DENTAL AND SKELETAL MATURATION IN TRISOMY 21 (DOWN'S SYNDROME)

A Thesis

Presented to

The Faculty of Graduate Studies and Research

University of Manitoba

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

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by

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March 1973

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by

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ABSTRACT

Previous studies of individuals affected with trisomy 21 have indicated that the maturation process is altered by this condition. The purpose of the present cross-sectional investigation was to quantitate maturation of the skeletal and dental systems in a group of 295 individuals karyotyped and found to have trisomy 21.

A method of calculating dental eruption age and dental calcification age for each subject was developed. Skeletal maturation was measured from radiographs of the hand and wrist using the atlas technique of Greulich and Pyle (1959) as well as the single bone technique of Tanner, Whitehouse, and Healy (1961). Standing height was recorded for each subject, and mandibular length was measured from the lateral cephalometric radiographs.

Dental eruption was found to be delayed in the trisomy 21 group. Dental calcification was delayed as well, but to a lesser degree. Development of the carpal bones progressed relatively normally in the trisomy 21 group but epiphyseal maturation did not. The epiphyses of the hand and wrist were initially retarded but progressed in

maturation with advancing chronological age much more rapidly than did the control group so that apparent maturity of these areas was achieved in the trisomy 21 group some two years earlier than in the control group.

Standing height and mandibular length were less in the trisomy 21 group at all age levels. The discrepancy between the two groups in both of these measures became greatest in adolescence when the trisomy 21 group showed no further increase in these dimensions while the mean values of the control group became larger with advancing chronological age.

ACKNOWLEDGEMENTS

There are a number of people to whom I would like to express my appreciation for the help and encouragement they have freely extended in the collection and analysis of data, and the preparation of this thesis.

To Dr. J. F. Cleall and Dr. A. S. G. Yip of the Department of Orthodontics, University of Manitoba, for their advice and guidance throughout.

To Dr. F. Chebib for his patient help with the statistical analysis.

To Dr. Irene A. Uchida, former director of Medical Genetics, Winnipeg Children's Hospital, and to Dr. J. L. Hamerton, director of Medical Genetics, Health Sciences Centre, Winnipeg, Manitoba, for making available the cytogenetic records of the trisomy 21 sample.

To Dr. G. H. Lowther of the Manitoba School for Retarded Children and to the Sisters and staff of the St. Amant Ward, St. Boniface Sanitorium, for their interest and assistance.

This investigation was supported by National Health and Welfare Grant No. 606-7-222.

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CHAPTER I

INTRODUCTION

The condition in humans known variously as mongolism, Down's syndrome, or trisomy 21 is caused by the presence of an extra chromosome identified as chromosome number 21. Individuals affected with trisomy 21 present a fairly consistent alteration of growth, in both timing and resultant morphology. Presumably these abnormalities are brought about by the extra genic material, but the mechanism is as yet unknown.

As mapping of the human chromosomes progresses, more and more is being learned of the functions of the individual chromosomes. At the same time, the trisomy 21 phenotype is being studied intensively at the biochemical, physiological and morphological levels. At some point in the future, these two pools of knowledge will be integrated to help solve some of the unanswered questions of developmental biology. It was felt that an examination of the emergence of the phenotype in trisomy 21 syndrome, in terms of maturation, would be a valuable addition to this body of knowledge. Elucidation of maturational anomalies resulting from this genetic imbalance may help to explain some of the morphological differences that have been described in the literature. As well, information of this kind may lead to a better understanding of the genetic

control of maturation.

The specific aims of this study were to examine several of the commonly used maturity indicators, and their interrelations in a group of trisomy 21 individuals as compared to a control group. In this regard, the following maturity indicators were recorded and analyzed:

1. chronological age
2. standing height
3. osseous calcification (bone age)

As well, indices were devised so that dental eruption age and dental calcification age could be calculated, and these parameters were included in the analysis of maturation.

Finally, mandibular length was determined as an indicator of facial maturation.

CHAPTER II

REVIEW OF THE LITERATURE

Down's Syndrome

According to Carter (1966) Down's syndrome or mongolism is the most common chromosomal disorder in man, and one of the most common mental retardation syndromes. The condition is caused by the presence of extra genic material carried by a small autosome identified as number 21. It presents a clinical picture typical enough to allow diagnosis without sophisticated tests, but Bartram (1969) has pointed out that the chromosomal anomaly is the most consistent finding and is essential for the etiologic diagnosis.

Although mongolism is an extremely old disease, apparently having occurred in the Saxons (Brothwell, 1960), the first reported description was by Esquirol (1838) who described a group of mentally retarded subjects with short stature, small head, depressed nasal root and with the external palpebral commisure higher than the internal one. E. Sequin (1846) added to this description the thick and furrowed tongue and the sensitivity of the lungs and integuments to infections.

Langdon Down in 1866 laid emphasis on the stereotyped physiognomy of these patients.

"When placed side by side it is difficult to believe

that the specimens compared are not children of the same parents. The hair is not black, as in the real mongol, but of a brownish color, straight and scanty. The face is flat and broad and destitute of prominence. The cheeks are roundish and extended laterally. The eyes are obliquely placed and the internal canthi more than normally distant from one another. The palpebral fissure is very narrow. The forehead is wrinkled transversely from the constant assistance which the levatores palpebrum derive from the occipito-frontalis muscle in the opening of the eyes. The lips are large and thick with transverse fissures. The tongue is long, thick, and much roughened. The nose is small. The skin has a slight dirty yellowish tinge and is deficient in elasticity - giving the appearance of being too large for the body."

This description was enlarged upon by Sequin (1866), Fraser and Mitchell (1876), Shuttleworth (1886), Jones (1890), Oliver (1891), Smith (1896), and Garrod (1899).

Brousseau and Brainerd (1928) in a monograph offered a thorough review of the literature up to that time and described mongolism clinically.

Benda (1946) published a monograph which analyzed the clinical pathology, neuropathology, and endocrinology of mongolism. In 1960 this was updated in the light of advances in the science of genetics, (Benda, 1960).

Oster (1953) reported on a large clinical and

genealogical investigation of Down's syndrome. Cytogenetics was first included in a clinical study of Down's syndrome by Gustavson (1964).

A large number of investigations of Down's syndrome have been reported on in recent years. Most of these are studies of one specific facet of the syndrome. Those pertinent to this work have been reviewed under separate headings.

Cytogenetics

The etiology of Down's syndrome was a challenge to many from its first description in the mid-nineteenth century, to 1959. Warkany (1960) compiled a list of 39 etiological theories proposed during this period.

Frasier and Mitchell (1876) drew attention to the observation that mongols tend to be the last born in their sibships. This was confirmed many times but it was never clear whether the important association was with birth order, maternal age or paternal age, since all three variables are highly correlated. Jenkins (1933) and Penrose (1934) applied proper statistical procedures to their data to determine that maternal age was the important factor.

After reviewing the literature relating to the occurrence of mongolism in twins, Allen and Baroff (1955) reported a 4 per cent concordance for the defect among dizygotic pairs and 100 per cent concordance among mono-

zygotic pairs. They concluded that mongolism must be determined before the earliest time at which the zygote may divide into two individuals.

Miller and Dill (1965) pointed out that among the many theories of etiology advanced prior to 1959, the one which might reasonably explain all of these aspects of the disease was that relating to chromosomal aberrations. This was first suggested by Waardenburg in 1932.

"I should like to suggest that cytologists investigate whether, in this specific case, it is not possible that there occurs in man an example of a chromosomal aberration. Why should this not also apply to human beings; and why should it not be possible that, when this chromosomal aberration has no lethal effect, it should cause a remarkable anomaly of the constitution?"

Miller and Dill (1965) reviewed the history of human cytogenetics in an effort to explain why it was not until 1959 that Waardenburg's theory was proved correct.

As far back as 1891 von Hanseman reported having counted 18, 24, and 40 chromosomes in three cells of normal human tissue (Turpin and LeJeune, 1969). In the early 1920's agreement was reached on the number of human chromosomes. Winiwarter (1912) numbered them at 47 in the male and 48 in the female. Painter (1921) discovered the Y-chromosome and concluded that 48 chromosomes existed in each sex.

These conclusions were largely accepted and for a period of 25 - 30 years the field of human cytogenetics lay dormant. Interest was stimulated again in 1952 when Hsu (1952) introduced a new technique. He observed that hypotonic shock shortly preceding fixation permitted dispersion of the chromosomes and allowed easier identification. In 1956, Tjio and Levan prepared cultures of living fibroblasts from four therapeutically aborted embryos, used the hypotonic shock technique and observed that most cells contained only 46 chromosomes. This was confirmed in human sex cells a few months later by Ford and Hamerton (1956).

Three years after the discovery by Tjio and Levan; LeJeune, Turpin, and Gautier (1959a)published their observations on the chromosomes of three mongols. They found 47 chromosomes, the extra one being a small acrocentric. In the same year (1959b) they verified their findings by the study of nine more cases. This discovery was confirmed shortly by Jacobs and others (1959), Ford and others (1959), and Book and others, (1959), all of whom suggested that the extra chromosome represented a trisomic state, i.e. that one of the members of the G group of chromosomes was present thrice, rather than twice.

In 1960 an expert study group met in Denver to devise a system of standard nomenclature for human chromosomes (Report, 1960). By the terms of this nomenclature the extra chromosome observed in mongols is generally be-

lieved to be number 21, and Down's syndrome can correctly be named trisomy 21 syndrome.

In 1960 Polani reported on a typical mongol who had four chromosomes in the 21-22 group rather than the five that would be expected. In addition, there was a chromosome missing from the 13-15 group and an extra body in the 6 - 12 and X group. This was a reciprocal translocation between a chromosome number 21 and one of the 13-15 group resulting in an effective or functional trisomy 21, with the two visible number 21 chromosomes plus the partial number 21 attached to the member of the 13-15 group. Similar patients were reported by Penrose and others (1960) and Carter and others (1960).

Other forms of translocation resulting in a functional trisomy 21 have been reported. Hamerton and others (1961), Penrose and others (1960), Zellweger and others (1963), Becker and others (1963), and Miller and Dill (1965).

In 1961, Clarke and others reported a case of a child with mongoloid facies and characteristic extremities. Her I.Q. was 100 at age two years and three months. Cytogenetic studies revealed a consistent mixture of two cell types, one with 46, the other with 47 chromosomes. The latter were trisomic for number 21. This situation is known as mosaicism.

The cytogenetic abnormality generally found in Down's

Syndrome is a trisomy of one of the small acrocentric chromosomes, traditionally called No. 21 (Report of the Denver study group, 1960). According to Mikkelson (1971) it is only possible to distinguish pair No. 21 from pair No. 22 on morphological grounds in very few cases.

Yunis and co-workers (1965a and b) have questioned whether the chromosome involved in Down's Syndrome is the largest of the two pairs. It has been suggested that G, would be the most correct description of the supernumerary chromosome (Therman and others, 1961). The term trisomy 21, however, is still being retained by authorities in the field (Mikkelson, 1971).

Epidemiology Of Down's Syndrome

Down's Syndrome is a relatively common abnormality. Incidences from 0.32 to 3.4 per 1000 live births have been reported (Lillienfeld, 1969). Combined data from newborn baby chromosomal surveys from Ontario, New Haven, and Edinburgh reported by Jacobs (1970) showed 9 cases of trisomy G in 9,983 births, an incidence of .9 per 1000. Uchida (1970) found incidences of 0.9 per 1000 to 1.35 per 1000 through a nine year period in Manitoba. Wahrman and Fried (1970) studied all hospital births in the Jerusalem district over a four year period, finding an incidence of 2.19 per 1000 live births. They attributed their relatively high incidence as being due to almost complete ascertainment.

Mikkelson (1971) pointed out that these different incidence rates may be caused by population differences or may reflect differences in the standard of diagnosis and degree of reporting. Her conclusion was that the population incidence seems to be between 1 and 2 per 1000 live births, as a mean value for all types of Down's syndrome and maternal ages.

The reported prevalence of Down's syndrome in the general population varies from 1:2000 to 1:4000 (Penrose and Smith, 1966). This discrepancy between birth incidence and general population incidence emphasizes the low life expectancy values for those affected by Down's syndrome (Collman and Stoller, 1963).

The incidence of the translocation form of the anomaly was examined by Mikkelson (1971). She reviewed 1,886 cases in unselected series from the literature and found 59 with translocations. This represented 3.2% Uchida (1970) found 2.9% of the Manitoba sample of 512 to be translocations, and 1.2% to be mosaics.

Phenotype - Karyotype Relationships

Recently, significant advances have been made in the understanding of information transfer from the genome of higher organisms, (Church, 1970). All cells of an organism, by virtue of their common descent from a zygote, can be supposed to contain identical sets of genetic information. These cells undergo differentiation and different-

ial growth to form a mature organism. Effective control mechanisms must exist which are capable of preferentially activating some of the genetic potential of each cell nucleus while at the same time suppressing the expression of other regions of the genome utilised earlier in development, or by another cell type.

The chromosomes of mammals are complex structures which carry the genetic information in large macromolecules of deoxyribonucleic acid (DNA). Each structural gene is a segment of base sequences in the DNA molecule. Church (1970) has pointed out that since there is approximately 3×10^{-9} mg. of DNA in the haploid genome, there is room for countless structural and regulator genes. If all of these genes were fully active simultaneously, the cell would literally burst open from the overabundance of protein production.

How this small amount of protein present in the fertilized zygote controls the differentiation and development of cells, and ultimately of the whole organism is one of the fundamental questions to be answered by modern science. Trisomy 21 presents a unique opportunity to examine the abnormalities in the development of humans caused by the addition of a small but specific amount of genetic material. As a consequence this condition is being studied from many different aspects.

In the translocation Down's syndrome, the long arms

of a number 21 chromosome are fused to the long arms of a D or G group chromosome. The genes on the long arm of chromosome 21, when present in triplicate, are evidently responsible for the Down's syndrome phenotype as the individuals are indistinguishable from the trisomy 21 syndrome (Shaw 1962; Gustavson 1964). The short arms of the two chromosomes, which are lost during subsequent mitotic divisions, apparently do not have any great discernible effect on the phenotype (Moore and Hay, 1962). Frostad (1969) has pointed out that this does not rule out minor differences which may be apparent after a detailed quantitative study of a large number of subjects.

Translocation carriers have a balanced translocation, with only the loss of the small arms from the two chromosomes involved, and appear phenotypically normal.

LeJeune and others (1964) described a mosaic individual with one normal cell line and one with monosomy 21. Other cases involving deletions of parts of chromosome No. 21 in an otherwise normal karyotype have been described (Reismann and others, 1966).

These subjects displayed "antimongoloid" signs, including hypertonia, downward slanting (antimongoloid) eyes, large ears, prominent nasal bridge, micrognathia, normal pelvis, and different palmar folds and triradius.

According to Shapiro (1971) it is obvious that trisomy disturbs genetic balance. He hypothesizes that the

genetic imbalance reduces the buffering capacity of the organism resulting in developmental instability and increased phenotypic variability. In support of this, Moss (1966) observed a significant increase in the variance of phenotypic traits in a study of the effects of supernumerary chromosomes occurring in the annual flowering plant rye.

Biochemical investigations reveal quantitative differences between affected subjects and controls for various metabolites (Berg and Stern, 1963). Thyroid antibodies have been found in a large percentage of Down's syndrome subjects (Mellon and others, 1963).

Maturation In Trisomy 21

Benda (1969) has pointed out that a "heterochrony" is present in Down's syndrome. That is, an irregularity in time relationships, specifically, a deviation from the typical sequence in time in the formation of organs or parts.

It is generally known that the person with Down's syndrome has really no true adult life. In the twenties, signs of premature aging are observed. In their thirties and forties, many show definite evidence of presenile changes (Benda, 1969).

Skeletal Maturation

Bone age has been used for some time as an indication of the physical development and maturation of the skeleton.

Standards obtained by means of radiographs have been used to determine the order, rate, time of appearance and progress of ossification of the bones of various parts of the body (Todd, 1937; Greulich and Pyle, 1950; Hoerr and Pyle, 1955; Pyle and Hoerr, 1955).

Ranke (1896) is considered to have been the first to study skeletal development by means of hand and wrist radiographs. The hand and wrist has received most attention in the literature because it is easy to radiograph and because it contains a wide range of bones for study (Acheson, 1954a).

The most popular method of assessing skeletal maturity has been to make a comparison with a series of films typical of the various age groups. Such pictorial standards have been published by Wilms (1902), Rotch (1909), Englebach and McMahon (1924), Siegert (1935), Flory (1936), Todd (1937), Vogt and Vickers (1938), Greulich and Pyle (1950) and Mackay (1952). The standards for hand and wrist developed by Greulich and Pyle (1950 and 1959) have been used by most investigators of skeletal maturation in Down's Syndrome.

A more recently developed method (Acheson 1954a, 1954b, 1966; Tanner and Whitehouse, 1959; Tanner, Whitehouse, and Healy, 1962) has established a series of standard stages through which each bone passes, and matches each bone of the given radiograph with these

stages. Each stage of each bone has a numerical score associated with it and the whole hand and wrist thus scores a total of so many maturity points. This is the Oxford method of assessment of skeletal maturation.

Tanner (1962) has pointed out that skeletal age is a measure which is less sensitive at some stages of growth than others. The standard deviation of the hand skeletal age calculated for age groups, all homogeneous at age 4.0 years, 5.0 years and so on increases from about 1 month at 6 months of age to 4 months at age 2, and, ultimately, 1 year at puberty (Greulich and Pyle, 1959).

There is a sex difference in skeletal maturation. Pryor (1905, 1923, 1925) was the first to discover this and his conclusion has been confirmed for practically every pre-natal and post-natal osseous appearance and fusion in the body (Tanner, 1962). At birth girls are ahead by a matter of weeks, at midgrowth by months, and at adolescence by the two years which separate the sexes in their growth spurts (Tanner 1962).

Examination of skeletal development in individuals with extra or missing sex chromosomes (Klinefelter's syndrome and Turner's syndrome) has led to the conclusion that genes on the Y chromosome retarding skeletal development are responsible for this sex difference (Tanner and others, 1959).

More recently it has been shown that the character of this sexual dimorphism is consistent with a hypothesis

of partial X-linkage (Garn and Rohman, 1962a, 1962b, 1966; Hunt, 1966; Acheson, 1966; Garn and McCreery, 1970).

According to Tanner (1962), the skeleton is advanced or retarded as a whole, so that skeletal ages obtained from different areas agree closely. Bayley (1943) fround that hand and knee assessments correlated from 0.85 to 0.90 even in the higher age groups. Besides this general factor common to all bones, there appear to be more restricted groupings that respond differently to the control of osseous development. Robinow (1942) recorded the age of appearance of ossification centers in a longitudinal radiographic series of 31 patients. Subjecting this data to factor analysis revealed two main factors; a "round bone" factor and an "epiphysis" factor. It has been shown that the carpals have a greater variability in times of appearance than the other hand bones, (Pyle and and Sontag, 1943; Garn and Rohman, 1959).

As long ago as 1907 Pryor stated that the variations in the ossification of bones were inherited. His conclusions were based on a study of carpal sequence and on the presence of extra epiphyses in members of the same family. A number of studies dealing, at least in part, with ossification in closely related children have confirmed Pryor's findings (Bushke 1934, 1935; Lund 1933; Hess and Abramson 1933; Flory 1936; Key 1936; and Rigler 1938). Sontag and Lipford (1943) examined a number of parameters

which might affect skeletal development and concluded that genetic factors were of primary importance.

Reynolds (1943) found that ranking from greatest to least similarity in ossification was twins, siblings, cousins, unrelated children. Sontag and Reynolds (1944) studied monovular triplets from the standpoint of ossification and concluded that there was a strong genetic component determining ossification, but, that environmental factors could modify it. Hewitt (1957) examined longitudinal series of radiographs of 172 children and found the pattern of correlation among related children to suggest that rate of skeletal maturation is inherited autosomally, with sex-linkage a possibility in the case of some genes which affect both height and rate of maturation.

That skeletal maturation is to some degree controlled by genetic factors has been well established. Exactly what it reflects in terms of hormone secretion and other physiologic processes is unclear. It is generally believed that growth hormone is concerned with increase in size and thyroid hormone with increase in differentiation (Becks and others, 1948; Simpson and others, 1950). In the prepuberal phase the active production of somatotropic and thyrotropic hormones from the pituitary is responsible for the initial statural development. A second spurt of growth occurs at puberty when the steroids, secreted by the gonads, stimulate epiphyseal growth, while inhibiting further release of growth hormone from the pituitary

(Greenblatt and others, 1969). These hormones, the androgens, have been shown to advance skeletal maturity in man (Sobel and others, 1956; Bayley and others, 1957).

Considerable controversy exists regarding the skeletal maturation of children with Down's Syndrome. A number of investigators have claimed that osseous development does not differ significantly from that of normal children. In the cases that Benda studied (1939), normal osseous age was the rule. Hefke (1940) compared hand wrist radiographs of 72 mongoloid subjects up to 15 years of age with Todd's standards for normal skeletal development. Seventy-nine per cent of subjects were within normal range. Of the rest, 14 per cent were advanced, while 5 per cent showed slight delay. Dutton (1959) analysed a mixed longitudinal series of fifty assessments on male mongoloids made by comparison of hand wrist radiographs to the standards of Greulich and Pyle. He found 80 per cent of the assessments to fall within the normal range.

Other investigators have found a delay to be present (Clift, 1922; Werner, 1939; Rarick and others, 1964).

Poszonyi and co-workers (1964) used Greulich and Pyle's standards to examine the bone age of one hundred mongoloid children from hand and wrist radiographs. They found retarded bone maturation up to the age of eight years. Beyond this age, bone development accelerated in advance of the theoretical norm. Roche (1964) reported on

a large longitudinal study of osseous development in Down's syndrome. He found a delay in bone maturation to be present in younger affected children but this delay was reduced as chronological age became greater indicating that bone age was actually progressing faster in the affected population than in the control population over a period of time.

Dental Maturation

The eruption of the permanent dentition provides a measure of dental maturity covering approximately the ages six years to thirteen years. Tables on eruption were published as early as 1837, when Saunders counted the individual teeth present in 1,046 children of 9 and 13 years. Cumulative incidence curves of percentages of children at each age with a given tooth erupted, have been given by various authors from cross-sectional data (Cattel, 1928; Boas, 1933; Hellman, 1943; Hurme, 1948, 1949; Dahlberg and Maunsbach, 1948; Leslie, 1951; Clements and others, 1953). Longitudinal studies have been reported by Stones and others, 1951; Fulton and Price, 1954; and Carr, 1962. Carr treated his data both cross-sectionally and longitudinally and found very close correlation between results.

A less crude measure of dental maturity is that of tooth development as seen radiographically. Bengston, (1935) studied root development radiographically, giving the ages at which each tooth had its root developed one

quarter, one half, three quarters and fully. Pinney, (1935) used lateral jaw radiographs and described successive stages of calcification for the mandibular teeth.

Gleiser and Hunt (1955) studied a longitudinal series of lateral jaw radiographs of 25 girls and 25 boys. A row of outline sketches was made of all the radiographic images of the permanent mandibular first molar for each child. From these sketches 15 stages of calcification were chosen:

1) no change in bone density, and no crypt visible.
2) crypt clearly visible, but no calcification.
3) coalescence of at least 2 centres.
4) outline of cusps completed.
5) half of crown completed.
6) 2/3 of crown completed.
7) crown completed.
8) minimal root formation.
9) 1/4 of root completed.
10) 1/3 of root completed.
11) 1/2 of root completed.
12) 2/3 of root completed.
13) 3/4 of root completed.
14) root canal terminally divergent.
15) root canal terminally convergent.

The reproduceability of this series of stages apparently was not tested by double determination.

Demisch and Wartmann (1956) adapted the stages of Gleiser and Hunt to study the mandibular third molar in lateral jaw radiographs. They eliminated stage 6 (2/3 of crown completed) as it could not be differentiated accurately from its neighbouring stages. A double determination revealed that disagreement was never more than one stage, and the range of identical ratings varied between 60 and 100% for the different stages.

Garn, Lewis, Koski, and Polacheck (1958) studied dental development of 255 subjects in a longitudinal series of oblique jaw radiographs. Although more stages could be identified, they chose the following 5 stages as constituting a reasonable number of definite and fairly well-spaced events in the developmental course of the teeth.

1) Stage of the full-follicle, immediately preceding the first evidence of cusp calcification.

2) Crown completion and beginning root formation.

3) Alveolar eruption, i.e., elevation of the crown above the alveolar margin.

4) Attainment of the occlusal level.

5) Apical closure.

By finding mean age of achievement of each stage they

established norms and a means of inter group comparisons.

Nolla (1960) adapted Pinney's technique to a longitudinal study of 25 girls. Her records included lateral jaw radiographs and periapical radiographs. Tooth development was staged as follows:

0) absence of crypt.
1) presence of crypt.
2) initial calcification.
3) one-third of crown completed.
4) two-thirds of crown completed.
5) crown almost completed.
6) crown completed.
7) one-third of root completed.
8) two-thirds of root completed.
9) root almost completed - open apex.
10) apical end of root completed.

Interpolations were made when necessary. Each individual assessment was repeated with the average being the stage recorded. Correlation between the two assessments was not reported.

Fanning (1961) studied a longitudinal series of lateral jaw radiographs of 48 boys and 51 girls. She adapted the stages of Gleiser and Hunt to assess the development of the cuspid, bicuspids and molars, adding three apical stages for precision:

apex 1/4 closed.

apex 1/2 closed.

apex 3/4 closed.

apex closure completed.

Tests for accuracy in assessment were made by independent ratings in 10 males. Complete agreement occurred in 73% of stagings, and disagreement of no more than one full stage in 27%.

There is a marked sex difference in eruption, with every permanent tooth appearing earlier in girls, by amounts varying from 2 months for the first molars to 11 months for the canines. (Clements and others, 1953; Carr, 1962; Tanner, 1962).

This same sex difference is seen in radiographic studies as well. Boys have a dental maturity age approximately 0.96 that of girls of the same chronological age as an average taken over all available teeth, whether calculated by eruption or calcification data (Gleiser and Hunt, 1955; Garn and others, 1958).

According to Tanner (1962), the rate of tooth development is chiefly controlled by hereditary factors. Boas (1933), has shown that eruption times are similar in pairs of twins and siblings. Hatton (1955) examined dental development in monozygotic and dizygotic twins and estimated the effect of heredity at 78 per cent. Garn, Lewis and Shoemaker (1956) found that the calcification sequence tends to

be the same in siblings more often than expected by chance. Pavlik (1968) examined a large group of twins radiographically and found that genetic factors were responsible for 80 per cent of the variance in dental maturity.

The hormonal control of tooth development in humans is not yet fully elucidated. Dental development is delayed in hypothyroidism, but advanced in hyperthyroidism (Salzmann, 1966).

Animal studies where the levels of pituitary and thyroid hormones could be altered led Baume (1954) to the conclusion that tooth eruption is presided over by the synergism of pituitary growth hormone and thyroid hormone, which controls differentiation or maturation. Testosterone has been shown to cause accelerated eruption in monkeys (van Wagenen and Hurme, 1950).

There are many reports that the eruption of permanent teeth is delayed in mongols, but no details have been supplied (Spitzer and Robinson, 1955; Spitzer and Quilliam, 1958; Hilliard and Kirman, 1965; Cohen and Winer, 1965). Silimbani (1962) examined 25 mongols, aged between 5 and 14 years, and reported a delay in the eruption of the permanent teeth. Oster (1953) made observations on more than 400 mongols and reported that the eruption of permanent teeth was delayed in many. None of the above observations include adequate statistical analyses. They do not allow

conclusions regarding the degree to which mongols vary from normal in median eruption ages for particular teeth. Neither do they allow an estimate of the incidence of delayed eruption in mongols.

Barkla (1966a) reported on a large cross-sectional study. He found that eruption age among mongoloids was delayed to a statistically significant extent for each tooth. The variances were very large, but, for each tooth, eruption would be expected within the normal range for less than 5 per cent of mongoloids.

Garn, Stimson and Lewis, (1970), reported the first study of dental development in a karyotyped trisomy 21 sample. Using oblique and lateral jaw radiographs, they assessed crown calcification, root development and alveolar eruption, and compared to a control group. Their 25 subjects ranged in age from 1 to 20 years. The trisomy 21 group exhibited an average delay of 0.7 years. This was a 13 per cent delay in dental development.

Height

Height in trisomy 21 syndrome is markedly retarded in development. Growth curves of individual cases indicate that growth slows down with increasing age and reaches an early standstill. At the end of the growth period, few persons with mongolism exceed a height of five feet (Benda, 1969).

Cross-sectional data derived from large numbers of mongols have been reported by Brousseau and Brainerd (1928), Benda, (1949)

and Oster (1953). These reports show that the rate of growth in stature of mongols is slow before birth and is much faster than the mean rate for normal children during the first two years of life. The rate of growth in stature is slightly slower than the normal mean between the ages of eight and ten years, but it is close to the rate for normal children between the ages of ten and thirteen years. After an age varying from thirteen to sixteen years, the mean rate is less rapid than the mean rate for normal children.

Roche (1965) reported similar findings in a longitudinal study. He found that adolescent spurts in stature occurred in most subjects. The range of occurrence did not differ markedly from that found in normal subjects. Increase in stature ceased at a much earlier age than in normal children.

Mandibular Length

Spitzer and Robinson (1955) described the mandible in Down's Syndrome as being underdeveloped and having a short ramus. This has been confirmed by other investigators who utilised cephalometric radiographs to quantitate mandibular size (Rezk, 1964; Kisling, 1966; and Ghiz, 1968).

Ghiz found both ramal length and body length to be less in the trisomy 21 group. His cross-sectional study contained subjects from four years of age to adults and he found mandibular size to be smaller in the trisomy 21

group at all age levels. The discrepancy in mandibular size between the control group and the trisomy 21 group was least during midchildhood and greatest in adults.

CHAPTER III

METHOD AND MATERIALS

The Sample

The sample consisted of 295 individuals, 160 males and 135 females, each upon cytogenetic analysis having a trisomy of chromosome number 21. All translocations and recognized mosaics were eliminated so that as far as was possible a sample with only trisomy 21 karyotype existed.

Cytogenetic records were made available by the Department of Medical Genetics of the Children's Hospital of Winnipeg, Winnipeg, Manitoba. The sample reported upon was drawn from a group of 512 Manitoba mongoloids studied by the Department of Genetics (Uchida, 1970). In Uchida's study cytogenetic analyses were confined to the leukocytes of peripheral blood samples. Where there was any suspicion of mosaicism repeat blood samples were taken, and additional cells totaling some 100 - 200 were counted, with detailed analysis confined to the G group.

All of the trisomy 21 sample resided within the province of Manitoba. 65.1 per cent were institutionalized in two schools, and 34.9 per cent lived at home. The trisomy 21 sample included all of the group studied by the Department of Genetics who could or would co-operate for the taking of the necessary records. In other words, the entire group was canvassed and those who presented them-

selves for examination were included.

The trisomy 21 sample ranged from 3 to 55 years of age. The age and sex distribution of the sample may be found in Table I.

The control sample consisted of 161 Caucasians, 73 males and 88 females. This group was randomly selected and included students from the University of Manitoba and individuals residing in and around Metropolitan Winnipeg. The age and sex distribution of the control sample is shown in Table I.

No attempt was made to determine the ethnic background of either the trisomy 21 group, or the control group. It was felt, however, that a similarity of backgrounds existed between the two groups.

The records obtained included lateral cephalometric radiographs, hand-wrist radiographs, panorex radiographs, alginate impressions of the upper and lower dental arches, and measurements of height and weight.

TABLE I

Age and Sex Distribution of Trisomy 21 and Control Sample

Age Ranges (in years)	Trisomy 21		Control	
	Male	Female	Male	Female
3 - 5	8	11	11	9
6 - 8	17	11	10	12
9 - 11	30	14	10	14
12 - 15	38	23	16	16
16 - 19	27	22	7	11
20 - 25	16	18	10	13
26 - 30	10	9	9	13
30 +	15	27	--	--
TOTAL	160	135	73	88

Assessment of Dental Eruption

Dental eruption was assessed by means of plaster models of the dentition. A tooth was considered to be erupted if any portion of it had pierced the gingival tissues. A tooth was considered to be non-erupted only if it could be identified radiographically, but had not yet emerged through the mucosa. Missing teeth, whether extracted or congenitally absent were scored separately and were not included in considerations of eruption.

For each subject having the appropriate records available, the eruption status of all permanent teeth with the exception of the third molars was assessed. Two groups were then segregated for further analysis; the entire control group which was balanced with regard to males and females, and a subgroup of the trisomy 21 sample balanced

with regard to sex. The age and sex distribution of the control group and of the trisomy subgroup is shown in Table II.

TABLE II

Age Distribution of Subjects Utilized for Probit Analysis of Dental Eruption

Age Ranges (in years)	Trisomy 21		Control	
	Male	Female	Male	Female
3 - 5	5	8	11	9
6 - 8	11	8	10	12
9 - 11	10	10	10	14
12 - 15	18	17	16	16
16 - 19	15	16	13	11
Adult	5	6	--	--
TOTAL	64	64	60	63

The subjects of the control group and the trisomy 21 subgroup were organized by chronological age into classes of three months each. The number of subjects with eruption of each tooth was calculated in each class. This data was then subjected to probit analysis to study the degree of eruption with advancing age.

The control sample was utilized to provide "normal eruption probabilities". These were derived from the best fitting probit curve for each tooth and are listed in Tables XXVI to XLI , Appendix "A".

An eruption index was then calculated for each subject

using the formula:

$$\text{Eruption Index} = \frac{N_e - P}{N} \times 100$$

Where: N_e = the number of erupted teeth; P = the sum of the normal eruption probabilities of all teeth assessed, for the chronological age of the subject; N = the number of teeth assessed.

The resulting index would theoretically range from -100 for a subject with no erupted teeth at an age where all teeth should have erupted, to +100 for a subject who had erupted all his permanent teeth at an incredibly early age. A subject whose teeth are erupted in a normal pattern at a normal chronological age would have an eruption index of zero. A meaningful index is calculable only for those subjects having some erupted permanent teeth, but who have not completed the eruption of their permanent dentition. In other words, the index applies only to subjects ranging in age from approximately five years to fifteen years, while the eruption of the permanent dentition is a dynamic process.

It was possible, as well, for any given subject, to calculate the chronological age to which his overall eruption status would normally correspond. That is, to calculate the chronological age that would give an eruption index of zero, for the eruption pattern recorded from the subject's dental models. A computer program was developed to calculate the eruption index and this "eruption age" of each

subject.

Assessment of Dental Calcification

Dental calcification was assessed utilizing panoral radiographs. An XRM Panorex unit was used with head stabilization achieved by means of the chin rest supplied by the manufacturer.

The Panorex technique uses the principle of curved surface laminagraphy, in which images of structures in selected planes are recorded distinctly. The focal trough of the Panorex is a region representing a one-half to two-thirds inch slice around the dental arches (Christen and Segreto, 1968). Anatomic structures that are not in focus in this trough are blurred or distorted on the radiograph. The subject's head remains stationary while the film and the radiation source rotate. Halfway through the exposure, the axis of rotation is changed from one side to the other by the automatic shifting of the chair. With this change the right and left sides of the patient's head are positioned in the film, distortion is minimized, and the spinal column is by-passed.

None of the previously described systems of staging the calcification of developing teeth were suitable for this study as they were designed for use with longitudinal samples and either periapical or lateral jaw radiographs (Pinney, 1939; Gleiser and Hunt, 1955; Demisch and Wartmann, 1956; Garn and others, 1958; Nolla, 1960; and Fanning, 1961).

The cross sectional nature of the sample in this study necessitated broader stages if the assessments were to be reproducible with a reasonable frequency. Furthermore, the radiographic technique used in this study produced images of less detail and definition, and more distortion than the lateral jaw and periapical techniques used by previous investigators.

A series of nine recognizable stages was arrived at for each tooth type, ranging from complete absence of the crypt, to closure of the apex or apices of the root(s). These are described in Figures 1, 2 & 3.[1] No interpolations were made. If a tooth fell between two stages it was recorded as being at the lower of the two.

This staging system was tested as follows. Panorex radiographs were taken from the files of 21 normal subjects evenly distributed over the age range 36 months to 146 months. Males and females were included in approximately equal numbers.

Using a lighted view box and magnifying glass all teeth were staged by one investigator. He was given no instructions other than the description of the stages as shown in Figures 1, 2 & 3. The same series of radiographs was then staged by the author. After a period of several weeks they were staged a second time by the author. Each staging was done without reference to previous values.

The number of assessments agreeing exactly were

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1. For Nomenclature of the Permanent Dentition see Appendix A, page 145a.

DEVELOPMENTAL STAGES INCISOR

STAGE A
ABSENCE OF CRYPT

STAGE B
THE CRYPT IS PRESENT BUT THERE IS NO CALCIFICATION.

STAGE C
THE CRYPT IS STILL VISIBLE AND THE INITIAL CALCIFICATION CAN BE SEEN.

STAGE D
ONE HALF THE CROWN IS CALCIFIED.

STAGE E
THE ENTIRE CROWN IS CALCIFIED.

STAGE F
THE ROOT IS ONE QUARTER CALCIFIED.

STAGE G
THE ROOT IS ONE HALF CALCIFIED.

STAGE H
THE ROOT IS THREE QUARTERS CALCIFIED.

STAGE I
THE ROOT HAS ACHIEVED ITS FULL LENGTH BUT THE APEX REMAINS OPEN.

STAGE J
THE APEX IS CLOSED.

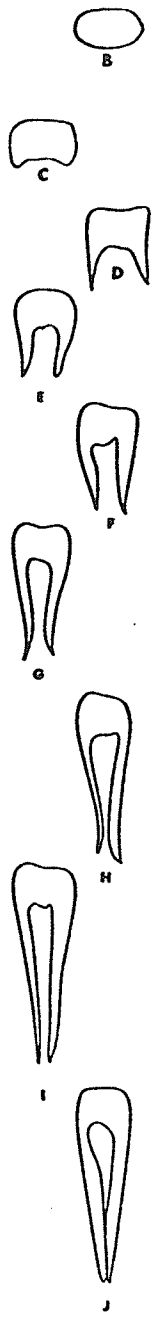

Figure 1. Configurational standards for development of incisor teeth.

DEVELOPMENTAL STAGES CUSPID/BICUSPID

STAGE A
ABSENCE OF CRYPT

STAGE B
THE CRYPT IS PRESENT BUT THERE IS NO CALCIFICATION.

STAGE C
THE CRYPT IS STILL VISIBLE AND THE INITIAL CALCIFICATION CAN BE SEEN.

STAGE D
ONE HALF THE CROWN IS CALCIFIED.

STAGE E
THE ENTIRE CROWN IS CALCIFIED.

STAGE F
THE ROOT IS ONE QUARTER CALCIFIED.

STAGE G
THE ROOT IS ONE HALF CALCIFIED.

STAGE H
THE ROOT IS THREE QUARTERS CALCIFIED.

STAGE I
THE ROOT HAS ACHIEVED ITS FULL LENGTH BUT THE APEX REMAINS OPEN.

STAGE J
THE APEX IS CLOSED.

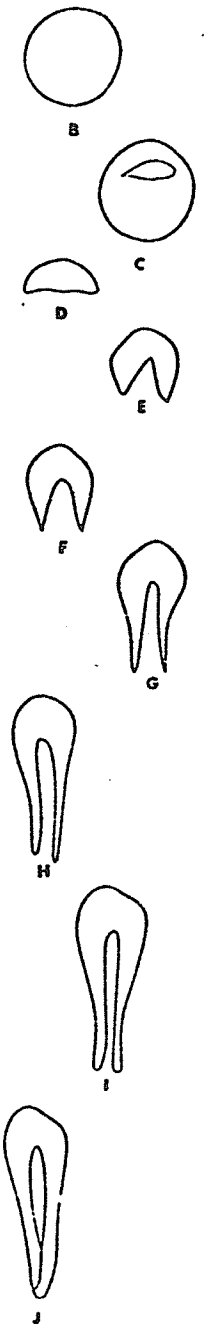

Figure 2. Configurational standards for development of cuspid/bicuspid teeth.

DEVELOPMENTAL STAGES MOLAR

STAGE A
ABSENCE OF CRYPT

STAGE B
THE CRYPT IS PRESENT BUT THERE IS NO CALCIFICATION.

STAGE C
THE CRYPT IS STILL VISIBLE AND THE INITIAL CALCIFICATION CAN BE SEEN.

STAGE D
ONE HALF THE CROWN IS CALCIFIED.

STAGE E
THE ENTIRE CROWN IS CALCIFIED.

STAGE F
THE ROOT IS ONE QUARTER CALCIFIED.

STAGE G
THE ROOT IS ONE HALF CALCIFIED.

STAGE H
THE ROOT IS THREE QUARTERS CALCIFIED.

STAGE I
THE ROOT HAS ACHIEVED ITS FULL LENGTH BUT THE APEX REMAINS OPEN.

STAGE J
THE APEX IS CLOSED.

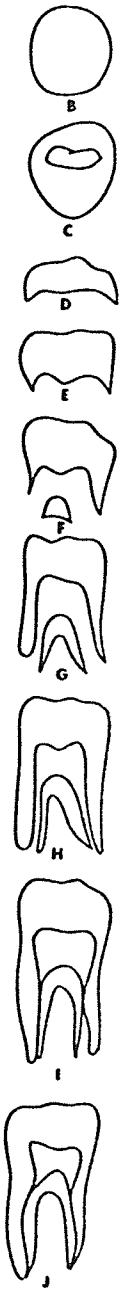

Figure 3. Configurational standards for development of molar teeth.

TABLE III

Agreement Between Separate Assessment of Developmental Stage From Panoramic Radiographs.

Tooth	Percent Agreement: Two Investigators Two Assessments	Percent Agreement: One Investigator Two Assessments
Maxillary		
1	90.4	95.2
2	95.3	100.0
3	67.4	87.1
4	72.8	69.3
5	80.8	90.4
6	79.4	88.1
7	75.2	87.6
Mandibular		
1	84.0	97.3
2	76.2	92.9
3	70.3	88.1
4	71.5	80.9
5	70.5	87.7
6	79.7	92.8
7	75.9	90.5
Mean	78.1	89.9

counted for each tooth. These are expressed as percentages of the total number of assessments made, and are presented in Table III. No disagreements between stages were found to be more than one stage. The mean overall agreement between different assessors was 78.1 per cent; and between two assessments by the author was 89.9 per cent.

TABLE IV

Mean, Standard Deviation and Significance of the Difference For Length to Width Ratios of Mature Permanent Teeth in the Trisomy 21 and Control Groups.

Tooth	Trisomy 21		Control	
	Mean	S.D.	Mean	S.D.
Maxillary				
1	2.292	0.333	2.538	0.260 *
2	3.500	0.526	3.242	0.389
3	3.073	0.330	3.233	0.261
4	2.722	0.341	2.909	0.493
5	2.814	0.321	2.781	0.309
6	1.680	0.386	1.750	0.395
7	1.806	0.379	1.914	0.410
Mandibular				
1	3.618	0.412	3.978	0.440 *
2	3.231	0.448	3.696	0.357 **
3	3.063	0.301	3.812	0.356 **
4	2.726	0.380	3.067	0.353 **
5	2.536	0.268	2.757	0.256 *
6	1.540	0.196	1.614	0.124
7	1.488	0.260	1.629	0.123 *

---

* Between group difference significant at 5 per cent level of confidence.

** Between group difference significant at 1 per cent level of confidence.

In order to assess the validity of applying the same configurational standards of tooth development to control and to trisomy 21 individuals the following procedures were carried out. Panorex films of 15 control individuals and 14 trisomy 21 individuals were randomly selected from the files. The only criterion of selection was that a relatively mature dentition be present. Males and females were present in approximately equal numbers.

Using measuring calipers with a Vernier scale the maximum length from incisal or occlusal surface to root tip was measured, for each tooth, as was maximum width of the crown. Rotated, restored or broken down teeth were not included. The ratio of length to width for each tooth was calculated. Two hundred and eighty-four teeth were included in the normal sample, two hundred and eleven in the trisomy 21 sample.

Since the application of the configurational standards of dental calcification described in Figures 1, 2 & 3 depended to a certain degree on the length of the calcifying tooth relative to its width, the resulting data was analyzed in terms of length/width ratios. The mean values for each tooth, along with their respective standard deviations are shown in Table IV.

The ratios were significantly smaller for the trisomy 21 group with respect to the maxillary central incisor and all the mandibular teeth except the first molar. This

blunting was considered when applying the standards to the trisomy group.

In using this system of measuring dental development of both the control and the trisomy 21 groups all assessable teeth as seen on the panoral radiographs were assigned a stage. This information was recorded for each tooth for each subject; along with the subject's chronological age. Then, for each tooth, the mean chronological age of all subjects displaying each stage could be calculated.

A subsample of the trisomy 21 group, balanced with respect to the sexes was analyzed in similar fashion. The age and sex distribution of this subsample may be found in Table V.

TABLE V

Age and Sex Distribution of Subjects Utilized For Calculation of Mean Calcification Values

Age Ranges (in years)	Trisomy 21		Control	
	Male	Female	Male	Female
3 - 5	2	5	11	9
6 - 8	4	2	10	12
9 - 11	7	6	10	14
12 - 15	14	12	16	16
16 - 19	13	10	13	11
Adult	4	4	--	--
TOTAL	44	39	60	63

Utilizing the mean values for each tooth-stage derived from the control sample a dental calcification age could be calculated for each subject. This was done using the formula:

$$\text{Dental calcification age} = \frac{\Sigma \bar{X}_c}{N}$$

where: $\Sigma \bar{X}_c$ is the sum of all normal mean ages corresponding to the tooth stages recorded for the subject; and N is the number of mean ages considered.

Stage J (apical closure) was not included in this calculation as it signifies the end of development and does not record a point in the dynamic process of dental calcification. In other words, in a cross sectional analysis the subject is seen at one point in time. The fact that an apex is closed is relatively meaningless as it may have been closed a significant time period prior to when the record was made. Only those teeth still in the process of calcification could be included in the calculation of calification age.

Assessment of Skeletal Development

Radiographs were taken of the left hand and wrist following the technique described by Tanner and Whitehouse (1959). The palm was faced downward in contact with the film, and the axis of the middle finger was in direct line with the axis of the forearm. The fingers were spread slightly and the thumb placed in a comfortable natural de-

gree of rotation with its axis making an angle of about 30 degrees with the first finger. The tube was centered above the head of the third metacarpal at a tube film distance of 30 inches. An exposure of 8 milliampere-seconds at 55 KV was found appropriate for an 8 - 10 year old child with corresponding adjustments for older or younger children.

Skeletal development was assessed by two methods, the Greulich-Pyle system (Greulich and Pyle, 1959), and the Oxford method (Tanner and Whitehouse, 1959; Tanner, Whitehouse and Healy, 1962). The former was chosen because most previous studies of skeletal maturation in trisomy 21 have used it - making it the basis of comparison. The latter was chosen, because it is more precise and differentiates between round bones and long bones.

The simpler Greulich-Pyle system matches the X-ray on an overall basis with one of fifty-eight photographs in an atlas. Each photograph is the standard for a particular skeletal age, with separate standards for each sex. The Greulich-Pyle standards were selected from the median of a hundred radiographs for each chronological age group, all of whom were radiographed within ±2% of their birthday. Most of the standards are a year apart and in assessing a radiograph against the standards an interpolation is made. The atlas photographs are based on a series of 2,500 child-

ren observed in Cleveland, Ohio, from 1932 to 1942, who were "....somewhat above average in economic and educational status". (Greulich and Pyle, 1959).

The Oxford method of skeletal developmental assessment was developed by Acheson (1954a, 1954b). According to Acheson if each of the more easily distinguished stages for any center of ossification is numbered, a maturity scale for that center is constructed. This can be done for a number of centers, and then, for a subject, a total maturity score can be derived by adding the individual ratings. No interpolations are made, a stage, or maturity indicator is either present or it is not. This is the essence of the Oxford method. Following the method of Tanner and Whitehouse (1959), and Tanner and Whitehouse and Healy (1962), the Oxford method was applied to the radiographs of the hand and wrist.

The radiographic images of each of twenty bones of the hand and wrist were compared with pictorial and verbal descriptions of the developmental stages for that particular bone, as published by Tanner and Whitehouse, 1959.

The bones evaluated were the radius, ulna; capitate, hamate, triquetral, lunate, navicular, greater multangular, lesser multangular; metacarpals 1, 3, 5; proximal phalanges 1, 3, 5; middle phalanges 1, 3, 5; and the distal phalanges 1, 3, 5. These may be seen in Figure 4.

The relative importance of each stage of a specific

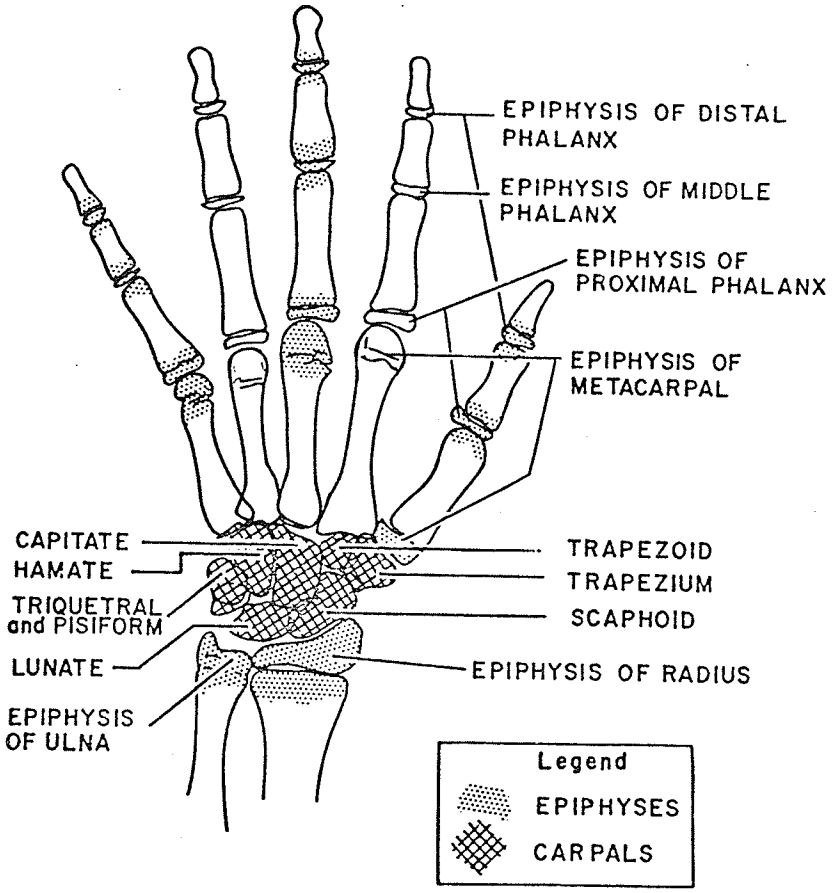

Figure 4. Areas of the hand and wrist skeleton assessed using the Oxford method.

bone had been previously assessed statistically to derive a score for each stage of the individual bone by Tanner, Whitehouse, and Healy, 1962. These scores were self-weighted and an overall score was arrived at by adding the scores of the individual bones.

The method assumes that:

1. There may be some truth to the notion that long bones and round bones are controlled by different factors, at least at certain times. Hence, a separate score for each is desirable.
2. A simple average of all bones would be overweighted by the large number of metacarpals and phalanges whose maturation is very closely linked.

The metacarpals and phalanges of the second and fourth fingers were omitted, consequently, and a weighting was reached for long bones in which the radius and ulna each contributed 20% of the score, and the first, third and fifth fingers, each considered as a whole, each contributed 20% also. Each carpal bone contributed 14% to the round bone score. The long bone score and the carpal score each contributed equally to the total score.

All subjects for whom hand and wrist films were available were rated according to the Greulich-Pyle system, and the Oxford system. The age and sex distributions of the trisomy 21 and control sample are contained in Table VI.

TABLE VI

Age and Sex Distribution of Subjects Utilized for Assessment of Skeletal Development

Age Ranges (in years)	Trisomy 21		Control	
	Male	Female	Male	Female
3 - 5	8	10	11	9
6 - 8	14	9	10	12
9 - 11	13	8	10	14
12 - 15	24	16	16	16
16 - 19	31	16	13	11
Adult	20	30	--	--
TOTAL	100	89	60	63

Measurement of Standing Height

Standing height was measured following standard procedures. Each subject was asked to remove his shoes and stand as erect as possible with feet flat on the floor, next to a vertical scale. A horizontal arm was moved down the vertical scale until it made firm contact with the subject's head. At this point the height reading was taken.

The age and sex distribution of the subjects utilised for assessment of standing height is contained in Table VII.

TABLE VII

Age and Sex Distribution of Sample

Utilised for Assessment of Standing Height

Age Ranges (in years)	Trisomy 21		Control	
	Male	Female	Male	Female
3 - 5	4	7	11	9
6 - 8	9	4	10	12
9 - 11	13	11	10	14
12 - 15	34	18	15	16
16 - 19	24	17	17	13
Adult	25	38	8	9
TOTAL	109	95	71	73

Lateral Cephalometric Radiographs

The lateral cephalometric radiographs were obtained using the now conventional technique first developed by Broadbent (1931). The radiographs were taken with the teeth in centric occlusion, and in the mouth wide open position. Three cephalometric X-ray machines were used. A Broadbent-Bolton cephalometer was used on a portion of the trisomy 21 group living in private homes. A Cephalometrix* cephalometer was used on the control group and a portion of the trisomy 21 group. Some of the trisomy 21 group residing in institutions were radiographed with a specially built portable cephalometer. The portable cephalometer was built along the lines of a conventional

* Moss Corporation, Chicago, Illinois.

cephalometer utilizing a General Electric* 90 kv X-ray head and control panel, a standard cephalostat, and an easily dismantled plywood base. These three sections were so constructed that the machine could easily be transported, set up, and dismantled.

All machines had an approximate focal point to film distance of 5 feet, 6 inches. Magnification factors for each of the machines had been previously established (Frostad, 1969). The magnification averaged 7 per cent on the Broadbent-Bolton and portable cephalometer between individuals. On the Cephalometrix cephalometer the magnification averaged 9 per cent between individuals. All linear dimensions were corrected for the magnification to absolute units. Therefore, the linear dimensions taken from the three machines were comparable.

Measurement of Mandibular Length

For the purposes of this study mandibular length was defined as the distance between the points condylion and gnathion. These points are defined as follows:

Gnathion - An arbitrarily defined point taken as the most anterior and inferior point, visually, on the outline of the mandible (Krogman and Sassouni, 1957).

Condylion - Radiographic condylion, as described by Krogman and Sassouni, 1957, was used. This was arbitrarily defined as the point on the superior border of the

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* General Electric of Canada Ltd., Toronto, Ontario.

condyle where a line parallel to the long axis of the condyle in the midline of the condyle intersected the superior border.

Because the condyle is not a spherical structure, the outline varies on a lateral cephalogram depending on the position of the X-ray beam. From one aspect, the outline resembles an ellipse and from another a sphere. Regardless of the technique used (example, occlusal, rest, or "wide-open" cephalometric radiographs), this is an inherent difficulty in any radiographic study involving the condyle. A second problem is the presence of the meniscus which may tend to obscure the superior border of the condyle giving either a different outline or a blurring of the outline. These difficulties were at least partly overcome by comparison between films taken in rest position, occlusal contact, and wide-open position. It was on the latter that the measurement from condylion to gnathion was made. If two condylar images were present, the measurements were averaged.

The radiographs were traced on the matte surface of acetate paper over a varying intensity illuminator with a hard pencil. The distance condylion-gnathion was measured to not less than 0.5 mm. using a standard millimeter gauge.

The age and sex distribution of the subjects included in the assessment of mandibular length is contained in

Table VIII.

TABLE VIII

Age and Sex Distribution of Sample

Utilised for Assessment of Mandibular Length

Age Ranges (in years)	Trisomy 21		Control	
	Male	Female	Male	Female
3 - 5	6	9	11	9
6 - 8	16	9	10	12
9 - 11	17	13	10	14
12 - 15	36	21	16	16
16 - 19	23	22	7	11
Adult	32	49	19	26
TOTAL	130	123	73	88

Analysis of the Data

Using the techniques outlined in the previous sections it was possible to describe each set of related measures by means of one "index". For each subject, indices were calculated to describe dental eruption, dental calcification, round bone ossification, long bone ossification and a composite of both long bone and round bone ossification. The resulting indices, each being a function of a number of measures are more amenable to statistical analysis than the original measures. These were subjected to further statistical treatment together with the values for standing height, mandibular length and chronological age.

The effect of chronological age on each of the de-

pendent variables dental eruption, dental calcification, round bone ossification, long bone ossification, overall ossification, standing height and mandibular length was examined for both the control and the trisomy 21 group. The significance of differences between groups, in both the slope of the resulting curves (rate of maturation) and the elevation of the resulting curves was tested in the following manner.

In the hope of transforming into straight lines the asymptoting curves found when the effect of chronological age was studied, each value of each dependent variable was computed as a percentage of the maximum possible for that variable. In the case of standing height and mandifular length, the mean adult values for each sex and each group were arbitrarily considered to be the maximum possible. These percentages were then subjected to the arc sine square root transformation (Steele and Torrie, 1960). Testing this procedure by plotting the transformed percentages against chronological age showed that it did, in fact, result in a straight line for each of the relationships studied.

The transformed values were subjected to analysis of covariance in order to test the significance of difference between group means adjusted for age, and the significance of difference in slopes between groups. The I.B.M. 360-65 computer system of the University of Manitoba was used to process the data.

CHAPTER IV

RESULTS

Dental Eruption

As was described in the previous section, the method of probits was used to determine the chronological age at which there is a fifty per cent probability of a given tooth having erupted. This was done separately for the control group and the trisomy 21 group, and was used as a method of comparing the eruption of individual teeth between groups. Since the control group in this study represented a sample much smaller than those usually used for determinations of eruption times, a comparison with previously reported data was desirable. The control values from the present study along with those from five other studies are presented in Table IX.

The values for the control group agreed well with those found by previous investigators of normal populations.

The values for the control group and the trisomy 21 group along with their standard errors and significance of the difference are presented in Table X. The trisomy 21 group showed greater age than the control group at the fifty per cent probability of eruption level for each of the fourteen teeth studied. This retardation of eruption in the trisomy 21 group was most pronounced for the mandi-

TABLE IX

A Comparison of "Normal" Tooth Eruption Data from Six Studies. The Values Represent the Age in Months at Which There is a Fifty Per Cent Probability of Eruption.

	Manitoban 1970	Australian 1960	British 1950		Western & Northern European 1857-1940	Pima Indian 1958
	N = 112	N=3952	N=625	N=1039		N=957
	Nevile	Carr		Clements	Hurmé	Dahlberg
			Rural	Urban	(from 18 sources)	
Tooth						
Maxillary						
1	86	85	83	82	87	92
2	99	99	97	96	100	102
3	134	134	127	133	---	136
4	123	125	120	121	---	119
5	135	131	128	135	---	132
6	76	76	74	72	76	71
7	144	143	143	141	---	138
Mandibular						
1	71	75	73	71	76	75
2	87	88	87	86	89	90
3	122	123	125	120	---	123
4	127	128	123	131	---	122
5	140	136	136	144	---	132
6	71	76	73	72	73	68
7	139	141	135	136	---	132

TABLE X

Mean, Standard Error, and Significance of the Difference for the 50 Per Cent Eruption Ages of Each Tooth (in Months).

	Trisomy 21		Control		
Tooth	50% Erupted	S.E.	50% Erupted	S.E.	
Maxillary					
1	93.13	2.70	85.84	2.52	*
2	117.28	3.47	98.58	1.80	**
3	156.73	3.64	133.90	2.54	**
4	138.92	2.80	123.07	2.40	**
5	145.53	3.62	134.72	2.68	*
6	84.69	2.48	76.50	2.46	*
7	164.46	3.44	144.24	2.84	**
Mandibular					
1	84.80	2.78	71.36	2.53	**
2	93.56	2.77	86.53	1.98	*
3	128.36	2.87	122.39	2.15	*
4	141.78	3.79	126.81	2.91	**
5	152.69	3.39	139.63	2.95	**
6	86.40	2.48	71.39	2.29	**
7	163.22	4.00	138.56	1.75	**

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* between group difference significant at 5 per cent level of confidence.

** between group difference significant at 1 per cent level of confidence.

bular central incisor and first molar, the maxillary central incisor and cuspid, and the second molars in both jaws. This pattern was evident whether the retardation was measured in months or in a relative manner, as a per cent of normal values.

The values for both groups are represented as bars in Figure 5, and ranked in order of chronological age at fifty per cent probability of eruption of the control group. It can be seen that the degree of retardation varies slightly from tooth to tooth but that no clear trend toward or away from the control values exists. The early developing teeth are not more or less retarded than the later developing teeth.

In addition to an overall retardation in eruption time, the trisomy 21 group showed a much greater variability in eruption time. This is evidenced by the standard errors for the fifty per cent eruption times (Table X). Even though the trisomy 21 group contained many more subjects, the standard errors are uniformly much larger than those of the control group.

The findings upon examination of dental eruption age, which is an index of the eruption of all of the teeth, were consistent with the findings for individual teeth. The mean, standard deviation, standard error and number for each age class, for both the trisomy 21 group and the control group are presented in Table XI. The relationship of

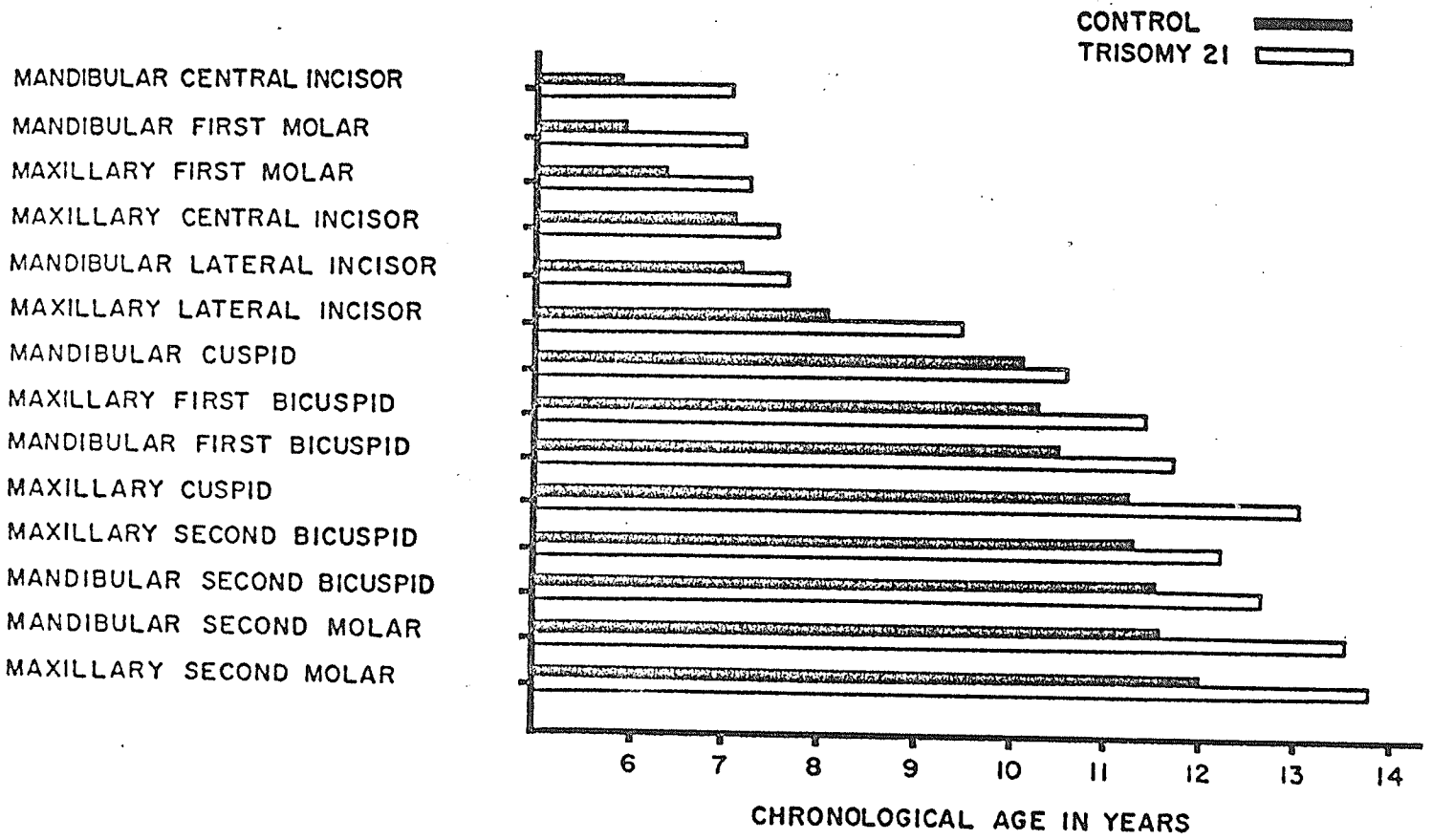

Figure 5. Median eruption age of the permanent teeth for the control group and the trisomy 21 group ranked in chronological order according to the control group.

TABLE XI

Mean, Standard Deviation, Standard Error, and Number for Dental Eruption Age. (Males and Females Combined).

Mid-point of Age Class (Months)	Group	Mean (Months)	SD	SE	No.
66	Control	60.5	2.446	1.000	6
	Trisomy 21	none with erupted permanent teeth			
78	Control	79.2	8.60	3.25	7
	Trisomy 21	69.5	8.50	6.00	2
90	Control	91.8	6.86	2.80	6
	Trisomy 21	81.3	16.85	5.96	8
102	Control	99.7	7.78	2.59	9
	Trisomy 21	103.1	22.65	10.13	5
114	Control	110.6	8.43	2.81	9
	Trisomy 21	99.5	3.27	1.63	4
126	Control	126.0	13.74	5.19	7
	Trisomy 21	112.4	15.01	5.67	7
138	Control	143.8	21.45	7.58	8
	Trisomy 21	124.2	28.11	9.37	9
150	Control	168.4	21.43	7.14	9
	Trisomy 21	142.5	18.26	5.78	10
162	Control	168.8	23.48	9.59	6
	Trisomy 21	150.8	27.52	6.88	16
174	Control	173.5	24.15	8.01	9
	Trisomy 21	172.4	21.47	8.12	7
186	Control	180.0	21.47	9.60	5
	Trisomy 21	180.2	18.63	6.21	9

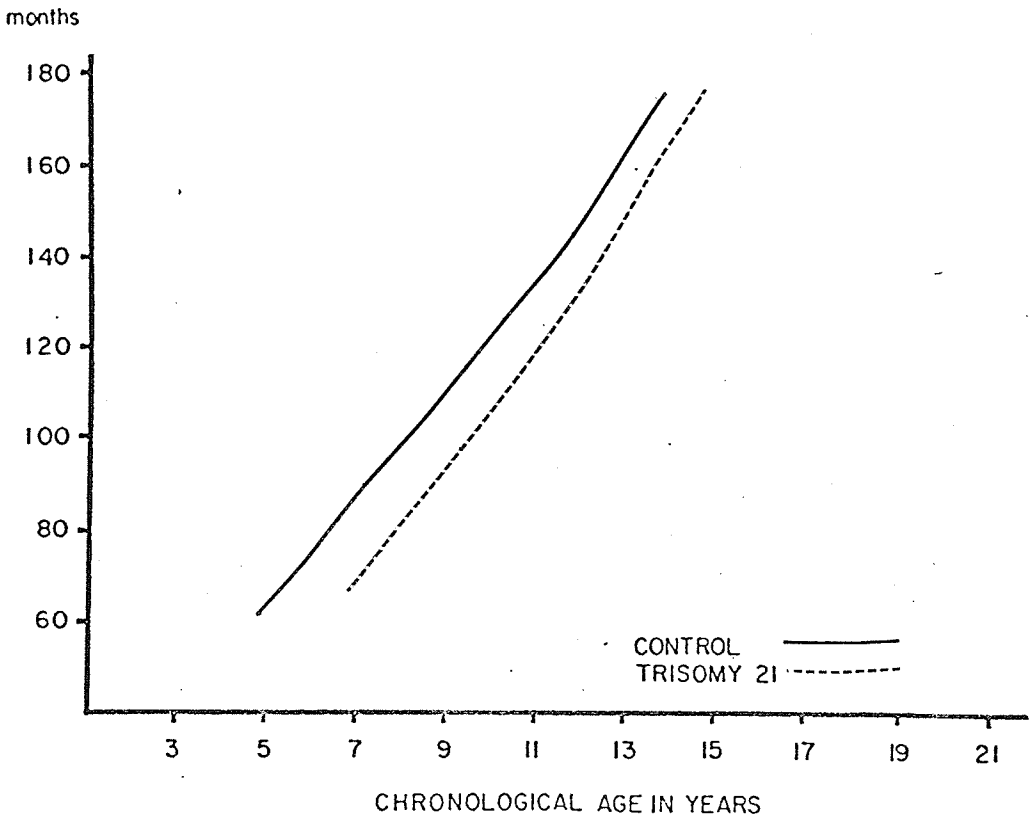

Figure 6 : Effect of Chronological Age on Dental Eruption Age.

the mean scores of both groups to chronological age can be seen in Figure 6. The trisomy 21 group had a smaller mean index at all age levels. In other words they began erupting their teeth later than the control subjects and they completed their eruption later than the control subjects. This difference in eruption time in terms of the dental eruption age calculated, was significant at the one per cent level of confidence. No significant differences could be detected in the rate of increase in dental eruption age between the control group and the trisomy 21 group. This can be seen in the parallel slopes of the lines depicting the relationship of dental eruption age to chronological age for both groups (Figure 6).

Dental Calcification

The calcification of individual teeth was examined in both the control group and the trisomy 21 group by calculating for each developmental stage of each tooth the mean age of all the subjects of each group who were found to have that tooth in that stage. These mean ages, along with their standard deviations and number of subjects are presented in Tables XLII to LVII, Appendix B.

Comparing the two groups on the basis of these values revealed that all teeth developed more slowly in the trisomy 21 group. The retardation in calcification was greatest for the mandibular cuspid, first bicuspid and maxillary cuspid. The difference between the control and trisomy 21 groups was significant for all of the teeth except the maxillary central and lateral incisors and the maxillary first molar.

Calcification rates for individual teeth were assessed by plotting the mean age of attainment for each stage against an arbitrary but standard scale of development. This was done separately for the control group and the trisomy 21 group and is shown in Figures 31 to 46 , Appendix B.

Examining the data in this way revealed a high degree of parallelism in the calcification curves of the trisomy 21 group and the control group. In other words, although there was a delay in calcification of each tooth in the trisomy 21 group, the rate of calcification was similar to

that of the control group.

The standard deviations in mean age at each stage showed little difference between the two groups for most of the teeth studied. Those that did have a larger standard deviation in the trisomy 21 group were the maxillary central incisor, lateral incisor, cuspid and second molar, and the mandibular second molar.

The relationship of dental calcification age to chronological age in both groups is shown in Figure 7. The mean scores for each age group, along with their standard deviations and standard errors are presented for both groups in Table XII. Differences between the trisomy 21 and control groups cannot be adequately assessed in the earliest age groups due to the small number of subjects in the trisomy group at that age.

After age seven years the trisomy 21 group had mean dental calcification ages retarded relative to the control mean ages. The amount of retardation remained relatively constant with advancing chronological age until age fifteen when both groups were mature in terms of dental calcification. The overall retardation in dental calcification calculated as a percentage of the control scores for each age group was 3.5 per cent.

TABLE XII

Mean, Standard Deviation, Standard Error, and Number for Dental Calcification Age. (Males and Females Combined).

Mid-point of Age Class (Months)	Group	Mean (Months)	SD	SE	No.
42	Control	43.3	2.3	1.0	5
	Trisomy 21	---	---	---	--
54	Control	58.3	8.5	2.8	9
	Trisomy 21	46.5	2.0	1.2	3
66	Control	67.2	3.0	1.2	6
	Trisomy 21	71.2	4.6	2.7	3
78	Control	78.8	9.5	3.6	4
	Trisomy 21	85.5	9.9	7.0	2
90	Control	89.2	8.5	3.5	6
	Trisomy 21	65.8	9.0	5.2	3
102	Control	104.1	7.2	2.4	9
	Trisomy 21	94.5	---	---	1
114	Control	117.2	7.4	2.5	9
	Trisomy 21	---	---	---	--
126	Control	126.5	6.2	2.4	7
	Trisomy 21	122.5	13.6	5.2	7
138	Control	134.3	10.6	3.7	8
	Trisomy 21	134.8	8.9	3.6	6
150	Control	153.6	12.5	4.2	9
	Trisomy 21	149.3	7.9	2.8	8
162	Control	158.9	7.2	3.2	5
	Trisomy 21	151.9	8.9	2.7	11
174	Control	162.7	9.6	3.2	9
	Trisomy 21	161.3	9.9	4.4	5
186	Control	166.5	5.9	2.0	8
	Trisomy 21	163.1	6.6	2.5	7

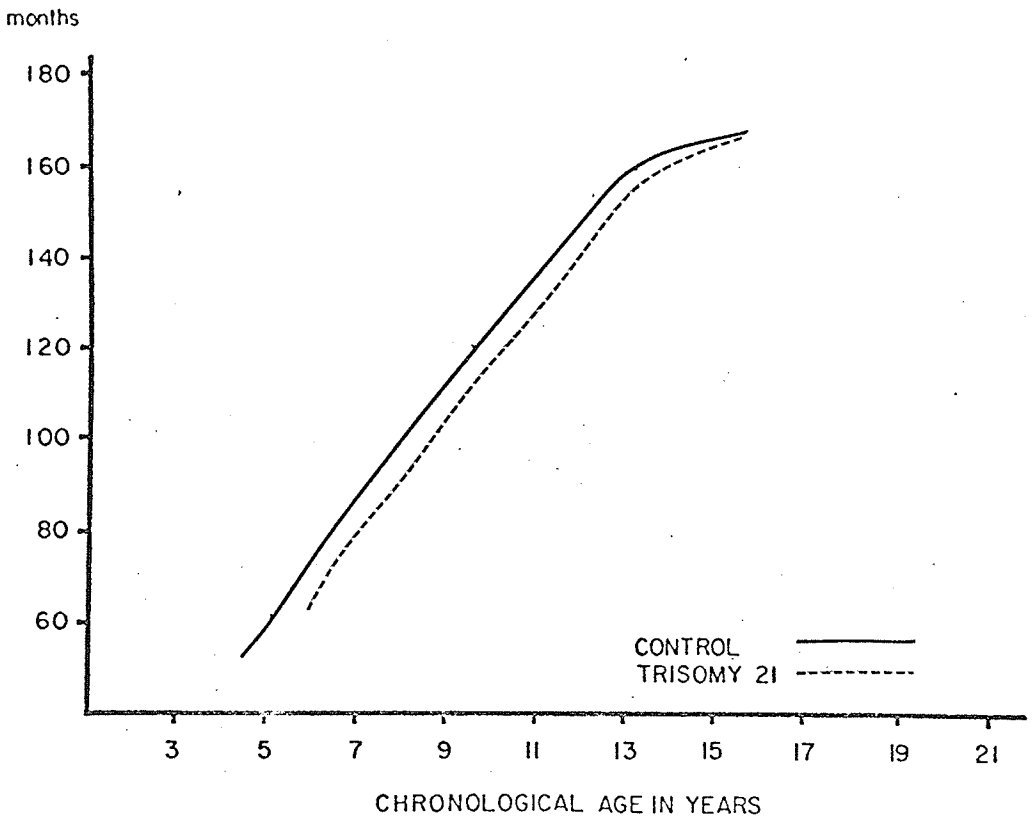

Figure 7 : Effect of Chronological Age on Dental Calcification Age.

Skeletal Maturation

Greulich-Pyle Score

The mean, standard deviation and number for the Greulich-Pyle Score for each age class are presented in Table XIII for the control group and Table XIV for the trisomy 21 group. The relationship of these mean scores to chronological age is shown in Figure 8 for the control group and Figure 9 for the trisomy 21 group. It was found that the males were consistently behind the females throughout the age span studied for both the control group and the trisomy 21 group. This difference was significant at the one per cent level of confidence.

When the trisomy 21 females were compared to the control females (Figure 10) it was found that the trisomy 21 means were less for the early age classes, but by age thirteen years the trisomy 21 means were greater than those of the control females. This trend persisted as chronological age increased with the trisomy 21 females achieving a mature mean score by age sixteen while the control females did not have a mean score at the mature level until age eighteen. This difference was significant at the one per cent level of confidence.

A similar interaction was displayed by the mean Greulich-Pyle Scores for the males (Figure 11). The trisomy 21 males had mean scores much less than those of the control males until approximately age thirteen years.

After this age the trisomy 21 mean scores were greater than those of the control group. The trisomy 21 males achieved a mean score at the mature level by age seventeen years, while the control males had not achieved maturity in this measure by age nineteen years. This difference was also significant at the one per cent level of confidence.

TABLE XIII

Mean, Standard Deviation and Number for Greulich-Pyle Score by Chronological Age Class for the Control Group.

Mid-point Age Class (Months)	Males			Females		
	Mean	SD	No.	Mean	SD	No.
42	30.5	3.0	4	29.0	0.0	1
54	38.8	7.5	4	47.0	7.3	5
66	44.0	9.0	3	48.5	2.1	2
78	62.0	4.2	2	81.5	3.0	4
90	83.0	16.9	2	72.0	9.6	3
102	82.3	9.9	4	86.8	12.8	4
114	95.0	16.9	4	108.2	21.8	5
126	113.0	26.2	3	116.0	12.5	4
138	105.0	22.7	3	127.0	18.3	3
150	133.4	13.8	5	139.0	20.8	4
162	161.0	8.5	2	153.0	9.2	3
174	150.0	32.5	6	164.0	5.2	3
186	177.0	19.3	3	179.0	12.0	3
198	191.2	24.6	4	191.0	11.1	4
210	204.1	21.5	4	206.0	12.7	3
222	211.3	23.4	4	215.0	0.0	3

TABLE XIV

Mean, Standard Deviation and Number for Greulich-Pyle Score by Chronological Age Class for the Trisomy 21 Group.

Mid-point of Age Class (Months)	Males			Females		
	Mean	SD	No.	Mean	SD	No.
42	23.0	0.0	1	11.0	0.0	1
54	30.0	1.7	3	30.5	10.7	6
66	45.5	13.3	4	40.0	14.2	3
78	44.0	7.9	3	65.6	17.7	5
90	65.6	17.8	5	67.3	11.3	4
102	76.0	9.6	6	---	---	-
114	101.1	20.8	4	56.0	0.0	1
126	105.0	22.0	6	111.0	25.0	3
138	105.0	28.4	3	138.2	16.1	5
150	143.0	18.0	3	148.0	22.5	6
162	166.3	33.6	9	156.5	27.9	4
174	186.0	12.2	6	---	---	1
186	183.5	5.7	4	209.0	4.5	5
198	207.0	25.0	3	215.0	0.0	3
210	227.0	0.0	4	215.0	0.0	5
222	227.0	0.0	5	215.0	0.0	4

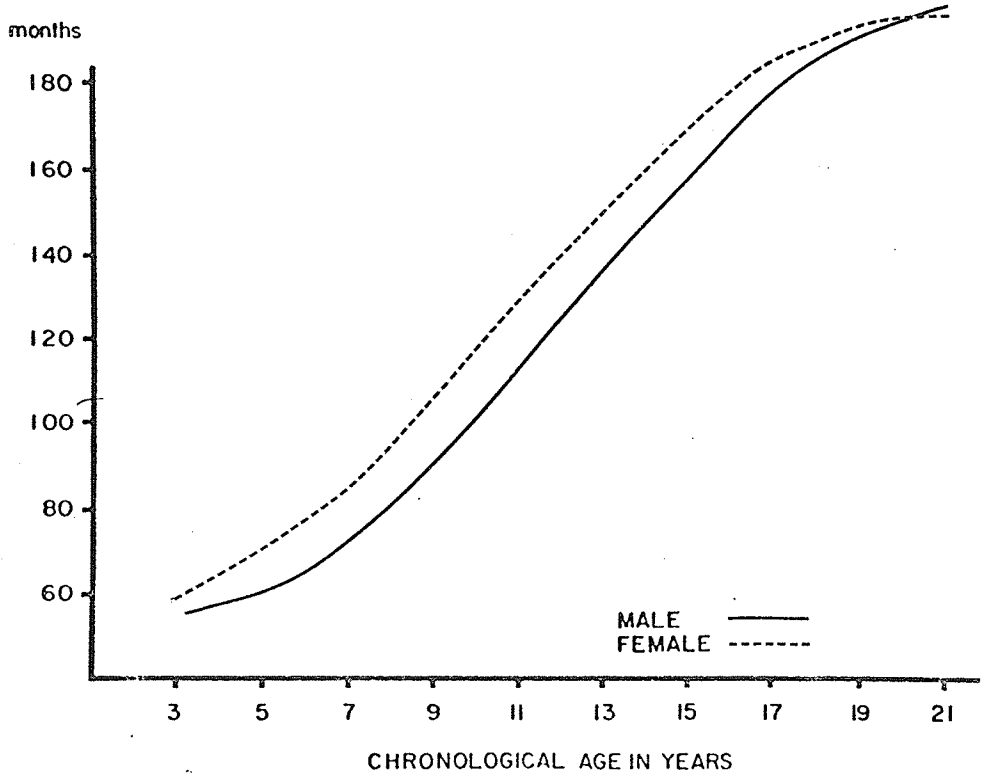

Figure 8. Effect of chronological age on Greulich-Pyle Score for the control group.

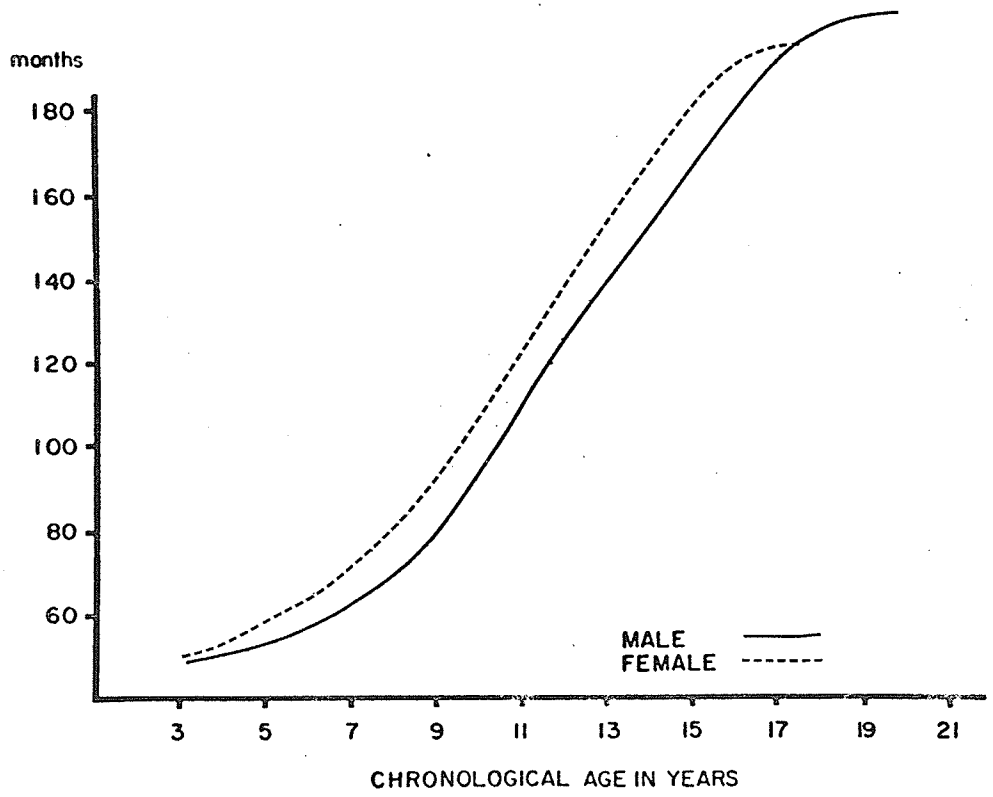

Figure 9. Effect of chronological age on Greulich-Pyle Score for the trisomy 21 group.

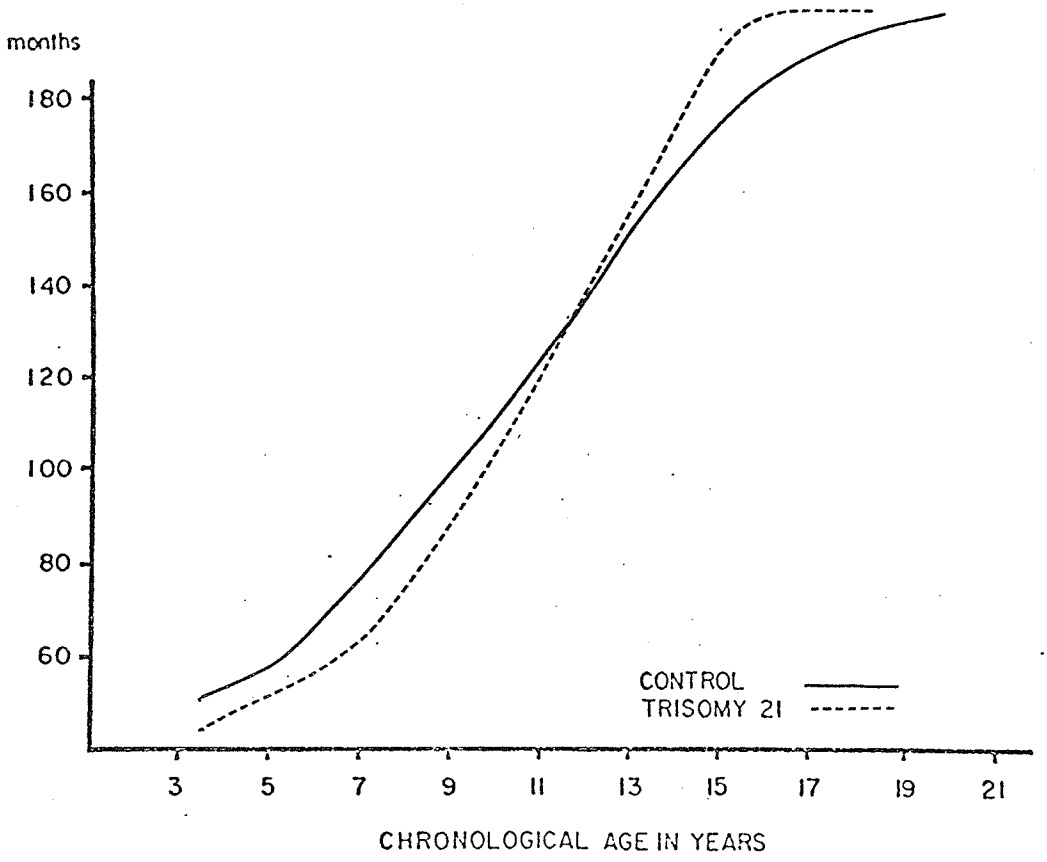

Figure 10. Effect of Chronological Age on Greulich-Pyle Score for Females.

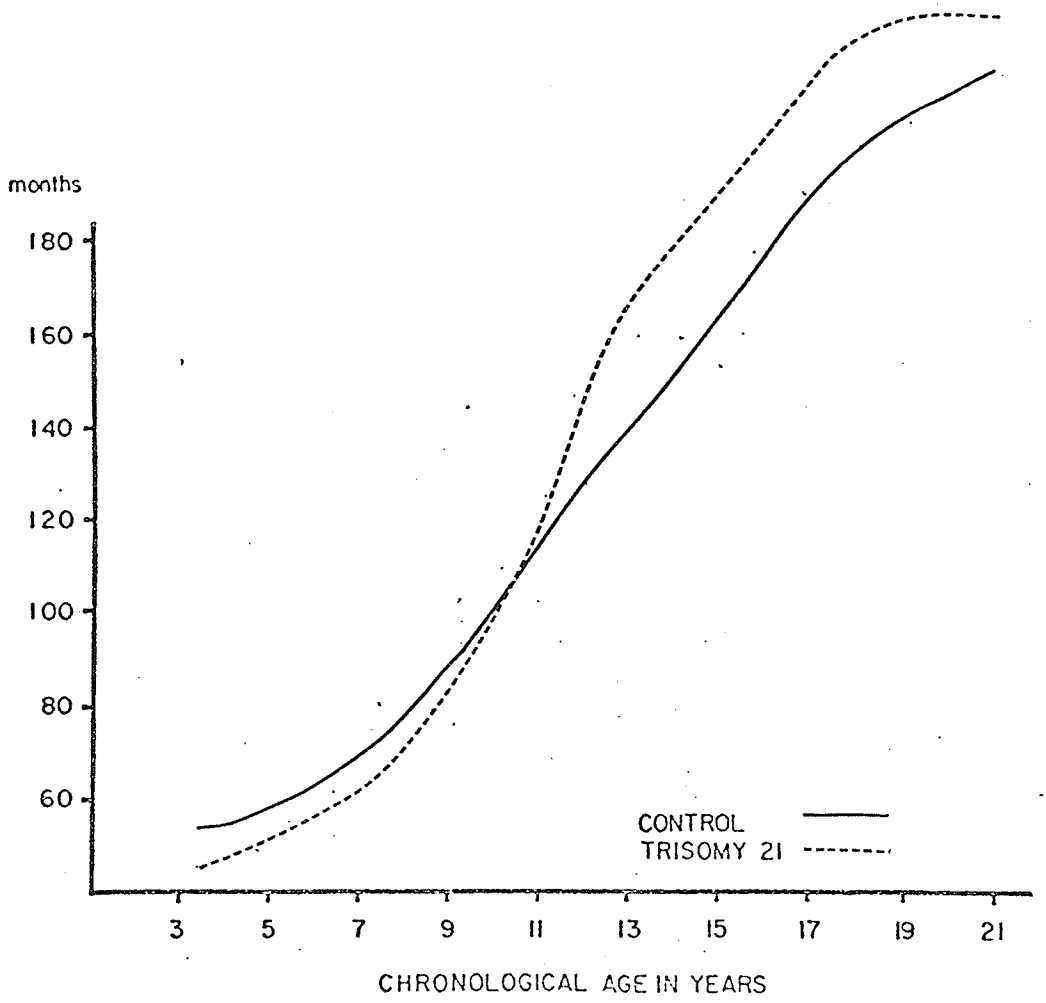

Figure 11. Effect of Chronological Age on Greulich-Pyle Score for Males.

Total Oxford Score

The mean, standard deviation and number for Total Oxford Score for each age class are presented in Table XV for the control group, and Table XVI for the trisomy 21 group. The relationship of these mean scores to chronological age is displayed in Figure 12 for the control group and Figure 13 for the trisomy 21 group. The sex difference in timing of maturation is evident in both groups and is of a similar magnitude in each.

The relationship between the scores of the trisomy 21 females and the control females is shown in Figure 14. As was seen with the mean Greulich-Pyle Scores, the relationship is one of interaction. The early trisomy 21 scores were less than those of the control group but after approximately age thirteen years the trisomy 21 scores were greater. This interaction was significant at the one per cent level of confidence. The trisomy 21 females showed mature mean scores some two to three years ahead of the control females.

The males followed a similar pattern (Figure 15). The trisomy 21 mean scores were less in the early age groups, but after approximately age twelve the trisomy 21 mean scores were greater than those of the control group. Mature scores were reached by the trisomy 21 males by age eighteen years but at that age the control males did not yet show mature scores. This difference in maturation

rate between the trisomy 21 males and the control males was significant at the one per cent level of confidence.

TABLE XV

Mean, Standard Deviation and Number for Total Oxford Score by Chronological Age Class for the Control Group.

Mid-point of Age Class (Months)	Males			Females		
	Mean	SD	No.	Mean	SD	No.
42	50.5	12.9	4	45.5	0.0	1
54	98.0	22.2	4	183.5	49.7	5
66	115.5	20.0	3	195.5	14.1	2
78	195.5	84.9	2	303.0	38.6	4
90	250.5	21.2	2	265.5	34.6	3
102	280.5	52.6	4	370.5	110.3	4
114	358.0	92.5	4	477.5	138.1	5
126	358.3	73.7	3	523.0	149.3	4
138	498.5	58.6	3	624.4	170.0	3
150	537.5	127.5	5	730.5	159.3	4
162	755.5	169.7	2	798.8	81.4	3
174	685.2	270.5	6	908.8	20.8	3
186	822.5	105.0	3	928.8	50.3	3
198	845.5	77.2	4	975.5	45.0	4
210	851.2	65.4	4	955.5	56.5	3
222	920.1	103.2	4	1000.0	0.0	3

TABLE XVI

Mean, Standard Deviation and Number for Total Oxford Score by Chronological Age Class for the Trisomy 21 Group.

Mid-point of Age Class (Months)	Males			Females		
	Mean	SD	No.	Mean	SD	No.
42	55.5	0.0	1	----	--	-
54	58.8	11.5	3	90.5	48.1	6
66	150.5	61.9	4	188.8	46.2	3
78	145.5	43.6	3	247.5	73.9	5
90	247.5	79.8	5	295.5	37.4	4
102	275.5	42.4	6	----	--	-
114	365.5	106.7	4	205.5	0.0	1
126	422.2	133.5	6	522.2	243.5	3
138	438.8	123.4	3	715.5	104.2	5
150	632.2	162.9	3	730.5	177.6	6
162	723.3	181.5	9	773.0	129.7	4
174	824.1	94.6	7	1000	0.0	1
186	883.5	110.3	5	987.5	17.9	5
198	964.3	58.4	8	918.7	132.8	3
210	828.8	288.7	3	1000	0.0	5
222	988.8	10.3	6	1000	0.0	4
	1000	0.0	4	1000	0.0	4
	1000	0.0	3			

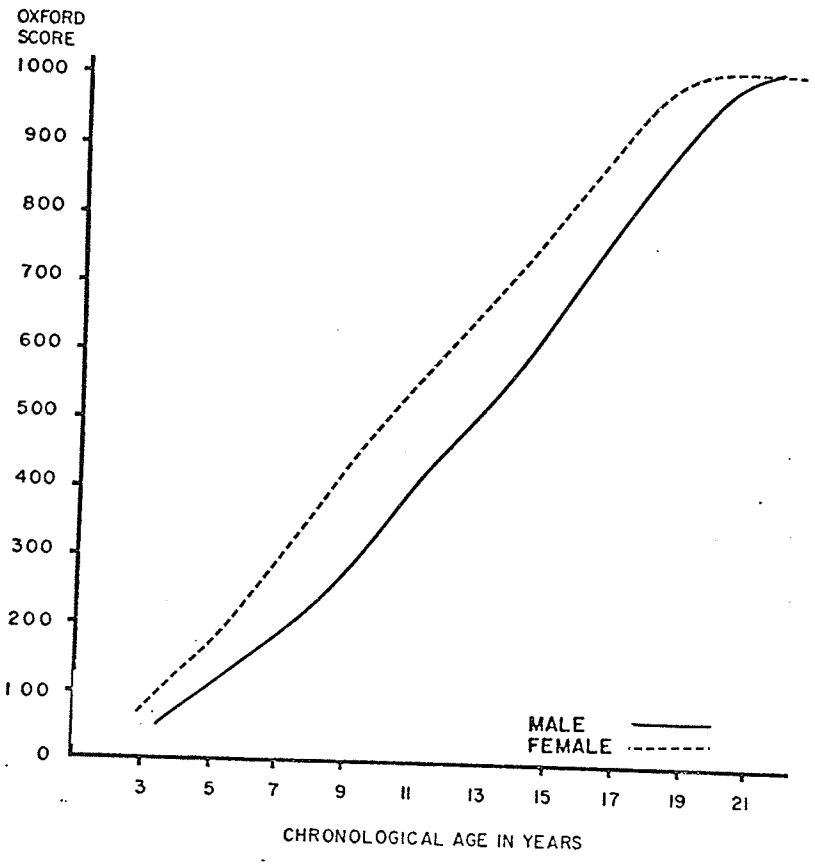

Figure 12. Effect of chronological age on Total Oxford Score for the control group.

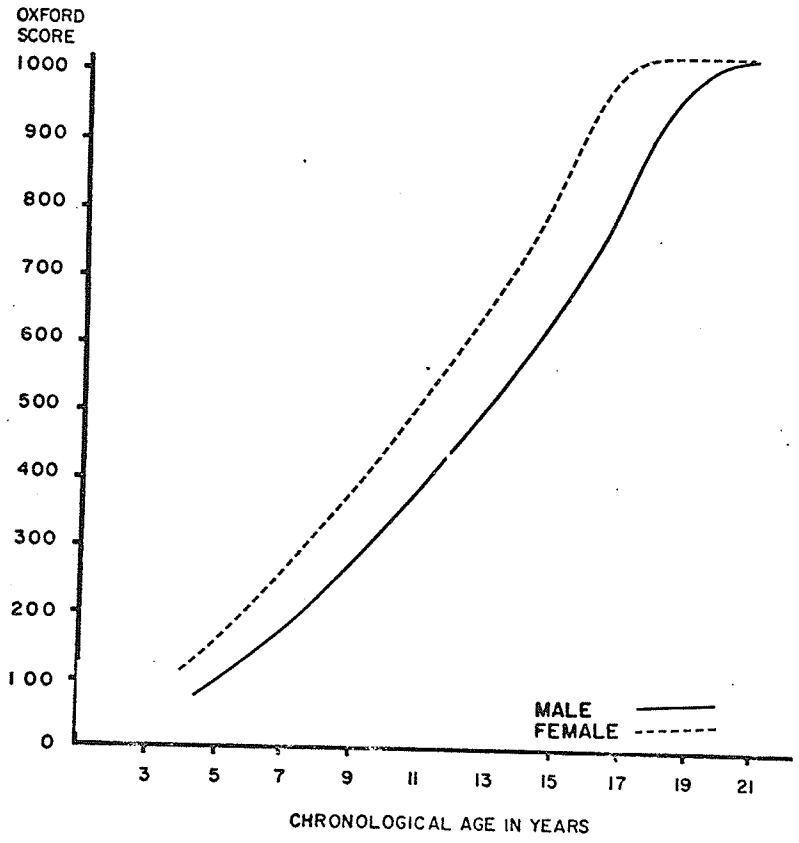

Figure 13. Effect of chronological age on Total Oxford Score for the trisomy 21 group.

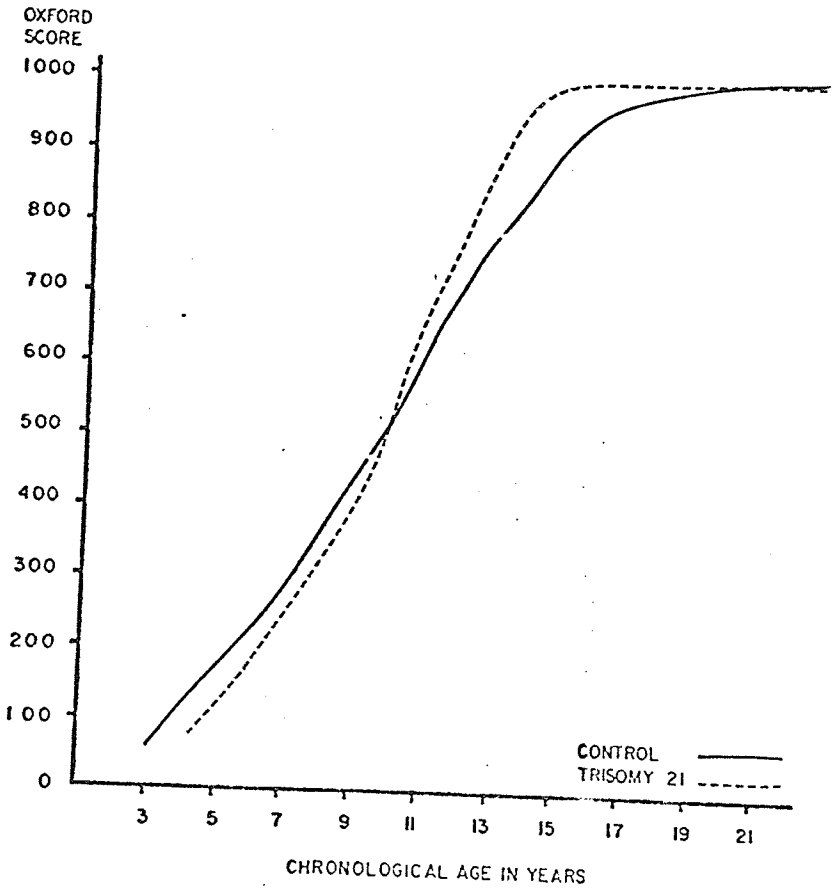

Figure 14. Effect of Chronological Age on Total Oxford Score for Females.

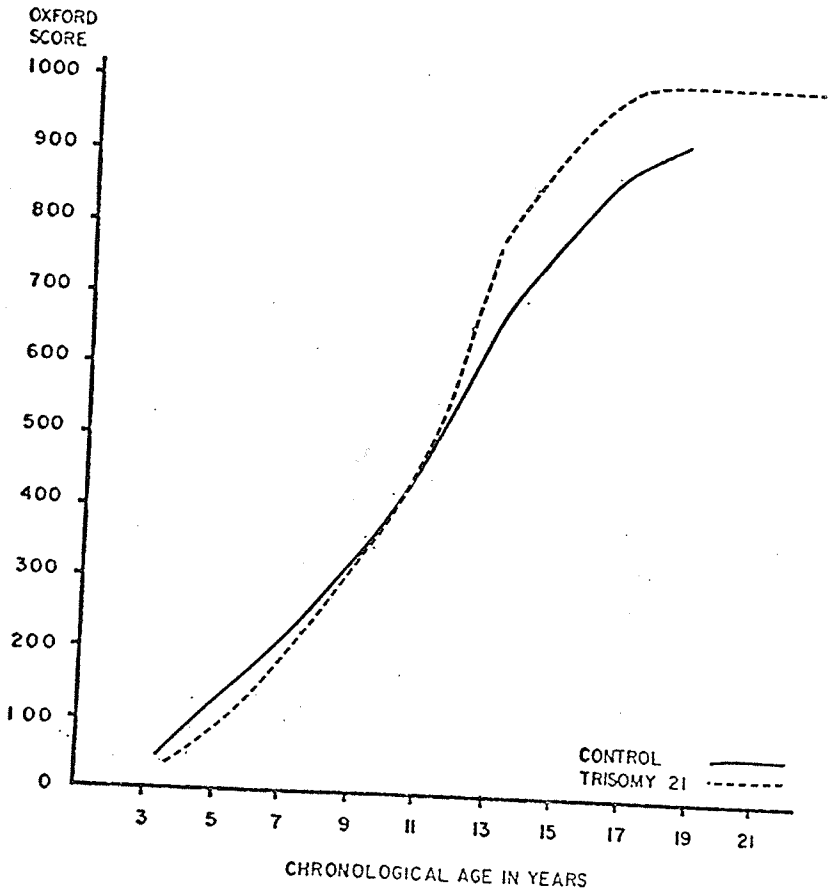

Figure 15. Effect of Chronological Age on Total Oxford Score for Males.

Oxford Carpal Score

One component of the Total Oxford Score is the Oxford Carpal Score. The mean, standard deviation and number for the carpal score are presented in Table XVII for the control group and Table XVIII for the trisomy 21 group. The relationship of these scores to chronological age is shown in Figure 16 for for the control group and Figure 17 for the trisomy 21 group. Again, for both groups the males were found to be behind the females in carpal ossification at all age levels. The sex difference shown by the trisomy 21 group was very similar to that shown by the controls.

When the trisomy 21 females were compared to the control females (Figure 18) it was found that there was no significant difference between the two either in mean score for age or in rate of increase. As well, the time of achievement of mature scores was essentially the same between the two groups at age sixteen years.

Examination of the relationship between the trisomy 21 males and the control males revealed a similar situation (Figure 19). There was no significant difference in carpal development for age, or rate of maturation between the two groups. The trisomy 21 males did show mature scores by age eighteen years but control males did not.

TABLE XVII

Mean, Standard Deviation and Number for Carpal Score by Chronological Age Class for the Control Group.

Mid-point of Age Class (Months)	Males			Females		
	Mean	SD	No.	Mean	SD	No.
42	14.3	7.5	4	18.0	0.0	1
54	26.8	14.4	4	75.0	28.9	5
66	39.7	12.6	3	75.5	10.6	2
78	78.0	42.4	2	136.8	21.4	4
90	125.5	10.6	2	128.0	10.0	3
102	119.3	21.7	4	166.8	40.9	4
114	144.3	22.1	4	204.0	71.9	5
126	156.3	20.8	3	213.0	48.0	4
138	118.0	35.0	3	286.3	112.5	3
150	232.0	65.7	5	348.0	90.6	4
162	390.5	95.5	2	343.0	83.5	3
174	343.0	150.8	6	436.0	36.9	3
186	404.7	30.6	3	443.0	51.9	3
198	421.3	35.0	4	485.0	34.2	4
210	440.4	29.3	4	490.0	33.1	3
222	439.7	32.1	4	492.1	28.6	3

TABLE XVIII

Mean, Standard Deviation and Number for Carpal Score by Chronological Age Class for the Trisomy 21 Group.

Mid-point of Age Class	Males			Females		
	Mean	SD	No.	Mean	SD	No.
42	8.0	0.0	1	--	--	-
54	16.3	7.6	3	38.0	36.2	6
66	60.5	28.7	4	73.0	15.0	3
78	56.3	33.3	3	123.0	23.7	5
90	112.0	38.3	5	140.5	19.4	4
102	128.8	41.2	6	--	--	-
114	160.5	45.6	4	118.0	0.0	1
126	198.8	94.3	6	244.7	113.4	3
138	196.3	62.5	3	316.0	94.8	5
150	296.3	72.9	3	322.2	105.9	6
162	320.8	86.9	9	333.0	72.2	4
174	375.3	51.0	7	500.0	0.0	1
186	440.5	82.1	5	495.0	24.7	5
198	480.2	40.9	8	500.0	0.0	3
210	485.6	32.3	3	500.0	0.0	5
222	500.0	0.0	6	500.0	0.0	4
234	500.0	0.0	4	500.0	0.0	4
246	500.0	0.0	3			

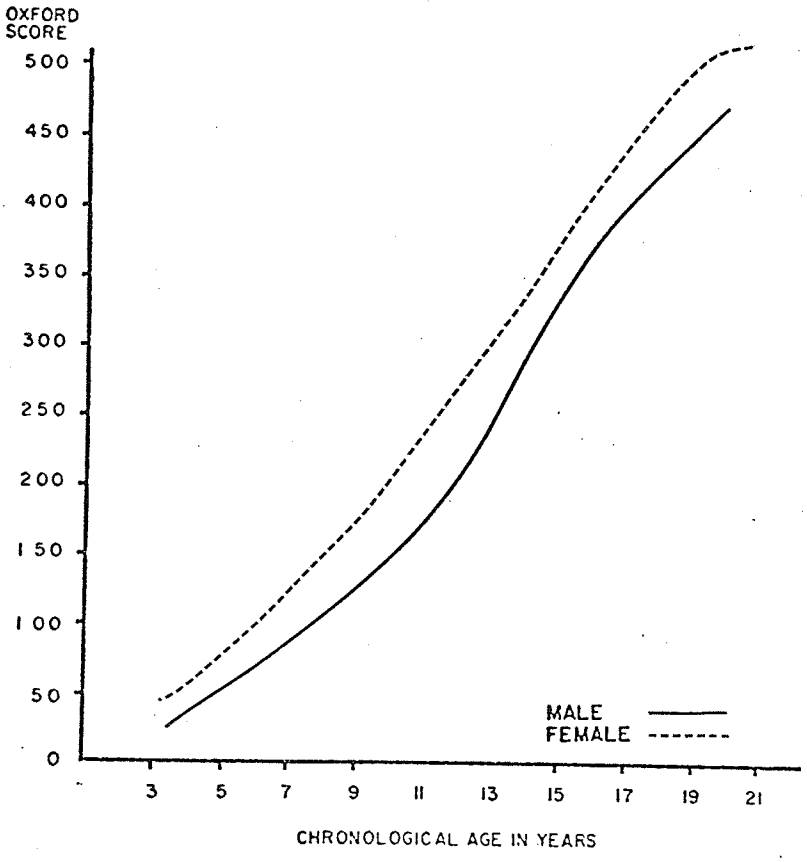

Figure 16. Effect of chronological age on Oxford Carpal Score for the control group.

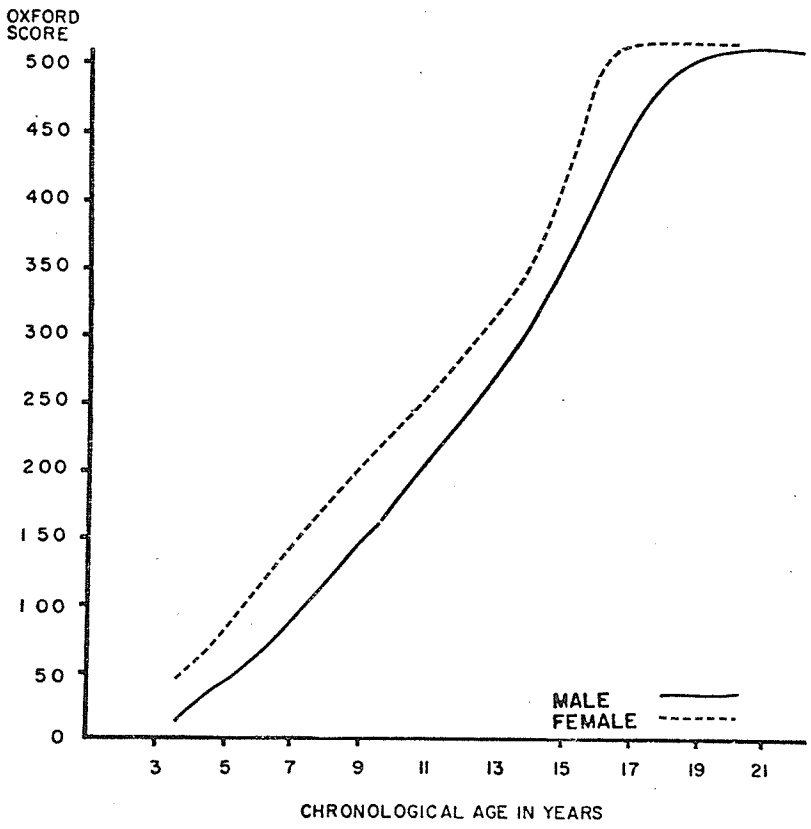

Figure 17. Effect of chronological age on Oxford Carpal Score for the trisomy 21 group.

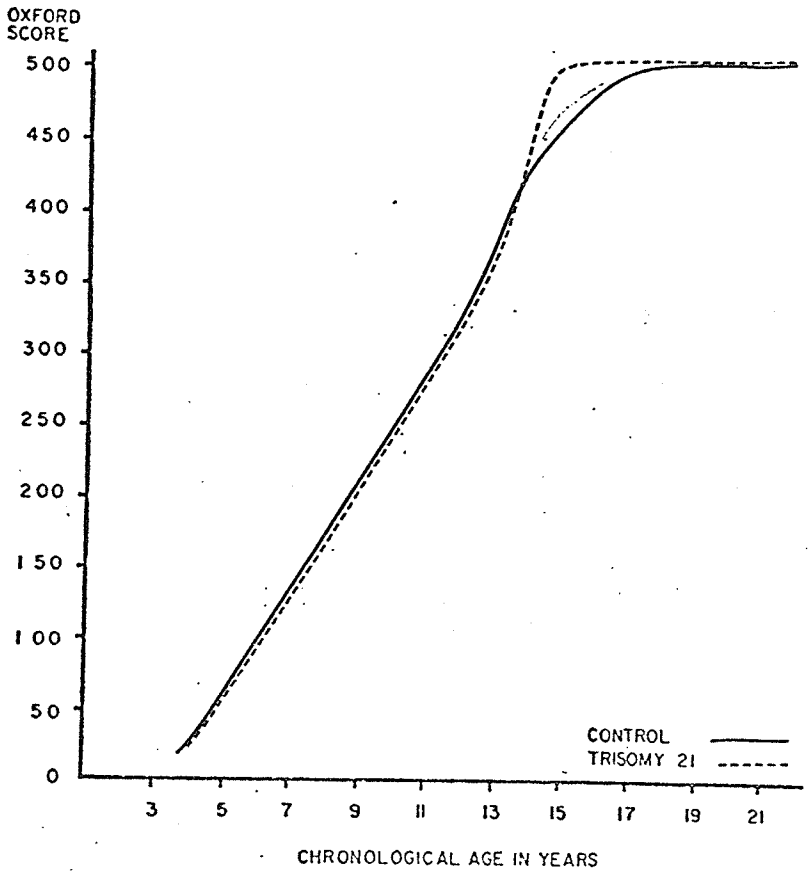

Figure 18. Effect of Chronological Age on Oxford Carpal Score for Females.

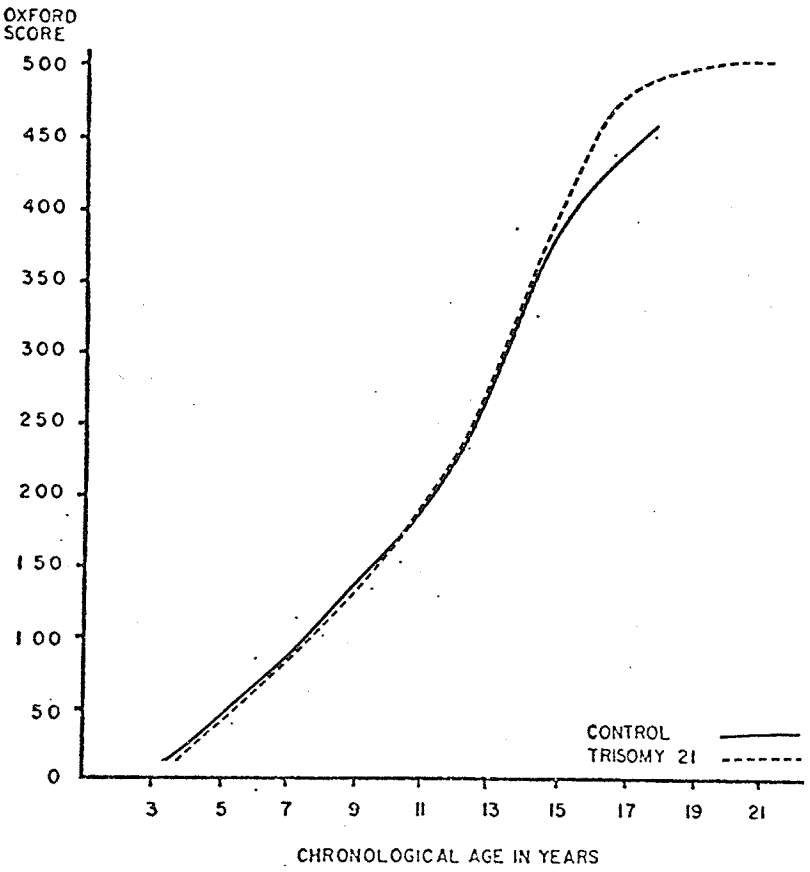

Figure 19. Effect of Chronological Age on Oxford Carpal Score for Males.

Oxford Epiphyseal Score

The second component of Total Oxford Score is the Epiphyseal Score. The mean, standard deviation and number for this score for each age class are presented in Table XIX for the control group and Table XX for the trisomy 21 group. The relationship of these mean scores to chronological age is shown in Figure 20 for the control group and Figure 21 for the trisomy 21 group. Again, the males of both groups were consistently behind the females. In each case the difference was found to be significant at the one per cent level of confidence.

When the trisomy 21 females were compared to the control females (Figure 22) it was found that the trisomy 21 means were less for the early age classes but after age eleven years they were greater. This difference in rate of maturation was significant at the one per cent level of confidence. The trisomy 21 females showed mature scores at age fifteen years while the control females did not until age seventeen years.

When the relationship between trisomy 21 males and control males was examined it was found that a similar situation existed (Figure 23). The initial scores were somewhat lower in the trisomy 21 males than the control males, but after age eleven years the trisomy 21 scores were significantly higher than those of the control males. This difference was significant at the one per cent level

of confidence. The trisomy 21 males showed mean scores in the mature range by age seventeen years while at eighteen years the control males had not yet reached maturity in this measure.

TABLE XIX

Mean, Standard Deviation and Number for Epiphyseal Score by Chronological Age Class for the Control Group.

Mid-point of Age Class (Months)	Males			Females		
	Mean	SD	No.	Mean	SD	No.
42	34.3	15.5	4	33.0	0.0	1
54	69.3	11.1	4	104.0	30.7	5
66	79.7	5.8	3	120.5	31.8	2
78	118.0	35.4	2	166.8	24.9	4
90	120.5	10.6	2	139.7	24.7	3
102	161.8	30.9	4	204.3	70.8	4
114	186.8	37.1	4	275.0	72.2	5
126	201.3	55.1	3	306.8	100.6	4
138	179.7	24.7	3	338.0	60.0	3
150	306.0	69.3	5	380.5	68.5	4
162	365.5	74.2	2	424.7	30.6	3
174	343.0	124.3	6	473.0	22.9	3
186	413.0	88.9	3	484.7	18.9	3
198	413.0	73.1	4	500.0	0.0	4
210	411.6	55.2	4	500.0	0.0	3
222	415.3	53.1	4	500.0	0.0	3

TABLE XX

Mean, Standard Deviation and Number for Epiphyseal Score by Chronological Age Class for the Trisomy 21 Group.

Mid-point of Age Class (Months)	Males			Females		
	Mean	SD	No.	Mean	SD	No.
42	43.0	0.0	1	--	--	-
54	39.7	12.6	3	52.2	15.6	6
66	89.3	37.3	4	113.0	26.1	3
78	88.0	13.2	3	122.0	48.9	5
90	134.0	43.8	5	154.3	21.4	4
102	146.3	19.1	6	--	--	-
114	205.5	62.0	4	88.0	0.0	1
126	213.8	52.0	6	279.7	127.5	2
138	241.3	62.9	3	396.0	36.3	5
150	336.3	94.4	3	408.8	73.5	6
162	401.9	105.6	9	440.5	58.1	4
174	458.0	19.2	6	500.0	0.0	1
186	458.0	27.1	4	498.0	0.0	5
198	496.3	2.9	3	500.0	0.0	3
210	490.0	14.7	4	500.0	0.0	5
222	500.0	0.0	5	500.0	0.0	4

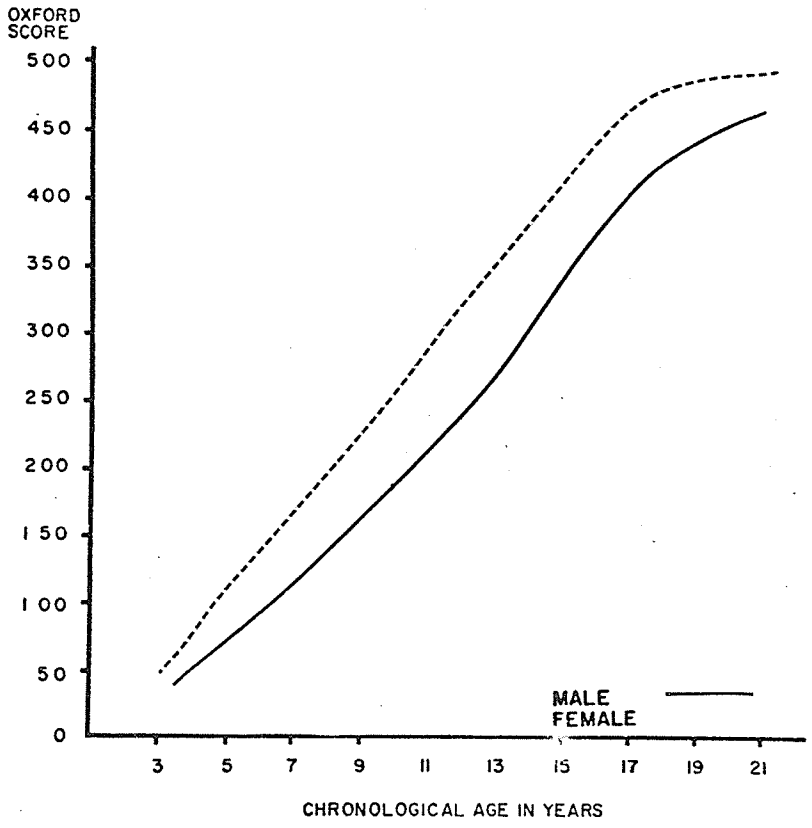

Figure 20. Effect of chronological age on Oxford Epiphyseal Score for the control group.

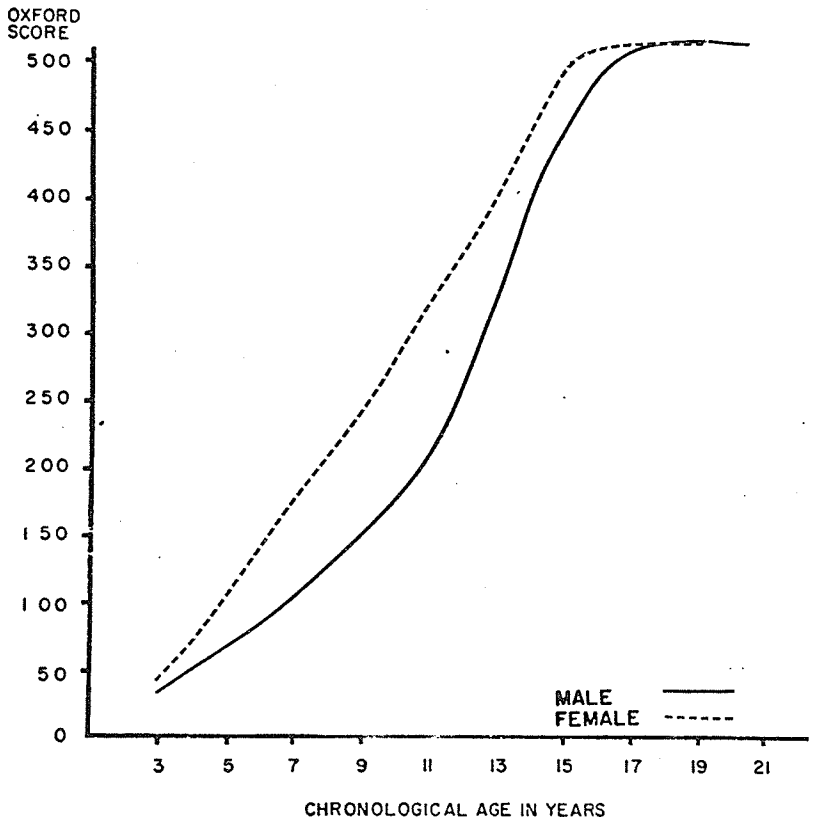

Figure 21. Effect of chronological age on Oxford Epiphyseal Score for the trisomy 21 group.

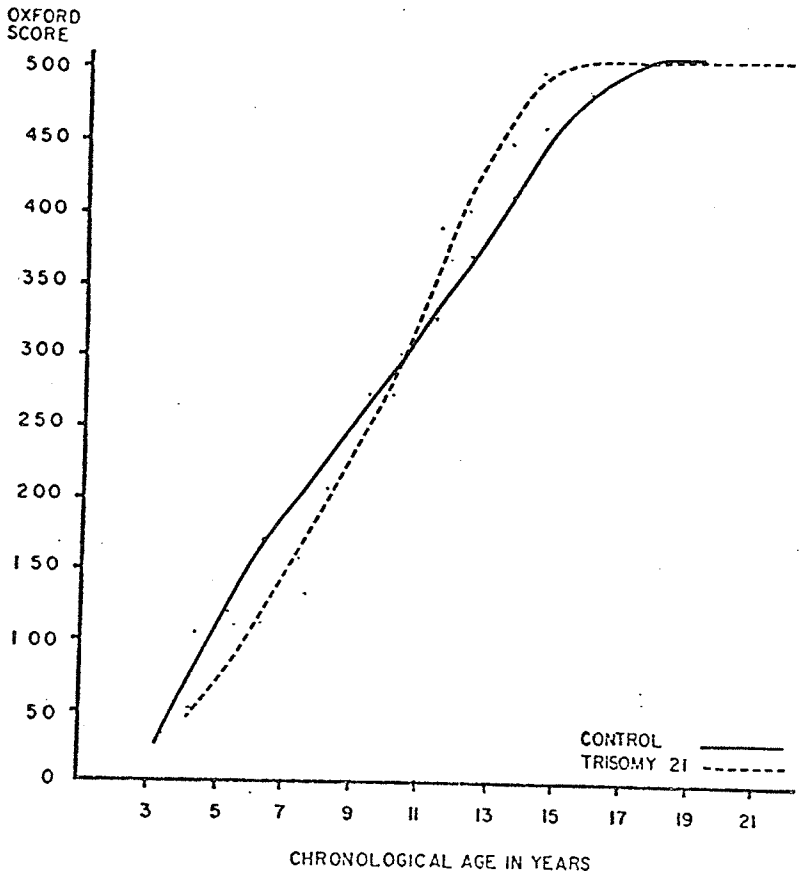

Figure 22 . Effect of Chronological Age on Oxford Epiphyseal Score for Females.

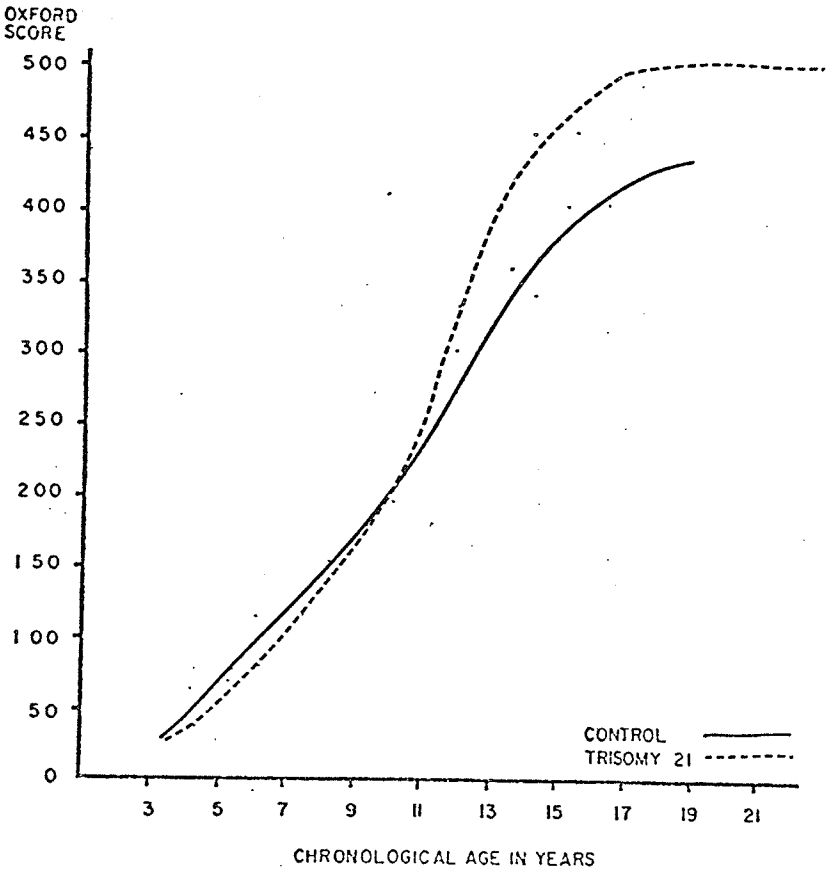

Figure 23. Effect of Chronological Age on Oxford Epiphyseal Score for Males.

Standing Height

The effect of chronological age on the linear measurement standing height is shown in Figure 24 for females and Figure 25 for males. The mean values for each sex of both groups are presented, along with their standard deviations and numbers of subjects in Tables XXI and XXII.

It was found that the mean standing height of the trisomy 21 individuals was less than that of the controls at all age levels for both sexes. The disparity between the mean heights of the trisomy 21 individuals and the controls remained relatively constant in magnitude until age fifteen years in males, and age thirteen years in females. At these age levels the rate of increase in mean standing height with advancing chronological age became much less in the trisomy 21 group, while the control group retained its initial rate of increase until age 17 years in males and age fifteen years in females.

The differences seen in magnitude of standing height between the trisomy 21 group and the control group in both males and females were significant at the one per cent level of confidence. The differences in rate of increase of standing height were also significant at the one per cent level of confidence.

TABLE XXI

Mean, Standard Deviation and Number for the Linear Dimension Standing Height (in inches) for the Control Sample.

Mid-point of Age Class (Months)	Males			Females		
	Mean	SD	No.	Mean	SD	No.
42	37.1	0.7	4	39.6	--	1
54	41.9	3.4	4	42.8	1.3	5
66	42.6	1.0	3	42.3	3.0	3
78	45.6	2.1	3	47.0	1.6	4
90	50.6	1.2	3	48.8	1.8	3
102	50.5	1.2	4	52.3	3.5	5
114	51.7	0.8	4	50.8	1.6	5
126	54.5	2.7	3	53.9	2.0	4
138	54.1	2.7	3	57.2	3.1	5
150	58.9	0.8	4	59.5	4.7	4
162	61.2	5.9	2	61.3	4.4	4
174	63.7	4.7	6	64.9	1.0	3
186	65.7	3.3	3	65.1	3.2	5
198	66.1	4.2	4	63.1	2.5	2
210	67.2	5.1	5	64.4	1.5	4
222	67.2	3.5	4	65.1	1.7	4
234	68.0	3.1	4	65.1	1.8	3

TABLE XXII

Mean, Standard Deviation and Number for the Linear Dimension Standing Height (in inches) for the Trisomy 21 Sample.

Mid-point of Age Class (Months)	Males			Females		
	Mean	SD	No.	Mean	SD	No.
42	---	--	-	25.2	--	1
54	37.3	1.7	2	39.0	2.6	3
66	41.1	0.4	2	39.2	1.3	4
78	43.9	--	1	42.8	6.9	3
90	48.4	4.4	3	43.8	--	1
102	48.1	3.2	5	---	--	-
114	48.1	5.3	3	48.0	--	1
126	49.1	3.8	7	51.5	4.0	5
138	51.6	3.1	3	50.9	4.0	5
150	55.5	3.7	8	55.3	4.2	6
162	57.9	3.7	10	57.3	3.1	7
174	59.0	2.1	8	---	--	-
186	61.5	2.0	8	56.4	1.1	5
198	60.2	2.0	10	59.3	5.2	3
210	59.7	3.3	3	58.1	5.2	5
222	62.1	3.2	7	55.1	2.0	5
234	63.1	2.3	4	57.1	3.9	4
246	64.0	2.1	3	59.2	1.5	2

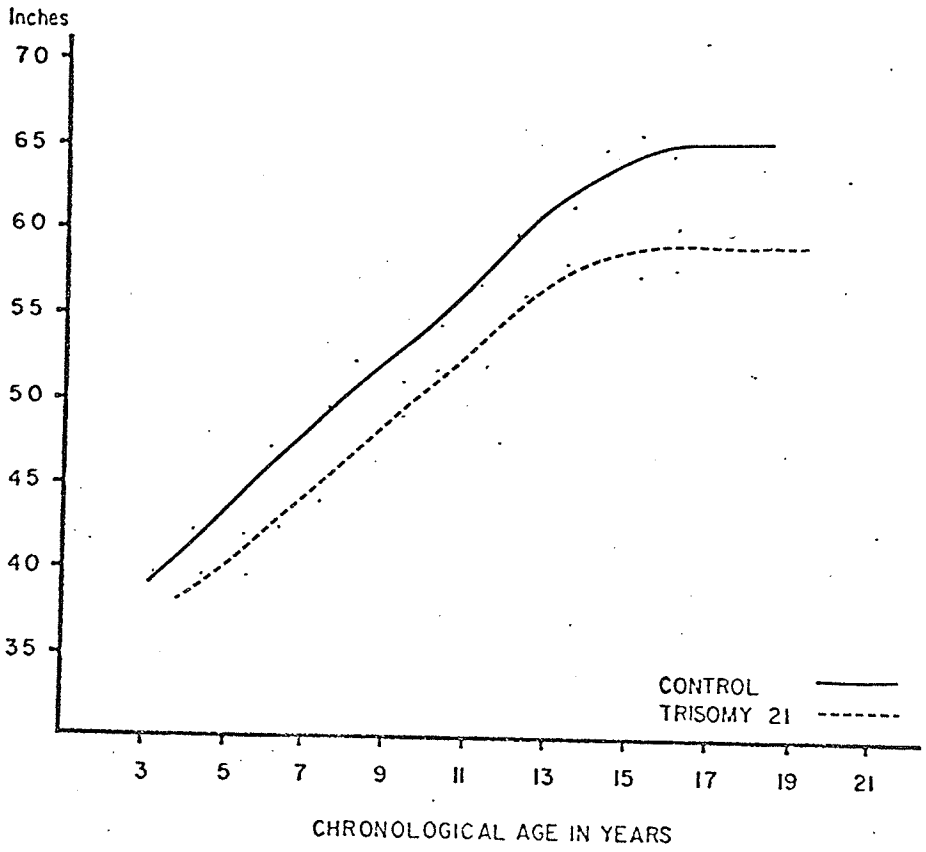

Figure 24 . Effect of Chronological Age on Standing Height for Females.

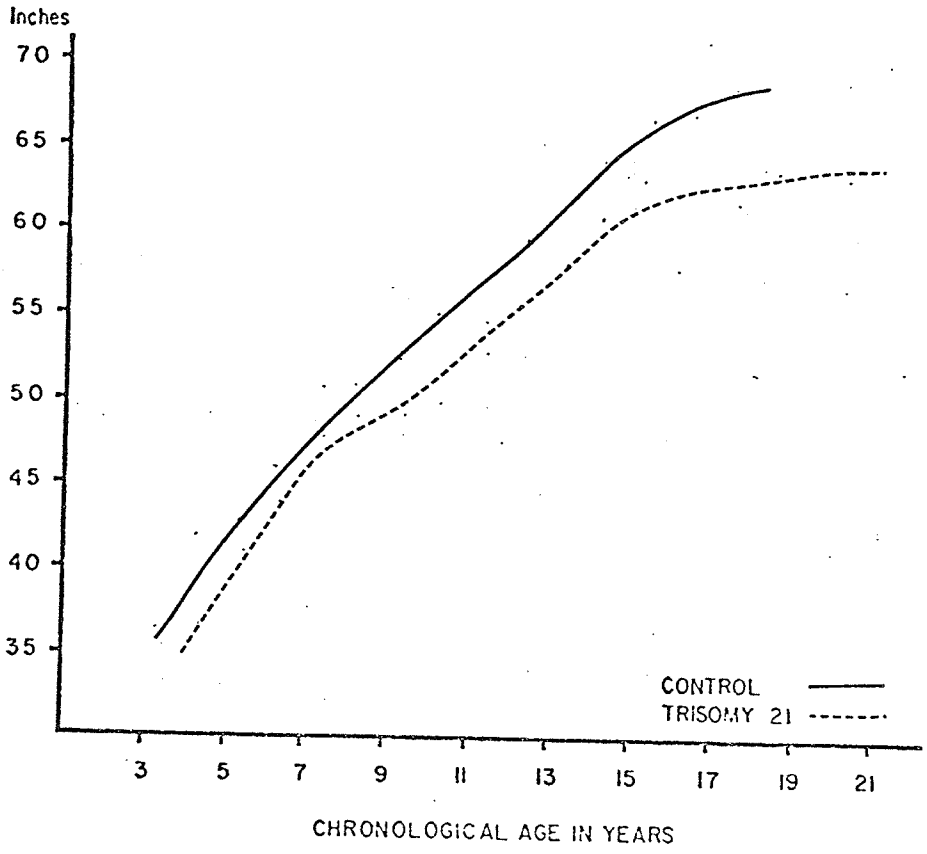

Figure 25 . Effect of Chronological Age on Standing Height for Males.

Mandibular Length

The effect of chronological age on the measurement of mandibular length is shown in Figure 26 for females, and Figure 27 for males. The mean, standard deviation and number of subjects in each age class for each sex for both groups are presented in Table XXIII and Table XXIV.

The trisomy 21 individuals of both sexes were smaller in this dimension than the controls at all age levels. This difference, which was significant at the one per cent level of confidence was largest in the age range three to nine years, diminished somewhat from ten to fifteen years in males and from nine to thirteen years in females. After approximately age fifteen years in males and age thirteen years in females the increase in this dimension appeared to cease in the trisomy 21 group. The female control group showed an increase in mean mandibular length until age sixteen to seventeen years while the control males showed an increase in this dimension until age nineteen years. These differences in rate of increase were significant at the one per cent level of confidence.

TABLE XXIII

Mean, Standard Deviation and Number for the Linear Dimension Mandibular Length (in millimeters) for the Control Sample.

Mid-point of Age Class (Months)	Males			Females		
	Mean	SD	No.	Mean	SD	No.
42	77.5	4.2	4	81.3	--	1
54	85.7	6.8	4	81.3	4.1	5
66	85.3	2.8	3	83.9	4.1	3
78	87.9	2.2	3	89.3	1.6	4
90	92.3	4.4	3	90.1	5.5	3
102	95.3	1.7	4	96.2	6.3	5
114	96.4	2.8	4	93.8	6.1	5
126	101.8	9.9	3	96.1	4.6	4
138	99.6	6.0	3	100.6	3.9	5
150	101.9	4.2	5	104.4	5.9	4
162	107.1	5.4	2	105.2	3.6	4
174	109.3	6.2	6	103.3	5.5	3
186	107.7	3.8	3	109.6	6.1	5
198	113.2	7.1	4	111.5	3.9	2
210	116.2	4.3	4	107.9	6.0	5
222	118.3	5.0	3	111.0	3.6	4
234	118.4	5.1	4	111.3	2.2	3

TABLE XXIV

Mean, Standard Deviation and Number for the Linear Dimension Mandibular Length (in millimeters) for the Trisomy 21 Sample.

Mid-point of Age Class (in months)	Males			Females		
	Mean	SD	No.	Mean	SD	No.
42	----	--	-	50.5	--	1
54	71.4	6.1	3	69.6	7.3	5
66	80.2	9.0	3	77.3	7.9	3
78	75.4	3.5	3	77.2	5.0	4
90	79.9	3.2	5	77.3	7.0	5
102	85.5	8.0	8	----	--	-
114	85.0	6.1	5	81.3	--	1
126	84.8	7.5	7	88.5	8.9	7
138	94.1	3.3	5	87.6	3.1	5
150	94.6	5.1	9	96.9	3.6	6
162	97.4	6.9	10	93.0	6.2	8
174	102.1	4.0	9	93.4	9.3	2
186	103.4	7.0	8	96.9	5.5	5
198	102.2	5.2	11	97.3	5.5	5
210	106.9	3.5	3	94.9	4.3	7
222	106.1	6.1	6	95.6	3.3	5
234	110.6	8.8	3	96.7	2.1	5
246	101.8	4.1	3	99.4	0.7	2

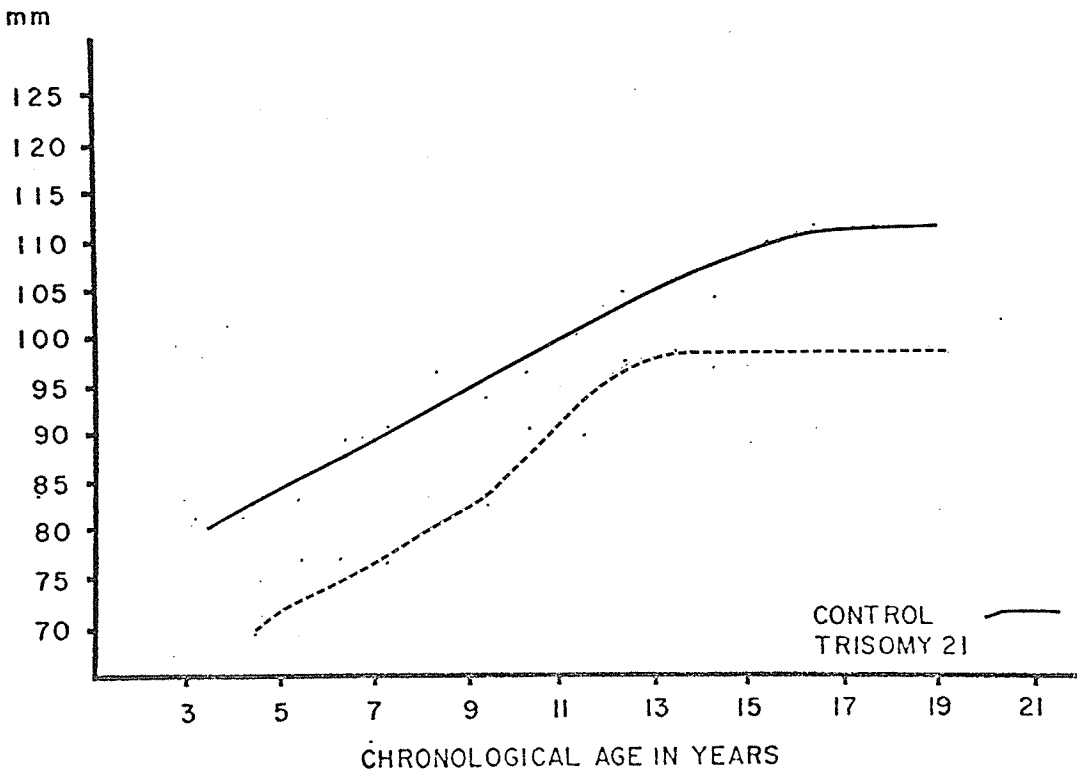

Figure 26. Effect of chronological age on mandibular length for females.

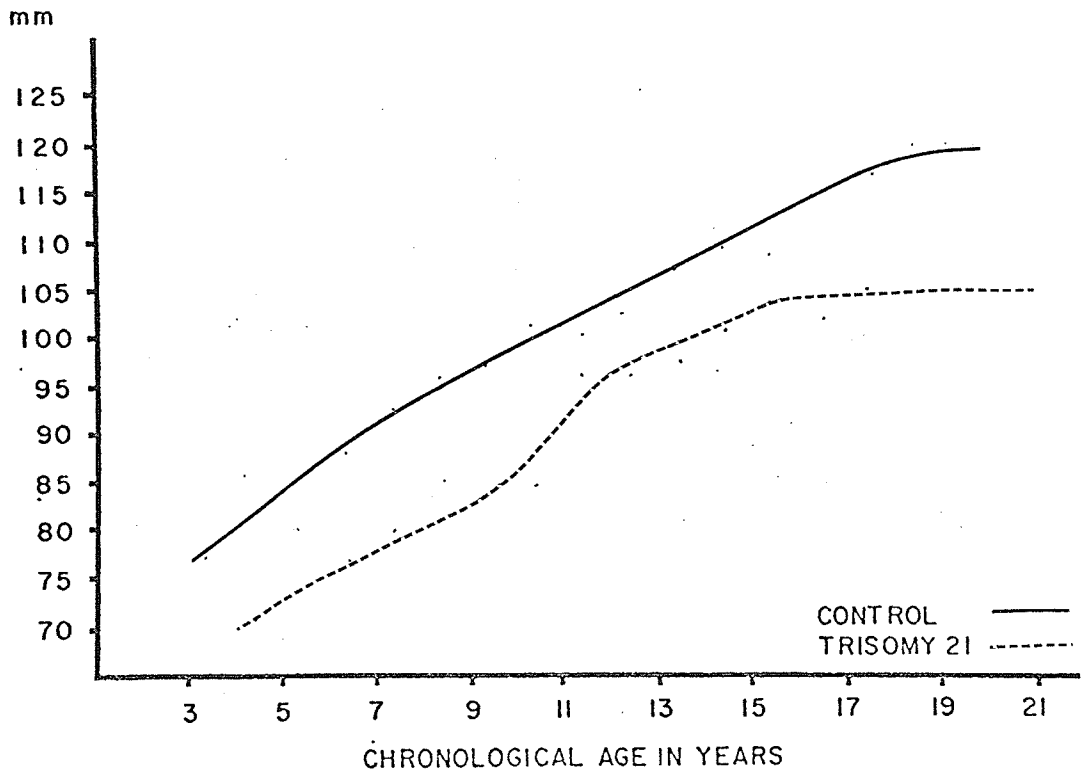

Figure 27. Effect of chronological age on mandibular length for males.

CHAPTER V

DISCUSSION

Maturation of Individual Teeth

The findings of this study with respect to dental eruption confirm the previously reported findings of Barkla (1966 and Cutress (1971), in that all of the teeth studied were delayed in eruption time in the trisomy 21 group, and all showed a greater variability in time of eruption than did those of the control group.

The magnitude of delay, however, varied considerably from that found by these previous investigators. The median eruption times for trisomy 21 subjects reported by Barkla (1966) and Cutress (1971) were uniformly higher than those found in this study. This discrepancy was greatest for the maxillary second bicuspid, where the median reported by Barkla was approximately thirty-two months greater than that found for the trisomy 21 subjects in this study. It is unlikely that this difference between the present study and previous studies can be adequately explained on the basis of sampling differences. All of the studies utilized a primarily Cavcasian sample with roughly equal numbers of individuals living at home and in institutions. The most likely explanation of the difference between these studies lies in the methodology. The data reported on in this

study was derived from both plaster models and panoramic jaw radiographs while the previous studies utilized only visual examination. In this study then, congenitally absent or extracted teeth were not erroneously classified as unerupted teeth. This is no small factor considering the well known high incidence of congenitally missing teeth in trisomy 21 individuals (Barkla, 1966b Odani, 1969).

The teeth showing the most severe retardation in the trisomy 21 group were the maxillary cuspid and the mandibular second molar. The median eruption time of the maxillary cuspid in the trisomy 21 group was 22.8 months greater than that of the control group. The median eruption time of the mandibular second molar was 24.7 months greater than that of the control group. Both of these teeth showed a great amount of variability in eruption time. It was subjectively noted on examination of the panoramic jaw radiographs that many of the maxillary cuspids were impacted. These were classed as unerupted as no clear cut means could be devised to distinguish between impacted and unerupted teeth. In the case of the mandibular second molars, it was noted radiographically that many of these teeth in the trisomy 21 group exhibited an unusual distal inclination associated with non-eruption. This occurred in subjects with and without third molars and with and without apparently adequate space for eruption (Figure 28 to 30).

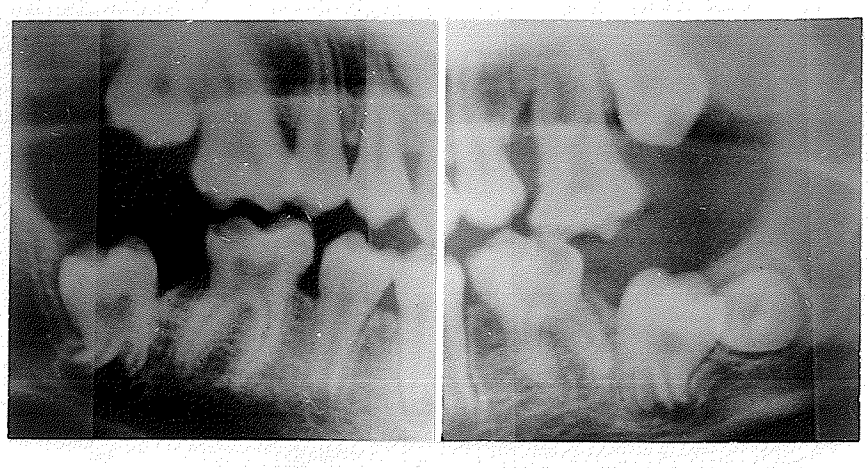

Figure 28. Right and left sides of subject number 186 trisomy 21 female aged 13 years 2 months.

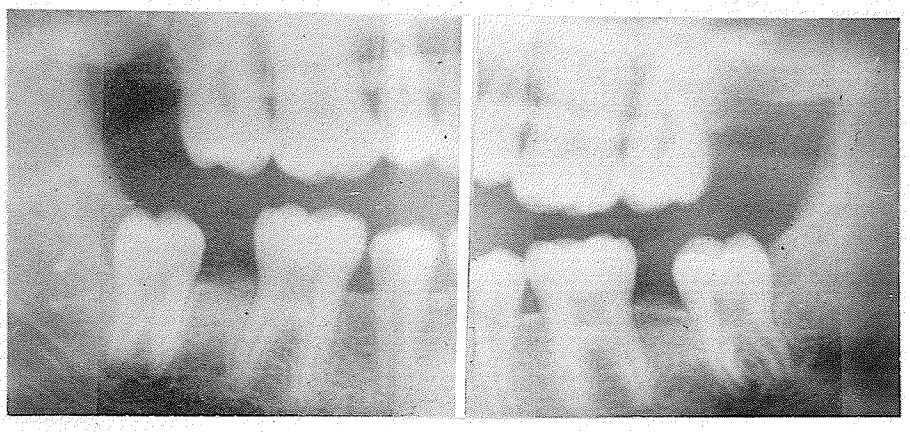

Figure 29. Right and left sides of subject number 90 trisomy 21 male aged 13 years 8 months.

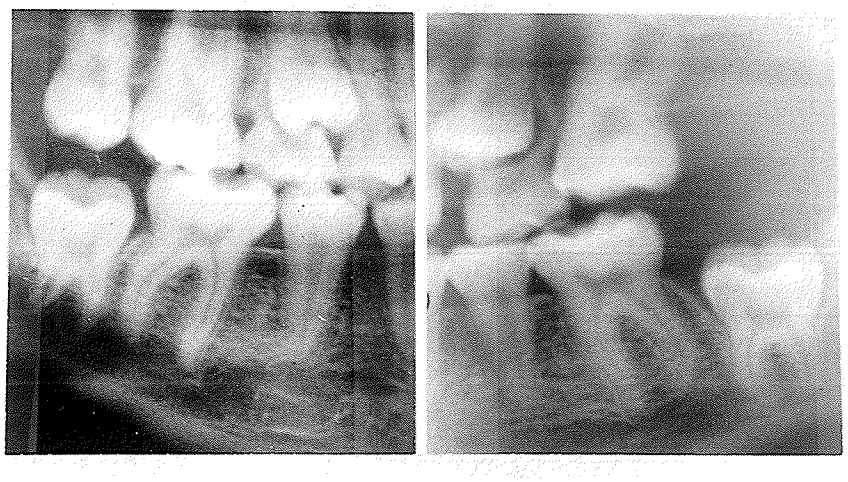

Figure 30. Right and left sides of subject number 222 trisomy 21 male aged 16 years.

In Figure 5 the median eruption ages for both the control and trisomy 21 group are represented by bars. They are ordered vertically according to magnitude of median eruption time in the control group. The only variation from this order in the trisomy 21 group is the maxillary cuspid which was more delayed in median eruption time than one would expect on the basis of the delay seen for the other teeth. This may represent a specific retardation of the eruption process for this tooth, but it seems more likely that it is the result of certain other factors. In normal individuals the maxillary cuspid follows a tortuous path of eruption which is in rather delicate balance. Moreover, it is the last tooth to erupt anterior to the second molars. If conditions become unfavorable for eruption of the maxillary cuspid it frequently becomes impacted. This is especially true when maxillary growth is deficient. A high incidence of horizontal impaction was noted for maxillary cuspids in the trisomy 21 group. This is probably related to the lack of maxillary growth reported for this condition (Kisling, 1966; Ghiz, 1968). If some way to exclude impacted teeth from the analysis of dental eruption could be arrived at it would, in all likelihood, become apparent that the maxillary cuspid in the trisomy 21 group was actually retarded to the same extent as the other teeth. The data on dental calcification show that the

maxillary cuspid is not significantly more retarded in this second measure of dental development than the other teeth examined. In other words there is no retardation of calcification specific to the maxillary cuspid.

The trisomy 21 group showed a retardation to be present in the formation and calcification of each of the fourteen teeth studied. This was present in the earliest stages assessable and persisted throughout development. The rate of progress of the teeth through the stages of development equalled that of the control group. In other words, initiation appeared to be delayed, but subsequent development progressed at a normal rate. It is important to remember that in assessing the stages of development of the teeth in the trisomy 21 group, the overall blunting of the roots was taken into consideration. If they were compared with the controls on the basis of the same ultimate root length a marked retardation would have been evident during the period of root formation. In this study, the development of the teeth was measured in terms of its progress toward the mature configuration in each group and the trisomy 21 group was found to progress at a rate similar to the control group.

The calcification curves for the maxillary and mandibular second bicuspids of the trisomy 21 group displayed an irregularity in that the mean age exhibiting stage "A" (absence of crypt) was much greater than the mean age of

those showing stage "B" (presence of crypt with no calcification) (Figure 34 and Figure 42, Appendix B). This can be explained on the basis of the high incidence of congenital absence of teeth in the trisomy 21 group. No doubt the subjects included in the calculation of mean age showing stage "A" for these teeth included some subjects who were never going to progress to stage "B" due to congenital absence, thus skewing the distribution of ages at this stage in the direction of greater age.

It is interesting to note that in both eruption and calcification the dentition of the trisomy 21 group appeared to be affected as a whole. This is quite different from a characteristic such as congenital absence which has a definite predilection for certain teeth both in "normal" populations and trisomy 21 populations. Presumably dental maturation is determined by multiple genes with additive effects. There is some evidence to indicate that absence of a tooth is a quasi-continuous character directly related to a continuous variation involving the size of the tooth when present (Gruneberg, 1951, 1952; Garn and Lewis, 1969; Garn & others, 1970). In other words, congenital absence is a "threshold effect". If the size of a tooth falls below a certain threshold, it is absent altogether. In support of this is the fact that those teeth most susceptible to absence are the teeth that show the greatest variability in size. In

this connection one might expect to find a similar relation between variability in maturation and congenital absence. "Lateness" in development might have a threshold beyond which no development at all occurs. If this were true, teeth "stable" in terms of congenital absence would show less disturbance of maturation than less stable teeth in a condition such as trisomy 21. No such relationship could be shown to exist.

Dental Eruption Age and Dental Calcification Age

When the control group and the trisomy 21 group were compared on the basis of dental eruption age it was evident that the trisomy 21 group was delayed significantly but that a very parallel relationship existed between the two groups. Calculating the delay shown by the trisomy 21 group gave the following results:

TABLE XXV

Mean Delay in Dental Eruption Age Shown by Trisomy 21 Group.

Mid-point of Age Class. (months)	Mean Delay in Dental Eruption Age Shown by Trisomy 21 Group
78	12.3%
90	11.4%
102	-3.3%
114	9.1%
126	9.3%
138	13.6%
150	15.4%
162	10.7%
174	0.6%
186	0.0%

It can be seen that except for minor variations the trisomy 21 group progressed in eruption at the same rate as the control group, with an average delay of 9.8 per cent until age fourteen to fifteen years when eruption was complete in the trisomy 21 group and no difference in dental eruption age could be distinguished between the control group and the trisomy 21 group.

It has been suggested that a trend toward "normalization" exists in the trisomy 21 phenotype, with regard to certain clinical features (Hall, 1970). The findings reported here would seem to indicate that as far as eruption of the permanent teeth is concerned, a delay is present when the first permanent teeth erupt and remains relatively unchanged with advancing chronological age until the last permanent teeth erupt. The evidence of Roche and Barkla (1964) suggests that a similar relationship exists in the eruption of the primary teeth.

Dental calcification is similar to dental eruption in the trisomy 21 group in that the rate of progress in maturation is equal to that of the control group. There is no evidence of "catch-up" maturation to compensate for the initial delay.

According to the findings of this study calcification of the teeth in trisomy 21 is only slightly retarded when compared to the control group. The retardation was calculated to be 3.5 per cent overall. This is considerably

less than the 9.8 per cent delay seen in dental eruption, and is much less than the 13 per cent delay reported by Garn, Stimson and Lewis (1970). This may be explained by several factors. The study of Garn and co-workers involved a sample of only 25 subjects. Their index of dental development included dental eruption which, as has been shown in this study, is significantly more retarded than dental calcification, and can be affected by impacted teeth. More important, however, is the fact that the standards of root development were not adjusted to allow for the smaller length to width ratios found for the teeth of individuals affected with trisomy 21. This results in an apparent retardation in maturation which is, in reality, an altered morphology.

The greater retardation of dental eruption as opposed to dental calcification in the trisomy 21 group is consistent with current knowledge of these two processes. It is well known that dental calcification is one of the maturity indicators least affected in a wide variety of endocrinopathies and size diminutions (Garn, Lewis and Blizzard, 1965; Keller and others, 1970). Dental eruption, on the other hand, is more likely to show changes secondary to endogenous factors such as nutritional and hormonal imbalances, as well as to exogenous factors such as early loss of deciduous teeth or crowding of the dentition (Bjork, 1956; Garn and others, 1958; Lewis and

Garn, 1960; Fanning, 1961).

It is interesting to note that the variability in dental calcification age in the trisomy 21 group is no greater than that of the control group. This is in contrast to most other measures of maturity or morphology in this condition where an extremely high variability is found.

Genetic, functional, nutritional, endocrine and metabolic factors all play a role in dental development but the quantitative and qualitative effects of each have not been well elucidated as yet (Garn and others, 1965). Longitudinal studies of normal twins and triplets have led to the conclusion that as much as 90 per cent of the variability in normal dental maturation has a genetic basis (Hatton, 1955; Garn and others, 1965; Pavlik, 1968). Whether the effects on dental development of trisomy 21 seen in this study are caused directly by genes affecting dental maturation and carried on the supernumerary chromosome or whether they are secondary to endocrine or metabolic disturbances is impossible to determine at this time. One possible explanation lies in the theory propounded by Bailit and others (1968) in an attempt to explain the generalized delay in dental development seen in children affected with cleft palate. The addition of the extra genic material carried on the supernumerary chromosome in trisomy 21 may cause a breakdown in the polygenic system that controls the development

of the organism and buffers it against environmental stresses. Blakeslee (1959) has reported a number of trisomic plants of the genus Datura. All show morphologic anomalies in most visible characters as well as being slower in growth than normal plants. In competition they are liable to be crowded out by the latter. This failure to thrive is seen dramatically in the other trisomy states known in humans, E group trisomy and D group trisomy (Nelson & others,1969). An obvious exception to this pattern are the sex chromosome aneuploidies (Horowitz, 1972). Individuals with Klinefelter's syndrome have a supernumerary chromosome but are not apparently growth retarded. This can be explained on the basis of X-inactivation (Lyon, 1961, 1962). Even though these individuals have extra chromosomal material their phenotype is expected to be and is much less affected than in autosomal aneuploidies (Lyon, 1970).

Shapiro (1971) has also suggested that a major effect of trisomy is the disruption of evolved chromosomal balance leading to less well-buffered developmental pathways. He predicts that developmental pathways that are relatively less stable in the normal individual would be even more unstable in aneuploid individuals, and accordingly would show more disruption in a condition such as trisomy 21. The findings of this study with regard to dental maturation support this hypothesis. Eruption, known to be an extreme-

ly variable phenomenon in terms of timing was much more affected in the trisomy 21 group than was dental calcification which is known to be a very stable process normally.

Skeletal Development

The skeletal maturation displayed by the control group in this study agreed well with the pattern that has been shown to exist in a large number of "normal" populations that have been investigated in the last half century. Mean development appeared to progress at a steady rate but there was a great deal of individual variation in spite of the fact that the control sample was apparently free of pathological conditions.

Each of the four different measures of skeletal maturity examined showed the control females to be ahead of the control males of the same chronological age. This consistent and normal relationship was paralleled very closely by the trisomy 21 group for each of the four measures. The sex difference in skeletal maturity is thought to be related to genes on the Y chromosome (Tanner and others, 1959), or to genes on the X chromosome (Garn and McCreery,1970). It is in accordance with these views that the autosomal aneuploidy, trisomy 21 displayed a sex difference in skeletal maturation similar in size and character to that seen in a group of control individuals.

The Greulich-Pyle method of assessing skeletal devel-

opment theoretically rules out sex differences by using a separate set of standards for each sex. In spite of this, the males of both the control and the trisomy 21 group scored significantly less than the females of the same group in this measure. This finding would seem to indicate that the difference in skeletal maturation rates between males and females is greater in Manitoba children at present than it was in the Ohio population recorded by Greulich and Pyle in the 1930's. Studies utilizing larger samples than were possible in this work would be necessary to investigate this trend more thoroughly.

In general, the skeletal maturation recorded for the trisomy 21 group in this study was retarded in the youngest age groups, not different from that of the control groups in midchildhood, and accelerated in the later age groups. This is in complete agreement with the findings of Poszonyi and co-workers (1964), and in general agreement with the results reported by Roche (1964). It is, however, at variance with much of the previous literature. The confusion in the literature with regard to skeletal maturation in Down's syndrome can be explained to some extent on the basis of the present findings. From the nature of the relationship shown to exist between the control group and the trisomy 21 group in this study, one can see that if inadequate attention were paid to

grouping the data on the basis of chronological age the true relationship would be obscured. As well, the age of the sample is extremely important. If the sample were predominantly younger an overall retardation in skeletal maturation would be evident. If it were predominantly older the impression would be that skeletal maturation is advanced in Down's syndrome. A sample containing only children in midchildhood would show no difference from a control sample. All of these varying results have been reported. Several additional sources of error are possible. Small samples have been the rule, and this, combined with the large variability that has been shown to exist in individuals affected with trisomy 21 may account for some of the confusing results reported. As well, none of the previous studies utilized control groups geographically and secularly similar to the Down's syndrome group that was examined.

It might be argued that in a cross sectional study an increase in maturation rates in the later age groups is only apparent because there is selection by death of the more severely affected individuals. This may be partly true, but Roche (1964) found a definite difference between early and late skeletal maturation rates in Down's syndrome subjects followed longitudinally. The longitudinal nature and handling of his data ruled out selection by death.

The difference in early and late maturation rates reported by Roche was similar in character to that seen in this study with the exception that Roche did not find the mean skeletal development of the later age groups to exceed that of his control. He pointed out that some affected individuals, however, did mature faster than the control. This difference from the present study may be because Greulich-Pyle standards were used as a control by Roche, rather than utilizing an actual control group. As well, his sample was almost completely institutional, and presumably included the entire institutional population. The sample utilized in this study included only those subjects who, it was felt, could cooperate in the taking of cephalometric radiographs. Bedridden and severely retarded individuals were thus selected out of the sample.

When skeletal maturation was broken down into its epiphyseal and carpal components it became relatively clear that the majority of the difference between the control group and the trisomy 21 group lay in epiphyseal development. Carpal development was almost normal in character.

Differences between the development of round bones and long bones have been reported previously for normal children (Robinow, 1942; Garn and Rohmann, 1959; and Pyle and Sontag, 1943). It is unclear what a difference

such as is seen in the trisomy 21 group means. One cannot assume that genetic factors influencing skeletal growth do so by directly affecting some metabolic or enzymic process in the developing cartilaginous or skeletal tissue. Altered skeletal development may well be secondary to an effect on the hormonal control of the individual. A case in point is the condition of hereditary pituitary dwarfism in the mouse where the primary genetic defect involves the anterior lobe of the pituitary (Gruneberg, 1947).

Altered hormonal control may be due to aberrant hormone production, either quantitatively or qualitatively, genetically altered end organ response, or autoimmune phenomena. Current evidence in the field of endocrine control of osseous development indicates that growth hormone, thyroid hormone, gonadal and adrenal hormones all are sufficiently involved in the control of ossification for imbalances in these to be considered to be possible etiological factors. Roche (1964) has pointed out that a consideration of the incomplete and sometimes conflicting nature of the information available relating to the hormonal changes associated with trisomy 21 makes it clear that their exact nature is still uncertain. The hormonal changes in this condition may well be as variable as are the clinical signs.

The fact that the carpal bones are not as affected as

the epiphyseal areas might lead one to suspect that bone growth involving proliferation of cartilage is more affected than appositional bone growth. The gross appearance of the hand would appear to bear this out. The hands in trisomy 21 are extremely short and broad which could occur if epiphyseal growth were stunted while apposition was relatively unimpaired.

Craniofacial morphology of individuals affected with trisomy 21 is consistent with a hypothesis of greater interference with cartilaginous growth. The middle third of the face is deficient, much as is seen in achondroplastic dwarfs (Mitchell, 1966). The cranial base is short, the maxilla small, and the nasal cartilage reduced in size (Ghiz, 1967; Frostad, 1969; Alimchandani, 1973).

Standing Height

The present findings with respect to standing height in the trisomy 21 group are in general agreement with those previously reported (Brousseau, 1928; Benda, 1949; Oster, 1953; and Roche, 1965). Mean trisomy 21 heights were less than the mean control heights for all age groups. This discrepancy became more pronounced at age thirteen years in females and at age fifteen years in males. Roche (1965) in a large longitudinal study of Down's syndrome clearly demonstrated a similar effect.

In normal individuals there is a close correlation between maturation of bones and elongation of bones (Bayley

and Pinneau, 1952). It would seem reasonable to assume, then, that the pattern seen in growth in standing height in the trisomy 21 group is related to the aberrant skeletal development shown by this group. The early cessation of growth in standing height seen may well be secondary to the early maturation of epiphyseal growth sites and loss of further growth potential.

Roche (1965) found that stature in Down's syndrome actually increased more rapidly than in control individuals during the period from approximately age seven years to age twelve years. This finding, although not apparent in the limited cross sectional data of this study, fits in well with the pattern of skeletal maturation seen. This period of accelerated growth in height corresponds closely with the period of acceleration in epiphyseal maturation seen in this study.

Mandibular Length

This study confirms the findings of previous investigators who have reported the mandible in Down's syndrome to be smaller than normal (Spitzer and Robinson, 1955; Kisling, 1966; and Ghiz, 1967).

The rate of growth in mandibular length in the trisomy 21 group is interesting in that it closely parallels the rate of growth in standing height. Both show some "catch-up" growth in the mid-juvenile period but cease to increase in dimension much earlier than the control individuals.

Ghiz (1967) reported similar results for growth in length of the body of the mandible and growth in height of the ramus of the mandible.

As growth in standing height largely reflects growth at the epiphyses it follows that there should be a close relationship between growth in this dimension and epiphyseal maturation. As was pointed out on page 124 this was in fact the case. Increase in length of the mandible occurs primarily at the mandibular condyle. It has been well documented that this site is not typical of an epiphyseal growth centre. This is true on a histological basis and on the basis of its reactions to pathological situations such as acromegaly or achondroplasia (Sicher, 1957).

Sicher explains these different responses on the basis of the histological evidence. The condylar cartilage of the mandible enlarges primarily by appositional growth involving the proliferation of undifferentiated chrondrogenic mesenchymal cells. The cartilage of an epiphyseal area grows by interstitial cell division of chondrocytes which are in a differentiated state. Among many other things differentiation implies the activation of different enzyme systems of a cell. It is for this reason that genetic defects or hormonal changes can affect mandibular growth in a way different from their effect on epiphyseal growth or different from their effect on cranial base

growth which is also interstitial.

The fact that mandibular and epiphyseal growth rates appear to be affected in a similar manner in trisomy 21 individuals might indicate that the disturbance in cartilaginous growth is due to a more general factor than that seen for example in the autosomal defect known as achondroplasia where the mandible is relatively unaffected (Mitchell, 1966). As well, since growth potential appears to be lost prematurely for mandibular length as well as for standing height it may be reasonable to assume that this is due to something more than simply early epiphyseal fusion as is seen in short stature secondary to hyperthyroidism.

Ghiz (1967) measured maxillary length in a group of trisomy 21 individuals and found the same pattern to be present. There was a spurt of growth evident from age nine years to age thirteen years and then growth ceased earlier than in the control group. Alimchandani (1973) demonstrated a similar pattern for increase in maxillary width. This is evidence in support of a general factor operating to increase growth in the mid-juvenile age period, but it does not rule out cartilage as being the primarily affected growing tissue. Affected growth of the nasal septal cartilage may well be responsible for this pattern of maxillary growth.

CHAPTER VI

SUMMARY AND CONCLUSIONS

The object of the present study was to evaluate maturation of the skeletal and dental systems in the human aneuploid state trisomy 21. The morphological development of the bones of the hand and wrist was assessed as well as growth in standing height and mandibular length. Dental maturation was measured in terms of eruption and calcification.

The sample consisted of 295 individuals ranging in age from three to fifty-five years, all karyotyped and found to have trisomy 21. They were compared with a control sample made up of 161 normal individuals.

Records made included panoramic jaw radiographs, cephalometric radiographs, plaster models of the dental arches and measurement of standing height.

Indices were developed so that dental eruption age and dental calcification age could be calculated for each individual. Skeletal development was assessed using the atlas technique of Greulich and Pyle (1959) as well as the single bone technique of Tanner, Whitehouse and Healy (1961). The findings were evaluated statistically and led to the following conclusions:

1. The trisomy 21 group showed delayed eruption of all permanent teeth. The mean delay in eruption age was 918 per cent.

2. The permanent teeth were each delayed in eruption to a relatively equal extent. Exceptions to this were the maxillary cuspid which was often impacted, and the mandibular second molar which frequently was seen unerupted and in a disto-angular position.

3. Eruption in the trisomy 21 group was much more variable than in the control group.

4. Calcification of the permanent teeth in the trisomy 21 group progressed at the same rate as in the control group, but was initially and throughout retarded an average of 3.5 per cent.

5. The permanent teeth of the trisomy 21 group were all affected in calcification to a similar degree.

6. Dental calcification in the trisomy 21 group was no more variable than in the control group.

7. Sex differences in skeletal maturation in the trisomy 21 group were found to be similar to those of the control group.

8. Maturation of the carpal bones in the trisomy 21 group progressed at a rate very similar to that of the control group, and no differences between the two groups in this measure could be ascertained.

9. Maturation of the epiphyseal areas in the hand and wrist in the trisomy 21 group was retarded in the youngest age groups but was equal to the control values in mid-childhood and was actually greater than control values at

puberty so that finally, epiphyseal maturity was reached by the trisomy 21 group approximately 2 years earlier than the control group.

10. Mean standing height of the trisomy 21 group was less than that of the control group for all age groups. The discrepancy between the two groups became greater at age thirteen years in females and age fifteen years in males as trisomy 21 mean height failed to increase further with advancing age while the control group increased in this dimension for several more years.

11. Mean mandibular length of the trisomy 21 group was smaller than that of the control group at all age levels. An increased rate of growth shown by the trisomy 21 group in midchildhood caused this discrepancy to lessen, but then an early cessation of growth in the trisomy 21 group caused the difference in size between the two groups to increase in the older age groups.

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APPENDIX A

NOMENCLATURE OF THE PERMANENT DENTITION

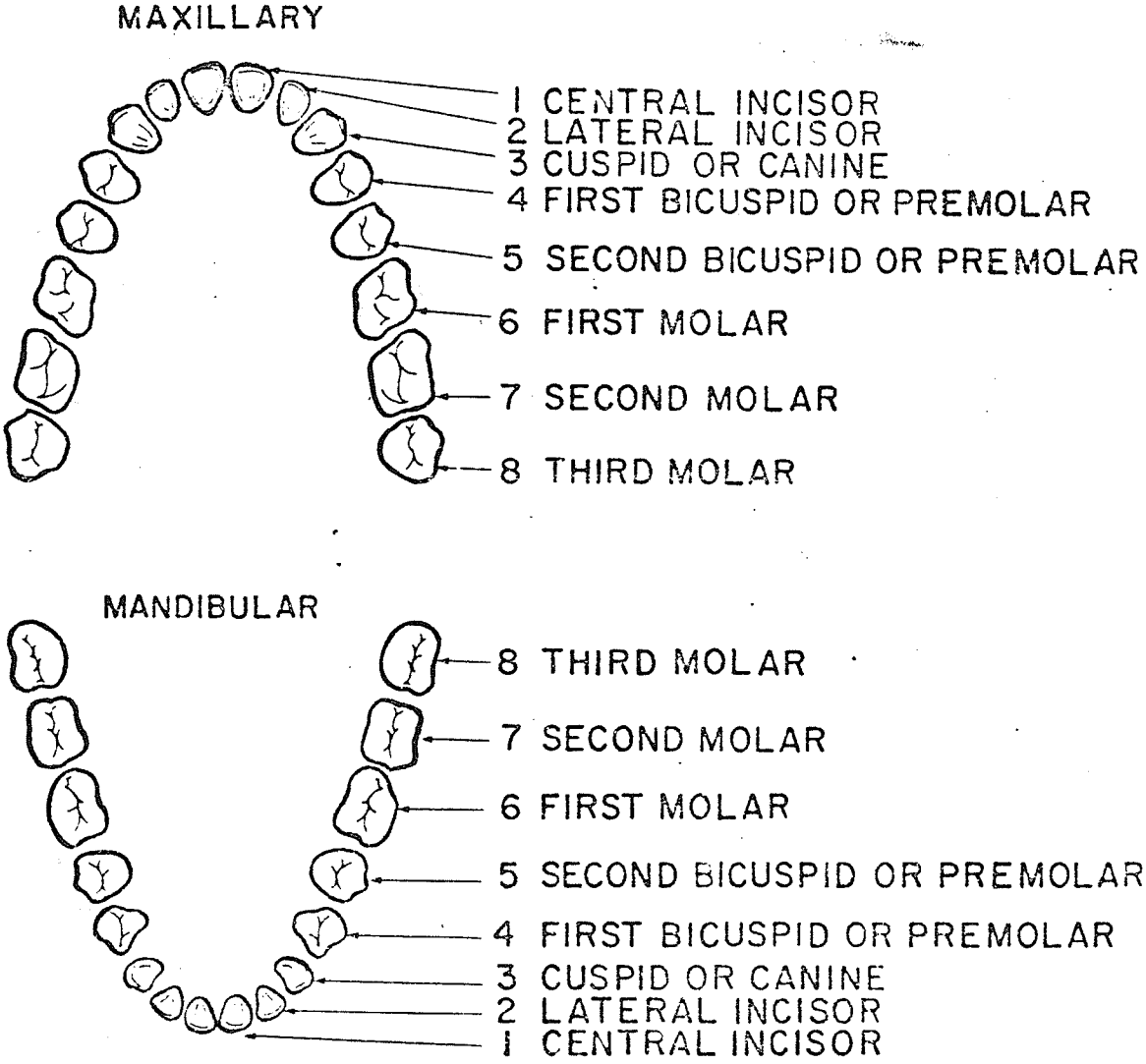

TABLE XXV

Probability of Eruption (from Probit Analysis of Control Data)

MAXILLARY CENTRAL INCISOR

Chronological Age (months)	Probability of Eruption	Chronological Age (months)	Probability of Eruption
less than 54	.00	87	.53
54	.01	88	.56
58	.02	89	.59
60	.03	90	.62
62	.04	91	.65
64	.05	92	.67
65	.06	93	.70
66	.07	94	.73
67	.08	95	.75
68	.09	96	.77
69	.11	97	.79
70	.12	98	.81
71	.14	99	.83
72	.15	100	.85
73	.17	101	.87
74	.19	102	.88
75	.21	103	.90
76	.24	104	.91
77	.26	105	.92
78	.28	106	.93
79	.31	107	.94
80	.33	108	.95
81	.36	110	.96
82	.39	112	.97
83	.42	114	.98
84	.45	118	.99
85	.48	more than 118	1.00
86	.50		

TABLE XXVI

Probability of Eruption (from Probit Analysis of Control Data)

MAXILLARY LATERAL INCISOR

Chronological Age (months)	Probability of Eruption	Chronological Age (months)	Probability of Eruption
less than 81	.00	99	.53
81	.01	100	.58
83	.02	101	.63
84	.03	102	.67
85	.04	103	.73
86	.05	104	.77
87	.07	105	.81
88	.09	106	.84
89	.11	107	.87
90	.13	108	.90
91	.16	109	.92
92	.20	110	.94
93	.24	111	.95
94	.28	112	.96
95	.32	113	.97
96	.37	114	.98
97	.42	116	.99
98	.48	more than 116	1.00

TABLE XXVII

Probability of Eruption (from Probit Analysis of Control Data)

MAXILLARY CUSPID

Chronological Age (months)	Probability of Eruption	Chronological Age (months)	Probability of Eruption
less than 98	.00	134	.50
98	.01	135	.53
102	.02	136	.56
105	.03	137	.58
107	.04	138	.61
109	.05	139	.63
110	.06	140	.65
111	.07	141	.68
112	.08	142	.70
113	.09	143	.72
114	.10	144	.75
115	.11	145	.76
116	.12	146	.78
117	.14	147	.80
118	.15	148	.82
119	.17	149	.84
120	.19	150	.85
121	.21	151	.87
122	.23	152	.88
123	.25	153	.89
124	.27	154	.90
125	.29	155	.91
126	.31	156	.92
127	.33	157	.93
128	.36	158	.94
129	.38	159	.95
130	.40	161	.96
131	.43	163	.97
132	.46	166	.98
133	.48	170	.99
		more than 170	1.00

TABLE XXVIII

Probability of Eruption (from Probit Analysis of Control Data)

MAXILLARY FIRST BICUSPID

Chronological Age (months)	Probability of Eruption	Chronological Age (months)	Probability of Eruption
less than 90	.00	124	.53
90	.01	125	.55
94	.02	126	.58
96	.03	127	.61
98	.04	128	.64
100	.05	129	.66
101	.06	130	.69
102	.07	131	.71
103	.08	132	.74
104	.09	133	.76
105	.10	134	.78
106	.12	135	.80
107	.13	136	.82
108	.15	137	.84
109	.16	138	.85
110	.18	139	.87
111	.20	140	.88
112	.22	141	.90
113	.24	142	.91
114	.26	143	.92
115	.29	144	.93
116	.31	145	.94
117	.34	146	.95
118	.36	148	.96
119	.39	150	.97
120	.42	152	.98
121	.44	156	.99
122	.47	more than 156	1.00
123	.50		

TABLE XXIX

Probability of Eruption (from Probit Analysis of Control Data)

MAXILLARY SECOND BICUSPID

Chronological Age (months)	Probability of Eruption	Chronological Age (months)	Probability of Eruption
less than 95	.00	135	.51
95	.01	136	.53
100	.02	137	.55
103	.03	138	.58
105	.04	139	.60
107	.05	140	.62
108	.06	141	.64
110	.07	142	.67
111	.08	143	.69
112	.09	144	.71
113	.10	145	.73
114	.11	146	.75
115	.12	147	.76
116	.14	148	.78
117	.15	149	.80
118	.16	150	.82
119	.18	151	.83
120	.19	152	.85
121	.21	153	.86
122	.23	154	.87
123	.25	155	.88
124	.26	156	.90
125	.28	157	.91
126	.30	159	.92
127	.33	160	.93
128	.35	161	.94
129	.37	163	.95
130	.39	164	.96
131	.41	167	.97
132	.44	170	.98
133	.46	174	.99
134	.49	more than 174	1.00

TABLE XXX

Probability of Eruption (from Probit Analysis of Control Data)

MAXILLARY FIRST MOLAR

Chronological Age (months)	Probability of Eruption	Chronological Age (months)	Probability of Eruption
less than 47	.00	77	.52
47	.01	78	.55
50	.02	79	.58
52	.03	80	.61
55	.04	81	.64
56	.05	82	.67
57	.06	83	.70
58	.07	84	.72
59	.09	85	.75
60	.10	86	.77
61	.11	87	.79
62	.13	88	.82
63	.15	89	.84
64	.16	90	.86
65	.18	91	.87
66	.21	92	.89
67	.23	93	.90
68	.25	94	.91
69	.28	95	.93
70	.31	96	.94
71	.33	97	.95
72	.36	99	.96
73	.39	101	.97
74	.42	103	.98
75	.45	106	.99
76	.49	more than 106	1.00

TABLE XXXI

Probability of Eruption (from Probit Analysis of Control Data)

MAXILLARY SECOND MOLAR

Chronological Age (months)	Probability of Eruption	Chronological Age (months)	Probability of Eruption
less than 101	.00	144	.50
101	.01	145	.52
106	.02	146	.54
109	.03	147	.56
112	.04	148	.58
114	.05	149	.60
115	.06	150	.62
117	.07	151	.64
118	.08	152	.66
119	.09	153	.68
120	.10	154	.70
121	.11	155	.72
122	.12	156	.74
123	.13	157	.75
124	.14	158	.77
125	.15	159	.79
126	.16	160	.80
127	.18	161	.82
128	.19	162	.83
129	.21	163	.84
130	.22	164	.86
131	.24	165	.87
132	.25	166	.88
133	.27	167	.89
134	.29	168	.90
135	.31	169	.91
136	.33	170	.92
137	.35	171	.93
138	.37	173	.94
139	.39	175	.95
140	.41	177	.96
141	.43	179	.97
142	.45	182	.98
143	.47	188	.99
		more than 188	1.00

TABLE XXXII

Probability of Eruption (from Probit Analysis of Control Data)

MANDIBULAR CENTRAL INCISOR

Chronological Age (months)	Probability of Eruption	Chronological Age (months)	Probability of Eruption
less than 40	.00		
40	.01	72	.52
44	.02	73	.55
46	.03	74	.58
48	.04	75	.61
49	.05	76	.64
51	.06	77	.66
52	.07	78	.69
53	.09	79	.72
54	.10	80	.74
55	.11	81	.76
56	.12	82	.79
57	.14	83	.81
58	.16	84	.83
59	.18	85	.85
60	.20	86	.86
61	.22	87	.88
62	.25	89	.90
63	.27	90	.92
64	.29	91	.93
65	.32	92	.94
66	.35	93	.95
67	.37	95	.96
68	.40	97	.97
69	.43	99	.98
70	.46	103	.99
71	.49	more than 103	1.00

TABLE XXXIII

Probability of Eruption (from Probit Analysis of Control Data)

MANDIBULAR LATERAL INCISOR

Chronological Age (months)	Probability of Eruption	Chronological Age (months)	Probability of Eruption
less than 69	.00	87	.52
69	.01	88	.58
71	.02	89	.63
72	.03	90	.68
73	.04	91	.72
74	.05	92	.76
75	.06	93	.80
76	.08	94	.84
77	.10	95	.87
78	.13	96	.89
79	.16	97	.91
80	.19	98	.93
81	.23	99	.95
82	.28	100	.96
83	.32	101	.97
84	.37	102	.98
85	.42	104	.99
86	.48	more than 104	1.00

TABLE XXXIV

Probability of Eruption (from Probit Analysis of Control Data)

MANDIBULAR CUSPID

Chronological Age (months)	Probability of Eruption	Chronological Age (months)	Probability of Eruption
less than 96	.00	123	.52
96	.01	124	.56
99	.02	125	.59
101	.03	126	.63
103	.04	127	.66
104	.05	128	.69
105	.06	129	.72
106	.07	130	.75
107	.09	131	.78
108	.10	132	.80
109	.12	133	.83
110	.14	134	.85
111	.16	135	.87
112	.18	136	.89
113	.20	137	.90
114	.23	138	.92
115	.26	139	.93
116	.29	140	.94
117	.32	141	.95
118	.35	142	.96
119	.38	144	.97
120	.42	146	.98
121	.45	149	.99
122	.49	more than 149	1.00

TABLE XXXV

Probability of Eruption (from Probit Analysis of Control Data)

MANDIBULAR FIRST BICUSPID

Chronological Age (months)	Probability of Eruption	Chronological Age (months)	Probability of Eruption
less than 80	.00	127	.50
80	.01	128	.52
85	.02	129	.54
89	.03	130	.56
92	.04	131	.58
94	.05	132	.60
96	.06	133	.62
97	.07	134	.64
98	.08	135	.66
100	.09	136	.68
101	.10	137	.70
102	.11	138	.71
103	.12	139	.73
104	.13	140	.75
105	.14	141	.76
106	.15	142	.77
107	.16	143	.79
108	.17	144	.80
109	.19	145	.81
110	.20	146	.83
111	.22	147	.84
112	.23	148	.85
113	.25	149	.86
114	.26	150	.87
115	.28	151	.88
116	.29	152	.89
117	.31	153	.90
118	.33	154	.91
119	.35	155	.92
120	.37	157	.93
121	.39	158	.94
122	.41	160	.95
123	.43	162	.96
124	.45	165	.97
125	.47	168	.98
126	.49	174	.99
		more than 174	1.00

TABLE XXXVI

Probability of Eruption (from Probit Analysis of Control Data)

MANDIBULAR SECOND BICUSPID

Chronological Age (months)	Probability of Eruption	Chronological Age (months)	Probability of Eruption
less than 93	.00	139	.49
93	.01	140	.51
98	.02	141	.53
102	.03	142	.55
104	.04	143	.57
106	.05	144	.58
108	.06	145	.60
110	.07	146	.62
111	.08	147	.64
113	.09	148	.66
114	.10	149	.68
115	.11	150	.70
116	.12	151	.72
117	.13	152	.73
118	.14	153	.75
119	.15	154	.77
120	.16	155	.78
121	.18	156	.80
122	.19	157	.81
123	.20	159	.83
124	.22	160	.84
125	.24	161	.85
126	.25	162	.87
127	.26	163	.88
128	.28	164	.89
129	.30	165	.90
130	.32	167	.91
131	.33	168	.92
132	.35	170	.93
133	.37	171	.94
134	.39	173	.95
135	.41	175	.96
136	.43	178	.97
137	.45	181	.98
138	.47	187	.99
		over 187	1.00

TABLE XXXVII

Probability of Eruption (from Probit Analysis of Control Data)

MANDIBULAR FIRST MOLAR

Chronological Age (months)	Probability of Eruption	Chronological Age (months	Probability of Eruption
less than 45	.00	72	.52
45	.01	73	.56
49	.02	74	.59
50	.03	75	.63
52	.04	76	.66
53	.05	77	.70
54	.06	78	.73
55	.07	79	.75
56	.08	80	.78
57	.10	81	.81
58	.12	82	.83
59	.14	83	.85
60	.16	84	.87
61	.18	85	.89
62	.20	86	.91
63	.23	87	.92
64	.25	88	.93
65	.28	89	.94
66	.32	90	.95
67	.35	91	.96
68	.38	92	.97
69	.42	94	.98
70	.45	97	.99
71	.49	more than 97	1.00

TABLE XXXVIII

Probability of Eruption (from Probit Analysis of Control Data)

MANDIBULAR SECOND MOLAR

Chronological Age (months)	Probability of Eruption	Chronological Age (months)	Probability of Eruption
less than 121	.00	139	.52
121	.01	140	.58
124	.02	141	.63
125	.03	142	.68
126	.04	143	.73
127	.05	144	.77
128	.07	145	.81
129	.09	146	.85
130	.12	147	.87
131	.15	148	.90
132	.19	149	.92
133	.23	150	.94
134	.27	151	.96
135	.31	152	.97
136	.36	154	.98
137	.41	156	.99
138	.47	more than 156	1.00

TABLE XXXIX

Probability of Eruption (from Probit Analysis of Control Data)

MAXILLARY CUSPID

Chronological Age (months)	Probability of Eruption	Chronological Age (months)	Probability of Eruption
less than 98	.00	134	.50
98	.01	135	.53
102	.02	136	.56
105	.03	137	.58
107	.04	138	.61
109	.05	139	.63
110	.06	140	.65
111	.07	141	.68
112	.08	142	.70
113	.09	143	.72
114	.10	144	.75
115	.11	145	.76
116	.12	146	.78
117	.14	147	.80
118	.15	148	.82
119	.17	149	.84
120	.19	150	.85
121	.21	151	.87
122	.23	152	.88
123	.25	153	.89
124	.27	154	.90
125	.29	155	.91
126	.31	156	.92
127	.33	157	.93
128	.36	158	.94
129	.38	159	.95
130	.40	161	.96
131	.43	163	.97
132	.46	166	.98
133	.48	170	.99
		more than 170	1.00

APPENDIX B

TABLE XL

Mean, Standard Deviation and Number for Each Dental Calcification Stage of the Maxillary Central Incisor. (Males and Females Combined).

Dental Calcification Stage	Trisomy 21			Control		
	Mean (Months)	SD	No.	Mean (Months)	SD	No.
A	—	—	—	—	—	—
B	—	—	—	—	—	—
C	—	—	—	—	—	—
D	—	—	—	—	—	—
E	58.0	—	1	63.1	9.9	7
F	80.5	14.8	2	69.5	8.1	5
G	83.0	12.1	6	81.2	7.5	7
H	93.0	24.2	3	102.2	9.7	15
I	152.6	30.4	17	135.1	18.4	40
J	—	—	—	—	—	—

TABLE XLI

Mean, Standard Deviation and Number for Each Dental Calcification Stage of the Maxillary Lateral Incisor. (Males and Females Combined.)

Dental Calcification Stage	Trisomy 21			Control		
	Mean (Months)	SD	No.	Mean (Months)	SD	No.
A	—	—	—	—	—	—
B	—	—	—	—	—	—
C	—	—	—	37.0	0.0	1
D	—	—	—	45.7	9.7	8
E	—	—	—	68.8	14.3	15
F	70.0	—	1	80.2	15.5	12
G	83.7	17.6	7	96.8	11.0	14
H	130.0	72.1	2	108.6	8.1	8
I	148.1	29.2	19	134.6	16.6	46
J	—	—	—	—	—	—

TABLE XLII

Mean, Standard Deviation and Number for Each Dental Calcification Stage of the Maxillary Cuspid. (Males and Females Combined).

Dental Calcification Stage	Trisomy 21			Control		
	Mean (Months)	SD	No.	Mean (Months)	SD	No.
A	—	—	—	—	—	—
B	—	—	—	—	—	—
C	58.0	—	1	37.0	0.0	2
D	72.3	22.0	4	54.6	13.7	21
E	93.0	25.8	3	71.0	16.9	18
F	86.0	10.7	6	84.2	15.0	23
G	131.7	28.0	9	107.0	11.7	24
H	150.7	16.0	18	128.4	12.5	33
I	170.0	29.0	28	162.9	20.4	51
J	—	—	—	—	—	—

TABLE XLIII

Mean, Standard Deviation and Number for Each Dental Calcification Stage of the Maxillary First Bicuspid. (Males and Females Combined).

Dental Calcification Stage	Trisomy 21			Control		
	Mean (Months)	SD	No.	Mean (Months)	SD	No.
A	—	—	—	—	—	—
B	—	—	—	37.0	0.0	1
C	53.5	6.4	2	41.7	7.4	9
D	61.0	20.8	3	57.4	8.7	24
E	83.7	10.9	12	83.4	13.4	25
F	116.5	25.7	4	100.9	12.0	24
G	127.8	5.0	8	120.4	14.0	23
H	151.8	16.6	16	138.8	20.7	30
I	162.0	18.9	33	167.3	15.9	38
J	—	—	—	—	—	—

TABLE XLIV

Mean, Standard Deviation and Number for Each Dental Calcification Stage of the Maxillary Second Bicuspid. (Males and Females Combined.)

Dental Calcification Stage	Trisomy 21			Control		
	Mean (Months)	SD	No.	Mean (Months)	SD	No.
A	82.0	5.2	3	42.5	6.7	11
B	65.0	20.4	3	46.6	9.3	5
C	49.0	0.0	2	61.0	8.0	12
D	84.5	12.2	6	70.7	11.3	18
E	94.8	26.6	4	92.6	11.8	27
F	127.0	35.2	4	113.2	17.6	20
G	134.2	13.4	11	129.1	17.3	23
H	147.4	15.9	12	140.8	17.4	22
I	163.9	19.3	32	170.0	18.6	41
J	—	—	—	—	—	—

TABLE XLV

Mean, Standard Deviation and Number for Each Dental Calcification Stage of the Maxillary First Molar. (Males and Females Combined.)

Dental Calcification Stage	Trisomy 21			Control		
	Mean (Months)	SD	No.	Mean (Months)	SD	No.
A	—	—	—	—	—	—
B	—	—	—	—	—	—
C	—	—	—	—	—	—
D	—	—	—	41.0	6.2	6
E	51.3	4.5	4	45.1	7.7	10
F	68.5	2.1	2	62.3	10.8	14
G	80.1	10.8	7	70.2	11.0	19
H	81.3	11.2	9	91.3	13.2	23
I	134.9	18.5	17	122.6	19.1	60
J	—	—		—	—	—

TABLE XLVI

Mean, Standard Deviation and Number for Each Dental Calcification Stage of the Maxillary Second Molar. (Males and Females Combined.)

Dental Calcification Stage	Trisomy 21			Control		
	Mean (Months)	SD	No.	Mean (Months)	SD	No.
A	—	—	—	41.9	10.9	11
B	52.0	5.2	3	50.0	1.5	6
C	85.0	—	1	57.6	6.6	7
D	76.0	11.7	6	65.7	7.4	16
E	94.3	21.0	10	83.7	17.1	23
F	104.5	36.0	2	108.0	15.6	39
G	149.6	26.8	14	124.7	9.7	21
H	149.8	14.0	23	149.0	16.4	13
I	177.8	29.6	30	174.3	20.3	54
J	—	—	—	—	—	—

TABLE XLVII

Mean, Standard Deviation and Number for Each Dental Calcification Stage of the Mandibular Central Incisor. (Males and Females Combined.)

Dental Calcification Stage	Trisomy 21			Control		
	Mean (Months)	SD	No.	Mean (Months)	SD	No.
A	—	—	—	—	—	—
B	—	—	—	—	—	—
C	—	—	—	—	—	—
D	—	—	—	37.0	0.0	6
E	58.0	—	2	46.4	6.5	7
F	70.6	—	2	57.0	1.5	6
G	79.6	7.5	5	64.9	6.3	14
H	78.4	9.8	5	83.4	7.0	11
I	125.7	16.9	11	110.8	16.0	46
J	—	—	—		—	—

TABLE XLVIII

Mean, Standard Deviation and Number for Each Dental Calcification Stage of the Mandibular Lateral Incisor. (Males and Females Combined.)

Dental Calcification Stage	Trisomy 21			Control		
	Mean (Months)	SD	No.	Mean (Months)	SD	No.
A	—	—	—	—	—	—
B	—	—	—	—	—	—
C	—	—	—	—	—	—
D	—	—	—	38.7	4.5	7
E	58.0	—	2	46.5	6.6	7
F	70.0	—	3	63.0	7.7	17
G	80.8	7.7	8	73.4	11.3	14
H	97.0	38.1	2	90.7	7.8	11
I	119.5	12.5	8	115.9	13.7	40
J	—		—	—		—

TABLE XLIX

Mean, Standard Deviation and Number for Each Dental Calcification Stage of the Mandibular Cuspid. (Males and Females Combined.)

Dental Calcification Stage	Trisomy 21			Control		
	Mean (Months)	SD	No.	Mean (Months)	SD	No.
A	—	—	—	—	—	—
B	—	—	—	—	—	—
C	—	—	—	37.0	0.0	1
D	80.5	18.0	6	44.2	10.4	13
E	70.0	—	1	55.8	7.0	9
F	79.0	11.9	8	67.9	9.6	28
G	112.5	31.0	8	92.7	9.6	25
H	140.3	14.8	9	117.6	10.8	36
I	152.3	20.5	33	152.9	20.7	39
J	—	—		—	—	—

TABLE L

Mean, Standard Deviation and Number for Each Dental Calcification Stage of the Mandibular First Bicuspid. (Males and Females Combined.)

Dental Calcification Stage	Trisomy 21			Control		
	Mean (Months)	SD	No.	Mean (Months)	SD	No.
A	—	—	—	—	—	—
B	49.0	—	1	—	—	—
C	52.0	5.2	3	39.3	4.7	9
D	88.0	4.2	2	53.1	8.2	14
E	82.5	12.7	10	66.6	7.8	26
F	85.6	20.1	5	88.0	8.3	18
G	131.0	13.6	8	108.2	11.6	34
H	141.1	15.6	21	130.7	14.3	33
I	162.3	17.1	31	146.9	15.8	32
J	—	—	—		—	—

TABLE LI

Mean, Standard Deviation and Number for Each Dental Calcification Stage of the Mandibular Second Bicuspid. (Males and Females Combined.)

Dental Calcification Stage	Trisomy 21			Control		
	Mean (Months)	SD	No.	Mean (Months)	SD	No.
A	83.5	6.4	2	41.7	6.0	7
B	51.3	4.5	4	47.4	10.8	11
C	77.5	10.5	4	63.5	8.8	11
D	81.5	14.7	6	67.8	9.3	16
E	91.0	—	1	83.4	12.5	22
F	100.8	25.2	4	104.2	10.1	26
G	134.0	9.6	16	125.9	16.4	21
H	150.1	16.7	14	140.1	15.6	28
I	165.4	19.1	24	160.9	16.0	28
J	—		—	—	—	—

TABLE LII

Mean, Standard Deviation and Number for Each Dental Calcification Stage of the Mandibular First Molar. (Males and Females Combined.)

Dental Calcification Stage	Trisomy 21			Control		
	Mean (Months)	SD	No.	Mean (Months)	SD	No.
A	—	—	—	—	—	—
B	—	—	—	—	—	—
C	—	—	—	—	—	—
D	—	—	—	—	—	—
E	49.0	—	1	38.8	3.8	10
F	65.2	18.3	5	51.4	2.5	10
G	72.1	8.4	7	63.7	5.9	22
H	83.3	5.5	7	86.4	10.2	26
I	125.6	14.8	15	117.9	16.1	58
J	—		—	—	—	—

TABLE LIII

Mean, Standard Deviation and Number for Each Dental Calcification Stage of the Mandibular Second Molar. (Males and Females Combined.)

Dental Calcification Stage	Trisomy 21			Control		
	Mean (Months)	SD	No.	Mean (Months)	SD	No.
A	—	—	—	53.5	2.1	4
B	52.0	5.2	3	43.0	6.6	16
C	85.0	0.0	2	56.5	2.1	4
D	84.0	12.1	3	64.0	4.2	10
E	80.1	17.5	9	78.1	10.8	26
F	109.5	20.9	12	104.4	13.9	30
G	134.9	10.3	11	117.8	10.6	28
H	151.9	18.8	27	143.5	13.9	24
I	180.2	21.8	27	174.1	17.9	54
J	—	—	—	—	—	—

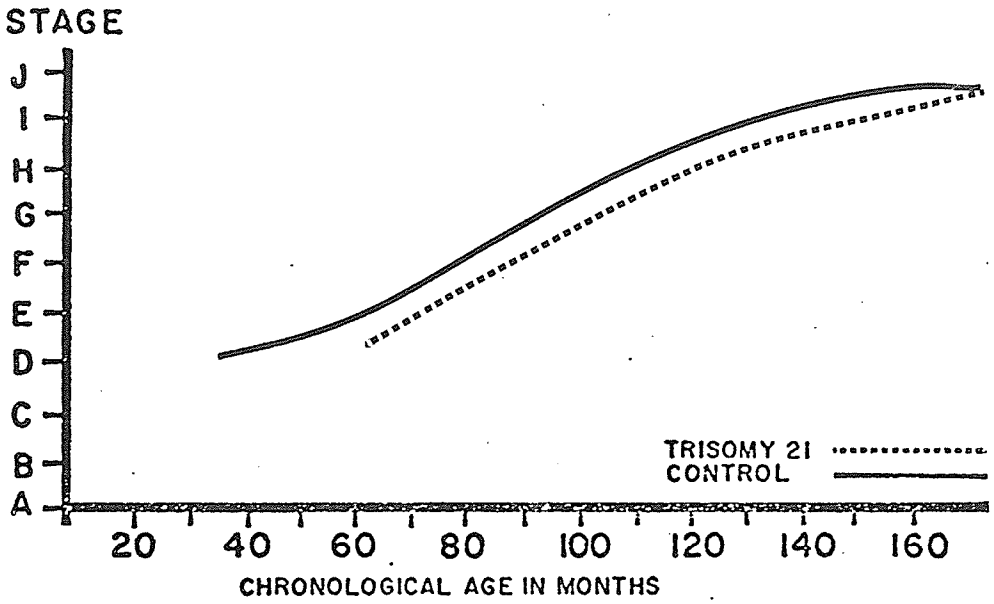

Figure 31. Main effect of chronological age on dental calcification stage - maxillary central incisor.

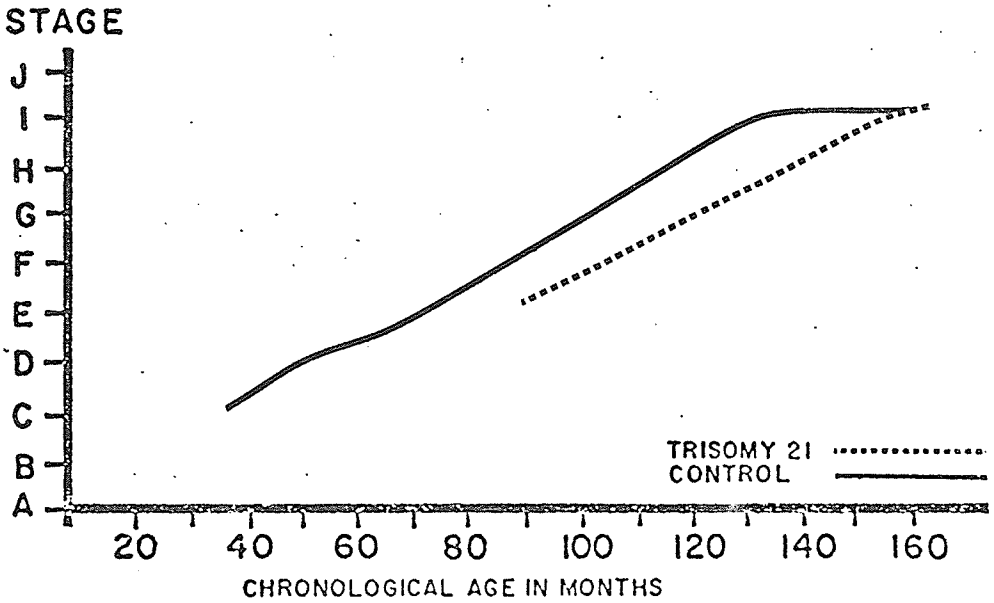

Figure 32. Main effect of chronological age on dental calcification stage - maxillary lateral incisor.

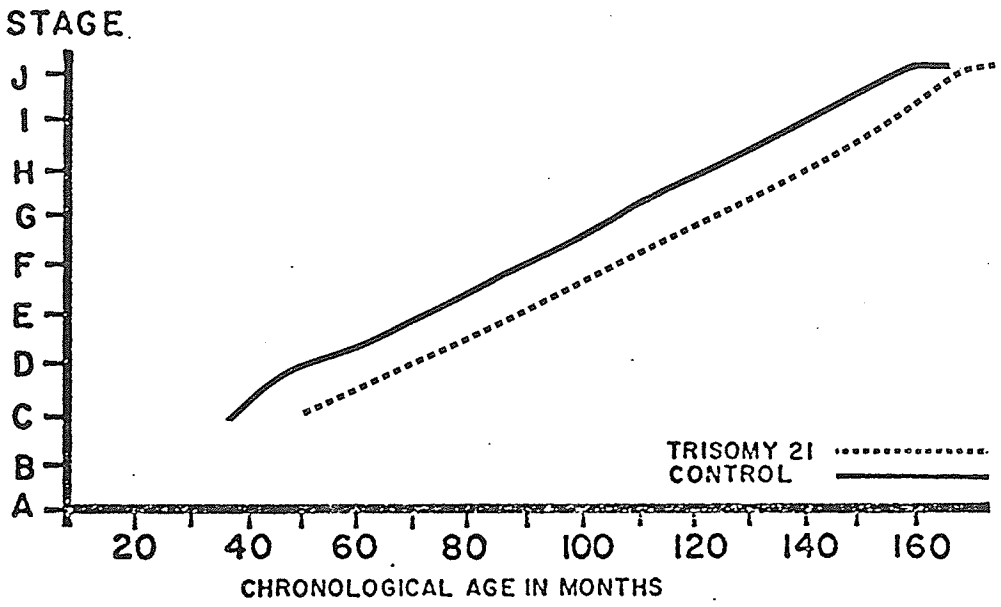

Figure 33. Main effect of chronological age on dental calcification stage - maxillary cuspid.

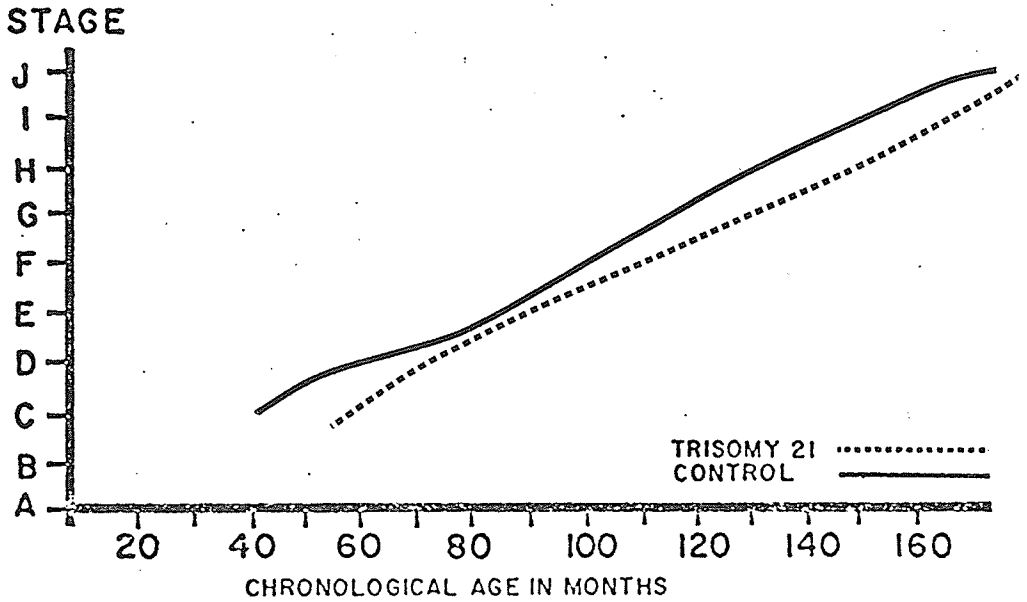

Figure 34. Main effect of chronological age on dental calcification stage - maxillary first bicuspid.

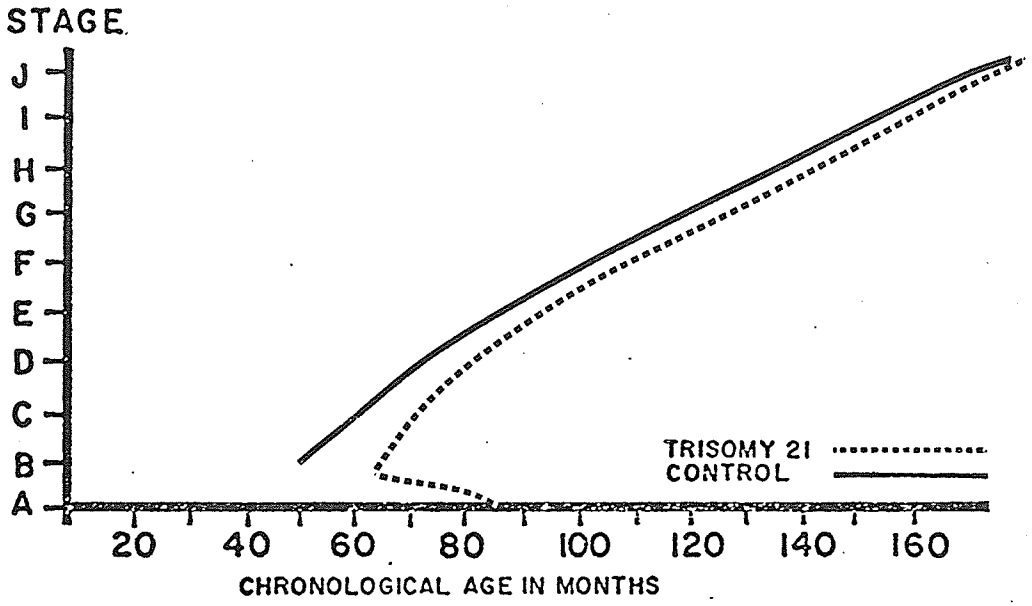

Figure 35. Main effect of chronological age on dental calcification stage - maxillary second bicuspid.

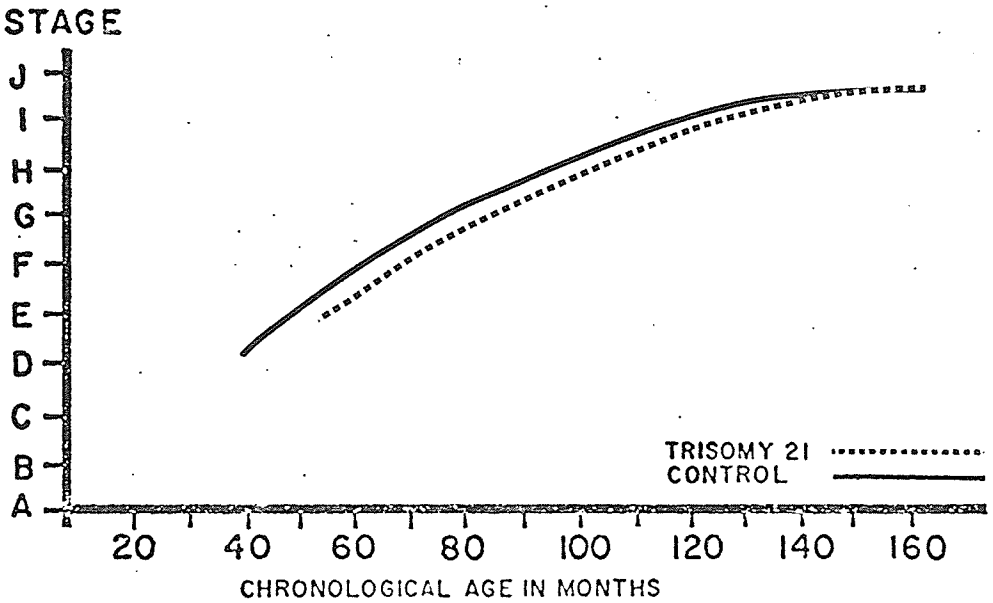

Figure 36. Main effect of chronological age on dental calcification stage - maxillary first molar.

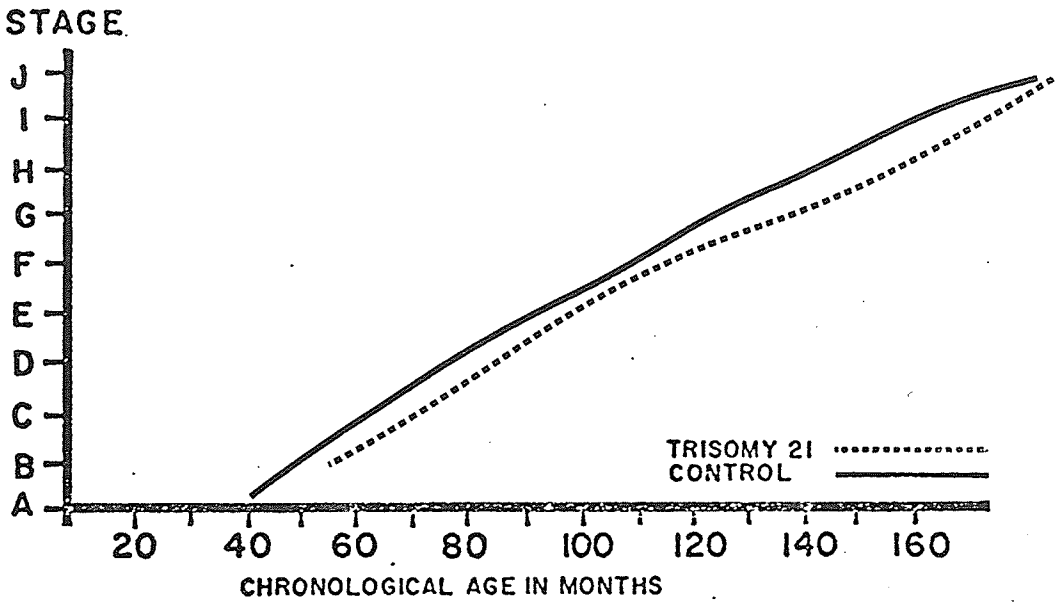

Figure 37. Main effect of chronological age on dental calcification stage - maxillary second molar.

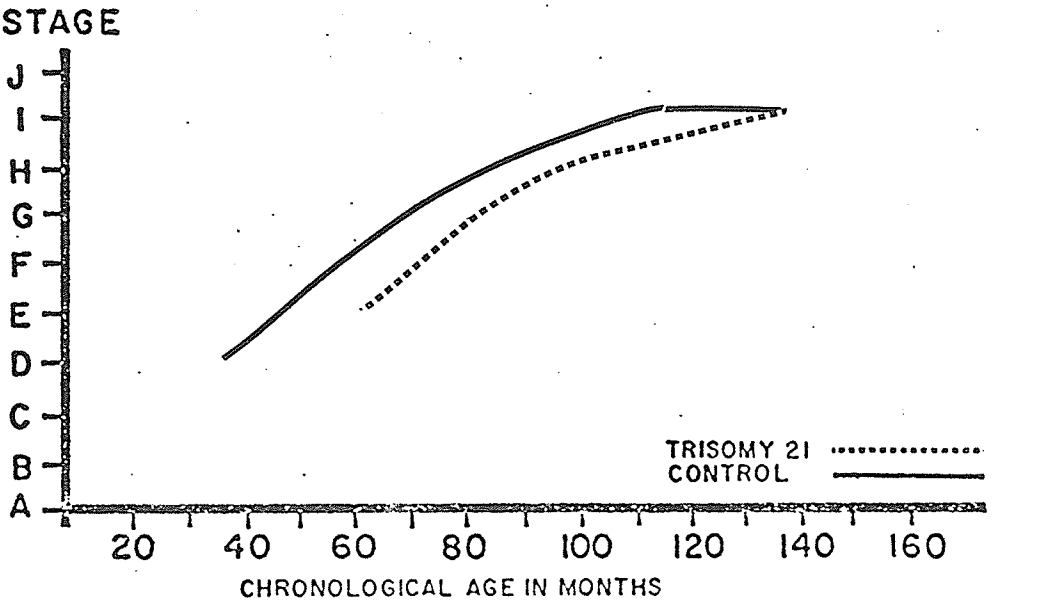

Figure 38. Main effect of chronological age on dental calcification stage - mandibular central incisor.

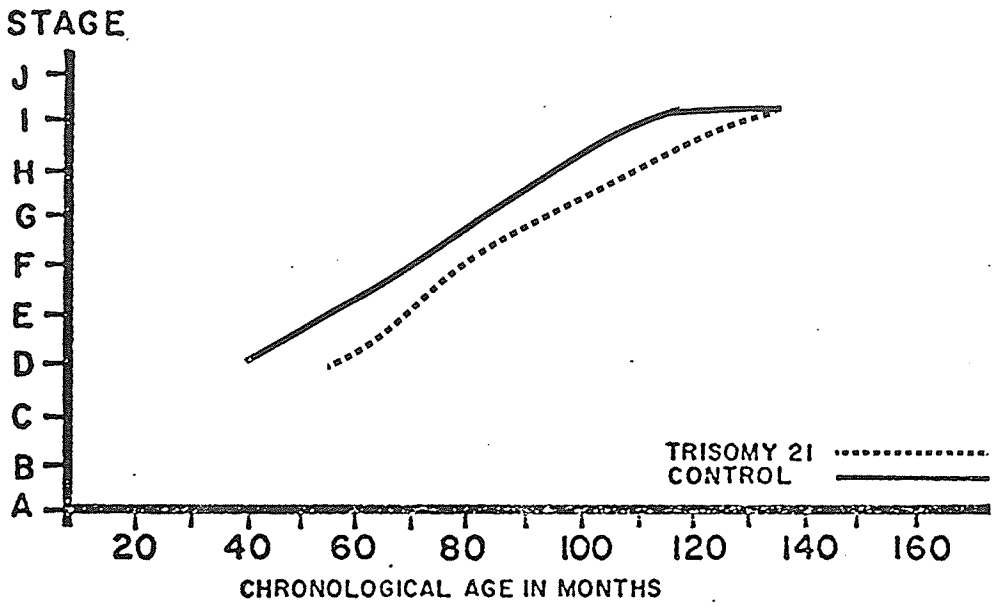

Figure 39. Main effect of chronological age on dental calcification stage - mandibular lateral incisor.

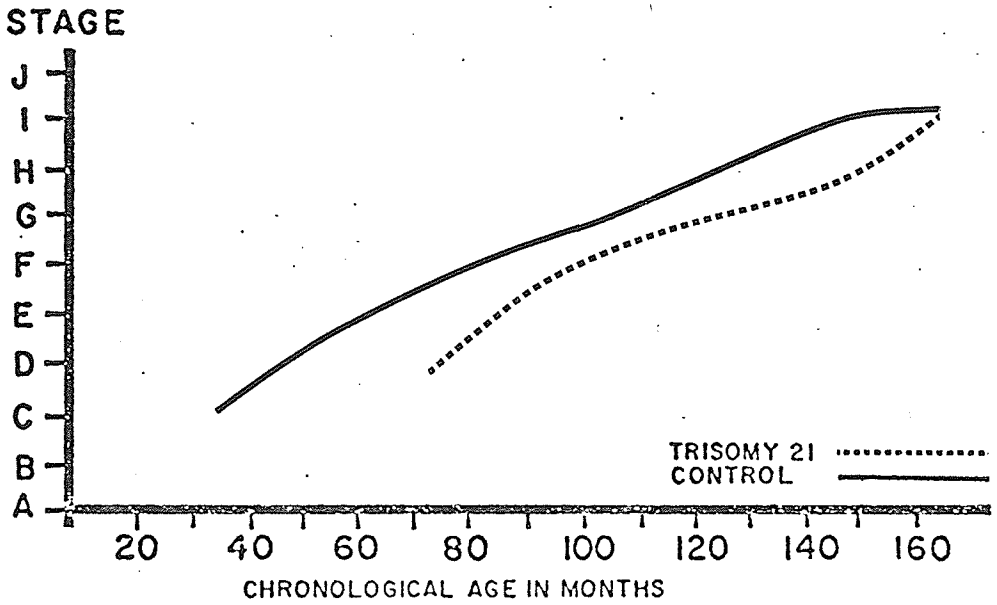

Figure 40. Main effect of chronological age on dental calcification stage - mandibular cuspid.

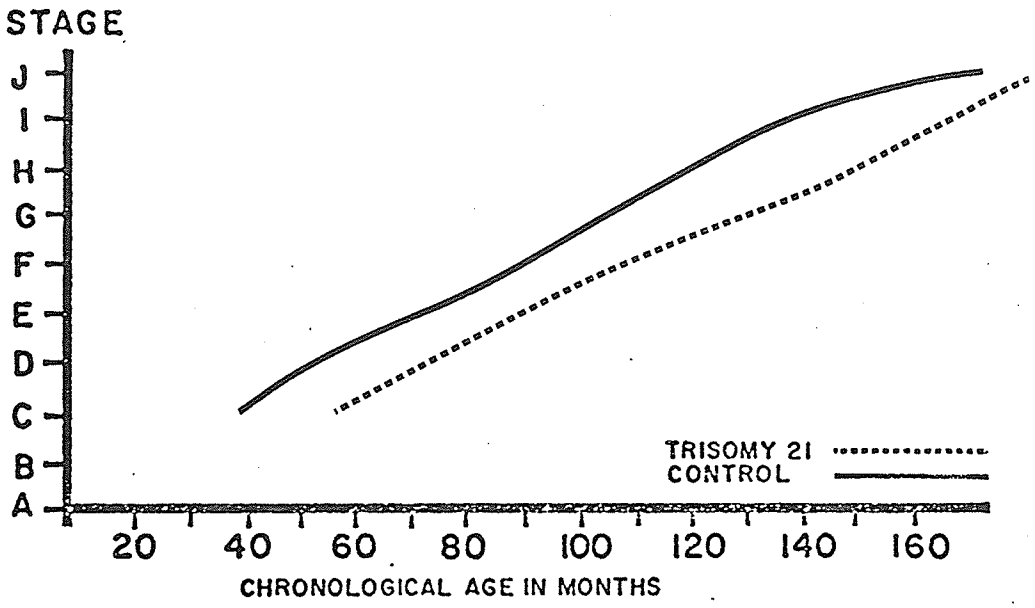

Figure 41. Main effect of chronological age on dental calcification stage - mandibular first bicuspid.

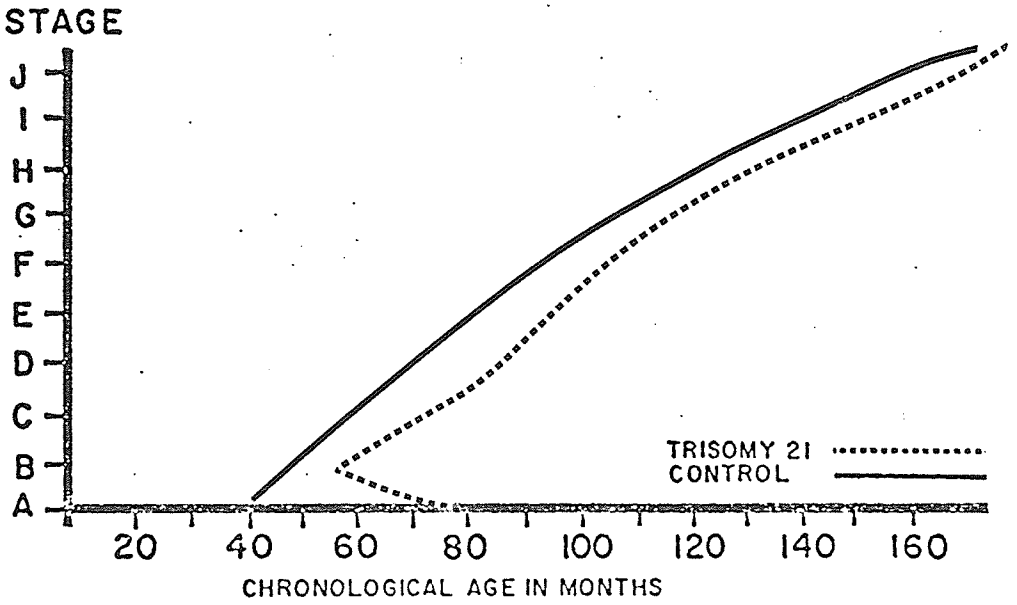

Figure 42. Main effect of chronological age on dental calcification stage - mandibular second bicuspid.

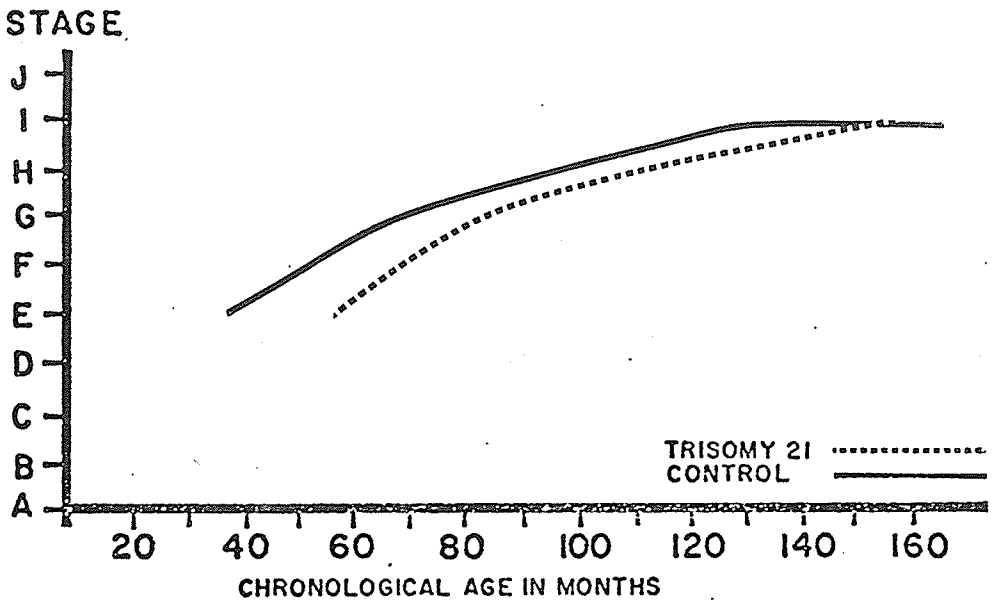

Figure 43. Main effect of chronological age on dental calcification stage - mandibular first molar.

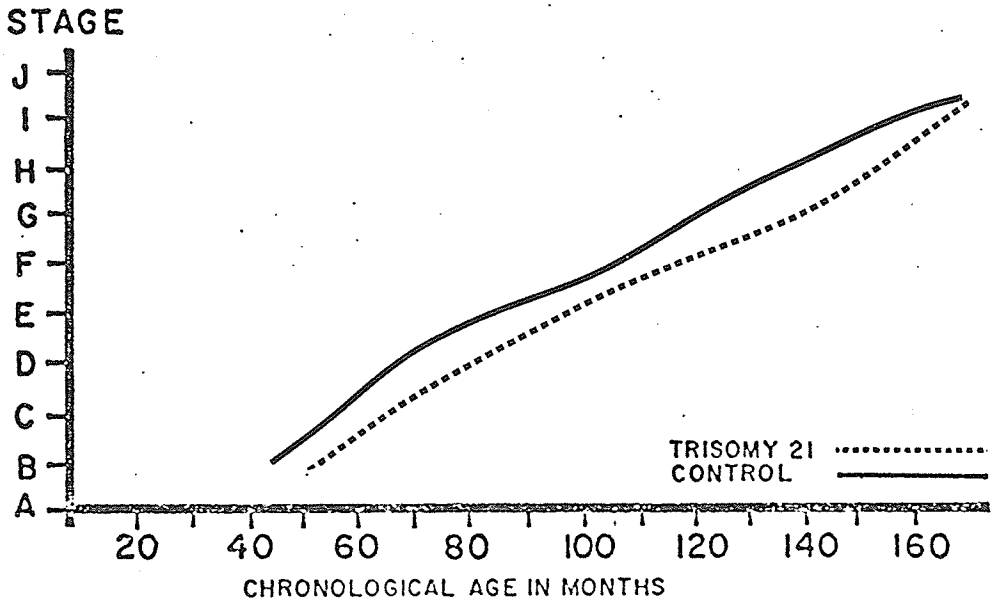

Figure 44. Main effect of chronological age on dental calcification stage - mandibular second molar.