CLEIDOCRANIAL DYSPLASTIC MUTANT IN THE MOUSE: DENTAL FINDINGS.

With an overview of human cleidocranial dysplasia.

Cathryn Vasseleu
B.D.S. (Hons), (Syd. Univ.)

A thesis submitted in partial requirement for the degree of Master of Dental Science.

DEPARTMENT OF PREVENTIVE DENTISTRY,
FACULTY OF DENTISTRY,
UNIVERSITY OF SYDNEY

1986.

ACKNOWLEDGEMENTS

I would like to thank Associate Professor Keith Godfrey, who, in the course of supervising this thesis, has given much valuable guidance, advice and encouragement. I also wish to thank Professor David Sillence, Director of the Commonwealth Institute of Health, for giving me the opportunity to be involved in his mouse mutation research project and for providing me with all necessary facilities and much information. Special thanks are due to Helen Ritchie for her extensive assistance and collaboration in the capacity of fellow research student, and to radiographer Joy Mahant of the Department of Surgery, Faculty of Medicine, who contributed invaluable expertise and many hours to this project. The radiographic work was undertaken in the Department of Surgery, Faculty of Medicine, and I would like to thank Professor Janet McCredie for generously putting the department's radiographic facilities at my disposal. I gratefully acknowledge the advice and assistance of Associate Professor Peter Barnard, of the Department of Preventive Dentistry, Professor Eugene Seneta, of the Department of Mathematical Statistics, Dr Toshiko Mori, of the Department of Prosthetic Dentistry, Dental Faculty librarians Joan Thwaite, Kay Daniels and Roslyn Gibb, and from the Photography Department of the Faculty of Dentistry - Bob Van Luyn, Bob Johnson and Peter Holloman. Thanks are also due to Sue Elliott, Kate Gilroy, Peter Vaughan, Kit Chan, Jenny Vasseleu, and to Maureen Hatherley, who has typed this manuscript.

CONTENTS

INTRODUCTION

Cleidocranial dysplasia is a genetic disorder which affects not only processes of osteogenesis, but also processes of tooth eruption, tooth induction, and craniofacial growth. These last three complications make the condition one which may interest those working in the fields of oral and craniofacial biology. The condition is neither life-threatening nor incapacitating. However, elucidation of the pathological process which it embodies may provide valuable insights into the normal mechanisms of tooth eruption, tooth induction and craniofacial growth, each of which remains a largely unsolved puzzle. The discovery of a mouse mutant which appears to have a genetic disorder homologous to the condition found in humans may provide scientists with an opportunity to study aspects of the disorder in a detailed manner which might otherwise be impossible. The extent to which the condition affects craniofacial growth and the dentition of the Ccd mutant has not been investigated, but if such processes are similarly affected in both mice and humans, then elucidation of these in the mouse may assist scientists not only in achieving an understanding of human cleidocranial dysplasia, but may also help with the unravelling of normal mechanisms of craniofacial and dental development.

It is intended that this study will provide an overview of cleidocranial dysplasia in humans (with particular emphasis on craniofacial aspects), a discussion of aetiology and treatment, and a description of the condition in the Ccd mouse mutant, which is being studied by Sillence, Ritchie & Selby (in press). The original contribution being made is an investigation of the dentition of the Ccd mouse mutant, with the intention of assessing whether the homology between human cleidocranial dysplasia and the Ccd mouse mutant extends to aspects of the dentition.

CHAPTER I

A. HISTORICAL INTRODUCTION

The description by Greig (1933) of a neanderthaloid skull with features indicative of cleidocranial dysplasia has prompted the comment that the disease may have an ancestry dating from the dawn of civilization (Barrett 1970). Other evidence from antiquity is presented by Bartsocas (1982), who entertains the possibility that a skeleton without clavicles of a woman dating from the 16th century B.C. might be an early instance of the condition, and by Carter (1973), who suggests that Homer describes in Thersites (Iliad) a possible case: "He was the ugliest man who came to Troy. He was bandy-legged and lame in one foot. His shoulders were bent and met over his chest. Above he had an egg-shaped head and on it sprouted some scanty hairs."

The first known description of an inherited deformity of the clavicles was made by Martin in 1765 (quoted by Bjorn & Grahnen, 1966; and Walter, 1967). Scheuthauer, in 1871, (quoted by Walter, 1967) made observations associating clavicular deformity with deficient ossification of cranial sutures in two skeletons in the Pathological Museum in Vienna.

Although case reports had been made since 1766 (Morand, quoted by McCurdy & Baer, 1923), it was not until 1896 that Marie and Sainton published the classic paper describing the condition as a syndrome: "dysostose cleido-cranienne". The essential characteristics were listed as:-

A. An exaggerated development of the transverse diameter of the cranium coincident with a retarded ossification of fontanelles.

B. An aplasia more or less pronounced of the clavicles.

C. Hereditary transmission of these malformations.

Disturbances of the teeth and palatal vault were also noted. Marie and Sainton gave original credit for recognition of the syndrome to

P.-A. Pierre, whose Doctoral thesis on the subject may have lain buried and forgotten in a university library except for the attention given it by the two practising physicians (Marie and Sainton, 1898).

In 1910, Fitzwilliams reviewed 58 published cases and added two of his own. Two years before this, Hultkrantz made the observation that all parts of the cranium participate in the deformity, and that the cranial base and facial skeleton are also involved. An abstract and discussion of his 1908 article are included in Fitchet's comprehensive review of contributions on the subject up to 1929 (Hultkrantz, 1908, in Fitchet, 1929). Interest in the effects on the dentition was stimulated by Hesse, who in 1925 carried out an extensive roentgenographic study of the jaws in cleidocranial dysplasia and published a report with particular emphasis on dental findings (Hesse, 1925, in Gorlin and Pindborg, 1976).

By 1929 there were 151 cases reported; by 1937 there were 228. By 1946, 505 cases had been reported, and by 1962, about 600 cases (Kalliala & Taskinen, 1962). To date, over 700 cases have been documented in the medical and dental literature (Gorlin & Pindborg, 1976). As many cases go unnoticed, it is probable that cleidocranial dysplasia is even commoner that this figure suggests (Beighton, 1978). Although not all of the documented cases will be included here, authors who have made contributions of particular interest will be discussed at the appropriate places in the text, and particular emphasis will be given to cases reported in the last twenty years.

B. NOMENCLATURE

Marie and Sainton had originally placed their findings in the class of "hydrocephalics" and had been criticized for doing so. When naming their syndrome "dysostose cleido-cranienne" they explained that the word "dysostosis" had no other pretention than to designate a "disturbance in the ossification" (Marie & Sainton, 1898). This term was adopted and remained in use until its reclassification in the International Nomenclature of Constitutional

Diseases of Bone of 1977. Prior to this, various alterations to the nomenclature had been proposed. Soule (1946) had agreed with Rhinehart's suggestion (Rhinehart, 1936, in Soule, 1946) that "mutational dysostosis" would be more appropriate because of the great variability in defects found, while others, more interested in the dental anomalies of the syndrome, had argued that the nomenclature should reflect this constant and significant feature - hence "osteodental dystrophy" (Lebourg et al 1953, quoted by Thoma & Goldman, 1960), "osteodental dysplasia" (Jackson, 1951; Walter, 1967) and "cleidocraniodental dysostosis" (Forest & Fontaine, 1967; Kelly & Nakamoto, 1974).

With the intention of developing a uniform nomenclature for the large heterogeneous groups of constitutional disorders of the skeleton which have been, or are being, elucidated, an International Nomenclature of Constitutional Diseases of Bone was developed in 1969 and updated in 1977 (Rimoin, 1975; Maroteaux, 1983). This International Nomenclature divides the constitutional disorders of the skeleton into five major groups:

Osteochondrodysplasias - abnormalities of cartilage or bone growth and development or both.

Dysostoses - malformations of individual bones singly or in combination.

Idiopathic osteolyses

Chromosomal aberrations

Primary metabolic abnormalities

The osteochondrodysplasias are further divided into:

1. Defects of growth of tubular bones and/or spine, which are frequently referred to as chondrodysplasias.
2. Disorganized development of cartilage and fibrous components of the skeleton.
3. Abnormalities of density or cortical diaphyseal structure or metaphyseal modelling.

The condition formerly referred to as "cleidocranial dysostosis" has been included in the first subsection of the group of osteochondrodysplasias, as "cleidocranial dysplasia".

The term dysostosis" applies specifically to malformations of the skeleton. A malformation is a morphologic defect of an organ, part of an organ or larger region of the body resulting from an intrinsically abnormal developmental process (Spranger, Benirschke, Hall, Lenz, Lowry, Opitz, Pinsky, Schwarzacher, Smith, 1982). The malformation may be agenesis (complete failure of embryonic primordium, or anlagen), aplasia (failure of anlagen to differentiate) or hypoplasia (failure of anlagen to grow to normal size due to intrinsic deficiency) (Sillence, 1985).

Abnormalities of tissue development and their anatomical results are not malformations but dysplasias. A dysplasia is an abnormal organisation of cells into tissue(s) and its morphologic result(s); a dysplasia is the process and consequence of dyshistogenesis. (For example, osteogenesis imperfecta is a dysplasia because the abnormality can be reduced to a defect in connective tissue). Because the defect involves all anatomical sites which contain the affected tissue, dysplasias often show widespread involvement rather than being confined to a single organ system (Spranger et al, 1982). Cleidocranial dysplasia is designated a dysplasia because there is widespread involvement, and the pattern of skeletal abnormalities at any age prior to maturity is not the final pattern found at maturity. Therefore it is not a simple malformation syndrome (dysostosis) (Sillence, Ritchie, Selby, 1985).

The current nomenclature is based primarily on the part of the skeleton which is affected radiologically, but it is intended that progress be made towards a pathogenetic classification of skeletal dysplasias as morphologic studies add to precision of diagnosis and help define heterogeneity and modes of inheritance of disorders (Sillence, Rimoin, Lachman, 1978; Sillence, Rimoin, 1982). As the structure, pathogenesis, and particularly the basic biochemical defect of disorders are elucidated, it is hoped that the nomenclature will be changed to refer to the specific pathogenetic or metabolic defect (Rimoin & Sillence, 1982).

Finally, a note on the use of the term "syndrome": this is a pattern of mutiple anomalies thought to be pathogenetically related

and not known to represent a single sequence or a polytopic field defect. A sequence is a pattern of multiple anomalies derived from a single known or presumed prior anomaly or mechanical factor (a malformation, disruption or a mechanical factor may give rise to a cascade of secondary problems in subsequent morphogenesis). A polytopic field defect is a pattern of anomalies derived from the disturbance of a single developmental field (dysmorphogenetically, the anomalies are derivatives of a single malformative or disruptive process). The present use of the word "syndrome" implies a lower level of understanding - only that the anomalies are considered to be part of the same developmental field defect, while knowledge of the initiating event and ensuing cascade of secondary events means that a syndrome may turn out to represent a polytopic field defect or a sequence (Spranger et al, 1982).

CHAPTER II

DESCRIPTION OF FEATURES

A. GENERAL CHARACTERISTICS

Cleidocranial dysplasia (to be referred to hereafter as CCD, as distinguished from the mouse mutation Ccd) is characterized by multiple variable anomalies, principally of the skeleton and dentition. Racial, ethnic and regional variation is widespread, with cases being reported from every continent (Soule, 1946), and apart from the bias towards Caucasians which is likely to be a reflection of the predominance of Europe, America and Australia in the generation of medical and dental literature, incidence in Hindu, Jewish, Mestizo, Chinese and Negro groups among others has been reported (Lasker, 1946).

Many of the defects are present at birth, but some of them, craniofacial and dental anomalies in particular, become apparent with growth and development. Despite defective early ossification, increase in ossification of hands, pelvis and calvarium occurs with age (Jackson, 1951; Jarvis & Keats, 1974).

1. GENERAL APPEARANCE

In their large surveys of CCD both Soule (1946) and Jarvis & Keats (1974) commented on the strikingly similar physical appearance among affected individuals. The cranium is large and broad, with prominent frontal bosses and depressed sagittal suture. The face appears to be recessed and small, with wide-spaced, sunken eyes, broad, depressed nasal bridge, and prominent mandible. Many are small of stature, with long necks, slightly drooped shoulders and sloping chests. Almost every case report includes a photograph of the patient demonstrating his or her ability to approximate the shoulders. The hands have prominent knuckles, unusually long index fingers, and small, tapering terminal phalanges.

2. HEREDITARY PATTERN

Marie and Sainton included hereditary transmission in their classification of the syndrome in 1898. In 1929, Fitchet, after reviewing most cases which had been reported, recognised that both hereditary and non-hereditary (approximately 46%) forms occurred. By 1946, Soule had found 125 cases (approximately 39%) in the literature where no family influence could be determined. In the same year, Lasker came to the conclusion that inherited cases complied with dominant Mendelian ratios, that the mutation had high penetrance, and that both sexes were equally affected. He suggested that cases of spontaneous occurrence (he assessed these as comprising approximately 16%, which is at variance with Soule, even though they both reviewed the same material) could perhaps be explained if the responsible gene recurs as a mutant. Herndon (1951) concentrated on the spontaneous cases, considering them in terms of three possible explanations. He ruled out phenocopies (environmental factors which mimic genetic mutations) because the environmental factors would have to work at one stage of embryological development, and this did not seem appropriate for CCD. The inheritance of the condition by offspring of spontaneous cases (reported, for example, by Winter, 1943; Forland, 1962; Winther & Khan, 1972; as well as Herndon, 1951) would also argue against this alternative. The second alternative, of recessive homozygotes, was ruled out on the basis that observed case distribution pointed to this being so rare as to be negligible. That the disease has not been observed to miss a generation then reappear further substantiates this view (Soule, 1946; Forland, 1962; Walter, 1967). The third alternative, that spontaneous cases represent a fresh mutation of the same dominant gene, best fitted all previous observations, and Herndon concluded that all cases of CCD are due to a dominant gene with virtually complete penetrance and an unusually high mutation rate. He suggested that mating selection might explain why the mutation was not maintained in any family for more than five generations, but Jackson (1951) and Jarvis & Keats (1974) have both traced the disease through six generations.

Recent pedigree studies by Bjorn & Grahnen (1966) and Jarvis & Keats (1974) support the view that both spontaneous and inherited cases of CCD are explicable in terms of an autosomal dominant

mutation with high penetrance. On the other hand, Goodman, Tadmor, Zaritsky & Becker (1975) found offspring of two sets of consanguinous parents to have CCD and presented this as possible evidence for an autosomal recessive form of the disease, with apparently sporadic cases inheriting the condition in its recessive form.

Cytogenetic analyses of several cases have been made by Forland (1962) and Bjorn and Grahnen (1966), none of whom found any chromosomal abnormalities. On the other hand, Srivastava, Pai, Kolbhandara & Kant (1971) reported a case with consistent presence of exaggerated constriction in one of the chromosomes in the 13-15 group. Hall (1982) observed that some chromosomal disorders, partial trisomy 11q and partial trisomy 11q/22q had been reported to have a high incidence of congenital clavicular hypoplasia or agenesis (CCHA), and concluded that 11q is likely to be the chromosome responsible for the occurrence of CCHA in this particular group. CCD is one of the syndromes (in fact the prototype syndrome) associated with CCHA. (See TABLE 1)

B. CLINICAL, RADIOGRAPHIC & HISTOLOGICAL FINDINGS

In the following sections, clinical, radiographic and histological findings in CCD are described. These features will then be referred to and discussed in a subsequent chapter dealing with aetiology of CCD.

1. SKELETON

Instead of recording every case report in which a particular anomaly has been described, the following summary is based on several articles where extensive collations have been made. The first of these is the tabulation by Fitzwilliam (1910) of two of his own and 58 other reported cases; the second is the survey of all case reports and articles in Cumulus Index Medicus from 1929 to 1944 made by Soule (1946); and the third is the review of forty new cases collected by Jarvis & Keats in 1974. Where additional findings to those described in these articles have been reported in the case studies and more specialized material (for example

TABLE 1

ENTITIES WITH SIGNIFICANT FREQUENCY OF CONGENITAL CLAVICULAR HYPOPLASIA OR AGENESIS (CCHA)

I. Skeletal Dysplasia
   - A. Cleidocranial Dysplasia, Classic Autosomal Dominant
   - B. Cleidocranial Dysplasia, Rare Autosomal Recessive (Goodman et al)

II. Skeletal Dysostosis
   - A. Congenital Clavicular Pseudoarthrosis
   - B. Parietal Foramina/Lateral Clavicular Deficiency (Eckstein and Hoare)

III. Chromosome Disorder
   - A. 11q Partial Trisomy
   - B. 11q/22q Partial Trisomy
   - C. 20p Trisomy (Schinzel)

IV. Multiple Congenital Anomaly
   - A. Dysplasia Cleido-Facialis (Kozlowski et al)
   - B. Digit/Mandible/Clavicle Hypoplasia (Yunis and Varon)
   - C. Microcephaly/Micrognathic/Contracture Dwarfism (Bixler and Antley)
   - D. Imperforate Anus/Psoriasis/Clavicle Deficiency (Fukuda et al)
   - E. Focal Dermal Hypoplasia of Goltz
   - F. Coffin-Siris?
   - G. Crane/Heise Syndrome

(From Hall B.D; Proceedings of the Third International Clinical Genetics Seminar, 1982, p 286, Table IV)

otorhinolarygology and orthodontics) read by this author, they have been included in the following text.

i. Calvarium

The skull is usually brachycephalic, with a cephalic index of more than 80 degrees (transverse diameter is more than 80% of longitudinal diameter). There is a marked prominence of the frontal, parietal and occipital bosses, with increased biparietal diameter and reduced fronto-occipital diameter (Fitzwilliam, 1910; Soule, 1946; Jarvis & Keats, 1974). There is deformity and enlargement of the foramen magnum associated with dysplastic changes in the basi-occiput (Soule, 1946; Jarvis & Keats, 1974).

The sagittal suture is depressed, and the metopic suture (which separates the lateral portions of the frontal bones in the foetus) persists into childhood or often never fuses at all (Soule, 1946; Jarvis & Keats, 1974). Similarly there is delayed and often incomplete closure of the fontanelles with persistence of large irregular defects in the anterior, posterior, mastoid and sphenoid fontanelles. Heavy fascia or thin bone may develop over these defects, but there is seldom complete bone closure with tables of normal thickness (Soule, 1946). Complete absence of parietal bones at birth has been reported (Tan & Tan, 1981).

Suture lines tend to be wide, depressed and tortuous. Secondary centres of ossification appear in the suture lines and many wormian bones may form. Overdevelopment and defects of the supra-orbital ridges are common (Fitzwilliam, 1910; Soule, 1946; Jarvis & Keats, 1974) and there may be mild exophthalmos associated with a depressed orbital roof (Fitzwilliam, 1910). Jarvis & Keats (1974) noted segmental calvarial thickening and sclerosis of diploeic space in not only the supra-orbital portion of the frontal bone and the squama of the temporal and occipital bones, but also unusual bony shelves in the temporal bones at the squamoparietal suture, and the inferior margin of the squamous portion of the occipital bone. These shelves may measure up to 1 cm in adults with the condition.

The mastoids are often unpneumatized (Jaffee, 1968; Jorgenson, Morgenstein, Becker, 1971). Gorlin & Pindborg (1976) consider that this is because of altered function of the sternocleidomastoid muscles, but this does not explain the absence of pneumatization in other areas which are normally pneumatized, such as the frontal sinuses (reported by Rock, 1969, - although Soule, 1946 comments that these may be disproportionately large) and maxillary sinuses (to be described in the following section).

ii. Facial bones

The facial bones, especially those of the midface, are underdeveloped. The distance between the anterior nasal spine and rim of the orbit is reduced (Fernex, Chouvet, Fourquez, 1974) and the suborbital region is depressed due to deficient and malformed nasal, lacrymal and zygomatic bones. Maxillary and paranasal sinuses may be small or absent (Fitzwilliam, 1910; Soule, 1946; Jarvis & Keats, 1974). Asymmetry of nasal bones may also occur (Fitzwilliam, 1910; Pou, 1971) and a gap representing absence of the zygoma may occur between the zygomatic process of the temporal bone and the maxilla (Soule, 1946). Hypertelorism is also an occasional finding (Kalliala & Taskinen, 1962; Jorgenson et al, 1971; Jarvis & Keats, 1974; Dann, Crump, Ringenberg, 1980). The palate is frequently described as high-vaulted, and occasionally, cleft (Fitzwilliam, 1910; Soule, 1946; Jorgenson et al, 1971; Monasky, Winkler, Icenhower, Ruane, Fielding, Defrancisis, 1983).

Mandibular anomalies reported include prolonged patency of the mental suture (Fitzwilliam, 1910; Soule, 1946), greatly enlarged genial tubercles (Rushton, 1938; Soule, 1946) and elongation and thinning of the neck of the condyle (Fernex et al, 1974; Jarvinen, 1981).

iii. Cranial base

Hultkrantz (summarized by Fitchet, 1929) recognised that the cranial base is considerably involved in CCD. He reported a reduced longitudinal diameter, and a reduction in width, particularly in the middle part. Denting of the clivus between the sphenoid and occipital portions with abrupt decline and shortening, and a turning forward of the foramen magnum in conjunction with the depression of

the posterior portion of the cranial base was also identified. These observations have been substantiated in later studies, by Soule (1946), Fernex, et al (1974), and Kreiborg, Leth Jensen, Bjork & Skeiller (1981). These last researchers found that in addition to flexion distortion of the clivus (with convexity towards the endocranium) and reduction in cranial base length (which they discovered to be manifest as shortness of both anterior and posterior portions), all seventeen of the CCD patients in their sample had a bulbous dorsum sella, and eight (almost half) had a small pituitary fossa. Migliorisi and Blenkinsopp (1980) also report the finding of a shallow pituitary fossa. A finding of unpneumatized sphenoid sinuses has been described in one case presentation (Rock, 1969).

iv. Auditory bones

Nager (1936, quoted by Thoma & Goldman, 1960) reported otologic symptoms in patients with CCD, which he believed to be associated with malformations of the malleus and stapes. Subsequent workers have also reported the findings of dense, bulky, distorted, clumped and fixated auditory ossicles, and furthermore, pronounced narrowing of the external auditory canals (Fons, 1969; Pou, 1971; Hawkins, Shapiro, Petrillo, 1975). Dense sclerosis of the middle ear and absence of pneumatization of mastoids is also described (Jaffee, 1968; Fons, 1969; Hawkins et al, 1975). Defects of auditory bones are not a universal finding in CCD; Fons (1969) presented a case of CCD with hearing defects where the mother, twin and sibling had no middle ear malformations despite being diagnosed as having CCD.

v. Upper extremities

Total absence or defects of the clavicles are among the commonest, and arguably, universal findings in CCD. Defects may be bilateral or unilateral, with a right-sided selectivity. In about ten percent of all reported cases the clavicles are entirely absent. Frequently, sternal and acromial ends are present but ununited, or united by a fibrous cord or pseudoarthrosis. The acromial end is more likely to be absent, and where there are two portions, smaller than the sternal portion. Three separate fragments have also been described (Fitzwilliam, 1910; Fitchet, 1929; Soule, 1946; Jarvis & Keats, 1974). Cases with no clavicular defects (Fitchet, 1929;

Flynn, 1966) and cases with complete but hypoplastic clavicles (Kalliala & Taskinen, 1962) have been reported. Jarvis & Keats (1974) identified flaring of the normally tubular medial third with an under-funnelization type of modelling defect as a feature which had previously been unnoticed, and Eventov, Reider-Grosswasser, Weiss, Legum & Schorr (1979) presented some cases which had this defect but would otherwise have been considered normal. The defects of the clavicles give unusual mobility to the shoulders.

The scapulae are typically small and primitive in appearance, lie higher and nearer the axilla than usual, and anomalies of the acromial ends are occasionally found. Defects of the humerus, ulna and radius are unusual, although the shafts may be shorter than average. Persistence of the epiphyseal lines at the lower extremities of ulna and radius is fairly frequent (Soule, 1946).

Anomalies of the metacarpals and phalanges are common. "Zaphen" epiphyses (abnormal or underdevloped epiphyses with pine-cone shape - Kalliala & Taskinen, 1962) and extra epiphyses in the proximal ends of one or more metacarpals and in the distal ends of one or more phalanges (especially the proximal) are found in children with CCD. The metacarpals are wide at the end and narrowed in the shaft. The second metacarpal is usually disproportionately long. Variations in the shape and density of the proximal phalanges are found and all phalanges of the little finger are unusually short (Soule, 1946; Jarvis & Keats, 1974). The fingers are tapered due to failure of development of the terminal tufts at the free extremities of the phalanges (Brailsford, 1953; Forest & Fontaine, 1967; Jarvis & Keats, 1974). Some case reports which include hand-wrist radiographs showing the various defects mentioned above are those made by Kalliala & Taskinen (1962), Stiff & Lally (1969), and Srivastava et al (1971).

vi. Spine, pelvis & thorax

Spinal abnormalities occur in most patients with CCD. Kyphosis, lordosis and scoliosis, fusion defects of the laminae and spinous processes (spina bifida, accessory vertebrae, missing vertebrae and hemivertebrae), spondylolysis, and spondylolisthesis are the spinal anomalies most frequently encountered. Cervical ribs

are an occasional finding (Soule, 1946; Jarvis & Keats, 1974).

Pelvic involvement is invariably found. The pelvic bones are usually smaller than normal, with hypoplasia of the iliac wing and wide sacro-iliac joints. The most common defect is underdevelopment and mesial deficiency of the ossa pubes, with resultant widening of the symphysis pubis. Closure with sclerosis and distortion may occur by about twenty-five years of age. Asymmetry of the pelvic canal may predispose to delivery difficulties in females (Soule, 1946; Jarvis & Keats, 1974).

The sternum may be normal or small and irregular in outline. The ribs are rounded behind and flattened in front (Soule, 1946). Unduly elevated first ribs have also been noticed (Lloyd-Roberts, Apley, Owen, 1975). The thorax is often cone-shaped, apparently incident to hypoplasia or delayed development of a segment of the posterior part of the vertebral body (Jarvis & Keats, 1974).

vii. Lower extremities

The femoral necks are frequently deformed, widened or absent. Femora, tibiae and fibulae may have shorter shafts than average. Coxa vara or coxa valga is sometimes encountered. Changes in the ankles and feet similar to those in the wrists and hands may be found (Soule, 1946; Jarvis & Keats, 1974).

2. EXTRA SKELETAL ANOMALIES

i. Nervous system

Nervous system changes which have been reported in association with CCD include agenesis of cingula gyri and several basal cell nuclei, syringomyelic or hydromyelic spinal cord changes, and cysts of frontal or occipital lobes (Soule 1946; Moriarty & Klingman, 1962). The incidence of epilepsy is also reported to be higher in CCD (1.8%) than in the average population (0.26%) (Henderson & Gillespie, 1951 - quoted by Giaccai, Salaam & Zellweger, 1954). In the vast majority of cases the mental capacity of patients is normal, although occasional reports of feeblemindedness have been made; in both the reports of this made by Thomsen & Guttadauro (1952) and Giaccai et al (1954) CCD was associated with

osteosclerosis. A case of neuralgia associated with pressure of clavicular fragments on the brachial plexus has been reported (Poynton 1913-14 - quoted by Fitchet, 1929). Hawkins et al (1975) entertain the possibility that the hearing defect occasionally encountered might be associated with encroachment of sclerotic bone on the vestibulo-cochlear nerve, but also reason that an unaffected facial nerve contradicts this suggestion.

ii. Muscles

Variations in size, origin and insertion of muscles related to the clavicles and scapulae are found, particulary sternocleidomastoid, sternohyoid, trapezius, deltoid and pectoralis. Function appears to be unaffected. (Fitzwilliam, 1929; Soule, 1946).

iii. Blood

Blood calcium and blood phosphatase levels are usually within normal limits (Soule, 1946). Blood dyscrasias have been reported (Alexander & Ferguson, 1980) but are probably coincidental.

3. DENTITION

i. Eruption anomalies

Over-retention of deciduous teeth and failure of eruption of many permanent teeth is the commonest reason for presentation of patients. Eruption of the full deciduous dentition occurs, although delay in onset and progress of eruption has been frequently reported (Alderson, 1960; Kalliala & Taskinen, 1962; Flynn, 1966; Winkler & Jung, 1971; Winkler, Drinnan & Puengphob, 1976; Abbas & Prabhu, 1982). The permanent teeth most likely to erupt are the first permanent molars and lower incisors. According to Rushton (1937A, 1938), those teeth which normally appear first are the teeth which are most likely to erupt. There are exceptions to this, with several cases reported where such teeth have not erupted (Alderson, 1960; Winch & Armstrong, 1962; Stiff & Lally, 1969; Winther & Khan, 1972; Fardy, 1984). Other authors (Winter, 1943; Kalliala & Taskinen, 1962) considered that those teeth without predecessors are more likely to erupt normally. However, as Rushton (1937A) pointed out, eruption of lower incisors and common failure of eruption of

second and third molars contradicts this view.

Where permanent teeth erupt they are often ectopic, malaligned or rotated, and their eruption (particularly first molars) may be late or slow (Rushton, 1938; Winch & Armstrong, 1962; Elomaa & Elomaa, 1967; Walter, 1967; Winther & Khan, 1972; Hutton, Bixler, Garner, 1981; Farrer & Van Sickels, 1983). Eruption of upper second molars over three and a half years (Elomaa & Elomaa, 1967) and eruption of teeth in adults, often under dentures, has been observed (Winter, 1943; Barrett, 1970; Hylton & Albright, 1970; Jarvis & Keats, 1974). In a patient being treated by this author, a lower incisor erupted at 15 years, and upper first molars erupted at 16 years.

An association has been made between common sites of non-exfoliation of deciduous teeth, delayed or non-eruption of permanent teeth and regions of common supernumerary formation (that is, premolar and upper incisor regions) (Bjorn & Grahnen, 1966). However, as will be discussed in the section on treatment, eruption of permanent teeth does not often occur after the removal of deciduous precursors, which may be ankylosed (Hitchin & Fairley, 1974), or following the removal of possibly impacting supernumerary teeth.

There is a high incidence of dentigerous cysts associated with unerupted teeth in CCD (Rushton, 1938; Wilbanks, 1964; Douglas & Greene, 1969; Winkler & Jung, 1971; Levin, 1972; Oatis, Robertson, Sugg & Firtell, 1975 - who claim to report the first case; and Koch & Hammer, 1978).

It has not been possible to make a table showing distribution of unerupted/erupted teeth because of the inadequate reporting of such information in most case presentations.

ii. Anomalies of number

In many cases, supernumeraries of the permanent dentition are formed. One supernumerary of the deciduous series - an upper canine - has been reported (Winther & Khan, 1972). Late formation and mineralization, and recurrence after removal has been found

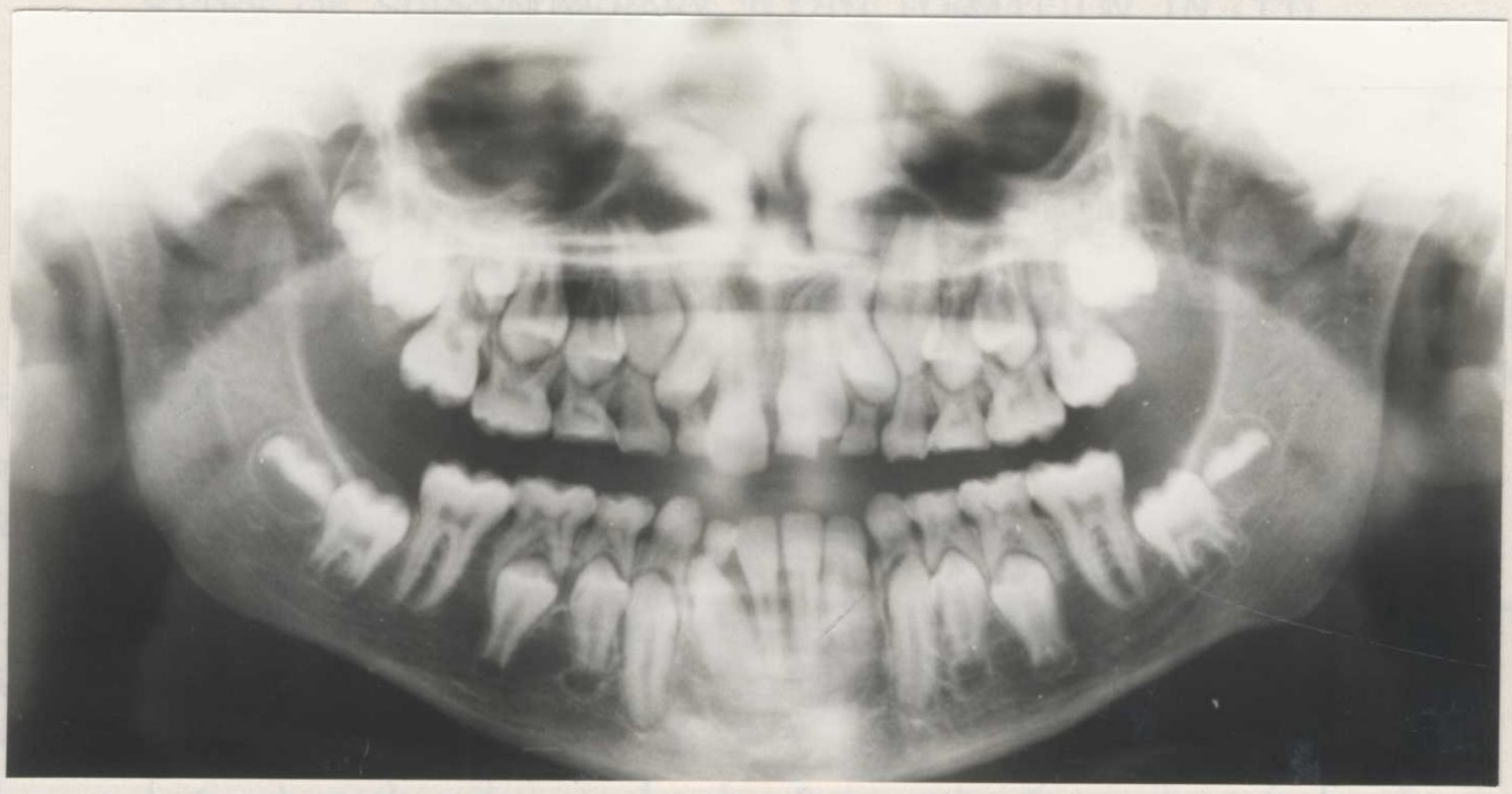
(Kalliala & Taskinen, 1962; Elomaa & Elomaa, 1967; Winther & Khan, 1972; Jarvinen, 1980A; and this author - see FIG. 1). Although most cases show an increase in odontogenic activity, congenital absence of upper laterals has also been described by Smylski, Woodside & Harnett (1974) and Chapnick & Main (1976). (Neither of these patients nor an affected sibling of one had any supernumeraries).

The commonest sites for the supernumerary teeth are the premolar and anterior regions (Rushton 1938), particularly lower premolar and upper anterior regions (see TABLE 2, which presents a distribution of supernumeraries in cases from the literature where sufficient detail regarding their position and number has been given). Supernumeraries in the first molar regions and (supernumerary) fourth molars are occasionally found (Rushton, 1938; Archer & Henderson, 1951; Kalliala & Taskinen, 1962; Elomaa & Elomaa, 1967; Walter, 1967; Winther & Khan, 1972; Migliorisi & Blenkinsopp, 1980). Symmetry is not consistent.

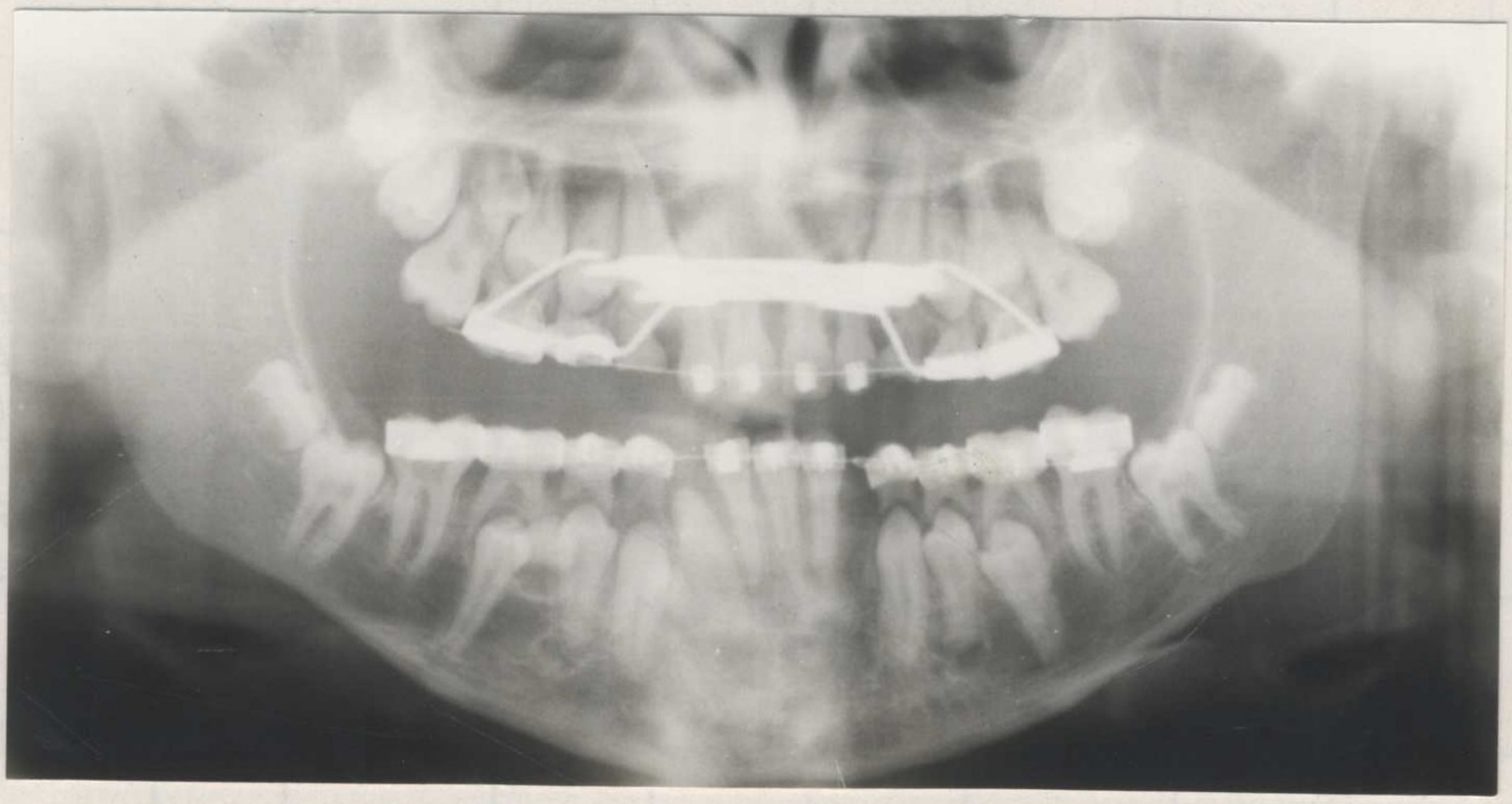
Unlike supernumeraries reported in normal children, where additional mandibular teeth are usually located apically of the teeth of the permanent series (Berendt, 1951; Morgan, Morgan & Crouch, 1970; Jarvinen 1976), Archer & Henderson (1951) recognised an occasional "capping" effect of supernumeraries over the normal succedaneous teeth. Radiographs of cases presented by Levin (1972), Smylski et al (1974) and Jarvinen (1980A) demonstrate this effect well. (See FIG. 2).

iii. Anomalies of tooth morphology

The crowns of unerupted teeth in CCD may be misshapen, spheroidal (appearing flattened), conical (with narrowing incisally), dilacerated, or have deep central fossae (Rushton, 1937B; Rock, 1969; Barrett, 1970; Hitchin & Fairley, 1974; Hall & Hyland, 1978). Rushton (1937B) also found the enamel from a series of extracted teeth to be ridged and pitted. He commented that because of distortion, the distinction between unerupted normal and supernumerary teeth was sometimes difficult to make. A single case involving fusion of an erupted deciduous lower canine and incisor has been reported (Jarvinen, 1980A), which may possibly be incidental.



a)



b)

FIGURE 1. a) Panoramic radiograph of a twelve year old boy with cleidocranial dysplasia. Note the supernumerary tooth distal to the upper right second premolar.
b) Panoramic radiograph of the same boy at fifteen. Note the development of an additional supernumerary tooth between the lower right first and second premolars.

TABLE 2

SITES OF SUPERNUMERARY TOOTH FORMATION IN CCD

	Case No/.	MAXILLA				MANDIBLE			
		Incisors & Canines	Pre-molars	Molars	4th Molars	Incisors & Canines	Pre-molars	Molars	4th Molars
ARCHER & HENDERSON (1951)	1	2	1		1		2		
KALLIALA & TASKINEN (1962)	1		1			1	5		
	2	3		1		2	2	1	
	3	4	2	2		3	5		
	4	2				3	3		
ELOMAA & ELOMAA (1967)	1	5	1		(2)		3		
WALTER (1967)	1	2	2				2	1	
ROCK (1969)	1		4			1	3		
WINTHER & KHAN (1972)	3	6							
	4	4	4			4	4(2)		(2)
JARVINEN (1980)	1	2(1)				1	2(2)		
	2	2(1)							
	3	2					2(2)		
BISHOP (1984)	1	2	1		1		1	2	
FARDY (1984)	1	2	1		1		3	2	
TOTALS		40	17	3	4	16	44	4	2

Numbers in brackets represent supernumerary teeth which developed subsequently after first examination.

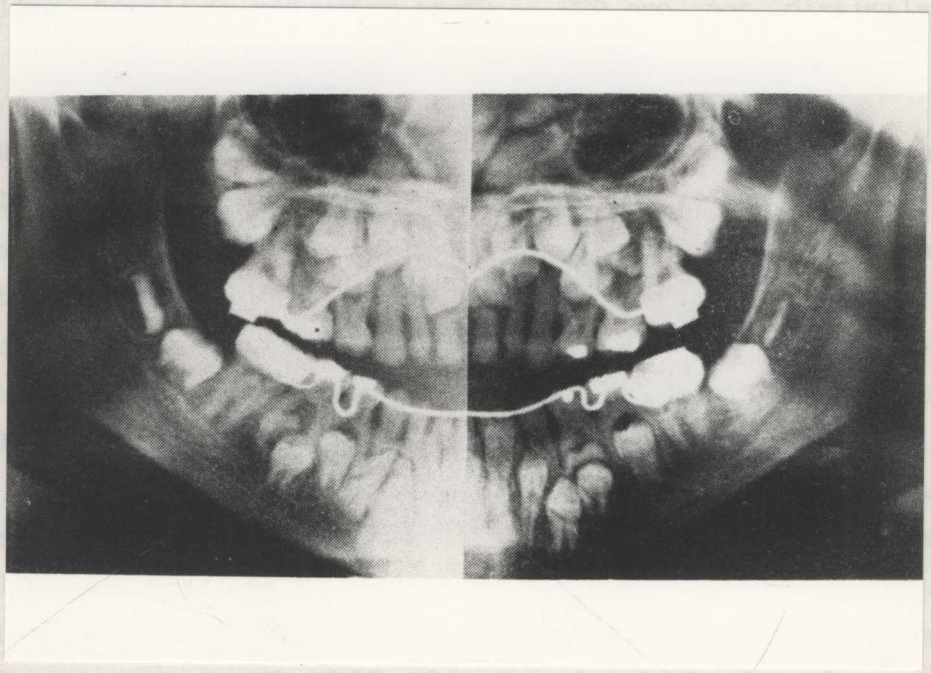


FIGURE 2. Panoramic radiograph (reproduced from Smylski P.T., Woodside D.G., Harnett B.E.; Int. J. Oral Surg. 3, 1974, Fig. 8, p384) which illustrates the occasional "capping" effect of supernumerary teeth over normal succedaneous premolars in cleidocranial dysplasia.

The roots of unerupted teeth are often distorted, short, conical, hooked, bifurcated, spirally twisted, and may display spike-like apices (Rushton, 1937B; Wilbanks, 1964; Barrett, 1970; Hitchin & Fairley, 1974; Hitchin, 1975; Hall & Hyland, 1978; Miller, Sakamoto, Zell, Arthur, Stratigos, 1978). Rushton (1937B) noted that the roots are often transversely ridged and direction of growth appears to change abruptly and often. He further commented that the anomalies found in unerupted teeth in CCD are not dissimilar to those often found in otherwise normal individuals.

Rushton (1956) found an extreme deficiency of cellular cementum in all but one of nine extracted teeth from CCD patients. In both erupted and unerupted teeth only small patches of cellular cementum were found, filling hollows or grooves rather than on free surfaces. Acellular cementum, on the other hand, was present in normal amounts, and the deciduous teeth studied had normal distribution of cellular and acellular cementum. The findings of Alderson (1960), Smith (1968), Chapnick & Main (1976), Hitchin (1975) and Hall & Hyland (1978) are in agreement with Rushton's observations regarding cellular cementum, but Smith (1968) found very little cellular cementum on deciduous teeth and Chapnick & Main (1976) found no cellular cementum and half the normal thickness of acellular cementum on deciduous teeth. Also, reduction in thickness of acellular cementum in unerupted teeth was found by Hitchin (1975) and Hall & Hyland (1978).

Additional histological observations include poor attachment of Sharpey's fibres and less than normal collagen in the periodontal membrane (Chapnick & Main, 1976). The inclusion of what appear to be "vascular trees" (the remains of periodontal blood supply) in the acellular cementum, led Hitchin (1975) to describe the cementum as "vasocementum", (conjecturally neither cellular nor acellular cementum, but calcified periodontal membrane).

Hitchin (1975) found that in contrast to unerupted or spontaneously erupting teeth in CCD, teeth which were assisted to erupt by surgical exposure had normal distribution of cellular and acellular cementum, had no spike-like apices, and were of normal length and shape. Migliorisi & Blenkinsopp (1980) also found normal

straight roots where eruption was encouraged surgically.

No studies of progress of tooth mineralization in CCD have been undertaken.

iv. Anomalies of alveolar bone and mucosa

Clinically, the mucosa overlying unerupted teeth in CCD has been found to be dense and fibrotic (Miller et al, 1978), and histologically, a thick, dense, continuous collagen layer with the presence of foci of calcified tissue within the submucosa has been described (Hall & Hyland, 1978).

There may be hypoplasia of alveolar bone, with apices of maxillary teeth well into the antrum (Hall & Hyland, 1978; Dann et al, 1980). During oral surgery, dense, sclerotic, cancellous and cortical bone has been encountered (Wilbanks, 1964; Smylski et al, 1974), and histologically, abnormally dense trabeculation and multiple reversal lines have been found (Hitchin & Fairley, 1974; Migliorisi & Blenkinsopp, 1980).

4. MALOCCLUSION

Delay or failure of eruption of permanent teeth, with over-retention and occasional ankylosis of deciduous teeth, as well as rotation and malalignment of those teeth which do erupt are features which have been described in the previous sections. Transposed maxillary canines and incisors have also been reported (Wilbanks, 1964; Lubowitz, 1968). The frequent finding of high-vaulted palate, and occasionally, clefting, has also been mentioned previously, and transverse discrepancies (lingual posterior crossbites) have been reported (Elomaa & Elomaa, 1967; Hall & Hyland, 1978; Hutton et al, 1981). It is possible that anteroposterior discrepancies may contribute to apparent transverse problems.

Vertical discrepancies are a significant feature of malocclusions found in CCD patients. Large interocclusal freeway space and overclosure (estimated up to 15 millimetres) has been reported (Lubowitz, 1968; Kelly & Nakamoto, 1974; Smylski et al, 1974; Hall & Hyland, 1978; Dann et al, 1980). Lubowitz (1968) considered that lack of occlusal contacts between erupted opposing

teeth was associated with failure of bone formation at alveolar crests, and suggested that CCD cases demonstrated that the relationship between growth of the jaws and eruption of teeth is largely independent. It is difficult to agree with this suggestion because there is a pathological process occurring in CCD, affecting not only dental eruption but also growth of the entire craniofacial skeleton, and this would be likely to disrupt any normal inter-relationship. Reduced alveolar height, also described by other authors (Hall & Hyland, 1978; Dann et al, 1980) may have contributed to the anterior open-bites reported by Harris, Gaston, Avery, McCuen (1977) and Bishop (1984), but the amount of vertical deficiency often appears to be more than that which could be accounted for by alveolar hypoplasia alone, and may be related to sagittal deficiency of the cranial base (Hall & Hyland, 1978; Dann et al, 1980). Fernex et al (1974) reported findings of increased subnasal height, large gonial angle and large mandibular/occlusal plane angle, but the paucity of details given make it difficult to comment further on these findings.

With regard to sagittal discrepancy, the commonest problem found by clinical assessment is maxillary hypoplasia with relative mandibular prognathism (Winch & Armstrong, 1962; Kalliala & Taskinen, 1962; Wilbanks, 1964; Hitchin & Fairley, 1974; Winkler et al, 1976; Weintraub & Yalisove, 1978; Monasky et al, 1983). Cephalometric analyses give more variable assessments. While diagnoses of maxillary hypoplasia and relative mandibular prognathism have been made (Dann et al, 1980; Trimble, West & McNeill, 1982), actual mandibular prognathism (Harris et al, 1977) and normal skeletal relationships (Hutton et al, 1981) have also been reported. The findings of Lubowitz (1968) and Jarvinen (1981) are interesting. Lubowitz (1968) reported pseudo-prognathism and underdeveloped maxilla, with the entire face posterior to normal limits, despite an SNA of 89° and SNB of 97°, both of which are well forward of the norm. From the published photograph, the patient does appear to have a retruded face and it is possible that the very prominent frontal bossing exaggerates this effect. Jarvinen (1981) also found high SNA and SNB angles in three cases and from these made a diagnosis of real maxillary prognathism, which he regarded as an atypical finding, perhaps indicative of individual variation in

CCD. However, the high SNA and SNB angles found by these authors does not contradict the clinical impression of facial retrognathism or maxillary hypoplasia. Jarvinen (1980B) demonstrated a relationship between small NSAr angles and significantly larger SNA angles, and in CCD the cranial base angle (NSAr) is often unusually small - consistent with bending of the clivus (Kreiborg et al, 1981; Jarvinen, 1981). The anterior and posterior cranial base may also be significantly shorter (Kreiborg et al, 1981) which could also affect SNA and SNB measurements (Jacobson, 1975). Lubowitz (1968) and Jarvinen (1981) both acknowledged that abnormalities of the cranial base may affect measurements derived from sella-nasion, but did not modify their analyses on this account.

C. DIFFERENTIAL DIAGNOSIS & ASSOCIATED ANOMALIES

Several of the orofacial features found in CCD are also reported in a variety of other disorders, many of which are also genetic disorders. This is not surprising when it is considered that orofacial abnormalities are associated with approximately 25 percent of disorders in which Mendelian inheritance is suggested or established, and that orofacial abnormalities are present in practically all syndromes recognised to be associated with chromosomal abnormalities (Salinas, 1982).

Failure/delay of eruption	-Osteosclerosis (osteopetrosis) (Wolpowitz & Matisonn, 1974)
	-Incontinentia pigmenti (Shokeir, 1974)
	-Gorlin/Gotz syndrome (Shokeir, 1974)
	-Pyknodysostosis (Shokeir, 1974)
	-Complete failure of eruption of all permanent teeth (autosomal dominant disorder) (Shokeir, 1974)
	-Craniofacial Dysostosis (Crouzon's disease) (Winter, 1943)
	-Achondroplasia (Winter, 1943)
	-Hypopituitarism, hypogonadism, cretinism (Winter, 1943)
	-Hereditary Gingivofibromatosis (Di Biase, 1971)

	-Cryptodontic brachymetacarpalia (Bixler, 1976)
	-Focal dermal hypoplasia (Bixler, 1976)
Supernumerary teeth	-Gardner syndrome (Burzynski & Escobar, 1983)
	-Hallermann-Streiff syndrome (Burzynski & Escobar, 1983)
	-Orofacialdigital I syndrome (Burzynski & Escobar, 1983)
	-Cleft lip/palate (Burzynski & Escobar, 1983)
Brachycephaly/ Frontal bossing	-Pyknodysostosis (Wolpowitz & Matisonn, 1974; Gorlin & Pindborg, 1976)
	-Rickets (Gorlin & Pindborg, 1976)
	-Prenatal Syphilis (Gorlin & Pindborg, 1976)
	-Achondroplasia (Winter, 1943; Gorlin & Pindborg, 1976)
Open fontanelles and sutures	-Pyknodysostosis (Wolpowitz & Matisonn, 1974)
	-Familial Idiopathic Acro-osteolysis (Wolpowitz & Matisonn, 1974)
	-Spina Bifida Occulta (Epstein & Epstein, 1967)
	-Meningeocele (Epstein & Epstein, 1967)
	-Craniofacial Dysostosis (Crouzon's disease) (Epstein & Epstein, 1967)
	-Osteogenesis Imperfecta (Winter, 1943)
	-Cretinism (Winter, 1943)
Multiple Wormian bones	-Pyknodysostosis (Wolpowitz & Matisonn, 1974)
	-Familial Idiopathic Acro-osteolysis (Wolpowitz & Matisonn, 1974)
	-Osteogenesis Imperfecta (Winter, 1943)
Hypoplastic facial sinuses	-Osteosclerosis (osteopetrosis) (Wolpowitz & Matisonn, 1974)
	-Pyknodysostosis (Wolpowitz & Matisonn, 1974)
	-Familial Idiopathic Acro-osteolysis (Wolpowitz & Matisonn, 1974)
	-Craniofacial Dysostois (Crouzon's disease) (Winter, 1943)

Maxillary hypoplasia
-Apert's syndrome (Gorlin & Pindborg, 1976)
-Craniofacial Dysostosis (Crouzon's syndrome) (Winter, 1943; Gorlin & Pindborg, 1976)
-Achondroplasia (Winter, 1943)
-Cleft lip/palate
-Trisomy 21 (Down's syndrome) (Stewart, 1976)

Clavicular defects are, arguably, a universal finding in CCD. However, there are a number of disorders other than CCD which are associated with congenital clavicular hypoplasia or agenesis (CCHA). (See TABLE 1). In addition to these, clavicular anomalies are found in several rare syndromes associated with significant upper limb deficiency, lethal neonatal dwarfism, or minimal, inconsistent rare hypogenesis, and also, entities where postnatal clavicular hypoplasia or dysgenesis occurs - Progeria, Acro-osteolytic Entities, Pyknodysostosis (debated) and Post-natal Onset Pseudo-arthrosis (Hall, 1982). Pseudoarthrosis of the clavicle may occur as a result of birth or later traumatic fracture, or as a congenital defect with unknown aetiology. This last group appears to have autosomal dominant transmission (Hall, 1982) and right-sidedness is an almost constant feature (Lloyd-Roberts et al, 1975). In several cases in the literature where diagnosis of CCD has been made on the basis of clavicular defects but absence of other abnormalities characteristic of CCD, pseudoarthrosis of the clavicle is a more likely diagnosis; Alldred (1963) gives the example of a case described by Fitchett (1910), and this author suspects that the two cases presented by Williams (1962) are erroneously diagnosed as cases of CCD.

In the interests of differential diagnosis, a number of syndromes which display similarities to CCD warrant discussion.

Osteosclerosis (or Ostepetrosis) is an hereditary condition, thought to be both autosomal recessive (fatal) and autosomal dominant (benign). It is characterised by uniform density of bone between cortical and medullary bone of epiphyses and absence of diploeic spaces in membrane bone. Fractures after minimal trauma are common, paranasal sinuses are hypoplastic, mastoids unpneumatized, the sella may be unusually small, and dental eruption

may be delayed (Wolpowitz & Matisonn, 1974). As well as similarities between the two conditions, features of osteosclerosis, particularly recurrent fracture and condensed epiphyses, have been found in association with CCD (Giaccai et al, 1954; Thomsen & Guttadauro, 1952; Thoms, 1958; Kalliala & Taskinen, 1962).

Craniofacial Dysostosis is characterised by autosomal dominant inheritance, brachycephaly, ocular disturbances and atrophy of the optic nerve, hypoplasia of maxillary and nasal bones, underdeveloped sinuses, and ectopic and retarded dental eruption. However, in contrast to CCD, premature synostosis occurs in the coronal and lambdoid sutures and possibly in sutures of the cranial base and maxillary sutures (Winter, 1943; Glass, 1969; Fernex et al, 1974; Dahl, 1976).

Pyknodysostosis has an autosomal recessive pattern of inheritance, and has many features in common with CCD: frontal and occipital bulging, high palate, widened anterior fontanelles and sutures, persistent metopic sutures, wormians in the parietal bones, unpneumatized mastoids, hypoplastic paranasal and maxillary bones, total clavicular aplasia or hypoplasia of acromial ends, coxa valga or coxa vara, and short stature. Features which differ from CCD are receding chin, exophthalmia and blue sclera, parrot-like nose, aplasia of terminal phalanges and clubbing of fingers and toes, and in some cases, decreased alkaline phosphatase and increased calcium levels, thrombocytopenia and splenomegaly (Wolpowitz & Matisonn, 1974).

Another condition with many features in common with CCD is Familial Idiopathic Acro-osteolysis. Both familial dominant and non-familial forms have been described. Features shared with CCD are open fontanelles and sutures, persistent metopic suture, frequent occurrence of wormian bones, poorly developed nasal sinuses, hypoplastic maxilla, deficiency at acromioclavicular joints and margins of symphysis pubis. Features which differ from CCD are developmental anomalies of hand, wrist and knee joints, early tooth loss, and development of severe generalized osteopetrosis (Wolpowitz & Matisonn, 1974).

Apart from an occasional association with osteosclerosis (described above), CCD has been found in conjunction with post-stenotic dilation of the left sub-clavian artery (Short, 1979), squamous carcinoma of the face and maxilla (Weiss, 1964), Beta thalassemia minor (Alexander & Ferguson, 1980), and Achondroplasia (Alderson, 1960). Finally, Yunis and Varon (1980) have reported what they consider to be a new genetic syndrome with many features of CCD, but severe micrognathism and hand defects.

CHAPTER III

AETIOLOGY

A. GENERAL THEORIES

Before substantial information on defects found in the syndrome had been collected, CCD was thought to involve membrane bone only. Fitzwilliam (1910) concluded that defects of cartilage bones such as cranial base and nasal bones were secondary to delay in closure of the cranial vault. By 1929, Fitchet had gathered sufficient material to show that both membrane and cartilage bone were involved, and therefore considered the membrane bone hypothesis to be fallacious. Jackson (1951) reiterated this view, emphasising that defects of pure cartilage bones such as vertebrae, finger and long bones made it evident that the hypothesis of deficient membrane bone ossification could not explain all the defects found. He suggested that because dental defects were also a feature, perhaps all calcifying tissue was involved. He also noted a pattern of failure of midline ossification, for example, mandibular symphysis non-union, cleft sternum, spina bifida and widely separated pubic symphysis.

Despite the overwhelming evidence against the hypothesis that CCD involves ossification of membrane bone alone, it is still occasionally stated as fact - the most recent example is in an article by Fardy (1984). Aitchison (1962), who presented an atavistic theory as a possible explanation for the findings in CCD, also took for granted that membrane bone was the affected tissue. He argued that skin and membrane bones are more recent from a phylogenetic point than cartilaginous elements, and that arrested calcification of membranous bones may be an atavistic phenomenon.

Several authors, particulary earlier ones, have attempted and failed to discover any particular developmental period which would explain the multiple findings in CCD. For example, Jackson (1951) was puzzled to find that although the period in which the dysplastic agent was operating appeared to him to be from 4-5 weeks in utero to

5 months in utero, the mandible was rarely affected despite developing in membrane at 6 weeks in utero, and although deciduous and permanent tooth germs formed in this period, only permanent teeth appeared to be affected. The view that a single developmental period may be responsible for the anomalies found in CCD has been superseded by the notion that an abnormality of tissue development is responsible. This notion is more consistent with the findings of widespread involvement and changing pattern of abnormalities with maturation, and is reflected by the change in nomenclature to "dysplasia".

It has been suggested that a factor which affects bone resorption may be operating in CCD. Gruneberg (1937) put forward the idea of "hereditary basis for response"; that is, that bone reacts by absorption to pressure only if the hereditary basis for doing so is undisturbed. Giaccai et al (1954) were the first to make an association between CCD and osteosclerosis, and they presented the hypothesis that a common aetiological factor was responsible for a two-directional derangement in the developmental processes of the mesenchyme. Hitchin (1975) suggested that root anomalies found in CCD were consistent with the hypothesis of disturbance in bone resorption, and Kreiborg et al (1981) considered that less than normal bone resorption would account for the cranial base anomalies found in CCD. (Both these views will be elaborated upon in the following sections). The auditory bone anomalies - dense, bulky, distorted and fixated auditory ossicles, pronounced narrowing of the external auditory meatus and absence of pneumatization of mastoids (Jaffee, 1968; Fons, 1969: Pou, 1971; Hawkins et al, 1975) are also consistent with a hypothesis of disturbed bone resorption, and the finding of multiple reversal lines in alveolar bone (Hitchin & Fairley, 1974; Migliorisi & Blenkinsopp, 1980) and under-developed facial sinuses (Fitzwilliam, 1910; Soule, 1946; Jarvis & Keats, 1974) also suggests that a disturbance in remodelling is occurring. The disturbed bone remodelling hypothesis does not, however, adequately explain the full spectrum of anomalies found. Failure of fusion of midline structures and fontanelles, shortened limbs, multiple epiphyses, vertebral anomalies, deficient clavicles, multiple wormian bones, and gaps between the zygomatic process of the temporal bone and

maxilla (normally occupied by the zygoma) are features which point to a disturbance of a fundamental component in the entire osteogenic process. Furthermore, this component would have to play a role in the processes of tooth eruption and tooth induction.

It has been proposed that autosomal dominant diseases in general are likely to be caused by mutations affecting structural proteins. Because a person with a dominantly inherited disease is a heterozygote, there would be a mixure of normal and mutant molecules if the protein functions as a subunit aggregate. The presence of abnormal and normal molecules together might possibly interfere with the proper formation of the aggregated protein (Searle, 1968, p 262). The aggregation of collagen in cartilage into amianthoid-like aggregates has been observed in one patient with CCD, which is suggestive of some defect in the proteoglycans or glycosaminoglycans of CCD connective tissue (Sillence, 1984 - unpublished research).

CCD appears to display a high degree of penetrance (the fraction of cases carrying a given gene that manifests a specific phenotype) (Lasker, 1946; Herndon, 1951), but is also characterzied by great variability in clinically detected anomalies. In many dominant conditions, the gene may manifest in all heterozygotes (Vogel & Motuloky, 1979, p 84), and it is also well known that dominant disorders in general are characterized by extreme variability in phenotypic expression (Rimoin, 1979). This last phenomenon is referred to as "variable expressivity"; that is, the variable manifestation of a given gene (Vogel & Motuloky, 1979, p 84). In reality, this is a blanket term which reflects our ignorance of the aetiological components of genetic disease (Young, 1983). Modifyer genes (for example, genes which supress the expression of another gene) and environmental modifiers (external agents which may modify expression of genes) are examples of mechanisms which have been proposed as possible explanations for variable expressivity.

B. SPECIFIC EMPHASIS: DEFECTIVE OSTEOGENESIS, TOOTH ERUPTION, AND TOOTH INDUCTION

1. DEFECTIVE OSTEOGENESIS

Osteogenesis involves the ossification and absorption of bone, the chemical and mechanical influences over these processes, and the general mechanisms whereby characteristic external form and internal structure are determined and maintained as integrated elements within the skeletal framework (Gardner, 1971). For the purposes of this discussion, only certain aspects of osteogenesis will be touched upon.

i) Osteogenesis of membrane and cartilage bone

All bones begin as mesenchymal condensations during the embryonic period. Some condensations are predominantly fibrous (or membranous), and these ossify directly to form membrane (or dermal) bones. Other bones begin as cellular proliferations which go through a chondrification stage which leads to the formation of cartilage. Bones which then form from this cartilage are referred to as cartilage or replacing bones. Although the environment in which ossification occurs differs for the two types of bone, the nature of the ossification process itself is the same (Gardner, 1971). Both types of bone undergo remodelling to become compact bone, and eventually the only way the two can be distinguished is by detection of traces of calcified cartilage which may have escaped the remodelling process in cartilage bone (Pritchard, 1972).

Membrane bones include most bones of the cranial vault, many around the sense organs and the facial skeleton, and in part, the clavicle and mandible. Intra-membranous ossification proceeds from fibrocellular proliferations in each bone, which are called primary centres. Mesenchymal cells differentiate into osteoblasts, which synthesize alkaline phosphatase and probably also secrete the matrix which contains complex mucopolysaccharides and other compounds which cement the collagen fibres together. This osteoid then becomes calcified by deposition of calcium phosphate crystals (Gardner, 1971).

In membrane bones, for example, parietal and frontal bones,

primary trabeculae become interconnected by secondary trabeculae which radiate out from the primary site, and increase in thickness and density of the trabeculae occurs at the centre. The bone continues to expand by the formation of new trabeculae at the periphery. When the bones come into close relationship with other bones, a bony border begins to form around peripheral edges as the trabeculae become interconnected. After this, reorganisation becomes the means whereby change in form is achieved. Reconstruction and formation of lamellar systems and resorptive mechanisms whereby diploe and sinuses are formed, all occur after birth. In other membrane bones, such as the maxilla, ossification is similar but the pattern of reconstructive growth and the general trabecular pattern is more complex (Gardner, 1971).

Cartilage bones begin as mesenchymal condensations in which cells with oval or round nuclei are packed together, and in the centre of these condensations an intercellular matrix containing the compounds characteristic of cartilage matrix is then formed. The deposition of matrix spreads peripherally to the margins of the original condensation, and the mesenchymal cells become oriented so as to form a perichondrium, the cells of which contribute to subsequent growth. This cartilage is then gradually replaced by bone (Gardner, 1971).

The ethmoid bone, inferior concha, sphenoid bone (lesser wings, basal portions of greater wings, and lateral plate of pterygoid process), petrosal portion of temporal bone, occipital bone (basilar, lateral and lower squamous portion), vertebral column and bones of the extremities are all formed in cartilage which is then replaced by bone through the process of endochondral ossification (Bhaskar, 1980; Bloom & Fawcett, 1975).

At a cellular level, endochondral growth proceeds by sequential zones which are responsible for multiplication, growth, and degeneration of cartilage cells, and chondro-osseous transformation. The "reserve zone" is the zone furthest from the zone of chondro-osseous transformation, the "zone of proliferation" has flattened chondrocytes, the "zone of hypertrophic chondrocytes" leads to the "zone of degenerative chondrocytes" and the zone of chondro-osseous

transformation. In this area, primary osseous trabeculae are formed by resorption of transverse matrix lamellae between the chondrocyte columns, remodelling of primary trabeculae is performed by chondroclasts, and deposition of bone matrix is the product of osteocytes. Further organisation leads to the development of mature lamellar bone (Rimoin & Sillence, 1981).

Using the long bone as an example, ossification begins at the middle of the cartilaginous model. A thin layer of osteoid is laid down between perichondrium and the portion of the shaft containing hypertrophied cells, forming a collar around the shaft. This becomes calcified, forming the primary bone collar. The inner cells of what is now the periosteum differentiate into osteoblasts, and trabeculae are formed in a manner similar to that which occurs in membranous ossification. In the cartilage itself, cartilage matrix which has been laid down in the central hypertrophied cellular area becomes calcified. Cellular masses derived from the periosteum invade the cartilage, and the cartilage cells are rapidly destroyed and replaced by the invading osteoblasts and undifferentiated cells. At a variable time after this invasion, osteoblasts form bone around the bits of calcified cartilage matrix which are left. The advance towards the ends of the bone leaves behind a loose network of endochondral trabeculae which fuses with the periosteal shell. Periosteal ossification also extends towards the ends of the bones by continuing deposition of bone matrix adjacent to the hypertrophied cartilage (Gardner, 1971). Growth involves both endochondral ossification and also membranous ossification (which accounts for growth in shaft diameter) (Sillence & Rimoin, 1982).

The tissue surrounding the early mesenchymal condensations is characterized by a matrix which contains significant amounts of Type III collagen. In cartilage bone, the mesenchymal chondroprogenitor cells undergo specialization which results in synthesis of Type II collagen from procollagen and concomitant accumulation of the cartilaginous matrix. Chondrocytes in the centres of the ossification hypertrophy which develop, switch from synthesis of Type II collagen to synthesis of Type I collagen. Further deposition of Type I collagen from procollagen by osteoblasts occurs, and eventually, after sufficient remodelling has occurred,

the lamellar bone matrix contains only Type I collagen. No mesenchymal cells of membranous bone undergo differentiation into cells which synthesize Type II collagen. Instead, osteoprogenitor cells induce a bony skeleton directly, and only Type I collagen is synthesized (Gay & Rhodes, 1980).

Collagen forms at least 90% of the organic matrix of bone and it has been supposed by many workers that it has a major function in calcification (see Hancox, 1972, p 85, for citations), but it is unlikely that it is the only factor which is concerned with calcification. The view that the protein-polysaccharide complex of bone (the amorphous part of the matrix) plays an important role has been put forward by many scientists, although most work which implicates protein-polysaccharides has been obtained from studies of calcification in cartilage rather than bone. However, bone contains very little protein-polysaccharide, and considerably less than cartilage matrix (see Hancox, 1972, p 87, for citations). It is also believed that an interaction between either calcium or phosphate ions in the plasma is an important prerequisite for calcification, but the mechanisms of binding are in dispute and the relative importance of calcium and phosphate ions in the process is also disputed (see Hancox, 1972, p 88-89, for citations).

The existence of inhibitor mechanisms in the calcification process has been postulated by Fleisch (1964). Collagens from a variety of tissues which normally do not calcify were found to induce nucleation in vitro from solutions containing prepared calcium and phosphate ion products at physiological levels, which suggests that some kind of inhibitor exists in normally non-mineralizing zones which is destroyed when calcification occurs. Experimental evidence indicated that very low concentrations of polyphosphates, or pyrophosphates, successfully prevented the in vitro calcification. Fleisch proposed that two essential conditions for tissue mineralization were 1) presence of a mineral nucleator such as collagen, elastin, keratin or other fibrous protein; and 2) the presence of pyrophosphatase to inactivate pyrophosphate. In answer to the criticism directed at this theory - that all tissues appear to contain pyrophosphatases, Russell & Fleisch (1970) suggested that variations in pyrophosphatase activity

might account for the differences between mineralizing and non-mineralizing tissues.

Cells such as osteoblasts appear to play an important role in calcification. Extracellular matrix vesicles derived from osteoblasts (and also implicated in calcification of dentine, growth cartilage and other tissue) appear to provide sites for hydroxyapatite deposition, and enzymes such as ATPase, which increase local calcium and phosphate concentrations or remove calcification inhibitors (perhaps proteoglycans or pyrophosphates may be produced. Also, calcium phospholipid complexes, phosphoproteins and glycoproteins may initiate mineral deposition (Boskey, Bullough & Dmitrovsky, 1980).

Calcification is almost certainly not the function of just one factor, but probably of many local factors. It is likely that a dynamic and reversible equilibrium exists between forces opposing mineralization and factors promoting it (Gardner, 1971; Boskey et al, 1980). On this basis, a missing, defective or deficient factor may disturb the equilibrium, altering perhaps its direction or rate of expression.

ii) The clavicle

The clavicular defects seen in CCD have intrigued those seeking an explanation for the syndrome's manifestations. The clavicular defects have been contrasted with the limited morphological defects seen in the mandible, despite the fact that ossification occurs first, and simultaneously in both these bones, at about 6 weeks i.u. (Jackson, 1951). The view of Gardner (1968, 1971) that both these bones are also formed in membrane with secondary cartilage formation makes the comparison seem even more intriguing. However, the development and ossification of the clavicle has been disputed by anatomists for many years.

Opinion varies as to whether the clavicle is preformed in cartilage or membrane, and whether one or two ossification centres occur. Fitzwilliam (1910) suggested that the sternal two-thirds arises in cartilage and the acromial third arises in membrane, and that ossification occurs from a single centre. Alldred (1963)

preferred the view of Fawcett (1913 - quoted by Alldred, 1963) that the clavicle forms from two cartilaginous masses, and that the condition of pseudoarthrosis represents a non-ossification of the precartilaginous bridge which connects the two portions. Anderson (1963) believed that the clavicle begins as a condensed mesenchymal cord in which two centres develop. Rapid ossification of the two centres results in their quick fusion. At the sternal and acromial ends, growth occurs through endochondral growth, with newly formed cartilage being immediately transformed into bone. Gardner (1968) considered there to be two centres of ossification in a membranous anlage which both unite to form a solid mass rather than being trabeculated in the way most other membrane bone is. Cells on the sternal and acromial ends become cartilaginous, but resemble articular rather than epiphyseal growth cartilage. Gibson and Carroll (1970) put forward the view that the clavicle is formed in pre-cartilage with enveloping membrane, and replacement hyaline cartilage at the ends, and that ossification is from a single centre.

Lloyd-Roberts et al (1975) observed that in cases of pseudo-arthrosis, right sidedness was almost a constant feature, and that it was often associated with the presence of unduly elevated first ribs. They proposed that the lesion might be due to pressure on the developing clavicle by the subclavian artery, and because the features of right-sided selectivity, cervical ribs and elevated first ribs were also common to CCD, the suggestion was made that the mechanism may also be involved in the clavicular defects seen in this condition.

One of the features of clavicular development is the rapid calcification which occurs (Andersen, 1963). This is one reason why the calcification pattern of the clavicle has been disputed by various researchers (as previously discussed). With respect to mice (which will be discussed in Chapter V), in the mouse strains C57BL and C3H being studied by Ritchie (1985 - personal communication) it has not been possible to obtain clavicular tissue which is only partly calcified - progress from uncalcified to calcified clavicle appears to be a very rapid event. It could be conjectured that if calcification depended on an appropriate environment and that if the

period during which a suitable environment existed was significantly shorter in the clavicle compared to other bones (the calvarial bones, for example, appear to continue ossifying for very long periods in CCD), then perhaps the expression of an abnormality which influenced the progress of calcification would be more marked in bones which normally ossify rapidly.

iii) Cranial base

The previous discussion has been in the area of early osteogenesis, but CCD is characterized by anomalies which become apparent with growth. One example of anomalous growth appears to be the cranial base, where, as has been previously mentioned, flexion distortion of the clivus, reduction in anterior and posterior length, bulbous dorsum sella and small or shallow pituitary fossa have been described (Hultkrantz - in Fitchet, 1929; Soule, 1946; Fernex et al, 1974; Migliorisi & Blenkinsopp, 1980; Kreiborg et al, 1981).

The cranial base, also known as the chondrocranium, arises from primordial cartilages which grow principally by endochondral bone formation and eventually fuse to form a contiguous structure (Stewart, 1976). Melsen (1974) has carried out an extensive histological study of the growth changes which occur in the cranial base. Increase in size of the sella turcica which occurs during growth is due to remodelling of the inner contour and resorption of the lower half of the posterior wall and floor. The spheno-occipital synchondrosis begins to close at about 12-13 years in girls and 14-15 years in boys, and there is an element of differentiated growth occurring within the synchondrosis which could give rise to a tilting of the basilar part of the occipital bone upwards and backwards relative to the sphenoid. In the absence of remodelling compensation, this might lead to flattening of the cranial base. In the clivus area, apposition occurs, throughout growth, on the nasopharyngeal surface of the occipital bone and anterior margin of foramen magnum. This mechanism provides for further lengthening of the clivus after closure of the spheno-occipital synchondrosis. There is also apposition on the sphenoidal surface, and resorption on the occipital surface. These processes combine to effect a bending of this portion of the cranial base

around the synchondrosis. This bending is partly compensated for by differentiated growth (as previously mentioned) of the synchondrosis. The height of the body of the sphenoid bone increases by apposition on the inferior face (see FIG. 3).

In contrast to the view of Brodie (1955) that uniform growth in all regions of the cranial base occurred so that shape remained constant, Melsen (1974) proposed that each area involved in the definition of cranial base angulation could be influenced by processes of remodelling as well as change in overall position of the bones. Stability of shape was considered to be the result of balance between factors causing flattening and factors causing increase in angulation. Changes in cranial base angle during growth would therefore be the consequence of change in balance of factors affecting cranial base angulation. According to Melsen (1974), increase in angulation of the cranial base reported in dysplasias such as achondrodysplasia and chondrodystrophia could be ascribed to a loss of the flattening effect produced by growth at the spheno-occipital synchondrosis. Fernex at al (1974) suggest that in CCD the excessive bowing and shortening of the clivus could possibly be explained by defective growth of the spheno-occipital synchondrosis.

Kreiborg et al (1981) thought that their finding of short anterior and posterior cranial base might be related either to the short stature of the patients, or to abnormal growth in the sutures and synchondroses of the cranial base. They considered that findings of shallow pituitary fossa and bulbous anterior margin of foramen magnum and dorsum sella, could, following the remodelling patterns described by Melsen (1974), be explained in terms of reduced bone resorption. However, with reference to Melsen's theory (1974), a contradiction emerges from the combination of remodelling deficiency and deficient growth of the spheno-occipital synchondrosis with respect to bowing of the clivus. Melsen considered that remodelling change leads to the appearance of "bending" of the clivus around the synchondrosis, which is counteracted by the flattening effect of growth of the synchondrosis. So, if the growth of the synchondrosis is deficient, then bending of the clivus might be excessive, but if remodelling was also deficient then the factor contributing to bending would also be reduced.

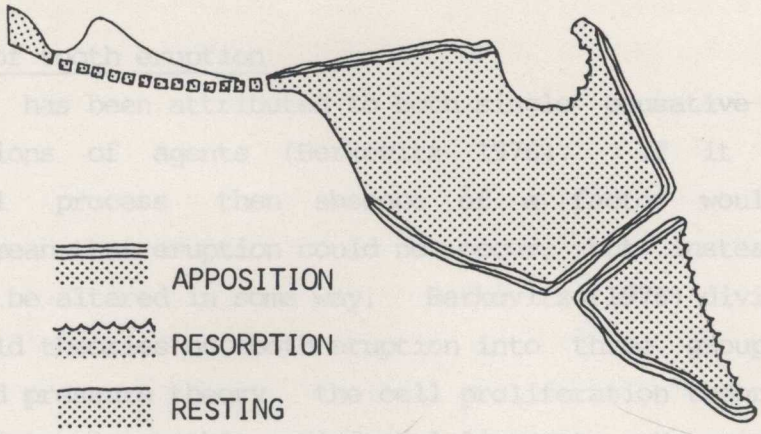


FIGURE 3. Diagrammatic representation of normal growth remodelling in the cranial base. (From Melsen, B.;Acta Odontol. Scand. 32:Suppl. 62, 1974, p 103.)

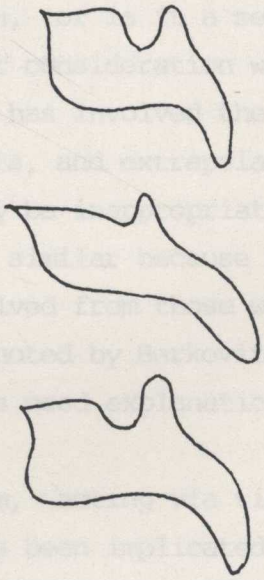


FIGURE 4. Tracings of the posterior cranial base from midsagittal tomograms of three patients with cleidocranial dysplasia. All three patients exhibited bulbous dorsun sella, flexion of clivus and bulbous anterior margin of foramen magnum. (Modified from Kreiborg, S. et al; Am. J. Orth., 79, 1981, Fig. 3, p 554.)

2. DEFECTIVE TOOTH ERUPTION

i) Theories of tooth eruption

Eruption has been attributed to both single causative agents and combinations of agents (Berkovitz 1976). If it were a multifactorial process then absence of a factor would not necessarily mean that eruption could not occur, but instead, the process might be altered in some way. Berkovitz (1976) divides the currently held theories on tooth eruption into three groups: the tissues fluid pressure theory, the cell proliferation theory, and the theory of tension within periodontal ligament. He points out two difficulties which confront those who are attempting to solve the riddle of tooth eruption. The first is that eruption may represent the resultant between forces causing eruption and those retarding it, so that distinguishing which of these two is affected by a testing agent may be difficult; (for example, is reduced eruption due to disruption of a stimulator or failure to override an inhibitor?). The second difficulty lies in separating cause and effect. For example, is the high rate of collagen turnover in the periodontal ligament evidence that this structure may be responsible for eruption, or is it a secondary process in response to eruption? A further consideration which must be made is that most work on eruption has involved the use of the continuously growing incisor of rodents, and extrapolation of findings onto teeth of limited eruption may be inappropriate. Although it is likely that the processes are similar because animals with continuously growing teeth have evolved from those whose teeth are of limited growth (Ness, 1956 - quoted by Berkovitz 1976), the differences between the two processes need explanation (Berkovitz, 1976).

The vascular system, acting via tissue fluid pressure around and beneath a tooth, has been implicated in the process of eruption (Bryer, 1957 - quoted by Berkovitz, 1976). There is evidence that a pressure gradient does exist, but the mechanisms responsible for maintaining these pressure gradients are not known (see Berkovitz, 1976, for citations). Nor is it established whether the tissue fluid pressure acts directly beneath the tooth and is therefore possibly related to pulp pressure, or (and) through pressure in the periodontal ligament (Berkovitz, 1976). It has been found that

human incisors undergo pulsatile movements which are synchronous with arterial pressure (Korber, 1970 - quoted in Berkovitz, 1976) which has been taken as showing that tissue fluid pressure can cause small tooth movements. Sympathectomies, inferior dental nerve blocks and alterations to blood pressure have been used in attempts to alter the tissue fluid pressure within periodontium and pulp tissue, without much success (see Berkovitz, 1976, for citations). Using a technique for continuous recording of movement, Moxham (1981) found that an increase in the mean rate of eruption occurred in rabbit incisors following cervical sympathectomy. During stimulation of the cut end of the nerve trunk for approximately 3 minutes, the tooth moved back into its socket in most animals.

It has been suggested that pressure generated by proliferating cells in dental tissues provides the main force responsible for tooth eruption (Sicher, 1942 - quoted in Berkovitz, 1976). The proliferating tissues at the base of the developing root exhibit considerable mitotic activity and have therefore been implicated (see Berkovitz, 1976, for citations). The administration of cytotoxic drugs, such as Demecolcine retarded eruption rates in mouse incisors almost immediately, (Chiba, 1968) but Berkovitz (1976) pointed out that cytotoxic agents could also affect the metabolism of many other cells and alter the molecular structure of metabolic chemicals. For example, reduction of collagen synthesis or increase in viscosity of hyaluronic acid have been reported (Castor & Prince, 1964; Bornstein, 1974 - both in Berkovitz, 1976). Some evidence that proliferative basal tissue may generate a force can be derived from the findings of Berkovitz (1972); continued proliferation of basal tissues and resorption of adjacent alveolar bone followed the gross retardation of eruption of rat incisors. On the other hand, Ohman & Ohman (1980) found that after surgical exposure, the apex of teeth moved in the opposite direction to the crown, and rate of eruption was not significantly influenced by root development, which suggested that in surgically exposed teeth, apical forces were not involved in eruption.

An experiment which casts doubt on the theories of tissue fluid pressure and cell proliferation (at least for continuously erupting teeth) is the root resection experiment performed by Berkovitz &

Thomas (1969). The apical or odontogenic region of rat incisors was removed, in conjunction with the alveolar wall at the base of the tooth. This procedure also destroyed the pulp. In 11 out of 16 rats, the unimpeded eruption rate equalled control levels 4 to 7 days after the operation, and was sustained until the base of the tooth reached the alveolar crest. These results suggested that several proposed mechanisms are not in fact essential to the eruptive process. Root elongation was prevented by root resection, pulp and dentine proliferation could not occur because the pulp was destroyed, fundic bone deposition did not keep pace with the base of the tooth, tissue fluid pressure was undermined by removal of the alveolar wall at the base of the tooth, and pressure from proliferation of periodontal tissue, if it had any effect, should have served to push the tooth back into the socket because the basal diameter of the incisor is greater that the coronal (Thomas, 1976). These findings were confirmed in subsequent root resection experiments undertaken by Pitaru, Michaeli, Zajicek and Weinreb (1976).

The root resection studies indicated that responsibility for tooth movement must lie with structures which are incisal to the surgical sites, which strongly implicated the periodontal ligament. It has been postulated that tension within the periodontal ligament is responsible for exerting a pulling force on teeth, thereby causing their eruption (see Berkovitz, 1976, for citations). Two theories have been forwarded to account for the creation of this tension, and will be described here.

The first theory involves collagen, of which mainly Type I and a little of Type III is found in the periodontal ligament (Sloan, 1982). The vast majority of collagen fibrils are believed to be grouped into bundles, although some fibrils, probably Type III, also occur in non-aggregated form. Thomas (1976) suggested that cross-linkage led to shortening of collagen fibres which insert via Sharpey's fibres into cementum. Tropocollagen macromolecules secreted into the extracellular compartment by fibroblasts polymerize to form fibrils which then aggregate through formation of intermolecular crosslinks, which causes a shrinkage in the overall length of the fibrils. This supplies a tractional force which might

be responsible for tooth eruption, given the isometric configuration of the oblique fibres of the periodontal ligament. This theory demands that a high turnover rate of collagen is occurring in periodontal ligament, a phenomenon which has been well demonstrated (see Berkovitz, 1976, for citations). Once again, this turnover could be a secondary effect of eruption rather than a cause (Berkovitz, 1976). However, interference with crosslinkage of collagen by administration of a lathyrogen (an agent which specifically inhibits collagen crosslinkage) produced retarded eruption in rodent incisors in vivo, while administration of collagen crosslinking agents such as gluteraldehyde produced an increased eruptive force in vitro and in vivo (Thomas, 1976). Other studies evaluating the effects of lathyrogens on eruption rate have been inconclusive (Sarnat & Sciaky, 1965; Berkovitz et al, 1972 - quoted in Berkovitz, 1976). Bailey (1976) has criticized the theory that crosslinking of collagen fibres causes a contraction force which would lead to eruption, on the basis that a highly organized fibre alignment and crosslink location would be required but has not been shown, and that if crosslinking between fibres did occur, there would be no flexibility in the tissue. Kardos and Simpson (1979) have suggested that the collagenous matrix of the periodontal ligament behaves like a thixotropic gel, and that isothermal viscosity changes within it might account for the eruption of teeth. Experiments where lathyrogen administration did not affect tooth eruption (see Kardos & Simpson, 1979 for citations) indicated that properties other than collagen crosslinkage are involved in tooth eruption, and the thixotropic properties of a gel are not affected by lathyrogens. In their extensive review of experimental evidence for and against the collagen contraction theory, Moxham and Berkovitz (1982) concluded that there was little evidence for, and much against the concept that collagen fibre contraction generated eruptive force. They did not rule out the role of collagen in eruption, but thought that this might be in the capacity of resistance to eruptive force or remodelling to allow eruptive movements to be maintained.

The second theory is that fibroblasts within the periodontal ligament are responsible for generating eruptive force, either by their contractility or locomotor activity (Ness, 1967 - quoted in

Berkovitz, 1976). Fibroblasts have been demonstrated to exert tractional force in vitro (James & Taylor, 1969 - quoted in Thomas, 1976), and fibroblasts from granulation tissue have been found to resemble smooth muscle cells due to the presence intracellularly of actomyosin-containing myofilaments and other similar cytoplasmic components (see Thomas, 1976, and Jacobson, 1983, for citations). If periodontal ligament fibroblasts were to exert an eruptive force they would have to have some form of direct contact with the teeth, or an indirect one, mediated perhaps through collagen fibres (Berkovitz, 1976). Administration of the cell contractant colchicine to rats was not found to have a significant effect on eruption rate of incisors, which does not support the fibroblast contraction theory (Main & Adams, 1966, quoted in Thomas, 1976). Microfilament networks have been found in fibroblasts and suggested as possible agents of locomotion (see Chiba, Ohshima, Takizawa, 1983, for citations). Chiba (1968) found evidence that fibroblasts migrate incisally within the mouse incisor periodontium, but whether such a finding is a cause or effect of eruption remains unclear (Berkovitz, 1976). Perera and Tonge (1981) also found fibroblast proliferation and apico-occlusal migration in erupting mouse molars and proposed this as a major causative factor in tooth eruption. Administration of a microfilament disrupting drug, cytochalalasin B, was not found to affect eruption rate in rat incisors (Chiba et al, 1983).

ii) Role of bone, cementum and mucous membrane in tooth eruption

At first, the deciduous tooth and its permanent successor develop within the same crypt. Bone surrounds both the teeth but does not completely enclose them. The occlusal surfaces of the deciduous teeth lie close to the crest of the alveolus. As the deciduous tooth erupts, the permanent tooth germ becomes situated apically and is entirely enclosed by bone except for the gubernacular canal which contains dental lamina and connective tissue remnants. It has been suggested that the gubernacular tissue may play a role in eruption (Scott, 1948 - quoted in Moxham & Berkovitz, 1982), but whether it provides a path of least resistance or is actively engaged in moving teeth has not been establilshed. It cannot be involved in the eruption of deciduous teeth because

these teeth lack a gubernaculum (Moxham & Berkovitz, 1982).

During the eruptive phase, root formation is initiated by proliferation of the Hertwig root sheath. Bone is resorbed ahead of the developing root (which means that root formation cannot be responsible for generating eruptive force), but later in the eruptive process, rate of eruption may exceed root formation, in which case bone deposition occurs on the crypt floor (Jacobson, 1983). The importance of bone resorption in the process of tooth eruption is suggested by mouse mutants which are thought to demonstrate defective bone resorption. In the grey lethal (gl), there is complete failure of eruption, with distortion of roots, as well as many other anomalies indicative of failure of secondary bone remodelling (Gruneberg, 1935). In the microphthalmic mouse (MI/MI), preliminary study has found delayed eruption of molars and incisors, diminished root development in molars and distortion of posterior growth of incisors, with reduction in number, functional activity and cytoplasmic volume of osteoclasts (Keys, 1984).

The rate of bone resorption may play a limiting role in eruption. Cahill (1969, 1970) found that in dogs, resorption of deciduous teeth and overlying bone occurred even when the succedaneous teeth had been ligated to the lower border of the mandible, but that after the ligated teeth had been released, they erupted at an accelerated rate compared to normal. Marks & Cahill (1984) found that even when dead crown shells or crown-shaped metal implants were substituted into dental follicles prior to eruption, resorption of overlying bone and eruption occurred as per normal. This evidence suggests that bone resorption occurs independently of eruptive movements. During the post-emergent phase of eruption, tooth movement in an axial direction is by active deposition of new bone at the base of the socket and crest of the alveolus (Jacobson, 1983). Steedle & Proffit (1985) suggested that the rate of bone resorption and also gingival remodelling are rate-limiting factors in pre-emergent eruption, while growth limitations of alveolar bone and gingiva, and also pressure from soft tissues and occlusal loading may play important roles in control of post-emergent tooth eruption.

During eruption, the tooth is separated from the oral cavity by both mucous membrane and dental follicle. As migration proceeds, the follicle unites with the connective tissue of the overlying mucosa (De Biase, 1971). However, the mechanism by which tissue penetration occurs remains speculative. Three possible theories are provided by Provenza (1964 - quoted in De Biase, 1971). The first is that the mechanical force of eruption causes a shearing of the tooth through the mucosa, the second is that pressure of eruption causes ischaemic atrophy of mucosa, and the third theory is that chemolytic activity of enzymes causes a breakdown of mucosa. Synthesis of acid hydrolases by connective tissue cells, with subsequent cell breakdown has been described during eruption (Ten Cate, 1971 - in Moxham & Berkovitz, 1982). Pressure alone is unlikely to account for collagen degradation because the connective tissue above erupting teeth always exhibits evidence of collagen formation (Moxham & Berkovitz, 1982). It is possible that mucosa may act as a barrier to eruption. De Biase (1971) found that a thickening of follicle around retained unerupted teeth was commonplace, and that remnants of enlarged follicle rather than mucous membrane appeared to act as a barrier to eruption. Failure of union between follicle and mucosa was suggested as a possible cause of delay in mucosal breakdown and eruption.

During root formation, cementum is deposited on the newly formed root surface by cells of the periodontal connective tissue. Cementoblasts synthesize collagen and proteoglycans which make up the organic matrix of cementum, and this cementoid is transformed into calcified cementum by deposition of calcium and phosphate ions (Armitage, 1980). There is also evidence that the innermost layer of cementum is odontoblastic in origin (see Bernick & Grant, 1982, for citations). The initial collagen fibres produced by cementoblasts are oriented at right angles to the root surface, and connective tissue fibres from the periodontal ligament also pass into the cementum. Odontogenic and cementogenic fibres are then mineralized. The process by which periodontal fibres become incorporated is still controversial, but their embedded portions are known as Sharpey's fibres (Armitage, 1980; Bernick & Grant, 1982). Where cementum remains relatively thin, Sharpey's fibres cross the entire thickness of cementum. With further apposition, a larger

proportion of the fibres is incorporated in the cementum. However, the attachment proper is confined to the most superficial, or recently formed layer, which suggests that increased cementum thickness does not enhance functional efficiency through increased strength of attachment of fibres. On the other hand, since collagen fibres of the periodontal ligament cannot be incorporated into dentine, a connective tissue attachment to the tooth is impossible without cementum (Armitage, 1980). Apart from its role as medium for attachment of collagen fibres that bind the tooth to alveolar bone, continuous deposition of cementum throughout life is considered to provide for functional tooth adaptations which occur with age (Armitage, 1980). It is unlikely that cementum plays a primary role in tooth eruption because cementum is found on the roots of teeth which have failed to erupt (Armitage, 1980).

iii) Failure/delay of eruption in CCD

A currently held view in the dental literature is that eruption anomalies found in CCD are the result of defective alveolar bone remodelling (Hitchin & Fairley, 1974; Hitchin, 1975; Migliorisi & Blenkinsopp, 1980). This view was proposed by Rushton (1937B), who recognised some similarity between the tooth morphology and eruption anomalies in CCD and those found in the grey lethal mouse mutant studied by Gruneberg (1935, 1937). In this mouse mutant, thought to suffer from a total lack of secondary bone remodelling, there is compression of molar crowns, kinking and spiral twisting of roots, spiking of apices, dense trabeculation, defective dentine and enamel, and total failure of eruption. The entire skeleton is severely affected and death occurs a few weeks after birth. Gruneberg (1935) explained the dental anomalies in terms of roots becoming bent and wrinkled due to resistant bone, with spikes formed where roots were pushed into small cavities in the spongiosa, crowns flattened because of failure of bone crypt resorption in response to pressure from growing teeth, and lack of co-ordination between dentine formation and calcification. Although the condition in the grey lethal mutant is not analogous to CCD, Rushton (1937B) argued that some of the dental findings in CCD - curved, twisted roots, spike-like apices and compressed crowns, were consistent with the view that growing teeth were being restricted by inadequate bone resorption.

The theory of defective bone resorption has been used to explain the phenomenon of deciduous tooth eruption despite failure of eruption of many permanent teeth. The deciduous tooth buds lie in a superficial position before eruption, only partly covered by bone, while the succedaneous teeth lie completely enclosed by bone (Proffit & Vig, 1981). It has been speculated that in CCD, because the first molars lie in similar relationship to overlying bone as deciduous teeth, they are more likely to erupt (Hitchin & Fairley, 1974; Koch & Hammer, 1978; Migliorisi & Blenkinsopp, 1980), but no authors account for the high frequency of eruption of the lower incisors, and relatively high frequency of eruption of upper incisors, which are succedaneous teeth. It could be argued that these teeth are covered by less bone than the premolars, which have a lower frequency of eruption. The histological finding of abnormally dense trabeculation and multiple reversal lines in alveolar bone of CCD patients gives further support to the view that defective bone remodelling is occurring (Hitchin & Fairley, 1974; Migliorisi & Blenkinsopp, 1980). The observation that teeth which are surgically exposed and orthodontically erupted do not display root distortions supports the view that mechanical obstruction is responsible for such defects in CCD (Hitchin, 1975; Migliorisi & Blenkinsopp, 1980).

If the problem was simply one of mechanical obstruction by bone, then it would be expected that following surgical exposure, buried teeth would erupt normally. This is not the case in CCD. Following exposure, many operators have reported the need for orthodontic traction to erupt the teeth more fully (Kjellgren, 1952; Hitchin & Fairley, 1974; Smylski et al, 1974; Miller et al, 1978; Farrer & Van Sickels, 1983), and it has been suggested that the limited eruption which is achieved by exposure alone is not the same process as that which occurs in spontaneous eruption, but instead, analogous to filling in of a cystic cavity (Ohman & Ohman, 1980; Farrer & Van Sickels, 1983). That the buried teeth often respond well to orthodontic traction after exposure suggests that a process which supplies an equivalent force during eruption is deficient. In the section "Theories of tooth eruption", the possible tractional contribution made by periodontal components such as collagen and fibroblasts was discussed. Histological observation of periodontal

ligament in CCD patients includes poor attachment of Sharpey's fibres and less than normal collagen in the periodontal ligament (Chapnick & Main, 1976). Despite the use of orthodontic traction to erupt teeth, there is still a deficiency of alveolar bone, contributing to severe reduction in vertical facial height (Hall & Hyland, 1978; Dann et al, 1980). This could be seen as indicative that the normal apposition which accompanies the post-emergent phase of tooth eruption (Jacobson, 1983) is affected as well as bone resorption in CCD.

With respect to the anomalies of cementum described in CCD, Rushton (1956) was intrigued by the observations that erupted as well as unerupted teeth in CCD displayed very little cellular cementum, which was confined to hollows or grooves in the teeth. Hitchin (1975) found that when teeth were surgically exposed, they exhibited normal cementum, but when they erupted without any intervention they did not. He took this as evidence in favour of the theory that defective bone resorption was responsible for mechanical obstruction, which affected formation of cementum. Where teeth had erupted unaided, it was considered that they had been subjected to large mechanical resistance in the process. Chapnick & Main (1976) also suggested that if eruptive force is derived from tractional forces of cells of the periodontal membrane, then in CCD, lack of cementum would preclude sound attachment of fibres to the tooth (a view substantiated by their finding of poor attachment of Sharpey's fibres in CCD patients). Even if the role of periodontal fibres in eruption is not a primary one, but one of remodelling or maintenance of eruptive movements (Moxham & Berkovitz, 1982), defective attachment of fibres to the tooth could undermine the eruptive process.

As mentioned in the previous section, De Biase (1971) found that a thickening of follicle around unerupted teeth was commonplace and that follicular enlargement may be responsible for failure of mucosal breakdown during eruption. The mucosa overlying unerupted teeth in CCD has been described as dense and fibrotic (Miller et al, 1978; Hall & Hyland, 1978), and there is a high incidence of dentigerous cysts (Rushton, 1938; Wilbanks, 1964; Douglas & Greene, 1969; Winkler & Jung, 1971; Levin, 1972; Oatis et al, 1975; Koch &

Hammer, 1978). It has been suggested that dense fibrotic mucosa may provide mechanical inhibition to eruption in CCD (Proffit & Vig, 1981), but because teeth often do not erupt even after surgical exposure, the mucosa cannot be considered to contribute to failure of eruption in a significant way.

The evidence accumulating seems to point towards a multi-factorial disruption of eruption in CCD. It appears that defective bone remodelling is contributing a mechanical resistance to the eruptive process where resorption does not occur, and that insufficient deposition of alveolar bone is occurring in the post-emergent phase of eruption. Mechanical resistance may also play a role in cementum deficiency, which might indirectly affect periodontal attachment. There may also be a defect in the periodontal fibre system, affecting eruption directly, or indirectly, through perhaps defective attachment to the teeth. It is suggested that in CCD, dyshistogenesis is affecting a tissue component or process which is common to both periodontal tissue and alveolar bone.

3. DEFECTIVE TOOTH INDUCTION

i. Tooth induction

The first visible sign of tooth morphogenesis in a modern mammalian embryo is the proliferation of cells of the basal layer of epithelium along the ridge of the dental arch. The thickened dental lamina gives rise to a species - specific number of buds which penetrate the underlying mesenchyme. The bud cell mass expands to form an inverted cap of epithelium surrounding a papilla of mesenchyme, and this is surrounded in turn by mesenchyme of the developing jaw bone. A basement membrane separates the epithelial cells from the mesenchyme. Mesenchymal cells of the enclosed papilla adjacent to this basement membrane differentiate into odontoblasts (Brown, 1983).

The buds of the human deciduous teeth are initiated in the second month in utero, and the buds of the succedaneous permanent dentition form from extensions of the dental lamina on the lingual side of the primary tooth bud. This proliferation occurs from about

five months in utero for the permanent central incisor to about ten months of age for the second premolar. The permanent molars arise directly from distal extension of the original dental lamina, from about four months in utero for the first permanent molar until about the fourth or fifth year for the third permanent molars. The dental lamina may still be active in the third molar region after it has regressed following initiation of tooth buds in the rest of the jaws (Bhussry, 1980).

It has been shown that the essential stimulus for tooth development comes from the mesenchyme. Kollar and Baird (1970A, 1970B) demonstrated that incisor and molar teeth could be induced by confronting mouse lip-furrow epithelium or foot epithelium with papillary mesenchyme from incisor and molar regions respectively, and concluded that the dental mesenchyme was responsible for the induction and structural specificity of teeth. It appears that collagen might exert an important function during morphogenesis. Kollar (1978) quotes several studies in which agents known to disrupt collagen structure, synthesis or secretion were able to prevent tooth morphogenesis, but that morphogenesis resumed if the tissue was returned to control medium. There is also increasing evidence of the importance of proteoglycans of the ground substance of the extracellular compartment, which interact with collagens and modify morphogenesis (Kollar, 1978). Changes in the distribution of collagenous and non-collagenous glycoproteins and basement membrane proteoglycan have been observed to be closely associated with cell differentiation and matrix secretion in developing teeth (Thesleff, Barrach, Foidart, Vaheri, Pratt, Martin, 1981; Hurmerinta, 1982).

It has also been shown that long term culture of dental papillae does not destroy their ability to induce teeth; in other words, cultured dental papillae retain their morphogenetic capabilities even after severe and prolonged inhibition (Kollar, 1978).

According to Ruch (1983), odontogenesis cannot be explained by a spontaneous unfolding of a "genetic endogenous programme". Different dental cells transcribe different combinations of genes, which may include selective gene activation and/or repression.

These sequential differential transcriptions are, in some way influenced by cell interactions.

ii. Hyperdontia in CCD

Supernumerary teeth are recorded for a large number of mammalian teeth. Ferrets in particular have a high incidence, and the number of molars in the manatee is so variable that the dental formula is in doubt (Schwartz, 1984). The incidence of supernumerary tooth formation in humans has been given as 0.64% (Saarenmaa, 1951), 0.1-3.6% (Salinas, 1982) and 0.5% (Burzynski & Escobar, 1983). The incidence is higher in males, and all tooth bearing areas may be involved, although maxillary incisors and maxillary molars (fourth molars) are the commonest sites affected (Saarenmaa, 1951; Salinas, 1982; Burzynsky & Escobar, 1983).

There are several different theories of the origin of supernumerary teeth. These include an atavistic theory, a post-permanent dentition theory, a tooth germ division theory, and theories of hyperproductivity (Saarenmaa, 1951).

The location of supernumerary teeth provides evidence against the atavistic theory. The original mammalian formula is 3I, 1C, 4PM, 3M, which means that humans have lost one incisor and two premolars from each quadrant. It would be expected that the highest incidence of supernumerary teeth would be in the premolar regions but this is not the case. Nor is the incidence of upper and lower incisor supernumeraries equivalent, which one would expect if the atavistic theory was consistent. Furthermore, incidence of additional canines and four incisors has been reported, which is not found in any mammalian dentition (Saarenmaa, 1951). The recurrence of supernumerary teeth following removal (Jarvinen, 1976) is not explained by the atavistic theory.

Supernumerary teeth usually develop at about the same time as the permanent dentition and may appear as well developed as the adjacent permanent teeth. They do not usually cause resorption of the roots of the permanent teeth. These observations argue against considering supernumerary teeth to be the expression of a post-permanent dentition (Saarenmaa, 1951).

Bolk's theory of schizogenous division of a tooth germ (Bolk, 1914 - in Saarenmaa 1951) has been criticized because it implies that the extra tooth should always be situated lingually to the normal series, and both the protomer and deuteromer should have no grooves or cusps, which is not always the case (Saarenmaa, 1951). However, credibility has been given to the theory that supernumerary teeth could be the result of splitting of the normal tooth germ by a study of Berkovitz & Thomson (1973), in which shared enamel organ and pulp chamber were demonstrated in normal and supernumerary teeth in the ferret. Although there is agreement that this process does occur, most supernumerary teeth are typically rudimentary structures or fully formed teeth that are serial complements to the normal dentition rather than identical to an immediate neighbour (Schwartz, 1984).

It has been suggested that hyperactivity of the dental lamina may be responsible for additional tooth formation (Saarenmaa, 1951). Osborn (1978) and Lumsden (1979) have suggested that proliferating tooth class zones could continue to produce teeth at the ends of that tooth class. Supernumeraries would thus be seen anterior or posterior to the normal incisors, canines or molars. The number of teeth horizontally within a tooth class would be limited by the mitotic potential of the elongating ends. There is also evidence that supernumerary teeth may occur interstitially within a tooth class (Berkovitz & Thomson, 1973). Thus, inhibition of expansion of progress zones at the proliferating ends of a tooth class, and inhibition of expansion between bud interstices are possible mechanisms which may operate to limit the number of teeth. Virtually all kinds of supernumerary teeth and their occurrences in any tooth class can be understood within the context of uninhibited normal growth (Schwartz, 1984).

The ability of a given region of dental lamina to proliferate and give rise to new tooth germs may be retained after the time when normal tooth germ formation in that region has been completed (Sofaer, 1975B). The proximity of established tooth germs has been suggested as a mechanism by which a still potentially active lamina may be prevented from proliferating further (Gillette, 1955; Osborn, 1971 - both in Sofaer, 1975B). Sofaer (1969, 1975B) proposed that

this process might explain the dental anomalies found in the Tabby, crinkled, downless and sleek mouse mutants. In these mutants, the incisors may be reduced or absent, the first molar crown reduced, the second molar may be larger than normal, third molars may be absent, and supernumerary teeth may be found adjacent to or fused to the incisor or anterior to the first molar of the normal series. It was suggested that proliferation of the dental lamina sometimes develops anterior to the first molar in response to the small size of the first molar, and this may develop into a supernumerary tooth. Supernumerary tooth formation did not occur if the first molar was of normal size. It was suggested that interaction between tooth germs and between tooth germs and dental lamina might provide a developmental mechanism whereby the length of the tooth row tends to be stabilized (Sofaer, 1975B). Abnormality of dermally derived structures which develop by down-growth of solid epithelial buds into an underlying mesenchyme has been suggested as a feature of the Tabby mutant (Gruneberg, 1966) and demonstrated in the downless mutant (Sofaer, 1975A). The four mouse mutants described above demonstrate that there are gene-controlled interactions which affect tooth development. They show that there are at least four mutant genes in the mouse, each of which is capable of producing a similar syndrome of dental anomalies. The simplest explanation for this phenomena is that each allele is responsible for one of a number of steps at a biochemical level of cell or tissue interactions (Sofaer, 1977).

As has been discussed, tooth induction depends on interaction between proliferating dental epithelium and underlying mesenchyme. It has also been demonstrated that papillary mesenchyme retains its morphogenetic capacity even after prolonged inhibition in vitro (Kollar, 1978), and that tooth morphogenesis can be inhibited in vitro by administration of agents which disrupt collagen, then recommenced by their removal (Kollar, 1978). This suggests the possibility that an agent might operate to inhibit tooth development in vivo, operating via mesenchymal tissue components.

It has been suggested that in CCD, the supernumerary teeth tend to be confined to the areas of the jaws supporting the primary dentition, while those teeth which develop from distal extension of

the dental lamina are not affected (Migliorisi & Blenkinsopp, 1980). This is not the case; supernumeraries have been reported in all areas of the permanent dentition in CCD (see TABLE 2). Hyperactivity of the dental lamina has been proposed as an explanation of the high incidence and recurrence of supernumerary teeth (Saarenmaa, 1951; Migliorisi & Blenkinsopp, 1980). However, the dental lamina is epithelial tissue and other epithelial tissue does not appear to be affected in CCD. On the other hand, mesenchymal tissue is certainly affected. Bearing in mind that tooth induction is dependent on mesenchyme, it is suggested that if supernumerary tooth formation in CCD was the expression of a dyshistogenesis affecting mesenchyme, this would provide an albeit basic link in the puzzle as to why tooth induction as well as osteogenesis and tooth eruption are all affected in CCD.

CHAPTER IV

DENTAL MANAGEMENT OF CLEIDOCRANIAL DYSPLASIA

A. TREATMENT NEEDS

While hearing loss and cephalopelvic disproportion (with consequent delivery complications for pregnant women) are significant medical problems encountered (Soule, 1946; Hawkins et al, 1975), problems associated with the dental anomalies are the most likely reasons for presentation of individuals with CCD. These may include concern about unerupted, supernumerary or malpositioned teeth (Winch & Armstrong, 1962), infected dentigerous cysts (Soule, 1946; Koch & Hammer, 1978), pain from unerupted teeth or erupting teeth under dentures (Wilbanks, 1964; Kirson, Scheiber & Tomaro, 1982), or masticatory deficiency (Stiff & Lally, 1969; Dann et al, 1980). Concern about dental appearance is a common finding, and several authors comment on the marked psychological improvements which accompany restoration of dentofacial aesthetics (Seldin, Seldin & Rakower, 1950; Lubowitz, 1968; Winkler & Jung, 1971, Kelly & Nakamoto, 1974; Monasky et al, 1983). Aitchison (1962) gives two case histories of patients with CCD who have sustained head injuries, and draws attention to this risk associated with faulty calcification of cranial bones.

Not all patients with CCD have problems - in fact some find that their condition gives them unique abilities such as the facility to escape from strait-jackets, through ships' scuttles or down drainpipes (Maddox, 1946, quoted by Herndon, 1951), or if a wrestler, to wriggle out of any hold (Davis, 1954). One Englishman even earned his living from his condition by occasionally allowing his shoulder to be caught in the closing door of a public conveyance, and then using convincing X-ray evidence to substantiate his claim for supposed injury (Fitchet, 1929). One author makes a fanciful conjecture that the artist Marino Marini may have chosen a model with CCD for a sculpture of a horse and rider because the positioning permitted him to develop a certain line in the sculpture to express a unity of form in the man and the horse (Nyham, 1973).

The problems which must be dealt with in the dental management of patients with CCD include:

-Delay or failure of eruption of permanent teeth, with over-retention, ankylosis and caries of deciduous dentition.

-Supernumerary teeth.

-Dentigerous cysts.

-Impaction and abnormal positions of unerupted permanent teeth.

-Anomalies of tooth and crown morphology.

-Rotated, ectopic and malaligned erupted teeth.

-Reduced alveolar bone height.

-Pseudoprognathism and Class III malocclusion associated with underdeveloped midface, and sagittal, transverse and vertical deficiency of the maxilla.

-Congenitally missing teeth or teeth which cannot be saved because of abnormal position, malformation, cystic involvement or other reasons.

-Risk of pathological fracture of the mandible.

-Aesthetic and functional problems associated with the above factors.

B. METHODS OF TREATMENT

Alternative treatment rationales for dealing with the above problems have given cause for considerable debate among clinicians, particularly regarding the widsom or otherwise of leaving unerupted teeth in the jaws, or whether unerupted teeth can be brought into occlusion, and if so, the best method for achieving this. Treatment

rationales also differ depending on the age of the patient at initial presentation, with increasing emphasis in the literature on the need to begin treatment planning early, in the mixed dentition where possible.

1. REMOVAL OF ALL UNERUPTED TEETH (in conjunction with prosthetic treatment)

The reasons given for the need to remove all unerupted supernumerary and permanent teeth are that they are prone to cystic involvement or likely to erupt and cause discomfort under dentures (Alderson, 1960; Aitchison, 1962; Smylski et al, 1974; Koch & Hammer, 1978), or the contradictory view that because eruptive forces are retarded, attempts to remove deciduous teeth and overlying bone in the hope of stimulating eruption are likely to fail (Douglas & Greene, 1969). With regard to the former reasons, Winter (1943) and Jarvis & Keats (1974) report cases where permanent teeth erupted under full dentures, while Wilbanks (1964) reports a case where full dentures had been worn for six years over 18 unerupted teeth, none of which had erupted, but two of which had become cystically involved. Winkler & Jung (1971) followed a case for ten years where unerupted teeth had been left under upper and lower partial dentures. Although they report that there was no follicular enlargement around unerupted teeth, two teeth had been removed because of cystic involvement during the ten year period. However, removal of all unerupted teeth does not necessarily eliminate the risk of dentigerous cyst formation, because late development or recurrence of supernumeraries after removal has been commonly reported (Elomaa & Elomaa, 1967; Winther & Khan, 1972; Migliorisi & Blenkinsopp, 1980). With regard to the view that unerupted teeth should be removed because the likelihood of stimulating eruption is remote, several authors have had success in bringing unerupted teeth into occlusion by various methods, and these will be discussed in the following sections.

Fear of creating iatrogenic fracture of the jaw is a reason given by those who do not favour removal of all impacted teeth (Hylton & Albright, 1970; Kirson et al, 1982). However Walter (1967) comments on the possibility of pathological fractures of the mandible where there are many supernumeraries, and Maw (1978) argues

that this fear of future traumatic fracture, with multiple impacted teeth in the line of fracture, non-union and infection if unerupted teeth are left in the jaw far outweighs the fear of iatrogenic fracture. Support for the argument that future problems may be worse if teeth are left in situ than iatrogenic ones if they are removed is given by a case report of squamous cell carcinoma combined with CCD, where osteoradionecrosis in conjunction with unerupted teeth which could not be subsequently removed was a complication of radiation therapy (Weiss, 1964). On the other hand, the removal of all 38 unerupted teeth from a twenty-four year old woman was complicated by perforation into the maxillary antrum, mandibular fracture, blood loss which required a 2 unit transfusion, and because all alveolar bone was lost in the procedure, the need for a second operation for bone chip grafting and deepening of labio/lingual sulci so that dentures could be worn. An unforeseen complication in the management of the iatrogenic fracture was that expected post-operative oedema prohibited immobilization because of risk to airways. Removal of supernumerary teeth before root completion was recommended (Hopkins, 1979-1980). Jarvis & Keats (1974) also reported a case of iatrogenic mandibular fracture during removal of supernumerary teeth. Cases where no complications accompanied removal of all teeth (usually in stages) and construction of dentures have been reported (Douglas & Green, 1969, who performed a two-stage full clearance; Seldin et al, 1950, who removed all deciduous and unerupted teeth in two procedures; Wilbanks, 1964, who removed teeth by quadrants; and Tucker, 1966).

2. SELECTIVE REMOVAL OF UNERUPTED TEETH (in conjunction with prosthetic treatment)

Where the treatment plan is for prosthetic replacement of missing teeth, the principal argument against the removal of all unerupted teeth is that this leads to unwarranted destruction of bone and jeopardises the success of any prosthesis (Alderson, 1960; Frommer & Lapeyrolerie, 1964; Hylton & Albright, 1970; Magnus & Sands, 1974). The ridges for support of denture bases are generally full and rounded if embedded teeth are left in situ, and are considered very suitable for prostheses (Kelly & Nakamoto, 1974). Permanent and deciduous teeth are only removed if they are useless or a potential prosthetic problem (Hylton & Albright, 1970; Magnus &

Sands, 1974). It is regarded as preferable to preserve denture bearing areas rather than to avoid the problem of occasional eruption of buried teeth under a prosthesis. These can be removed as they erupt if necessary (Alderson, 1960; Hylton & Albright, 1970). The case against this approach is made by Seldin et al (1950), who argue that this may lead to many surgical operations with many renewals or rebasings of the dentures. However, there are no cases reported in the literature where more than a couple of teeth have erupted under dentures, and in an era of innovations in overlay denture construction, these erupting teeth might well be incorporated into such a prosthesis. Dentigerous cysts are more likely to cause problems, and it has been suggested that checks be made for these. Overlay dentures have been advocated and used in the treatment of CCD (Hitchin & Fairley, 1974; Kelly & Nakamoto, 1974; Magnus & Sands, 1974; Winkler et al, 1976; Weintraub & Yalisove, 1978; Monasky et al, 1983), and cases in recent literature where full or partial dentures have been constructed over unerupted teeth are reported by Sandler (1951), Rock (1969), Hylton & Albright (1970), Hasler & Vandermer (1974), Kelly & Nakamoto (1974), Koch & Hammer (1978), and Illic (1980).

The advantages of prosthetic appliances for CCD patients are considered to be that they can improve appearance, establish functional occlusion, build out the maxilla and increase vertical dimension (as much as 13mm has been well tolerated - Kelly & Nakamoto, 1974). Argument against prosthetic treatment is made by Lubowitz (1975) who considers it unacceptable practice to leave the deciduous dentition or unerupted teeth in place and construct dentures over these. Instead, skilful treatment to erupt unerupted teeth will obviate the need for dentures. This argument introduces another treatment rationale.

3. TREATMENT TO ERUPT TEETH

Attempts to stimulate the eruption of teeth with and without the aid of orthodontic traction have been made. Archer & Henderson (1951) used thyroid hormones on a 16 year old boy, hoping to stimulate tooth eruption, but had no success. Removal of the deciduous dentition and supernumerary teeth in the expectation that eruption of the permanent dentition would follow has met with

failure (Muller, 1965; Miller et al, 1978).

More success has followed surgical exposure of permanent teeth. Kjellgren (1952) found that removal of supernumeraries and surgical exposure of permanent teeth hastened eruption, but not sufficiently for acceptable results. He concluded that if there is some tendency towards eruption, enhanced by extraction of supernumeraries and exposure of permanent teeth, then positive results with orthodontics may be possible. Hutton et al (1981) were able to obtain a relatively normal sequence of tooth eruption by removing remaining deciduous teeth and underlying alveolar bone as permanent teeth began to show evidence of root development. However, 12 months of orthodontic treatment was needed to align and erupt teeth into better occlusion. Hitchin & Fairley (1974) had used a similar technique earlier, removing bone above permanent teeth at the time of normal eruption, and found that the permanent teeth moved occlusally without traction but eruption was still deficient. They carried out this procedure in the mandible only, preferring to restore the maxilla with an overlay denture which permitted some compensation for the skeletal deficiency. Farrer & Van Sickels (1983) found that if the wound was packed open after surgical exposure of permanent teeth, they would erupt spontaneously. Fardy (1984) had only limited success using this method. The same approach was used to erupted deeply embedded supernumeraries which were subsequently removed. However, the erupted teeth were so badly rotated and malaligned that orthodontic correction was deemed necessary. They explained their success in terms of the hypothesis made by Ohman & Ohman (1980) that surgically exposed teeth were moved occlusally by the same processes which were responsible for filling in a cyst cavity from its base after marsupialization. The reduction in the rate of movement after an initial spurt following surgical exposure of teeth was thought to indicate that this eruption process was not quite the same as that in normal eruption. Miller et al (1978) found that although teeth could be visualized intraorally after surgical exposure, there was no change in their relative position and no appreciable eruption occurred until orthodontic traction was applied. They stressed that any mechanical obstruction appears to inhibit the rate of eruption and this observation was taken to heart by Migliorisi & Blenkinsopp (1980),

who not only removed deciduous teeth and supernumeraries, but also buccal alveolar plates as well as elevating some teeth into better positions in their efforts to erupt permanent teeth. Despite some ability of the teeth to erupt, the possible need for additional exposure and orthodontic traction was noted. Smylski et al (1974) surgically exposed permanent teeth, but found that orthodontic traction was needed to produce sufficient alveolar development. Although their conclusion that orthodontic treatment was necessary for proper eruption was based on only a short time of observation before institution of orthodontic traction, the experience of other clinicians tends to substantiate their view.

The advent of direct bonding meant that problems of bone loss and avulsion of conically shaped roots during surgical exposure and circumdental wiring could be eliminated (Hall & Hyland, 1978; Miller et al, 1978) although Trimble et al (1982) found that difficulty in obtaining a dry surgical field could make direct bonding impossible. Excellent results following exposure of and orthodontic traction to unerupted permanent teeth have been reported by Elomaa & Elomaa (1967), Lubowitz (1968), Jorgenson et al (1971), Smylski et al (1974), Hall & Hyland (1978), Miller et al (1978), Hutton et al (1981) and Bishop (1984).

Hall & Hyland (1978) described a nine point management plan based on the treatment rationale developed by Smylski et al (1974) which involves a two-stage surgical approach to eruption. At 5-6 years and again at 9-10 years the deciduous teeth and bony crypts overlying the developing permanent teeth are removed. The actual surgical exposures and removal of supernumerary teeth are delayed until the first permanent molars erupt and can be banded. Teeth in the incisor region are then exposed and supernumeraries removed, followed by a similar procedure in the premolar regions between 9-12 years. Orthodontic tooth movement is performed, with an early treatment objective being the establishment of a suitable occlusal plane. The teeth respond to very light forces, but conservation of already deficient alveolar bone is essential for successful movement.

The need for early treatment is stressed by several authors.

This may maximise inherent growth potential of alveolar bone which may obviate the need for future orthognathic surgery and prevent abnormalities of root morphology (Migliorisi & Blenkinsopp, 1980; Bishop, 1984). Hitchin (1975) found that exposure of unerupted teeth led to normal root morphology with both acellular and cellular cementum and no spiked apices. Elomaa & Elomaa (1967) felt that early treatment with rapid maxillary expansion before apices closed might improve the prognosis by gaining space and perhaps stimulating eruption. Hall & Hyland (1978) point outed that delay in root development (also noted by Elomaa & Elomaa, 1967) may conflict with the need to institute treatment as early as possible, and also that if exposures are made too early, thick mucosa may recover the crowns.

One of the major orthodontic problems is the adjustment of vertical dimension required due to vertical maxillary deficiency and alveolar hypoplasia (Smylski et al, 1974; Hall & Hyland, 1978). Weintraub & Yalisove (1978) treated this problem prosthetically, using crowns on erupted teeth to establish an appropriate vertical dimension before exposing and moving teeth orthodontically to establish a reasonable mandibular plane. A maxillary overlay partial denture was then constructed on prepared maxillary teeth. Others have resorted to orthognathic surgery to correct vertical and also anteroposterior discrepancy, and this option will be discussed in the following section. Treatment of the transverse discrepancies by the use of rapid maxillary expansion (Elomaa & Elomaa, 1967), and expanded orthodontic archwires (successfully by Hall & Hyland, 1978, and unsuccessfully by Hutton et al, 1981) has been reported.

Despite some limitations of orthodontic treatment, the number of successful cases where combined surgical exposure and orthodontic treatment have been employed tends to contradict the opinion of Magnus & Sands (1974) that orthodontic treatment does not seem advisable to correct the malocclusion. The advantages of this type of management include the avoidance of problems related to unerupted teeth (dentigerous cysts, infections, fractures), conservation of alveolar bone, achievement of a more aesthetic and functional result, the avoidance of prostheses, and, if necessary, the establishment of a more stable alveolus for prostheses (Smylski et

al, 1974; Lubowitz, 1975; Hall & Hyland, 1978; Migliorisi & Blenkinsopp, 1980).

4. TRANSPLANTATION

Several authors have had success transplanting unerupted teeth in patients with CCD. The first of these was Muller (1965), who selected several teeth with suitable morphology and installed these in situ, fixed to erupted teeth by an acrylic plate for 28 days. Five years later the structure of bone and roots was satisfactory, but no vitality tests were reported. Oksala & Fagerstrom (1971) transplanted 14 unerupted teeth in two operations for an 18 year old patient. Three years post-operatively there was a healthy functioning occlusion with no evidence of apical resorption and normal gingival pocket depth in all but two transplanted teeth, but there was no response to an electric pulp tester from the transplanted teeth. Nordenram (1971) treated a 48 year old patient who had previously worn full dentures over multiple impacted teeth for 22 years by extirpation of all but seven of the impacted teeth because of infection or abnormal morphology. The seven lower anterior teeth were extirpated and transplanted and a full/partial denture was constructed after crown and bridge treatment of the transplanted teeth. Nineteen months after transplantation, one tooth was lost because of deep gingival pocketing.

Transplantation of teeth is considered a viable treatment alternative where orthodontics would be unsuitable or give unsatisfactory results, or where prosthetics is undesirable (Oksala & Fagerstrom, 1971). Its advantages are that it places the patient's own teeth into functional position within a short treatment time, eliminates the pathological potential of retained teeth and possibly stimulates the formation of alveolar bone through function (Muller, 1965; Nordenram, 1971; Oksala & Fagerstrom, 1971).

5. ORTHOGNATHIC SURGERY

Although orthodontic treatment can successfully achieve desired dental movements, resort to orthognathic surgery for correction of skeletal discrepancies may be necessary for optimal results. As mentioned previously, institution of early treatment to maximise growth potential by functional stimulus is suggested as a possible

way to reduce this need.

Maxillary deficiency is related not only to hypoplastic alveolar development but also to the sagittal deficiency of cranial base (Hall & Hyland, 1978; Dann et al, 1980). Maxillary and mandibular hypoplasia may be marked (the root apices of maxillary teeth have been found well into the antrum) but the amount of vertical maxillary deficiency may be more than that accounted for by alveolar hypoplasia alone (Dann et al, 1980).

Both overclosure and open-bite may be found in patients with CCD. Dann et al (1980) reported a case where deficiency in the lower third facial height had not been corrected by a 3 millimeter increase in vertical dimension achieved by orthodontic means. Subsequent insertion of an occlusal splint which increased the vertical dimension by 15 millimeters was well tolerated, and a Le Fort 1 osteotomy (with interpositional grafting) which repositioned the maxilla inferiorly and increased lower face height appeared to be within neuromuscular tolerance.

Bishop (1984) reported the management of open-bite in a patient who underwent two years of orthodontic treatment after removal of deciduous and supernumerary teeth and surgical exposure of permanent teeth. After optimal alignment, the anterior open-bite was corrected by Le Fort 1 osteotomy of the maxilla with sectioning of the hard palate to allow advancement and inferior repositioning of the premaxilla. Harris et al (1977) reported a case of open-bite which they diagnosed to be associated with mandibular prognathism. A bilateral mandibular osteotomy with posterior positioning and rotation to correct the open-bite was undertaken.

Trimble, West & McNeill (1982) outlined a comprehensive treatment plan for the dentofacial abnormalities accompanying CCD. This involved (1) simultaneous extraction of primary and supernumerary teeth with banding of the erupted permanent dentition when the crowns and 50% of the roots of canines and pre-molars were formed, (2) active orthodontic co-ordination of maxillary and mandibular arches, (3) surgical correction of facial-skeletal deformities, (4) post-surgical orthodontic finishing and (5) any

supplementary treatment (such as prosthetics or periodontics). They emphasized the need to retain any deciduous teeth as vertical stops until such time as they could be replaced by opposing permanent teeth, and also the need for serial standardized lateral cephalometric radiographs to assist in the diagnosis of patterns of facial growth and prediction of future surgical requirements.

There are some specific considerations when planning orthognathic surgery for patients with CCD. Abnormal root form and osseous anatomy frequently requires different lines of cut for osteotomy. Advancement of the maxilla may accentuate the flared base, shallow nose and flat bridge which are often characteristic nasal features, thus requiring thought to be given to the need for rhinoplasty. Different incision sites may also be needed because there is often less buccal and labial sulcus depth and less attached marginal gingiva than normal (Trimble et al, 1982). A further consideration is that in cases where the maxillary sinuses are unpneumaticized, osteotomy may be precluded (Migliorisi & Blenkinsop, 1980).

CHAPTER V

CLEIDOCRANIAL DYSPLASIA AND MOUSE MUTATION RESEARCH

A. USE OF THE MOUSE AS AN ANIMAL MODEL

An animal model is a living organism with an inherited, naturally acquired or induced pathological process which in one or more respects closely resembles the same phenomenon in humans (Wessler, 1976, in Held, 1983). The existence of homologous animal models is possible because of conservation of protein and gene structure derived from a common evolutionary ancestor (Searle, 1968, p 25). Eighty million years separate mouse and human, but certain groups of gene loci are known to have been conserved in close physical relation ship, some of them functionally related, others not related, and extending across large areas of chromosomes (Francke, 1980).

Although there is no a priori reason to choose one species of mammal over another as a source of models of human genetic disease, practical considerations make some species more suitable than others for certain types of investigation. For example, where large numbers of progeny or inbred backgrounds are required, small laboratory rodents such as mice are appropriate, but where large volumes of tissue fluids, surgical procedures, or measurements are required, larger mammals might be more appropriate (Patterson, Haskins & Jezyk, 1982).

Another reason why mice are preferred animals for a systematic approach to the production of models for human genetic disorders is that they are genetically the best characterized mammals besides humans. Over 700 genes are known in the mouse, and 500 of these have been mapped out (Francke, 1980). Many human genetic disorders, for example lysosome storage diseases and A and B thalassemias have parallels in the mouse (Lewis, 1984). However, it is possible that a similar mutation in an homologous locus could be expressed differently in mouse and human, and therefore the validity of a mouse model cannot be established on the basis of similarities in

phenotypic expression alone. Demonstration of a comparable defect at molecular level, for example mutation in homologous structural enzyme loci, would be more appropriate proof (Francke, 1980).

Animal models are particularly useful in the study of genetic disorders in which the chain of events between the underlying cause and the pathological phenotype cannot be practically studied in humans. Francke (1980) lists possible avenues of research once mouse models for human genetic disorders have been established. These are 1) the possibility of manipulating developmental mechanisms in mutations causing abnormal foetal development, and study of timing of induction of specific malformations; 2) mouse models would provide easy access to tissues and organs for study purposes; 3) manipulation of genetic disorders in vivo; and 4) therapeutic experimentation such as direct genetic therapy by gene transfer.

The sequence and nature of osteogenesis in the mouse is very similar to human osteogenesis, and, as in humans, the genetic disorders of the skeleton in the mouse are a heterogeneous group which manifest as generalized defects of cartilage and/or bone growth and development, and consequently, abnormal craniofacial growth and disproportionately short stature (Rimoin, 1975). Over 150 constitutional disorders of the skeleton in the mouse have been reported (210 entities have been listed in humans - Sillence et al, 1985). Subsequent to the establishment of an International Nomenclature of Constitutional Diseases of Bone in 1969 (Rimoin, 1978), Eteson et al (1985) have organized the mouse skeletal mutants in a manner similar to the human nomenclature; in other words, osteochondro-dysplasias, dysostoses, idiopathic osteolyses, chromosomal aberrations, and primary metabolic abnormalities.

With reference to the human skeletal dysplasias, before a mouse mutant can be regarded as a model for one of these, there must be a tight correlation found in terms of the clinical disease, extraskeletal abnormalities, mode of inheritance, radiographic skeletal abnormalities, histological and ultrastructural appearance of cartilage, and eventually, the basic biochemical defect. Unless a tight correlation is found, an animal mutant cannot be considered

a model of a human disease, or be used for drawing conclusions about the possible pathological defect in the human disorder (Rimoin, 1975). Only a few of the mouse skeletal mutants have been established as analogous to human disorders: hypophosphatemia (hyp) with X-linked hypophosphatemic rickets, mottled (Mo) with Menkes syndrome, and bare-patches (Bpa) with X-linked chondrodysplasia punctata (Prins & Van Den Hamer, 1970; Eicher et al, 1976; Happle et al, 1983 - all cited in Eteson et al, 1985). Sillence et al (1985) also propose that cleidocranial dysplasia (Ccd) is analogous to the human condition of the same name.

B. MUTATION 320

Mutation 320 was one of thirty-one confirmed autosomal dominant skeletal mutations found in a mutation rate experiment involving irradiation of male mice undertaken by Selby & Selby (1977). A similarity between the anomalies found in mutation 320 and those found in cleidocranial dysplasia in humans was commented upon and the anomalies found in the mutation were described (Selby & Selby, 1977, 1978).

In a study of the genetic segregation and skeletal manifestations of mutation 320 on both C57BL and C3H inbred strains of mice compared with normal mice of the same inbred strains, Sillence et al (1985) confirmed that mutation 320 is a fully penetrant dominant trait with variable expressivity, and that it is strictly homologous to CCD in humans at a clinical and radiographic level. (See TABLE 3). They proposed that the name "cleidocranial dysplasia" (Ccd) be given to mutation 320 mice. Several features of these mice were studied in detail.

In the clavicles, several patterns of defective ossification were observed. The acromial end was always present, sometimes with aplasia of the remainder of the clavicle, sometimes with normal anatomical length and appearance of the clavicle, sometimes with a "pseudo-arthrosis" at the acromial end, sometimes with more than one ossification centre (clavicular fragments). The clavicular centres also varied in shape from mutant to mutant. Hypoplasia was often

TABLE 3

COMPARISON OF MOUSE MUTATION 320 AND HUMAN CCD

HUMAN Dominant		MUTATION 320 Dominant
SKULL		
Patent anterior fontanelle	++	
Brachycephaly	+	
Hypertelorism	?	
Wormian bones		Interparietal fragmented
Delayed suture closure	+	
Deformity of foramen magnum	?	
Calvarial thickening	?	
Maxillary hypoplasia	?	
Hypoplastic nasal bones	++	
Hypoplastic zygomatic bones	++	
CLAVICLES		
Normal	++	
Aplasia	x	
Pseudoarthrosis	++	
Bilateral sternal hypoplasia	++	
Bilateral acromial hypoplasia	x	
Combination of the above	++	
OTHER		
Spina bifida-cervico thoracic	++	
Scoliosis	x	
Coxa vara/valga	?	
Delayed ossification of pubis	++	
Unossified symphysis pubis	++	
Brachymesophalangia 2nd & 5th Metacarpal	?	Delayed ossification of metacarpal/tarsal
Long 2nd metacarpal	?	
Point of terminal tufts	?	
Hypoplasia of scapulae	++	Hypoplastic deltoid tuberosity.
(Findings of Sillence & Ritchie, unpublished research, 1985)		
DENTAL		
Delay/failure eruption permanent teeth	?	To be investigated in this study.
Delayed onset eruption deciduous teeth	?	
Supernumerary teeth	?	

+/noted ++/noted and quantified ?/not yet looked for

asymmetrical, and no sex difference was observed.

The mutant showed retarded as well as dysplastic ossification of the cranial bones. There was delayed closure with wide anterior and posterior fontanelles and although there was progressive ossification, the anterior fontanelle was still open in some 2 year old mice (sexual maturity in female mice is reached at around 45 days). The interparietal bones (not present in humans) had wide sutures and fragmentation - up to 6 ossification centres were found, and were considered to correspond to the wormian bones surrounding the lambdoid and parietal sutures observed in human skulls. Delayed ossification in interparietal, occipital and frontal bones occurred during development, but ossification was almost complete by maturity. Other cranial elements which showed particular abnormality were the nasal bones, which were invariably hypoplastic, and the post-tympanic hook of the squamosal bone, which was frequently hypoplastic in the C57BL strain (but rarely in the C3H strain) and led to a gap in the zygomatic arch. (See FIG. 5 & 6).

At 30 days, the pubes and ischia had fused in normal mice, but were incompletely ossified and separated by a wide gap in the mutants. Retarded ossification was less noticeable at maturity than in 5 day old mice. Retarded ossification of cervical vertebrae, metatarsals and the anterior border of the scapulae was observed in some mutants, and in some mutants the deltoid tuberosity of the humerus was reduced or missing.

The pathogenesis of the skeletal abnormalities is still to be defined. With reference to clavicular development, the clavicle of the foetal mouse was represented by a fibrous connective tissue (mesenchymal) condensation at day 14 of gestation. In normal mice the clavicle ossified at day 15 of gestation. In the mutant, the mesenchymal condensation was reduced in size and usually present only at the acromial end. Thus, the mechanism of clavicular hypoplasia is related to hypoplasia/aplasia of mesenchymal condensation prior to the normal timing of ossification (Sillence et al, 1985).

The dentition of the mutant was not studied.

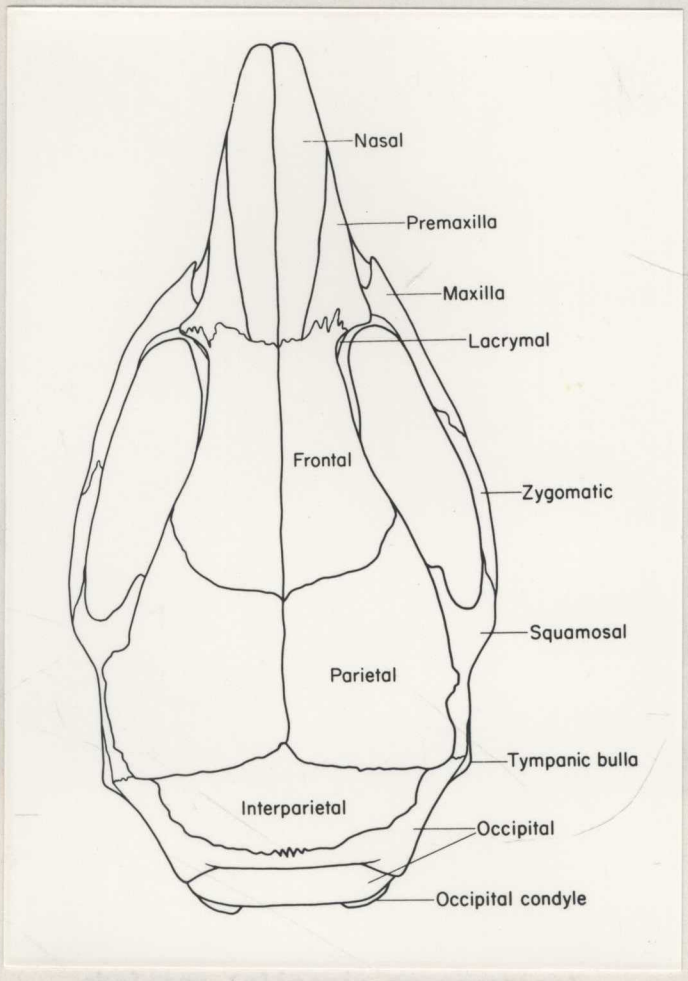
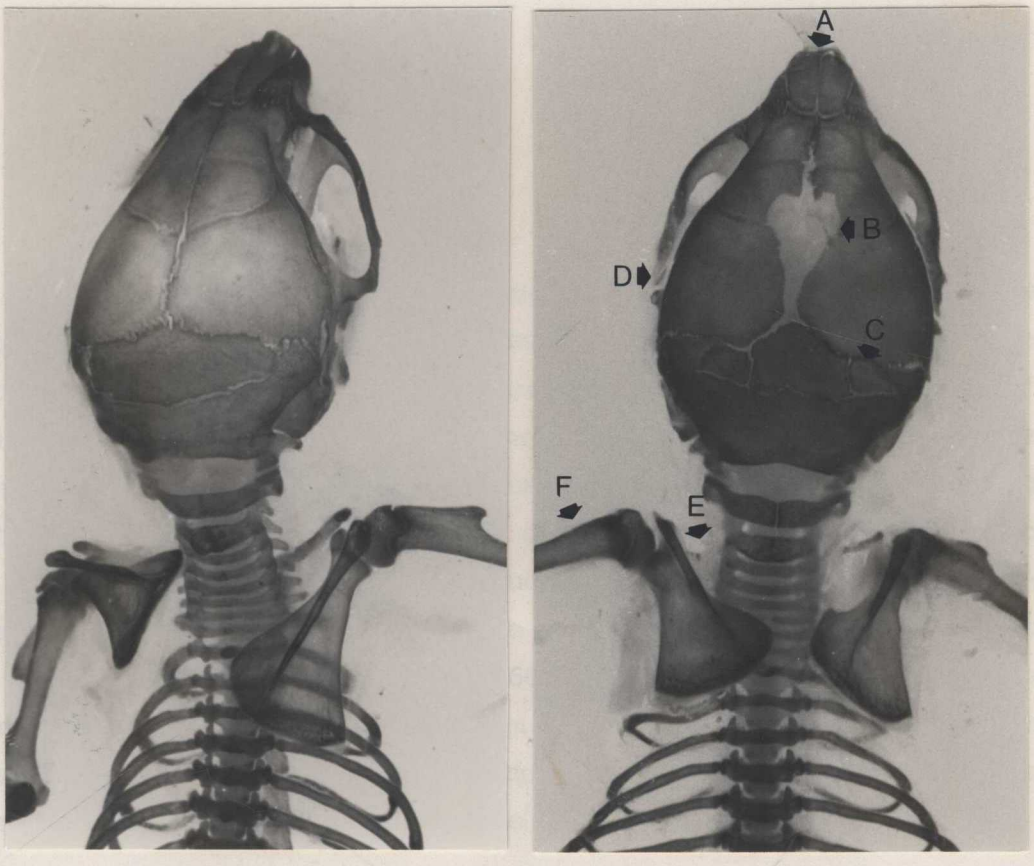


FIGURE 5. Diagrammatic representation of the dorsal surface of a mouse skull. (Reproduced from Cook M.J.; The Anatomy of the Laboratory Mouse. Academic Press, 1965. Fig. 11,p 18.)



a) b)

FIGURE 6. a) Head and shoulders of a normal C57/BL mouse skeleton (alizarin preparation).
b) Head and shoulders of a Ccd phenotype C57/BL mouse skeleton (alizarin preparation).
Note-
A: hypoplastic nasal bones
B: patent fontanelles
C: fragmented interparietal bones
D: hypoplastic post-tympanic hook of squamosal bone
E: hypoplastic clavicles
F: missing deltoid tuberosity

(Photographs courtesy of Helen Ritchie.)

C. MOUSE DENTITION

The dental formula for the mouse is:

incisors	1/1	
cuspids	0/0	
premolars	0/0	
molars	3/3	(Cohn, 1957)

Unlike the majority of placental mammals, the mouse is a monophyodont. The question arises as to whether this single dentition is homologous to the deciduous or permanent series of typical diphyodont placental mammals. Gaunt (1966) was of the opinion that the molars of the mouse are equivalent to persisting members of the diphyodont deciduous dentition, and that the free end of the dental lamina fails to produce further tooth germs. Moss-Salentijn (1978) concluded that the incisor teeth also belonged to the deciduous series. Gaunt (1966) also observed that the mouse enamel organs arise directly from oral epithelium without the presence of a definitive dental lamina. A dental lamina grows out subsequent to the development of the enamel organs.

The molars are structurally similar to those in humans, although the anatomy of their crowns is different. The UM1 has eight cusps, all of which are tilted posteriorly. There are three buccal, three central and two lingual cusps. The UM2 differs by having one less central cusp. The crown of LM1 has seven cusps, most of which are tilted anteriorly. There are three buccal, three lingual and one posterior central cusp. LM2 differs by missing the first lingual cusp. The cusps of the third molars are simpler and subject to some variation (Gruneberg, 1965; Sofaer, 1977). The third molars are small and poorly developed. In some strains they may be entirely absent (Sofaer, 1969; 1975A; 1977). In the strain of mice being used in this study, C57BL, the incidence of agenesis of one or more third molars is 1% (Sofaer, 1975A).

The root configurations of the molar teeth are similar to their equivalents in the human series:

M1(3)	M2(3)	M3(3)	
M1(2)	M2(2)	M3(1)	(Cohn, 1957)

The third molars may display some variability; UM3 may have a single root which shows a tendency towards division into three towards the apex, and LM3 may similarly divide into two (Sofaer, 1977). (See FIG. 7).

The molar teeth undergo considerable attrition and there is gradual deposition of cellular cementum at the apical portions, which is presumably a compensatory mechanism. Distinct hypercementosis of molar teeth develops with age (Cohn, 1957). Continuous apposition of cementum and increase in thickness with age also occurs in human teeth (Zander, 1958). Distinctive trabecular patterns of alveolar bone, and varying thicknesses of periodontal membrane have been observed in different strains of mice (Baer & Lieberman, 1959).

The incisors of mice are arc shaped and have no separate crown and root. The incisal edge undergoes continual attrition, and to compensate for wear, there is continual, equivalent synthesis of tooth material apically. The superior surface of the incisors is covered only by cementum and is attached to alveolar bone by periodontal ligament. Hertwig's root sheath is found only on the superior surface of the tooth. The inferior surface is covered by enamel. The tissue at the apical portion is similar, but in different arrangement to tooth germs which give rise to teeth of limited eruption. Progenitor cells provide ameloblasts, odontoblasts, cementoblasts and periodontal ligament cells continuously throughout life (Jacobson, 1983). (See FIG. 8). Jacobson lists three differences between teeth of continuous and limited eruption. The first is that an intermediate plexus is purported to exist in continuously erupting teeth, which allows teeth to erupt while supporting bone remains stationary. The

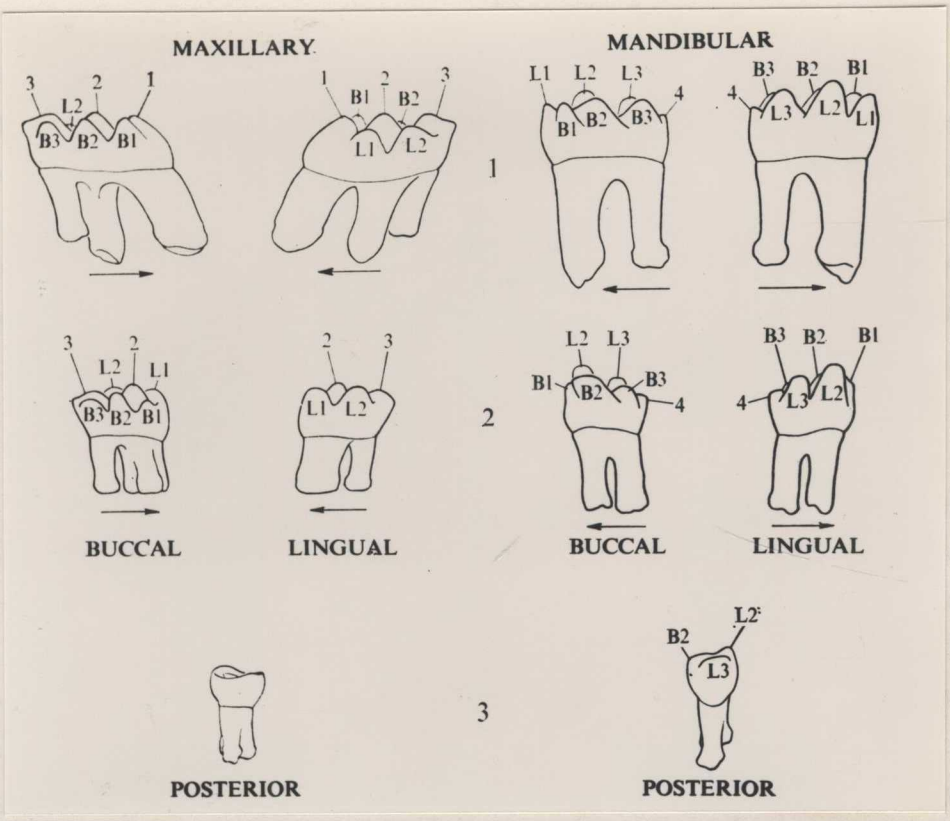


FIGURE 7. Outline drawings of the left molars of a 60-day-old normal female mouse. The arrows point forward. (From Gruneberg, H., J. Embryol. exp. Morph. 14, Fig 1, p 138.1965)

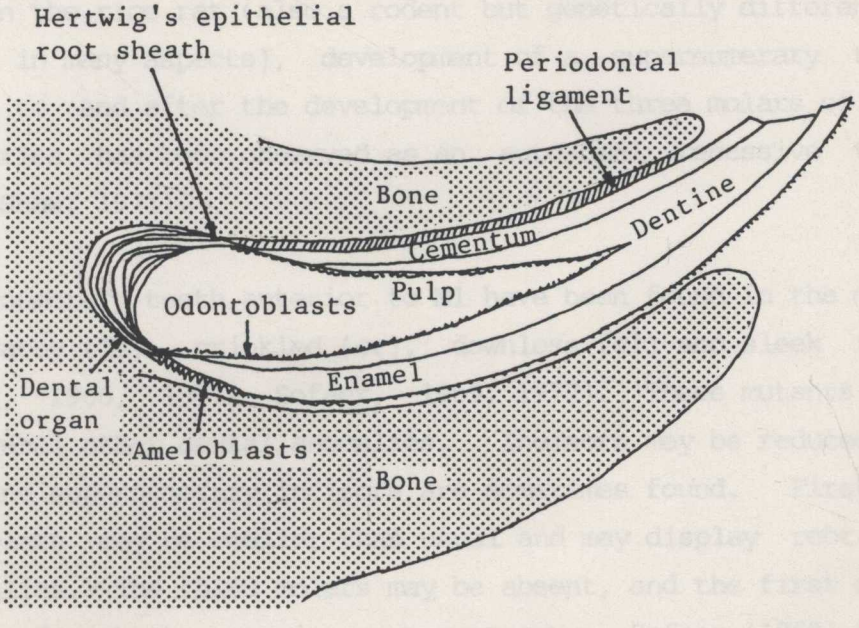


FIGURE 8. Anatomy of rat and mouse incisor. (Modified from Jacobson, A.; Birth Defects: Original Article, Series, 19, 1983, Fig 3. p 71.)

existence of this structure in human teeth has been the subject of much debate. The second difference is that continuously erupting teeth continue to erupt even if unopposed, while teeth of limited eruption cease to erupt after a period if they lose their antagonists. The third difference is that the periodontal ligament of unopposed continuously erupting incisors shows no atrophy, unlike teeth of limited eruption, whose supporting bone and periodontal ligament may undergo atrophy when there is loss of antagonists.

The tooth germs are derived from three separate ingrowths of oral epithelium: two proximal ingrowths which give rise to the molars, and an anterior ingrowth which gives rise to the two incisors and the lip furrow band. The ingrowths for the molar teeth begin to develop before those of the incisors. In the early stages, the incisor and molar regions are separate, but the incisors gradually grow backwards, until at birth they lie under the first molars and later, all molars (Hay, 1961). See TABLE 4 for sequence of development.

The dentition of mice is not generally known for the occurrence of an excess number of teeth. Experimentally induced supernumerary teeth, adjacent to the lateral aspect of M3 were found in 5 out of 44 (11%) transplanted 18 day C57BL M2-M3 grafts (Kerley & Kollar, 1977). In the rice rat (also a rodent but genetically different to the mouse in many aspects), development of a supernumerary tooth posterior to and after the development of the three molars of the normal series has been observed as an autosomal recessive trait (Sofaer & Shaw, 1971).

Supernumerary teeth anterior to M1 have been found in the mouse mutants Tabby (Ta), crinkled (cr), downless (dl) and sleek (slk) (Gruneberg, 1966, 1971; Sofaer, 1969, 1977). These mutants also share several other dental anomalies. Incisors may be reduced or absent, and supernumerary incisors are sometimes found. First and second molars may be smaller than usual and may display root and cusp anomalies. The third molars may be absent, and the first molar may be fused with the anterior supernumerary. Sofaer (1969) found that in normal A strain mice there was a small extension of the dental lamina anteriorly and somewhat lingually from the point of

TABLE 4

SEQUENCE OF DEVELOPMENT OF TEETH IN THE MOUSE

DAY	COHN (1957)	HAY (1961)
12 i.u.	First sign of differentiation of dental lamina	Well defined dental lamina
13 i.u.		M1/M1: bud shaped swelling
14 i.u.	Enamel organ M1/M1	
15 i.u.		Dental lamina for M2/M2 present
16 i.u.	Tooth buds for M2/M2	
POSTNATAL		
4-6	Tooth buds for M3/M3	
10	Eruption M1/M1 begins (bone which encapsulated M1/M1 is being resorbed occlusally)	
15		Incisors erupt into oral cavity
16-17	M1/M1 erupt into oral cavity	
18-19	M2/M2 erupt into oral cavity	
24	Full root length M1/M1 achieved	
25	Full root length M2/M2 achieved (cellular cementum appears near apical ends just prior to or at time teeth attain functional occlusion)	
28-29	M3/M3 erupt into oral cavity	
35	M3/M3 in functional occlusion, roots have cellular cementum	

origin of the first molar tooth germ (See FIG. 9), which, in the Tabby mutant, sometimes proliferated to form an epithelial downgrowth anterior to the developing first molar. In some cases, a supernumerary tooth formed from this epithelial downgrowth. Incidence of supernumerary formation was greater in the mandible. The overall impression formed was a partial suppression of growth and differentiation of dental epithelium, with occasional localized points of abnormal overgrowth, due perhaps to failure of inhibitory interaction between tooth germs and dental lamina (Sofaer, 1975B). In each of the descriptions of supernumerary formation presented here, derivation from proliferation of the anterior or posterior ends of the dental lamina has occurred, and the supernumeraries have developed after the adjacent teeth of the normal series. Lumsden (1979) has shown that in the development of the mouse dentition the M1 is the stem progenitor and that M2 and M3 arise as a result of posteriorly directed proliferation of the initial cell mass.

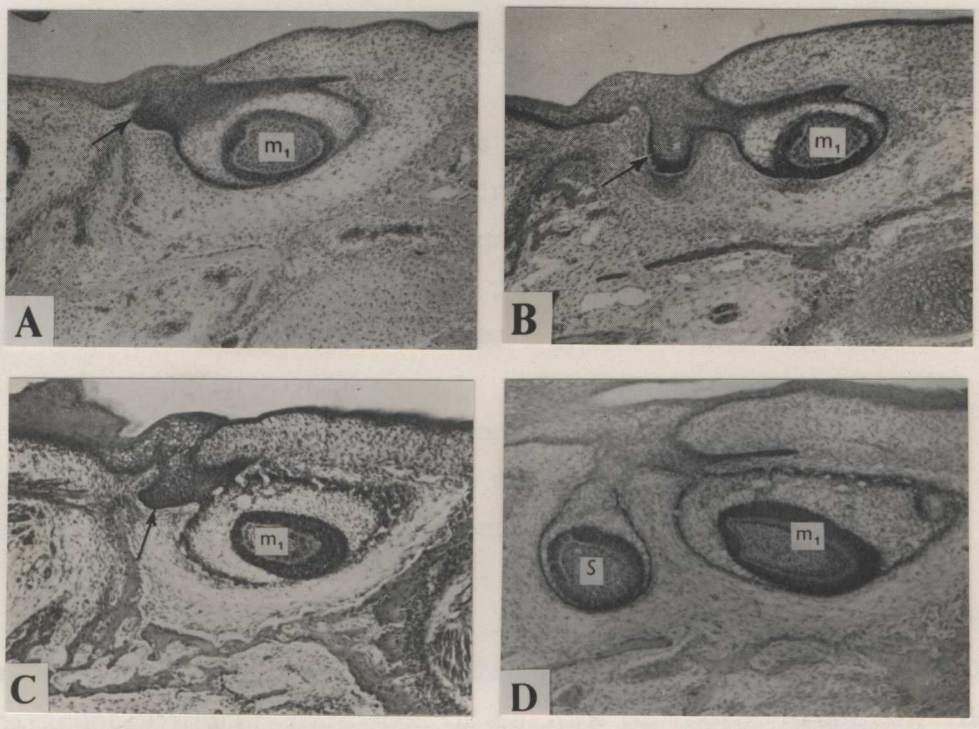


FIGURE 9. Supernumerary tooth formation in the Tabby mouse mutant.

A: Control lower first molar germ at 17 days, sectioned lingually to show the normal anterior extension of dental lamina (indicated by the arrow).

B: Tabby heterozygote at 17 days, with lower first molar sectioned lingually. There is a large bud of dental lamina anteriorly (indicated by the arrow).

C: Control lower first molar at 19 days, sectioned lingually to show the normal anterior extension at this stage.

D: Tabby heterozygote at 19 days with lower first molar sectioned lingually. There is a small supernumerary tooth germ anteriorly with its own laminal connections.

(From Sofaer J.A.; J. Embryol. exp. Morph. 22, 1962. Fig. 2D, 2E, 3C, 3D, p 186 & 189.)

CHAPTER VI

EXPERIMENT

A. AIM

The aim of the experiment was to study aspects of the dentition of the mutation 320 mouse, comparing it to features of the dentition found in humans with CCD. Significant features of the human dentition in CCD which might practically be compared to the dentition of the mutation 320 mouse include:

1) failure of tooth eruption.
2) delay in onset of tooth eruption.
3) higher incidence of supernumerary teeth.

The hypothesis proposed was that if, compared to litter-mates with normal phenotype, mice with Ccd phenotype were observed to display a significantly higher incidence of failure of tooth eruption, delay in onset of eruption, or higher incidence of supernumerary teeth, then such observations would provide further evidence, in terms of extraskeletal abnormalities characteristic of the clinical disease, for the proposition that mouse mutation 320 (Ccd) is homologous to CCD in humans.

B. MATERIALS AND METHODS

The mice used in this experiment were provided by the Commonwealth Institute of Health, Sydney, where various mouse skeletal dysplastic mutants were being investigated by Professor D. Sillence in a project which was approved and funded by the National Health and Medical Research Council (1984).

Aspects of the dentition of mutation 320 on C57BL inbred mouse background were compared with normal mice of the same inbred strain. Offspring of matings of heterozygotes (320/+ x 320/+) and heterozygotes with normal homozygotes (320/+ x +/+) were used. Homozygote 320 mutants are lethal in utero (Sillence et al, 1985).

The mice were killed in an ether chamber, and the phenotype of each mouse was identified by radiographic assessment, using a Torrex 120, low kV, fully shielded bench x-ray unit. Exposures were taken on Polaroid Land Film (Polapan 52) at 40 kV, 3mA, with average time of 5 seconds for 16 day old mice (Sillence, Ritchie, Koltai, McCredie, Mahant, Selby, 1984). The mice were classified as mutants if they possessed one or more of the following features (see FIG. 10):

1) Hypoplasia of clavicular bones.
2) Failure of ossification in the region of the suture between zygoma and squamosal bones.
3) Reduction or absence of the deltoid tuberosity of the humerus.
4) Patent anterior fontanelle. (This feature was identified by dissection).

The study was divided into three parts:

PART 1: Incidence of failure of tooth eruption
PART 2: Timing of first molar eruption
PART 3: Incidence of supernumerary tooth formation

PART 1: Incidence of failure of tooth eruption

55 mice from 11 litters of 45 days old mice (28 of 320/+, 27 of

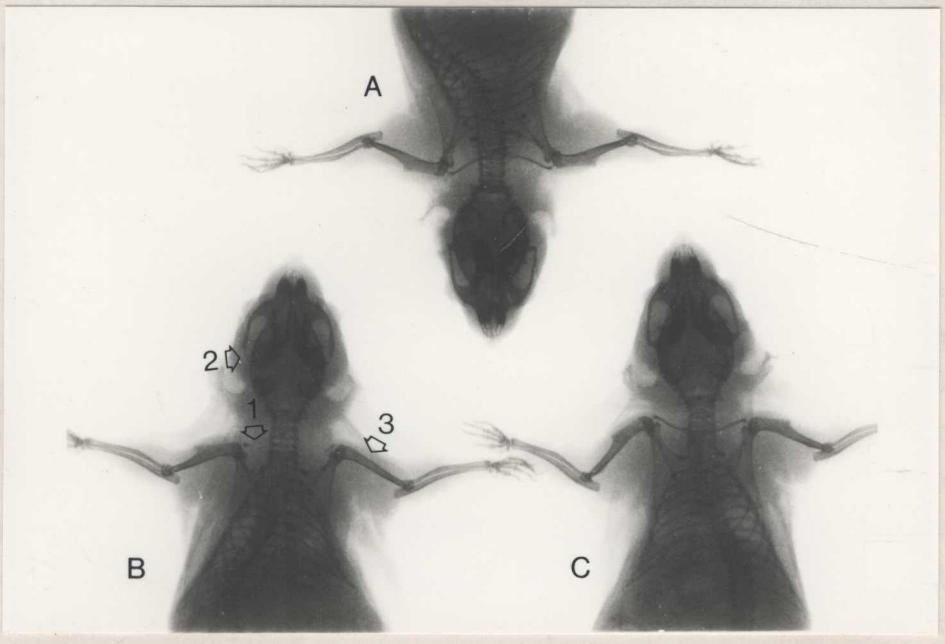


FIGURE 10. Photograph of a Polaroid radiographic film (Polapan) taken to identify mouse phenotype. Mouse A and C are normal, while mouse B is a Ccd mutant. Arrow 1 indicates hypoplasia of clavicular bones. Arrow 2 indicates failure of ossification in the region of the suture between zygoma and squamosal bone. Arrow 3 indicates unilateral absence of the deltoid tuberosity of the humerus.

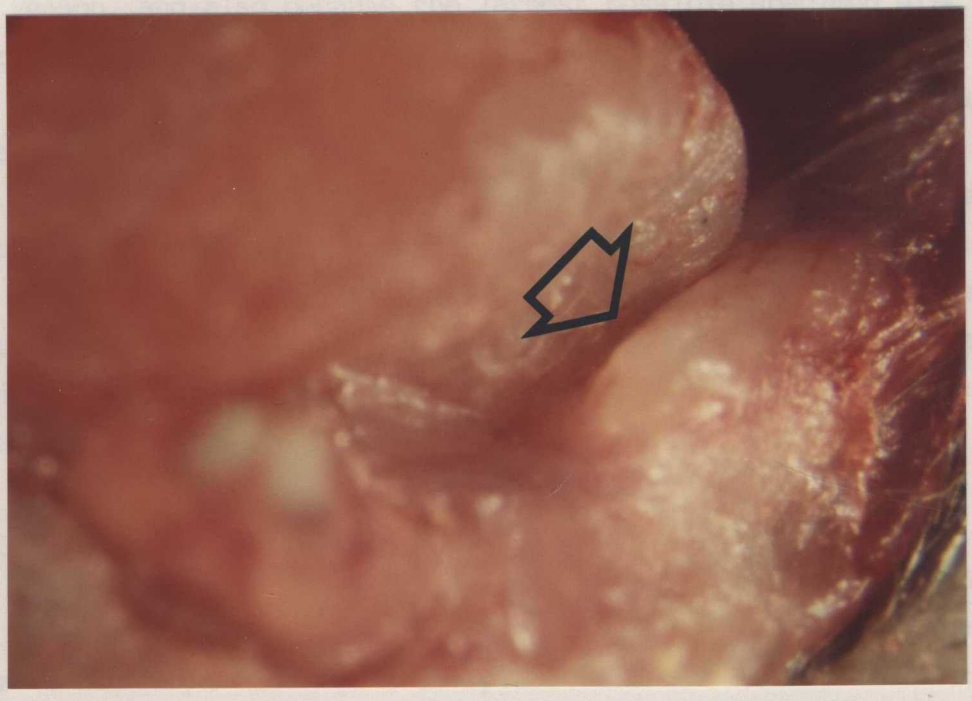
+/+, and 58 mice from 10 litters of mice which were 90 days or older (28 of 320/+, 30 of +/+) were used. Normal mice in both these groups would be expected to have a fully erupted dentition. After the mice were killed and phenotyped, the mandibles were partially disarticulated from the head in order to allow direct observation of the dental arches of both jaws, using a stereoscopic macroscope. The number of teeth erupted in both arches was recorded, and the heads were then removed and preserved in 10% neutral buffered formalin.

PART 2: Timing of first molar eruption

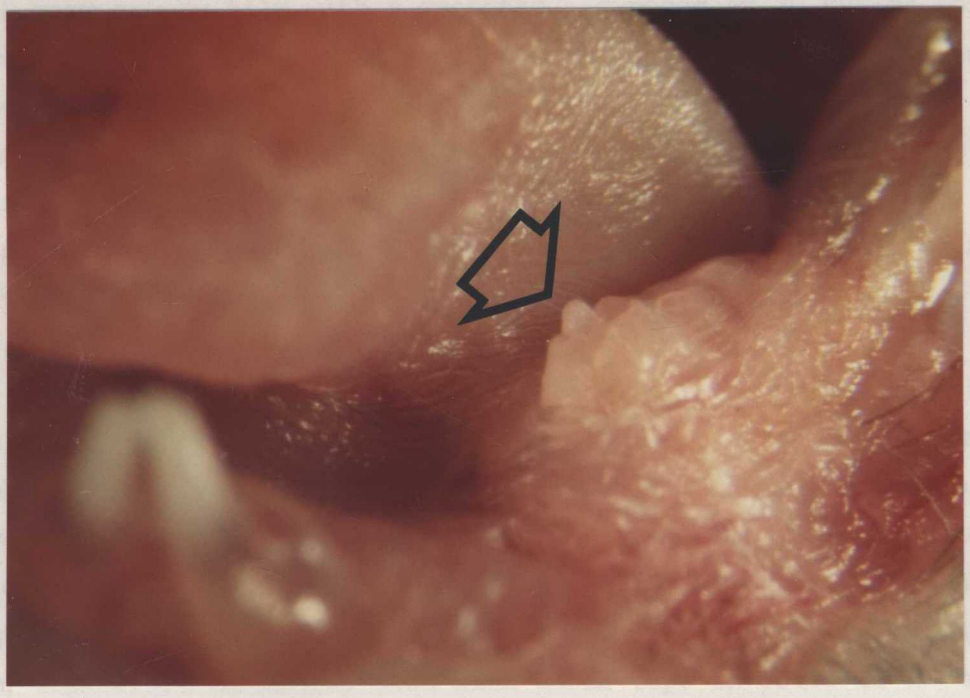
This part of the experiment was intended as a study of timing of first tooth eruption in view of the reports of delay in onset and progress of eruption of deciduous dentitions in humans with CCD (Alderson, 1960; Kalliala & Taskinen, 1962; Flynn, 1966; Winkler & Jung, 1971; Winkler et al, 1976; Abbas & Prabhu, 1982). However, the first teeth to erupt in the mouse are the incisors. These teeth have no equivalent in the human dentition, being structurally different and undergoing continuous eruption rather than limited eruption. However, the molar teeth are structurally similar to those in humans and undergo limited eruption. Therefore, the event chosen for comparative study between normal and mutant mice was eruption of first molar tooth. After a preliminary investigation of normal mice, the approximate time of eruption of the first molar (bilateral or unilateral lower first molar) was ascertained to be at 16 days. The formal investigation comprised 95 16 day old mice from 19 litters (41 of 320/+, 54 of +/+). The mice were killed, then weighed on a Mettler weighing machine. The mandibles were partially disarticulated from the head in order to allow direct observation of the dental arches of both jaws, using a stereroscopic macroscope. Eruption was deemed to have occurred if any portion of the crown of a molar tooth had penetrated the mucosa (see FIG. 11). Examination was made by one observer, who was unaware of the phenotype of each mouse being studied. Following examination, the heads were removed and preserved in 10% netural buffered formalin.

PART 3: Incidence of supernumerary tooth formation

In humans with CCD, supernumerary teeth develop at the time of permanent dentition formation and may also occur later in life. For



a)



b)

FIGURE 11. a) Lower left alveolus of a 16-day-old mouse. Molar eruption has been deemed to have not yet occurred.
b) Lower left alveolus of a 16-day-old mouse. Eruption of the first molar has been deemed to have occurred.

this reason, and also because the largest possible specimen size was desirable for radiographic purposes, adult mice were selected for this part of the study. 58 mice from 10 litters of mice which were 90 days or older (28 of 320/+, 30 of +/+) were used. These were the same mice which had been used for Part 1 of the experiment. Following observation of erupted teeth, the mandible of each mouse was disarticulated from the skull and dissected from the soft tissue, then hemi-sectioned at the mandibular symphysis. The hemi-sectioned mandibles were then stored in 10% neutral buffered formalin.

Note on Radiography:

Radiographs of the mandibles were taken using a fully shielded low kV Faxitron 405 x-ray unit. Several types of film were tried before a technique which gave acceptable detail was obtained. Kodak Min R mammography film with a cassette, exposed at 30 kV 3mA for 14 seconds produced excessive graininess which was not sufficiently reduced when the film was hand-wrapped in black polyethylene and exposed without the use of the cassette, and at lower kV. There was insufficient tissue penetration below 20 kV. Better, but not acceptable results were obtained using Kodak M double emulsion individually packaged film at 20 kV 3mA for 10 minutes.

In order to reduce graininess, attention turned to high resolution film because of the fineness of the emulsions used. Kodak High Resolution SO-343 film was individually packaged in black polyethylene using a heat-sealer in a dark room. Contact micro-radiography techniques were not employed. The mandibles, which are slightly curved, were simply placed lingual side up on the wrapped film; taping the mandibles down with clear tape in order to increase contact with the film made no appreciable difference. Because the three mouse molar teeth are progressively more lingually inclined from the anterior to posterior portions of the jaw, some over-lapping of teeth occurred. Attempts to avoid this problem by altering the angulation of the mandibles resulted in portions being out of focus because of their distance from the film. Exposures were for 3 hours at 40 kV, 3mA. The film was processed using Kodak D19 liquid developer and Kodak liquid fixer according to manufacturer's instructions.

The processed radiographs were examined for evidence of supernumerary teeth, using a microfiche viewing screen, and with a Wild M400 photomacroscope. A line drawing of the molar teeth of C57 mice was used to assist in interpretation of the radiographs (See FIG. 12 & 13).

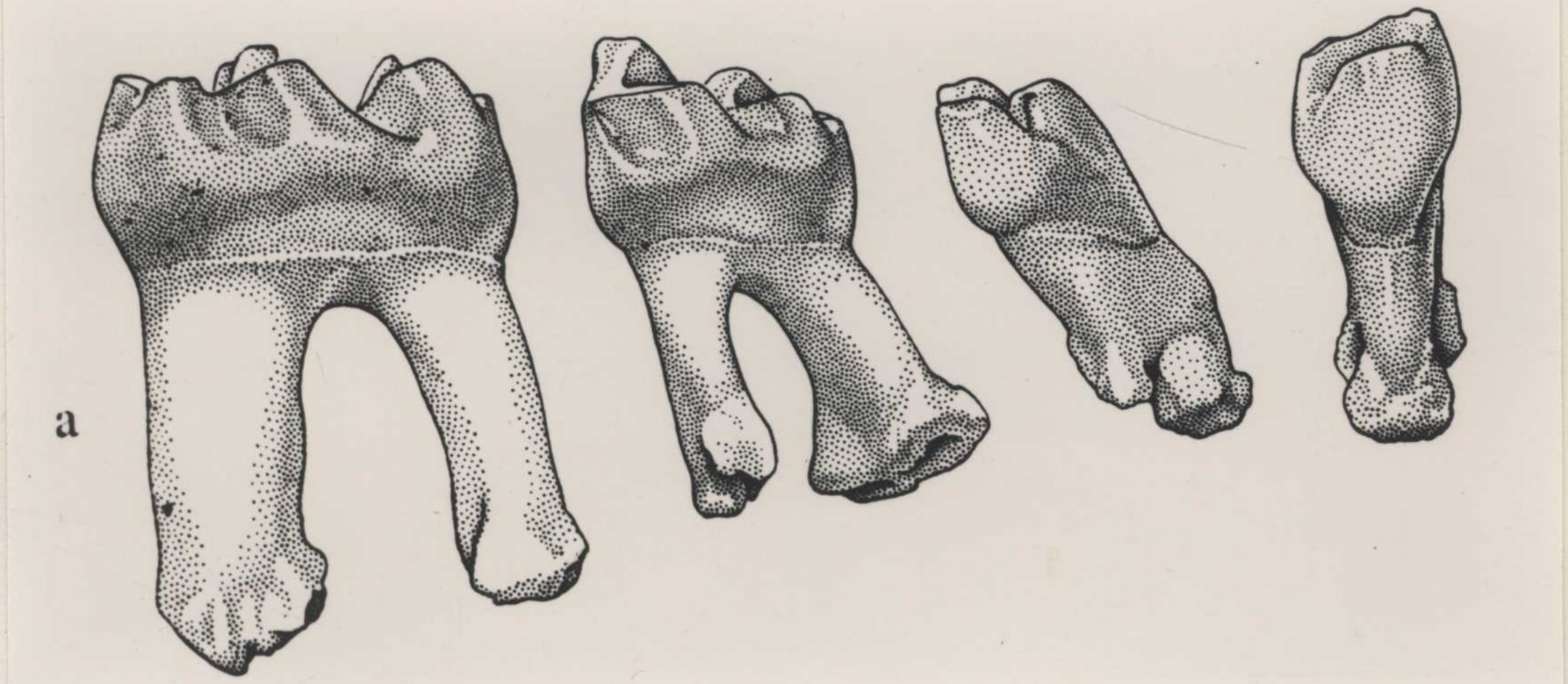


FIGURE 12. The mandibular molar teeth of the C57/BL mouse, 65 day-old male. Buccal views of M1, M2, M3, together with posterior views of M3 normal to its axis. (From Gruneberg H.; J. Embryol. exp. Morph. 14, 1965. Fig. 16a, p 151.)

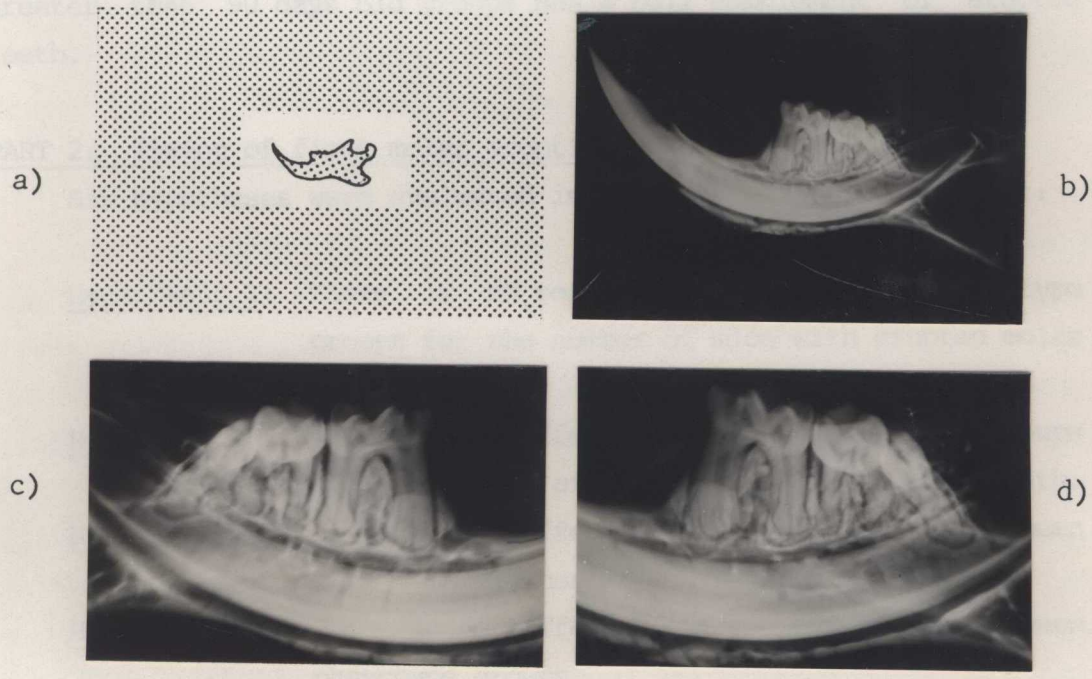


FIGURE 13. Radiographs of disarticulated hemisectioned mandibles of adult male C57/BL mice, obtained using Kodak SO-343 high resolution film exposed at 40kV, 3mA for 3 hours.
a) Line drawing demonstrating actual size.
b) Right mandible of normal mouse, depicted to assist with orientation.
c) Left molars and alveolus of a Ccd phenotype mouse.
d) Right molars and alveolus of the same normal mouse shown in b).

C. RESULTS

PART 1: Incidence of failure of tooth eruption

All normal and mutant mice examined from both 45 days old and greater than 90 days old groups had a full complement of erupted teeth.

PART 2: Timing of first molar eruption

Six hypotheses were evaluated in this part of the experiment:

Hypothesis 1: There is no sex difference within phenotype groups for the number of mice with erupted molar teeth.

Hypothesis 2: There is no difference between phenotype groups for the number of mice with erupted molar teeth.

Hypothesis 3: There is no difference in weight (grams) between sexes within phenotype groups.

Hypothesis 4: There is no difference in weight (grams) between phenotype groups.

Hypothesis 5: There is no difference between the weight (grams) of abnormal mice with erupted molar teeth and abnormal mice with unerupted molar teeth.

Hypothesis 6: There is no difference between the weight (grams) of normal mice with erupted molar teeth and normal mice with unerupted molar teeth.

There was no significant sex difference within phenotypes as shown by Chi square test (thus supporting Hypothesis 1), so male and female mice within each phenotype were combined. Eruption of at least one molar tooth (lower first molar) had occurred in 43 of the 54 normal mice, and 4 of the 41 mice with Ccd/+ phenotype. A Chi square test showed that there was a significant difference at 5% level between phenotypes for the number of mice with erupted molar teeth (thus refuting Hypothesis 2).

With regard to weight, there was no sex difference found within phenotype groups using a 2-tail T test (thus supporting Hypothesis 3), so sexes were combined within each phenotype group. The mean

weight for normal mice was 7.46g, and the mean weight for Ccd phenotype mice was 6.81g. A significant difference at 5% level was found between phenotype groups using a 2-tail T test (thus refuting Hypothesis 4).

No significant difference (at 5% level) in weight was found between Ccd mice which had erupted molar teeth and those which had no erupted molar teeth (thus supporting Hypothesis 5).

The mean weight of normal mice with erupted teeth was 7.61g and the mean weight of normal mice with no erupted teeth was 6.89g. However, comparison of the variances (F ratio) showed that there was too great a variation to allow a 2-tail T test to be carried out. Because the sample size of normal mice with erupted teeth was large (43) compared to the sample size of normal mice with no erupted molar teeth (11), the mean weight of the former was treated as a population mean, and a one-sample T-test was carried out, using the weights of the sample of normal mice with no erupted molar teeth. A significant difference at the 5% level was found between the two groups (thus refuting Hypothesis 6).

PART 3: Incidence of supernumerary tooth formation

No evidence of supernumerary tooth formation was observed in radiographs of either normal or Ccd mice.

D. DISCUSSION

Although the intention of this study has been to establish whether the dentition of mouse mutation 320 has anomalies which are homologous to those found in humans with CCD, the differences between human and mouse dentitions need to be taken into account. As was discussed (see "Mouse Dentition"), the mouse has continuously erupting incisors, and although the molar teeth undergo limited eruption and are structurally similar to human molars, the mouse is monophyodont while humans are diphyodont. Whether this monophyodont dentition corresponds to the primary or secondary human dentition is uncertain. Gaunt (1966) and Moss-Salentijn (1978) are of the opinion that the single dentition of the mouse is homologous to the deciduous series of typical diphyodont mammals. This last factor becomes significant when it is considered that in human CCD, the secondary dentition is the one which is affected by failure of eruption and development of supernumerary teeth. The only anomaly reported which appears also to affect the deciduous dentition is delay in onset of eruption. (Alderson, 1960; Kalliala & Taskinen, 1962; Flynn, 1966; Winkler & Jung, 1971; Winkler et al, 1976; Abbas & Prabhu, 1982).

No failure of eruption of teeth or occurrence of supernumerary teeth was observed in this study. It was expected that if supernumerary teeth were found, they would be likely to have formed as mesial or distal extensions of the normal molar tooth rows, because these are the sites where supernumerary teeth have been reported in other mice (Gruneberg 1966, 1971; Sofaer 1969, 1977; Kerley & Kollar, 1977). The significance of the negative findings in Part 1 and Part 3 of this study is difficult to establish. It could not be claimed that the case for homology between human CCD and mouse Ccd is weakened by these findings, because, as has been discussed, it is thought that the monophyodont dentition of the mouse is equivalent to the human deciduous dentition, and in human CCD the deciduous dentition is not affected by failure of eruption or formation of supernumerary teeth. On the other hand, the corollary between mouse dentition and human deciduous dentition is not a firmly established fact and the negative findings in Part 1 and Part 3 of this study might indicate a dissimilarity between the mouse and the human

condition. Finally, assuming that the corollary between the mouse and human deciduous dentition is appropriate, the negative findings in Part 1 and Part 3 would indicate that a factor specific to the secondary dentition was significant in CCD. For example, in the case of failure of tooth eruption, it has been suggested that the deciduous teeth lie in a superficial position before eruption, only partially covered by bone, and that in the presence of an underlying bone remodelling defect, are more likely to erupt than fully enclosed, deeply positioned succedaneous teeth (Hitchin & Fairley, 1974). This may also explain why the dentitions of mutation 320 mice observed in this study all erupted fully.

As regards supernumerary tooth formation, if this anomaly is specific to formation of a secondary dentition, perhaps a factor associated with reactivation (or disinhibition) of the original dental lamina at the time of secondary proliferation to establish the secondary dentition may be involved. In the case of the mouse, there would not normally be a secondary proliferative stage. Also, the mouse dentition does not appear to form from a definite dental lamina, as it does in humans. Instead, each tooth row is formed from a posteriorly directed proliferation of a dental lamina derived from the initial tooth bud mass (Gaunt, 1966; Lumsden, 1979).

The results of Part 2 of this study showed that there was a statistically significant difference between the number of normal and mutant mice which had erupted a molar tooth by 16 days. This finding would be consistent with the expectation that, as in humans with CCD, onset of eruption would be delayed in mice with a homologous condition. However, the weight of Ccd/+ mice was significantly less than that of the normal mice in this study, and the contribution which this factor may have had with respect to maturation and tooth eruption in the mice requires consideration. Many humans with CCD have also been reported to be small of stature (Soule, 1946; Jarvis & Keats, 1974), and the same consideration regarding onset of eruption should be made. Delgardo, Habicht, Yarbrough, Lechtig, Martorell, Malina, Klein (1975) found no correlation between nutritional status and the emergence of the deciduous dentition in humans, while El Lozy, Reed, Kerr, Boutourline, Tesi, Ghamry, Stare, Kallal, Turki, Hemaidan (1975)

found that severe malnutrition led to delayed emergence of deciduous teeth. Lee, Chan, Low, Chang (1965), Garn, Sandusky, Nagy, Trowbridge (1973), and Billewicz & McGregor (1975) all came to the conclusion that although nutritional factors may have an impact on general somatic growth, the effect on eruption is either non-existent or statistically insignificant. Jellife & Jellife (1973, quoted in Demirjian, 1978) suggested that current information indicates that formation and emergence patterns of the deciduous dentition in humans seem to be "programmed" in foetal life.

Comparison of the weight of normal mice with erupted molar teeth and normal mice with no erupted molar teeth was difficult because the majority of normal mice had erupted molar teeth, leaving a very small number of mice in the latter group. An F-test showed that the two groups were not homogeneous, thus precluding analysis using a 2-tail T-test. Comparison of the weights of mutant mice with erupted molar teeth and mutant mice with no erupted molar teeth was able to be made using a 2-tail T-test, but once again, the number of mice in one of the groups (erupted molar) was extremely small. Overall, statistical analysis revealed a significant difference between the weights of normal mice with erupted teeth and normal mice with no erupted teeth, but no significant difference between the weights of abnormal mice with erupted teeth and abnormal mice with no erupted teeth. No conclusion regarding the significance of weight on the progress of tooth eruption in the mice in this study could be made from these results.

The finding that most of the normal mice had erupted at least one molar tooth by day 16 suggests that 16 days was an appropriate age for assessing the event of initial molar eruption in normal and mutant mice. However, further information concerning the extent of the delay in onset of molar eruption in mutant mice, that is, whether the delay is only a matter of days or more marked, might have been obtained if a study of subsequent age groups (for example 18 day old, and 20 day old mice) had been undertaken to establish at what age molar eruption occurred in mutant mice. Limitations of time and resources of mice precluded this.

Some incidental observations were made during the study. In

all mice studied, all incisor teeth had erupted and were in normal interincisal relationship. No evidence of cleft palate was found, and all erupted teeth were in normal alignment.

E. SUMMARY

1) No evidence of failure of eruption was observed in normal or mutant mice.

2) No evidence of supernumerary tooth formation was observed in normal or mutant mice.

3) The number of normal 16 day old mice with erupted molar teeth was significantly greater than the number of mutant 16 day old mice with erupted molar teeth.

4) Although the weight of 16 day old normal mice was significantly greater than the weight of 16 day old mutant mice, conclusions could not be drawn regarding the possible influence weight differences might have had on eruption progress.

The differences between the dentitions of mice and humans make comparisons for the purposes of evaluating the extent of homology difficult. However, the finding of Part 2 of this study (that is, the observation of a delay in tooth eruption at 16 days in mutant mice) is consistent with the dental findings reported in humans with CCD (assuming that the dentition of the mouse corresponds with the human primary dentition).

CONCLUSION

A study was undertaken in order to establish whether mouse mutation 320 (Ccd) displayed dental abnormalities similar to those found in humans with cleidocranial dysplasia. Although differences between human and mouse dentitions may have complicated the comparison, the observation of delay in molar tooth eruption at 16 days in mutant mice was a positive finding in terms of homology between human CCD and the Ccd mouse mutant (assuming that the mouse dentition corresponds with the human primary dentition). Further study of this feature is indicated in order to assess the degree of delay, and a histological study might provide aetiological clues regarding the observed delay in eruption.

It is possible that the underlying biochemical defect which is occurring in cleidocranial dysplasia will be elucidated in the future. In the event of such a discovery, explanation of the anomalies seen in the dentition in cleidocranial dysplasia might be facilitated. Such explanations might also provide scientists with valuable insights into normal processes of tooth eruption and tooth induction. Although may workers have been puzzled by the fact that this particular dysplasia affects tooth eruption and tooth induction processes, it has been suggested in this thesis that both processes involve mesenchymal tissues and that certain proteins or protein complexes may be common to them as well as to processes of osteogenesis.

Another area in which the Ccd mouse mutant may yield valuable information is that of craniofacial growth. If, as in humans with cleidocranial dysplasia, the shape of the skull and growth of the cranial base is affected in Ccd mutant mice, an opportunity exists for a systematic study of abnormal craniofacial development.

APPENDIX

APPENDIX TABLE 1

WEIGHT AND MOLAR ERUPTION STATUS 16 day old MICE

Ccd/+				+/+			
FEMALE		MALE		FEMALE		MALE	
WEIGHT (g)	MOLAR ERUPTED	WEIGHT (g)	MOLAR ERUPTED	WEIGHT (g)	MOLAR ERUPTED	WEIGHT (g)	MOLAR ERUPTED
7.3	-	6.5	-	6.9	-	9.5	✓
7.0	-	6.3	-	7.2	-	9.2	✓
6.3	-	5.6	-	9.8	✓	9.6	✓
5.2	-	5.8	-	9.4	✓	6.8	-
4.0	-	8.9	-	9.7	✓	7.1	-
7.5	-	5.5	-	5.8	✓	7.7	✓
6.1	-	5.7	✓	6.0	✓	6.8	✓
5.2	-	7.6	-	6.9	✓	6.0	✓
5.0	-	7.4	-	7.9	✓	7.1	✓
7.8	-	7.1	-	6.7	-	5.3	✓
8.1	-	4.7	-	6.8	-	7.0	✓
5.2	-	6.0	-	6.7	✓	6.9	-
9.0	✓	9.1	-	6.6	✓	6.5	✓
7.1	-	8.1	-	8.9	✓	8.1	✓
6.3	-	8.1	-	5.1	✓	6.1	✓
6.9	-	8.4	✓	6.5	-	6.6	-
7.6	✓	7.6	-	4.7	✓	6.2	✓
7.7	-	6.6	-	7.5	✓	3.6	✓
		6.4	-	7.5	✓	9.5	✓
		6.7	-	7.3	-	8.6	✓
		6.8	-	8.8	✓	9.2	✓
		7.9	-	8.5	✓	7.0	-
		7.3	-	8.3	✓	7.7	✓
				7.9	✓	7.0	✓
				7.6	✓	8.7	✓
				8.4	✓	8.5	✓
				8.7	✓		
				8.5	✓		
Total 119.3	2	160.1	2	210.6	22	192.3	21
Mean 6.63		6.96		7.52		7.40	
S^2 1.62		1.27		1.63		2.01	

APPENDIX TABLE 2

WEIGHT (grams) OF Ccd/+ AND +/+ MICE, 16 days, WITH AND WITHOUT ERUPTED MOLAR TEETH

Ccd/+		+/+	
Erupted	Unerupted	Erupted	Unerupted
9.0	7.3	9.8	6.9
7.6	7.0	9.4	7.2
5.7	6.3	9.7	6.7
8.4	5.2	5.8	6.8
	4.0	6.0	6.5
	7.5	6.9	7.3
	6.1	7.9	6.8
	5.2	6.7	7.1
	5.0	6.6	6.9
	7.8	8.9	6.6
	8.1	5.1	7.0
	5.2	4.7	
	7.1	7.5	
	6.3	7.5	
	6.9	8.8	
	7.7	8.5	
	6.5	8.3	
	6.3	7.9	
	5.6	7.6	
	5.8	8.4	
	8.9	8.7	
	5.5	8.5	
	7.6	9.5	
	7.4	9.2	
	7.1	9.6	
	4.7	7.7	
	6.0	6.8	
	9.1	6.0	
	8.1	7.1	
	8.1	5.3	
	7.6	7.0	
	6.6	6.5	
	6.4	8.1	
	6.7	6.1	
	6.8	6.2	
	7.9	3.6	
	7.3	9.5	
		8.6	
		9.2	
		7.7	
		7.0	
		8.7	
		8.5	

Hypothesis 1: There is no sex difference within phenotype groups for the number of mice with erupted molar teeth.

CCD/+

	C1	♀	C2	♂	
Erupted	R1	2	R1	2	4
Unerupted	R2	16	R2	21	37
Σ		18		23	41

	F	f	f-F	|f-F|-0.5	(|f-F|-0.5)²	$\frac{(\lvert f-F\rvert-0.5)^2}{F}$
R1C1	1.76	2	0.24	-0.26	0.07	0.04
R1C2	2.24	2	-0.24	-0.26	0.07	0.03
R2C1	16.24	16	-0.24	-0.26	0.07	0.00
R2C2	20.76	21	0.24	-0.26	0.07	0.00

$$\chi^2 = \sum \frac{(\lvert f-f\rvert-0.5)^2}{F} \quad *$$

f = observed
F = expected.

$= 0.07$

$\chi^2_{[1]}(0.05) = 3.84$ (from tables)

$0.07 < 3.84$

Observed and expected ratios do not differ significantly.
∴ ♀/♂ can be added.

+/+

	C1	♀	C2	♂	
Erupted	R1	22	R1	21	43
Unerupted	R2	6	R2	5	11
Σ		28		26	54

	F	f	f-F	|f-F|-0.5	(|f-F|-0.5)²	$\frac{(\lvert f-F\rvert-0.5)^2}{F}$
R1C1	22.30	22	-0.3	-0.20	.04	0.001
R1C2	20.70	21	0.3	-0.20	.04	0.001
R2C1	5.70	6	0.3	-0.20	.04	0.007
R2C2	5.29	5	-0.29	-0.20	.04	0.007

$$\chi^2 = \sum \frac{(\lvert f-F\rvert-0.5)^2}{F}$$

$= 0.02$

$\chi^2_{[1]}(0.05) = 3.84$ (from tables)

$0.02 < 3.84$

Observed and expected ratios do not differ significantly.
∴ ♀/♂ can be added.

---

* Statistical Methods. 6th Ed.
Snedecor G.W., Cochran W.G.
The Iowa State University Press, 1967,
p. 217.

Hypothesis 2: There is no difference between phenotype groups for the number of mice with erupted molar teeth.

	C1	Ccd/+	C2	+/+	
Erupted	R1	4	R1	43	47
Unerupted	R2	37	R2	11	48
Σ		41		54	95

	F	f	f-F	$\lvert f-F \rvert -0.5$	$(\lvert f-F \rvert -0.5)^2$	$\frac{(\lvert f-F \rvert -0.5)^2}{F}$
R1C1	20.28	4	-16.28	15.78	249.00	12.28
R1C2	26.72	43	16.28	15.78	249.00	9.32
R2C1	20.72	37	16.28	15.78	249.00	12.02
R2C2	27.28	11	-16.28	15.78	249.00	9.12

$$\chi^2 = \sum \frac{(\lvert f-F \rvert -0.5)^2}{F}$$

$$= 42.74$$

$\chi^2_{[1]}(0.05) = 3.84$ (from tables)

42.74 is $>$ 3.84

Observed and expected ratios differ significantly.

$\therefore$ Hypothesis 2 is disproved; there is a difference between phenotype groups for the number of mice with erupted teeth.

Hypothesis 3: There is no difference in weight (grams) between sexes within phenotype groups.

	Ccd/+		+/+	
	♀	♂	♀	♂
$\bar{y}$	6.63	6.96	7.52	7.40
n	18	23	28	26
s^2	1.62	1.27	1.63	2.01
df	17	22	27	25

* $F = \frac{\text{Greater } s^2}{\text{Lesser } s^2}$

$= \frac{1.62}{1.28}$

$= 1.28$

$F_{18,23}(.025) = 2.57$

$F = \frac{\text{Greater } s^2}{\text{Lesser } s^2}$

$= \frac{2.01}{1.63}$

$= 1.23$

$F_{26,28}(.025) = 2.27$

** $T = \frac{\bar{y}1-\bar{y}2}{\sqrt{\frac{[(n_1-1)s_1^2+(n_2-1)s_2^2]x\ \frac{1}{n_1}+\frac{1}{n_2}}{(n_1+n_2)-2}}}$

$= \frac{6.63-6.96}{\sqrt{\frac{[(17x1.62)+(22x1.27)]x\ \frac{1}{18}+\frac{1}{23}}{(18+23)-2}}}$

$= \frac{-0.33}{\sqrt{\frac{55.48\ x\ 0.1}{39}}}$

$= \frac{-0.33}{\sqrt{0.14}}$

$= \frac{-0.33}{0.37}$

$= -0.89$

$T_{39}(.025) = 2.03$

-0.89 is $<$ 2.03

Null hypothesis applies
$\therefore$ ♀/♂ can be combined.

$T = \frac{\bar{y}1-\bar{y}2}{\sqrt{\frac{[(n_1-1)s_1^2+(n_2-1)s_2^2]x\ \frac{1}{n_1}+\frac{1}{n_2}}{(n_1+n_2)-2}}}$

$= \frac{7.52-7.4}{\sqrt{\frac{[(27x1.63)+(25x2.01)]x(\frac{1}{28}+\frac{1}{26})}{(28+26)-2}}}$

$= \frac{0.12}{\sqrt{\frac{94.26\ x\ .07}{52}}}$

$= \frac{0.12}{\sqrt{0.13}}$

$= \frac{0.12}{0.36}$

$= 0.33$

$T_{52}(.025) = 2.01$

$.33$ is $<$ 2.01

Null hypothesis applies
$\therefore$ ♀/♂ can be combined.

* Statistical Methods. 6th Ed.
Snedecor G.W., Cochran W.G.
The Iowa State University Press, 1967, p 117.

** Op. Cit. p 105.

Hypothesis 4: There is no difference in weight (grams) between phenotype groups.

	Ccd/+	+/+
$\bar{y}$	6.81	7.46
n	41	54
s^2	1.55	3.09
df	40	53

$$F = \frac{3.09}{1.55}$$
$$= 1.99$$
$$F_{41,54}(.005) = 2.00$$

$$T = \frac{6.81 - 7.46}{\sqrt{\frac{[(40 \times 1.55) + (53 \times 3.09)] \times (\frac{1}{41} \times \frac{1}{54})}{(41 + 54) - 2}}}$$

$$= \frac{-0.65}{\sqrt{\frac{(62 + 163.77) \times .04}{93}}}$$

$$= \frac{-0.65}{\sqrt{\frac{9.03}{93}}}$$

$$= \frac{-0.65}{\sqrt{0.10}}$$

$$= \frac{-0.65}{0.32}$$

$$= -2.03$$

$$T_{93}(.025) = 1.99.$$

-2.03 is $<$ than $\pm$ 1.99

$\therefore$ Null hypothesis does not apply.

Hypothesis 5: There is no difference between the weight (grams) of abnormal mice with erupted molar teeth and abnormal mice with unerupted molar teeth.

Ccd/+

	Erupted	Unerupted
$\bar{y}$	7.68	6.72
n	4	37
s^2	1.94	1.52
df	3	36

$$F = \frac{1.94}{1.52}$$
$$= 1.28$$

$$F_{4,37}(.025) = 3.72$$

$$T = \frac{7.68 - 6.72}{\sqrt{\frac{[(3 \times 1.94) + (36 \times 6.72)] \times (\frac{1}{4} \times \frac{1}{37})}{(4 + 37) - 2}}}$$

$$= \frac{0.96}{\sqrt{\frac{247.74 \times 0.25}{39}}}$$

$$= \frac{0.96}{\sqrt{1.59}}$$

$$= \frac{0.96}{1.26}$$

$$= 0.76$$

$$T_{39}(.025) = 2.03$$

0.76 is $<$ 2.03

$\therefore$ The null hypothesis is satisfied.

Hypothesis 6: There is no difference between the weight (grams) of normal mice with erupted molar teeth and normal mice with uneruppted molar teeth.

+/+

	Erupted	Unerupted
$\bar{y}$	7.61	6.89
n	43	11
s^2	1.82	0.075
df	42	10

$$F = \frac{1.821}{0.075}$$
$$= 24.28$$

$$F_{43,11}(.005) = 3.86$$

$\therefore$ F Test is not satisfied.

One Sample T-test

Comparing sample of normal mice with unerupted molar teeth (n = 11) to "population" weight : i.e. mean weight of normal mice with erupted molar teeth (n = 43).

μ ("population" mean) = 7.61

S(unerupted)= $\sqrt{0.075}$ = 0.273

$$T = \sqrt{n}\ (\frac{\bar{y} - \mu}{S})$$

$$= \sqrt{11}\ (\frac{6.89 - 7.61}{.273})$$

$$= -8.76$$

$$T_{10}(.05) = \pm 2.228$$

-8.76 is $< \pm 2.228$

$\therefore$ Hypothesis must be rejected.

BIBLIOGRAPHY

ABBAS K.E.D., PRABHU S.R. (1982)
Cleidocranial Dysplasia in a Sudanese Female.
J. Oral Med., 37(2) : 45-48.

AITCHISON J. (1962)
Early recognition of congenital osteodystrophies.
N.Z. Dent. J., 58(July) : 123-128.

ALDERSON C.G.P. (1960)
Hereditary Cleido-cranial Dysostosis. (A Case Report).
Brit Dent. J., 108(Feb 16) : 157-159.

ALEXANDER W.N., FERGUSON R.L. (1980)
Beta thalassemia minor and cleidocranial dysplasia : A rare combination of genetic abnormalities in one family.
OS.OM.OP., 49(5) : 413-418.

ANDERSEN H. (1963)
Histochemistry and development of the human shoulder and acromio - clavicular joints with particular reference to the early development of the clavicle.
Acta Anat., 55 : 124-165.

ALLDRED A.J. (1963)
Congenital pseudoarthrosis of the clavicle.
J. Bone. Jt. Surg., 45B(2) : 312-319.

ARCHER W.H., HENDERSON S.G. (1951)
Cleidocranial dysostosis. (Report of Two Cases).
OS.OM.OP., 4(July) : 1201-1213.

ARMITAGE G.C. (1980)
Cementum.
In Orban's Oral Histology and Embryology (9th Ed.).
Ch 6, p 180-203.
Ed: S.N. Bhaskar. The C.V. Mosby Company.

BAER R.N., LIEBERMAN J.E. (1959)
Observation on some genetic characteristics of the periodontium in three strains of inbred mice.
OS.OM.OP., 12(7) : 820-829.

BAILEY A.J. (1976)
Discussion.
In The Eruption and Occlusion of Teeth (Colston Papers). p 306.
Eds: D.F.G. Poole, M.V. Stack. Butterworths.

BARRETT P.O. (1970)
Cleidocranial dysostosis : report of a case.
J. Oral Surg., 28(9) : 679-681.

BARTSOCAS C.S. (1982)
An Introduction to Ancient Greek Genetics & Skeletal Dysplasias.
In Skeletal Dysplasias: Proceedings of the 3rd Int. Clin. Genetics Seminar, Greece. p 3-13.
Eds: C.S. Papadatos, C.S. Bartsocos. Alan R. Liss Inc., N.Y.

BEIGHTON P. (1978)
Miscellaneous skeletal dysplasias.
In Inherited Disorders of the Skeleton.
p 57-79. Churchill Livingstone.

BERENDT H.C. (1951)
Report on a case of multiple supernumerary teeth.
OS.OM.OP., 4(July) : 1132-1135.

BERKOVITZ B.K.B., THOMAS N.R. (1969)
Unimpeded eruption in the root-resected lower incisor of the rat with a preliminary note on root transection.
Arch. Oral Biol., 14(7) : 771-780.

BERKOVITZ B.K.B. (1972)
The effect of preventing eruption on the proliferative basal tissues of the rat lower incisor.
Arch. Oral Biol., 17(9) : 1279-1288.

BERKOVITZ B.K.B., THOMSON P. (1973)
Observations on the aetiology of supernumerary upper incisors in the albino ferret (Mustela putorius)
Arch. Oral Biol., 18(4) : 457-463.

BERKOVITZ B.K.B. (1976)
Theories of tooth eruption.
In The Eruption and Occlusion of Teeth (Colston Papers).
p 193-204.
Eds: D.F.G. Poole, M.V. Stack. Butterworths.

BERNICK S., GRANT D.A. (1982)
Development of the periodontal ligament.
In The Periodontal Ligament in Health & Disease
Ch 9, p 197-213.
Eds: B.K.B. Berkovitz, B.J. Moxham, H.N. Newman.
Pergamon Press.

BHASKAR S.N. (1980)
Maxilla and mandible (alveolar process).
In Orban's Oral Histology and Embryology
(9th Ed.). Ch 8, p 240-260. Ed: S.N. Bhaskar.
The C.V. Mosby Company.

BHUSSRY B.R. (1980)
Development and growth of teeth.
In Orban's Oral Histology and Embryology
(9th Ed.). Ch 2, p 24-45. Ed: S.N. Bhaskar.
The C.V. Mosby Company.

BILLEWICZ W.Z., McGREGOR I.A. (1975)
Eruption of permanent teeth in West African (Gambian)
children in relation to age, sex and physique.
Ann. Hum. Biol., 2 : 117-124.

BISHOP R.G. (1984)
Dental management of cleido-cranial dysostosis.
Case Report.
Aust. Dent. J., 29(1) : 1-4.

BIXLER D. (1976)
Heritable disorders affecting cementum and the periodontal
structure.
In Oral Facial Genetics. Ch 9, p 262-287.
Eds: R.E. Stewart, G.H. Prescott. The C.V.
Mosby Company.

BJORN H., GRAHNEN H. (1966)
Cleido-cranial Dysostosis.
Odontol. Revy., 17 : 167-175.

BLOOM W., FAWCETT D.W. (1975)
Bone.
In A Textbook of Histology (10th ed.).
Ch 10, p 244-287. W.B. Saunders Company.

BOSKEY A.L., BULLOUGH P.G., DMITROVSKY E. (1980)
The Biochemistry of the Mineralization Front.
In Bone Histomorphometry. Third International Workshop.
p 61-67. Societe Nouvelle de Publications Medicales et
Dentaires, Paris.

BRAILSFORD J.F. (1953)
The Radiology of Bones and Joints
p 32. Williams & Wilkins Co., Baltimore.

BRODIE A.G. (1955)
The Behaviour Of The Cranial Base And Its Components As Revealed By Serial Cephalometric Roentgenograms.
Angle Orth., 25(3) : 148-160.

BROWN K.S. (1983)
Evolution and Development of the Dentition.
Birth Defects, 19(1) : 29-66.

BURZYNSKI N.J., ESCOBAR V.H. (1983)
Classification and Genetics of Numeric Anomalies of Dentition.
Birth Defects, 19(1) : 95-106.

CAHILL D.R. (1969)
Eruption pathway formation in the presence of experimental tooth impaction in puppies.
Anat. Rec., 164(May) : 67-77.

CAHILL D.R. (1970)
The histology and rate of tooth eruption with and without temporary impaction in the dog.
Anat. Rec., 166(Feb) : 225-237.

CARTER C.O. (1973)
Cleidocranial Dysostosis in the Iliad.
The Lancet, 2(Aug 11) : 323.

CHAPNICK L.A., MAIN J.H.P. (1976)
Cementum in cleidocranial dysostosis.
J. Canad. Dent. Ass., 42(3) : 139-142.

CHIBA M. (1968)
Movement during unimpeded eruption of the position of cells, and of material incorporating tritiated proline, in the lingual periodontal membrane of the mandibular incisors of adult male mice.
J. Dent. Res., 47 : 986 (Abstract).

CHIBA M., OHSHIMA S., TAKIZAWA K. (1983)
The effect of a microfilament-disrupting drug, cytochalisin B, on 6-hourly and daily eruption rates of the rate mandibular incisor.
Arch. Oral Biol., 28(7) : 651-653.

COHN S.A. (1957)
Development of the Molar Teeth in the Albino Mouse.
Am J. Anat., 101(2) : 295-319.

DAHL E. (1976)
Genetic Aspects of Some Orofacial Anomalies.
Acta Otolaryngol., 82(3-4) : 226-229.

DANN J.J., CRUMP P., RINGENBERG Q.M. (1980)
Vertical maxillary deficiency with cleidocranial dysplasia.
Am. J. Orth., 78(5) : 564-574.

DAVIS P.L. (1954)
Deafness and cranio-cleido-dysostosis.
Arch. Otolaryngol., 59(May) : 602-603.

DELGADO H., HABICHT J.P., YARBROUGH C., LECHTIG A., MARTORELL R., MALINA R.M., KLEIN R.E. (1975)
Nutritional status and timing of deciduous tooth eruption.
Am J. Clin Nutr., 28(3) : 216-224.

DEMIRJIAN A. (1978)
Dentition.
In Human Growth. 2. Postnatal Growth. Ch V, p 413-444.
Eds: F. Faulker, J.M. Tanner. Plenum Press.

DI BIASE D.D. (1971)
Mucous membrane and delayed eruption.
Dent. Practit. & Dent. Rec., 21(7) : 241-250.

DOUGLAS B.L., GREENE H.J. (1969)
Cleidocranial dysostosis: report of a case.
J. Oral Surg., 27(1) : 39-43.

EL LOZY M., REED R.B., KERR G.R., BOUTOURLINE E., TESI G., GHAMRY M.T., STARE F.J., KALLAL Z., TURKI M., HEMAIDAN N. (1975)
Nutritional correlates of child development in southern Tunisia. IV: Relation of deciduous dental eruption to somatic development.
Growth, 39(2) : 209-221.

ELOMAA E., ELOMAA M. (1967)
Orthodontic Treatment of a Case of Cleidocranial Dysostosis.
Suom. Hammaslaak Toim, 63(3-4) : 139-149.

EPSTEIN J.A., EPSTEIN B.S. (1967)
Deformities of the skull surfaces in infancy and childhood.
J. Pediatr., 70(4) : 636-647.

ETESON D.J., SILLENCE D.O., LACHMAN R.S., RIMOIN D.L. (1985)
The mouse skeletal mutants: models for the human skeletal dysplasias.
In Normal and Abnormal Bone Growth: Basic and Clinical Research. p 411-151. Alan R. Liss Inc., N.Y.

EVENTOV I., REIDER-GROSSWASSER I., WEISS S., LEGUM C., SCHORR S. (1979)
Cleidocranial Dysplasia : A Family Study.
Clin. Radiol., 30(3) : 323-328.

FARDY M.J. (1984)
Cleidocranial Dysostosis : Some Problems in the Dental Management of Occlusion.
Dental Update, 11(6) : 363-368.

FARRER E.L., VAN SICKELS J.E. (1983)
Early Surgical Management of Cleidocranial Dysplasia : A Preliminary Report.
J. Oral Maxillofac. Surg., 41(8) : 527-529.

FERNEX E., CHOUVET G., FOURQUEZ M. (1974)
Some Observations on Cleido-cranial Dysostosis and Craniostenosis.
Trans. Eur. Orth. Soc., 91-96.

FITCHET S.M. (1929)
Cleidocranial dysostosis: hereditary and familial.
J. Bone & Jt. Surg., 11(New Series) : 838-865.

FITZWILLIAMS D.C.L. (1910)
Hereditary Cranio-cleido-dysostosis.
The Lancet: (ii) : 1466-1475.

FLEISCH H. (1964)
Role of nucleation and inhibition in Calcification.
Clin. Orthop., 32 : 170-180.

FLYNN D.M. (1966)
Family with Cleido-cranial Dysostosis Showing Normal and Abnormal Calvicles.
Proc. Royal Soc. Med., 59(May) : 491-492.

FONS M. (1969)
Ear malformations in cleidocranial dysostosis.
Acta oto-laryngol., 67(May) : 483-489.

FOREST D., FONTAINE J.M. (1967)
Cleidocranio-dental dysostosis: a case report.
J. Can. Dent. Ass., 33(3) : 141 (English Abstract).

FORLAND M. (1962)
Cleidocranial Dysostosis.
Am. J. Med., 33(Nov) : 792-799.

FRANCKE U. (1980)
Cytogenetic Approaches to Mouse Models of Human Genetic Diseases.
Workshop on needs for new animal models of human disease.
Am. J. Path., 101 (35) Supplement Dec : S41-S51.

FROMMER H.H., LAPEYROLERIE F.M. (1964)
Two Case Reports of Cleidocranial Dyostosis [sic].
N.Y. Journal of Dent., 34(3) : 103-107.

GARDNER E. (1968)
The Embryology of the Clavicle.
Clin. Orthop. & Related Res., 58(May-June) : 9-16.

GARDNER E. (1971)
Osteogenesis in the Human Embryo and Fetus.
In The Biochemistry and Physiology of Bone. Vol III.
Ch 2, p 77-118. Ed: G.H. Bourne. Academic Press.

GARN S.M., SANDUSKY S.T., NAGY J.M., TROWBRIDGE F.L. (1973)
Negro-caucasoid differences in permanent tooth emergence at a constant income level.
Arch. Oral. Biol., 18(5) : 609-615.

GAUNT W.A. (1966)
The disposition of the developing cheek teeth in the albino mouse.
Acta Anat., 64 : 572-585.

GAY S., RHODES R.K. (1980)
Immunohistochemical Demonstration of the Genetically Distinct Collagen Types in Human Skeletal Tissues.
In Bone Histomorphometry. Third International Workshop.
p 97-101. Eds: W.S.S. Lee, A.M. Parfitt. Societe Nouvelle De Publications Medicales et Dentaires, Paris.

GIACCAI L., SALAAM M., ZELLWEGER H. (1954)
Cleidocranial dysostosis with osteopetrosis.
Acta Radiol., 41(4) : 417-424.

GIBSON D.A., CARROLL N. (1970)
Congenital pseudoarthrosis of the clavicle.
J. Bone & Jt Surg., 52B(4) : 629-643.

GLASS D. (1969)
The recognition of bilateral craniofacial deformities.
Brit. Soc. Study Orth., 70 : 105-116.

GOODMAN R.M., TADMOR R., ZARITSKY A., BECKER S.A. (1975)
Evidence for an autosomal recessive form of cleidocranial dysostosis.
Clin. Genet., 8 : 20-29.

GORLIN R.J., PINDBORG J.J. (1976)
Cleidocranial Dysplasia.
In Syndromes of the Head and Neck. (2nd Ed)
Ch 33, p 180-184. McGraw Hill Inc.

GREIG D.M. (1933)
Neanderthaloid skull presenting features of cleidocranial dysostosis and other pecularіarities.
Edinburgh Med. J., 40(Nov) : 497-557.

GRUNEBERG H. (1935)
A New Sub-Lethal Colour Mutation in the House Mouse.
Proc. Royal Soc. Lond., 118B : 321-345.

GRUNEBERG H. (1937)
The relations of endogenous and exogenous factors in bone and tooth development. (The teeth of the grey-lethal mouse).
J. Anat., 71(2) : 236-244.

GRUNEBERG H. (1965)
Genes and genotypes affecting the teeth of the mouse.
J. Embryol. exp. Morph., 14(2) : 137-159.

GRUNEBERG H. (1966)
The molars of the tabby mouse, and a test of the "single-active X- chromosome" hypothesis.
J. Embryol. exp. Morph., 15(4) : 223-244.

GRUNEBERG H. (1971)
The tabby syndrome in the mouse.
Proc. Royal Soc. Lond., 179B : 139-156.

HALL B.D. (1982)
Syndromes and Situations Associated With Congenital Clavicular Hypoplasia or Agenesis.
In Skeletal Dysplasias: Proceedings of the 3rd Int. Clin. Genetics Seminar, Greece. p 279-288.
Eds: C.S. Papadatos, C.S. Bartsocas.
Alan R. Liss Inc., N.Y.

HALL R.K., HYLAND A.L. (1978)
Combined surgical and orthodontic management of the oral abnormalities in children with cleidocranial dysplasia.
Int. J. Oral Surg., 7(4) : 267-273.

HANCOX N.M. (1972)
Calcification of Bone.
In Biology of Bone. Ch 8, p 82-92.
Cambridge University Press.

HARRIS R.J., GASTON G.W., AVERY J.E., McCUEN J.M. (1977)
Mandibular prognathism and apertognathia associated with cleidocranial dysostosis in a father and son.
OS.OM.OP., 44(6) : 830-836.

HASLER J.F., VANDERMER J. (1974)
Cleidocranial Dysplasia.
Birth Defects, 10(2) : 524-6.

HAWKINS H.B., SHAPIRO R., PETRILLO C.J. (1975)
The Association of Cleidocranial Dysostosis With Hearing Loss.
Am. J. Roent., 125(4) : 944-947.

HAY M.F. (1961)
The development in vivo and in vitro of the lower incisor and molars of the mouse.
Arch. Oral Biol., 3(2) : 86-109.

HELD J.R. (1983)
Appropriate animal models.
In The role of animals in biomedical research p 13-19. Ed: J.A. Sechzer. Annals of the New York Academy of Sciences, N.Y.

HERNDON C.N. (1951)
Cleidocranial Dysostosis
Am. J. Human Genetics, 3(4) : 314-324.

HITCHIN A.D., FAIRLEY J.M. (1974)
Dental Management in Cleido-cranial Dysostosis.
Brit. J. Oral Surg., 12(1) : 46-55.

HITCHIN A.D. (1975)
Cementum and Other Root Abnormalities of Permanent Teeth in Cleidocranial Dysostosis.
Brit. Dent. J., 139(Oct 21) : 313-318.

HOPKINS R. (1979-1980)
Cleido-cranial dysostosis - a case report.
Brit. J. Oral Surg., 17 : 232-243.

HURMERINTA K. (1982)
Cell interactions during tooth development.
Proc. Fin. Dent. Soc., 78(Supl V) : 1-73.

HUTTON C.E., BIXLER D., GARNER L.D. (1981)
Cleidocranial dysplasia - treatment of dental problems.
J. Dent. Child., 48(6) : 456-462.

HYLTON R.P., ALBRIGHT J.E. (1970)
Cleidocranial dysostosis : report of case.
J. Oral Surg., 28(9) : 682-685.

ILLIC D. (1980)
Cleidocranial Dyostotis [sic].
Proc. Europ. Prosth Assoc., 4th Annual Meeting, Warsaw, Poland : 101-105.

JACKSON W.P.U. (1951)
Osteo-dental dysplasia (cleidocranial dysostosis).
Acta med. Scand., 139(3) : 292-303.

JACOBSON A. (1975)
The "Wits" appraisal of jaw disharmony.
Am. J. Orth., 67(2) : 125-138.

JACOBSON A. (1983)
The Physiology of Tooth Eruption.
Birth Defects, 19(1) : 67-82.

JAFFEE I.S. (1968)
Congenital Shoulder - Neck - Auditory Anomalies.
Laryngoscope, 78(Dec) : 2119-2139.

JARVINEN S. (1976)
Formation of Multiple Supernumerary Teeth in Early Teenage. (A Case Report).
Proc. Finn. Dent. Soc., 72(4) : 132-134.

JARVINEN S. (1980A)
Dental findings in three cases of cleidocranial dysostosis.
Proc. Finn. Dent. Soc., 76(2) : 56-61.

JARVINEN S. (1980B)
Relation of the SNA angle to the saddle angle.
Am. J. Orth., 78(6) : 670-673.

JARVINEN S. (1981)
Cephalometric findings in three cases of cleidocranial dysostosis.
Am. J. Orth., 79(2) : 184-191.

JARVIS J.L., KEATS T.E. (1974)
Cleidocranial Dysostosis. (A Review of 40 New Cases).
Am. J. Roent., 121(1) : 5-16.

JORGENSON R.J., MORGENSTEIN R.S., BECKER M.A. (1971)
Cleidocranial Dysplasia (Formerly Cleidocranial Dysostosis) with Dental Anomalies (Two Cases).
Birth Defects, 7(7) : 289-290.

KALLIALA E., TASKINEN P.J. (1962)
Cleidocranial Dysostosis. Report of Six Typical Cases and One Atypical Case.
OS.OM.OP., 15(7) : 808-822.

KARDOS T.B., SIMPSON L.O. (1979)
A theoretical consideration of the periodontal membrane as a collagenous thixotropic system and its relationship to tooth eruption.
J. Perio. Res., 14(5) : 444-451.

KELLY E., NAKAMOTO R.Y. (1974)
Cleidocranial dysostosis - A prosthetic problem.
J. Pros. Dent., 31(5) : 518-526.

KERLEY M.A., KOLLAR D.J. (1977)
Supernumerary Tooth Formation in Mouse Molar Transplants.
J. Dent. Res., 56(11) : 1344 (Annotation).

KEYS J. (1984)
Tooth development and bone resorption in microphthalmic (M1/M1) mice.
Aust. Dent. J., 29(4) : 261 (Abstract).

KIRSON L.E., SCHEIBER R.E., TOMARO A.J. (1982)
Multiple Impacted Teeth in Cleidocranial Dysostosis.
OS.OM.OP., 54(2) : 604.

KJELLGREN B. (1952)
Bite conditions and treatment in cases of cleido-cranial dysostosis.
Int. Dent J., 3(1) : 83-85.

KOCH P.E., HAMMER W.B. (1978)
Cleidocranial dysostosis : review of the literature and report of case.
J. Oral Surg., 36(1) : 39-42.

KOLLAR E.J., BAIRD G.R. (1970A)
Tissue interactions in embryonic mouse tooth germs.
I: Reorganisation of the dental epithelium during tooth-germ reconstruction.
J. Embryol. exp. Morph., 24(1) : 159-171.

KOLLAR E.J., BAIRD G.R. (1970B)
Tissue interactions in embryonic mouse tooth germs.
II: The inductive role of the dental papilla.
J. Embryol. exp. Morph., 24(1) : 173-186.

KOLLAR E.J. (1978)
The Role of Collagen During Tooth Morphogenesis : Some Genetic Implications.
In Development, Function and Evaluation of Teeth. p 1-12.
Eds: P.M. Butler, K.A. Joysey. Academic Press.

KREIBORG S., LETH JENSEN B., BJORK A., SKIELLER V. (1981)
Abnormalities of the cranial base in cleidocranial dysostosis.
Am. J. Orth., 79(5) : 549-557.

LASKER G.W. (1946)
The inheritance of cleidocranial dysostosis.
Human Biol., 18(2) : 81-126.

LEE M.M.C., CHAN S.T., LOW W.D., CHANG K.S.F. (1965)
Eruption of the permanent dentition of southern Chinese children in Hong Kong.
Arch. Oral Biol., 10(5) : 849-861.

LEVIN M.P. (1972)
Multiple Impacted Teeth in Cleidocranial Dysostosis.
OS.OM.OP., 33(4) : 669.

LEWIS S.E. (1984)
The mouse as a model system for mutation testing and evaluation of risk in mammals.
Terat. Carcinog. Mutag., 4 : 129-136.

LLOYD-ROBERTS G.C., APLEY A.G., OWEN R. (1975)
Reflections Upon the Aetiology of Congenital Pseudoarthrosis of the Clavicle.
J. Bone & Jt. Surg., 51B(1) : 24-29.

LUBOWITZ A.H. (1968)
Cleidocranial Dysostosis: A Case Report.
Angle Orth., 38(2) : 150-154.

LUBOWITZ A.H. (1975)
Cleidocranial dysostosis (Letter to Editor).
Am. J. Orth., 67(2) : 217.

LUMSDEN A.G.S. (1979)
Pattern formation in the molar dentition of the mouse.
J. Biol. buccale, 7(1) : 77-103.

McCURDY J., BAER R.W. (1923)
Hereditary Cleidocranial Dysostosis.
J.A.M.A., 81(1) : 9-11.

MAGNUS W.W., SANDS N.R. (1974)
Cleidocranial dysostosis.
Am. J. Orth., 65(6) : 638-643.

MARKS S.C., CAHILL D.R. (1984)
Experimental study in the dog of the non-active role of the tooth in the eruptive process.
Arch. Oral Biol., 29(4) : 311-322.

MARIE P., SAINTON P. (1898)
On Hereditary Cleido-cranial Dysostosis.
(Trans. E.M. Bick, of the original: Sur la dysostose cleido-cranienne herediataire.
Rev. neurol., 6 : 835, 1898).
Clin. Orthop. & Related Res., 58(May-June) : 5-7.

MAROTEAUX P. (1983)
International nomenclature of constitutional diseases of bone.
Annales de Radiologie 26 : 457-462.

MAW R.B. (1978)
Cleidocranial dysostosis: report of case.
J.A.D.A., 96(2) : 306-309.

MELSEN B. (1974)
The cranial base.
Acta. odont. Scand., 32(Suppl.62) : 1-126.

MIGLIORISI J.A., BLENKINSOPP P.T. (1980)
Oral Surgical Management of Cleidocranial Dysostosis.
Brit. J. Oral Surg., 18(3) : 212-220.

MILLER R., SAKAMOTO E., ZELL A., ARTHUR A., STRATIGOS G.T. (1978)
Cleidocranial dysostosis: a multidisciplinary approach to treatment.
J.A.D.A., 96(2) : 296-309.

MONASKY G.E., WINKLER S., ICENHOWER J.B., RUANE A.S., FIELDING A.F., DEFRANCISIS D. (1983)
Cleidocranial Dysostosis - Two Case Reports.
N.Y. State Dent. J., 49(4) : 236-238.

MORGAN G.A., MORGAN P.R., CROUCH L.D.S. (1970)
Recurring mandibular supplemental premolars.
Oral Surg., 30(4) : 501-504.

MORIARTY J.A., KLINGMAN W.O. (1962)
Congenital and prenatal diseases.
In Clinical Neurology (2nd Ed.) Vol 4. Ch 41, p 1985-1986.
Ed: A.B. Baker. Hoeber-Harper.

MOSS-SALENTIJN L. (1978)
Vestigal Teeth in the Rabbit, Rat and Mouse; their Relationship to the Problem of Lacteal Dentitions.
In Development, Function and Evolution of Teeth. p 13-29.
Eds: P.M. Butler, K.A. Joysey. Academic Press.

MOXHAM B.J. (1981)
The effects of section and stimulation of the cervical sympathetic trunk on eruption of the rabbit mandibular incisor.
Arch. Oral Biol., 26(11) : 887-891.

MOXHAM B.J., BERKOVITZ B.K.B. (1982)
The periodontal ligament and physiological tooth movement.
In The Periodontal Ligament in Health & Disease.
Ch 10, p 215-247.
Eds: B.K.B. Berkovitz, B.J. Moxham,, N.H. Newman.
Pergamon Press.

MULLER E.E. (1965)
Transplantation of Teeth in Cleidocranial Dysostosis.
Transactions 2nd Congress Int. Assoc. Oral Surgeons : 375-379.

NORDENRAM A. (1971)
Autotransplantation of teeth in cleidocranial dysostosis.
Odont. Revy., 22 : 363-370.

NYHAM W.L. (1973)
Malformation Syndromes in Human Genetic Disease.
Plast. Reconst. Surg., 52(3) : 237-245.

OATIS G.W., ROBERTSON G.R., SUGG W.E., FIRTELL D.N. (1975)
Cleidoncranial dysostosis with mandibular cyst.
OS.OM.OP., 40(1) : 62-67.

OHMAN I., OHMAN A. (1980)
The eruption tendency and changes of direction of impacted teeth following surgical exposure.
OS.OM.OP., 49(5) : 383-389.

OKSALA E., FAGERSTROM G. (1971)
A Two-stage Autotransplantation of 14 Teeth in a Patient with Cleidocranial Dysostosis.
Suom. Hammaslaak Toim, 67(6) : 333-338.

OSBORN J.W. (1978)
Morphogenetic gradients : fields versus clones.
In Development, Function and Evolution of Teeth.
p 171-201. Eds: P.M. Butler, K.A. Joysey, Academic Press.

PATTERSON D.F., HASKINS M.E., JEZYK P.F. (1982)
Models of Human Genetic Disease in Domestic Animals.
Advances in Human Genetics, Vol. 12. Ch 4, p 163-339.
Eds: Harris & Hirschhorn. Plenum Publishing Co.

PERERA K.A., TONGE C.H. (1981)
Fibroblast cell proliferation in the mouse molar periodontal ligament.
J. Anat., 133(Part 1) : 77-90.

PITARU S., MICHAELI Y., ZAJICEK G., WEINREB M.N. (1976)
Role of Attrition and Occlusion Contact in the Physiology of the Rat Incisor :
X : The Part Played by the Periodontal Ligament in the Eruptive Process.
J. Dent. Res., 55 : 819-824.

POU J.W. (1971)
Congenital Anomalies of the Middle Ear : Presentation of Two Cases.
Laryngoscope, 81(June) : 831-839.

PRITCHARD J.J. (1972)
General Histology of Bone.
In The Biochemistry and Physiology of Bone.
Vol I. Ch 1, p 1-20. Ed: G.H. Bourne. Academic Press.

PROFFITT W.R., VIG K.W.L. (1981)
Primary failure of eruption : A possible cause of posterior open-bite.
Am. J. Orth., 80(2) : 173-190.

RIMOIN D.L. (1975)
The chondrodystrophies.
Advances in Hum. Genet., 5 : 1-118.

RIMOIN D.L. (1978)
International Nomenclature of constitutional diseases of bone.
J. Pediatr., 93(4) : 614-616.

RIMOIN D.L. (1979)
Variable Expressivity in the Skeletal Dysplasias.
Birth Defects, 15(5B) : 91-112.

RIMOIN D.L., SILLENCE D.O. (1981)
Chondro-Osseous Morphology and Biochemistry in the Skeletal Dysplasias.
Birth Defects, 17(1) : 249-265.

RIMOIN D.L., SILLENCE D.O. (1982)
The skeletal dysplasias : nomenclature, classification, and clinical education.
In Heritable Disorders of Connective Tissue
Ch 27, p 324-332. Eds: W. Akeson, P. Bornstein, M. Glimcher. The C.V. Mosby Company.

ROCK W.P. (1969)
Cleido-cranial Dysostosis : A Case Report.
Brit. Dent J., 126(Jan 21) : 85-57.

RUCH J.V. (1983)
Epithelial-mesenchymal interactions in tooth germs : mechanisms of differentiation.
J. Biol. buccale, 11(3) : 173-193.

RUSHTON M.A. (1937A)
The Dental Condition in Cleido-Cranial Dysostosis.
Dent. Rec., 57 : 554-561.

RUSHTON M.A. (1937B)
The Failure of Eruption in Cleido-Cranial Dysostosis.
Brit. Dent. J., 63(11) : 641-645.

RUSHTON M.A. (1938)
Dental abnormalities in cleido-cranial dysostosis.
J. Hered., 29(4) : 129-135.

RUSHTON M.A. (1956)
An Anomaly of Cementum in Cleidocranial Dysostosis.
Brit. Dent J., 100(3) : 81-83.

RUSSELL R.G.E., FLEISCH H. (1970)
Inorganic pyrophosphate and pyrophosphatases in calcification and calcium homeostasis.
Clin. Orthop., 69 : 101-107.

SAARENMAA L. (1951)
The origin of supernumerary teeth.
Acta Odont. Scand., 9(3-4) : 293-301.

SALINAS C.F. (1982)
Orodental Findings and Genetic Disorders.
Birth Defects, 18(1) : 79-120.

SANDLER H.C. (1951)
Cleidocranial Dysostosis in Four Siblings.
Am. J. Orth., 37(8) : 584-593.

SCHWARTZ J.H. (1984)
Supernumerary teeth in anthropoid primates and models of tooth development.
Arch. Oral Biol., 29(10) : 833-842.

SEARLE A.G. (1968)
Comparative genetics of coat colour in mammals.
(page no/.s quoted in text).
Logos Press Ltd., London.

SELBY P.B., SELBY P.R. (1977)
Gamma - Ray - Induced Dominant Mutations That Cause Skeletal Abnormalities in Mice.
I: Plan, summary of results and discussion.
Mutation Research, 43 : 337-375.

SELBY P.B., SELBY P.R. (1978)
Gamma - Ray - Induced Dominant Mutations That Cause Skeletal Abnormalities in Mice.
II: Description of proved mutations.
Mutation Research, 51 : 199-236.

SELDIN H.M., SELDIN S.D., RAKOWER W. (1950)
Cleidocranial dysostosis.
J. Oral Surg., 8(July) : 236-241.

SHOKEIR M.H.K. (1974)
Complete failure of eruption of all permanent teeth : An autosomal dominant disorder.
Clin. Genet., 5 : 322-326.

SHORT D.W. (1979)
A case of craniocleidal dysostosis presenting with vascular complications.
Brit. J. Surg., 66(8) : 596-598.

SILLENCE D.O., RIMOIN D.L., LACHMAN R. (1978)
Neonatal Dwarfism.
Pediatr. Clin. Nth. Am., 25(3) : 453-483.

SILLENCE D.O., RIMOIN D.L. (1982)
Chondroosseous morphology in the skeletal dysplasias.
In Heritable Disorders of Connective Tissue.
Ch 28, p 333-352. Eds: W. Akeson, P. Bornstein, M. Glimcher. The C.V. Mosby Company.

SILLENCE D., RITCHIE H., KOLTAI A., McCREDIE J., MAHANT J., SELBY P. (1984)
The radiology of cleidocranial dysplasia in the laboratory mouse.
Vet. Radiol., 25 : 31.

SILLENCE D.O., RITCHIE H., SELBY P. (1985)
The cleidocranial dysplastic mutant in the mouse.
In Press.

SILLENCE D.O. (1985)
Congenital malformations and dysmorphic syndromes.
In Press.

SLOAN P. (1982)
Structural organization of the fibres of the periodontal ligament.
In The Periodontal Ligament in Health & Disease.
Ch 3, p 51-72. Eds: B.K.B. Berkovitz, B.J. Moxham, H.N. Newman. Pergamon Press.

SMITH N.H.H. (1968)
A histological study of cementum in a case of cleidocranial dysostosis.
OS.OM.OP., 25(3) : 470-478.

SMYLSKI P.T., WOODSIDE D.G., HARNETT B.E. (1974)
Surgical and orthodontic treatment of cleidocranial dysostosis.
Int. J. Oral Surg., 3(6) : 380-385.

SOFAER J.A. (1969)
Aspects of the Tabby - crinkled - downless syndrome. Part I.
J. Embryol. exp. Morph., 22(2) : 181-205.

SOFAER J.A., SHAW J.H. (1971)
The genetics and development of fused and supernumerary molars in the rice rat.
J. Embryol. exp. Morph., 26(1) : 99-109.

SOFAER J.A. (1975A)
Genetic variation and tooth development.
Brit. Med. Bull., 31(2) : 107-110.

SOFAER J.A. (1975B)
Interactions between tooth germs and the adjacent dental lamina in the mouse.
Arch. Oral. Biol., 20(1) : 56-61.

SOFAER J.A. (1977)
The teeth of the "sleek" mouse.
Arch. Oral. Biol., 22(4) : 299-301.

SOULE A.B. (1946)
Mutational dysostosis (cleidocranial dysostosis).
J. Bone & Jt. Surg., 28(1) : 81-102.

SPRANGER J., BENIRSCHKE K., HALL J.G., LENZ W., LOWRY R.B., OPITZ J.M., PINSKY L., SCHWARZACHER H.G., SMITH D.W. (1982)
Errors of morphogenesis : Concepts and terms.
J. Pediatr., 100(1) : 160-165.

SRIVASTAVA K.K., PAI R.A., KOLBHANDARA M.P., KANT K. (1971)
Cleidocranial dysostosis. (A clinical and cytological study).
Clin. Genet., 2 : 104-110.

STEEDLE J.R., PROFITT W.R. (1985)
The pattern and control of eruptive tooth movements.
Am. J. Orth., 87(1) : 56-66.

STEWART R.E. (1976)
Genetic factors in craniofacial morphogenesis.
In Oral Facial Genetics. Ch 2, p 46-80.
Eds: R.E. Stewart, G.H. Prescott. The C.V. Mosby Company.

STIFF R.H., LALLY E.T. (1969)
Cleidocranial dysostotis. (Report of a case).
OS.OM.OP., 27(2) : 202-207.

TAN K.L., TAN L.K.A. (1981)
Cleidocranial Dysostosis in Infancy.
Pediatr. Radiol., 11 : 114-116.

THESLEFF I., BARRACH H.J., FOIDART J.M., VAHERI A., PRATT R.M. MARTIN G.R. (1981)
Changes in the Distribution of Type IV Collagen, Laminin, Proteoglycan, and Fibronectin during Mouse Tooth Development.
Develop. Biol., 81(1) : 182-192.

THOMA K.H., GOLDMAN H.M. (1960)
Anomalies and diseases of the head and jaws: Cleidocranial Dysostosis.
In Oral Pathology (5th Ed). p 608-615.
The C.V. Mosby Company.

THOMAS N.R. (1965)
The Effect of Inhibition of Collagen Maturation on Eruption in Rats.
J. Dent. Res., 44(6, Suppl.) 1159 (Abstract).

THOMAS N.R. (1976)
Collagen as the generator of tooth eruption.
In The Eruption and Occlusion of Teeth (Colston Papers). p 290-301.
Eds: D.F.G. Poole, M.V. Stack. Butterworths.

THOMS J. (1958)
Cleidocranial dysostosis : report of two cases with special characteristics.
Acta Radiol., 50(Dec) : 514-520.

THOMSEN G., GUTTADAURO M. (1952)
Cleidocranial dysostosis associated with osteosclerosis and bone fragility.
Acta Radiol., 37(June) : 559-567.

TRIMBLE L.D., WEST R.A., McNEILL R.W. (1982)
Cleidocranial dysplasia : comprehensive treatment of the dentofacial abnormalities.
J.A.D.A., 105(4) : 661-666.

TUCKER K.M. (1966)
Cleidocranial dysostosis : dental treatment of a patient.
Dent. Survey : 42(June) : 41-44.

VOGEL F., MOTULOKY A.G. (1979)
Human Genetics : Problems and Approaches.
Ch 3, p 82-188. Springer Verlag.

WALTER J.D. (1967)
Osteo-Dental Dysplasia.
Dental Mag. Oral. Topics., 86(1) : 16-19.

WEINTRAUB G.S., YALISOVE I.L. (1978)
Prosthodontic therapy for cleidocranial dysostosis : report of case.
J.A.D.A., 96(2) : 301-305.

WEISS L. (1964)
Squamous cell carcinoma of face and maxilla combined with cleidocranial dysostosis.
J. Oral Surg. Anaesth. & Hosp. D. Serv.
22(May) : 249-251.

WILBANKS J.L. (1964)
Cleidocranial Dysostosis. (Report of a Case).
OS.OM.OP., 17(6) : 797-801.

WILLIAMS T.H. (1962)
Cleidocranial dysostosis : a progress report on two cases.
J.A.D.A., 64(2) : 201-208.

WINCH R., ARMSTRONG C.J. (1962)
Cleido-cranial dysostosis.
Aust. Dent. J., 7(3) : 205-253.

WINKLER S., JUNG E.L. (1971)
Cleidocranial dysostosis : Report of a case.
Dental Digest, 77(1) : 24-28.

WINKLER S., DRINNAN A.J., PUENGPHOB R. (1976)
Cleidocranial Dysostosis. (A review and Case Report).
N.Y. State Dent. J., 42(1) : 24-26.

WINTER G.R. (1943)
Dental conditions in cleidocranial dysostosis.
Am. J. Orth. & Oral Surg., 29(2) : 61-89.

WINTHER J.E., KHAN M.W. (1972)
Cleidocranial dysostosis : report of 4 cases.
Dent. Pract. Dent. Rec., 22(6) : 215-219.

WOLPOWITZ A., MATISONN A. (1974)
A Comparative Study of Pycnodysostosis, Cleidocranial Dysostosis, Osteopetrosis and Acro-osteolysis.
Sth. African Med. J., 48(May 18) : 1011-1018.

YOUNG R.S. (1983)
Genetic Heterogeneity : Implications and Methods of Detection.
Birth Defects, 19(1) : 145-153.

YUNIS E., VARON H. (1980)
Cleidocranial Dysostosis, Severe Micrognathism, Bilateral Absence of Thumb and First Metatarsal Bone, and Distal Aphalangia. (A New Genetic Syndrome).
Am. J. Dis. Child., 134(7) : 649-653.

ZANDER H.A. (1958)
Continuous cementum apposition.
J. Dent.Res., 37(1) : 44 (Abstract).