any facial or cervical structure.

We used the bilateral measurements of facial, cervical, and cranial base asymmetry previously described to determine if asymmetry was present. We computed the Pearson Correlation Coefficient (r) for the differences between each pair of asymmetry measurements to determine whether there was correlation between different asymmetries, or a specific correlation to asymmetry in particular points.

Results

Consecutive patients were screened until the target population of 120 was achieved; 139 patients were screened, and 19 were excluded. The study population of 120 patients comprised 33 males (27%) and 87 females (73%). The age of participants ranged from 22-72 years, with a mean of 43.38 years. Of the 19 exclusions, 2 were excluded due to radiation scatter from restorations, two due to lack of a genial foramen, and the remaining 15 cases due to our inability

to visualize all of the required radiographic points on the CBCT scan. Of the 19 excluded, 12 were male (80%) and 7 female (20%) (Table1).

When midline measurements taken were to the left of the CBML they were given a negative value, and when they were to the right of the CBML they were positive. Measurements including the positive and negative signs were recorded ("raw values"), as were distances from the CBML with no indication of directionality ("absolute values"). Both raw and absolute values are referenced; raw values are labeled when used. The abbreviations and description of the anatomic points measured are listed in Appendix 16.

Coincidence of Facial and Upper Cervical Skeletal Midline Points, and Soft Tissue Midline Points of the face with the Cranial Base Midline.

Table 2 gives the mean absolute distance from the CBML, SD, the percentages of times the measurements for each point was to the left, coincident with and to the right of the CBML, the absolute range of values from the CBML, and the absolute and raw CIs. The frontonasal suture (FNS), (FNS mean absolute distance from the CBML 0.22mm,SD 0.38,), raw CI.(-0.06,0.1)) and the posterior nasal spine (PNS), (PNS mean absolute distance from the CBML 0.32mm,SD 0.46, raw CI(-0.18,0.02)) were the 2 hard tissue points that were markers of the CBML, and had absolute means that were within 0.5mm from the CBML.

The tip of dens (TD), FNS, anterior inferior aspect of the incisive foramen (AIIF), and the anterior nasal spine (ANS), were within 1-1.5mm of the CBML. The genial foramen (GF) and midline of the hyoid bone (HB) were within 1-1.5mm from the CBML. The tip of the spinous process of C2 (TPC2) was 2.5mm from the CBML (TPC2 mean absolute distance from the CBML 2.56mm, SD 2.24, raw CI(0.37,1.55)), and had a mean absolute distance of greater than 1.5mm from the CBML (Table 2).

There were no soft tissue midline points that were able to be used as markers of the CBML. Table 3 provides the mean absolute distance from the CBML, SD, percentages of times the measurements are to the left, coincident, and to the right of the CBML, median, absolute range, and absolute and raw CIs for the soft tissue midline markers. STN was the closest to the CBML, (STN mean absolute distance from the CBML 0.83mm, SD 0.8, raw CI(-0.32,0.1)).The MaMF was the most distant from the CBML(MaMF mean absolute distance from the CBML 1.25mm, SD 1.19, raw CI.(-0.7,-0.09)) . The MMF was 0.87mm from the CBML, (MMF mean absolute distance from the CBML 0.87mm, SD 0.84, raw CI (.34,0.09)). The soft tissue midline points which were immediately adjacent to skeletal midline points did not directly overlay the hard tissue points, and were often not to the same side of the CBML as the hard tissue points (Table 4).

The skeletal midline points were more reliable markers of the CBML than the soft tissue markers of the midline. The order of reliability as a marker of the CBML for all skeletal and soft tissue

midline points from the most rliable to the least reliable was FNS, PNS, TD, buccal maxillary midline suture (BMMS), AIIF, ANS, STN, MMF, IMP, SMP, MaMF, GF, HB, SPC2 .

Coincidence of the Maxillary and Mandibular Midline Frena with the Skeletal Midline Structures of the Maxilla and Mandible.

Table 5 compares the maxillary and mandibular midline frena with their associated skeletal midline points in the palate and mandible, and gives the mean absolute distance of the frenum from the skeletal midline point, SD, percentage of times the frenum is to the left, coincident, and to the right of the skeletal midline point, the median and absolute range of values, and the absolute and raw CIs for the distance of the maxillary and mandibular frenum from the skeletal midline point. BMMS was the only skeletal midline point of the maxilla that was within the 0.5mm needed to be accepted as coincident with the MMF (BMMS mean absolute distance from the MMF 0.49mm, SD 0.54, raw CI(-0.06,0.21)) . The AIIF, the ANS and the PNS were within 0.5-1mm from the maxillary midline frenum. The PNS was the most distant from the MMF (PNS mean absolute distance from the maxillary midline frenum0.92mm, SD 0.78, raw CI(-0.26,0.18)).

The MaMF was outside of the 0.5mm to the left or right of the GF taken as coincidence, with the midline of the mandible (MaMF mean distance from the GF 0.84mm, SD 0.83, raw CI (0.13,

0.54)). Therefore, the MaMF was not a reliable clinical indicator of the midline of the mandible under the parameters of this study, although the MaMF was closer to the CBML than the GF.

The MMF had similar distributions both on, and to either side of the BMMS. The AIIF, the ANS, and the PNS were more frequently to the left or right than coincident with the MMF. The MaMF was most often to the right of the GF (Table 5).

The Amount of Cranial Base, Facial and Upper Cervical Asymmetry and its Correlation with Midline Asymmetry.

There was asymmetry at every facial, cervical, and cranial base measurement point. There were no cranial base or facial asymmetry measurements which were equal for any subject on the left and the right sides.

Table 6 gives measurements for the differences in the left and right measurements of cranial base and facial asymmetry from the CBML. These include the absolute mean distance from the CBML, SD, median, absolute range, the percentages of time the difference was to the left or

right of the CBML, and the absolute and raw CIs for the differences in the distance from the CBML. There were no measurements for which the measurements of cranial base and facial asymmetry were equal.

All of the absolute means of the difference between the left and right measurements of cranial base and upper cervical asymmetry, and most of the facial asymmetry measurements were within 0- 2mm of the CBML. Facial asymmetry measurements that had absolute means that were within 2-3mm of the CBML were the difference in the distance on the left and right from the CBML to the palatal alveolar crest at the level of the incisive foramen (DPCIF), the difference in the distance on the left and right from the CBML to the lateral surface of the mandible at the level of the genial foramen (DLSGF), the difference in the distance on the left and right from the CBML to the angle of the coronoid process at the level of pogonion (DACP), the difference in the distance on the left and right from the CBML to the lateral surface of the skull at the level of the FNS (DLSFNS). The difference in the distance on the left and right from the CBML to the lateral surface of the skull at the level of the ANS, and the difference in the distance on the left and right from the CBML to the lateral surface of the skull at the level of basion (DLSB), the difference in the distance on the left and right from the CBML to the medial aspect of the external wall of the eye socket at the level of the hypophyseal fossa (DEWE), and DLSFNS were to the right of the CBML on average. The difference in the distance on the left and right from the CBML to the distal aspect of the optic canals (DDOC), the difference in the distance on the left and right from

the CBML to the tip of the transverse process of C1 (DTPC1), DLSGF, DLSIIF, and DACP, were to the left of the CBML on average.

In general there was statistically significant strong correlation between asymmetry of the various skeletal midline facial elements (Table 7). There was no statistically significant correlation between any skeletal or soft tissue facial midline points and TD, or the midline position of the spinous process of C2 (SPC2). However there was no statistically significant correlation between the skeletal midline structures FNS, and PNS ($r= 0.080$, $p >0.05$).

Statistically significant strong correlations existed for the distance to the CBML from ANS with BMMS ($r=0.710$, $p<0.001$), and AIIF($r=0.730$,$p<0.001$). There was also a statistically significant strong correlation between the distance to the CBML of BMMS and AIIF ($r=0.891$,$p<0.001$).

Moderate significant positive correlations existed between the distance to the CBML of GF and the following skeletal midline structures (Table 7): BMMS ($r=0.425$,$p<0.001$), AIIF ($r=0.454$,$p<0.001$), and HB ($r=0.617$,$p<0.001$).

The soft tissue midline structures had strong positive correlations with each other (Table 8), with the exception of the MaMF with STN, which were weakly correlated ($r=0.263$,$p<0.01$).

Statistically significant strong positive correlations existed between the distance to the CBML from MMF and the following skeletal midline structures (Table 8); ANS($r=0.703, p<0.001$), BMMS ($r=0.800, p<0.001$), and AIIF ($r=0.731, p<0.001$). A statistically significant strong positive correlation existed between the distance to the CBML from GF and MaMF ($r=0.779, p<0.001$).

Moderate statistically significant positive correlations existed between the distance to the CBML from the MaMF and the following skeletal midline structures; ANS ($r= 0.500, p<0.001$), BMMS ($r=0.486, p<0.001$), and AIIF ($r=0.494, p<0.001$).

There was little correlation between the distance to the CBML from hard or soft tissue midline structures and the left and right differences in cranial base measurements to the CBML (Table 10). There was mild significant negative correlation between the vertical asymmetry at the sphenoid sinus (VASS) and GF ($r= -0.245$, $p <0.01$), ANS ($r=-0.182, p<0.05$),PNS ($r=-0.180, p<0.05$), MMF ($r=-0.199, p<0.05$), and MaMF ($r=-0.240, p<0.01$).There was no statistically significant correlation between the vertical discrepancy at the pterygoid plates (VDPP) and any skeletal midline points. There was mild negative statistical significance between VDPP and MaMF ($r=-0.212, p<0.05$).

There were no significant correlations between the difference in the distance on the left and right from the CBML to the medial aspect of the medial pterygoid plates (DMMP) or the difference in

the distance on the left and right from the CBML to the distal aspect of the distal pterygoid plates (DDDP) and any of the soft tissue midline points. There was moderate significant positive correlation between the distance to the CBML from PNS and DMMP ($r=0.410, p<0.001$) and DDDP ($r=0.342, p<0.001$) to the CBML. There was no significant correlation between GF and DMMP ($r=0.069, p>0.05$), or DDDP ($r=0.043, p>0.05$).

There were many facial asymmetry measurements that had significant correlations with midline skeletal and soft tissue points (Tables 11, 12). The difference in the distance on the left and right from the CBML to the palatal alveolar crest at the level of PNS (DPCPNS), the difference in the distance on the left and right from the CBML to the medial aspect of the lacrimal foramen (DMLF), DLSIIF, DLSGF, DPCIIF, and DACP had the most significant correlations with the midline skeletal and soft tissue points. DACP had significant moderate positive correlation with BMMS ($r=0.397, p< 0.001$), and AIIF ($r = 0.409, p<0.001$), and weak significant correlation with ANS ($r=0 .281, p<0.01$), and GF($r=0 .297, p <0.01$). GF had moderate positive correlations with the frenal deviation (FD), ($r=0 .559, p< 0.001$), and strong correlation with the skeletal midline deviation (SMD), ($r=0 .827, p< 0.001$).

There were only a few measurements with significant correlation between the differences between the left and right sides of facial measurements and cervical midline points (Table 11).

The Amount of Rotational Asymmetry and its Correlation with Midline Asymmetry

Rotational asymmetry was present at most measurements. Table 13 gives values for absolute mean, SD, median, absolute range, percentage rotated to the left, percentage with no rotation, percentage rotated to the right, and absolute and raw CIs. SPC2 was most often rotated to the left of the CBML in an axial view with the teeth together and natural head posture (mean absolute value for rotation from the CBML 4.44 degrees, SD3.65 degrees, raw CI.(0.54,2.55)). A negative value was given if the spinous process was rotated to the left of the CBML. A positive value was given if SPC2 was rotated to the right of the CBML.

FNS had mild statistically significant correlation with the difference in the angular measurements on the left and right of the inferior surface of the occiptial condyles (DAIOC), ($r=0.221, p<0.05$). There were no other significant correlations between the hard or soft tissue midline markers of the face and any of the rotational measurements taken (Table 14). There were some significant correlations among the rotational measurements, and the cervical midline measurements TD and SPC2.

Correlation of Facial and Cervical Asymmetry with Cranial Base Asymmetry

There were no anatomic points for which the absolute values of the differences in the measurements between the left and right sides were significantly correlated with all other points.

Only a few significant correlations were found between cervical and cranial base asymmetry (Table 15).

In general the level of correlation between the elements of lateral cranial base asymmetry was poor. DMMP and DDDP had correlations with all measurements of lateral cranial base asymmetry except for the difference in the distance on the left and right from the CBML to the inferomedial aspect of the occipital condyles (DIMOC), which had no correlations with any other cranial base or facial asymmetry measurement, and a few mildly significant correlations with cervical asymmetry (Table15).

The correlations between DMMP and DDDP with other measurements of lateral cranial base asymmetry were similar. Mild statistically significant correlations existed for both DMMP ($r=0.338, p<0.001$))and DDDP ($r=0.322, p<0.001$) and the difference in the distance on the left and right from the CBML to the base of the styloid process (DBS). There were mild statistically significant correlations between DDOC and DMMP ($r=0.240, p<0.01$) and DDDP

($r=0.283, p<0.01$). There was moderate statistically significant positive correlation ($r=0.471$ $p< 0.001$) between DMMP and DDDP (Table 15).

VASS had weak significant positive correlation with VDPP (r=0.363, p< 0.001). There was mild statistically significant correlation between VDPP and DMMP (r=0.388,p<0.001), but not DDDP (r=-0.044,p>0.05), or any other measures of cranial base asymmetry (Table 15).

DMMP and DDDP were the cranial base asymmetry measurements that had the most number of significant correlations with facial asymmetry. The correlations between differences in lateral facial asymmetry measurements and DMMP (Table 16), included moderate significant positive correlations with the difference in the distance on the left and right from the medial poles of the mandibular condyles (DMMC), (r=0.482,p< 0.001), and DLSIIF(r=0.427,p<0.001). DDDP had weak correlation with DMMC (r=0.366,p<0.001).

VDPP had mild statistically significant correlations to facial asymmetry measurements (Table 16), DLSANS (r=0.275,p<0.01), and DLSB (r=0.183,p<0.05).There was no statistically significant correlation between VDPP and DPCIF (r=0.058,p>0.05), or DPCPNS (r=0.042,p>0.05), or DSGF (r=0.001,p>0.05).

Facial asymmetry measurements that had weak statistically significant correlations with VASS (table 16) included; DLSFNS(r=0.286,p<0.01), DPCIF(r=-0.259,p<0.01), DLSB(r=0.185,p<0.05), and DLSGF(r=-0.181,p<0.05). There was no statistically significant correlation between VASS and DMMC (r=0.109,p>0.05), or DACP (r=-0.074,p>0.05).

In general there was good correlation of facial asymmetry values (Table 17). The measurements involving the maxilla, DLSANS, DLSIIF, DPCIF, and DPSPNS, had good general levels of correlation with other facial asymmetry measurements.

DACP had no significant correlations with any cranial base asymmetries (Table 16), but was significantly positively correlated with several measurements of facial asymmetry (table 17), including moderate correlations with DLSIIF ($r=0.486, p< 0.001$); and DLSGF($r=0.515$, $p< 0.001$). There were mild correlations with DPCIF ($r=0.389, p< 0.001$), DPCPNS ($r=0.237$ $p<0.01$), DLSANS ($r=0.354$, $p< 0.001$), and DMLF($r=0.365$, $p< 0.001$).

SMD (Table 17), had moderate statistically significant correlation with DLSGF($r=0.471, p<0.001$), and weak statistically significant negative correlation with DLSFNS($r=-0.209, p<0.05$), and DSMC ($r=-0.208, p<0.05$).

Discussion

We found that there was no coincidence of any soft tissue midline point with the CBML. Eskelsen et al[15] and Bidra[335] have investigated the coincidence of facial midline points with the facial midline. Eskelsen et al [15] found that the interpupillary distance was not coincident with the dental midline. Bidra et al[335] found that the ascending order of deviation of soft tissue landmarks from the facial midline during smile was the midline of the oral commisures, the dental midline, tip of philtrum, nasion and the tip of the nose. Both studies agree with our finding that there is no coincidence of the soft tissue midline features with the facial midline. Bidra et al[335] excluded subjects with obvious asymmetry, and used a soft tissue based midline reference plane, which may explain minor differences in our results.

The FNS and PNS were the only 2 skeletal midline points within the 0.5mm taken as coincident with the CBML in this study. Neither BMMS, nor AIIF were reliable markers of the CBML. There was no correlation between the midline positions of FNS, and PNS. The posterior palatal area is subject to different genetic [336-338] and transcriptional[339] factors than the anterior palatal region. This may account for the slight differences in midline coincidence between the anterior and posterior palatal midline skeletal points. It may be that both the FNS and the PNS can be used as markers of the CBML, but are subject to different growth processes due to their position in the facial skeleton[340]. FNS is closest to the cranial base, but is subject to environmental

[341,342]and endogenous growth modifiers [340].The PNS may not have as many myofunctional and airway related factors affecting its growth as the other skeletal midline points of the palate[61, 62, 64, 91, 94, 215, 343-345].

Our results show that the various soft tissue and skeletal midline points have different distributions around the CBML. STN, BMMS, and MMF, were distributed evenly on and to the left and right of the CBML, in this study population. The GF, MaMF, and the HB were most often to the left of the CBML. Most studies on facial asymmetry describe left or right facial dominance, and have found that the mandible is a defining asymmetric facial feature[346, 347,316,348], and is most often deviated to the left side[347, 349, 350], which is in agreeance with our results for the position of the GF, MaMf and the HB. Ferrario[290], Song [348]and Haraguchi[346, 347] reported right sided facial dominance in photographic studies, whereas we found that the underlying skeletal lateral asymmetries are mixed to the left and right in agreement with the CT study done by Kwon et al[317]. Reasons for the contrast in findings may be the differences in midline symmetry which we found between the soft tissue and skeletal midline points, the generally minor nature of the facial asymmetry in a general population, and the differences in reference midline planes used in each study. A visual facial plane does not reference underlying skeletal asymmetries unless those asymmetries are severe enough to be visually noticeable.

The literature supports a close relationship between the growth, anatomy and function of the face and cervical spine[387, 211, 258, 259, 261, 263, 264, 351-353]. TD and SPC2 were most often to the right of the

CBML, and GF was most often to the left of the CBML. We found no correlation between the skeletal cervical and facial midline points, including SPC2 and GF. This lack of correlation is in agreement with Korbmacher et al [245] who found no correlation between laterality of occlusion and cervical elements. It is possible that the lack of correlations between midline elements of the upper cervical and facial skeleton reflects changes that have occurred in the cervical spine related to trauma, as well as functional discrepancies after growth of the cervical and facial structures have been completed.

SPC2 was the only skeletal midline point which was more than 1.5mm from the CBML. There is very little in the literature about the normal range of the neutral relationship between C1 and C2 and the skull. It may be that the rotations that we measured in the cervical spine are due to ligament laxity [275, 354, 355], and are normal variations of C1 and C2 position, or they may also be the result of head tilts and rotations that exist in the population, and were not corrected because of our use of natural head posture. It would be helpful if future research included palpation of the cervical spine in the C1, C2 area for prominent or tender facet joints prior to taking a CBCT scan. Korbmacher et al [245] found high levels of agreement between palpation and radiographic findings in the upper cervical spine. Although we were measuring lateral asymmetry, the actual cervical asymmetry is a complex 3 dimensional change in relationship, and so our study does not provide a complete description of the change in cervical relationships.

Sakaguchi et al[7] and Ceneviz et al[8] have used the frenal midlines as indicators of the facial midline in studies on electromyographic, posture, or gait changes. The frenal midline has been used as a marker of facial midline in many facets of dentistry [10, 297, 299,356] . Fu et al [6] found that when the frenal midline discrepancy approaches 0.5mm there is relief of the symptoms of temporomandibular disorders during treatment with a flat plane appliance. Our study showed that there is no reliable soft tissue marker of the CBML. It may be that coincidence with the CBML is not a clinical requirement for successful treatment of temporomandibular disorders. It is possible that alignment of soft tissue structures has more relevance to the successful outcome of therapy for TMD than the position of the skeletal structures. It may be that the soft tissue midlines do not accurately reflect the underlying skeletal midlines, as the MaMF was shown not to be a reliable indicator of the mandibular midline in the present study. In our study population there were individuals who demonstrated more asymmetry than others. For those individuals who had less asymmetry, the midline frena may well be acceptable markers of the maxillary and mandibular midlines. It may be that the clinician will still need to make a clinical decision about whether they are dealing with a symmetric or asymmetric individual, and give the soft tissue markers the appropriate weight as midline markers based on that decision.

This study population was predominantly female and Caucasian. This reflects the location of the study, that females are more prevalent in the general dental population [357-360], and that part of the inclusion criteria was the ability to visualize all of the required skeletal and soft tissue points. Although females suffer from TMD more frequently than males [361-363], the rate of disc displacement in the general population is 30- 70%[142-145, 364, 365]. It is not certain if the female

predominance of the study has affected our results, and more studies would need to be done using CBCT to ascertain the differences caused by ethnicity, gender, and other temporomandibular disorder types on facial and midline asymmetry, as disc displacement is known to affect condylar, maxillary , mandibular and cranial base growth [137-140]. Although Visual analogue scale, Routine Diagnostic Criteria for Temporomandibular Disorders, sleep hypiene and Epworth Scale of Daytime Tiredness data were all collected, these were not analysed as part of this study.

The medial and lateral pterygoid muscles are thought to be related to the midline positioning of the mandible[191, 192, 196, 198, 206, 238, 366, 367], and increase their activity during lateral mandibular movements [208, 209]. As both muscles have attachments to the lateral pterygoid plate, it was reasonable to expect that there would be some correlations between the midline positions of the medial and lateral pterygoid plates, and the genial foramen of the mandible. Matsunaga et al [368]found that the part of the lateral pterygoid muscle that arises from the anterior part of the pterygoid plates inserts into the pterygoid fovea, and those from the posterior part insert into the medial of the condyle. The lateral pterygoid muscle attaches to the medial aspect of the condylar disc in 30% of cases [204, 369], and may affect medial condylar position by acting on the disc or directly on the condyle. Cases with insertion into the disc were found by MRI to be more likely to have disc displacement without reduction [370]. The discal and medial condylar attachments of the lateral pterygoid muscles inserting in the area that we were measuring may explain the moderate correlations that we found between DMMC, DDDP and DMMP.

We found moderate correlations between DDDP, DMMP, and PNS, which could be expected because of the close anatomical connection of the pterygoid plates to the posterior part of the maxilla. The lack of correlation between the lateral and medial pterygoid plates, GF, and MaMF may reflect compensation in mandibular growth and position, and muscle force or attachment that is not reflected in the skeletal relationship. The muscles may compensate for asymmetrical skeletal development [179,175, 371, 372,189]. CBCT measures skeletal anatomic points, but tells us nothing directly about the size of the muscles atttached to those points or the forces they exert. The measurement of muscle activity or size of the muscles was beyond the scope of this study.

There were multiple weak negative correlations between the vertical discrepancy of pneumatisation of the sphenoid sinus and skeletal and soft tissue midline points, including ANS, PNS, GF, MMF and MaMF. Due to the numbers of structures involved, it is likely that there may be a relationship between sphenoid sinus pneumatisation and midline asymmetry of the face. It is not necessary that the relationship exclusively involves vertical pneumatisation of the sinus, as pneumatisation occurs in many directions throughout the sphenoid bone, and can extend into the maxillary sinus [373], the anterior clinoid process, and the pterygoid plates [374]. This may account for the weak nature of the correlations, as we measured only the vertical aspect of sphenoid sinus pneumatisation at a specific point.

Sphenoid sinus pneumatisation is often asymmetric [375,374] and may become arrested for as yet unknown reasons [376] . Pneumatisation of the sphenoid bone occurs after birth[377], and was once

thought to peak during adolescence[376], but is now thought to continue until the third decade, and then decrease to 71% of its maximum volume around 70 years of age [378]. The pneumatisation of the pterygoid plates of the sphenoid bone may occur after closure of the spheno-occipital synchondrosis [378]. Very little is known about sinus pneumatisation. It may be related to local changes in blood supply [376], but there is evidence that it is responsive to climatic influences [341, 379] there is some doubt as to whether masticatory forces are involved [380].

The cranial base has been shown to be asymmetric [317, 381, 382]. The pterygoid plates have been observed to be a coordinating feature of the cranial base[383] which may be partly due to their placement in the centre of the cranial base. The central placement of the pterygoid plates may explain their correlation with our other measurements of cranial base asymmetry. Kwon et al[317] did not find a relationship between facial asymmetry and cranial base asymmetry, whereas other studies have found a relationship between facial and cranial base anatomy[384,385-387], and especially between lateral cranial base and facial anatomy[74, 388]. The conclusions of Kwon et al were based on their findings that both their normal and asymmetric study populations had similar cranial base symmetry. Our population was not graded by asymmetry. Cranial base and facial asymmetry were common findings, and they were correlated with general facial asymmetries. There was little correlation between cranial base and midline asymmetry.

The cranial base positions chosen for measurements of asymmetry are situated on the periphery of the cranial base. The lateral positioning of these points may account for the lack of correlation

observed between them in this study, especially if the multi-modular theory of growth between the face and the cranial base is correct [389-391]. A module is a growth unit with strong relationships of growth among its components[391], similar to the concept of functional matrices[56, 60, 66, 67, 392, 393]. Given the limits of what can be concluded from a study of linear measurements, our results may be consistent with the concept of modular growth, as multiple correlations between midline and lateral asymmetry were found for certain anatomical features such as the angle of the coronoid process, vertical pneumatisation of the sphenoid sinus, and the pterygoid plates, with elements of the palate. These elements are all situated in the middle area of the skull. More research needs to be done to detail the nature of the modules, and exactly how they interact during the growth of an individual. It is likely that if modules exist, they overlap, and have complex interactions with other modules as the structures of the face grow as an integrated unit. Structures that are closer together are likely to have a greater reciprocal influence on growth than more distant structures.

In summary, there were elements of our results that showed many correlations and others which showed fewer than may have been expected in a closed system with an integrated pattern of growth such as the facial and cervical structures. Some of the reasons for lack of correlation, or a correlation that was not as strong as expected may be

1. In adult subjects the relationships that are established during growth may be altered during aging by factors such as positional changes in the cervical structures, and the continued effects of differing environmental inputs.

2. A continued close relationship may be defined by anatomical proximity, interactions and differences in functional forces between areas, and systemic and metabolic growth issues.

3. We were measuring only a two-dimensional aspect of a complex three-dimensional relationship. A simple lateral midline mesasurement does not necessarily define the most important aspect of the spatial relationships that exists between structures, so that a lack of correlation of midline or lateral asymmetry measurements does not mean that a relationship does not exist between structures.

4. We had no way of determining the direction or magnitude of the muscular forces acting on the measured points for each individual. These may have either compensated for, or caused some of the asymmetry that existed.

Several factors may have influenced outcomes of this study which can be improved on in future work. This study was done on a general population of consecutive patients. Our study population heavily favored female Caucasian subjects. We did not categorize these subjects into a symptomatic versus a non-symptomatic group to determine if any differences in asymmetry between the 2 groups exist. Although participants in the study completed VAS forms for orofacial pain and the Routine Diagnostic Criteria for Temporomandibular Disorder, this information was not analysed as part of this study. Similarly, we did not classify our population into those who required orthodontic therapy for malocclusion and those who did not. It can be reasonably expected that those who have a malocclusion may have more asymmetry than those who don’t.

We did not classify our population by levels of asymmetry. It is likely that the soft tissue markers will be more reliable as markers of the midline in more symmetric individuals. We did not measure muscle activity in the masticatory and cervical muscles, and so could not relate that to our results. We also did not palpate the cervical spine in a neutral position before taking the CBCT scan, and have no baseline for comparison with our findings of cervical rotation. The large numbers of correlations involved in this study means that at least some of them will have occurred by chance.

Future work could target populations differing by sex, ethnicity, symptoms and malocclusion to see whether there are differences in the levels of asymmetry found on CBCT scans. Alterations to skeletal and soft tissue midline, and general asymmetry during orthodontic therapy and splint therapy for temporomandibular disorder could be investigated, especially in relation to the finishing positions of the maxillary and mandibular midline frena, and activity in the masticatory and cervical muscles.

More investigation is needed into the relationship between the paranasal sinuses and facial growth and symmetry. Particular attention could be given to the interaction between the sphenoid sinus in normalcy and disease, and the pterygoid plates at different stages of growth and conditions of dentition including disc displacement, parafunction, and edentulousness.

Conclusions

In a nonsyndromic, predominantly female, general dental population, FNS and PNS were within 0.5mm of the CBML, and were the only skeletal markers of the CBML. There were no soft tissue midline points that were within the 0.5mm of the CBML needed to be considered coincident with the CBML.

The order of distance from the CBML for all skeletal and soft tissue midline points was FNS, PNS, TD, BMMS, AIIF, ANS, STN, MMF, IMP, SMP, MaMF, GF, HB, and SPC2. BMMS was the only skeletal midline point of the palate coincident with the MMF. GF was not coincident with the MaMF.

The cervical midline points had no correlations with any facial skeletal or soft tissue midline point. The degree of correlation was largely dependent on the proximity of the structures.

In general there was poor correlation between skeletal and soft tissue midline points and cranial base asymmetry. VASS had mild correlations with several skeletal and soft tissue midline points. There were no facial points that had strong correlations with skeletal and soft tissue midline points. There was no correlation between the medial or lateral pterygoid plates and GF or any

soft tissue midline points. There was mild correlation between DMMC and DDDP, and moderate correlation between DMMC and DDDP.

Mild to moderate correlations existed between cervical midline points and the cervical rotational values. In general the level of correlation between midline and rotational values was low. The spinous process of C2 was most often rotated from the CBML.

There were a number of mild correlations between cranial base and facial asymmetry. These were most common between the medial and lateral pterygoid plates and facial measurement points. Most pterygoid plate correlations were with midface or palatal measurements.

The maxillary midline frenum may be an acceptable indicator of the CBML in more symmetric individuals. Absolute alignment of the skeletal structures may not be a clinical requirement for obtaining the correctly midlined bite.

Table 1

Study Population Demographics

	Number (%) Total = 120
Sex	
Female	87 (72.5)
Male	33 (27.5)
Ethnicity	
Caucasian	113 (94.2)
Asian	3 (2.5)
Indian	1 (0.8)
Polynesian	3 (2.5)
Age	
Range	22-72
Mean (SD)	43.38 (12.31)

Table 2

Descriptive Statistics for the Relationship of the CBML and Skeletal Midline Points

	Absolute Values			Raw Values			
	[2]Mean(SD)	Range	95% C.I.	95% C.I	(%) to the Left of CBML	(%) on the CBML	(%) to the Right of CBML
FNS[1]	0.22(0.38)	0-1.95	(0.15,0.28)	(-0.06,0.10)	13	70	17
ANS	0.78(0.84)	0-3.25	(0.63,0.94)	(-0.35,0.06)	33	40	27
BMMS	0.66(0.69)	0-2.68	(0.53,0.79)	(-0.37,-0.03)	36	36	28
AIIF	0.71(0.69)	0-2.45	(0.58,0.83)	(-0.30.050)	36	35	29
PNS	0.32(0.46)	0-1.69	(0.23,0.40)	(-0.180.020)	23	62	15
GF	1.31(1.34)	0-6.44	(1.06,1.55)	(-1.04-0.41)	53	28	19
HB	1.47(1.45)	0-6.92	(1.21,1.73)	(-0.96,-0.25)	47	23	30
TD	0.63(0.62)	0-2.39	(0.52,0.74)	(0.12,0.42)	19	36	45
SPC2	2.56(2.24)	0-11.3	(2.15,2.96)	(0.37,1.55)	37	13	50

[1]For explanation of abbreviations see Appendix 16

[2] Measurements are given in millimeters

Table 3

Descriptive Statistics for the Relationship of the CBML and Soft Tissue Midline Points

	Absolute Values				Raw Values			
	[2]Mean(SD)	Median	Range	95% C.I.	95%C.I.	% to the Left of CBML	% on the CBML	% to the right of CBML
MMF[1]	0.87(0.84)	0.71	0-3.18	(0.71,1.02)	(-0.34,0.09)	37	34	29
MaMF	1.25(1.19)	0.95	0-6.17	(1.04,1.47)	(-0.7,-0.09)	48	20	32
STN	0.83(0.8)	0.71	0-4.92	(0.68,0.97)	(-0.32,0.10)	41	23	36
SMP	1.21(1.04)	0.96	0-3.93	(1.02,1.40)	(-0.69,-0.13)	48	22	30
IMP	1.20(1.24)	0.85	0-6.92	(0.98,1.43)	(-0.81,-0.21)	49	23	28

[1]For explanation of abbreviations see Appendix 16

[2] Measurements are given in millimeters

Table 4

Descriptive Statistics for the Relationship of the Adjacent Skeletal and Soft Tissue Midline Points to the CBML

Absolute Values			Raw Values			
Hard Tissue and Adjacent Soft Tissue Midline Point	[2]Mean(SD)	95%C.I.	95% C.I.	% to the Left of CBML	% on the CBML	% to the Right of CBML
FNS[1]	0.22(0.38)	(0.15,0.28)	(-0.06,0.10)	13	70	17
STN	0.83(0.80)	(0.68,0.97)	(-0.32,0.10)	41	23	36
ANS	0.78(0.84)	(0.63,0.94)	(-0.35.0.06)	33	40	27
SMP	1.21(1.04)	(1.02,1.40)	(-0.69,-0.13)	48	22	30
BMMS	0.66(0.69)	(0.53,0.79)	(-0.37,-0.03)	36	36	28
MMF	0.87(0.84)	(0.71,1.02)	(-0.34,0.09)	37	34	29
GF	1.31(1.34	(1.06,1.55)	(-1.04,0.41)	53	28	19
MaMF	1.25(1.19))	(1.04,1.47)	(-0.70,-0.09)	48	20	32

[1]For explanation of abbreviations see Appendix 16

[2] Measurements are given in millimeters

Table 5

Descriptive Statistics for the Coincidence of Hard and Soft Tissue Midline Points of the Maxilla and Mandible with the Maxillary and Mandibular Midline Frena

	Absolute Values				Raw Values			
Skeletal Midline Point and Associated Frenum	[2]Mean(SD)	Median	Range	95% C.I.	95% C.I.	% Frenum to the Left	% Frenum coincident	% Frenum to the right
[1]**BMMS-MMF**	0.49(0.54)	0.45	0-2.45	(0.39,0.59)	(-0.06,0.21)	37	28	35
ANS-MMF	0.67(0.61)	0.49	0-2.45	(0.55,0.78)	(-0.14,0.19)	40	22	38
AIIF-MMF	0.56(0.6)	0.45	0-2.45	(0.46,0.67)	(-0.15,0.15)	38	25	37
PNS-MMF	0.92(0.78)	0.73	0-4.38	(0.78,1.06)	(-0.26,0.18)	41	21	38
GF-MaMF	0.84(0.83)	0.71	0-5.9	(0.69,0.99)	(0.13,0.54)	31	11	58

[1]For explanation of abbreviations see Appendix 16

[2] Measurements are given in millimeters

Table 6

Descriptive Statistics for Cranial Base and Facial Asymmetry Relative to the CBML

		Absolute Values				Raw Values		
		[2]Mean(SD)	Median	Range	95% C.I.	95% C.I.	% to the Left of CBML	% to the Right of CBML
Cranial Base Asymmetry	**[1]DDOC**	1.69(1.26)	1.46	7.93	(1.46,1.92)	(-1.18,-0.48)	70	30
	DIMOC	1.09(0.86)	0.91	4.01	(0.94,1.25)	(-0.32,0.16)	51	49
	DBS	1.84(1.45)	1.53	7.38	(1.58,2.10)	(-0.13,0.55)	46	54
	DMMP	1.23(0.99)	1.01	5.02	(1.05,1.41)	(-0.31,0.27)	52	48
	DDDP	1.53(1.15)	1.37	6.1	(1.32,1.74)	(-0.43,0.26)	48	52
Facial Asymmetry	**DEWE**	1.14(1.16)	0.85	0.060-9.95	(0.93,1.35)	(0.05,0.63)	42	58
	DLSFNS	2.58(1.82)	2.38	8.12	(2.25,2.91)	(0.68,1.74)	34	66
	DLSANS	1.72(1.28)	1.5	6.07	(1.48,1.95)	(0.12,0.88)	45	55
	DLSIIF	1.8(1.31)	1.56	6.67	(1.56,2.04)	(-0.77,0.02)	54	46
	DLSB	1.81(1.66)	1.39	8.3	(1.51,2.11)	(0.53,1.35)	38	62
	DLSGF	2.38(1.94)	1.87	9.64	(2.03,2.73)	(-1.15,-0.05)	58	42
	DPCIF	2.07(1.87)	1.64	12.39	(1.73,2.41)	(-1.18,-0.20)	58	42
	DPCPNS	1.9(1.39)	1.72	8.1	(1.65,2.15)	(-0.80,0.04)	55	45
	DMLF	1.11(0.84)	0.98	3.75	(0.96,1.26)	(-0.37,0.13)	49	51
	DMMC	1.65(1.17)	1.41	4.89	(1.43,1.86)	(-0.15,0.57)	44	56
	DSMC	1.93(1.60)	1.59	8.82	(1.64,2.22)	(-0.43,0.48)	48	52
	DACP	2.1(1.82)	1.66	11.53	(1.77,2.42)	(-0.99,-5.55)	54	46
	DTPC1	1.94(1.66)	1.53	10.14	(1.64,2.24)	(0.44,1.31)	35	65
	DIMC1	1.89(1.47)	1.44	6.94	(1.63,2.16)	(0.23,1.07)	39	61

[1]For explanations of abbreviations please see Appendix 16
[2]Measurements are given in millimeters

Table 7

Correlation Coefficients for the Relationships between Skeletal Midline Structures

	ANS	BMMS	AIIF	PNS	GF	H	TD	SPC2
[1]FNS	0.309**	0.184*	0.228*	0.080	0.200*	0.059	0.107	-0.012
ANS		0.710***	0.730***	0.254**	0.378***	0.259**	-0.040	0.006
BMMS			0.891***	0.317***	0.425***	0.351***	-.006	-.011
AIIF				0.391***	0.454***	0.385***	0.002	-0.017
PNS					0.271**	0.284**	0.164	-0.086
GF						0.647***	0.025	0.111
H							0.101	0.124
TD								0.128

*p<0.05
**p<0.01
***p<0.001
[1]For explanation of abbreviations see Appendix 16

Table 8

Correlation Coefficients for the Relationships of the Soft Tissue Midline Structures

	[1]MaMF	STN	SMP	IMP
MMF	0.531***	0.422***	0.669***	0.633***
MaMF		0.263**	0.476***	0.534***
STN			0.519***	0.426***
SMP				0.753***

**p<0.01
***p<0.001
[1]For explanation of abbreviations see Appendix 16

Table 9

Correlation Coefficients for the Relationships of the Skeletal and Soft Tissue Midline Structures

	[1]FNS	ANS	BMMS	AIIF	PNS	GF	H	TD	SPC2
MMF	0.184*	0.703***	0.800**	0.713***	0.216*	0.402***	0.327***	-0.040	0.086
MaMF	0.216*	0.500***	0.486***	0.494***	0.193*	0.779***	0.384***	0.016	0.175
STN	0.531***	0.488***	0.305**	0.311**	0.018	0.181*	-0.016	0.026	0.047
SMP	0.362***	0.692***	0.565***	0.577***	0.102	0.385***	0.181*	-0.063	0.009
IMP	0.283**	0.631***	0.593***	0.532***	0.061	0.471***	0.218*	-0.056	0.157

*p<0.05
**p<0.01
***p<0.001
[1]For explanation of abbreviations see Appendix 16

Table 10

Correlation Coefficients for the Relationships of Cranial Base Asymmetry and Skeletal and Soft Tissue Midline Points

	[1]DDOC	DIMOC	DBS	DMMP	DDDP	VDPP	VASS
FNS	-0.016	-0.016	-0.077	-0.058	0.164	-0.149	-0.045
ANS	-0.185	-0.018	0.008	0.191*	0.138	0.006	-0.182*
BMMS	-0.093	-0.118	0.061	0.172	0.183*	-0.011	-0.178
AIIF	-0.042	-0.057	0.141	0.231*	0.176	-0.052	-0.157
PNS	-0.009	0.009	0.269**	0.410***	0.342***	-1.116	-0.180*
GF	-0.081	0.065	0.001	0.069	0.043	-0.176	-0.245**
H	-0.056	0.073	0.125	0.110	0.089	-0.010	--0.144
TD	-0.073	0.191*	-0.014	-0.027	-0.011	-0.081	0.043
SPC2	-0.048	0.136	-0.097	-0.164	0.027	-0.178	-0.152
MMF	-0.246	-0.020	-0.019	0.124	0.110	-0.020	-0.199
MaMF	-0.116	-0.065	0.011	0.048	0.049	-0.212*	-0.240**
STN	-0.165	-0.042	-0.245*	-0.002	0.120	-0.009	-0.152
SMP	-0.167	0.012	-0.081	0.154	0.120	0.000	-0.066
IMP	-0.131	0.050	-0.133	0.076	0.139	-0.050	-0/110

*p<0.05
**p<0.01
***p<0.001
[1]For explanation of abbreviations see Appendix 16

Table 11

Correlation Coefficients for the Relationships of Facial Asymmetry and Skeletal Midline Points

	[1]FNS	ANS	BMMS	AIIF	PNS	GF	H	TD	SPC2
DEWE	0.324***	0.244**	0.185	0.307**	0.137	0.060	-0.067	0.038	-0.072
DLSFNS	-0.113	0.220*	-0.318***	-0.258**	-0.068	-0.132	-0.057	-0.093	0.055
DLSANS	-0.181*	0.251**	0.386***	0.385***	0.220*	0.003	0.140	0.079	-0.162
DLSIIF	0.180*	0.476***	0.569***	0.607***	0.430***	0.439***	0.448*	0.016	0.033
DLSB	0.212*	0.068	0.024	0.070	-0.017	-0.053	-0.019	0.007	-0.163
DLSGF	0.232*	0.394***	0.427***	0.433***	0.382***	0.613**	0.463***	0.049	0.107
DPCIF	0.129	0.585***	0.629***	0.653***	0.366***	0.379***	0.399***	-0.009	-0.089
DPCPNS	0.142	0.331***	0.385***	0.335***	0.377***	0.288**	0.257**	-0.033	0.135
DMLF	0.397***	0.491***	0.546***	0.563***	0.367***	0.264**	0.228*	-0.059	-0.048
DMMC	-0.031	-0.036	-0.018	0.012	0.335***	-0.011	-0.005	-0.109	-0.110
DSMC	0.112	0.103	0.070	0.070	0.105	-0.156	-0.177	0.272**	-0.074
DACP	-0.213*	0.2178**	0.409***	0.409***	0.000	0.292**	0.139	0.019	0.052
DTPC1	-0.013	0.005	0.100	0.079	0.140	0.085	0.198*	0.530***	0.170
DIMC1	0.067	0.028	0.146	0.136	0.115	0.134	0.159	0.696***	0.307**
SMD	0.098	-0.005	-0.105	-0.010	0.125	0.827***	0.512***	0.003	0.111
FD	0.110	0.000	-0.069	-0.012	0.036	0.559***	0.173	0.051	0.130

*p<0.05 **p<0.01 ***p<0.001 [1]For explanation abbreviations see Appendix 16

Table 12

Correlation Coefficients for the Relationships of Facial Asymmetry and Soft Tissue Midline Points

	MMF	MaMF	STN	SMP	IMP
DEWE	0.169	0.070	0.377***	0.270**	0.098
DLSFNS	0.315**	-0.169	-0.268**	-0.233*	-0.255**
DLSANS	0.221*	0.054	0.064	0.199*	0.035
DLSIIF	0.516***	0.467***	0.176	0.415***	0.340***
DLSB	-0.055	-0.018	0.114	0.164	0.000
DLSGF	0.390***	0.586***	0.152	0.2197**	0.297
DPCIF	0.587***	0.461***	0.233*	0.436***	0.381***
DPCPNS	0.367***	0.247**	0.113	0.237**	0.175
DMLF	0.449***	0.297**	0.356***	0.305**	0.226*
DMMC	-0.108	-0.114	-0.172	-0.035	-0.107
DSMC	0.098	0.031	0.145	0.105	0.046
DACP	0.383***	0.383***	0.184*	0.240**	0.289**
DTPC1	0.076	0.081	-0.081	0.044	-0.017
DIMC1	0.103	0.108	-0.051	0.038	0.092
SMD	-0.028	0.563***	0.000	0.012	0.013
FD	-0.185*	0.722***	-0.033	0.028	0.117

*p<0.05 **p<0.01 ***p<0.001 [1]For explanation abbreviations see Appendix 16

Table 13

Descriptive Statistics for Rotational Values

	Absolute Values				Raw Values			
	[2]Mean(SD)	Median	Range	95%C.I.	95%C.I.	% to the Left of CBML	% on the CBML	% to the Right of CBML
[1]DAC	4.76(3.68)	4.00	0-14.30	(4.10,5.43)	(0.07,2.22)	41*	2	57
DAIOC	6.46(4.79)	5.50	0-24.80	(5.59,7.32)	(-4.31,-1.59)	65	1	34
DAIC1	3.75(3.09)	3.00	0.10-14.90	(3.19,4.31)	(-1.40,0.35)	52	0	48
ATTPC1	1.97(1.67)	1.9	7.4	(1.66,2.27)	(-0.26,0.67)	42	42	26
AMC2	4.44(3.68)	3.35	17.7	(3.78,5.10)	(0.54,2.55)	39	8	53

*A value of n/a indicates that the measurement did not have a left/right direction, and so did not have negative and positive values, or raw values.
[1]For explanation of abbreviations see Appendix 16
[2]Measurements are given in millimeters

Table 14

Correlation Coefficients for the Relationships of Skeletal and Soft tissue Midline Points and Rotational Values

	DAC	DAIOC	DAIC1	ATTPC1	AMC2
[1]FNS	-0.156	0.221*	-0.073	0.017	-0.047
ANS	-0.075	0.046	-0.163	-0.092	0.054
BMMS	-0.053	0.088	-0.077	0.043	0.082
AIIF	-0.055	0.049	-0.026	0.060	-0.011
PNS	0.115	-0.066	-0.156	-0.094	-0.100
GF	-0.032	0.107	-0.114	-0.095	0.060
H	-0.016	-0.017	-0.174	-0.106	0.109
TD	-0.133	0.327***	-0.460***	0.077	0.042
SPC2	0.099	0.103	-0.419***	-0.251**	0.761***
MMF	-0.073	-0.012	-0.055	-0.040	0.056
MaMF	-0.035	0.046	-0.067	-0.040	0.065
STN	-0.205*	0.112	-0.036	0.108	-0.049
SMP	-0.050	0.065	-0.027	0.054	-0.064
IMP	0.000	0.136	-0.165	-0.088	0.054

*p<0.05
**p<0.01
***p<0.001
[1]For explanation of abbreviations see Appendix 16

Table 15

Correlation Coefficients for the Relationships of Cranial Base and Cervical Asymmetry

	DIMOC	DBS	DMMP	DDDP	VDPP	VASS	[2]DTPC1	[2]DIMC1
[1]DDOC	-0.117	0.157	0.240**	0.283**	0.137	0.191*	-0.015	0.035
DIMOC		0.157	-0.015	-0.055	-0.149	-0.050	0.278**	0.255**
DBS			0.338***	0.322***	-0.013	0.052	0.244*	0.035
DMMP				0.388***	0.388***	0.143	0.166	0.046
DDDP					-0.044	0.109	0.143	0.096
VDPP						0.363***	-0.007	-0.049
VASS							-0.139	-0.101
[2]DTPC1								0.729***

[2] Cervical Asymmetry values
*p<0.05
**p<0.01
***p<0.001

[1]For explanation of abbreviations see Appendix 16

Table 16

Correlation Coefficients for the Relationships of Cranial Base, Cervical and Facial Asymmetry

	[1]VDPP	[1]VASS	[1]DDOC	[1]DIMOC	[1]DBS	[1]DMMP	[1]DDDP	[2]DTPC1	[2]DIMC1
[3]DEWE	0.059	0.057	0.151	-0.017	-0.039	0.180*	0.246**	0.077	-0.021
DLSFNS	0.136	0.286**	0.370**	-0.021	0.202*	0.095	0.016	0.011	-0.107
DLSANS	0.275**	0.131	0.130	-0.056	0.291**	0.365***	0.313**	0.142	0.056
DLSIIF	0.105	-0.156	-0.066	0.054	0.251**	0.427***	0.314***	0.166	0.136
DLSB	0.183*	0.185*	0.232*	-0.064	0.195	0.074	0.217*	-0.043	-0.107
DLSGF	0.001	-0.181*	-0.094	0.062	0.239**	0.309**	0.312**	0.259**	0.186*
DPCIF	0.058	-0.259**	-0.168	0.053	0.132	0.338***	0.227*	0.200*	0.143
DPCPNS	0.042	-0.146	-0.074	0.022	0.275**	0.397***	0.235**	0.199*	0.108
DMLF	-0.052	-0.101	-0.059	-0.119	0.068	0.209*	0.329***	0.060	0.043
DMMC	0.052	0.109	0.294**	0.008	0.569***	0.482***	0.366***	0.087	-0.023
DSMC	-0.012	0.008	-0.012	0.067	0.008	0.152	0.150	0.138	0.198*
DACP	0.126	-0.074	0.048	-0.035	0.047	0.136	0.047	0.168	0.185*

[1]Cranial base asymmetry
[2]Cervical asymmetry
*p<0.05
**p<0.01
***p<0.001
[3]For explanation of abbreviations see Appendix 16

Table 17
Correlation Coefficients for the Relationships of Facial Asymmetry

	[1]DLSFNS	DLSANS	DLSIIF	DLSB	DLSGF	DPCIF	DPCPNS	DMLF	DMMC	DSMC	DACP	SMD	FD
DEWE	0.058	0.404***	0.285**	0.339***	0.137	0.176	0.159	0.389***	0.066	-0.043	0.090	-.035	-0.045
DLSFNS		0.008	-0.209*	0.268**	-0.147	-0.308**	-0.090	0.234**	0.309**	-0.411***	-0.170	-.010	0.056
DLSANS			0.521***	0.471***	0.350***	0.395***	0.304**	0.420***	0.283**	0.095	0.354***	-.209*	-0.103
DLSIIF				0.050	0.725***	0.759***	0.554***	0.539***	0.140	0.095	0.486***	0.198*	0.168
DLSB					0.098	-0.067	-0.067	0.153	0.175	-0.151	0.137	-0.088	0.038
DLSGF						0.666***	0.511***	0.545***	0.182*	0.045	0.515***	0.471***	0.383***
DPCIF							0.541***	0.608***	0.052	0.105	0.389***	0.103	0.088
DPCPNS								0.434***	0.271**	0.023	0.237	0.115	-0.008
DMLF									0.074	0.063	0.365***	0.034	0.000
DMMC										0.020	-0.059	0.017	-0.029
DSMC											0.186*	-0.208*	-0.036
DACP												0.102	0.175
SMD													0.656***

*p<0.05
**p<0.01
***p<0.001
[1]For explanation of abbreviations see Appendix 16

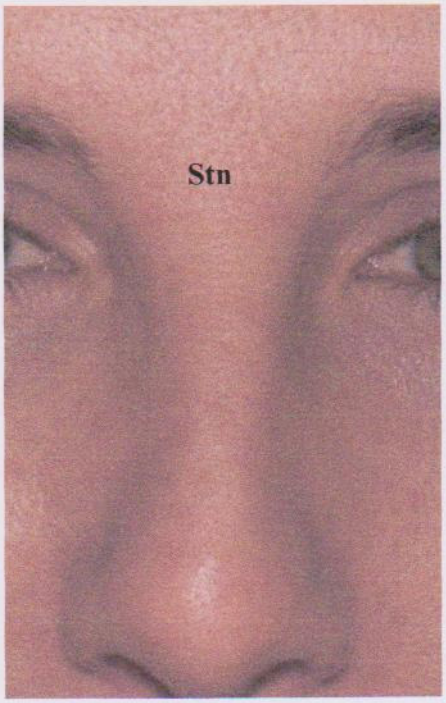


Figure 1
Soft tissue Markers of the Face
Stn Soft tissue nasion

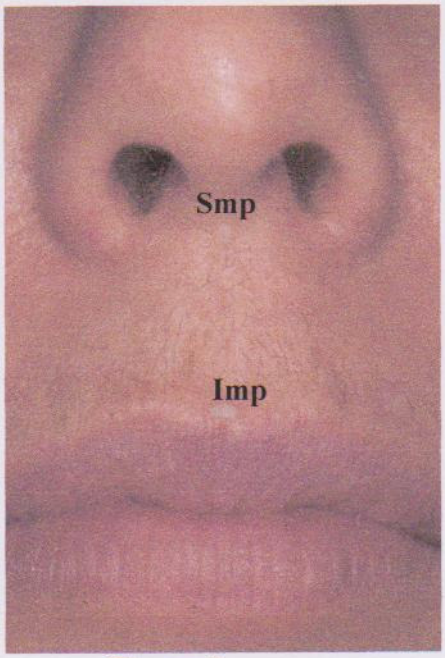


Figure 2
Soft Tissue Markers of the Face
Smp Superior midline of the philtrum
Imp Inferior midline of the philtrum

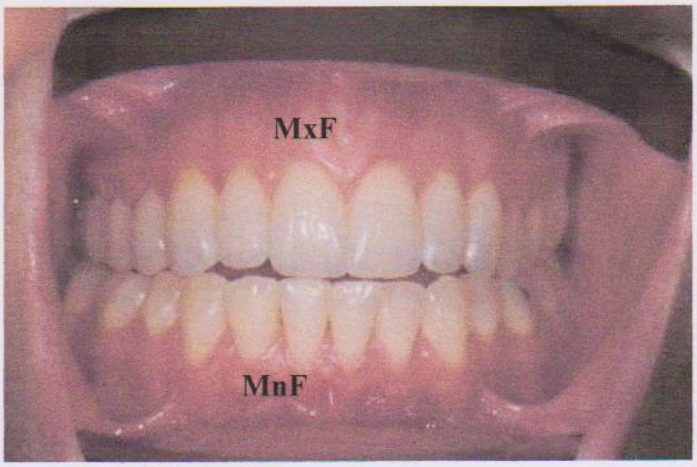


Figure 3
Soft tissue Markers of the Face
MxF Maxillary midline frenum
MnF Mandibular midline frenum

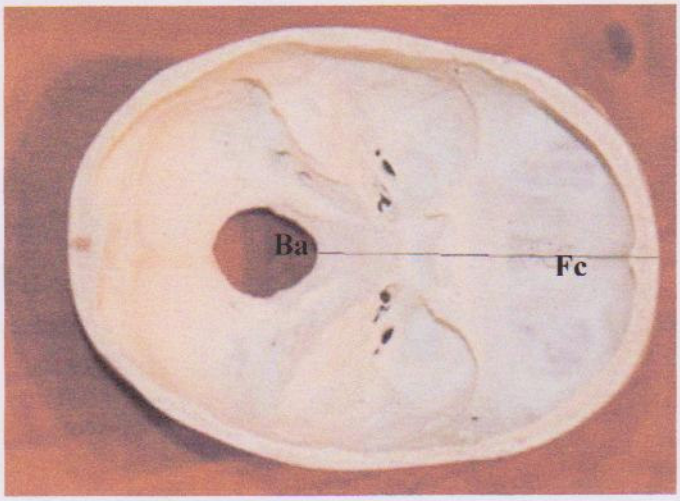


Figure 4
The cranial base midline

A line is drawn extending from foramen cecum anteriorly to basion at the posterior extent of the cranial base
Fc Foramen cecum
Ba Basion

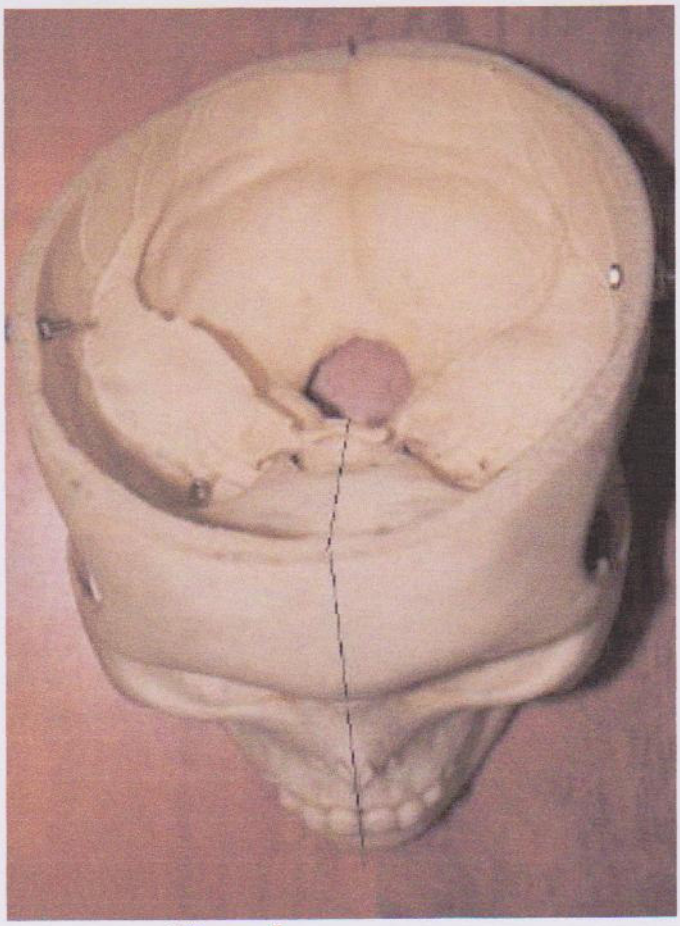


Figure 5
Extension of the Cranial Base Midline onto the face

The line from basion to foramen cecum is extended vertically
On to the face and becomes the facial midline

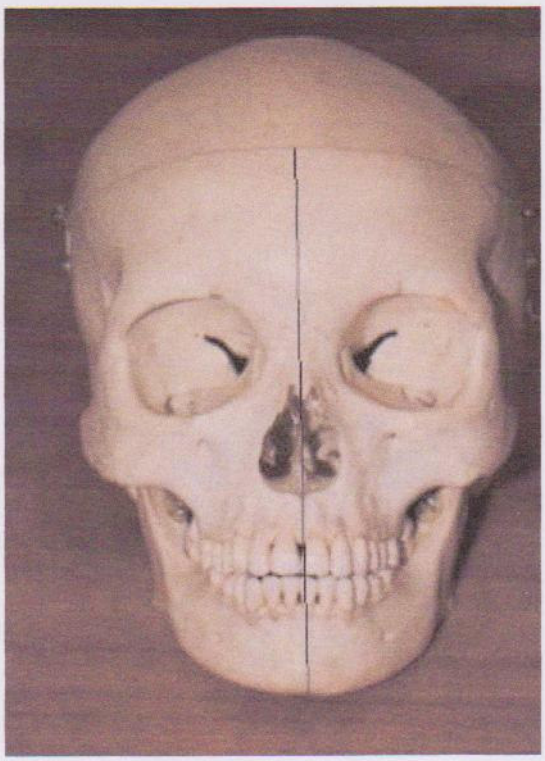


Figure 6
The Facial Midline
The final extension of the cranial base midline on to the face

1. Helms JA, Schneider RA. Cranial skeletal biology. Nature. 2003;423:326-31.

2. Young DL, Schneider RA, Hu D, Helms JA. Genetic and teratogenic approaches to craniofacial development. Crit Rev Oral Biol Med. 2000;11:304-17.

3. Mao JJ, Nah HD. Growth and development: Hereditary and mechanical modulations.[see comment]. Am J Orthod Dentofacial Orthop. 2004;125:676-89.

4. Francis-West PH, Robson L, Evans DJ. Craniofacial development: The tissue and molecular interactions that control development of the head. Adv Anat Embryol Cell Biol. 2003;169:III,VI, 1-138.

5. Francis-West P, Ladher R, Barlow A, Graveson A. Signalling interactions during facial development. Mech Dev. 1998;75:3-28.

6. Fu AS, Mehta NR, Forgione AG, Al-Badawi EA, Zawawi KH. Maxillomandibular relationship in TMD patients before and after short-term flat plane bite plate therapy. Cranio. 2003;21:172-9.

7. Sakaguchi K, Mehta NR, Abdallah EF, et al. Examination of the relationship between mandibular position and body posture. Cranio. 2007;25:237-49.

8. Ceneviz C, Mehta NR, Forgione A, et al. The immediate effect of changing mandibular position on the EMG activity of the masseter, temporalis, sternocleidomastoid, and trapezius muscles. Cranio. 2006;24:237-44.

9. Pradham NS, White GE, Mehta N, Forgione A. Mandibular deviations in TMD and non-TMD groups related to eye dominance and head posture. J Clin Pediatr Dent. 2001;25:147-55.

10. Latta GH,Jr. The midline and its relation to anatomic landmarks in the edentulous patient. J Prosthet Dent. 1988;59:681-3.

11. Carstens MH. Development of the facial midline. J Craniofac Surg. 2002;13:129-87.

12. Zhang Y, Xiao L, Li J, Peng Y, Zhao Z. Young people's esthetic perception of dental midline deviation. . Accessed 3, 80.

13. Cardash HS, Ormanier Z, Laufer BZ. Observable deviation of the facial and anterior tooth midlines. J Prosthet Dent. 2003;89:282-5.

14. Bidra AS, Uribe F, Taylor TD, Agar JR, Rungruanganunt P, Neace WP. The relationship of facial anatomic landmarks with midlines of the face and mouth. .

15. Eskelsen E, Fernandes CB, Pelogia F, et al. Concurrence between the maxillary midline and bisector to the interpupillary line. J Esthet Restor Dent. 2009;21:37-41.

16. Siebert JR. Prenatal growth of the median face. Am J Med Genet. 1986;25:369-79. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med2&AN=3777030.

17. Shiratori H, Hamada H. The left-right axis in the mouse: From origin to morphology. Development. 2006;133:2095-104.

18. Opitz JM, Utkus A. Comments on biological asymmetry. Am J Med Genet. 2001;101:359-69.

19. Meyers EN, Martin GR. Differences in left-right axis pathways in mouse and chick: Functions of FGF8 and SHH. Science. 1999;285:403-6.

20. Zhang XM, Ramalho-Santos M, McMahon AP. Smoothened mutants reveal redundant roles for shh and ihh signaling including regulation of L/R symmetry by the mouse node. Cell. 2001;106:781-92.

21. MacKenzie A, Ferguson MW, Sharpe PT. Hox-7 expression during murine craniofacial development. Development. 1991;113:601-11.

22. Hu D, Marcucio RS. A SHH-responsive signaling center in the forebrain regulates craniofacial morphogenesis via the facial ectoderm. Development. 2009;136:107-16.

23. Hu D, Marcucio RS. Unique organization of the frontonasal ectodermal zone in birds and mammals. Dev Biol. 2009;325:200-10.

24. Eames BF, Schneider RA. Quail-duck chimeras reveal spatiotemporal plasticity in molecular and histogenic programs of cranial feather development. Development. 2005;132:1499-509.

25. Morin-Kensicki EM, Melancon E, Eisen JS. Segmental relationship between somites and vertebral column in zebrafish. Development. 2002;129:3851-60.

26. Kjaer I. Ossification of the human fetal basicranium. J Craniofac Genet Dev Biol. 1990;10:29-38.

27. Kjaer I. Prenatal traces of aberrant neurofacial growth. Acta Odontol Scand. 1998;56:326-30.

28. Kjaer I. Neuro-osteology. Crit Rev Oral Biol Med. 1998;9:224-44.

29. Kjaer I. Correlated appearance of ossification and nerve tissue in human fetal jaws. J Craniofac Genet Dev Biol. 1990;10:329-36.

30. Radlanski RJ, Renz H. Genes, forces, and forms: Mechanical aspects of prenatal craniofacial development. Dev Dyn. 2006;235:1219-29.

31. Sonnesen L, Kjaer I. Anomalies of the cervical vertebrae in patients with skeletal class II malocclusion and horizontal maxillary overjet. Am J Orthod Dentofacial Orthop. 2008;133:188.e15,188.e20.

32. Sonnesen L, Nolting D, Kjaer KW, Kjaer I. Association between the development of the body axis and the craniofacial skeleton studied by immunohistochemical analyses using collagen II, Pax9, Pax1, and noggin antibodies. Spine. 2008;33:1622-6.

33. Sonnesen L, Nolting D, Engel U, Kjaer I. Cervical vertebrae, cranial base, and mandibular retrognathia in human triploid fetuses. Am J Med Genet A. 2009;149A:177-87.

34. Sperber GH. Craniofacial Development. Hamilton, Ont. ; London; Lewiston, NY: B.C. Decker; Sales and distribution, U.S., B.C. Decker; 2001:220.

35. Gong SG, Gong TW, Shum L. Identification of markers of the midface. J Dent Res. 2005;84:69-72.

36. Radlanski RJ, van der Linden FP, Ohnesorge I. 4D-computerized visualisation of human craniofacial skeletal growth and of the development of the dentition. Ann Anat. 1999;181:3-8.

37. Radlanski RJ. Prenatal craniofacial morphogenesis: Four-dimensional visualization of morphogenetic processes. Orthod Craniofac Res. 2003;6:89-94.

38. Radlanski RJ, Emmerich S, Renz H. Prenatal morphogenesis of the human incisive canal. Anat Embryol (Berl). 2004;208:265-71.

39. Lieberman DE, Crompton AW. Why fuse the mandibular symphysis? A comparative analysis. Am J Phys Anthropol. 2000;112:517-40.

40. Liang X, Jacobs R, Lambrichts I. An assessment on spiral CT scan of the superior and inferior genial spinal foramina and canals. Surg Radiol Anat. 2006;28:98-104.

41. Vandewalle G, Liang X, Jacobs R, Lambrichts I. Macroanatomic and radiologic characteristics of the superior genial spinal foramen and its bony canal. Int J Oral Maxillofac Implants. 2006;21:581-6.

42. Liang X, Jacobs R, Lambrichts I, Vandewalle G. Lingual foramina on the mandibular midline revisited: A macroanatomical study. Clin Anat. 2007;20:246-51.

43. Jacobs R, Lambrichts I, Liang X, et al. Neurovascularization of the anterior jaw bones revisited using high-resolution magnetic resonance imaging. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;103:683-93.

44. Noden DM, Francis-West P. The differentiation and morphogenesis of craniofacial muscles. Dev Dyn. 2006;235:1194-218.

45. Jiang R, Bush JO, Lidral AC. Development of the upper lip: Morphogenetic and molecular mechanisms. Dev Dyn. 2006;235:1152-66.

46. Rogers CR, Weinberg SM, Smith TD, Deleyiannis FW, Mooney MP, Marazita ML. Anatomical basis for apparent subepithelial cleft lip: A histological and ultrasonographic survey of the orbicularis oris muscle. Cleft Palate Craniofac J. 2008;45:518-24.

47. Marazita ML. Subclinical features in non-syndromic cleft lip with or without cleft palate (CL/P): Review of the evidence that subepithelial orbicularis oris muscle defects are part of an expanded phenotype for CL/P. Orthod Craniofac Res. 2007;10:82-7.

48. Stelnicki EJ, Hoffman WY, Vanderwall K, Harrison MR, Foster R, Longaker MT. A new in utero model for lateral facial clefts. J Craniofac Surg. 1997;8:460-5.

49. Lipinski RJ, Hutson PR, Hannam PW, et al. Dose- and route-dependent teratogenicity, toxicity, and pharmacokinetic profiles of the hedgehog signaling antagonist cyclopamine in the mouse. Toxicol Sci. 2008;104:189-97.

50. Park D, Jeon JH, Shin S, et al. Green tea extract increases cyclophosphamide-induced teratogenesis by modulating the expression of cytochrome P-450 mRNA. Reprod Toxicol. 2009;27:79-84.

51. Lu SJ, He W, Shi B, Meng T, Li XY, Liu YR. A preliminary study on the teratogenesis of dexamethasone and the preventive effect of vitamin B12 on murine embryonic palatal shelf fusion in vitro. J Zhejiang Univ Sci B. 2008;9:306-12.

52. Juriloff DM, Harris MJ. Mouse genetic models of cleft lip with or without cleft palate. Birth Defects Res Part A Clin Mol Teratol. 2008;82:63-77.

53. Jang JY, Park D, Shin S, et al. Antiteratogenic effect of resveratrol in mice exposed in utero to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Eur J Pharmacol. 2008;591:280-3.

54. Webster WS, Abela D. The effect of hypoxia in development. Birth Defects Res Part C Embryo Today. 2007;81:215-28.

55. Scott J. The doctrine of functional matrices. Am J Orthod. 1969;56:38-44.

56. Moss ML. The functional matrix hypothesis revisited. 4. the epigenetic antithesis and the resolving synthesis. Am J Orthod Dentofacial Orthop. 1997;112:410-7.

57. McGonnell IM, Clarke JD, Tickle C. Fate map of the developing chick face: Analysis of expansion of facial primordia and establishment of the primary palate. Dev Dyn. 1998;212:102-18.

58. Chierici G, Harvold EP, Vargervik K. Morphogenetic experiments in facial asymmetry: The nasal cavity. Am J Phys Anthropol. 1973;38:291-9.

59. Chierici G, Harvold EP, Dawson WJ. Morphologic adaptations secondary to the production of experimental cleft palate in primates. Cleft Palate J. 1970;7:59-67.

60. Moss ML. The primacy of functional matrices in orofacial growth. Dent Pract Dent Rec. 1968;19:65-73.

61. Abed GS, Buschang PH, Taylor R, Hinton RJ. Maturational and functional related differences in rat craniofacial growth. Arch Oral Biol. 2007;52:1018-25.

62. Vargervik K, Harvold EP. Experiments on the interaction between orofacial function and morphology. Ear Nose Throat J. 1987;66:201-8.

63. Prince ME, Nasser JG, Pass BB. Effect of upper-airway passages on craniofacial growth in an animal model: A pilot study. J Otolaryngol. 1997;26:306-15.

64. Harvold EP, Tomer BS, Vargervik K, Chierici G. Primate experiments on oral respiration. Am J Orthod. 1981;79:359-72.

65. Tomer BS, Harvold EP. Primate experiments on mandibular growth direction. Am J Orthod. 1982;82:114-9.

66. Moss ML. The functional matrix hypothesis revisited. 1. the role of mechanotransduction. Am J Orthod Dentofacial Orthop. 1997;112:8-11.

67. Moss ML. The functional matrix hypothesis revisited. 2. the role of an osseous connected cellular network. Am J Orthod Dentofacial Orthop. 1997;112:221-6.

68. Enlow DH, Hans MG. Essentials of Facial Growth. Ann Arbor, Mich: Needham Press; 1996:303.

69. Hayakawa K, Konishi Y, Matsuda T, et al. Development and aging of brain midline structures: Assessment with MR imaging. Radiology. 1989;172:171-7.

70. Hammond P, Forster-Gibson C, Chudley AE, et al. Face-brain asymmetry in autism spectrum disorders. Mol Psychiatry. 2008;13:614-23.

71. Burdi AR, Lawton TJ, Grosslight J. Prenatal pattern emergence in early human facial development. Cleft Palate J. 1988;25:8-15.

72. Bastir M, Rosas A, Stringer C, et al. Effects of brain and facial size on basicranial form in human and primate evolution. . Accessed 5, 58.

73. Bastir M. A systems-model for the morphological analysis of integration and modularity in human craniofacial evolution. 86.

74. Bastir M, Rosas A. Correlated variation between the lateral basicranium and the face: A geometric morphometric study in different human groups. . Accessed 9, 51.

75. Bastir M, Rosas A. Hierarchical nature of morphological integration and modularity in the human posterior face. . Accessed 1, 128.

76. Rosas A, Bastir M, Alarcón JA, Kuroe K. Thin-plate spline analysis of the cranial base in african, asian and european populations and its relationship with different malocclusions. .

77. Sgouros S, Natarajan K, Hockley AD, Goldin JH, Wake M. Skull base growth in childhood. Pediatr Neurosurg. 1999;31:259-68.

78. Thilander B. Basic mechanisms in craniofacial growth. Acta Odontol Scand. 1995;53:144-51.

79. Kantomaa T, Pirttiniemi P, Tuominen M. Cranial base and the growth of the cranial vault: An experimental study on the rabbit. Proc Finn Dent Soc. 1991;87:93-8.

80. Cendekiawan T, Wong RW, Rabie AB. Temporal expression of SOX9 and type II collagen in spheno-occipital synchondrosis of mice after mechanical tension stimuli. Angle Orthod. 2008;78:83-8.

81. Lei WY, Wong RW, Rabie AB. Factors regulating endochondral ossification in the spheno-occipital synchondrosis. Angle Orthod. 2008;78:215-20.

82. Tang M, Mao JJ. Matrix and gene expression in the rat cranial base growth plate. Cell Tissue Res. 2006;324:467-74.

83. Wang X, Mao JJ. Chondrocyte proliferation of the cranial base cartilage upon in vivo mechanical stresses. J Dent Res. 2002;81:701-5.

84. Wang X, Mao JJ. Accelerated chondrogenesis of the rabbit cranial base growth plate by oscillatory mechanical stimuli. J Bone Miner Res. 2002;17:1843-50.

85. Mann SS, Naidich TP, Towbin RB, Doundoulakis SH. Imaging of postnatal maturation of the skull base. Neuroimaging Clin N Am. 2000;10:1-21.

86. O'Higgins P, Bastir M, Kupczik K. Shaping the human face. Int Congr Ser. 2006;1296:55-73.

87. Smith TD, Rossie JB, Cooper GM, et al. The maxillary sinus in three genera of new world monkeys: Factors that constrain secondary pneumatization.; secretory otitis media in adults: II. the role of mastoid pneumatization as a prognostic factor.; A morphogenetic model of cranial pneumatization based on the invasive tissue hypothesis.; independence of biomechanical forces and craniofacial pneumatization in cebus.; A morphogenetic model of cranial pneumatization based on the invasive tissue hypothesis.; fate of the mesenchyme in the process of pneumatization. Otol Neurotol. 2002;293; 106; 23:91; 37; 291(11); 291(11); 291(11); 192,2010 Jan; 40; 2008 No; 2008 No; 2008 No; 199.

88. Coben SE. The spheno-occipital synchondrosis: The missing link between the profession's concept of craniofacial growth and orthodontic treatment.[see comment]. Am J Orthod Dentofacial Orthop. 1998;114:709-12.

89. Lieberman DE. Sphenoid shortening and the evolution of modern human cranial shape. Nature. 1998;393:158-62.

90. Linder-Aronson S. Effects of adenoidectomy on dentition and nasopharynx. Trans Eur Orthod Soc. 1972:177-86.

91. Linder-Aronson S. Adenoids. their effect on mode of breathing and nasal airflow and their relationship to characteristics of the facial skeleton and the denition. A biometric, rhino-

manometric and cephalometro-radiographic study on children with and without adenoids. Acta Otolaryngol Suppl (Stockh). 1970;265:1-132.

92. Mahony D, Karsten A, Linder-Aronson S. Effects of adenoidectomy and changed mode of breathing on incisor and molar dentoalveolar heights and anterior face heights. Aust Orthod J. 2004;20:93-8.

93. Moyers RE, McNamara JA, Ribbens KA, University of Michigan, Center for Human Growth and Development. Naso-Respiratory Function and Craniofacial Growth. Ann Arbor, Mich: Center for Human Growth and Development, University of Michigan; 1979:332.

94. Zettergren-Wijk L, Forsberg CM, Linder-Aronson S. Changes in dentofacial morphology after adeno-/tonsillectomy in young children with obstructive sleep apnoea--a 5-year follow-up study. Eur J Orthod. 2006;28:319-26.

95. Harvold EP. The role of function in the etiology and treatment of malocclusion. Am J Orthod. 1968;54:883-98.

96. Chierici G, Harvold EP, Dawson WJ. Primate experiments on facial asymmetry. J Dent Res. 1970;49:847-51.

97. Backlund E. Facial growth, and the significance of oral habits, mouthbreathing and soft tissues for malocclusion. A study on children around the age of 10. Acta Odontol Scand. 1963;21:9-139.

98. Behrents RG. The biological basis for understanding craniofacial growth during adulthood. Prog Clin Biol Res. 1985;187:307-19.

99. Dager MM, McNamara JA, Baccetti T, Franchi L. Aging in the craniofacial complex. Angle Orthod. 2008;78:440-4.

100. Pecora NG, Baccetti T, McNamara JA,Jr. The aging craniofacial complex: A longitudinal cephalometric study from late adolescence to late adulthood. Am J Orthod Dentofacial Orthop. 2008;134:496-505.

101. Bachler M, Neubuser A. Expression of members of the fgf family and their receptors during midfacial development. Mech Dev. 2001;100:313-6.

102. Roessler E, Belloni E, Gaudenz K, et al. Mutations in the human sonic hedgehog gene cause holoprosencephaly. Nat Genet. 1996;14:357-60.

103. Kjaer I, Keeling JW, Graem N. The midline craniofacial skeleton in holoprosencephalic fetuses. J Med Genet. 1991;28:846-55.

104. Seppala M, Depew MJ, Martinelli DC, Fan CM, Sharpe PT, Cobourne MT. Gas1 is a modifier for holoprosencephaly and genetically interacts with sonic hedgehog. J Clin Invest. 2007;117:1575-84.

105. Cordero D, Marcucio R, Hu D, Gaffield W, Tapadia M, Helms JA. Temporal perturbations in sonic hedgehog signaling elicit the spectrum of holoprosencephaly phenotypes. J Clin Invest. 2004;114:485-94.

106. Burdine RD, Schier AF. Conserved and divergent mechanisms in left-right axis formation. Genes Dev. 2000;14:763-76.

107. Abzhanov A, Tabin CJ. Shh and Fgf8 act synergistically to drive cartilage outgrowth during cranial development. Dev Biol. 2004;273:134-48.

108. Young B, Minugh-Purvis N, Shimo T, et al. Indian and sonic hedgehogs regulate synchondrosis growth plate and cranial base development and function. Dev Biol. 2006;299:272-82.

109. Goodnough LH, Brugmann SA, Hu D, Helms JA. Stage-dependent craniofacial defects resulting from Sprouty2 overexpression. Dev Dyn. 2007;236:1918-28.

110. Chiang C, Litingtung Y, Lee E, et al. Cyclopia and defective axial patterning in mice lacking sonic hedgehog gene function. Nature. 1996;383:407-13.

111. Behnan SM, Guo C, Gong TW, Shum L, Gong SG. Gene and protein expression of transforming growth factor beta 2 gene during murine primary palatogenesis. Differentiation. 2005;73:233-9.

112. Choi JK, Kim SC. Environmental effects on gene expression phenotype have regional biases in the human genome. Genetics. 2007;175:1607-13.

113. Choi JK, Kim YJ. Epigenetic regulation and the variability of gene expression. Nat Genet. 2008;40:141-7.

114. Jaenisch R, Bird A. Epigenetic regulation of gene expression: How the genome integrates intrinsic and environmental signals. Nat Genet. 2003;33:245-54.

115. Cutfield WS, Hofman PL, Mitchell M, Morison IM. Could epigenetics play a role in the developmental origins of health and disease? Pediatr Res. 2007;61:68R-75R.

116. McEwen BS. Understanding the potency of stressful early life experiences on brain and body function. Metabolism: Clinical & Experimental. 2008;57:S11-5.

117. Roach HI, Aigner T. DNA methylation in osteoarthritic chondrocytes: A new molecular target. Osteoarthritis & Cartilage. 2007;15:128-37.

118. Zeisel SH. Epigenetic mechanisms for nutrition determinants of later health outcomes. Am J Clin Nutr. 2009;89:1488S-93S.

119. Wang J, Wu G, Zhou H, Wang F. Emerging technologies for amino acid nutrition research in the post-genome era. Amino Acids. 2009;37:177-86.

120. Fraga MF, Ballestar E, Paz MF, et al. Epigenetic differences arise during the lifetime of monozygotic twins. Proc Natl Acad Sci U S A. 2005;102:10604-9.

121. Boughner JC, Wat S, Diewert VM, Young NM, Browder LW, Hallgrimsson B. Short-faced mice and developmental interactions between the brain and the face. J Anat. 2008;213:646-62. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=19094181.

122. Lipinski RJ, Dengler E, Kiehn M, Peterson RE, Bushman W. Identification and characterization of several dietary alkaloids as weak inhibitors of hedgehog signaling. Toxicol Sci. 2007;100:456-63.

123. Lipinski RJ, Hutson PR, Hannam PW, et al. Dose- and route-dependent teratogenicity, toxicity, and pharmacokinetic profiles of the hedgehog signaling antagonist cyclopamine in the mouse. Toxicol Sci. 2008;104:189-97.

124. Zhou FC, Sari Y, Powrozek T, Goodlett CR, Li TK. Moderate alcohol exposure compromises neural tube midline development in prenatal brain. Brain Res Dev Brain Res. 2003;144:43-55.

125. Aoto K, Shikata Y, Higashiyama D, Shiota K, Motoyama J. Fetal ethanol exposure activates protein kinase A and impairs shh expression in prechordal mesendoderm cells in the pathogenesis of holoprosencephaly. Birth Defects Res Part A Clin Mol Teratol. 2008;82:224-31.

126. Chudley AE. Fetal alcohol spectrum disorder: Counting the invisible - mission impossible?[comment]. Arch Dis Child. 2008;93:721-2.

127. Chudley AE, Kilgour AR, Cranston M, Edwards M. Challenges of diagnosis in fetal alcohol syndrome and fetal alcohol spectrum disorder in the adult. Am J Med Genet C Semin Med Genet. 2007;145C:261-72.

128. Neri G, Sammito V, Romano C, Sanfilippo S, Opitz JM. Facial midline defect in the fetal alcohol syndrome: Embryogenetic considerations in two clinical cases. Am J Med Genet. 1988;29:477-82.

129. Schneider RA, Hu D, Rubenstein JL, Maden M, Helms JA. Local retinoid signaling coordinates forebrain and facial morphogenesis by maintaining FGF8 and SHH. Development. 2001;128:2755-67.

130. Jang JY, Shin S, Choi BI, et al. Antiteratogenic effects of alpha-naphthoflavone on 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposed mice in utero. Reprod Toxicol. 2007;24:303-9.

131. Hirschfelder U, Piechot E, Schulte M, Leher A. Abnormalities of the TMJ and the musculature in the oculo-auriculo-vertebral spectrum (OAV). A CT study. J Orofac Orthop. 2004;65:204-16.

132. Figueroa AA, Friede H. Craniovertebral malformations in hemifacial microsomia. J Craniofac Genet Dev Biol Suppl. 1985;1:167-78.

133. Nakata S, Mizuno M, Koyano K, Nakayama E, Watanabe M, Murakami T. Functional masticatory evaluation in hemifacial microsomia. Eur J Orthod. 1995;17:273-80.

134. Gidarakou IK, Tallents RH, Kyrkanides S, Stein S, Moss ME. Comparison of skeletal and dental morphology in asymptomatic volunteers and symptomatic patients with bilateral disk displacement without reduction. Angle Orthod. 2004;74:684-90.

135. Gidarakou IK, Tallents RH, Stein S, Kyrkanides S, Moss ME. Comparison of skeletal and dental morphology in asymptomatic volunteers and symptomatic patients with unilateral disk displacement with reduction. Angle Orthod. 2004;74:212-9.

136. Qadan S, Macher DJ, Tallents RH, Kyrkanides S, Moss ME. The effect of surgically induced anterior disc displacement of the temporomandibular joint on the midface and cranial base. Clin Orthod Res. 1999;2:124-32.

137. Legrell PE, Isberg A. Mandibular length and midline asymmetry after experimentally induced temporomandibular joint disk displacement in rabbits. Am J Orthod Dentofacial Orthop. 1999;115:247-53.

138. Legrell PE, Reibel J, Nylander K, Horstedt P, Isberg A. Temporomandibular joint condyle changes after surgically induced non-reducing disk displacement in rabbits: A macroscopic and microscopic study. Acta Odontol Scand. 1999;57:290-300.

139. Qadan S, Macher DJ, Tallents RH, Kyrkanides S, Moss ME. The effect of surgically induced anterior disc displacement of the temporomandibular joint on the midface and cranial base. Clin Orthod Res. 1999;2:124-32.

140. Bryndahl F, Eriksson L, Legrell PE, Isberg A. Bilateral TMJ disk displacement induces mandibular retrognathia. J Dent Res. 2006;85:1118-23.

141. Paesani D, Salas E, Martinez A, Isberg A. Prevalence of temporomandibular joint disk displacement in infants and young children. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999;87:15-9.

142. Katzberg RW, Westesson PL, Tallents RH, Drake CM. Anatomic disorders of the temporomandibular joint disc in asymptomatic subjects. J Oral Maxillofac Surg. 1996;54:147-53.

143. Schellhas KP, Pollei SR, Wilkes CH. Pediatric internal derangements of the temporomandibular joint: Effect on facial development. Am J Orthod Dentofacial Orthop. 1993;104:51-9.

144. Nebbe B, Major PW. Prevalence of TMJ disc displacement in a pre-orthodontic adolescent sample. Angle Orthod. 2000;70:454-63.

145. Sanchez-Woodworth RE, Katzberg RW, Tallents RH, Guay JA. Radiographic assessment of temporomandibular joint pain and dysfunction in the pediatric age-group. J Dent Child. 1988;55:278-81.

146. Elias DL, Kawamoto HK,Jr, Wilson LF. Holoprosencephaly and midline facial anomalies: Redefining classification and management. Plast Reconstr Surg. 1992;90:951-8.

147. Hu D, Helms JA. The role of sonic hedgehog in normal and abnormal craniofacial morphogenesis. Development. 1999;126:4873-84.

148. Maity T, Fuse N, Beachy PA. Molecular mechanisms of sonic hedgehog mutant effects in holoprosencephaly. Proc Natl Acad Sci U S A. 2005;102:17026-31.

149. Neri G, Sammito V, Romano C, Sanfilippo S, Opitz JM. Facial midline defect in the fetal alcohol syndrome: Embryogenetic considerations in two clinical cases. Am J Med Genet. 1988;29:477-82.

150. El-Hawrani A, Sohn M, Noga M, El-Hakim H. The face does predict the brain--midline facial and forebrain defects uncovered during the investigation of nasal obstruction and rhinorrhea. case report and a review of holoprosencephaly and its classifications. Int J Pediatr Otorhinolaryngol. 2006;70:935-40.

151. Kjaer I, Becktor KB, Lisson J, Gormsen C, Russell BG. Face, palate, and craniofacial morphology in patients with a solitary median maxillary central incisor. Eur J Orthod. 2001;23:63-73.

152. Becktor KB, Sverrild L, Pallisgaard C, Burhoj J, Kjaer I. Eruption of the central incisor, the intermaxillary suture, and maxillary growth in patients with a single median maxillary central incisor. Acta Odontol Scand. 2001;59:361-6.

153. Tabatabaie F, Sonnesen L, Kjaer I. The neurocranial and craniofacial morphology in children with solitary median maxillary central incisor (SMMCI). Orthod Craniofac Res. 2008;11:96-104.

154. Losee JE, Feldman E, Ketkar M, et al. Nonsynostotic occipital plagiocephaly: Radiographic diagnosis of the "sticky suture". Plast Reconstr Surg. 2005;116:1860-9.

155. Bjoerk A, Bjoerk L. ARTIFICIAL DEFORMATION AND CRANIO-FACIAL ASYMMETRY IN ANCIENT PERUVIANS. J Dent Res. 1964;43:353-62.

156. Stellwagen L, Hubbard E, Chambers C, Jones KL. Torticollis, facial asymmetry and plagiocephaly in normal newborns. Arch Dis Child. 2008;93:827-31.

157. Kreiborg S, Moller E, Bjork A. Skeletal and functional craniofacial adaptations in plagiocephaly. J Craniofac Genet Dev Biol Suppl. 1985;1:199-210.

158. Abramson DL, Janecka IP, Mulliken JB. Abnormalities of the cranial base in synostotic frontal plagiocephaly. J Craniofac Surg. 1996;7:426-8.

159. Losee JE, Mason AC, Dudas J, Hua LB, Mooney MP. Nonsynostotic occipital plagiocephaly: Factors impacting onset, treatment, and outcomes. Plast Reconstr Surg. 2007;119:1866-73.

160. Losee JE, Mason AC. Deformational plagiocephaly: Diagnosis, prevention, and treatment. Clin Plast Surg. 2005;32:53-64.

161. Du Tolt DF, Nortje C. The maxillae: Integrated and applied anatomy relevant to dentistry. SADJ. 2003;58:325-30.

162. Woodside DG, Linder-Aronson S, Lundstrom A, McWilliam J. Mandibular and maxillary growth after changed mode of breathing. Am J Orthod Dentofacial Orthop. 1991;100:1-18.

163. Ravosa MJ, Kunwar R, Stock SR, Stack MS. Pushing the limit: Masticatory stress and adaptive plasticity in mammalian craniomandibular joints. J Exp Biol. 2007;210:628-41.

164. Taylor AB, Jones KE, Kunwar R, Ravosa MJ. Dietary consistency and plasticity of masseter fiber architecture in postweaning rabbits. Anat Rec A Discov Mol Cell Evol Biol. 2006;288:1105-11.

165. Beecher RM, Corruccini RS. Effects of dietary consistency on craniofacial and occlusal development in the rat. Angle Orthod. 1981;51:61-9.

166. Beecher RM, Corruccini RS. Effects of dietary consistency on maxillary arch breadth in macaques. J Dent Res. 1981;60:68.

167. Beecher RM, Corruccini RS, Freeman M. Craniofacial correlates of dietary consistency in a nonhuman primate. J Craniofac Genet Dev Biol. 1983;3:193-202.

168. Corruccini RS, Beecher RM. Occlusofacial morphological integration lowered in baboons raised on soft diet. J Craniofac Genet Dev Biol. 1984;4:135-42.

169. Corruccini RS, Beecher RM. Occlusal variation related to soft diet in a nonhuman primate. Science. 1982;218:74-6.

170. Kuboyama N, Moriya Y. Influence of diet composition and malocclusion on masticatory organs in rats. J Nihon Univ Sch Dent. 1995;37:91-6.

171. Yu CC, Wong FH, Lo LJ, Chen YR. Craniofacial deformity in patients with uncorrected congenital muscular torticollis: An assessment from three-dimensional computed tomography imaging. Plast Reconstr Surg. 2004;113:24-33.

172. Gedrange T, Harzer W. Muscle influence on postnatal craniofacial development and diagnostics. J Orofac Orthop. 2004;65:451-66.

173. Inoue N, Sakashita R, Kamegai T. Reduction of masseter muscle activity in bottle-fed babies. Early Hum Dev. 1995;42:185-93.

174. Korbmacher H, Koch LE, Kahl-Nieke B. Orofacial myofunctional disorders in children with asymmetry of the posture and locomotion apparatus. Int J Orofacial Myology. 2005;31:26-38.

175. Kwon TG, Park HS, Lee SH, Park IS, An CH. Influence of unilateral masseter muscle atrophy on craniofacial morphology in growing rabbits. J Oral Maxillofac Surg. 2007;65:1530-7.

176. Kylamarkula S. Growth changes in the skull and upper cervical skeleton after partial detachment of neck muscles. an experimental study in the rat. J Anat. 1988;159:197-205.

177. Lifshitz J. Comparative anatomic study of mandibular growth in rats after bilateral resections of superficial masseter, posterior temporal, and anterior digastric muscles. J Dent Res. 1976;55:854-8.

178. Matsuyuki T, Kitahara T, Nakashima A. Developmental changes in craniofacial morphology in subjects with duchenne muscular dystrophy. Eur J Orthod. 2006;28:42-50.

179. Nakata S. Relationship between the development and growth of cranial bones and masticatory muscles in postnatal mice. J Dent Res. 1981;60:1440-50.

180. Poikela A, Kantomaa T, Pirttiniemi P. Craniofacial growth after a period of unilateral masticatory function in young rabbits. Eur J Oral Sci. 1997;105:331-7.

181. Poyak J. Effects of pacifiers on early oral development. Int J Orthod Milwaukee. 2006;17:13-6.

182. Raadsheer MC, Kiliaridis S, Van Eijden TM, Van Ginkel FC, Prahl-Andersen B. Masseter muscle thickness in growing individuals and its relation to facial morphology. Arch Oral Biol. 1996;41:323-32.

183. Solow B, Kreiborg S. Soft-tissue stretching: A possible control factor in craniofacial morphogenesis. Scand J Dent Res. 1977;85:505-7.

184. Drevensek M, Papic JS. The influence of the respiration disturbances on the growth and development of the orofacial complex. Coll Antropol. 2005;29:221-5.

185. Drevensek M, Stefanac-Papic J, Farcnik F. The influence of incompetent lip seal on the growth and development of craniofacial complex. Coll Antropol. 2005;29:429-34.

186. Pirttiniemi P, Lahtela P, Huggare J, Serlo W. Head posture and dentofacial asymmetries in surgically treated muscular torticollis patients. Acta Odontol Scand. 1989;47:193-7.

187. Satiroglu F, Arun T, Isik F. Comparative data on facial morphology and muscle thickness using ultrasonography. Eur J Orthod. 2005;27:562-7.

188. Sakurai M, Yonemitsu I, Muramoto T, Soma K. Effects of masticatory muscle force on temporomandibular joint disc growth in rats. Arch Oral Biol. 2007;52:1186-93.

189. Nakano H, Maki K, Shibasaki Y, Miller AJ. Three-dimensional changes in the condyle during development of an asymmetrical mandible in a rat: A microcomputed tomography study. Am J Orthod Dentofacial Orthop. 2004;126:410-20.

190. Kwon TG, Lee KH, Park HS, Ryoo HM, Kim HJ, Lee SH. Relationship between the masticatory muscles and mandibular skeleton in mandibular prognathism with and without asymmetry. J Oral Maxillofac Surg. 2007;65:1538-43.

191. Murray GM, Phanachet I, Uchida S, Whittle T. The human lateral pterygoid muscle: A review of some experimental aspects and possible clinical relevance. Aust Dent J. 2004;49:2-8.

192. Murray GM, Phanachet I, Uchida S, Whittle T. The role of the human lateral pterygoid muscle in the control of horizontal jaw movements. J Orofac Pain. 2001;15:279-92.

193. Fujita S, Iizuka T, Dauber W. Variation of heads of lateral pterygoid muscle and morphology of articular disc of human temporomandibular joint--anatomical and histological analysis. J Oral Rehabil. 2001;28:560-71.

194. Alomar X, Medrano J, Cabratosa J, et al. Anatomy of the temporomandibular joint. Semin Ultrasound CT MR. 2007;28:170-83.

195. Hiraba K, Hibino K, Hiranuma K, Negoro T. EMG activities of two heads of the human lateral pterygoid muscle in relation to mandibular condyle movement and biting force. J Neurophysiol. 2000;83:2120-37.

196. Bhutada MK, Phanachet I, Whittle T, Peck CC, Murray GM. Activity of superior head of human lateral pterygoid increases with increases in contralateral and protrusive jaw displacement. Eur J Oral Sci. 2007;115:257-64.

197. Bhutada MK, Phanachet I, Whittle T, Peck CC, Murray GM. Regional properties of the superior head of human lateral pterygoid muscle. Eur J Oral Sci. 2008;116:518-24.

198. Huang BY, Whittle T, Murray GM. Activity of inferior head of human lateral pterygoid muscle during standardized lateral jaw movements. Arch Oral Biol. 2005;50:49-64.

199. Murray GM, Phanachet I, Uchida S, Whittle T. The human lateral pterygoid muscle: A review of some experimental aspects and possible clinical relevance. Aust Dent J. 2004;49:2-8.

200. Taskaya-Yilmaz N, Ceylan G, Incesu L, Muglali M. A possible etiology of the internal derangement of the temporomandibular joint based on the MRI observations of the lateral pterygoid muscle. Surg Radiol Anat. 2005;27:19-24.

201. Taskaya-Yylmaz N, Ogutcen-Toller M. Clinical correlation of MRI findings of internal derangements of the temporomandibular joints. Br J Oral Maxillofac Surg. 2002;40:317-21.

202. Bakke M, Moller E, Werdelin LM, Dalager T, Kitai N, Kreiborg S. Treatment of severe temporomandibular joint clicking with botulinum toxin in the lateral pterygoid muscle in two cases of anterior disc displacement. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;100:693-700.

203. Liu C, Kaneko S, Soma K. Glenoid fossa responses to mandibular lateral shift in growing rats. Angle Orthod. 2007;77:660-7.

204. Bittar GT, Bibb CA, Pullinger AG. Histologic characteristics of the lateral pterygoid muscle insertion to the temporomandibular joint. J Orofac Pain. 1994;8:243-9.

205. Carpentier P, Yung JP, Marguelles-Bonnet R, Meunissier M. Insertions of the lateral pterygoid muscle: An anatomic study of the human temporomandibular joint. J Oral Maxillofac Surg. 1988;46:477-82.

206. Bhutada MK. Functions of the lateral pterygoid muscle. Ann R Australas Coll Dent Surg. 2004;17:68-9.

207. Usui A, Akita K, Yamaguchi K. An anatomic study of the divisions of the lateral pterygoid muscle based on the findings of the origins and insertions. Surg Radiol Anat. 2008;30:327-33.

208. Schindler HJ, Rues S, Turp JC, Schweizerhof K, Lenz J. Jaw clenching: Muscle and joint forces, optimization strategies. J Dent Res. 2007;86:843-7. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=17720852.

209. Yamaguchi S, Rikimaru H, Yamaguchi K, Itoh M, Watanabe M. Overall activity of all masticatory muscles during lateral excursion. J Dent Res. 2006;85:69-73. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med4&AN=16373684.

210. Huggare J, Kylamarkula S. Morphology of the first cervical vertebra in children with enlarged adenoids. Eur J Orthod. 1985;7:93-6.

211. Kylamarkula S, Huggare J. Head posture and the morphology of the first cervical vertebra. Eur J Orthod. 1985;7:151-6.

212. Sandikcioglu M, Skov S, Solow B. Atlas morphology in relation to craniofacial morphology and head posture. Eur J Orthod. 1994;16:96-103.

213. Singh GD, McNamara JA,Jr, Lozanoff S. Morphometry of the midfacial complex in subjects with class III malocclusions: Procrustes, euclidean, and cephalometric analyses. Clin Anat. 1998;11:162-70.

214. Baccetti T, Antonini A, Franchi L, Tonti M, Tollaro I. Glenoid fossa position in different facial types: A cephalometric study. Br J Orthod. 1997;24:55-9.

215. Singh GD. Morphologic determinants in the etiology of class III malocclusions: A review. Clin Anat. 1999;12:382-405.

216. Giuntini V, De Toffol L, Franchi L, Baccetti T. Glenoid fossa position in class II malocclusion associated with mandibular retrusion. Angle Orthod. 2008;78:808-12.

217. Innocenti C, Giuntini V, Defraia E, Baccetti T. Glenoid fossa position in class III malocclusion associated with mandibular protrusion. Am J Orthod Dentofacial Orthop. 2009;135:438-41.

218. Kilic N, Kiki A, Oktay H. Condylar asymmetry in unilateral posterior crossbite patients. Am J Orthod Dentofacial Orthop. 2008;133:382-7.

219. Nakano H, Watahiki J, Kubota M, et al. Micro X-ray computed tomography analysis for the evaluation of asymmetrical condylar growth in the rat. Orthod Craniofac Res. 2003;6:168-72.

220. Pinto AS, Buschang PH, Throckmorton GS, Chen P. Morphological and positional asymmetries of young children with functional unilateral posterior crossbite. Am J Orthod Dentofacial Orthop. 2001;120:513-20.

221. Poikela A, Pirttiniemi P, Kantomaa T. Location of the glenoid fossa after a period of unilateral masticatory function in young rabbits. Eur J Orthod. 2000;22:105-12.

222. Akahane Y, Deguchi T, Hunt NP. Morphology of the temporomandibular joint in skeletal class iii symmetrical and asymmetrical cases: A study by cephalometric laminography. J Orthod. 2001;28:119-28.

223. Voudouris JC, Woodside DG, Altuna G, et al. Condyle-fossa modifications and muscle interactions during herbst treatment, part 2. results and conclusions. Am J Orthod Dentofacial Orthop. 2003;124:13-29.

224. Voudouris JC, Woodside DG, Altuna G, Kuftinec MM, Angelopoulos G, Bourque PJ. Condyle-fossa modifications and muscle interactions during herbst treatment, part 1. new technological methods. Am J Orthod Dentofacial Orthop. 2003;123:604-13.

225. Rabie AB, Wong L, Tsai M. Replicating mesenchymal cells in the condyle and the glenoid fossa during mandibular forward positioning. Am J Orthod Dentofacial Orthop. 2003;123:49-57.

226. Rabie AB, Xiong H, Hagg U. Forward mandibular positioning enhances condylar adaptation in adult rats. Eur J Orthod. 2004;26:353-8.

227. Rabie AB, Zhao Z, Shen G, Hagg EU, Dr O, Robinson W. Osteogenesis in the glenoid fossa in response to mandibular advancement. Am J Orthod Dentofacial Orthop. 2001;119:390-400.

228. Woodside DG, Metaxas A, Altuna G. The influence of functional appliance therapy on glenoid fossa remodeling. Am J Orthod Dentofacial Orthop. 1987;92:181-98.

229. Voudouris JC, Woodside DG, Altuna G, Kuftinec MM, Angelopoulos G, Bourque PJ. Condyle-fossa modifications and muscle interactions during herbst treatment, part 1. new technological methods. Am J Orthod Dentofacial Orthop. 2003;123:604-13.

230. de Leeuw R, American Academy of Orofacial Pain. Orofacial Pain : Guidelines for Assessment, Diagnosis, and Management. 4th ed. Chicago: Quintessence Books; 2008:316.

231. Pirttiniemi P, Kantomaa T, Tuominen M. Associations between the location of the glenoid fossa and its remodeling. an experimental study in the rabbit. Acta Odontol Scand. 1991;49:255-9.

232. Pirttiniemi P, Kantomaa T, Tuominen M, Salo L. Articular disc and eminence modeling after experimental relocation of the glenoid fossa in growing rabbits. J Dent Res. 1994;73:536-43.

233. Cordray FE. Three-dimensional analysis of models articulated in the seated condylar position from a deprogrammed asymptomatic population: A prospective study. part 1. Am J Orthod Dentofacial Orthop. 2006;129:619-30.

234. Pullinger AG, Seligman DA, Gornbein JA. A multiple logistic regression analysis of the risk and relative odds of temporomandibular disorders as a function of common occlusal features. J Dent Res. 1993;72:968-79.

235. Mackie A, Lyons K. The role of occlusion in temporomandibular disorders--a review of the literature. N Z Dent J. 2008;104:54-9.

236. Niemi PM, Le Bell Y, Kylmala M, Jamsa T, Alanen P. Psychological factors and responses to artificial interferences in subjects with and without a history of temporomandibular disorders. Acta Odontol Scand. 2006;64:300-5.

237. Le Bell Y, Niemi PM, Jamsa T, Kylmala M, Alanen P. Subjective reactions to intervention with artificial interferences in subjects with and without a history of temporomandibular disorders. Acta Odontol Scand. 2006;64:59-63.

238. Huang BY, Whittle T, Murray GM. A working-side change to lateral tooth guidance increases lateral pterygoid muscle activity. Arch Oral Biol. 2006;51:689-96.

239. Rottner K, Richter EJ, Fanghanel J, et al. Effects of centric relation prematurities of the frontal teeth. Ann Anat. 2007;189:397-403.

240. Mehta NR, Forgione AG, Maloney G, Greene R. Different effects of nocturnal parafunction on the masticatory system: The weak link theory. Cranio. 2000;18:280-6.

241. Cholasueksa P, Warita H, Soma K. Alterations of the rat temporomandibular joint in functional posterior displacement of the mandible. Angle Orthod. 2004;74:677-83.

242. Kokai S, Yabushita T, Zeredo JL, Toda K, Soma K. Functional changes of the temporomandibular joint mechanoreceptors induced by a lateral mandibular shift in rats. Angle Orthod. 2007;77:436-41.

243. Rilo B, da Silva JL, Mora MJ, Cadarso-Suarez C, Santana U. Unilateral posterior crossbite and mastication. Arch Oral Biol. 2007;52:474-8.

244. Rilo B, da Silva JL, Mora MJ, Cadarso-Suarez C, Santana U. Midline shift and lateral guidance angle in adults with unilateral posterior crossbite. Am J Orthod Dentofacial Orthop. 2008;133:804-8.

245. Korbmacher H, Koch L, Eggers-Stroeder G, Kahl-Nieke B. Associations between orthopaedic disturbances and unilateral crossbite in children with asymmetry of the upper cervical spine. Eur J Orthod. 2007;29:100-4.

246. Korbmacher H, Eggers-Stroeder G, Koch L, Kahl-Nieke B. Correlations between dentition anomalies and diseases of the of the postural and movement apparatus--a literature review. J Orofac Orthop. 2004;65:190-203.

247. Korbmacher H, Koch LE, Kahl-Nieke B. Orofacial myofunctional disorders in children with asymmetry of the posture and locomotion apparatus. Int J Orofacial Myology. 2005;31:26-38.

248. Segatto E, Lippold C, Vegh A. Craniofacial features of children with spinal deformities. BMC Musculoskelet Disord. 2008;9:169.

249. Ben-Bassat Y, Yitschaky M, Kaplan L, Brin I. Occlusal patterns in patients with idiopathic scoliosis. Am J Orthod Dentofacial Orthop. 2006;130:629-33.

250. D'Attilio M, Filippi MR, Femminella B, Festa F, Tecco S. The influence of an experimentally-induced malocclusion on vertebral alignment in rats: A controlled pilot study. Cranio. 2005;23:119-29.

251. Rocabado M. Biomechanical relationship of the cranial, cervical, and hyoid regions. J Craniomandibular Pract. 1983;1:61-6.

252. Sahin Saglam AM, Uydas NE. Relationship between head posture and hyoid position in adult females and males. J Craniomaxillofac Surg. 2006;34:85-92.

253. Valenzuela S, Miralles R, Ravera MJ, et al. Does head posture have a significant effect on the hyoid bone position and sternocleidomastoid electromyographic activity in young adults?. Cranio. 2005;23:204-11.

254. Crompton AW, Cook P, Hiiemae K, Thexton AJ. Movement of the hyoid apparatus during chewing. Nature. 1975;258:69-70.

255. Hannam AG, Stavness I, Lloyd JE, Fels S. A dynamic model of jaw and hyoid biomechanics during chewing. J Biomech. 2008;41:1069-76.

256. Hiiemae KM, Palmer JB, Medicis SW, Hegener J, Jackson BS, Lieberman DE. Hyoid and tongue surface movements in speaking and eating. Arch Oral Biol. 2002;47:11-27.

257. Eriksson PO, Haggman-Henrikson B, Nordh E, Zafar H. Co-ordinated mandibular and head-neck movements during rhythmic jaw activities in man. J Dent Res. 2000;79:1378-84.

258. Haggman-Henrikson B, Nordh E, Zafar H, Eriksson PO. Head immobilization can impair jaw function. J Dent Res. 2006;85:1001-5.

259. Haggman-Henrikson B, Eriksson PO. Head movements during chewing: Relation to size and texture of bolus. J Dent Res. 2004;83:864-8.

260. Sale H, Isberg A. Delayed temporomandibular joint pain and dysfunction induced by whiplash trauma: A controlled prospective study. J Am Dent Assoc. 2007;138:1084-91.

261. Haggman-Henrikson B, Osterlund C, Eriksson PO. Endurance during chewing in whiplash-associated disorders and TMD. J Dent Res. 2004;83:946-50.

262. Haggman-Henrikson B, Zafar H, Eriksson PO. Disturbed jaw behavior in whiplash-associated disorders during rhythmic jaw movements. J Dent Res. 2002;81:747-51.

263. Eriksson PO, Haggman-Henrikson B, Zafar H. Jaw-neck dysfunction in whiplash-associated disorders. Arch Oral Biol. 2007;52:404-8.

264. Eriksson PO, Zafar H, Haggman-Henrikson B. Deranged jaw-neck motor control in whiplash-associated disorders. Eur J Oral Sci. 2004;112:25-32.

265. Bergman H, Andersson F, Isberg A. Incidence of temporomandibular joint changes after whiplash trauma: A prospective study using MR imaging. AJR Am J Roentgenol. 1998;171:1237-43.

266. Abdallah EF, Mehta NR, Forgione AG, Clark RE. Affecting upper extremity strength by changing maxillo-mandibular vertical dimension in deep bite subjects. Cranio. 2004;22:268-75.

267. Abduljabbar T, Mehta NR, Forgione AG, et al. Effect of increased maxillo-mandibular relationship on isometric strength in TMD patients with loss of vertical dimension of occlusion. Cranio. 1997;15:57-67.

268. Chakfa AM, Mehta NR, Forgione AG, Al-Badawi EA, Lobo SL, Zawawi KH. The effect of stepwise increases in vertical dimension of occlusion on isometric strength of cervical flexors and deltoid muscles in nonsymptomatic females. Cranio. 2002;20:264-73.

269. Miralles R, Moya H, Ravera MJ, et al. Increase of the vertical occlusal dimension by means of a removable orthodontic appliance and its effect on craniocervical relationships and position of the cervical spine in children. Cranio. 1997;15:221-8.

270. Moya H, Miralles R, Zuniga C, Carvajal R, Rocabado M, Santander H. Influence of stabilization occlusal splint on craniocervical relationships. part I: Cephalometric analysis. Cranio. 1994;12:47-51.

271. Bergamini M, Pierleoni F, Gizdulich A, Bergamini C. Dental occlusion and body posture: A surface EMG study. Cranio. 2008;26:25-32.

272. Fujimoto M, Hayakawa L, Hirano S, Watanabe I. Changes in gait stability induced by alteration of mandibular position. J Med Dent Sci. 2001;48:131-6.

273. Gangloff P, Louis JP, Perrin PP. Dental occlusion modifies gaze and posture stabilization in human subjects. Neurosci Lett. 2000;293:203-6.

274. Tardieu C, Dumitrescu M, Giraudeau A, Blanc JL, Cheynet F, Borel L. Dental occlusion and postural control in adults. Neurosci Lett. 2009;450:221-4.

275. Dangerfield PH, Roche CJ, King SE, Carty HM, Dorgan JC. Rotation of the atlantico-axial joint, investigated using CT and MRI. Stud Health Technol Inform. 2002;88:336-9.

276. Chang W, Alexander MT, Mirvis SE. Diagnostic determinants of craniocervical distraction injury in adults. AJR Am J Roentgenol. 2009;192:52-8.

277. Bono CM, Vaccaro AR, Fehlings M, et al. Measurement techniques for upper cervical spine injuries: Consensus statement of the spine trauma study group. Spine. 2007;32:593-600.

278. Patijn J, Wilmink J, ter Linden FH, Kingma H. CT study of craniovertebral rotation in whiplash injury. Eur Spine J. 2001;10:38-43.

279. Pang D, Nemzek WR, Zovickian J. Atlanto-occipital dislocation--part 2: The clinical use of (occipital) condyle-C1 interval, comparison with other diagnostic methods, and the manifestation, management, and outcome of atlanto-occipital dislocation in children. Neurosurgery. 2007;61:995-1015.

280. Sugimoto Y, Tanaka M, Nakanishi K, Misawa H, Takigawa T, Ozaki T. Assessing the range of cervical rotation in patients with rheumatoid arthritis after atlantoaxial screw fixation using axial CT. Spine. 2007;32:2318-21.

281. Ostensen H, Gudmundsen TE, Haakonsen M, Lagerqvist H, Kaufmann C, Ostensen M. Three dimensional CT evaluation of occipito-atlanto-axial dislocation in rheumatoid arthritis. Scand J Rheumatol. 1998;27:352-6.

282. Cronin CG, Lohan DG, Mhuircheartigh JN, Meehan CP, Murphy J, Roche C. CT evaluation of chamberlain's, McGregor's, and McRae's skull-base lines. Clin Radiol. 2009;64:64-9.

283. Dvorak J, Hayek J, Zehnder R. CT-functional diagnostics of the rotatory instability of the upper cervical spine. part 2. an evaluation on healthy adults and patients with suspected instability. Spine. 1987;12:726-31.

284. Dvorak J, Penning L, Hayek J, Panjabi MM, Grob D, Zehnder R. Functional diagnostics of the cervical spine using computer tomography. Neuroradiology. 1988;30:132-7.

285. Rocabado M, Tapia V. Radiographic study of the craniocervical relation in patients under orthodontic treatment and the incidence of related symptoms. Cranio. 1987;5:36-42.

286. Gradl G, Maier-Bosse T, Penning R, Stabler A. Quantification of C2 cervical spine rotatory fixation by X-ray, MRI and CT. Eur Radiol. 2005;15:376-82.

287. Pang D, Nemzek WR, Zovickian J. Atlanto-occipital dislocation: Part 1--normal occipital condyle-C1 interval in 89 children. Neurosurgery. 2007;61:514-21.

288. Burke PH. Serial observation of asymmetry in the growing face. Br J Orthod. 1992;19:273-85.

289. Jerrold L, Lowenstein LJ. The midline: Diagnosis and treatment. Am J Orthod Dentofacial Orthop. 1990;97:453-62.

290. Ferrario VF, Sforza C, Miani A,Jr, Serrao G. A three-dimensional evaluation of human facial asymmetry. J Anat. 1995;186:103-10.

291. Latta GH,Jr, Weaver JR, Conkin JE. The relationship between the width of the mouth, interalar width, bizygomatic width, and interpupillary distance in edentulous patients. J Prosthet Dent. 1991;65:250-4.

292. Hasanreisoglu U, Berksun S, Aras K, Arslan I. An analysis of maxillary anterior teeth: Facial and dental proportions. J Prosthet Dent. 2005;94:530-8.

293. Cesario VA,Jr, Latta GH,Jr. Relationship between the mesiodistal width of the maxillary central incisor and interpupillary distance. J Prosthet Dent. 1984;52:641-3.

294. Henry SW, Levin MP, Tsaknis PJ. Histologic features of the superior labial frenum. J Periodontol. 1976;47:25-8.

295. Ferguson MW, Rix C. Pathogenesis of abnormal midline spacing of human central incisors. A histological study of the involvement of the labial frenum. Br Dent J. 1983;154:212-8.

296. Edwards JG. The diastema, the frenum, the frenectomy: A clinical study. Am J Orthod. 1977;71:489-508.

297. Fialova S. The anatomy of soft tissues of the lower vestibule in relationship to periodontal tissues of the lower incisor teeth. epidemiological study. Acta Univ Palacki Olomuc Fac Med. 1988;120:357-65.

298. dos Santos VI, Korytnicki D, Ando T, Lascala NT. [Prevalence of different types of upper labial frenum in the deciduous dentition]. Rev Fac Odontol Sao Paulo. 1985;23:129-35.

299. Gartner LP, Schein D. The superior labial frenum: A histologic observation. Quintessence Int. 1991;22:443-5.

300. Martin RA, Jones KL. Absence of the superior labial frenulum in holoprosencephaly: A new diagnostic sign. J Pediatr. 1998;133:151-3.

301. Youko K, Satoshi F, Kubota K, Goto G. Clinical evaluation of a patient with single maxillary central incisor. J Clin Pediatr Dent. 2002;26:181-6.

302. Mintz SM, Siegel MA, Seider PJ. An overview of oral frena and their association with multiple syndromic and nonsyndromic conditions. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;99:321-4.

303. Gartner LP, Schein D. The superior labial frenum: A histologic observation. Quintessence Int. 1991;22:443-5.

304. Latta GH,Jr. The midline and its relation to anatomic landmarks in the edentulous patient. J Prosthet Dent. 1988;59:681-3.

305. Garcia de Mitchell CA, Pessa JE, Schaverien MV, Rohrich RJ. The philtrum: Anatomical observations from a new perspective. Plast Reconstr Surg. 2008;122:1756-60.

306. Gazit-Rappaport T, Weinreb M, Gazit E. Quantitative evaluation of lip symmetry in functional asymmetry. Eur J Orthod. 2003;25:443-50.

307. Gazit-Rappaport T, Gazit E, Weinreb M. Quantitative evaluation of lip symmetry in skeletal asymmetry. Eur J Orthod. 2007;29:345-9.

308. Trpkova B, Prasad NG, Lam EW, Raboud D, Glover KE, Major PW. Assessment of facial asymmetries from posteroanterior cephalograms: Validity of reference lines. Am J Orthod Dentofacial Orthop. 2003;123:512-20.

309. Kamiishi H, Miyasato Y, Kosaka M. Development of the 3D-cephalogram: A technical note. J Craniomaxillofac Surg. 2007;35:258-60.

310. Gu Y, McNamara JA,Jr. Cephalometric superimpositions. Angle Orthod. 2008;78:967-76.

311. Furst IM, Austin P, Pharoah M, Mahoney J. The use of computed tomography to define zygomatic complex position. J Oral Maxillofac Surg. 2001;59:647-54.

312. Hartmann J, Meyer-Marcotty P, Benz M, Hausler G, Stellzig-Eisenhauer A. Reliability of a method for computing facial symmetry plane and degree of asymmetry based on 3D-data. J Orofac Orthop. 2007;68:477-90.

313. Huisinga-Fischer CE, Zonneveld FW, Vaandrager JM, Prahl-Andersen B. CT-based size and shape determination of the craniofacial skeleton: A new scoring system to assess bony deformities in hemifacial microsomia. J Craniofac Surg. 2001;12:87-94.

314. Hwang HS, Hwang CH, Lee KH, Kang BC. Maxillofacial 3-dimensional image analysis for the diagnosis of facial asymmetry. Am J Orthod Dentofacial Orthop. 2006;130:779-85.

315. Hwang HS, Youn IS, Lee KH, Lim HJ. Classification of facial asymmetry by cluster analysis. Am J Orthod Dentofacial Orthop. 2007;132:279.e1,279.e6.

316. Katsumata A, Fujishita M, Maeda M, Ariji Y, Ariji E, Langlais RP. 3D-CT evaluation of facial asymmetry. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;99:212-20.

317. Kwon TG, Park HS, Ryoo HM, Lee SH. A comparison of craniofacial morphology in patients with and without facial asymmetry--a three-dimensional analysis with computed tomography. Int J Oral Maxillofac Surg. 2006;35:43-8.

318. Lagravere MO, Major PW. Proposed reference point for 3-dimensional cephalometric analysis with cone-beam computerized tomography. Am J Orthod Dentofacial Orthop. 2005;128:657-60.

319. Maeda M, Katsumata A, Ariji Y, et al. 3D-CT evaluation of facial asymmetry in patients with maxillofacial deformities. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;102:382-90.

320. Moate SJ, Geenty JP, Shen G, Darendeliler MA. A new craniofacial diagnostic technique: The sydney diagnostic system. Am J Orthod Dentofacial Orthop. 2007;131:334-42.

321. Netherway DJ, Abbott AH, Gulamhuseinwala N, et al. Three-dimensional computed tomography cephalometry of plagiocephaly: Asymmetry and shape analysis. Cleft Palate Craniofac J. 2006;43:201-10.

322. Ono I, Ohura T, Narumi E, et al. Three-dimensional analysis of craniofacial bones using three-dimensional computer tomography. J Craniomaxillofac Surg. 1992;20:49-60.

323. Cevidanes LH, Styner MA, Proffit WR. Image analysis and superimposition of 3-dimensional cone-beam computed tomography models. Am J Orthod Dentofacial Orthop. 2006;129:611-8.

324. Kyrkanides S, Klambani M, Subtelny JD. Cranial base and facial skeleton asymmetries in individuals with unilateral cleft lip and palate. Cleft Palate Craniofac J. 2000;37:556-61.

325. Baek SH, Cho IS, Chang YI, Kim MJ. Skeletodental factors affecting chin point deviation in female patients with class III malocclusion and facial asymmetry: A three-dimensional analysis using computed tomography. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;104:628-39.

326. Sonnesen L, Pedersen CE, Kjaer I. Cervical column morphology related to head posture, cranial base angle, and condylar malformation. Eur J Orthod. 2007;29:398-403.

327. Periago DR, Scarfe WC, Moshiri M, Scheetz JP, Silveira AM, Farman AG. Linear accuracy and reliability of cone beam CT derived 3-dimensional images constructed using an orthodontic volumetric rendering program. Angle Orthod. 2008;78:387-95.

328. Olszewski R, Reychler H, Cosnard G, Denis JM, Vynckier S, Zech F. Accuracy of three-dimensional (3D) craniofacial cephalometric landmarks on a low-dose 3D computed tomograph. Dentomaxillofac Radiol. 2008;37:261-7.

329. Loubele M, Jacobs R, Maes F, et al. Image quality vs radiation dose of four cone beam computed tomography scanners. Dentomaxillofac Radiol. 2008;37:309-18.

330. Lutz J, Jager V, Hempel MJ, Srivastav S, Reiser M, Jager L. Delineation of temporal bone anatomy: Feasibility of low-dose 64-row CT in regard to image quality. Eur Radiol. 2007;17:2638-45.

331. Lagravere MO, Carey J, Toogood RW, Major PW. Three-dimensional accuracy of measurements made with software on cone-beam computed tomography images. Am J Orthod Dentofacial Orthop. 2008;134:112-6.

332. Stratemann SA, Huang JC, Maki K, Miller AJ, Hatcher DC. Comparison of cone beam computed tomography imaging with physical measures. Dentomaxillofac Radiol. 2008;37:80-93.

333. Matteson SR, Bechtold W, Phillips C, Staab EV. A method for three-dimensional image reformation for quantitative cephalometric analysis. J Oral Maxillofac Surg. 1989;47:1053-61.

334. Horner K, Islam M, Flygare L, Tsiklakis K, Whaites E. Basic principles for use of dental cone beam computed tomography: Consensus guidelines of the european academy of dental and maxillofacial radiology. Dento-Maxillo-Facial Radiology. 2009;38:187-95.

335. Bidra AS, Uribe F, Taylor TD, Agar JR, Rungruanganunt P, Neace WP. The relationship of facial anatomic landmarks with midlines of the face and mouth. J Prosthet Dent. 2009;102:94-103.

336. Zhang Z, Song Y, Zhao X, Zhang X, Fermin C, Chen Y. Rescue of cleft palate in Msx1-deficient mice by transgenic Bmp4 reveals a network of BMP and shh signaling in the regulation of mammalian palatogenesis. Development. 2002;129:4135-46. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med4&AN=12163415.

337. Hilliard SA, Yu L, Gu S, Zhang Z, Chen YP. Regional regulation of palatal growth and patterning along the anterior-posterior axis in mice. . Accessed 5, 207.

338. Yu L, Gu S, Alappat S, et al. Shox2-deficient mice exhibit a rare type of incomplete clefting of the secondary palate. . Accessed 19, 132.

339. Liu KJ, Arron JR, Stankunas K, Crabtree GR, Longaker MT. Chemical rescue of cleft palate and midline defects in conditional GSK-3beta mice. Nature. 2007;446:79-82. Available from:

http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=17293880.

340. Shapiro R, Schorr S. A consideration of the systemic factors that influence frontal sinus pneumatization. Invest Radiol. 1980;15:191-202.

341. Marquez S, Laitman JT. Climatic effects on the nasal complex: A CT imaging, comparative anatomical, and morphometric investigation of macaca mulatta and macaca fascicularis. Anatomical Record (Hoboken, N.J.: 2007). :1420:291(11),2008 No. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=18951486.

342. Fatu C, Puisoru M, Rotaru M, Truta AM. Morphometric evaluation of the frontal sinus in relation to age. Annals of Anatomy. 2006;188:275-80. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med4&AN=16711167.

343. Bourdiol P, Mishellany-Dutour A, Abou-El-Karam S, Nicolas E, Woda A. Is the tongue position influenced by the palatal vault dimensions?. J Oral Rehabil. 2010;37:100-6. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=19925581.

344. Takada J, Ono T, Takahashi S, Honda E, Kurabayashi T. Changes in horizontal jaw position and intraoral pressure. Angle Orthod. 2008;78:254-61.

345. Kean MR, Houghton P. The role of function in the development of human craniofacial form--a perspective. Anat Rec. 1987;218:107-10.

346. Haraguchi S, Iguchi Y, Takada K. Asymmetry of the face in orthodontic patients. Angle Orthod. 2008;78:421-6.

347. Haraguchi S, Takada K, Yasuda Y. Facial asymmetry in subjects with skeletal class III deformity. .

348. Lee M, Chung DH, Lee J, Cha K. Assessing soft-tissue characteristics of facial asymmetry with photographs. . Accessed 1, 138.

349. Fong JH, Wu H, Huang M, et al. Analysis of facial skeletal characteristics in patients with chin deviation. . Accessed 1, 73.

350. Haraguchi S, Iguchi Y, Takada K. Asymmetry of the face in orthodontic patients. .

351. Huggare J, Houghton P. Associations between atlantoaxial and craniomandibular anatomy. . Accessed 1, 60.

352. Solow B, Sonnesen L. Head posture and malocclusions. Eur J Orthod. 1998;20:685-93.

353. Solow B, Sandham A. Cranio-cervical posture: A factor in the development and function of the dentofacial structures. Eur J Orthod. 2002;24:447-56.

354. Villas C, Arriagada C, Zubieta JL. Preliminary CT study of C1-C2 rotational mobility in normal subjects. Eur Spine J. 1999;8:223-8.

355. Rojas CA, Hayes A, Bertozzi JC, Guidi C, Martinez CR. Evaluation of the C1-C2 articulation on MDCT in healthy children and young adults. . Accessed 5, 193.

356. Eskelsen E, Fernandes CB, Pelogia F, et al. Concurrence between the maxillary midline and bisector to the interpupillary line. . Accessed 1, 21.

357. Maharani DA. Perceived need for and utilization of dental care in indonesia in 2006 and 2007: A secondary analysis. J Oral Sci. 2009;51:545-50. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=20032606.

358. Stahlnacke K, Soderfeldt B, Unell L, Halling A, Axtelius B. Changes over 5 years in utilization of dental care by a swedish age cohort. Community Dentistry & Oral Epidemiology. 2005;33:64-73. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med4&AN=15642048.

359. Skaret E, Raadal M, Kvale G, Berg E. Gender-based differences in factors related to non-utilization of dental care in young norwegians. A longitudinal study. Eur J Oral Sci. 2003;111:377-82. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med4&AN=12974679.

360. Swank ME, Vernon SW, Lairson DR. Patterns of preventive dental behavior. Public Health Rep. 1986;101:175-84. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med2&AN=3083472.

361. Marklund S, Wanman A. Incidence and prevalence of myofascial pain in the jaw-face region. A one-year prospective study on dental students. Acta Odontol Scand. 2008;66:113-21. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=18446553.

362. Jensen U, Ruf S. Longitudinal changes in temporomandibular disorders in young adults: Indication for systematic temporomandibular joint screening. Journal of Orofacial Orthopedics. 2007;68:501-9. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=18034290.

363. Goncalves DA, Dal Fabbro AL, Campos JA, Bigal ME, Speciali JG. Symptoms of temporomandibular disorders in the population: An epidemiological study. J Orofac Pain. 2010;24:270-8. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=20664828.

364. Ribeiro RF, Tallents RH, Katzberg RW, et al. The prevalence of disc displacement in symptomatic and asymptomatic volunteers aged 6 to 25 years. J Orofac Pain. 1997;11:37-47.

365. Flores-Mir C, Nebbe B, Heo G, Major PW. Longitudinal study of temporomandibular joint disc status and craniofacial growth. American Journal of Orthodontics & Dentofacial Orthopedics. 2006;130:324-30. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med4&AN=16979490.

366. Murray GM, Bhutada M, Peck CC, Phanachet I, Sae-Lee D, Whittle T. The human lateral pterygoid muscle. Arch Oral Biol. 2007;52:377-80.

367. Osborn JW. Biomechanical implications of lateral pterygoid contribution to biting and jaw opening in humans. Arch Oral Biol. 1995;40:1099-108.

368. Matsunaga K, Usui A, Yamaguchi K, Akita K. An anatomical study of the muscles that attach to the articular disc of the temporomandibular joint. Clinical Anatomy. 2009;22:932-40. Available from:

http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=19806671.

369. Peterson LJ, Naidoo LCD. Lateral pterygoid muscle and its relationship to the meniscus of the temporomandibular joint. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 1996;82:4-9.

370. Mazza D, Marini M, Impara L, et al. Anatomic examination of the upper head of the lateral pterygoid muscle using magnetic resonance imaging and clinical data. J Craniofac Surg. 2009;20:1508-11. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=19816287.

371. Matsumoto R, Ioi H, Goto TK, et al. Relationship between the unilateral TMJ osteoarthritis/osteoarthrosis, mandibular asymmetry and the EMG activity of the masticatory muscles: A retrospective study. .

372. Sinsel NK, Opdebeeck H, Guelinckx PJ. Mandibular condylar growth alterations after unilateral partial facial paralysis: An experimental study in the rabbit. Plast Reconstr Surg. 2002;109:181-9.

373. Ciobanu IC, Motoc A, Jianu AM, Cergan R, Banu MA, Rusu MC. The maxillary recess of the sphenoid sinus. Romanian Journal of Morphology & Embryology. 2009;50:487-9. Available from:

http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=19690779.

374. Lewin JS, Curtin HD, Eelkema E, Obuchowski N. Benign expansile lesions of the sphenoid sinus: Differentiation from normal asymmetry of the lateral recesses. Ajnr: American Journal of Neuroradiology. 1999;20:461-6. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med4&AN=10219412.

375. Spaeth J, Krugelstein U, Schlondorff G. The paranasal sinuses in CT-imaging: Development from birth to age 25. Int J Pediatr Otorhinolaryngol. 1997;39:25-40.

376. Welker KM, DeLone DR, Lane JI, Gilbertson JR. Arrested pneumatization of the skull base: Imaging characteristics. AJR.American Journal of Roentgenology. 2008;190:1691-6. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=18492926.

377. Shah RK, Dhingra JK, Carter BL, Rebeiz EE. Paranasal sinus development: A radiographic study. Laryngoscope. 2003;113:205-9.

378. Yonetsu K, Watanabe M, Nakamura T. Age-related expansion and reduction in aeration of the sphenoid sinus: Volume assessment by helical CT scanning. Ajnr: American Journal of Neuroradiology. 2000;21:179-82. Available from:

http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med4&AN=10669247.

379. Rae TC, Vidarsdottir US, Jeffery N, Steegmann AT. Developmental response to cold stress in cranial morphology of rattus: Implications for the interpretation of climatic adaptation in fossil hominins. Proc Biol Sci. 2006;273:2605-10.

380. Rae TC, Koppe T. Independence of biomechanical forces and craniofacial pneumatization in cebus. Anatomical Record (Hoboken, N.J.: 2007). :1414:291(11),2008 No. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=18951480.

381. Kim YH, Sato K, Mitani H, Shimizu Y, Kikuchi M. Asymmetry of the sphenoid bone and its suitability as a reference for analyzing craniofacial asymmetry. Am J Orthod Dentofacial Orthop. 2003;124:656-62.

382. Teul I, Czerwinski F, Gawlikowska A, Konstanty-Kurkiewicz V, Slawinski G. Asymmetry of the ovale and spinous foramina in mediaeval and contemporary skulls in radiological examinations. Folia Morphol (Warsz). 2002;61:147-52.

383. Sarac-Hadzihalilovic A, Dilberovic F. Study on skull asymmetry. . Accessed 3, 4.

384. Rosas A, Bastir M, Alarcon JA, Kuroe K. Thin-plate spline analysis of the cranial base in african, asian and european populations and its relationship with different malocclusions. .

385. Hayashi I. Morphological relationship between the cranial base and dentofacial complex obtained by reconstructive computer tomographic images. Eur J Orthod. 2003;25:385-91.

386. Richtsmeier JT, Deleon VB. Morphological integration of the skull in craniofacial anomalies. Orthod Craniofac Res. 2009;12:149-58.

387. McCane B, Kean MR. Integration of parts in the facial skeleton and cervical vertebrae. American Journal of Orthodontics & Dentofacial Orthopedics. 2011;139:e13-30. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=21195254.

388. Hallgrimsson B, Lieberman DE, Liu W, Ford-Hutchinson AF, Jirik FR. Epigenetic interactions and the structure of phenotypic variation in the cranium. Evol Dev. 2007;9:76-91. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=17227368.

389. Bastir M. A systems-model for the morphological analysis of integration and modularity in human craniofacial evolution. J anthropol sci. 2008;86:37-58.

390. Bastir M, Rosas A, O'higgins P. Craniofacial levels and the morphological maturation of the human skull. J Anat. 2006;209:637-54.

391. Neubauer S, Gunz P, Hublin JJ. The pattern of endocranial ontogenetic shape changes in humans. J Anat. 2009;215:240-55. Available from: http://ezproxy.library.tufts.edu/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=19531085.

392. Moss ML. The functional matrix hypothesis revisited. 3. the genomic thesis. Am J Orthod Dentofacial Orthop. 1997;112:338-42.

393. Singh GD, Levy-Bercowski D, Yanez MA, Santiago PE. Three-dimensional facial morphology following surgical repair of unilateral cleft lip and palate in patients after nasoalveolar molding. Orthod Craniofac Res. 2007;10:161-6.

V> APPENDICES

Appendix 1

Bellberry IRB Approval Letter

[illegible]
www.bellberry.com.au ABN [illegible]

Bb Bellberry Limited

MJ:ch
Ref No: C192/09

21 January 2010

Dr Karen McCloy
95 Morayfield Road
Caboolture QLD 4510

Dear Dr McCloy

Re: Coincidence of the Cranial Base, Facial, and Upper Cervical Midlines, and Soft Tissue Markers of the Face; and their Correlation with Cranial Base and Facial Asymmetry

- Letter dated 18/9/09 re Tufts approval of project and signatory page
- Protocol Version 2 dated 5/1/10
- Appendices:
  - 1. Informed Consent Form
  - 2. VAS Form Discomfort Scale
  - 3. RDC Diagnostic Criteria Form – History Questionnaire
  - 4. Medical History and Epworth Scale of Daytime Tiredness and Sleep Hygiene
  - Photographic Release Form

Date of Meeting:	**18 November 2009**
Date of Approval:	**21 January 2010**
Period of Approval:	**30 June 2011**

Thank you for your correspondence dated 6 January 2010 in response to the Bellberry Human Research Ethics Committee's further questions after review of the above study. I confirm that amendments to the documentation have been made in accordance with the recommendations made by the committee.

I now have pleasure in advising that the Bellberry Human Research Ethics Committee has approved this project subject to the conditions mentioned below.

CONDITIONS:-

- **THAT YOU ACKNOWLEDGE YOUR AGREEMENT TO THE UNDER MENTIONED CONDITIONS BY SIGNING AND RETURNING THE ATTACHED COPY OF THIS LETTER, PRIOR TO THE COMMENCEMENT OF THE RESEARCH**

- The data collected for the purpose of this research project cannot be used for any other purpose without the approval of the Bellberry Human Research Ethics Committee. Requests to use this data for other purposes must be made in the form of a formal research proposal.

- All research data, including electronic data is to be stored by the principal for 15 years after the research has been completed or after the last contact, whichever is the later. Data must be recorded in a durable and appropriately referenced form and comply with relevant privacy protocols.
- That copies of all completed consent forms and any other data used in this research may be inspected at any time by representatives of the Bellberry Human Research Ethics Committee.
- That a report on the progress of the research will be made to the Bellberry Human Research Ethics Committee in ***January 2011*** and then annually for the duration of the trial. This report is to indicate whether any ethical problems or complications have arisen, particularly side effects of drugs used or any other factor which may result in the investigation not producing any result (as distinct from the anticipated result).
- That you will notify the Bellberry Human Research Ethics Committee of any changes that may be required within the research proposal.
- Bellberry Human Research Ethics Committee approval is conditional upon your meeting any statutory obligations that you may have in relation to this project.
- That you will immediately notify the Bellberry Human Research Ethics Committee of any serious or unexpected adverse effect on participants as per guidelines posted on the website www.bellberry.com.au.
- Any extension to the initial approval period is to be requested in writing together with the inclusion of a progress report.
- That you will provide a copy of the final analysis report when this becomes available.

This study has been given the reference number C192/09. Please quote this number, plus the Protocol number and the Investigators name in all further correspondence.

Please do not hesitate to contact me if further clarification is required.

Yours sincerely

Michael James

DR MICHAEL JAMES
CHAIRMAN
BELLBERRY HUMAN RESEARCH ETHICS COMMITTEE

Appendix 2

Informed Consent Form

Title of Research Study : Coincidence of Midlines of Cranial Base, Facial and Upper Cervical Structures and Soft Tissue Markers in a Normal Population on Cone Beam Computerized Tomography.

Principal Investigator: Dr Karen McCloy BDSc
Co Investigator : Dr Steven Scrivani DMD,DMedSc

Emergency Contact: Dr Karen McCloy
McCloy Dental
95 Morayfield Road Caboolture 4510
Tel: 54 957988 E-mail: mccloy@skymesh.com.au

Purpose of the Study

It has been reported that midline positioning of the mandible, (lower jaw) is an important factor in the establishment of a therapeutic jaw position for treatment of jaw, head and neck pain. The purpose of this study is to investigate if the midlines of the face and upper structures of the neck are coincident with the midline of the skull base, and if there is a soft tissue facial point that can be used for identification of the correct midline position for the purposes of taking a bite. We want to know if midline points on the skin of the face and the middle of the base of the skull and face as seen and measured on an x-ray, all fall on the same line.

This study is conducted under the auspices of the Masters of Science programme of Distance Dental Education of Tufts University School of Dental Medicine and Tufts Cranio-facial Pain Centre in Boston, MA.

Participant Information

You are being invited asked to join this study because your treatment requires that you have a CBCT scan or x-ray using the i-Cat Classic machine. The purpose of this study is to determine a way to align the lower jaw to the correct facial midline position when a bite has to be taken for dental treatment .We wish to determine a way to align the jaws during treatment of facial pain in a general dental population.

You will be one of 120 adults whose radiographic data will be used for the purposes of this study. You will also have photographs of your mouth. face and posture taken, as well as plaster models made o f your teeth.

Location

You will be asked to come to McCloy Dental Practice at 95 Morayfield Rd Caboolture on a week day between 9.00am and 5.00 pm.

Study Procedures

1. Positions of 5 soft tissue points around your mouth and face will be marked with filling material, which can be removed with no residue after the procedure.
2. A 20 second x-ray will be taken on the I - Cat x-ray machine.
3. Impressions of your upper and lower teeth will be taken.
4. Photographs will be taken of your mouth, face and posture.

It is estimated that the study procedures should require 20 minutes

Risks

This research study involves exposure to ionising radiation. As part of every day living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 to 3 millisieverts (mSv) each year. The effective dose from this study is about .068mSv. At this dose level, no harmful effects of radiation have been demonstrated, and the risk is negligible.

Other possible risks include allergy to the filling or impression material, discomfort sitting in the x-ray chair or dental chair, and swallowing or inhaling impression material.

In any of the above cases, the subject you will be excused from the study. In addition the research team will make every effort to keep all of the information you tell us during the study strictly confidential, as required by law. All participant records will be kept under lock and key by the principle investigator, and will be available only to the investigators and research staff. After analyzing the results of the study, all data which can possibly identify you will be destroyed.

Benefits

The benefit to the participant is that the CBCT x-rays taken will be thoroughly analysed by the primary investigator. At the completion of the study, all participants will be contacted by telephone or email, and the details of these findings discussed if you wish. All of our 3dimensional x-rays are analysed by an oromaxillofacial radiologist. Any significant findings from that examination will be relayed to you immediately by your treating dentist.

Alternatives

You may choose to join the study, or you may choose not to join the study. Your participation is voluntary. You can stop participation at any time without any negative consequences. You do not have to answer any questions that you do not want to.

There is no penalty if you choose not to join the study. You will lose no benefits or advantages that are now coming to you, or would come to you in the future. If you do not choose to volunteer in the research study, your dental treatment will continue as
planned with your dentist. You will still have the radiograph that you will require, and it will not be used in the study.

Costs

There are no costs to participate in the study. You will be charged for your radiograph as decided between yourself and your dentist. Participants in the study will not incur a charge for their CBCT scan.

Investigators Benefits

Your study doctor is not being remunerated to conduct this study.

Payment

There will be no payment for participating in the study.

Compensation for Injury

If as a result of your participation in this study you become ill or get injured, immediately advise your study investigator of your condition. In the first instance your study doctor will evaluate your condition and then discuss treatment with both you and your regular treating doctor.

Since you are participating in a non-sponsored trial, any question about compensation must initially be directed to the study investigator who will advise their insurer to the matter. However, it would be prudent to seek independent legal advice before accepting any offer of monetary compensation.

Completion and Withdrawal.

This study is expected to end after all participants have completed all study related procedures, and all the information has been collected. The information collected may be used in a future study, or for educational purposes. The study may be stopped without your consent for the following reasons:

- The Principal Investigator feels it is best for your safety and/or health. You will be informed of the reasons why your participation has ceased.
- You have not followed the study instructions.
- The Principal Investigator or the Office of the Vice Provost at Tufts University can stop the study anytime.

You have the right to withdraw from the research study anytime during the study. You have the right to request that any or all of your information collected to date be withdrawn. There is no penalty or loss of benefits if you do so.

Advice and Information

If you have any further questions regarding this study, please do not hesitate to contact Dr Karen McCloy on 54 957988

The Bellberry Human Research Ethics Committee has reviewed this study in accordance with the National statement on Ethical Conduct in Human Research (2007). Should you wish to discuss the study or view a copy of the complaint procedure with someone not directly involved, particularly in relation to matters concerning policies, information or complaints about the conduct of the study or your rights as a participant, you may contact the Committee chair, Bellberry Human Research Ethics Committee on 08 8361 3222.

All study participants will be provided with a copy of the information sheet and consent form for their personal records.

Title of Research Study : Coincidence of Midlines of Cranial Base, Facial and Upper Cervical Structures and Soft Tissue Markers in a Normal Population on Cone Beam Computerized Tomography.

Consent Form

Title of Research Study : Coincidence of Midlines of Cranial Base, Facial and Upper Cervical Structures and Soft Tissue Markers in a Normal Population on Cone Beam Computerized Tomography.

I have read this consent form and have discussed with Dr._____ or his/her representative the procedures described above. I have been given the opportunity to ask questions, which have been answered to my satisfaction. I understand that any questions I might have will be answered verbally or, if I prefer, with a written statement.

I have been told that no information regarding my medical history will be divulged and the results of any tests involving me will not be published so as to reveal my identity.

I understand that I will be informed of any new findings developed during the course of this research study.

I understand that participation in this research study is voluntary. I understand that I may refuse to participate in this study. I also understand that if, for any reason, I wish to discontinue participation in this study at any time, I will be free to do so, and this will have no effect on my future care or treatment by my doctors or this practice.

I have been fully informed of the above described study with its risks and benefits, and I hereby consent to the procedures set forth above. I have received a signed copy of this consent form.

_____	_____	_____
Participant signature	Participant print name	Date

I have fully explained to _____ the nature and purpose of
Participant
the above described study and the risks that are involved in its performance. Consent was freely given by the participant, and I have answered all questions to the best of my ability.

_____
Principal Investigator or Representative

Appendix 3

Photographic Release Form

Title of Research Study : Coincidence of Midlines of Cranial Base, Facial and Upper Cervical Structures and Soft Tissue Markers in a Normal Population on Cone Beam Computerized Tomography.

Principal Investigator: Dr Karen McCloy BDSc
Co Investigator : Dr Steven Scrivani DMD,DMedSc

Emergency Contact: Dr Karen McCloy
McCloy Dental
95 Morayfield Road Caboolture 4510
Tel: 54 957988
E-mail: mccloy@skymesh.com.au

Date:_____**Participant**_____

By checking the appropriate box below, I do freely give my consent that photographs are taken as part of the procedures to be done for this study.

I agree to take part in the photography part of the study: Yes ❑ No ❑

If you ticked "Yes", you must sign this form in the nominated place, if you ticked "No" you do not need to sign this form.

For those that ticked the "Yes" box, you agree to be photographed at the records visit, and understand your identity will be kept confidential.

Your identity will be protected through alteration of the photos. You will not be identified by name in relation to any photo.

Participant Print Name: _____

Participant Signature: _____ Date:_____

Investigator Print Name: _____

Investigator Signature: _____ Date: _____

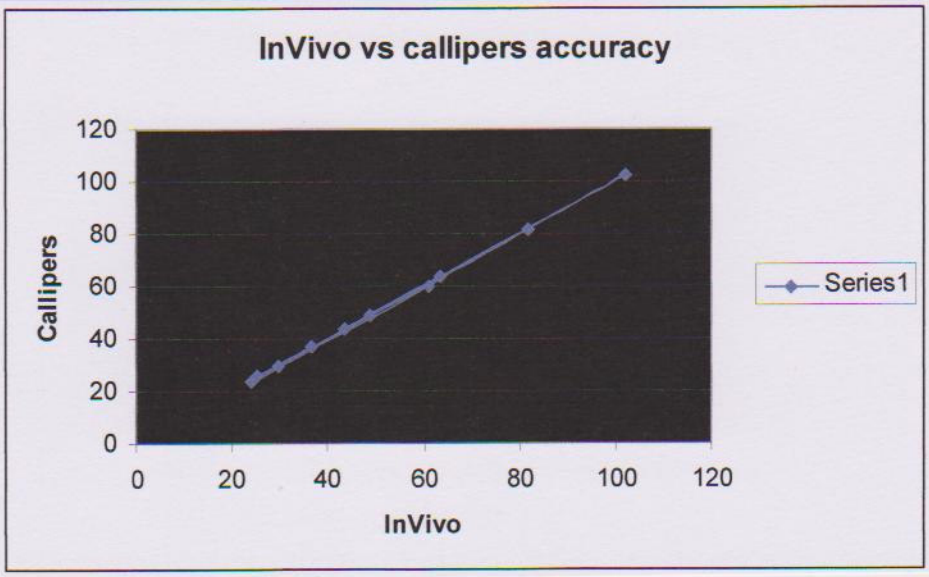
Appendix 4

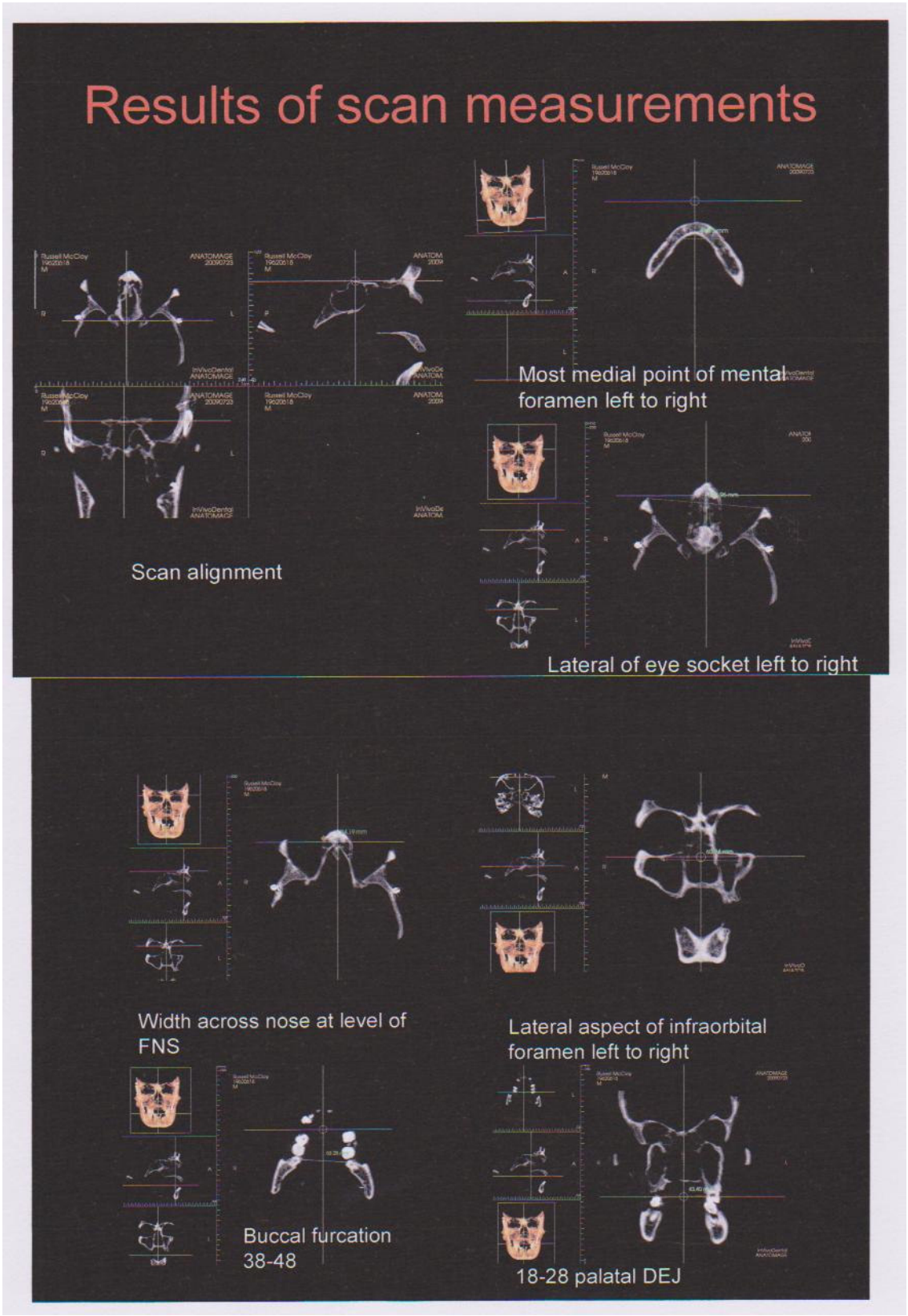
Trial measurements InVivoDental versus Digital Callipers on Skull

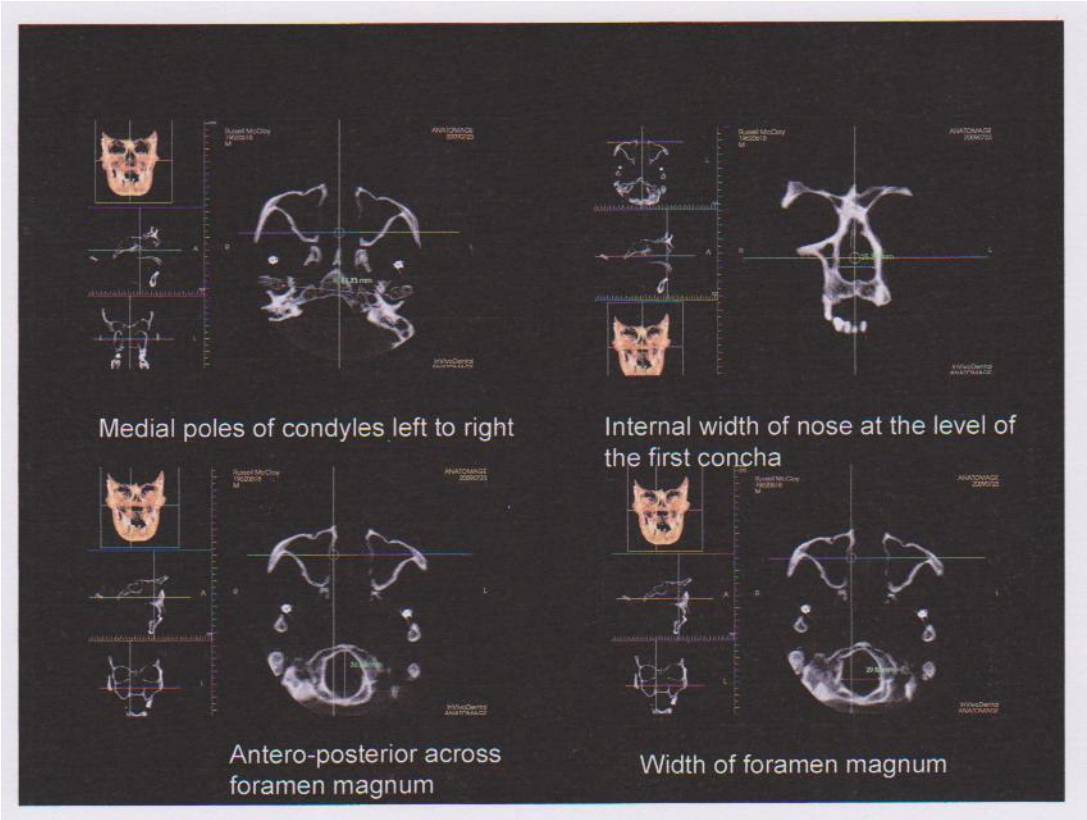
Points	InVivo	Callipers	Difference
Most medial point on mental foramen left to right	48.93	48.98	.05
Most lateral part of eye socket left to right	101.96	101.96	0
Width across nose at level of frontonasal suture	24.19	23.89	.30
Lateral aspect of infraorbital foramen left to right	60.94	60.1	.83
Buccal furcation of 38-48	63.28	63.43	.18
18-28 DEJ-DEJ on palatal	43.4	43.86	.46
Medial poles of condyles left to right	81.73	81.52	.21
Width of foramen magnum at the distal aspect of occipital condyles	29.82	29.65	.17
Anteroposterior measurement of foramen magnum	36.66	36.79	.13
Internal width of nose at level of first concha	25.39	25.66	.27

Conclusions

- The average difference in measurements between using digital callipers and the InVivo measuring tool was .26mm
- It is difficult using CBCT to repeatably measure from a number of different positions unless those positions are marked
- Empirical measurements made on the InVivo software from 1 anatomic point to another may not be accurate unless the anatomic point is marked, as it is very easy to measure from different starting and finishing points due to the delicacy of the tool.
- The inaccuracy stems not from the precision of the InVivo tool, but from the difficulty in placing such a small cursor in exactly the same position on an anatomically variable structure.
- Measurements made at the same time using the same reference point on an x-ray in InVivo should be proportionally accurate




Results of scan measurements
Scan alignment
Most medial point of mental foramen left to right
Lateral of eye socket left to right
Width across nose at level of FNS
Buccal furcation 38-48
Lateral aspect of infraorbital foramen left to right
18-28 palatal DEJ


Medial poles of condyles left to right
Internal width of nose at the level of the first concha
Antero-posterior across foramen magnum
Width of foramen magnum

Appendix 5

VAS Form

Name _____ Date _____

Discomfort Scale

These are discomfort scales. For each part of the body there are horizontal rows, one for the left and one for the right. Please report your average discomfort for the last 7 days by circling the rating from 0 to 10 which best reflects your discomfort.

0 being no pain – 10 being unbearable pain

Bite symptoms or bite changes	R	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
TMJ joint pain	R	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
TMJ joint sounds	R	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Headaches	R	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Facial pain	R	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Eye symptoms	R	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Ear pain	R	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Stuffy ears or ringing sounds	R	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Neck pain	R	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Arm/hand/finger (numbness, tingling or pain)	R	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Upper back pain	R	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Lower back pain	R	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Pain in shoulder	R	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Pain on raising shoulder	R	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Difficulty raising shoulder	R	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10

Other Questions – please tick & answer in space provided			
Have you suffered trauma? Where? Age when it happened -	YES ☐ NO ☐	Have you been involved in an accident? Age when it happened -	YES ☐ NO ☐
Have you had surgery? Where? When?	YES ☐ NO ☐	Do you have trouble swallowing? When?	YES ☐ NO ☐
Have you experienced Vertigo? (dizziness, head spins) When?	YES ☐ NO ☐	Do you grind or clench your teeth? When?	YES ☐ NO ☐

Signature _____ Date _____

Appendix 6

RDC Diagnostic Criteria Forms

HISTORY QUESTIONNAIRE

ID# _____ Date:__ / ___ / ____

Please read each question and respond accordingly.
For each of the questions below circle only one response.

1. Would you say your health in general is excellent, very good, good, fair or poor?				
Excellent 1	Very good 2	Good 3	Fair 4	Poor 5
2. Would you say your oral health in general is excellent, very good, good, fair or poor?				
Excellent 1	Very good 2	Good 3	Fair 4	Poor 5
3. Have you had pain in the face, jaw, temple, in front of the ear or in the ear in the past month?				
Yes 0	No 1	**If no pain in the past month, SKIP to question 14 If yes, go to question 4a**		
4.a. How many years ago did your facial pain begin for the first time? years ago				
If one year ago or more SKIP to question 5 , If less than one year ago, code 00				
4.b. How many months ago did your facial pain begin for the first time? months ago				
5. Is your facial pain persistent, recurrent or was it only a one-time problem?				
Persistent 1	Recurrent 2	One-Time 3		
6. Have you ever gone to a physician, dentist, chiropractor or other health professional for facial ache or pain?				
No 1	Yes, in the last 6 months. 2	Yes, more than 6 months ago 3		
7. How would you rate your facial pain on a 0 to 10 scale at the present time, that is right now, where 0 is "no pain" and 10 is "pain as bad as could be"?				
No pain 0 1 2 3 4 5 6 7 8 9 10 **Pain as bad as could be**				
8. In the past six months, how intense was your worst pain rated on a 0 to 10 scale where 0 is "no pain" and 10 is "pain as bad as could be"?				
No pain 0 1 2 3 4 5 6 7 8 9 10 **Pain as bad as could be**				
9. In the past six months, on the average, how intense was your pain rated on a 0 to 10 scale where 0 is "no pain" and 10 is "pain as bad as could be"? [That is, your usual pain at times you were experiencing pain].				
No pain 0 1 2 3 4 5 6 7 8 9 10 **Pain as bad as could be**				
10. About how many days in the last six months have you been kept from your usual activities (work, school or housework) because of facial pain? days				
11. In the past six months, how much has facial pain interfered with your daily activities rated on a 0 to 10 scale where 0 is "no interference" and 10 is "unable to carry on any activities"?				
No Interference 0 1 2 3 4 5 6 7 8 9 10 **Unable To Carry On Any Activities**				
12. In the past six months, how much has facial pain changed your ability to take part in recreational, social and family activities where 0 is "no change" and 10 is "extreme change"?				
No Change 0 1 2 3 4 5 6 7 8 9 10 **Extreme Change**				

13. In the past six months, how much has facial pain changed your ability to work including housework) where 0 is "no change" and 10 is "extreme change"?		
No Change 0 1 2 3 4 5 6 7 8 9 10 **Extreme Change**		
14.a. Have you ever had your jaw lock or catch so that it won't open all the way?		
Yes 0	No 1	**If no problem opening all the way, SKIP to question 15 If yes, go to question 14b**
14.b. Was this limitation in jaw opening severe enough to interfere with your ability to eat?		
Yes 1	No 0	
15. a. Does your jaw click or pop when you open or close your mouth or when chewing?		
Yes 1	No 0	
15.b. Does your jaw make a grating or grinding noise when it opens and closes or when chewing?		
Yes 1	No 0	
15.c. Have you been told, or do you notice that you grind your teeth or clench your jaw while sleeping at night?		
Yes 1	No 0	
15.d. During the day, do you grind your teeth or clench your jaw?		
Yes 1	No 0	
15.e. Does your jaw ache or feel stiff when you wake up in the morning?		
Yes 1	No 0	
15.f. Do you have noises or ringing in your ears?		
Yes 1	No 0	
15.g. Does your bite feel uncomfortable or unusual?		
Yes 1	No 0	
16.a. Do you have rheumatoid arthritis, lupus, or other systemic arthritic disease?		
Yes 1	No 0	
16.b. Do you know of anyone in your family who has had any of these diseases?		
Yes 1	No 0	
16.c. Have you had or do you have any swollen or painful joint(s) other than the joints close to your ears (TMJ)?		
Yes 1	No 0	**If no swollen or painful joints, SKIP to question 17a If Yes, go to question 16d**
16.d. Is this a persistent pain which you have had for at least one year?		
Yes 1	No 0	
17.a. Have you had a recent injury to your face or jaw?		
Yes 0	No 1	**If no recent injuries, SKIP to question 18 If Yes, go to question 17b**
17.b. Did you have jaw pain before the injury?		
Yes 1	No 0	
18. During the last six months have you had a problem with headaches or migraines?		
Yes 1	No 0	

19. What activities does your present jaw problem prevent or limit you from doing?		
a.Chewing	Yes 1	No 0
b. Drinking	Yes 1	No 0
c. Exercising	Yes 1	No 0
d. Eating hard foods	Yes 1	No 0
e. Eating soft foods	Yes 1	No 0
f. Smiling/laughing	Yes 1	No 0
g.Sexual activity	Yes 1	No 0
h. Cleaning teeth or face	Yes 1	No 0
i. Yawning	Yes 1	No 0
j. Swallowing	Yes 1	No 0
k. Talking	Yes 1	No 0
l. Having your usual facial appearance	Yes 1	No 0

20. In the last month, how much have you been distressed by: **Not At All (0) A Little Bit (1) Moderately (2) Quite A Bit (3) Extremely (4)**	
a. Headaches	0 1 2 3 4
b. Loss of sexual interest or pleasure	0 1 2 3 4
c. Faintness or dizziness	0 1 2 3 4
d. Pains in the heart or chest	0 1 2 3 4
e. Feeling low in energy or slowed down	0 1 2 3 4
f. Thoughts of death or dying	0 1 2 3 4
g. Poor appetite	0 1 2 3 4
h. Crying easily	0 1 2 3 4
i. Blaming yourself for things	0 1 2 3 4
j. Pains in the lower back	0 1 2 3 4
k. Feeling lonely	0 1 2 3 4
l. Feeling blue	0 1 2 3 4
m. Worrying too much about things	0 1 2 3 4
n. Feeling no interest in things	0 1 2 3 4
o. Nausea or upset stomach	0 1 2 3 4
p. Soreness of your muscles	0 1 2 3 4
q. Trouble falling asleep	0 1 2 3 4
r. Trouble getting your breath	0 1 2 3 4
s. Hot or cold spells	0 1 2 3 4
t. Numbness or tingling in parts of your body	0 1 2 3 4
u. A lump in your throat	0 1 2 3 4
v. Feeling hopeless about the future	0 1 2 3 4
w. Feeling weak in parts of your body	0 1 2 3 4
x. Heavy feelings in your arms or legs	0 1 2 3 4
y. Thoughts of ending your life	0 1 2 3 4
z. Overeating	0 1 2 3 4

20. (cont.) In the last month, how much have you been distressed by: **Not At All (0) A Little Bit (1) Moderately (2) Quite A Bit (3) Extremely (4)**				
aa. Awakening in the early morning	0 1 2 3 4			
bb. Sleep that is restless or disturbed	0 1 2 3 4			
cc. Feeling everything is an effort	0 1 2 3 4			
dd. Feelings of worthlessness	0 1 2 3 4			
ee. Feeling of being caught or trapped	0 1 2 3 4			
ff. Feelings of guilt	0 1 2 3 4			
21. How good a job do you feel you are doing in taking care of your health overall?				
Excellent 1	Very good 2	Good 3	Fair 4	Poor 5
22. How good a job do you feel you are doing in taking care of your oral health?				
Excellent 1	Very good 2	Good 3	Fair 4	Poor 5
23. When were you born? Month		Day	Year	
24. Are you male or female?	Male 1		Female 2	
25. Which of the following groups best represent your race?				
Aleut, Eskimo or American Indian 1	Asian or Pacific Islander 2	Black 3	White 4	Other 5 (please specify):
26. Are any of these groups your national origin or ancestry?				
Puerto Rican 1	Cuban 2	Mexican/Mexicano 3	Mexican American 4	Chicano 5
Other Latin American 6	Other Spanish 7	None of the above 8		
27. What is the highest grade or year of regular school that you have completed?				
Never attended or Kindergarten: 00		Elementary School: 1 2 3 4 5 6 7 8		
High School: 9 10 11 12		College: 13 14 15 16 17 18+		
28a. During the past 2 weeks, did you work at a job or business not counting work around the house (include unpaid work in the family farm/business)?				
Yes 1	No 2	**If Yes SKIP to question 29 If No, go to question 28b**		
28b. Even though you did not work during the past 2 weeks, did you have a job or business?				
Yes 1	No 2	**If Yes SKIP to question 29 If No, go to question 28c**		
28c. Were you looking for work or on layoff from a job during those 2 weeks?				
Yes, looking for work 1	Yes, layoff 2	Yes, both on layoff and looking for work 3	No 4	
29. Are you married, widowed, divorced, separated or never been married?				
Married-spouse in household 1	Married-spouse not in household 2			
Widowed 3	Divorced 4	Separated 5	Never Married 6	
30. Which of the following best represents your total combined household income during the past12 months?				
$0-$14,999	$25,000-$34,999	$15,000-$24,999	$35,000-$49,999	$50,000 or more
31. What is your 5-digit zip code?				

TMD BIOBEHAVIORAL ASSESSMENT
AXIS II: SCORING PROTOCOL FOR GRADED CHRONIC PAIN
Patient Name/Case #:
ANY TMD PAIN REPORTED IN THE PRIOR MONTH? (*History Questionnaire, Question 3*)
If NO, Chronic Pain Grade = 0
If YES, Continue
CHARACTERISTIC PAIN INTENSITY (CPI): (*CGP Scale, Questions 1, 2 and 3*) Calculate as follows:
CPI = + + = divided by 3 = x 10 =
(*Question #1.*) (*Question #2.*) (*Question #3.*)
DISABILITY POINTS:
Disability Days: (*GCP Scale, Question 7*) **Disability Score:** (*GCP Scale, Questions 4, 5 and 6*)
Number of Disability Days = . + + =
(*Question #7.*) (*Question #4.*) (*Question #5.*) (*Question #6.*)
divided by 3 =
0-6 days = **0** Disability Points x 10 = .
7-14 days = **1** Disability Point
15-30 days = **2** Disability Points Score of **0-29 = 0** Disability Points
31+ days = **3** Disability Points Score of **30-49 = 1** Disability Point
Score of **50-69 = 2** Disability Points
Score of **70+ = 3** Disability Points
+ = (DISABILITY POINTS)
(Points for Disability Days) (Points for Disability Score)
CHRONIC PAIN GRADE CLASSIFICATION:
Grade 0 No TMD pain in prior 6 months
Low Disability
Grade I *Low Intensity* Characteristic Pain Intensity < 50, and less than 3 Disability Points
Grade II *High Intensity* Characteristic Pain Intensity > 50, and less than 3 Disability Points
High Disability
Grade III *Moderately Limiting* 3 to 4 Disability Points, regardless of Characteristic Pain Intensity
Grade IV *Severely Limiting* 5 to 6 Disability Points regardless of Characteristic Pain Intensity

Research Diagnostic Criteria
TMD CLINICAL EXAMINATION FORM

1.a. Have you ever had your jaw lock catch so that it won't open all the way?		
Yes 1	No 0	**If no problem opening all the way, SKIP to question 2. If Yes, go to question 1b**
1.b. Was this limitation in jaw opening severe enough to interfere with your ability to eat?		
Yes 1	No 0	**If Yes SKIP to question 29 If No, go to question 28c**

2. Do you have pain on the right side of your face, the left side or both sides?				
None 0	Right 1	Left 2	Both 3	

3. Could you point to the areas where you feel pain?	
Left	**Right**
None 0	None 0
Jaw Joint 1	Jaw Joint 1
Muscles 2	Muscles 2
Both 3	Both 3
Examiner feels area subject points to, if it is unclear whether it is joint or muscle pain	
4. Opening Pattern Straight 0	Right Lateral Deviation (uncorrected) 1
Right Corrected ("S") Deviation 2	Left Lateral Deviation (uncorrected) 3
Left Corrected ("S") Deviation 4	Other 5 Type: (specify)
Comments:	
5. Vertical Range of Motion Maxillary incisor used	
a. Unassisted opening ____ ____mm	
MUSCLE PAIN	**JOINT PAIN**
None 0 Right 1 Left 2 Both 3	None 0 Right 1 Left 2 Both 3
b. Maximum unassisted opening ____ ____mm	
MUSCLE PAIN	**JOINT PAIN**
None 0 Right 1 Left 2 Both 3	None 0 Right 1 Left 2 Both 3
c. Maximum assisted opening ____ ____mm	
MUSCLE PAIN	**JOINT PAIN**
None 0 Right 1 Left 2 Both 3	None 0 Right 1 Left 2 Both 3
d. Vertical incisal overlap ____ ____mm	
MUSCLE PAIN	**JOINT PAIN**
None 0 Right 1 Left 2 Both 3	None 0 Right 1 Left 2 Both 3

6. Joint Sounds (palpation)	**Right**	**Left**
a. Opening	Click 1 Coarse Crepitus 2	Click 1 Coarse Crepitus 2
	Fine Crepitus 3	Fine Crepitus 3
	Measurement of Opening Click ____mm _____ mm	
b. Closing	Click 1 Coarse Crepitus 2	Click 1 Coarse Crepitus 2
	Fine Crepitus 3	Fine Crepitus 3
	Measurement of Closing Click _____mm _____mm	
c. Reciprocal click eliminated on protrusive opening	YES 1 NO 1 N/A 9	YES 1 NO 1 N/A 9
7.Excursions		
a. Right Lateral Excursion ____ ____mm		
MUSCLE PAIN	**JOINT PAIN**	
None 0 Right 1 Left 2 Both 3	None 0 Right 1 Left 2 Both 3	
b. Left Lateral Excursion ____ ____mm		
MUSCLE PAIN	**JOINT PAIN**	
None 0 Right 1 Left 2 Both 3	None 0 Right 1 Left 2 Both 3	
c. Protrusion ____ ____mm		
MUSCLE PAIN	**JOINT PAIN**	
None 0 Right 1 Left 2 Both 3	None 0 Right 1 Left 2 Both 3	
d.Midline Deviation mm	**RIGHT**	**LEFT**
	YES 1 NO 1 N/A 9	YES 1 NO 1 N/A 9
8..Joint Sounds on Excursions	**Right Sounds**	**Left Sounds**
Excursion Right	None 0 Click 1	None 0 Click 1
	Coarse Crepitus 2 Fine Crepitus 3	Coarse Crepitus 2 Fine Crepitus 3
Excursion Left	None 0 Click 1	None 0 Click 1
	Coarse Crepitus 2 Fine Crepitus 3	Coarse Crepitus 2 Fine Crepitus 3
Protrusion	None 0 Click 1	None 0 Click 1
	Coarse Crepitus 2 Fine Crepitus 3	Coarse Crepitus 2 Fine Crepitus 3

DIRECTIONS, ITEMS 9-11

The examiner will be palpating (touching) different areas of your face, head and neck. We would like you to indicate if you do not feel pain or just feel pressure (0), or pain (1-3). Please rate how much pain you feel for each of the palpations according to the scale below. Circle the number that corresponds to the amount of pain you feel. We would like you to make a separate rating for both the right and left palpations.

0 = No Pain/Pressure Only
1 = Mild Pain
2 = Moderate Pain
3 = Severe Pain

9. Extraoral muscle pain with palpation:	**RIGHT**	**LEFT**
a. Temporalis (posterior) "Back of temple	0 1 2 3	0 1 2 3
b. Temporalis (middle) "Middle of temple"	0 1 2 3	0 1 2 3
c. Temporalis (anterior) "Front of temple"	0 1 2 3	0 1 2 3
d. Masseter (origin [superior]) "Cheek/under cheekbone"	0 1 2 3	0 1 2 3
e. Masseter (body [middle]) "Cheek/side of face"	0 1 2 3	0 1 2 3
f. Masseter (insertion [inferior]) "Cheek/jawline"	0 1 2 3	0 1 2 3
g. Posterior mandibular region (Stylohyoid/posterior digastric region) "Jaw/throat region"	0 1 2 3	0 1 2 3
h. Submandibular region (Medial pterygoid/Suprahyoid/anterior digastric region) "Under chin"	0 1 2 3	0 1 2 3
10. Joint pain with palpation:	**RIGHT**	**LEFT**
a. Lateral pole"outside"	0 1 2 3	0 1 2 3
b. Posterior attachment "inside ear"	0 1 2 3	0 1 2 3
11. Intraoral muscle pain with palpation:	**RIGHT**	**LEFT**
a. Lateral pterygoid area "Behind upper molars"	0 1 2 3	0 1 2 3
b. Tendon of temporalis "Tendon"	0 1 2 3	0 1 2 3

Appendix 7

Medical History and Epworth Scale of Daytime Tiredness and Sleep Hygiene

PERSONAL DETAILS

Surname _____ Title _____
First Name/s _____ Birth Date _____
Address _____
_____ Postcode _____
Postal Address _____
_____ Postcode _____
Home Phone _____ Mobile Phone _____
Work Phone _____
Occupation _____ Email _____

	Yes	No	Please Specify
Are you in a health fund?	☐	☐	_____
Are you responsible for paying your account?	☐	☐	_____

How did you hear about us? ☐ Yellow Pages ☐ Website ☐ Friend ☐ Newspaper

Please Note **Payment is expected at each appointment.**

Do you have a specific reason for attending today?

☐ Broken Teeth	☐ Decay	☐ Toothache	☐ Tooth Sensitivity
☐ Jaw or Ear Pain	☐ Wisdom Teeth	☐ Missing Teeth	☐ Appearance
☐ Clean	☐ Regular Check-up	☐ Worn down teeth	☐ Bad breath

Are you happy with the appearance of your teeth? Yes ☐ No ☐
Would you like them to be whiter? Yes ☐ No ☐
Has your bite ever changed or been adjusted? Yes ☐ No ☐

On a scale of 1 – 5, how nervous would you say you are at the dentist?
Completely at ease 1 2 3 4 5 Very Nervous

"WE CATER FOR COWARDS"

MEDICAL HISTORY

Who is your regular medical practitioner? Name _____
Phone number _____
Have you gone to the dentist in the past year? _____

Have you had, or do you suffer from any of the following conditions? (Please tick)

☐ Angina	☐ Stroke	☐ Cancer Treatment	☐ Diabetes
☐ Blood Pressure	☐ Epilepsy	☐ Steroid Therapy	☐ Thyroid Problems
☐ Heart Attack	☐ CJD	☐ Blood Thinners	☐ Dry Mouth
☐ Rheumatic Fever	☐ Kidney Disease	☐ Hayfever	☐ Prolonged Bleeding
☐ Heart Murmur	☐ Liver Disease	☐ Asthma	☐ Gastric Reflux
☐ Prosthetic Valves	☐ Hepatitis	☐ Sinusitis	☐ Mouth Ulcers
☐ Joint Replacements	☐ Organ Transplant	☐ Tuberculosis	☐ Other Condition
☐ Shunts	☐ Rheumatoid Arthritis	☐ Psoriatic Arthritis	☐ Ankylosing Spondylitis
☐ Lupus (SLE)	☐ Multiple Sclerosis	☐ Sjogrens Disease	☐ Osteoporosis

Have you had any surgery in the last 6 months? ☐ YES ☐ NO

Have you seen other practitioners for this problem? ☐ YES ☐ NO

Signature _____ Date _____

Other Questions	**Yes**	Please Specify
Are you likely to be tested for banned substances? (e.g. professional sports).	☐	
Are you allergic to any drugs?	☐	
Are you Pregnant? If so, how many months?	☐	
Are you at high risk of acquiring HIV or Hepatitis?	☐	
Do you smoke cigarettes? If so, how many per day?	☐	
Do you have any other medical condition?	☐	
Are you taking any medications?	☐	**Please list below**
Are you taking any homeopathic preparations or vitamins?	☐	**Please list below**
Have you travelled overseas in the last 6 months?	☐	
Have you had overseas visitors in the last 6 months?	☐	
Do you drink town or tank water?	☐	

Medication/Herbal or Homeopathic preparation/ Vitamins	**Reason for Medication use**	**Dosage**	**Time Taken**

Signature _____ Date _____

Please fill in this form, to see if we can help you with your sleep.
We treat your healthcare beyond basic dentistry.

Epworth Sleepiness Scale

0 = no chance of dozing
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Situation	Chance of Dozing	Situation	Chance of Dozing
Sitting & reading		Watching TV	
Sitting inactive in a public place (e.g. a theatre or a meeting)		Lying down to rest in the Afternoon (when circumstances Permit)	
As a passenger in a car for an hour without a break		Sitting & talking to someone	
Sitting quietly after a lunch without alcohol		In a car, while stopped for a few minutes in traffic	

Other Questions – please tick & answer in space provided			
Do you snore?	YES □ NO □	Do you wake up choking?	YES □ NO □
Severity of snoring? 0 □ 1 □ 2 □ 3 □ 4 □ 5 □ (0 rating as none – 5 rating a severe)		Do you suffer from other parasomnia? e.g. sleep walking, sleep talking, other	YES □ NO□
Have you ever been diagnosed with Obstructive Sleep Apnoea? Were you diagnosed with mild, moderate or severe?	YES □ NO □	Do you wake during the night? If yes, how often?	YES□ NO □
Do you or have you used a C-PAP or oral appliance?	YES □ NO □	What time do you first wake up during the night?	
Do you wake with a headache? Do you suffer night sweats? Do you suffer from reflux or indigestion?	YES □ NO □ YES □ NO □ YES □ NO □	Is there a reason for you waking at this time? e.g. need a drink, go to toilet, can't get comfortable	YES □ NO□
Do you have a set sleep time? Do you wake feeling good?	YES □ NO □ YES □ NO □	How long does it take you to get back to sleep?	

Signature _____ Date _____

Name _____ Date _____

Discomfort Scale

These are discomfort scales. For each part of the body there are horizontal rows, one for the left and one for the right. Please report your average discomfort for the last 7 days by circling the rating from 0 to 10 which best reflects your discomfort.

0 being no pain – 10 being unbearable pain

Bite symptoms or bite changes	**R**	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
TMJ joint pain	**R**	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
TMJ joint sounds	**R**	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Headaches	**R**	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Facial pain	**R**	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Eye symptoms	**R**	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Ear pain	**R**	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Stuffy ears or ringing sounds	**R**	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Neck pain	**R**	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Arm/hand/finger (numbness, tingling or pain)	**R**	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Upper back pain	**R**	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Lower back pain	**R**	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Pain in shoulder	**R**	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Pain on raising shoulder	**R**	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10
Difficulty raising shoulder	**R**	0	1	2	3	4	5	6	7	8	9	10
	L	0	1	2	3	4	5	6	7	8	9	10

Other Questions – please tick & answer in space provided			
Have you suffered trauma? Where? Age when it happened -	YES ☐ NO ☐	Have you been involved in an accident? Age when it happened -	YES ☐ NO ☐
Have you had surgery? Where? When?	YES ☐ NO ☐	Do you have trouble swallowing? When?	YES ☐ NO ☐
Have you experienced Vertigo? (dizziness, head spins) When?	YES ☐ NO ☐	Do you grind or clench your teeth? When?	YES ☐ NO ☐

Signature _____ Date _____

McCloy Dental - Dr. Karen McCloy, Dr. Russell McCloy, Dr. Monica Smith, Dr. Pollyanna Lay

Appendix 8

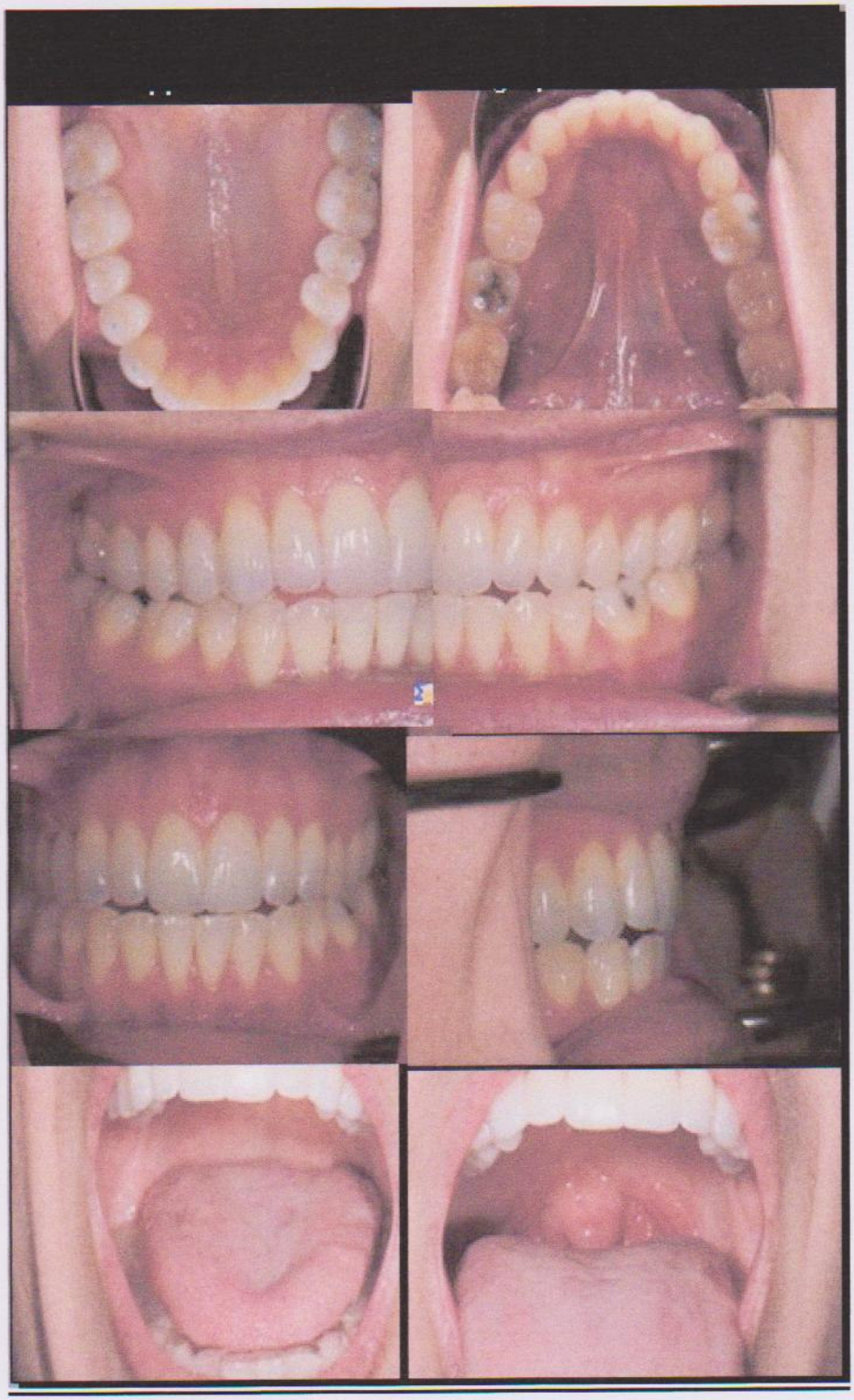
Tetric® EvoFlow Safety Data Sheet

Tetric EvoFlow MSDS - Material Safety Data Sheet Tetric EvoFlow

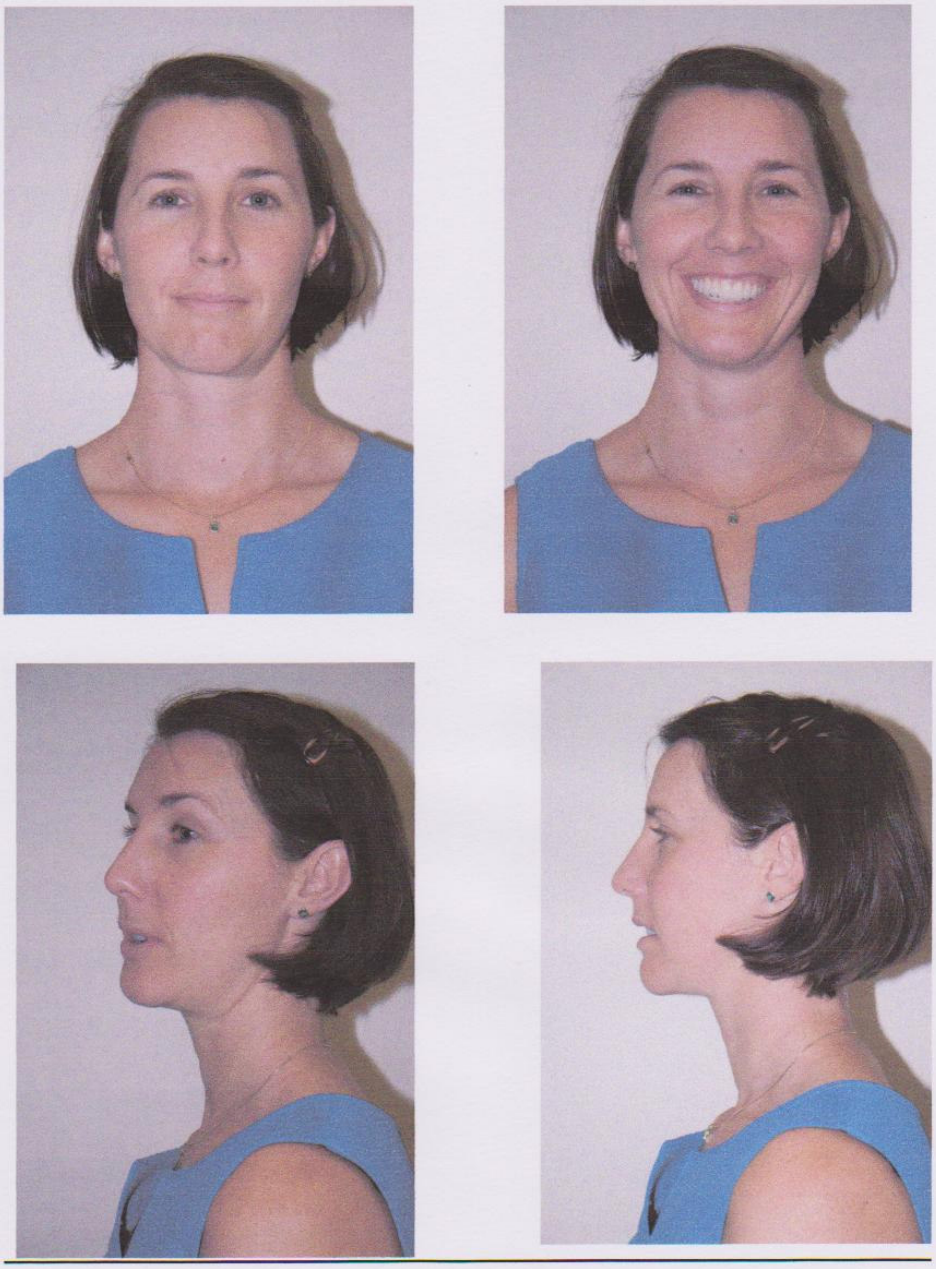
File Format: PDF/Adobe Acrobat - Quick View
MSDS prepared by Andejeet Gulati. Tel. No. 716 691-0010 **...** Sheet No. 1667. 01.10.2007. **Tetric EvoFlow**. Page 2 of 5. Skin contact **...**
www.endo**msds**.com/.../695_US-**Tetric_EvoFlow**_1667_1_2007.10.01.pdf

Appendix 9

Intraoral Photographs



Appendix 10 Extraoral Photographs




ARTICULOIAL PROTRACTOR

Appendix 11

Integra™ Alginate Safety Data Sheet

MATERIAL SAFETY DATA SHEET

INTEGRA

1 - IDENTIFICATION

Manufacturer:	Kerr Corporation
Address:	1717 West Collins Avenue
City, State, Zip:	Orange, CA 92867-5422
Telephone:	1-800-KERR-123
Emergency:	**Chemtrec 1-800-424-9300**
Date Prepared:	June 6, 2005

2 - COMPOSITION INFORMATION

Hazardous Ingredients

	CAS #	PEL	TLV	%
Cristobalite (Crystalline Silica)	14464-46-1	0.05mg/m^3	1.05mg/m^3	<60%

Other Ingredients
Metal salts of alginic acid, fumed silica

3 - PHYSICAL AND CHEMICAL PROPERTIES

Boiling Point: N/A
Specific Gravity (H_20 = 1): N/E
Vapor Pressure (mm Hg): N/A
Vapor Density (AIR = 1): N/A
Solubility in Water: Slightly soluble
Reactivity in Water: N/A
Appearance and Odor: A dustless alginate impression material.
Regular Set: A blue powder with a peppermint odor and flavor.
Fast Set: A pink powder with a cinnamon odor and flavor.

4 - FIRE AND EXPLOSION HAZARD DATA

Flash Point (Method Used): N/A
Flammable Limits: **LEL:** N/A **UEL:** N/A
Extinguishing Media: N/A
Special Fire Fighting Procedures: N/A
Unusual Fire and Explosion Hazards: N/A

5 - REACTIVITY DATA

Stability: Stable
Conditions to Avoid: None
Incompatibility (Material to Avoid): Hydrofluoric acid
Hazardous Decomposition Products: N/A
Hazardous Polymerization: Will not occur

6 - HEALTH HAZARD DATA

Routes of Entry:
Eyes: May cause irritation.
Skin: May cause a dry feeling.
Inhalation: Prolonged exposure to respirable crystalline silica may cause chronic lung injury (silicosis). Acute developing silicosis may occur in a short time in heavy exposure. Silicosis is a form of disabling pulmonary fibrosis which can be progressive and may lead to death. The International Agency for Research on Cancer (IARC) reports sufficient evidence of the carcinogenicity of crystalline silica to humans. IARC Group 1.
Ingestion: May result in an intestinal obstruction.
Carcinogenicity - **NTP:** No
IARC Monographs: Yes **OSHA Regulated Carcinogen:** No

7 - EMERGENCY FIRST AID PROCEDURES

Eyes: Flush eyes with water for at least 15 minutes.
Skin: Wash with soap and water. Use hand lotion.
Inhalation: Remove exposed person to fresh air.
Ingestion: Consult physician

8 - PRECAUTIONS FOR SAFE HANDLING & USE

Steps to be taken in case material is released or spilled: Ventilate area of spill or release. Vacuum or sweep up. Avoid unnecessary stirring or handling in order to prevent formation of dust.
Waste Disposal Method: Landfill
Precautions to be taken in handling and storing: Do not breathe dust. Keep container closed.
Other precautions: Use only according to directions.

9 - CONTROL MEASURES

Respiratory Protection (Specify Type): Respirator
VENTILATION:
Local Exhaust: Use sufficient local exhaust to reduce the level of respirable silica to the >PEL.
Mechanical (General): May be sufficient
Protective Gloves: Gloves optional
Eye Protection: Safety glasses
Work/Hygiene Practices: Handle in accordance with good personal hygiene and safety practices. These practices include avoiding unnecessary exposure.

10 - TRANSPORTATION INFORMATION

Not DOT regulated.

11 - SPECIAL INFORMATION

HMIS (Hazardous Material Identification System) Ratings:
H2 F0 R0
[Hazard Index: 4 - Severe Hazard; 3 - Serious Hazard; 2 - Moderate Hazard; 1 - Slight Hazard; 0 - Minimum Hazard]

State RTK: California Prop 65 Warning: This product contains crystalline silica, a chemical known to the State of California to cause cancer.

This MSDS was prepared in accordance with the requirements of the OSHA Hazard Communication Standard (29CFR 1910.1200) and is to be used only for this product. The information contained in this sheet is, to the best of our knowledge, believed to be accurate.

Appendix 12

VPM2 Vacuum Mixer

VPM2 Instruction Manual - Operation Manual

File Format: PDF/Adobe Acrobat - Quick View
Hands Free **Mixing** – The powerful **vacuum** allows the **unit** to hold the **... VPM2** Operation Manual. 4. Hold the bowl and paddle up until the **vacuum** supports **...**
*whipmix.com/wp-content/uploads/via.../**vpm2**_man_popt_crpd.pdf*

Appendix 13

i-CAT® Cone Beam 3D Dental Imaging System Version 3.0.34 Specifications

OPERATOR'S MANUAL

Cone Beam Volumetric Tomography and Panoramic Dental Imaging System

IMAGING SCIENCES INTERNATIONAL, INC.

1910 North Penn Road, Hatfield, PA 19440
United States of America
Phone 215-997-5666 Fax 215-997-5665, 5667
™

i-ii
Part number 990310 January 30, 2007

IMAGING SCIENCES INTERNATIONAL, INC.

1910 North Penn Road, Hatfield, PA 19440
United States of America
Phone 215-997-5666 Fax 215-997-5665, 5667

For more information or an original version of documentation on the i-CAT® Imaging System, by Imaging Sciences International, please write, call, or fax to Imaging Sciences International Inc. at the above address. This documentation has been drafted, approved & supplied in the English Language. Imaging Sciences International will make available under request any component parts, calibration instruments, circuit diagrams, etc.

Printed in the United States of America

i-iii
Part number 990310 January 30, 2007

Appendix 14

InVivoDental Application Version 4.0.78.0 Manual

***ANATOMAGE*, INC.**

Meet Your Anatomy™

InVivoDental 4.0

Reference Manual

Meet Your Anatomy™

™

111 N. Market St. # 899

San Jose, California 95113

info@anatomage.com

www.anatomage.com

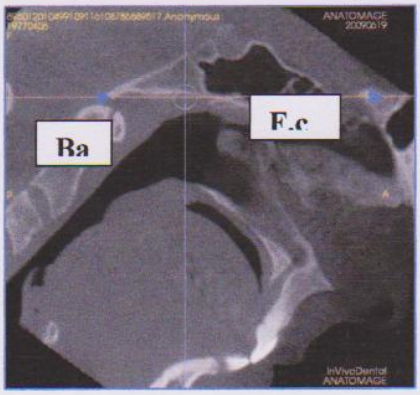
Invivo.exe

INVIVODENTAL®–PIONEERINGTHENEWDIMENSIONOFPATIENTCARE™

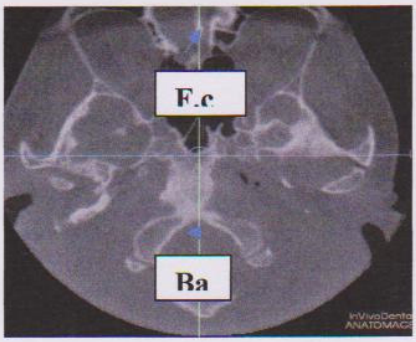
Appendix 15

Alignment of CBCT scans 15a Alignment of the Axial Scan

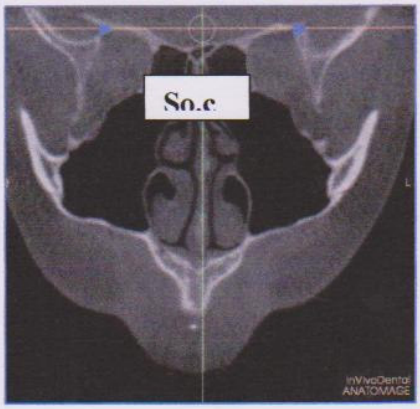
Ba Basion, F.c Foramen Caecum, Soc Superior aspect of the optic canals, Fns Frontonasal suture



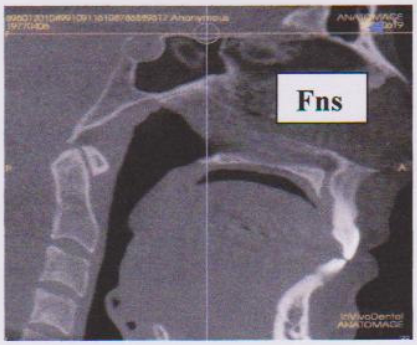
i)
Align the sagittal scan so that Ba and F.c are horizontal



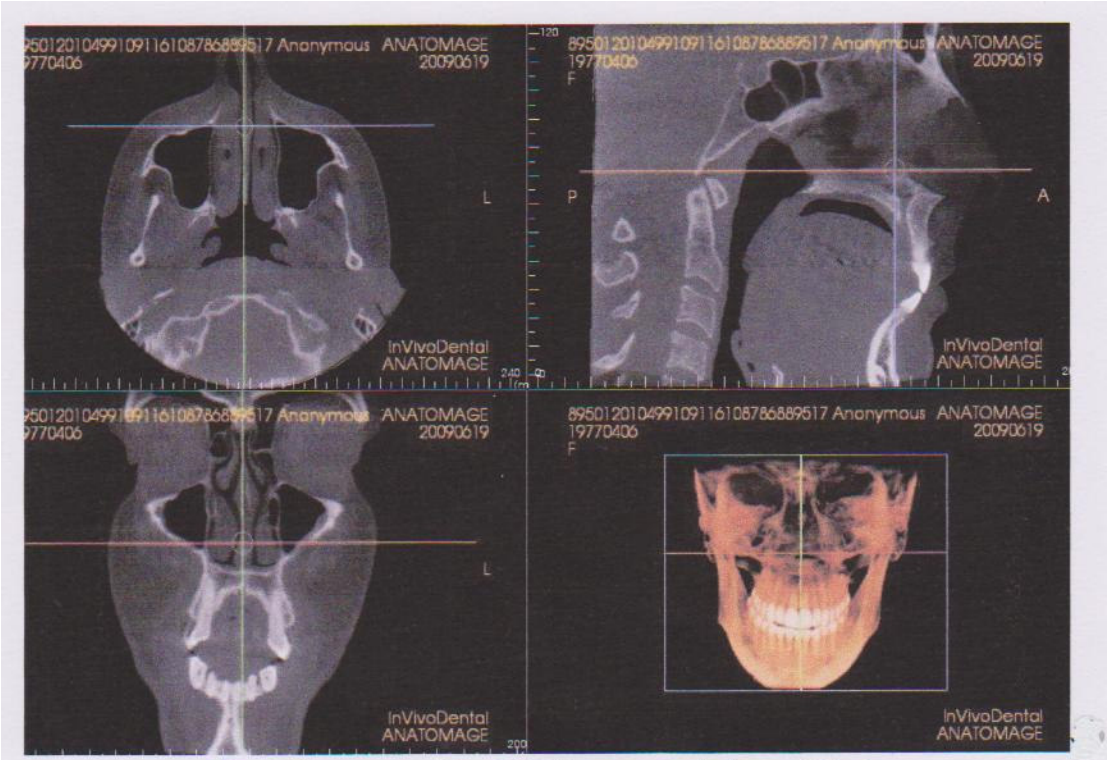
ii)
In the axial view, align the midpoints of basion and foramen cecum so that they are on a vertical line.
This line becomes the CBML, and is not moved at any stage during the mesurements.



iii)
In the coronal scan, the superior aspect of the optic canals is leveled to horizontal



iv)
The sagittal scan was then aligned so that the floor of the cranial base was on a horizontal line passing through the frontonasal suture.



Final alignment of the CBCT scans including a 3d view.

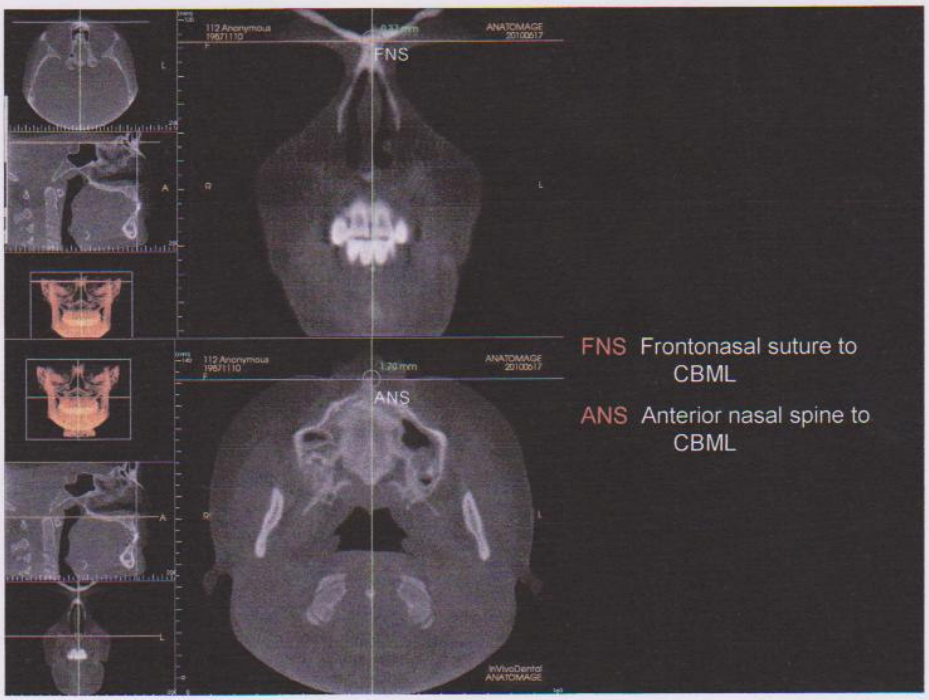
Appendix 16

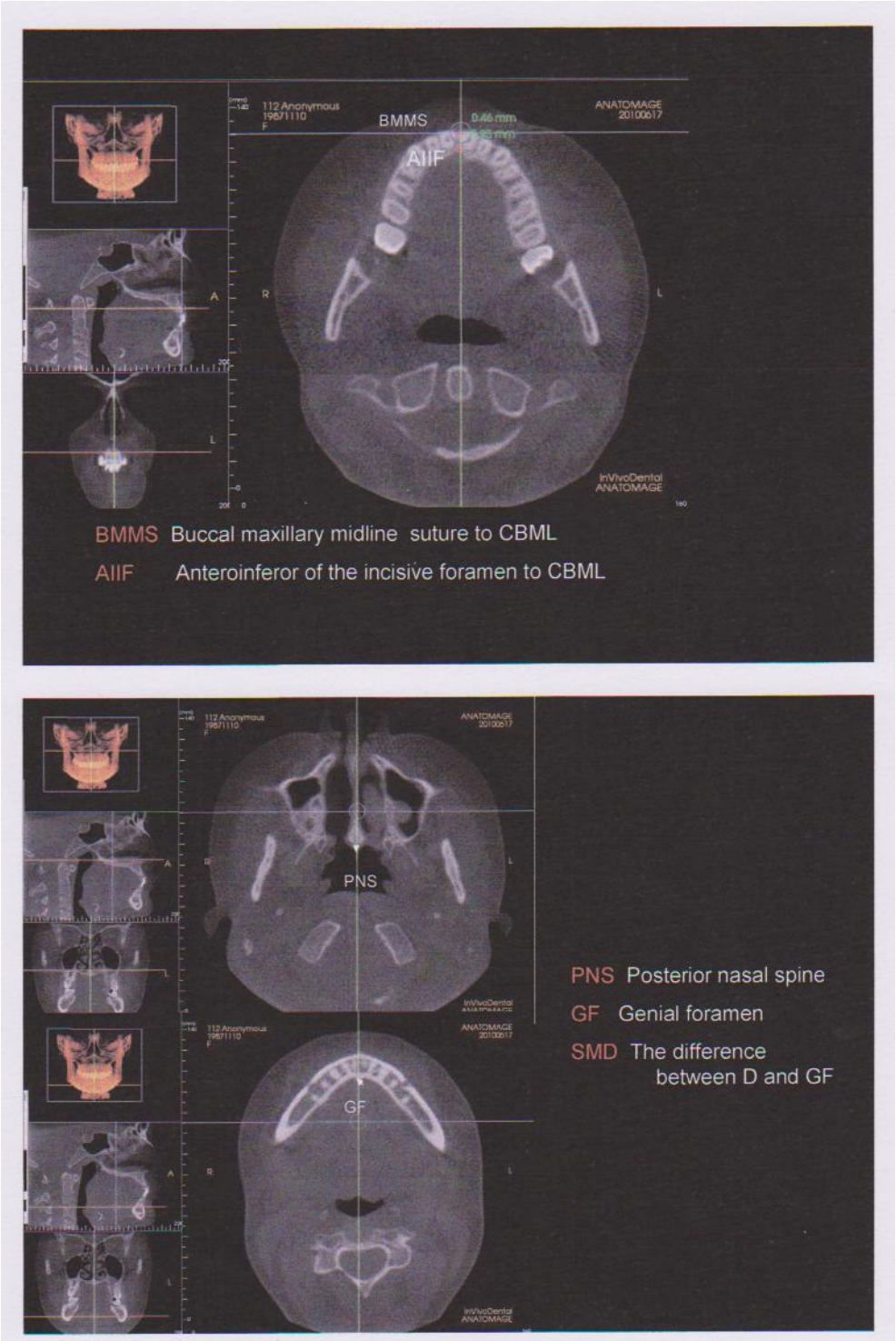
Measurements Used in the Study

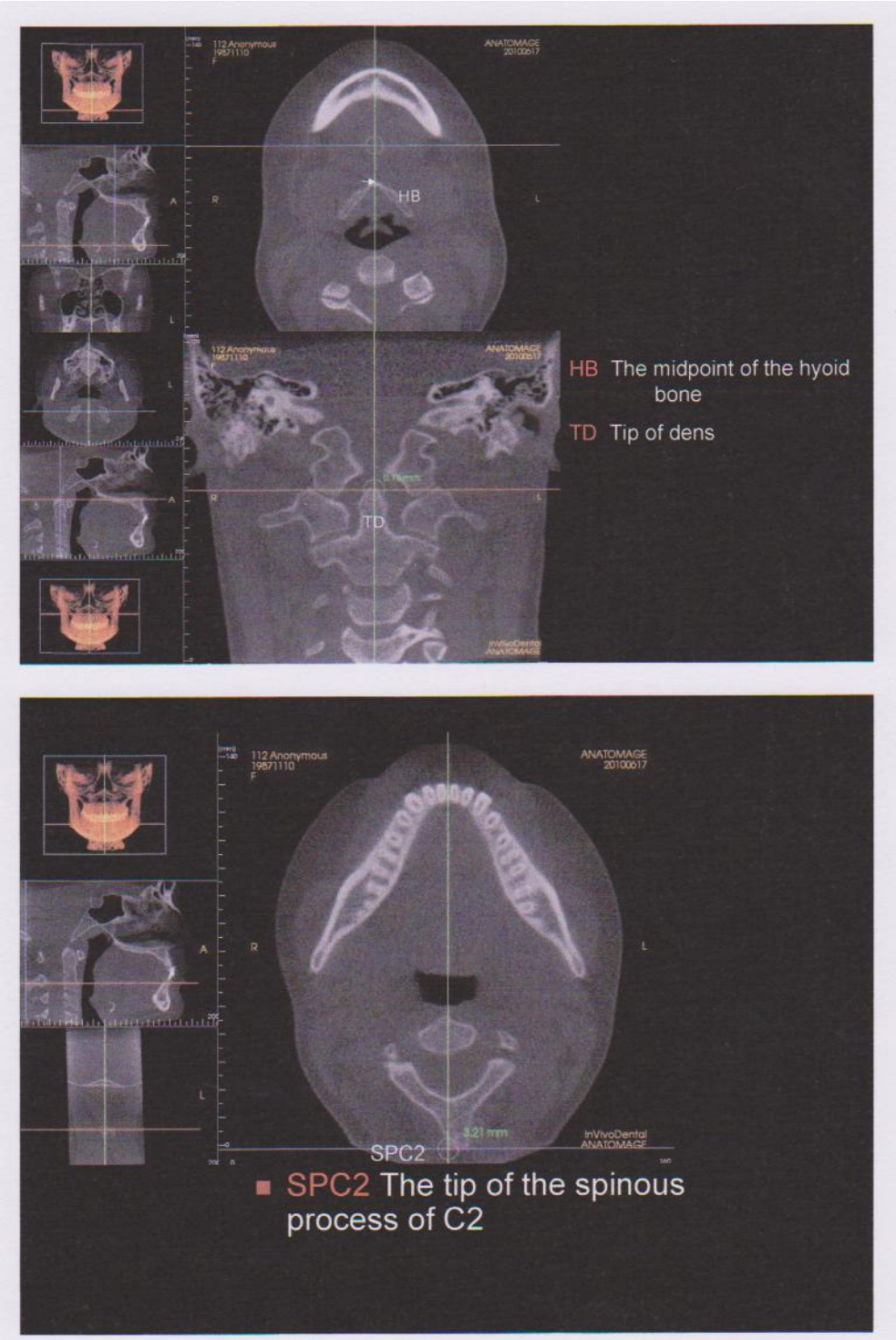
Measurements of Midline Coincidence of the Facial and Cervical Midline Bony Structures with the CBML

If facial growth has been symmetric in the midline, the cranial base midline should be equivalent to the facial skeletal midline. The facial midline skeletal and soft tissue structures, should lie on the continuation of the cranial base midline onto the face.

To determine the amount of midline asymmetry that existed we measured the relationship of the following hard tissue midline structures to the CBML. If the structure was on the CBML it was given a value of 0, to the left of the CBML was negative, and to the right of the CBML was given a positive value. Midline coincidence was taken as lying within 0.5mm to the left or right of the CBML.
This was measured at:

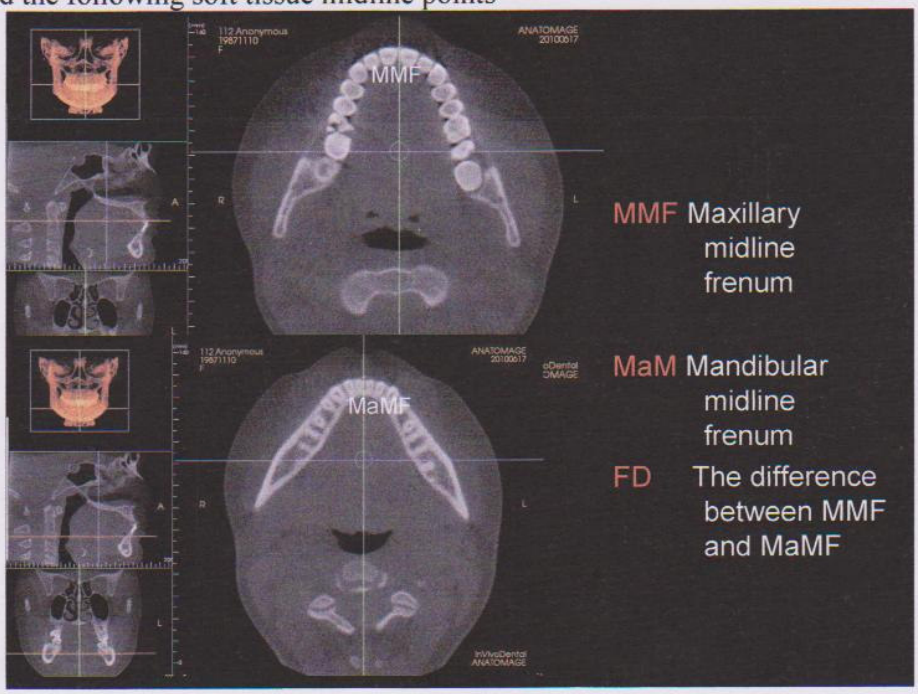


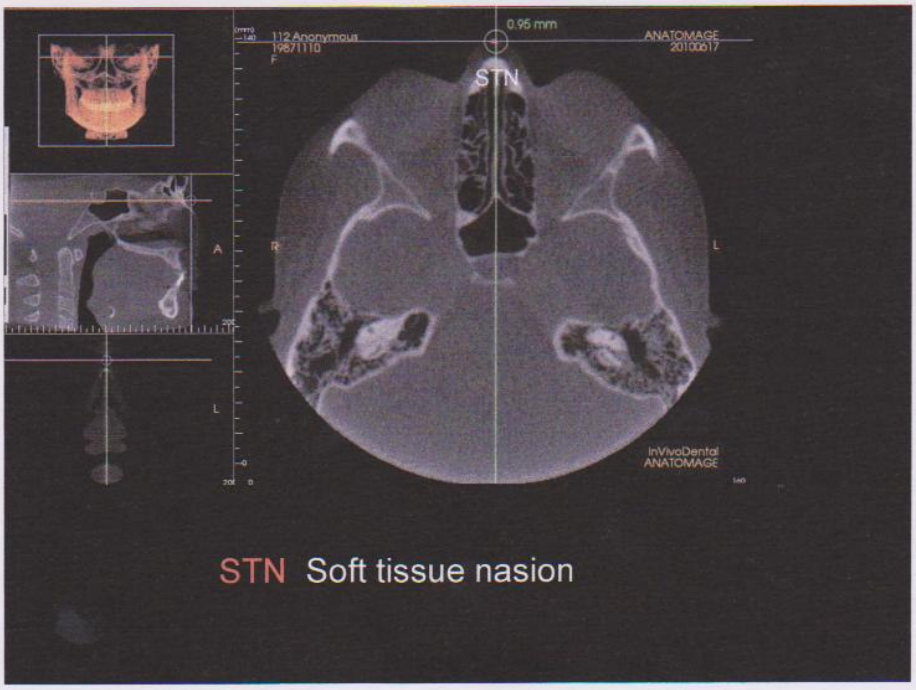

BMMS
AIIF
BMMS Buccal maxillary midline suture to CBML
AIIF Anteroinferor of the incisive foramen to CBML
PNS
GF
PNS Posterior nasal spine
GF Genial foramen
SMD The difference between D and GF

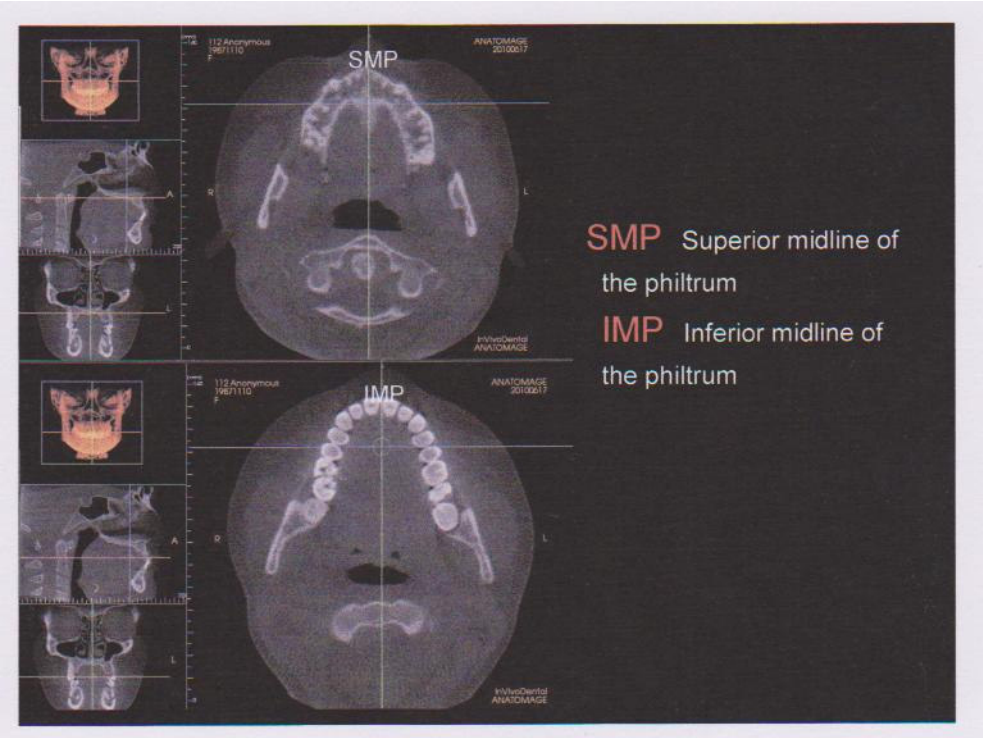

HB
TD
HB The midpoint of the hyoid bone
TD Tip of dens
SPC2
SPC2 The tip of the spinous process of C2

Measurments of Midline Coincidence of Facial Soft Tissue Midline Markers with the CBML

We measured the relationship of the following soft tissue midline structures to the CBML after marking them with flowable resin . The flowable resin appears on the CBCT scan as a white dot. We measured the distance to the CBML from the following soft tissue midline markers in millimeters. If they were on the CBML they were given a value of 0. If they were to the left of the CBML the value was negative, and to the right it was recorded as positive. Midline coincidence was accepted if the values were within 0.5mm to the left or right of the CBML.
We measured the following soft tissue midline points



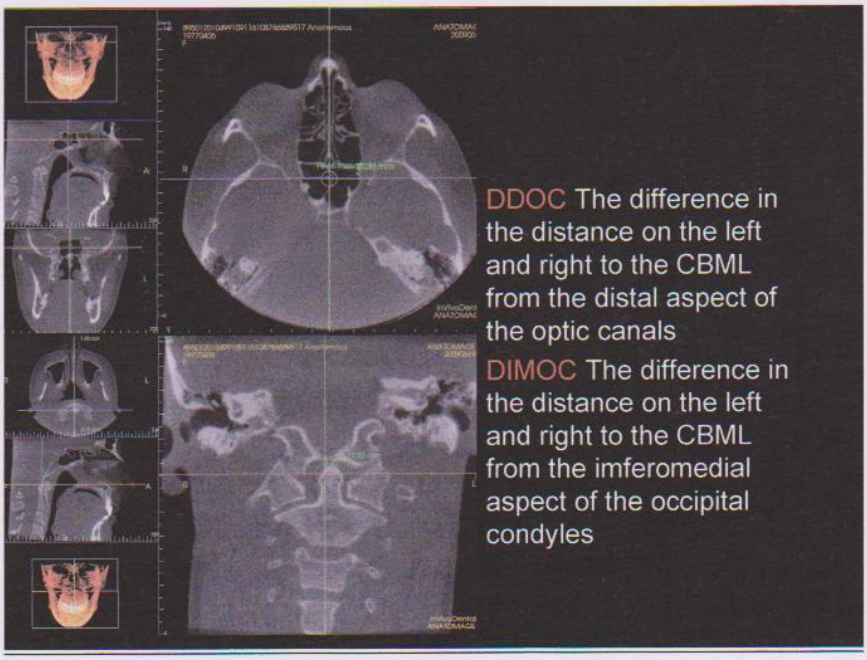


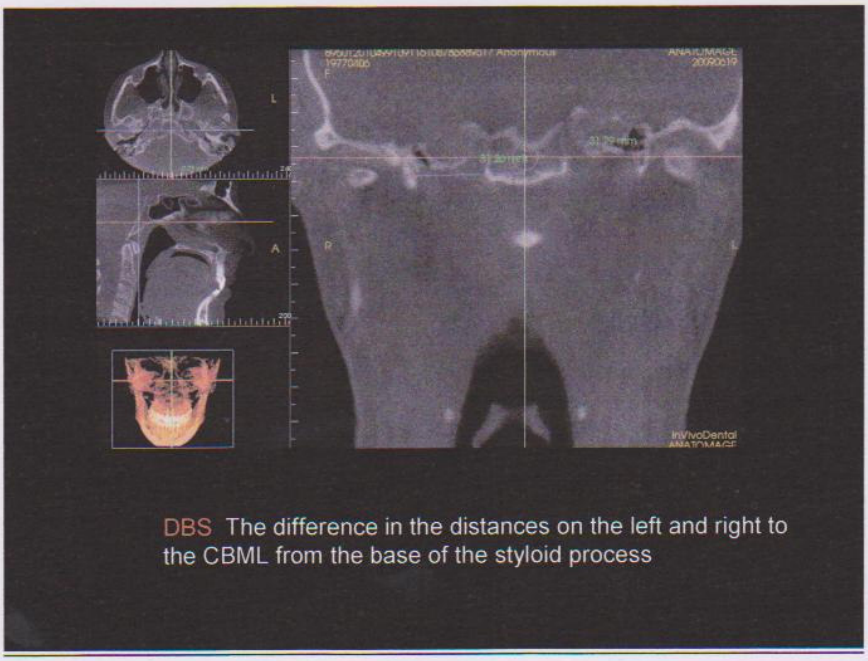

SMP
IMP
SMP Superior midline of the philtrum
IMP Inferior midline of the philtrum

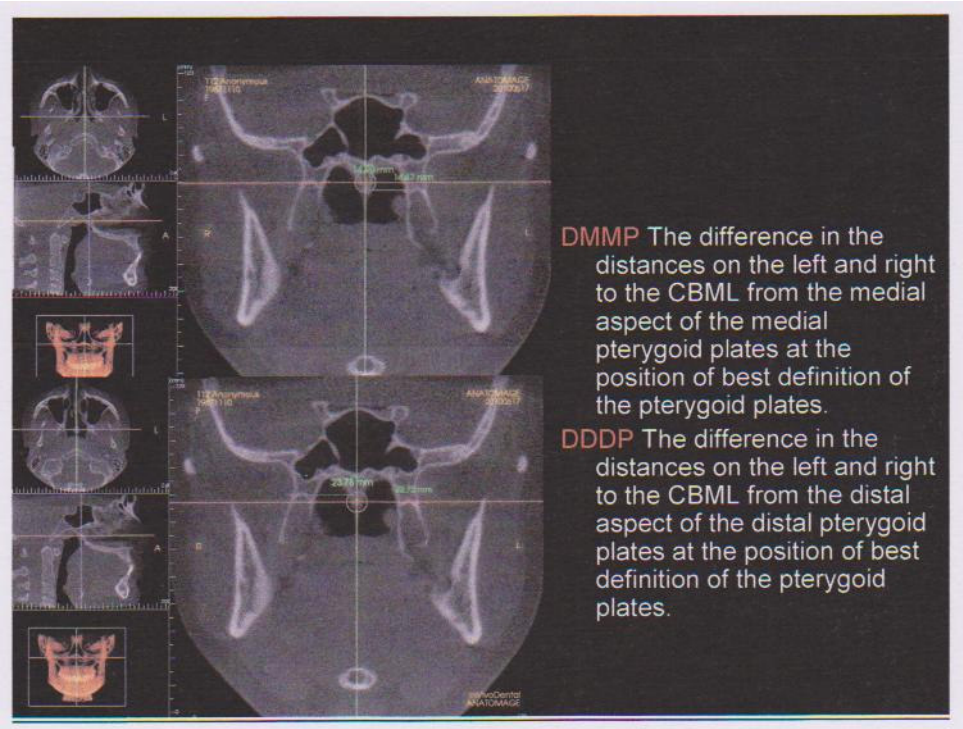
Bilateral Measurements of Cranial Base Asymmetry

To determine the level of asymmetry present in the cranial base, we measured the distance to the CBML from the following cranial base points in millimeters.
We then calculated the difference in the measurements. It was negative if the difference was larger to the left of the CBML, and positive if the difference was larger to the right.

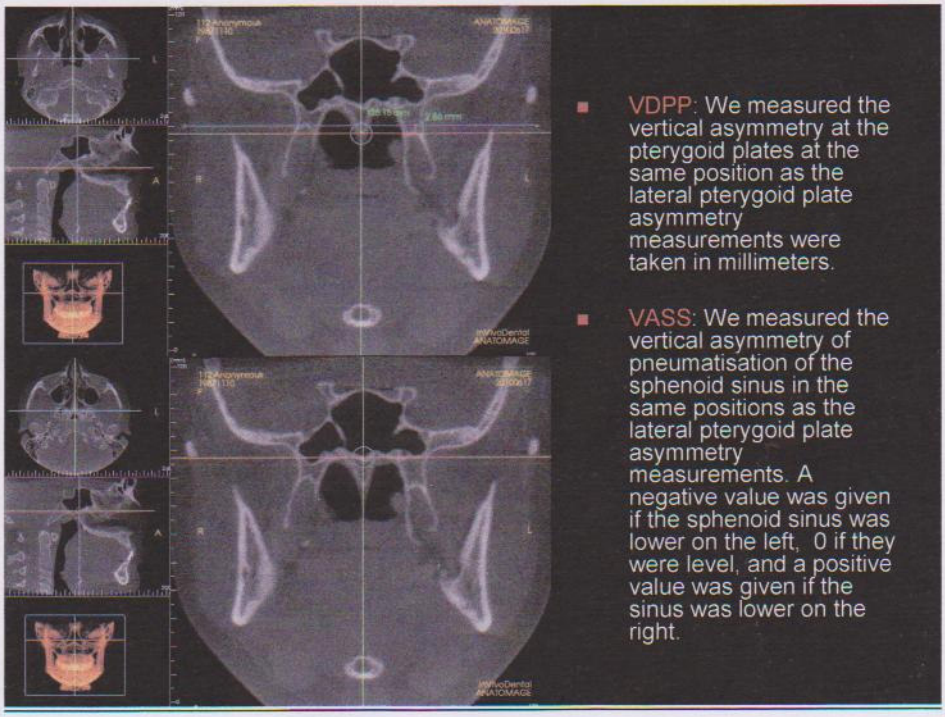
Measurements of Lateral Cranial Base Asymmetry





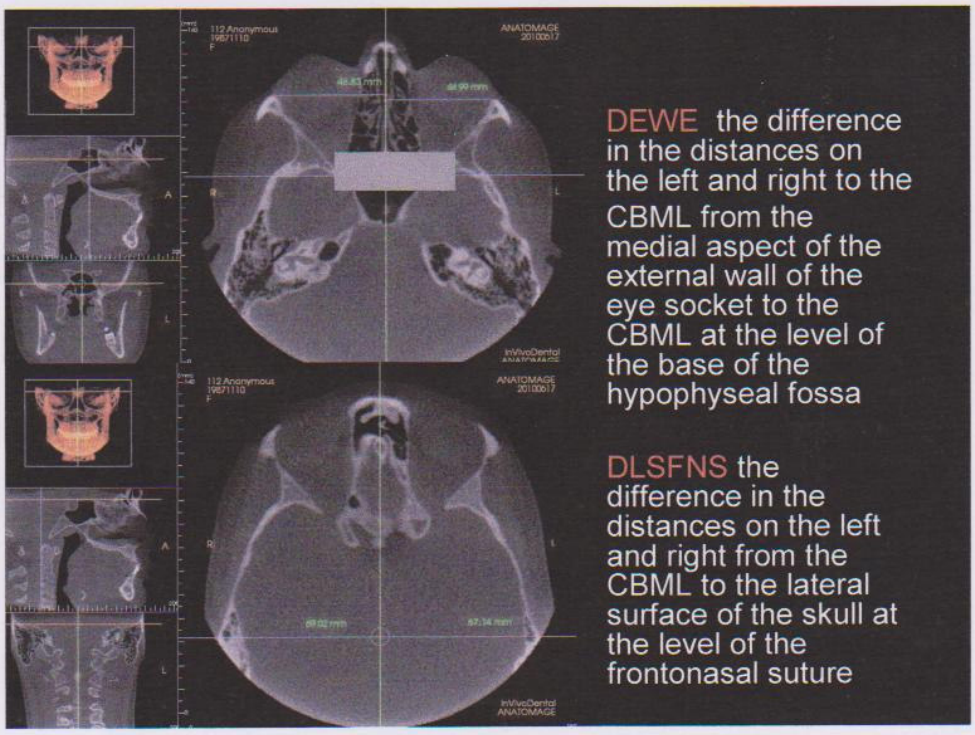


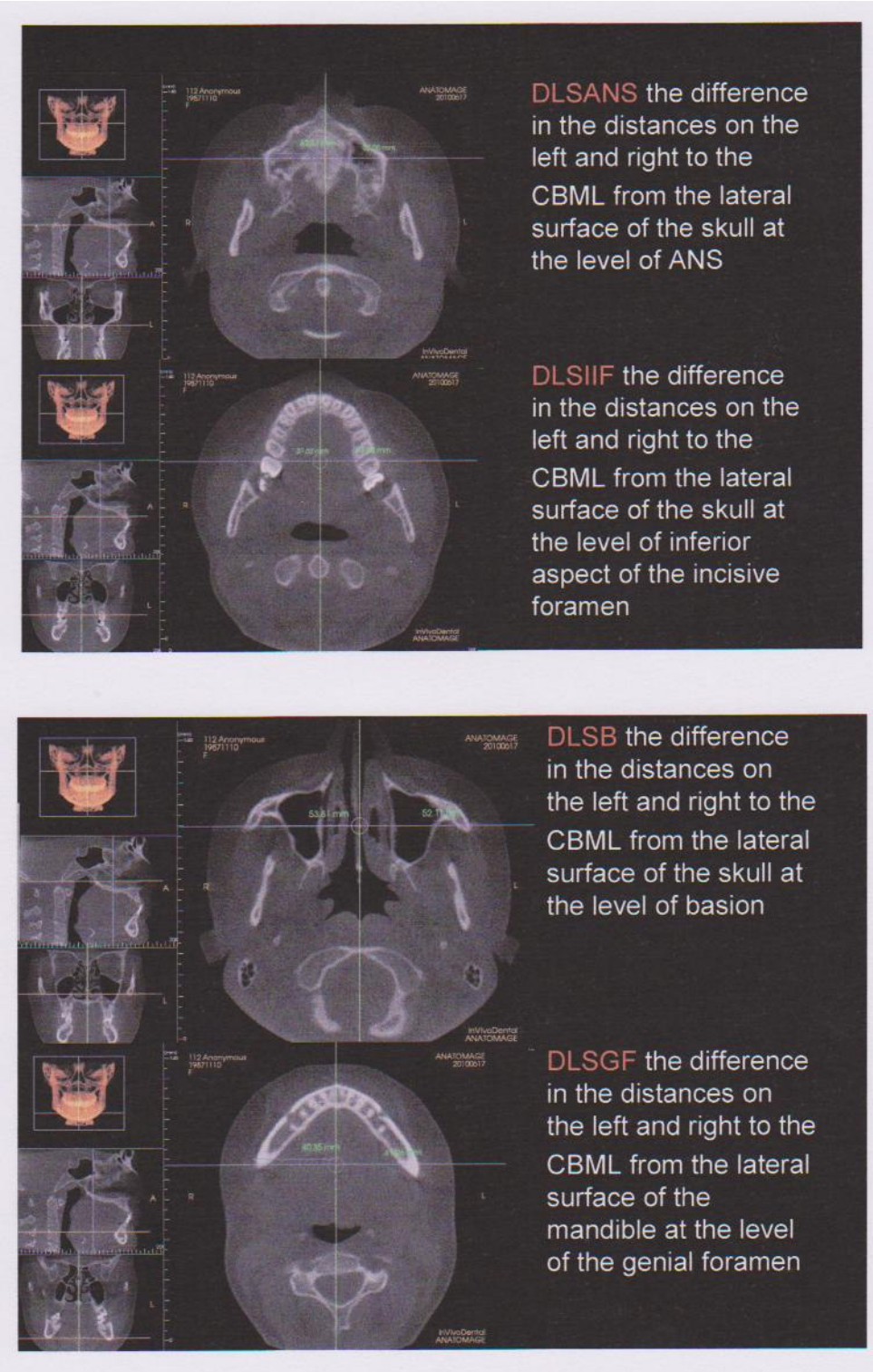
Measurements of Vertical Cranial Base Asymmetry

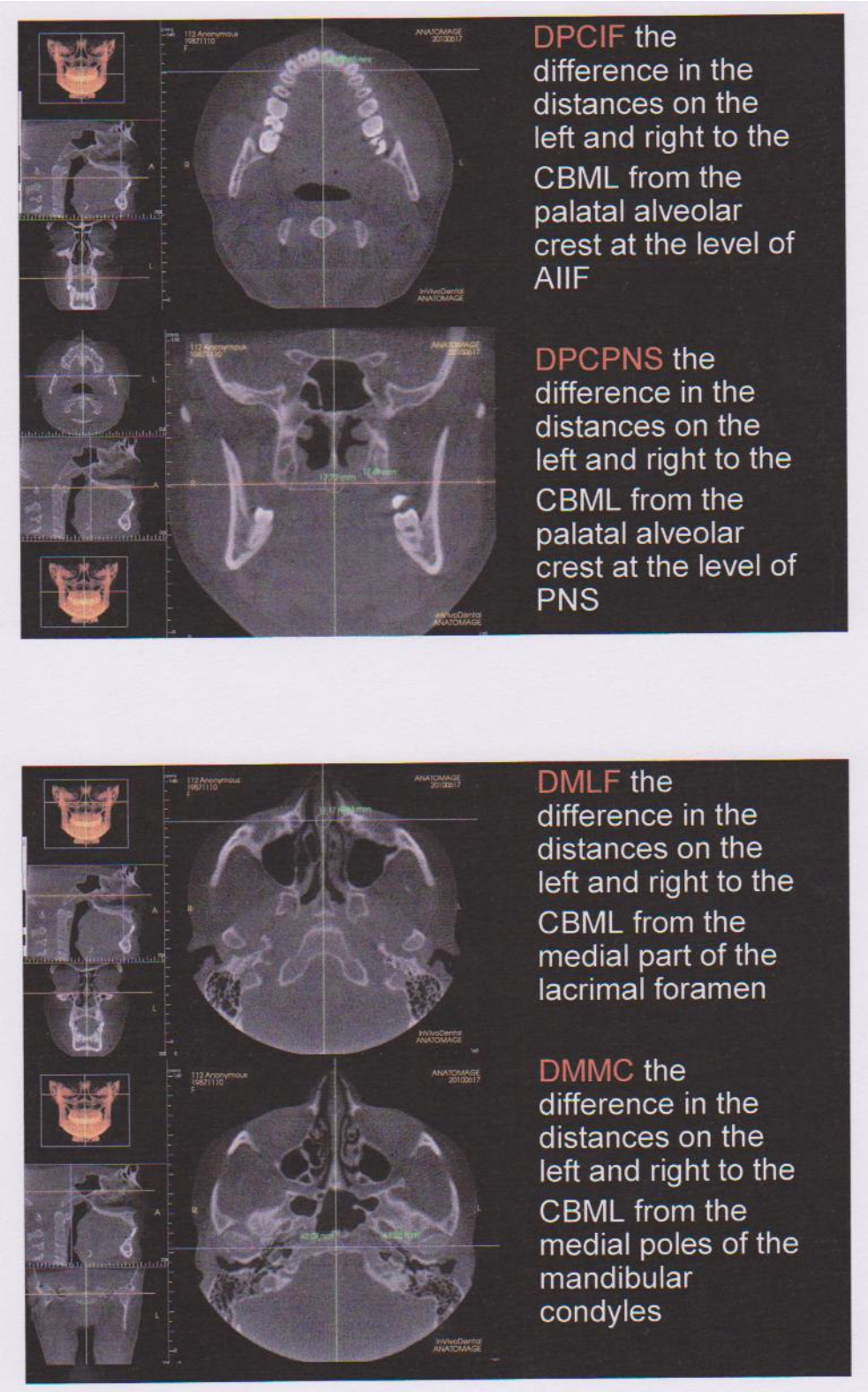


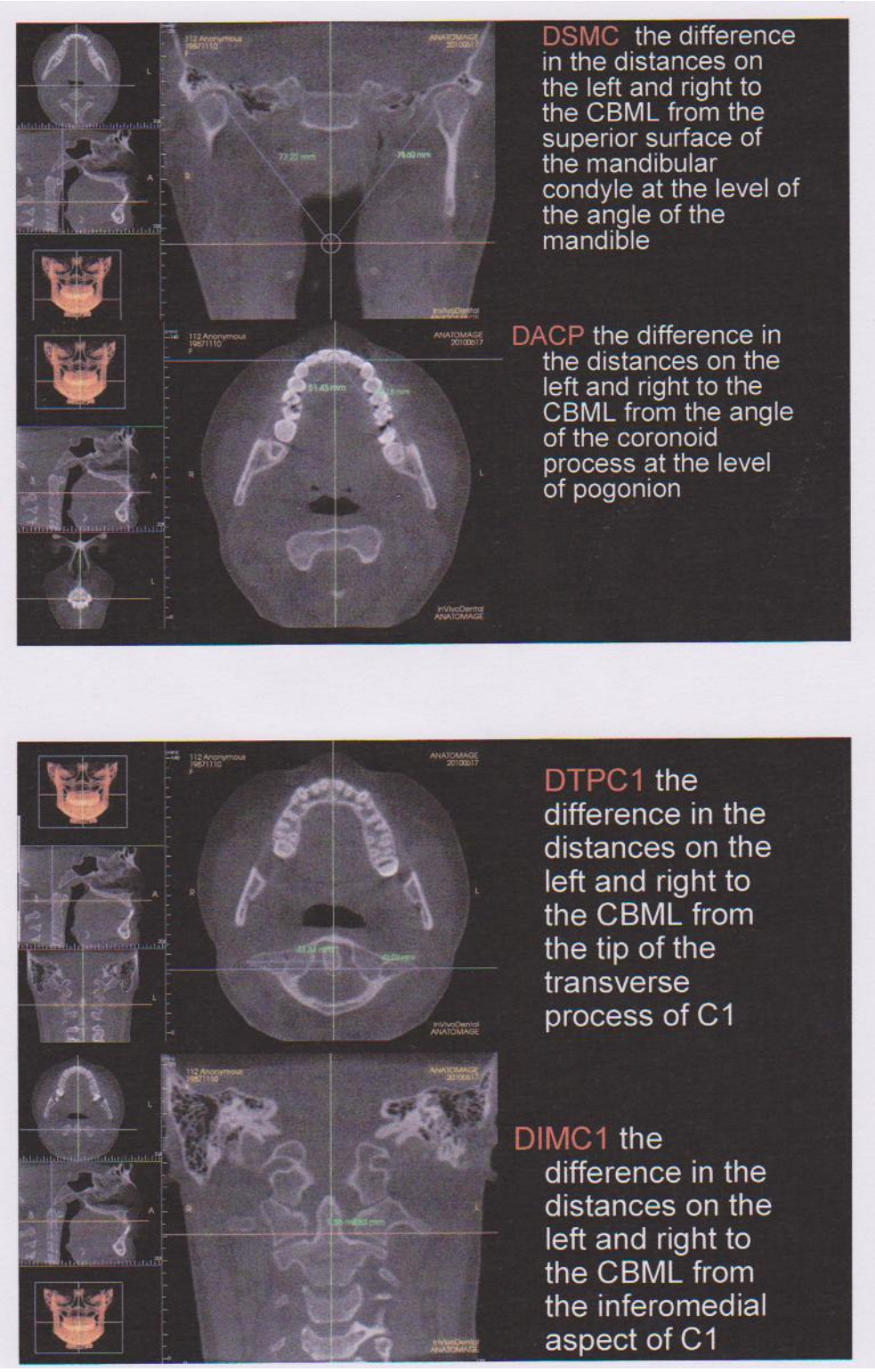
Bilateral Measurements of Facial Asymmetry to the CBML.

We took measurements of facial symmetry to the CBML at the following skeletal points. Measurements 1-6 are measurements of facial asymmetry to the CBML taken at the level of bony midline reference points. Measurements 7 and 8 are measurements of palatal asymmetry. Measurement 9 is a measurement of facial symmetry to the CBML at the level of the nasal airway. Measurements 10-12 are measurements of asymmetry of the mandible and mandibular condyle positioning to the CBML. Measurements 13-15 are measurements of upper cervical symmetry to the CBML.




DLSANS the difference in the distances on the left and right to the CBML from the lateral surface of the skull at the level of ANS
DLSIIF the difference in the distances on the left and right to the CBML from the lateral surface of the skull at the level of inferior aspect of the incisive foramen
DLSB the difference in the distances on the left and right to the CBML from the lateral surface of the skull at the level of basion
DLSGF the difference in the distances on the left and right to the CBML from the lateral surface of the mandible at the level of the genial foramen


DPCIF the difference in the distances on the left and right to the CBML from the palatal alveolar crest at the level of AIIF
DPCPNS the difference in the distances on the left and right to the CBML from the palatal alveolar crest at the level of PNS
DMLF the difference in the distances on the left and right to the CBML from the medial part of the lacrimal foramen
DMMC the difference in the distances on the left and right to the CBML from the medial poles of the mandibular condyles

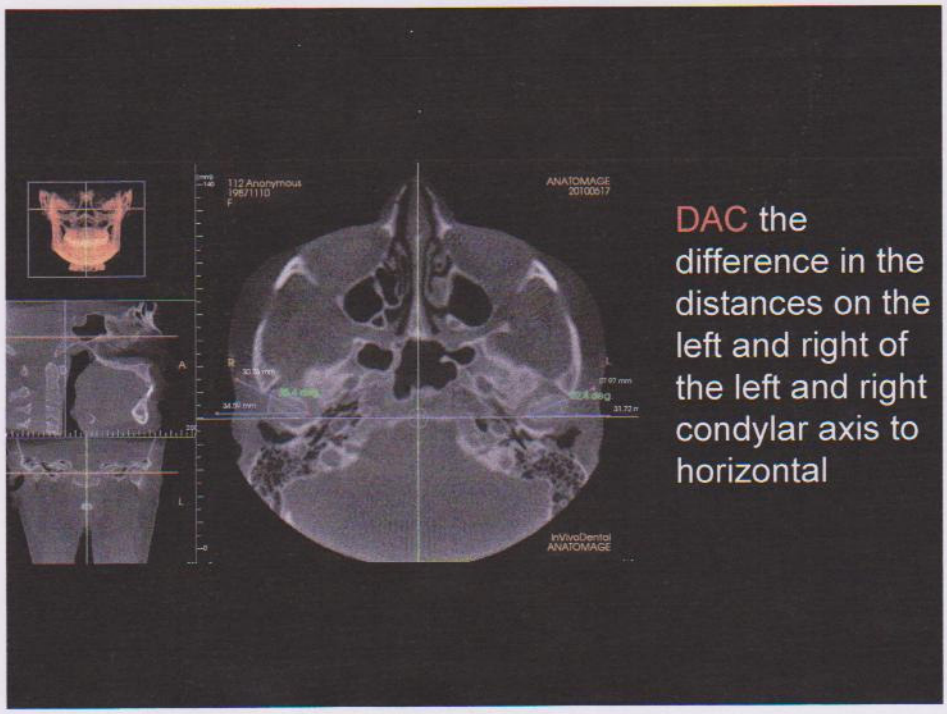

DSMC the difference in the distances on the left and right to the CBML from the superior surface of the mandibular condyle at the level of the angle of the mandible
DACP the difference in the distances on the left and right to the CBML from the angle of the coronoid process at the level of pogonion
DTPC1 the difference in the distances on the left and right to the CBML from the tip of the transverse process of C1
DIMC1 the difference in the distances on the left and right to the CBML from the inferomedial aspect of C1

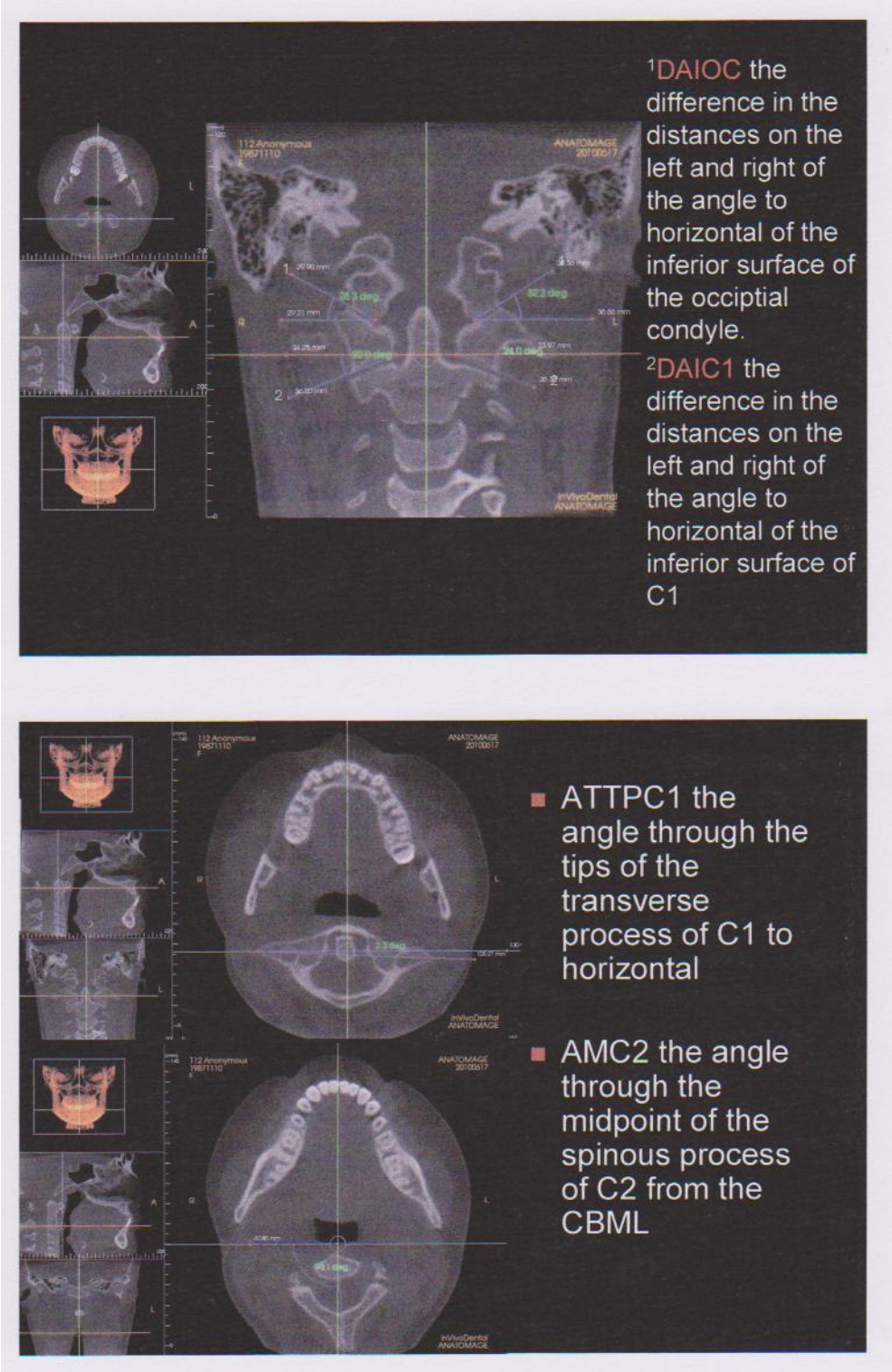
Rotational Measurements.

If correlation exists between midline asymmetry, facial asymmetry, and asymmetry of rotational measurements of the mandibular and occipital condyles, and the first and second cervical vertebrae (C1 and C2), then symmetric rotational measurements made on the left and right sides would be of equal value.

Rotational symmetry across the transverse processes of C1 was defined as a measurement of 0 degrees in the axial plane to a line that is perpendicular to the CBML. Rotational symmetry of the spinous process of C2 was defined as coincidence with the CBML when viewed in the axial plane.

The following measurements of rotational asymmetry were made.




[1]DAIOC the difference in the distances on the left and right of the angle to horizontal of the inferior surface of the occiptial condyle.
[2]DAIC1 the difference in the distances on the left and right of the angle to horizontal of the inferior surface of C1
ATTPC1 the angle through the tips of the transverse process of C1 to horizontal
AMC2 the angle through the midpoint of the spinous process of C2 from the CBML