AN EXAMINATION OF THE EFFECTS OF PRENATAL ALCOHOL EXPOSURE ON SCHOOL-AGE CHILDREN IN A MANITOBA FIRST NATION COMMUNITY.

A Study of Fetal Alcohol Syndrome Prevalence and Dysmorphology.

By

Debra L. Kowlessar

A Thesis
Submitted to the Faculty of Graduate Studies
in Partial Fulfilment of the Requirements
for the Degree of

MASTER OF SCIENCE

Department of Human Genetics
University of Manitoba
Winnipeg, Manitoba

THE UNIVERSITY OF MANITOBA

FACULTY OF GRADUATE STUDIES

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A STUDY OF FETAL ALCOHOL SYNDROME PREVALENCE AND DYSMORPHOLOGY

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Abstract

A cross-sectional survey was conducted in one First Nation Community in Manitoba to determine the prevalence of Fetal Alcohol Syndrome (FAS) among school-aged children (ages 5 years to 15 years). The study consisted of four parts: a maternal interview, where mothers were questioned about family dynamics, pregnancy and family histories, as well as alcohol use during pregnancy using the TWEAK screening questionnaire; review of the child's birth records, to confirm alcohol exposures reported by the mother; Dysmorphology assessment by a clinical geneticist; and psychoeducational testing by a trained retired teacher. The geneticist and teacher were blind to the alcohol exposure status of each child at the time of assessment.

Two hundred and seven consents were collected by two local coordinators, 178 of these were eligible for study (73% ascertainment rate). Forty-six percent of the children studied had been exposed to alcohol in utero, and 30% were exposed to high levels of alcohol. Out of the 178 children studied, 11 were identified as FAS. An additional 7 children were identified as Partial FAS . Thus, in total 10% (18/178) of children had physical evidence of being adversely affected by prenatal alcohol exposure. Prevalence of FAS in this community ranges from 31 to 62 per 1000 children, while the prevalence of alcohol related birth defects (FAS plus Partial FAS) ranges from 51 to 101 per 1000 children.

The dysmorphology parameters which differ significantly between the

alcohol exposed and unexposed groups are: decreased height, weight, head circumference and palpebral fissure lengths, and midface hypoplasia.

Growth parameter data of the "Normal" category of school-aged children were used to generate standard Native growth curves for school-aged children from this community. These curves were compared to the preexisting curves in the literature, primarily derived using Caucasian data, and showed significant differences between the two populations. With respect to postnatal growth, Native children from this community tend to be heavier, taller, have larger head circumferences, longer fingers, and more widely spaced eyes than their Caucasian counterparts. Comparison of the FAS and Partial FAS children with the Native curves, increased the number of children that would be considered "classic" FAS cases, as opposed to comparisons against Caucasian standards.

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1.0 Introduction

The following introduction is intended to provide the reader with some of the relevant background information on the subject of Fetal Alcohol Syndrome (FAS). It will cover the areas of alcohol use and abuse, with special reference to women, examine alcohol as a teratogen on the developing fetus through examination of various animal model studies, provide an historical account of FAS, detail criteria for FAS diagnosis, and review the available epidemiological data concerning FAS with special reference to Aboriginal epidemiology reports. Finally a review of the thesis and its hypotheses will be provided.

1.1 Alcohol use and abuse

Alcoholism is a growing concern in our society with the number of women abusing alcohol increasing steadily. In fact, during a five year period spanning 1973 to 1978 the number of women alcoholics in Canada increased from 90,000 to 400,000, and over the past twenty years the ratio of male to female alcoholics in Canada decreased from 8:1 to an equal distribution of 1:1 (Persaud, 1990). According to Golbus (1980), alcoholism is the most common drug abuse problem today affecting 1-2% of women of childbearing years. Other survey studies conducted in the United States concluded that as many as 10% of women of child bearing years are considered to be risk drinkers, that is these women consume on average greater than one drink per day (Dufour et al, 1994).

Recent research has shown that this trend maybe slowing down, as small

decreases in the number of women drinkers are beginning to be observed. According to the 1995 Canadian Profile on the use of alcohol, tobacco and other drugs by Canadians, in 1993 the number of Canadians (aged 15 years and older) who reported drinking was 74.4%, a small decrease as compared to 79% in 1990. These statistics also state that the highest drinking rates are being found among young Canadians between the ages of 15 and 24, and that the type of drinking reported is most often "binge-drinking" (consumption of five or more drinks on any one occasion). With respect to self-report, men tend to drink twice as much as women (5.9 drinks at a time versus 2.3 drinks respectively). However, it is possible that the estimate for women may be low, since women are less likely to report problems relating to their drinking (11.9% men versus 6.2% women). Low income Canadians tend to report drinking as being more problematic than when compared with their high income counterparts (17.9% versus 7.9 % respectively) (Canadian Centre on Substance Abuse, 1995).

The Canadian figures indicate that although overall consumption and reporting of alcohol problems has decreased slightly over the past 5 years, it is our youth, our next generation, that still are reporting the highest alcohol use figures. The figures cited are alarming given that alcohol has been identified as a teratogen, causing varying degrees of congenital malformations and mental retardation in infants (Weiner et al, 1989).

Several studies have been conducted over the years to determine women's awareness of risk drinking during pregnancy. Serdula et al (1991)

conducted a self-report survey of women during the years 1985 to 1988 to examine trends of alcohol consumption in pregnant women. They found a decrease in the number of women who consumed alcohol while pregnant over this time period, from 32% in 1985 to 20% in 1988. However, of those individuals who did drink during pregnancy, no decrease in the median number of drinks consumed per month was observed. They also point out that, although there was an overall decrease in the consumption rate of alcohol while pregnant, there was no significant decrease observed in young (less than 25 years of age) pregnant women, or in those who were less educated (high school or less).

Other studies have been conducted recently concerning awareness of the risks of heavy drinking and FAS in adults (Dufour et al, 1994) and in youths (McKinnon et al, 1995) in the United States. Both studies indicate that knowledge with respect to the risks of drinking during pregnancy is high (89% to 92% in the adult study versus 81% in the youth study) (Dufour et al, 1994; McKinnon et al, 1995). Also of interest, approximately 73% of adult women versus 72% of youths surveyed have heard of FAS. Unfortunately, only 39.0% of adult women and 46.9% of youths studied could correctly define FAS. In the study by McKinnon et al (1995), 47.8% thought that FAS was a baby born addicted to alcohol. An encouraging number of youths (95.0%) correctly believed that FAS is a preventable disorder. However, figures such as 50.3% believing FAS is curable, and 48.5% believing FAS is inheritable illustrate that stronger efforts must be made to ensure that FAS is accurately understood by

the general population, before prevention can begin.

1.1.1 Demographics of Women who abuse alcohol

According to epidemiological studies on the demographics of women who abuse alcohol, those women who drink heavily tend to be young, white, single, have higher education (greater than high school) and income, and work full time outside of the home (Day et al, 1993). Women who abuse alcohol during the first trimester of pregnancy can also be generally identified by these risk factors. However, these factors do not hold true and do not identify those women who abuse alcohol throughout pregnancy. According to Day et al. (1993), women who continue to drink in the third trimester more often tend to be older, black, less educated, lower socioeconomic status (SES), have more life events, and use other illicit drugs. Sokol et al (1980) reported similar findings, that older multigravidas, who were unmarried, were more likely to drink and abuse other drugs (both cigarettes and illicit drugs) during pregnancy. These women were also more likely to be clinically recognized to have psychosocial problems and as having a higher frequency of previous first trimester spontaneous abortions, low-birth weight infants and infants with congenital anomalies, in comparison with a non-alcohol abusing control group (Sokol et al, 1980). A recent study on the characteristics of a group of Canadian women who engaged in binge-drinking also reinforces the prototype of those women who engage in risky drinking patterns as being younger, single, Caucasians, who smoke and tend to

use illicit drugs, more often than their non-binging counterparts (Gladstone et al, 1997) . However, this study is limited as subjects were primarily of Caucasian background and were selected based on self referral to a counselling agency.

1.2 Teratogens

Teratology is the science that focuses on abnormal prenatal development including congenital fetal anomalies (Moore and Persaud, 1993). This branch of science examines both genetic etiologies (such as genetic inheritance, or chromosomal abberations) of birth defects as well as potential environmental factors which contribute to abnormal phenotypes observed in children. It might be assumed that the period between conception and birth would be a safe time, the child is shielded from the outside world and all its pollutants. However, is this environment as safe as we may like to believe? Studies are now showing that the womb is not the safehouse we once thought it was, as the unborn child can be exposed to many harmful agents which traverse the placenta and can cause a range of possible effects on the fetus, including both major and minor malformations, mental retardation, and death in some instances. These environmental agents that induce fetal damage following maternal exposure to them during the pregnancy are known as teratogens. Some teratogens include drugs (both prescription and street drugs), radiation, viruses, and alcohol (Zimmerman, 1991).

1.3 What is Fetal Alcohol Syndrome (FAS)?

Suspected teratogenic effects of alcohol date back to biblical times. In the Bible, Judges 13: 3-4, there is a warning that states "...you will soon be pregnant and have a son. Take care not to drink any wine or beer" (Good News Bible, 1976). During the gin epidemic in England during the early mid eighteenth century physicians noted that the children of alcoholic parents tended to be "weak, feeble and distempered" (Sokol, 1981). Even within the Amerindian culture, warnings concerning alcohol use and pregnancy were expressed. According to some Navajo elders "...if a woman about to bear a child drinks crazy water, the newborn will be crazy in the body and the mind" ("The Navajo Tribe" in Streissguth et al, 1988). Despite all of the historical suspicions, evidence confirming such warnings was not available until more recently. It has since been shown that many mothers who are chronic abusers of alcohol during pregnancy deliver children with a unique dysmorphic phenotype (Lemoine et al, 1968; Jones et al, 1973; Jones and Smith, 1973). First documented by Lemoine et al (1968) in France and independently observed by Jones et al (1973) in the United States, this unique phenotype, which includes central nervous system (CNS) dysfunction, growth deficiency, and craniofacial dysmorphology, came to be known as Fetal Alcohol Syndrome (FAS) (Jones and Smith, 1973)

To date there is no single test available that can positively identify

children who are affected with fetal alcohol syndrome (Osborn, 1993). Due to the great variability in types of abnormalities and severity of the anomalies observed in children exposed in utero to alcohol, fetal alcohol syndrome (FAS) is difficult to diagnose (Clarren and Smith, 1978; Clarren,1981) However, diagnostic criteria have been suggested by the Research Society on Alcoholism (RSA) in order to help simplify this task . The criteria for FAS diagnosis are based on a cluster of abnormalities that have been cited in nearly all cases of FAS dating back to the first reports by Lemoine et al, and Jones et al. The first important piece of information required before such a diagnosis can be made is a positive history of maternal alcohol abuse during the pregnancy (Osborn et al, 1993; Aase, 1994). Following that, the minimal criteria for FAS diagnosis are as follows:

(1) prenatal and/or postnatal growth deficiencies, which include height, weight, and / or head circumference below the tenth percentile when corrected for age.

(2) central nervous system (CNS) impairment, including developmental delay, behavioural disturbances such as Attention Deficit Disorder (ADD) and Attention Deficit Hyperactivity Disorder (ADHD) (which include impulsiveness, poor attention and concentration, and hyperactivity), intellectual impairment (mental retardation), and/or signs of other neurologic abnormality (structural or otherwise).

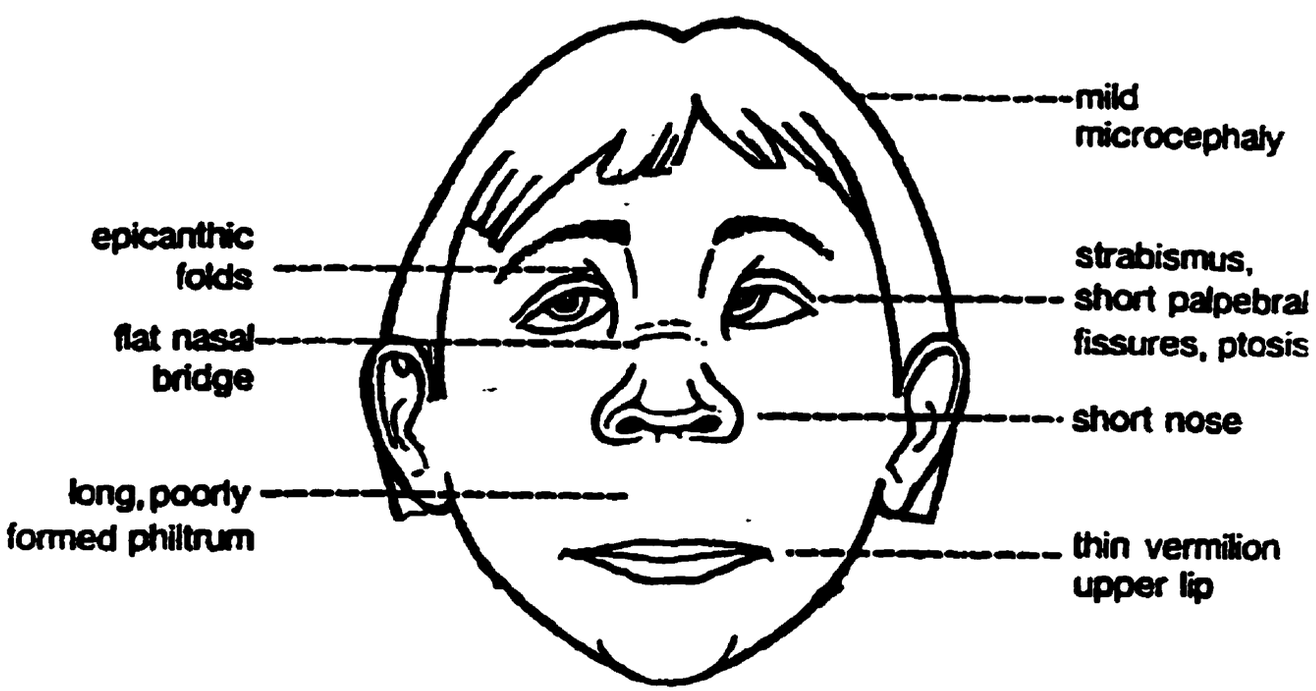
(3) characteristic craniofacial dysmorphology with at least two of the

following signs: microcephaly, (head circumference below the third percentile when corrected for age), microophthalmia and /or short palpebral fissures, poorly developed philtrum, thin upper lip and flattening of the maxillary area (Clarren and Smith, 1978; Rosett, 1980; Osborn et al, 1993; Spohr et al, 1993). Figure 1 illustrates these characteristic craniofacial abnormalities of the FAS face.

Some children may not exhibit all the required criteria for FAS diagnosis. However, they may still have positive histories of heavy maternal alcohol consumption during pregnancy and may exhibit only behavioural or cognitive difficulties and/or other nonspecific anomalies associated with the syndrome. These children are said to have a milder form of FAS known as Fetal Alcohol Effect (FAE) or Alcohol Related Birth Defects (ARBD) (Coles, 1993; Committee on Substance Abuse and Committee on Children with Disabilities, 1993; Spohr, 1993).

Alcohol is not unique in causing each of the previously mentioned signs and symptoms (Rosett, 1980). What does seem to be unique is the clustering of this subset of non-specific anomalies when a fetus has been exposed to high levels of alcohol in utero - the diagnostic criteria for full blown FAS (Clarren, 1981, Institute of Medicine, 1996). FAS is the tip of the iceberg - the severe extreme of a variable continuum of "possible fetal alcohol effects". Thus it has been suggested that any symptoms falling short of the minimum required criteria

Figure 1. Diagrammatic representation of the characteristic craniofacial features of FAS. (Modified from: Chudley, 1991)


mild microcephaly
epicanthic folds
strabismus, short palpebral fissures, ptosis
flat nasal bridge
short nose
long, poorly formed philtrum
thin vermilion upper lip

for FAS should not be considered as a separate and unique diagnosis of FAE. Instead FAE should be used in reference to the consideration that alcohol is a possible cause of the patient's birth defects (Osborn et al, 1993; Aase et al, 1995).

Since the time that the Research Society on Alcoholism set forth its minimum criteria for FAS diagnosis, a new diagnostic classification system has been suggested by the Institute of Medicine (1996). The new diagnostic criteria and diagnostic categories set forth by the Institute of Medicine is outlined in Table 1.

In this new five level classification system, the Institute of Medicine (1996) has attempted to provide a more accurate classification system, by ensuring that diagnostic criteria are reliable, and valid. Category number one in the new system is the classic FAS diagnosis, as before. In the Institute's new classification system, the term FAE as a unique diagnosis separate to that of FAS has been removed and been replace by the term "Partial FAS" (category number 3). A second prime difference between the old classification system and the newly described one, is that the Institute of Medicine acknowledges that one of the primary diagnostic criteria of the past for FAS - evidence of alcohol exposure during the pregnancy, is one of the most difficult to attain. Reasons for the difficulty in attaining accurate information regarding alcohol exposure histories range from the fact that some adoptive mothers may not know the alcohol history of their adopted child's prenatal life, while some mothers may

have difficulty remembering from a past pregnancy, and, in some cases, alcohol intake maybe denied for fear of stigmatization. For this reason, even if alcohol exposure cannot be confirmed, but the child illustrates all the phenotypic signs of FAS as assessed by an experienced dysmorphologist, FAS classification can still be made under category number 2 of the new system. The fourth and fifth categories represent a clustering of clinical conditions with confirmed alcohol exposure that is thought to be linked to the observed conditions. Category four represents a list of physical defects or congenital anomalies that includes malformations and dysplasias and is termed Alcohol-related Birth Defects (ARBD), while category five, Alcohol-related Neurodevelopmental Disorder (ARND), represents neurodevelopmental abnormalities and complex behaviour or cognitive abnormalities that cannot be explained by family background or environment alone. It is possible for both category four and category five to co-occur and thus should be stated as so, if the situation presents itself.

The anomalies associated with FAS are not unique to teratogenesis by alcohol. Many syndromes and other drug exposures have been found to present with similar anomalies. However, close examination will reveal to the trained eye that, although these syndromes illustrate growth deficiencies and facial anomalies, they are distinct from FAS (Institute of Medicine, 1996). Some syndromes which have been confused with FAS in the past include: Aarskog syndrome, Williams syndrome, Noonan syndrome, Dubowitz syndrome, Bloom syndrome, fetal hydantoin syndrome, maternal PKU fetal effects, and fetal

Table 1. New Diagnostic Criteria for FAS and Alcohol Related Effects as suggested by the Institute of Medicine (1996).

Fetal Alcohol Syndrome
1. FAS with confirmed maternal alcohol exposure A. Confirmed maternal alcohol exposure B. Evidence of characteristic pattern of facial anomalies such as short palpebral fissures, flat upper lip, flattened philtrum, and flat midface C. Evidence of growth retardation in at least one of the following: - low birth weight for gestational age - decelerating weight over time not due to nutrition - disproportional low weight to height D. Evidence of CNS neurodevelopmental abnormalities in at least one of the following: - decreased cranial size - structural brain abnormalities such as microcephaly, partial or complete agenesis of the corpus callosum, cerebellar hypoplasia - neurological hard or soft signs (as age appropriate) such as impaired fine motor skills, neurosensory hearing loss, poor tandem gait, poor eye-hand coordination
2. FAS without confirmed maternal alcohol exposure - B, C, and D as above
3. Partial FAS with confirmed maternal alcohol exposure A. Confirmed maternal alcohol exposure B. Evidence of some components of the pattern of characteristic facial anomalies **Either C, D, or E** C. Evidence of growth retardation in at least one of the following: -low birth weight for gestational age -decelerating weight over time not due to nutrition -disproportional low weight to height D. Evidence of CNS neurodevelopmental abnormalities in at least one of the following: -decreased cranial size -structural brain abnormalities such as microcephaly, partial or complete agenesis of the corpus callosum, cerebellar hypoplasia -neurological hard or soft signs (as age appropriate) such as impaired fine motor skills, neurosensory hearing loss, poor tandem gait, poor eye-hand coordination E. Evidence of a complex pattern of behaviour or cognitive abnormalities that are inconsistent with developmental level and cannot be explained by family background or environment alone, such as learning difficulties; deficits in school performance; poor impulse control; problems in social perception; deficits in higher level receptive and expressive language; poor capacity for abstraction or metacognition; specific deficits in mathematical skills; or problems in memory, attention, or judgment.

Alcohol-Related Effects
Clinical conditions in which there is a history of maternal alcohol exposure and where clinical or animal research has linked maternal alcohol ingestion to an observed outcome
4. Alcohol-related birth defects (ARBD) Cardiac: Atrial septal defects, ventricular septal defects, aberrant great vessels, Tetralogy of Fallot Skeletal: Hypoplastic nails, clinodactyly, shortened fifth digits, pectus excavatum and carinatum, radioulnar synostosis, Klippel - Feil syndrome, flexion contractures, hemivertebrae, camptodactyly, scoliosis Renal: aplastic, dysplastic, hypoplastic kidneys, horseshoe kidneys, ureteral duplications, hydronephrosis Ocular: Strabismus, refractive problems secondary to small globes, retinal vascular anomalies Auditory: Conductive hearing loss, neurosensory hearing loss Other: Virtually every malformation has been described in some patient with FAS. The etiologic specificity of most of these anomalies to alcohol teratogenesis remains uncertain.
5. Alcohol-related neurodevelopmental disorder (ARND) Presence of : A. Evidence of CNS neurodevelopmental abnormalities in at least one of the following: - decreased cranial size - structural brain abnormalities such as microcephaly, partial or complete agenesis of the corpus callosum, cerebellar hypoplasia - neurological hard or soft signs (as age appropriate) such as impaired fine motor skills, neurosensory hearing loss, poor tandem gait, poor eye-hand coordination and/or E. Evidence of a complex pattern of behaviour or cognitive abnormalities that are inconsistent with developmental level and cannot be explained by family background or environment alone, such as learning difficulties; deficits in school performance; poor impulse control; problems in social perception; deficits in higher level receptive and expressive language; poor capacity for abstraction or metacognition; specific deficits in mathematical skills; or problems in memory, attention, or judgment.

*From Institute of Medicine (1996), used with permission.

toluene syndrome (Institute of Medicine, 1996).

1.4 Effects of Alcohol on the Developing Fetus

1.4.1 Growth Retardation

Prenatal and/or postnatal growth retardation is one of the primary criteria in an FAS diagnosis. Children whose mothers were chronic abusers of alcohol throughout their pregnancy tend to suffer from symmetric growth deficiency, including weight, height (both below the tenth percentile for age or gestational age), as well as head circumferences below the third percentile (Jones et al, 1974; Cole, 1993; Spohr et al, 1993). Studies have illustrated the association of prenatal alcohol exposure with significantly lower birth weights in children (Jones et al, 1974; Little, 1977; Mills et al, 1984). Little (1977) suggests that alcohol exposure late in pregnancy will have a greater effect in decreasing birth weight than the same level of exposure early in pregnancy.

Despite adequate nutrition during postnatal life, the growth retardation of FAS affected individuals persists especially with respect to height and head circumference, as both parameters tend to remain well below average throughout life (Streissguth et al, 1991). It has been suggested that the slow growth in head circumference is an indicator of slowed brain growth, which tends to be a consistent feature in FAS affected individuals (Aase, 1994). The weight parameter differs slightly from the other two parameters in that a greater level of catch-up growth is observed. It has been found that, on average, males will

show some level of catch-up with respect to weight, but more dramatic catch up is noted in pubescent females, who have been said, in some reports, to become moderately obese during late adolescence (Streissguth et al, 1991; Spohr et al, 1993).

1.4.2 Craniofacial Dysmorphology

Craniofacial abnormalities are probably the most readily observable features of FAS. Some of the hallmark features of FAS facies are: short palpebral fissures which may give the illusion of the child's eyes being smaller and further apart than normal; hypoplastic midface; and long smooth philtrum with poor Cupid's bow formation and thinned upper lip (Aase, 1994). Other craniofacial anomalies associated with prenatal alcohol exposure include: epicanthus, strabismus and ptosis, with respect to eye anomalies; short upturned nose with anteverted nares; micrognathia; minor ear anomalies including low set posteriorly rotated ears and lop ears; high arched palate and cleft palate (Church and Gerkin, 1988; Autti-Ramo et al, 1992; Spohr et al, 1993; Aase, 1994).

According to longterm follow up studies, unlike the growth parameters, the distinctive craniofacial features of FAS tend to dissipate with time (Streissguth et al, 1991; Spohr et al, 1993). Streissguth et al (1991) report that increased growth of the nose, chin and midface, along with thickening of the philtral ridges during adolescence dramatically changes the overall facial appearance in many

patients. However, even in the older patient, relatively short palpebral fissures, smooth philtrum and thin upper lip can be important discriminating features.

1.4.3 Skeletal Abnormalities

Prenatal alcohol exposure has been associated with increased frequency of some nonspecific skeletal abnormalities, although these are less consistent than the cardinal FAS features. Some of these abnormalities include camptodactyly, clinodactyly, limited joint movement (such as incomplete rotation at the elbow) and abnormal dermatoglyphics (such as longitudinally oriented palmar creases) (Streissguth et al, 1991; Spohr et al, 1993; Aase, 1994). According to Spohr et al (1993), significant improvement of skeletal anomalies with time was observed. However, Streissguth et al (1991) cite that these minor anomalies remain important discriminating characteristics in older FAS patients.

1.4.4 Other Physical Anomalies associated with FAS

Exposure to alcohol in utero increases a child's chance of being affected with a number of nonspecific anomalies. Some of the more common, although still not consistent, anomalies include: congenital heart defects, minor external genital anomalies, renal defects, herniae, hemangiomata and spina bifida (Spohr et al, 1993; Aase, 1994). It has been stated that these anomalies occur up to 5 to 60 times more often in children who have been exposed to alcohol prenatally than in the general pediatric population (Aase, 1994). Other studies have

suggested an association between prenatal alcohol exposure and hearing disorders such as bilateral recurrent serous otitis media and bilateral sensorineural hearing loss, as well as a high incidence of speech and language disorders (Church and Gerkin, 1988). The speech of children with FAS has been described as being slurred, guttural, dysarthric and monotonous, and approximately 90 percent of children with FAS will demonstrate delays in both receptive and expressive language development (Lewis et al, 1994). Dental abnormalities have also been observed in patients with FAS (Coles, 1993).

1.4.5 Central Nervous System Impairment

(1) Behavioural Effects

One of the most striking symptoms of prenatal alcohol exposure is its effect on the developing central nervous system. Shortly after birth exposed infants illustrate behavioural deficits such as irritability, apparent hyperacusis, poor suck reflex and sleeping disturbances (Clarren and Smith, 1978; Clarren, 1981; Forrest et al, 1992; Lewis et al, 1994). One study noted a dose-dependent decrease in infant reaction time in infants exposed to alcohol in utero (Jacobson et al, 1994). During the preschool period, FAS children have been described as being affectionate, distractible and very active, with poor fine motor coordination, mild cerebellar dysfunction and hypotonicity also being common (Clarren and Smith, 1978; Clarren, 1981; Aase, 1994, Lewis et al, 1994).

It is during school ages that the behavioural deficits in these children may

cause problems. Studies have shown that one of the most common problems in children exposed to alcohol in utero is attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), and learning disabilities (Ouellette, 1985; Aase, 1994) Not only has chronic alcohol abuse been implicated in these disorders, but significant learning problems have been associated with binge drinking (consumption of five or more drinks on any occasion) during pregnancy, as well (Forrest et al, 1992). It has been suggested that these difficulties in learning may be associated with deficits in organization and processing aspects of information input, output, integration and memory. It is for these reasons—short attention span, hyperactivity and deficits in information organization and processing—that these children have problems with traditional means of education, and create a challenge for the educator to set up programs in a context-specific manner in order to teach the affected child (Weiner and Morse, 1994).

Affected adolescents and adults do not out grow these behavioural problems. In fact, adult patients have been said to have maladaptive behaviours which make them unsuitable for traditional job training programs (Streissguth et al, 1991). Attentional deficits, poor concentration, comprehension and judgement problems persist throughout adulthood. As well, problems with conduct become an issue, such as lying, defiance, and lack of consideration for others (Streissguth et al, 1991). Recent studies have illustrated that it is not just FAS affected individuals who are at risk for these secondary disabilities.

Individuals with FAE (Partial FAS) have been noted to have increased rates of secondary disabilities such as dropping out of school, and being in trouble with the law, compared to their FAS counterparts (Streissguth et al, 1996).

(2) Cognitive Difficulties

Mental retardation has been cited as one of the most common and serious effects of prenatal alcohol exposure on the developing fetus (Clarren and Smith, 1978). The more phenotypically severe patients were the ones who also had the lower IQs, suggesting that the lower intelligence is an effect of the alcohol exposure and not due to the postnatal environment of the child (Streissguth et al, 1978). Even in adulthood, lower intelligence persists. A follow up study of FAS-FAE patients by Streissguth et al (1991) noted the mean group IQ to be 68, which just falls into the mentally retarded range of IQ scores, with scores ranging from 20 (severely retarded) to 105 (normal). The normal scores were in the minority with approximately 58% of the scores being 70 or lower. FAE individuals showed, on average, 10 point higher IQ scores than their FAS counterparts, suggesting that alcohol dose may be an important factor in the severity of mental retardation. FAS affected adults and adolescents in this study frequently exhibited arithmetic deficits (second grade level), and significantly lower reading, and spelling skills (fourth and third grade levels, respectively) (Streissguth et al, 1991). Other longterm studies have illustrated the persistence of lower intelligence in affected adults (Spohr et al, 1993).

(3) Structural Abnormalities

One of the paramount features of FAS is microcephaly. According to Clarren (1981), microcephaly may be the first sign of CNS dysfunction. Autopsies of FAS patients indicate that the brains of these individuals exhibit similar malformations caused by failure or interruption of the neuronal and glial cell migration, with some of the consistent anomalies including cerebellar hypoplasia, and cerebral dysgenesis with heterotopic cell clusters (Jones and Smith, 1973; Clarren, 1981) Recently, magnetic resonance imaging (MRI) studies have identified reduction of size of the basal ganglia, reduced diencephalon and absence or reduction in size of the corpus callosum in children exposed to alcohol in utero as compared with both normal and other mentally retarded control subjects (Mattson et al, 1994). Mattson et al (1994) suggest that these reductions may be directly related to the cognitive and behavioural difficulties associated with FAS. For instance, decreased basal ganglia could be responsible for such features as spatial memory deficits, and lack of understanding concerning the consequences of their actions, while a hypoplastic corpus callosum could be responsible for ADHD, and the problems with the complex integrations between different brain systems.

1.5 Alcohol as a teratogen

Alcohol exposure in utero has been associated with many abnormalities in the developing fetus varying in type, number, and severity with the most severe affliction being FAS. The question remains how alcohol inflicts this damage on the fetus. Although not yet fully elucidated, the mechanisms of alcohol teratogenicity in the developing fetus are slowly being teased out.

In teratology, a few fundamental concepts are hallmarks to the effect a teratogen will have on the fetus. These fundamentals include: dose, timing and sensitivity. Ethanol, given its molecular weight, ionic nature and water/lipid solubility, is a molecule that can freely cross the placenta and thus interfere with proper embryonic development (Persaud, 1990). It is heavy maternal alcohol consumption during pregnancy that is associated with the occurrence of FAS. However, it has been estimated that FAS is only seen in 35-40% of offspring exposed in utero to high alcohol levels (Jones et al, 1974). Why does it not affect the other 60%? The answers to this question are varied. First, some reports cite that it is blood alcohol content rather than the total amount of alcohol consumed that predicts the congenital malformations associated with FAS (Persaud, 1990; Zajac and Abel, 1992). Recent research has determined that certain genotypes influence the rate of alcohol and/or acetaldehyde (an alcohol metabolite) metabolism within a given individual. Thus, the same dose of alcohol can have varying effects on different women and fetuses with respect to blood alcohol levels and length of time peak blood alcohol levels are maintained

(Zajac and Abel, 1992).

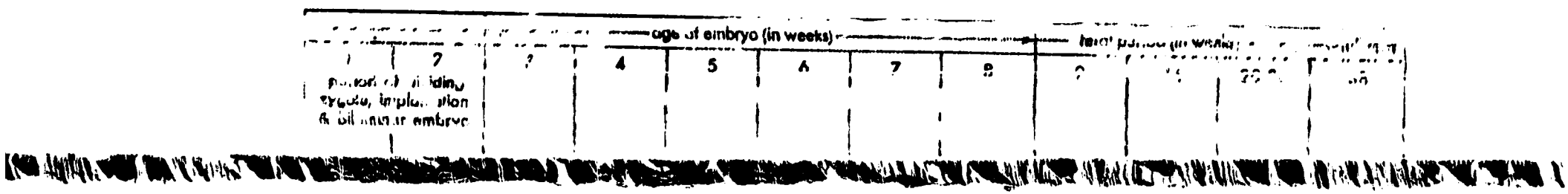
Second, timing of exposure is also critical in determining the type and severity of the anomalies (Moore and Persaud, 1993). Most studies on the effect of alcohol on critical developmental periods have been performed on animal models, specifically rats and mice due to their short gestation, large litters and the equivalence between trimesters of humans and rats (Zajac and Abel, 1992). One organ system which is particularly vulnerable to the teratogenic effects of alcohol is the central nervous system, due to its long critical period in humans extending from the third week of gestation to the end of the third trimester (see Figure 2) (Zajac and Abel, 1992; Moore and Persaud, 1993). According to Zajac and Abel (1992), alcohol exposure early in rodent development (equivalent to the first trimester in humans) leads to neural tube defects and modified neuronal proliferation. Maternal alcohol consumption during the second trimester has been associated with decreased, and disorganized neural tissue. This is due to alcohol's ability to interfere with neural differentiation and migration of both the glial (neural support cells) and neuronal cells (impulse conducting cells), such that patches of white matter are found in the cerebral cortex and vice versa. Alcohol exposure during the second trimester has also been associated with the delay of certain developmental landmarks leading to microcephaly in the fetus (Zajac and Abel, 1992). Both of these features have been documented by Jones and Smith (1973) in FAS autopsy cases. In the third trimester, the developing brain undergoes a growth

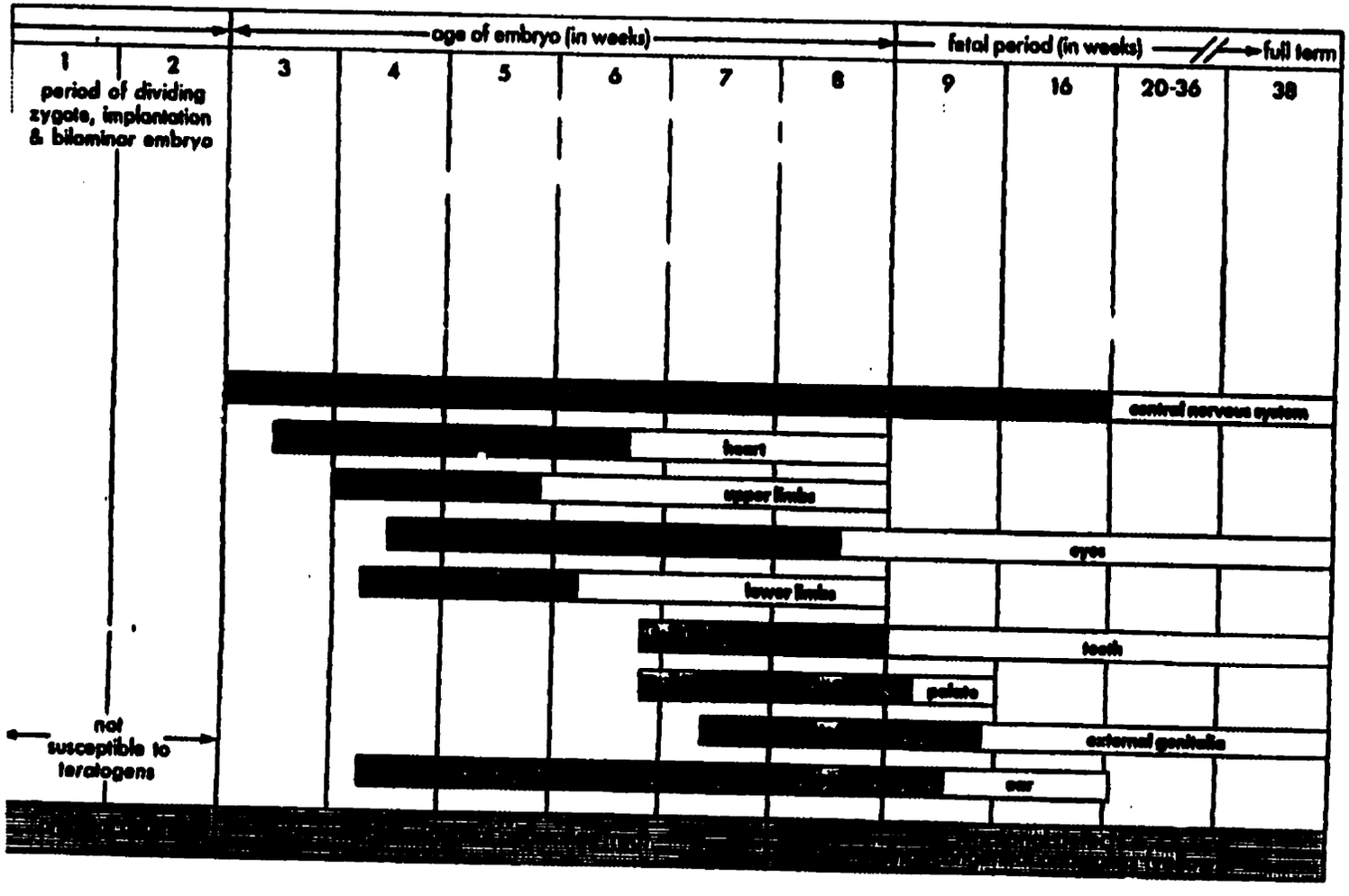
spurt. Alcohol exposure is more detrimental at this time than at previous times due to the increased sensitivity of specific areas of the brain. According to Zajac and Abel (1992) alcohol exposure during the third trimester interferes with glial, dendritic and synaptic proliferation, thus proper neural conducting pathways are adversely affected.

It has been suggested that alcohol may induce growth deficiency in the fetus by depletion of nutritional requirements for normal growth (Michaelis and Michaelis, 1994). Ethanol has been implicated in directly inhibiting the transportation of glucose and amino acids across the placenta to the fetus. This robs the fetal tissues of the energy and materials required for cell division, growth and differentiation, thus contributing to the smaller stature associated with prenatal alcohol exposure (Michaelis and Michaelis, 1994). Ethanol can also act as a vasoconstrictor. By increasing the umbilical artery resistance, it decreases the amount of oxygen that the fetus is receiving, and thus can also interfere with proper cell proliferation leading to intrauterine growth retardation (Persaud, 1990; Michaelis and Michaelis, 1994).

How alcohol induces the development of the unique facial features associated with FAS is still not completely understood. As many of the ear anomalies and other craniofacial anomalies associated with FAS are due to embryonic malformations of the first and second branchial arches, it is possible that alcohol exposure during this critical period may induce such dysmorphic features (Church and Gerkin, 1988). Others suggest that the some of the

Figure 2. Diagrammatic representation of the critical periods in human development. The first shaded portion of the bar graphs represent highly sensitive periods during which major anomalies may incur, while the latter portion represents stages less susceptible to teratogens, during which minor anomalies may result.
(Modified from: Moore and Persaud, 1993)


age of embryo (in weeks)
1
2
3
4
5
6
7
8
9


age of embryo (in weeks)
fetal period (in weeks)
full term
1
2
3
4
5
6
7
8
9
16
20-36
38
period of dividing zygote, implantation & bilaminar embryo
central nervous system
heart
upper limbs
eyes
lower limbs
teeth
palate
external genitalia
ear
not susceptible to teratogens

observed features may occur secondary to restricted brain/ head growth (Autti-Ramo et al, 1992). Other hypotheses suggest that the fetus would have to be exposed to a certain threshold blood alcohol level during the first trimester, or that pre-pregnancy alcohol consumption by the mother would be required to cause craniofacial dysmorphology (Larroque, 1992; Zajac and Abel, 1992).

Abel and Hannigan (1995) have developed a model which brings much of the research focussing on the teratogenic effects of alcohol on the developing fetus, as well as results of studies on maternal risk factors, to explain why alcohol does not act as an "equal opportunity" birth defect. They propose that there are certain "permissive factors" or sociobehavioural risk factors such as culture and socioeconomic status (SES) that the mother possesses, which interact with certain biological factors, or "provocative factors", such as blood alcohol levels, or presence or lack of certain enzymes, which create an internal environment, which exacerbates the effects of alcohol on the fetus. They hypothesize that the permissive and provocative factors act together to increase the action of maternal/fetal hypoxia, and free radical formation, which are thought to be two of the biological mechanisms by which alcohol teratogenesis works (Abel and Hannigan, 1995).

1.6 FAS Epidemiology

Abel and Sokol (1987) estimated the world wide incidence of FAS to be 1.9 per 1000 live births. This estimate was based on a survey of the literature on prospective and retrospective studies of FAS. They acknowledged that this estimate might be conservative due to difficulties in ascertainment, such as difficulties with FAS diagnosis, and increased infant mortality. They also noted that the incidence rates were variable based on the study sites, with the highest incidence being reported in mothers who were black or Indian and those who had a low SES. In these populations, the estimated incidence of FAS was 2.6 per 1000 livebirths as compared to 0.6 per 1000 livebirths in sites where mothers were predominantly white and of middle SES (Abel and Sokol, 1987).

In 1991, Abel and Sokol revised their previous estimate of the world wide incidence of FAS, which was based on prospectively gathered data. This revised estimate attempted to weed out the "false positives" that they believed were included in their previous estimate by excluding "less controlled" retrospective studies. In the revised study, Abel and Sokol (1991) attempted to control for the over-representation of certain racial groups who may be at higher risk than others of having a child with FAS, by basing their overall projections on the proportion of each of the ethnic subpopulations within the total population. This was carried out so that the higher risk groups would not inflate the overall incidence estimate. According to this new methodology, Abel and Sokol (1991) identified the incidence of FAS in the western world as being 0.33 per 1000

births, with a demographic breakdown of the incidence estimate being 0.29 per 1000 livebirths in whites versus 0.48 per 1000 livebirths in blacks. A third report of the world wide incidence of FAS was determined by Able in 1995, due to the increased availability of prospective studies regarding FAS since the last report. The world wide incidence of FAS was now calculated at 0.97 per 1000 livebirths. Abel noted great variability of FAS prevalence both between countries and within countries. For example he states that FAS was twenty times more prevalent in the United States versus other European countries (1.95 versus 0.08 per 1000), and that within the United States the observance of FAS was ten times higher in women who were black and of low SES compared with their Caucasian, middle to upper class counterparts (2.29 versus 0.26 per 1000) (Abel, 1995). However in both the 1991 and 1995 revised estimates, the authors acknowledge that Native Americans were not included in the study due to a lack of prospectively gathered data for that population. This ascertainment bias probably leads to an underestimate of the world wide incidence given that other studies have reported the highest incidence and prevalence rates in the Aboriginal communities (Sandor et al,1981; May et al, 1983; Robinson et al, 1987; Burd and Moffatt, 1994). In fact Chavez et al (1988) found that FAS rates were seven times higher in African Americans, and thirty times higher in Native Americans, than their Caucasian counterparts (Chavez et al, 1988). May et al (1983) have also shown that rates can vary greatly within a given race. For example, the Plains tribes in the South Western United States showed FAS prevalence rates approximately

10 times higher than the Navajo and Pueblo tribes found in the same region (19.5 per 1000, verses 2.5 and 2.7 per 1000 respectively).

Determining accurate estimates of the prevalence and incidence of FAE (partial FAS) or ARBD in a population proves even more challenging than that for FAS. The problem is that, unlike FAS, FAE/ARBD does not have clearly defined, widely accepted criteria on which to base a diagnosis. Consequently, some children will be labelled if the physician is aware that they were exposed to alcohol during the pregnancy, while others will be diagnosed as FAE when there are associated anomalies or other "FAS" characteristics detected in exposed children who do not meet the full criteria for FAS. That is why it is hoped that the diagnositic criteria outlined by the Institute of Medicine will be universally applied, and the new category "partial FAS' will replace the old catch phrase of FAE. It is expected that FAE/ARBD is much more frequent than FAS, with estimates being 3 to 5 times more frequent than FAS (Schorling, 1993).

1.7 FAS Epidemiology in Aboriginal Communities

As was previously stated, epidemiological data on the prevalence and incidence of FAS is limited, but even more scarce is good data on the prevalence and incidence rates for Aboriginal peoples. However, most of the available data suggest that American Indians and Canadian Aboriginals are at high risk for FAS (Aase, 1981; May et al, 1983; Robinson et al, 1987; Duimstra et al, 1993). In fact in the hallmark article of Jones et al (1973) originally

describing FAS, six of the eleven patients identified with FAS were of Native American origin.

The highest reported prevalence rate of FAS is by Robinson et al (1987) in a Native Indian community in British Columbia. In this study, all Native children in the community (between the ages of 1 and 18) were eligible to participate. Criteria for FAS diagnosis were based on the recommended criteria of the Fetal Alcohol Study Group of the Research Society on Alcoholism (Rosett, 1980) and diagnosis of FAS was made independent of knowledge of maternal alcohol consumption during the pregnancy. This study identified 22 affected children (FAS/FAE) out of 116 studied, with a sex distribution in the affected children being 13 male verses 9 female. Two thirds of the children identified as FAS/FAE were mentally retarded, one of the hallmark characteristics of in utero exposure to alcohol. The prevalence in this community was calculated as 190 FAS children per 1000 births. Robinson et al (1987) acknowledged that under-diagnosis of FAS could have occurred due to the anthropomorphic characteristics of the Native children which made measurements of certain landmarks (such as palpebral fissure size) difficult, and thus limited the comparability of these measurements to standards which are typically based on the "white" population measurements (Robinson et al, 1987; Abel and Sokol, 1991).

A second published report on the prevalence of FAS has been conducted by Sandor et al (1981) in British Columbia. Out of a sample of 76 FAS affected

children, 69 of the 76 were of Native origin, and the remaining 7 were Caucasian. In this report the authors state that there was a 10.9 to 1 ratio of FAS affected children in Native children versus Caucasians in the study (Sandor et al, 1981). However, it is possible that the number cited in this study may be an overestimate due to an ascertainment bias that exists within the methodology of the study (Bray and Anderson, 1989). All 76 FAS patients included in the study were found in two Vancouver hospitals, where it is possible that there might be an over-representation of affected native children who had been referred to these tertiary care units.

An unpublished report by Asante et al (1985) determined the prevalence of FAS in 36 communities in the Yukon and Northwest British Columbia. The basis of ascertainment of the 586 subjects between the ages of birth to 16 years of age, was via referrals by community agencies who had identified the children as being handicapped. This method of ascertainment could lead to a bias in the estimate of prevalence in the study, leading to the reporting of inflated prevalence figures among these Native populations (Bray and Anderson, 1989; Burd and Moffatt, 1994). The reported estimates of FAS/FAE prevalence in these populations were: 46 affected per 1000 Native children in the Yukon, and 25 affected per 1000 Native children in Northwest British Columbia, as compared to the prevalence rate of 0.4 affected per 1000 non-Native children in both regions (Asante et al, 1985).

One notable study of the prevalence of FAS in American Indians of the

Southwest was carried out by May et al in 1983. The basis of ascertainment for this study was via referrals, and those screened were from three distinctly different Native populations, the Navajo, Pueblo and Plains culture tribes. This study not only identified FAS/ FAE as a problem of the American Indians but also exemplified that there can be a great deal of variation between the different tribes, probably based on the varying social practices and traditions of each of the cultures. The highest prevalence rate was noted for the Southwest Plains Culture, with the prevalence rate being 19.5 FAS/FAE children per 1000 births. The Navajo and Pueblo cultures had considerably lower prevalence rates at 2.5 per 1000 births and 2.7 per 1000 births respectively (May et al, 1983). Also of interest was the frequent finding of mothers who had given birth to two or more "alcohol-damaged" children, with 85 FAS/FAE affected children being born to 65 mothers. May et al (1983) suggest that the differences in the prevalence between the three Native cultures is not solely due to a higher proportion of drinkers in the Plains culture tribe, but rather due to differences in the social regulations of each of the cultures. The Plains tribes encourage individuality and do not actively discourage behaviours such as risk-taking, drinking, and defiance. Conversely, both the Navajo and Pueblo tribes emphasize conformity to group norms, and thus exercise tighter control on alcohol-abusing behaviours, potentially explaining why lower prevalence rates are reported for these tribes.

Based on the data presented in the previous section, it would appear that Aboriginal mothers have a substantially increased risk of having children who

are affected with FAS. The question then remains, is this increase in incidence and prevalence rates due to a genetic susceptibility in Native peoples, or could the reported increases actually have nothing to do with FAS itself, but be artifacts of various methodological biases in the various studies? Although one cannot rule out an increased genetic susceptibility in Aboriginals until there is conclusive data to suggest it, in many of the studies that have been examined it is expected that methodological biases account for much of the observed increase in rates in this ethnic group. Table 2 provides a summary of some of the available literature concerning the rates of FAS and partial FAS .

In designing a study to examine the prevalence of FAS in a community, it is important that the individuals conducting the dysmorphology examinations be persons who are trained at diagnosing FAS/FAE and who use the widely accepted minimal criteria for FAS diagnosis. As has been previously stated, FAS can be a difficult diagnosis to make and thus, if one does not have experience in diagnosing such cases, many cases could be missed leading to an underestimateof the actual incidence/prevalence of FAS in a community. Conversely, an overestimate of the prevalence of FAS could be made if a large number of ethnic minorities are included in the study. This increase may not be due to an actual increase in the number of affected individuals, but rather due to similar physical characteristics of the populations to that of FAS patients. For example, some features which are normal for one ethnic group (such as the naturally occurring epicanthal folds and short palpebral fissures in Native Americans) may be considered anomalous when compared to the prevailing

Table 2. Summary of some of the available data on the Prevalence and Incidence rates of FAS and Partial FAS.

Study Type	First Author	Location	FAS rate (per 1000)
Clinic based	Dehaene et al (1977)	France	2.9
Clinic based	Hingson et al (1977)	U.S. (Boston)	0.6
Clinic based	Ouellette et al (1977)	U.S. (Boston)	3.1
Clinic based	Hanson et al (1978)	U.S. (Seattle)	1.3
Clinic based	Olegard et al (1979)	Sweden	1.7
Clinic based	Sokol et al (1980)	U.S. (Cleveland)	0.6
Clinic based	Dehaene et al (1981)	France	1.4
Clinic based	Sokol et al (1986)	U.S. (Cleveland)	3.0
Clinic based	Dehaene et al (1991)	France	1.2
Registry based	Wong (1983) unpublished	Native Canadians -British Columbia	4.7 - Native 0.4 - NN†
Registry based	Chavez et al (1988)	U.S. (1980 - 1986)	
		Native Americans	2.9
		African Americans	0.6
		Caucasian	0.09
		Hispanics	0.08
		Asians	0.03
Registry based	CDC (1993a)	U.S. (1979 - 1992)	0.2
Registry based	CDC (1993b)	U.S. (1992)	0.37
Population based	May et al (1983)	SW Native Americans (1969-1982)	2.0
		SW Native Americans (1978 - 1982)	4.2
Population based	Asante et al (1985) - unpublished	Native Canadians - British Columbia	25 *
		Native Canadians - Yukon	46 *
Population based	Robinson et al (1987)	NW Canadian Indians	190 *
Population based	Duimstra et al (1993)	Plains Indians	3.9 - 8.5

* denotes ARBD (FAS and Partial FAS), †denotes NonNative
After: Institute of Medicine (1996)

white standard, thus leading to a greater likelihood of FAS diagnosis in individuals of that particular ethnic group (Abel and Sokol, 1991).

Also of importance in the dysmorphology examination is for the examiner to be blind to information of maternal alcohol use, especially in Aboriginal populations where there already exists a stereotypic belief concerning increased levels of alcoholism. Thus, by blinding the diagnostician to knowledge of alcohol exposure the bias is minimized. This methodology was used in the study by Robinson et al (1987), but was not employed in most of the other studies.

A third important consideration in the dysmorphology assessment is the age group that is being studied. It has been stated that the ideal period of time for FAS diagnosis is between infancy and puberty. It has been reported that it is more difficult to diagnose infants with FAS, due to the fact that the hallmark characteristics of FAS are less discernible at this period of time. This could potentially lead to a decreased estimate of prevalence rates being reported. Diagnosis past puberty also presents problems as the identifying characteristics such as growth deficiency, and hypoplastic maxillary area become less distinct in the FAS adolescent and adult, although cognitive and behavioural problems do persist (Streissguth et al, 1991).

Another source of potential bias in the epidemiological studies of FAS is the method of ascertainment of the subjects. In order to obtain accurate prevalence rates in a specified region, it would be necessary to study every

family and child, which is time-consuming, costly and impractical (Robinson et al, 1987). In general, community surveys, where all children in the community are assessed, will provide a more reliable estimate of prevalence than those studies which ascertain their subjects through various referral methods. Relying on referrals as the ascertainment criterion, increases the chance of bias in the individuals seen. By this, we refer to the fact that there will be a higher proportion of affected individuals being seen in the study, and thus lead to an increase in the prevalence rates for that study.

Care must be taken when designing a community ascertainment study. First, given that FAS has been associated with increased morbidity and mortality (Burd and Moffatt, 1994), a substantial number of cases could be missed in the community, due to the fact that some affected persons are no longer living. In order to compensate for this potential under reporting of prevalence in the community, all death records should be assessed to identify the true number of affected individuals in the community. Burd and Moffatt (1994) also point out that, in some cases, community studies may also lead to a bias in the prevalence of FAS within an ethnic group, particularly if a community is surveyed because FAS is thought to be a major health problem there. It is possible that there may be a legitimate increase in prevalence in the defined geographic area, but caution should be used when generalizing from the particular area surveyed to the entire ethnic group.

A final, but important source of bias in the estimate of prevalence rates, is

the failure to separate confounding variables, which may produce characteristic features similar to those seen in FAS. For example, Bray and Anderson (1989) criticized the Robinson et al (1987) study on the basis that they did not separate out confounding variables, such as cigarette use in mothers, which could also account for the observed growth retardation, or maternal use of other teratogenic drugs which could cause similar dysmorphology and CNS dysfunction. Failure to adjust for such confounders can lead to over-estimates of the prevalence of FAS in the specified population.

1.8 Description of the FAS prevalence study on one Manitoba First Nations Community.

The general study from which this thesis stems was a collaborative effort on the part of the researchers and the band council. The researchers had received a grant from the Canadian Pediatric Society Committee on Indian and Inuit Health to develop a simple survey which could be eventually self-administered by the communities themselves to identify individuals with FAS, or other ARBD. This survey was to be conducted at minimal costs, and require minimal specialist input. At the same time, the community concerned had contacted one of the researchers, stating that the school was having an increased number of behavioural problems, which they thought could be attributable to alcohol exposure. Thus the team of investigators set forth to

develop such a survey, with a number of objectives in mind. The primary objectives of the overall study were :

(1) to develop a simple survey which could be administered with minimal cost and minimal specialist input;

(2) to determine the prevalence of FAS and partial FAS in one Manitoba First Nations Community;

(3) to provide diagnostic and rehabilitative services to FAS/partial FAS children in the community who had not previously been diagnosed;

(4) to assist the community with the development of preventive and rehabilitative programs for FAS/partial FAS.

Secondary objectives for the overall study included:

(5) examination of the relative contribution of alcohol during pregnancy compared with other sociodemographic variables to difficulties in school performance and behaviour.

(6) to develop norms for craniofacial morphometric analysis in a group of Aboriginal children of school age.

(7) to determine whether facial dysmorphology in Aboriginal children can be reliably determined from a photograph.

(8) to determine if parental report of school achievement on the Achenbach Child Behaviour Checklist is as reliable as teacher report on the same test and a more complex educational test battery (Woodcock-

Johnson).

(9) to determine the correlation between educational, social and behavioural findings with morphometric analysis.

This research proposal was approved by the University of Manitoba Faculty Committee on the use of Human Subjects in Research in July 1995.

This study is important not only from a developmental point of view, but also from an epidemiological standpoint. To date, very few epidemiological studies with regards to the rates of FAS, partial FAS, or Alcohol-related effects (ARBD and ARND), have been conducted in Canada. The studies that do exist have been conducted in Northwestern B.C. (Robinson et al, 1987; Assante et al, 1985; Wong, 1983), apart from one incidence study conducted in Saskatchewan (Habbick et al, 1996). No study to date has attempted to examine the magnitude of this problem within the Manitoban population in general, or in specific reference to the First Nation Communities within the province.

1.9 Focus of the Thesis

Data used for analysis in this thesis was collected as part of the larger Community FAS study. The thesis is intended to examine in detail the epidemiology and dysmorphology assessment aspects of the larger study. Prevalence rates will be calculated for this community and compared to previously reported literature rates within Canada. It is expected that this

community is not unique with respect to its drinking habits, and thus it is expected that the prevalence rates will fall within the previously reported ranges.

Examination of dysmorphology parameters, such as the craniofacial and other morphometric analyses, will be conducted to determine if the physical characteristics used to identify FAS or partial FAS in Caucasian populations, can be applied to Aboriginal populations, which are known to vary from the Caucasian population with respect to features such as the natural presence of epicanthal folds. It is hypothesized that, in general, the cardinal features such as growth retardation, telecanthus, and shortened palpebral fissures will be important physical characteristics in identifying those affected prenatally by alcohol.

Thirdly, the thesis will conduct an in depth analysis of the morphometric data collected on the "Normal", segment of the study population and will attempt to construct normal standard growth curves for all morphometric parameters collected, based on these data. It is expected that the Native school-aged population may differ with respect to size and craniofacial features, and that comparison of these children against normal standard curves which are primarily constructed based on morphometric data collected in Caucasian populations, may lead to erroneous (either inflated or deflated) estimates of the true prevalence of FAS and partial FAS in the community. In order to test such a hypothesis, percentile ranks for each of the morphometric data of the FAS and partial FAS individuals will be compared when plotted against the previously

established Caucasian standards and the newly generated Native ones to determine if an increase in anomalies can be detected.

2.0 Methods

2.1 Study Location

The Manitoba First Nation Community in which this study was conducted wishes to remain anonymous to avoid stigmatization that may result from the publication of the sensitive findings of this study. It can be said, however, that the community studied is a rural community which identifies itself as having had problems with alcohol. Further information concerning the characterization of the community rests with the author.

2.2 Informed Consent Collection

A list of all children born within the ten year study period which spanned 1981 to 1990 was obtained from Medical Services Branch (MSB), as well as a death list of those born within the cohort. According to MSB, 352 children were listed on the band list as being born within the specified cohort. It was not expected that all 352 children would be on reserve, as some may have been placed with CFS, been living off-reserve, attending school in other neighbouring towns, or have died. Examination of the cohort's death list indicated that 10 children in the cohort had died as of late 1995, none of whom had any evidence

of alcohol related birth defects. Secondly, a list of all children enrolled in the 1995 - 1996 school year was obtained from the local school. The student enrolment for the local school was 254, however, only 243 of the students fell within the birth cohort and thus were eligible for study. Another exclusion criterion was that the child had to attend the local school. This excluded children who did not attend the school regularly, and those who attended school off-reserve. This provided the base from which our study population was ascertained.

Researchers, in accordance with the band council's directives, hired and trained two local aboriginal workers to aid in the coordination of this study. The local coordinator was responsible for obtaining informed consent from parents, Legal Guardians or Child and Family Services (CFS) (depending on the status of the child), for the participation of their child in this local study. The job of the local coordinator was four-fold. The first responsibility was to visit the homes of children eligible for study participation based on the school list, and explain the study to the parents. If the parents agreed to allow their child to participate in the Community FAS study, then the coordinator read and explained to the parents the three consent forms to be signed (Appendix A), and witnessed the signing of the forms. The first form was a general consent, which explained the purpose of each aspect of the study, and the approximate length of time the child would be required to spend with the researchers. This form also stressed the voluntary nature of the study and that the child or parents could withdraw at

anytime during the study without penalty to the child. Anonymity of photographs and child's records were also stressed. The second consent form obtained permission from the parents, to release pertinent information to the school, so that appropriate measures could be set up to help the child learn according to his or her own special needs. The third consent form obtained parental consent to examine the child's birth records to obtain information such as growth parameters (height, weight, and head circumference), Apgar scores, and to check the Manitoba Nursing Database sheet to confirm whether alcohol was used during pregnancy.

2.3 Maternal Interview

The second part of the local coordinators' responsibilities included conducting a Maternal Interview (appendix B) with the mother (if more than one child was being registered in the study, a Maternal Interview for each child was completed), and administering the Parent form of the Achenbach Child Behaviour Checklist (CBCL) (Achenbach, 1978; 1979; 1979b). The Teacher form of the Achenbach CBCL was completed by the local teachers at the end of the 1995 school year for all children attending the local school.

The Maternal Interview itself consisted of questions regarding the status of the child (natural, adopted, or foster). If the child was a foster child or adopted, the parent was then asked whether alcohol was one of the reasons for placement. Other questions included information regarding the number of

people living in the house, source of income for the household, and the education level and occupations of the mother and head of the household. If the child was a foster child or adopted, the interview would stop at this point, unless the adoptive/foster parent was a close relative to the mother, who might be able to answer some of the other questions relating to pregnancy and family histories. In other cases, where the child was either in a foster home, or had been adopted, and the natural mother was still on reserve, attempts were made to contact the natural mother to complete the questionnaire.

The remainder of the interview concerned itself with alcohol use, or other drug use during pregnancy, questions regarding the birth of the child and postnatal life, numbers of children and stillbirths/ miscarriages had since the birth of this child, questions regarding mental retardation or birth defects in the family, both immediate and extended, and questions with regards to consanguinity of the parents.

The Maternal Interview provided the researchers with one retrospective, self-report source of information re-alcohol exposure during the pregnancy. In the Maternal interview, a version of the TWEAK (Russell, 1994) was used to identify high risk drinking during the pregnancy. The mothers were asked to recall the time that they were pregnant with the child in question, and answer the questions included in Table 3. The TWEAK test is a combination of other self-reporting screening tests such as a modified version of the Michigan Alcoholism Screening Test (MAST) representing questions two, four, and five (Selzer,

1971), T-ACE (Sokol et al, 1989) representing question one, and the CAGE (Ewing, 1984) representing question three. The TWEAK is scored on a seven point scale. Questions relating to using alcohol as an eye-opener (question three), amnesia (question four),and the Cut down question (question five) each score one point if a positive response is obtained. Two points are given if the woman answers five or more on the tolerance question (question one), and the same point value is scored if a positive response is obtained for the worry question (number two). A score of two or greater is considered to be indicative of "risk drinking". According to Russell (1994), the TWEAK test has been found to have sensitivity and specificity levels of 91 % and 77% respectively, in comparison to the same measures for the T-ACE (89% and 79%), and both have been shown to be more effective for screening than the MAST and CAGE questionnaires.

Two other sources of alcohol exposure information were also examined as part of this study. If the child was an adopted or foster child, the adoptive / foster mother was questioned at the start of the maternal interview as to whether, to their knowledge, alcohol was one of the reasons for the child's placement (Maternal Interview Question number three part three). An affirmative answer to this question was assumed to also mean that the child had probably been exposed prenatally to alcohol. The third source of information concerning alcohol use during pregnancy came from examination of the Nursing Database sheets in the child's birth records. This aspect of alcohol history collection will

be discussed further in the following section.

Table 3. The TWEAK Questionnaire.

Question #			Score
1	T	**Tolerance:** How many drinks can you hold? (if answer is ≥ 5 then score:	2
2	W	Have close friends or relatives **Worried** or complained about your drinking in the past year?	2
3	E	**Eye-opener:** Do you sometimes take a drink in the morning when you first get up?	1
4	A	**Amnesia:** Has a friend or family member ever told you about things you said or did while you were drinking that you could not remember?	1
5	K (C)	Do you sometimes feel the need to **Cut Down** on your drinking?	1
		TOTAL	7

After: Russell (1994).

2.4 Hospital Records Search

Consent was obtained from each parent or legal guardian to examine the child's hospital records at their hospital of birth. The majority of the children were born in 7 provincial hospitals, 4 within the city of Winnipeg, and 3 outside of the city. In the rare instance when a child was born outside of the province, hospital records could not be examined.

The purpose of examining the child's birth records was two-fold. The

primary purpose was to obtain information regarding alcohol use during the pregnancy. This information was to be obtained via review of the Nursing Data base sheet, a questionnaire which was developed for use in 1980. This sheet asks the mother questions regarding other pregnancies, health during the pregnancy, and includes one "yes / no" question with regards to alcohol use during the pregnancy. It has been found that there is a quite high reliability with respect to the completion of this question and questioning the mother with regards to the same question. Thus it was anticipated that this review would provide researchers with a method of confirming the maternally reported alcohol use during pregnancy, as in many cases the mother must remember far back in time to the pregnancy. However, the use of such forms by each hospital was voluntary. Many of the city hospitals had used the forms to document alcohol exposure, but the rural hospitals, where the majority of children were born, did not use this form at all, or use of the form by the institutions was irregular. Nursing, Physician, and Social Worker notes with regards to the birth and postnatal life of the child in hospital were also reviewed to see if any documentation existed regarding alcohol use during the pregnancy. Few hospital charts contained information regarding alcohol abuse during the pregnancy, and correlations between the hospital reports and the maternal recall could not be determined.

Secondly, the charts were reviewed to identify any problems during pregnancy, or post natal life (such as jaundice),apgar scores, and growth

parameters at birth. A copy of the hospital review form is appended as Appendix C.

2.5 Dysmorphology Assessment

All children on whom we had consent were examined by a dysmorphologist / geneticist and his assistant, both of whom at the time of assessment and categorization of the children were blind to the alcohol exposure histories, school performance, and behavioural status of all children. The Dysmorphology assessment consisted of three parts examining 46 different parameters, and took approximately 10 minutes per child.

The first aspect of the assessment involved taking two photographs of each child, a frontal (full face) photograph, and a lateral view of the child. The children were asked to place their hair behind their ears, so that the ears were visible, and asked not to smile, so that their faces would be in a natural position, to allow the researchers to perform some morphometric analyses of certain craniofacial landmarks on the pictures (Bookstein, 1986; Clarren et al 1987; Astley et al, 1992; Astley and Clarren, 1995; 1996). The photographs were taken at a standard distance of 24 cm, using a Polaroid Spectra camera, with a close-up F112 lens. The use of colour Polaroid grid film, where one grid block equalled 1 cm, was used to aid in the measurements of the facial landmarks to be studied. The photographs also served as a method to test interobserver reliability for FAS diagnosis. This aspect of the study will not be elaborated on

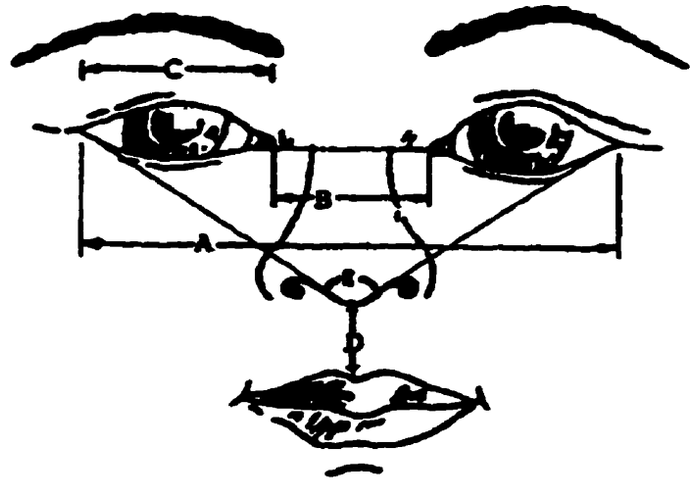
in this thesis, as it is the focus of a separate analysis.

The second aspect of the assessment involved the measurement of growth parameters such as height, weight, and head circumference, as well as several craniofacial landmarks such as inner and outer canthal lengths, palpebral fissure lengths, and philtrum length (see Figure 3). These measurements were made directly on the child using a physicians' measuring tape which was graded in millimetres. Each of the measurements was then plotted on a standard graph for each parameter (based on Caucasian norms), to determine the child's percentile rank for each parameter. One of the facial landmark measurements, the outer canthal, nasal, outer canthal (ONO) angle (Hall et al, 1989) was made using the frontal photograph of the child. This measurement allowed for a quantitative measure of the midface region of the child. A line was drawn from the outer canthus of each eye to the base of the columella (midline), the resultant angle (ONO) was then measured("E" in Figure 3), recorded, and the child's percentile rank was determined via plotting the ONO angle value on a standard graph. A ratio of palpebral fissure length/inner canthal distance was calculated based on the measurements obtained in the quantitative assessment of craniofacial features. This ratio has been shown to be a differentiating feature between "normal" and FAS individuals (Astley and Clarren, 1995; 1996).

Figure 3. Diagrammatic representation of craniofacial landmarks measured as part of the Dysmorphology Assessment section of the Community FAS study.

A: Outer Canthal Distance
B: Inner Canthal Distance
C: Palpebral Fissure Length
D: Philtrum Length
E: ONO Angle

Diagram modified from: Olsen and Tuntiseranee (1995).


C
B
A
D

The third aspect of the assessment involved qualitative observation of several other features of the children. Some of the features included: the slant of the palpebral fissures, formation of the philtrum (normal vs smooth) and palate (normal, cleft, or high-arched), appearance of the eyes, ears, and chin, finger anomalies, contractures, heart anomalies and others listed in Appendix D.

At the end of each assessment the dysmorphologist was asked to categorize the child in one of four categories based on the dysmorphology of the child alone. The four categories included: "normal", FAS, partial FAS, and dysmorphic, where the last category included children who do not appear normal, but it is expected that the differences observed are due to familial variants, or due to reasons other than alcohol exposure. Classification as FAS and partial FAS were based on the diagnostic criteria set forth by the Institute of Medicine (1996) (see Table 1).

2.6 Psychoeducational Testing Battery

A battery of psychoeducational tests were utilized to obtain information on how the child was functioning on the cognitive and behavioural levels. These tests were administered at the school by a retired teacher, who had received training on how to administer each of the tests, and was blind to the alcohol exposure status of each child. This part of the study generally spanned forty-five minutes to one hour in length. Given that this thesis will not focus on the

educational aspect of this study, the following provides a brief overview of the instruments utilized by the researchers in the general study:

(1) Woodcock Johnson Cognitive Battery (Woodcock and Johnson, 1977)

Two subtests of this battery were used: the Memory for Names test which tests long term retrieval in the children, and the Analysis-Synthesis test, which test fluid reasoning skills in the children.

(2) Beery Test of Visual Motor Integration (Beery, 1982)

This test was conducted in the standard way in which the child is asked to re-draw a pattern that they are shown, as well as a nonstandard method, whereby the pattern was shown to the child, he/she was asked to wait five seconds and then re-drawn the form from memory.

(3) Test of Visual Attention (T.O.V.A.®)

This test involved using a self-scoring computer program to test the visual attention levels of each child.

(4) Wechsler Intelligence Scales

The digit-span subtest was used to test memory.

(5) Canadian Test of Basic Skills (CTBS) and Canadian Achievement Test Scores.

The school provided the researchers with the scores of the CTBS (for those in K - grade 2), and CAT (grade 3-8). Both test academic

achievement.

2.7 Dysmorphology Diagnosis versus Full Chart Review Diagnosis

At the time of the Dysmorphology assessment, the dysmorphologist was asked to examine the child's growth parameters, morphometric percentiles, and general appearance, and classify the child into one of the four categories. This diagnostic classification by the dysmorphologist was based solely on dysmorphology, as the dysmorphologist and his assistant were both blind to alcohol exposure histories as well as the behavioural and psychoeducational assessment results. After all data collection was completed, the research team reviewed the research charts and data from those children with suspected FAS or suspected partial FAS. This review included the Dysmorphology assessment results, maternal interview results which included a recall assessment on alcohol exposure during the pregnancy, hospital chart review results, as well as the results of the Achenbach child behaviour checklist (both parent and teacher), and psychoeducational battery results. Based on the review of the charts, some of the children were then reclassified, based on diagnostic criteria used to identify the FAS and partial FAS children. Children were considered FAS, if they had been classified as such by the dysmorphologist, had a positive or undetermined alcohol exposure, and usually had behavioural and/or educational difficulties. Classification as to Partial FAS proved more difficult as there are not as strict guidelines for its diagnosis. However, in this study, children were

classified as partial FAS if they had been classified as such by the dysmorphologist, had a confirmed alcohol exposure, and had behavioural and/or educational difficulties. Children who were not exposed to alcohol prenatally but were originally classified as FAS or partial FAS based on dysmorphology alone were entered in a separate category, "Dysmorphic 2". After the new diagnostic categories were established, researchers then contacted the parents of these alcohol affected children via a letter, offering to meet and discuss the child's findings with the parents. Counselling, referrals to appropriate agencies and assistance in coping with the child's results were offered to the parents during this meeting. The meetings were in general a half hour in length.

2.8 Creation of Native Morphometric Normal Curves

Native normal curves were created through the mathematical manipulation of the morphometric data collected in the "Normal" diagnostic category, as per methods described in preexisting literature (Lucas and Pryor, 1935; Laestadius et al, 1969; Feingold and Bossert, 1974; Jones et al, 1978; Fuchs et al, 1980; Merlob et al, 1984) . The category was divided by sex and each category was then divided into one year divisions from age five to fifteen. Two-tailed student t-tests were performed on the male and female categories to determine if the results could be pooled for the sexes, or whether separate curves must be created for each sex for each particular morphometric parameter measured in this study. For each age category, the number of individuals were

noted, as were the range of measured values. Means and standard deviations were calculated for each age group. Normal curves for the morphometric data were constructed, by calculating and plotting the mean for each age group, plus and minus one and two standard deviations from the mean. Thus, on the actual generated curve, the standard deviations and mean would represent the second, sixteenth, fiftieth, eighty-fourth, and ninety-eighth percentiles respectively, assuming that 68% of all observations lie within the boundary $\mu \pm \sigma$, and approximately 95.4% are bound by $\mu \pm 2\sigma$ (Jekel et al, 1996). Previously established normative curves created based on Caucasian populations have been added as a shaded area behind the Native normative graphs, to allow for comparisons between the two graphs. Morphometric data from the FAS and partial FAS categories were then plotted on the new Native normal curves, to allow for comparison of affected individuals against their own peers. Differences between percentile ranks on the Caucasian curves, and the native curves were noted.

2.9 Statistical Analysis

Dysmorphology parameters were compared in the following analyses: exposure versus no exposure to alcohol; comparisons between graded levels of alcohol exposure; and comparisons between the diagnostic categories using univariate analysis. With respect to the graded levels of prenatal alcohol exposure, three categories were created: no exposure, low exposure, and high

exposure. The high prenatal alcohol exposure category included those individuals who were adopted or were in foster care, and for whom it was known that alcohol was a primary reason for placement. This category also included those children whose mothers had scored ≥ 2 on the TWEAK test. Low prenatal alcohol exposure was defined as evidence of exposure, but failure to meet the inclusion criteria of the high exposure group. Differences between groups were considered to be statistically significant at the $p \leq 0.01$ level, and considered to be of borderline statistical significance for the range $0.01 \leq p \leq 0.05$. The statistical significance level of $p \leq 0.01$ was chosen due to multiple comparisons which were made in the analyses.

In creating the Native normal curves, statistically different means between the males and females were detected using a two tailed Student t-test at the $p \leq 0.01$ level. If this level was noted between the means of the two groups ("normal" males versus "normal" females) on a given parameter (such as height, weight, etc) then graphs were created for each sex. If the difference between the means was not considered statistically different, the data between the two sexes were pooled to create the curves.

Comparison of the median lines on the normal Native curves, to those extrapolated from the normal Caucasian counterparts were tested for statistically significant differences using a paired Student t-test, with statistical significance being measured at the $p \leq 0.01$ level. Statistical tests were performed using the SAS (Statistical Analysis System) package (Release 6.08, 1989; SAS Institute,Inc.).

3.0 Results

Out of 243 possible candidates for participation in the study, 207 consents were collected, with only 7 refusals to participate in the study documented by the local coordinators (3% refusal rate). Twenty-nine individuals were not contacted by the coordinator for reasons unknown. In accordance with the exclusion criteria, another 29 individuals for whom consent was collected, were not eligible for analysis due to birth dates falling outside of the specified cohort, absenteeism from school on assessment dates, or due to moving off-reserve prior to assessment. Thus the final sample size for this study was 178 individuals, which corresponds to a 73% ascertainment rate.

3.1 Epidemiology Results

3.1.1 Alcohol Exposure

As can be seen in Table 4, 46% of the study sample had been exposed to alcohol in utero. This number can be stratified by graded level of exposure, in which case 30% of the sample had been exposed to high levels of alcohol, while the remaining 16% were considered low exposures.

Analysis of the number of children prenatally exposed to alcohol per year of the cohort indicate that the exposure rates observed in the early versus the later 1980's were 44% (32/73) and 42% (44/105) respectively (Table 5).

Table 4. Alcohol Exposure Data.

	Number of children Exposed (N= 165)	Exposure Rate
Total number of children exposed to Alcohol prenatally	76	46%
Total number (high exposure)	49	30%
Total number (low exposure)	27	16%

* 13 unknown exposures

Table 5. Break down of the Birth cohort, illustrating exposure levels per year of birth, and numbers of FAS / Partial FAS cases per year of birth.

Year of Birth	Number born per year	Number with positive alcohol exposures per year born	Exposure Percentages per year of birth	Number with ARBD per year of birth (FAS+partial FAS)
1981	12	6	50 %	2
1982	12	8	67 %	3
1983	13	5	38 %	0
1984	17	5	29 %	0
1985	19	8	42 %	3
1986	20	9	45 %	2
1987	21	13	62 %	4
1988	22	6	27 %	1
1989	19	7	37 %	0
1990	23	9	39 %	3

3.1.2 Diagnostic Classification Categories

Table 6 summarizes the number of children per diagnostic classification category. Prior to complete chart review, the Dysmorphologist, blind to alcohol exposure, was asked to categorize each child into one of the four categories listed, based on dysmorphology alone (Dx). At the end of the data collection phase of the study, full charts were reviewed for each child, and blinding to alcohol exposure was now abandoned. At this point in time, based on behavioural, educational, alcohol exposure information, and the dysmorphology assessment, a new diagnosis was given to each child based on all results obtained in the study (NDx). In the case of the FAS children, two were removed from the FAS group to the Dysmorphic 2 group based on no evidence of prenatal alcohol exposure. Individuals were included in the new category-Dysmorphic 2 if they had been excluded from the FAS and Partial FAS categories due to lack of alcohol exposure, but did not appear phenotypically "normal". It is thought that children in this category have abnormalities which are due to a normal familial variation or causes other than prenatal alcohol exposure. Even though the exposure numbers illustrate that only 9 were exposed, the NDx column indicates that 11 children were assessed as being FAS. This is due to the fact that exposure data was not available for the remaining two children, yet they met all other diagnostic criteria for inclusion in this category as expressed by the new diagnostic classification guidelines of the Institute of Medicine (1996). Similarly

only 8/13 previously classified partial FAS children had positive alcohol exposures. Five children were thus reclassified as Dysmorphic 2 based on the fact that they did not appear "normal" phenotypically, but their abnormalities could not be accounted for by prenatal alcohol exposure. One other child was removed from this group and added to the Dysmorphic 2 classification even though she had been exposed prenatally to alcohol. On initial observation the dysmorphologist thought she may have some but, not many of the features associated with FAS, such as telecanthus. However, the majority of the morphometric data did not fit this initial impression, as well, she was functioning normally in school, and was not assessed by teachers or parents as having behavioural problems. Thus, upon full chart review it was decided that she did not exhibit enough characteristic for adequate inclusion in the partial FAS category, despite her positive history of alcohol exposure. With respect to the Dysmorphic classification, 9/19 were exposed to alcohol in utero.

Finally, 50/133 (38%) of the "Normal" classification group had evidence of positive alcohol exposure in utero. This group provides a unique group to study as it allows one to look at the potential learning and behavioural effects of alcohol exposure on the child who does not manifest physical characteristics of such exposure. That is, the alcohol may affect the child behaviourally and cognitively, without observance of the classic FAS phenotype. It would be important for the school to identify these children, since, like their partial FAS counterparts, they may be the ones who do not receive additional resource

educational help.

Examination of the percentage of FAS and partial FAS children born per year of the study period (Table 5 and Figure 4) also reaffirms the alcohol exposure data, in that a significant decrease is not observed between the early and late 1980s [11% (8/73) versus 9.5% (10/105)]. The years of highest alcohol exposure rates, also correspond directly with the years in which the highest numbers of FAS and partial FAS children were born. For example, in 1982, a 67% exposure rate was documented with three FAS/ partial FAS children born, while in 1987, a 62% exposure rate was observed with the number of FAS/ partial FAS children born equalling four (Figure 4).

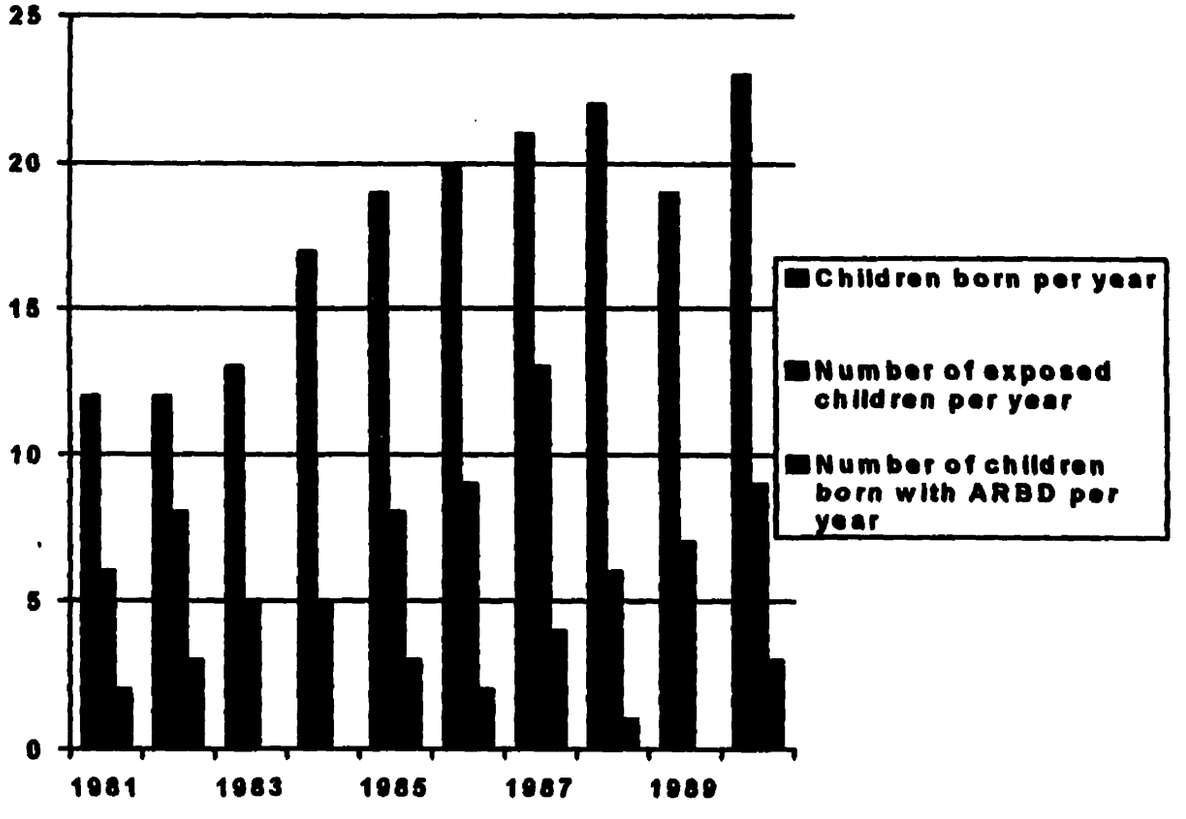
Based on the information presented in Table 4 and Table 6, it is possible to calculate the risk of FAS from pregnancies characterized by high levels of alcohol exposure. Based on these calculations it appears that 16.3% (8/49) of the high exposures resulted in FAS. This figure increases to 30.6% (15/49) if we include high exposure rates for FAS and Partial FAS combined. These numbers are based on a sample size of 165, as thirteen exposures were unknown.

Table 6. Breakdown of study sample by diagnostic classification categories based on the dysmorphology assessment only (Dx) and based on full chart review (NDx).

	Dx	Numbers exposed to alcohol prenatally	NDx
FAS	13	9	11
Partial FAS	13	8	7
Dysmorphic	19	9	19
Dysmorphic 2	0	0	8 (2 reclassified from FAS category, 6 reclassified from Partial FAS category)
"Normal"	133	50	133
Total	178	76	178

Figure 4. Graphic representation of the number of births per year of the cohort, number of exposures to alcohol per year and number of children born with FAS or Partial FAS per year of the cohort.

Breakdown of the Study Cohort by Birth Year illustrating number of exposures per year and the number of ARBD children born per year.



3.1.3 Prevalence

Prevalence rates of FAS and Partial FAS can be calculated for this particular community, based on the previous data. All calculations will be based on the new diagnostic categories, after full chart review (NDx), as this category takes into account all relevant data required in making an FAS diagnosis: dysmorphology, exposure histories, behavioural, and psychoeducational testing.

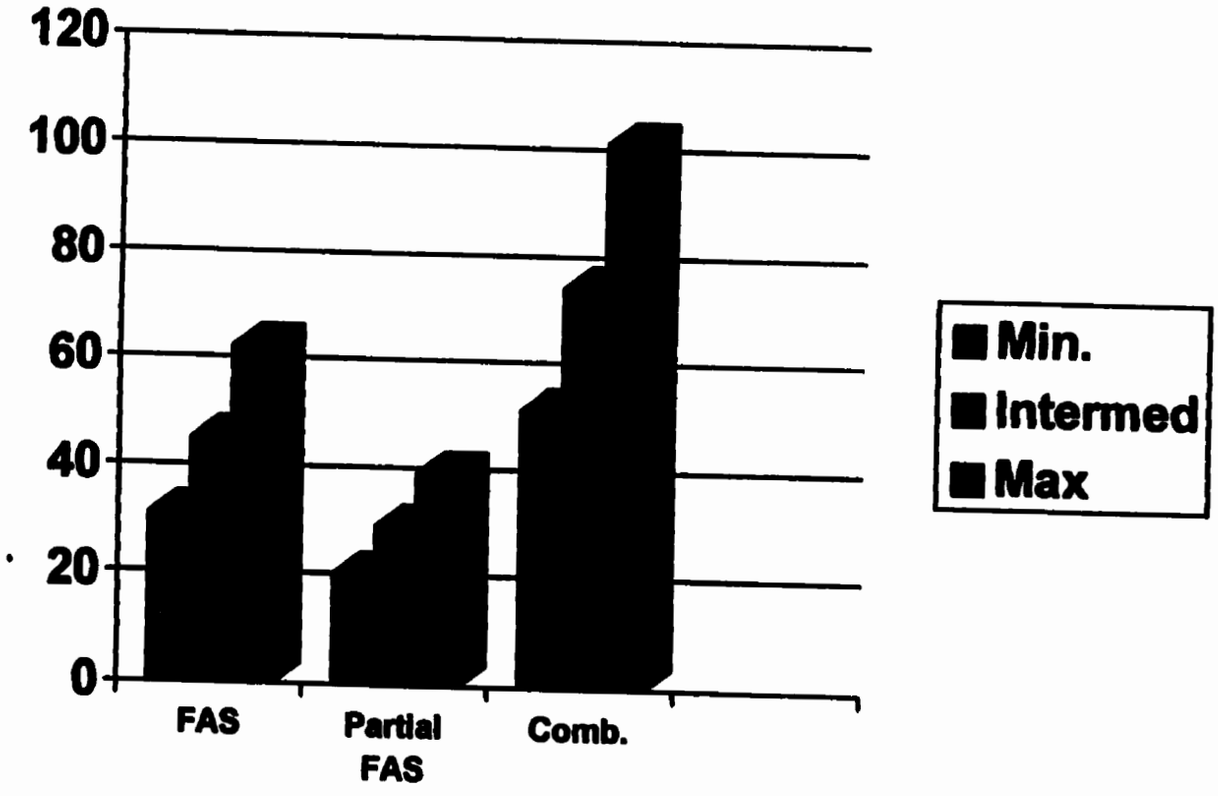
A range of prevalence rates can be determined based on which population size is used as the denominator of the calculation (Table 7 and Figure 5). A minimum prevalence rate is derived using the MSB cohort size of 352 children. Intermediate figures represent prevalence calculations using the school list population, of 243 children born within the specified cohort. In calculating both the minimum and intermediate figure, it is assumed that only the children enroled in the study are those affected with FAS or partial FAS, and that no other affected children would be found in the proportions of the populations not studied (49% and 27%, respectively). The maximum figure is calculated based on the assumption that the study sample is a random sample of the school-aged population in this community and thus the denominator for the calculation is the study sample size of 178 children. As noted in Table 7 and digrammatically depicted in Figure 5, the range for FAS in this community is between 31 - 62 cases per 1000 children, partial FAS ranges from 20 - 39 cases per 1000 children, and the combined figure for all forms of alcohol related birth defects ranges from 51 - 101 cases per 1000 children.

Table 7. Range of Prevalence (per 1000 children) for FAS, Partial FAS, and Combined ARBD in this study community.

	FAS	Partial FAS	Combined (FAS + Partial FAS)
Minimum Prevalence Figure	31	20	51
Intermediate Prevalence figure	45	29	74
Maximum Prevalence Figure	62	39	101

Figure 5. Graphic representation of the possible range of prevalence rates of FAS, partial FAS, and combined FAS and Partial FAS in the study Community (per 1000 children).

Prevalence Data



* number of cases per 1000 children

3.2 Dysmorphology Results

Examination of the dysmorphology assessment results by any level of prenatal exposure to alcohol (Table 8), illustrate that the only parameters that appear to differ statistically between the exposed group and the non-exposed group include: height ($p=0.0169$), weight ($p=0.0019$) and head circumference ($p<0.0001$) percentile values, as determined by use of the Caucasian normal standard graphs. The new diagnostic categories based on full chart review are also significantly different with respect to the exposed and non-exposed groups ($p<0.0001$). Accordingto Student t-test analysis, the exposed group was shorter (mean percentile rank: 58 exposed versus 68 non-exposed), weighed less (62 versus 76), and had smaller head circumferences (58 versus 77) than their unexposed counterparts. Other dysmorphology parameters that did not meet criteria of statistical significance at the $p=0.01$ level, but would be considered borderline significant ($0.05 \geq p \geq 0.01$) when examined with respect to alcohol exposure include brachydactyly ($p=0.059$), diagnosis based on dysmorphology alone ($p = 0.02$) and palpebral fissure length percentiles ($p=0.037$). With respect to brachydactyly, the exposed individuals showed a 4% rate of brachydactyly versus no cases observed in the unexposed individuals. Palpebral fissure length percentiles were lower for the exposed group in comparison to the unexposed group (mean percentile rank: 38 versus 47).

Data analyzed with respect to graded alcohol exposures (high, low, and no alcohol exposure) using the Wilcoxon signed rank sums test, indicate that the

same dysmorphology parameters significantly differ statistically between the groups (Table 9). These parameters include: height (p=0.0033), weight (p = 0.0001), and head circumference percentiles (p = 0.0001), diagnosis based on dysmorphology alone (p=0.003), as well as the new diagnosis based on dysmorphology and complete chart review (p<0.0001). According to the mean percentile ranks, individuals with high levels of alcohol exposure were shorter (high = 52, low =68 and no exposure = 68), lighter (high = 55, low =75, no exposure = 76), and had smaller head circumferences (high =52, low = 69, no exposure= 77). One dysmorphology parameter which was only considered to be of borderline statistical significance with respect to alcohol exposure, but which reaches statistical significance when alcohol exposure is graded, is the palpebral fissure length percentiles (p=0.0017). Individuals who were exposed to high levels of alcohol in utero exhibit the shortest palpebral fissure lengths (mean percentile rank: high = 32, low = 49, no exposure = 47). However, it is not the low exposure group who rank second with respect to short palpebral fissures, but rather the non-exposed group. As was observed with the alcohol exposure analysis, both midface and brachydactyly were considered to be of borderline statistical significance (p = 0.023 and p = 0.041 respectively), when analyzed with respect to graded alcohol exposure.

A description of the statistically significant results of the comparison of dysmorphology assessment parameters versus diagnostic categories based on dysmorphology alone is provided in Table 10. The Wilcoxon signed rank sums

Table 8. Results of Chi Square and Student t-test analysis of Dysmorphology Parameters in Exposed versus Non-exposed Individuals.

	Chi Sq Value	P value	Exposed	Not Exposed
Brachydactyly	3.578	0.059	4% *	0% *
Diagnosis by dysmorphology alone	9.884	0.020	-	-
New Diagnosis (after full chart review)	20.617	< 0.0001	-	-
	t values	P value	Mean Percentile Rank	
Height Percentile	2.4138	0.0169	58	68
Weight Percentile	3.1526	0.0019	62	76
Head Circumference Percentile	4.3019	< 0.0001	58	77
Palpebral Fissure Length Percentile	2.1038	0.0369	38	47

* denotes percentage of individuals affected

Table 9. Results of Chi Square and Wilcoxon Sums Rank analysis of Dysmorphology Parameters in Individuals with graded alcohol exposures (no exposure versus low exposure versus high exposure).

	Chi Sq Value	P value	Graded level of Exposure		
			High	Low	None
Midface	7.580	0.023	14%*	0%*	4%*
Brachydactyly	6.387	0.041	2%*	7%*	0%*
			Mean Percentile Rank		
Height Percentile	11.412	0.0033	52	68	68
Weight Percentile	20.131	0.0001	55	75	76
Head Circumference Percentile	22.689	0.0001	52	69	77
Palpebral Fissure Length Percentile	12.812	0.0017	32	49	47
Diagnosis by dysmorphology alone	19.604	0.003	-	-	-
Diagnosis post full chart review	31.677	< 0.0001	-	-	-

* denotes percentage of individuals affected

Table 10. Comparison of Dysmorphology Parameters by Diagnostic Categories based on the results of the dysmorphology assessment alone, and the proportion of individuals with abnormal features per category (qualitative data), or mean percentile rank per category (quantitative data).

	Chi Sq Value	P value	"Normal"	Dys-morphic	Partial FAS	FAS
Qualitative Data			Percentage of Affected Individuals			
Poor Cupid's Bow	14.544	0.002	11.6%	22.2%	33.3%	50.0%
Thin Upper lip	11.210	0.011	16.0%	22.2%	50.0%	41.7%
Recessed Midface	21.498	< 0.0001	2.4%	11.8%	10.0%	36.4%
Quantitative Data			Mean Percentile Rank			
Height Percentile	27.757	0.0001	68	64	46	22
Weight actual measurement (kg)	9.6894	0.0214	40*	34*	37*	29*
Weight - Percentile	31.609	0.0001	74	75	50	24
Head Circumference -actual measurement (cm)	15.658	0.0013	54*	54*	53*	51*
Head Circumference Percentile	24.860	0.0001	72	79	48	25
Outer Canthal Distance-actual measurement (cm)	7.7342	0.0518	8.6*	8.7*	8.5*	8.1*
Outer Canthal Distance %ile	19.832	0.0002	66	76	56	36
Palpebral Fissure Length - actual measurement (cm)	26.953	0.0001	2.68*	2.61*	2.55*	2.37*
Palpebral Fissure Length %ile	33.297	0.0001	47	38	24	11
Ratio of Palpebral fissure length to inner canthal distance	17.378	0.0006	0.83*	0.78*	0.78*	0.74*

* denotes mean actual measurement, not percentile rank score.

test was used to test for significant differences between the four diagnostic categories based on dysmorphology alone ("Normal", Dysmorphic (reasons other than possible alcohol exposure), FAS, and Partial FAS). This analysis revealed the significant dysmorphology parameters as being those which are used to make the FAS diagnosis. Poor Cupid's bow formation was noted to be statistically different between the groups (p=0.002), with 12% of the "normal" group (15/129) versus 50% (6/12) of the FAS , and 33% (4/12) of the partial FAS group being affected (information was not available for one FAS and one partial FAS individuals). Thin upper lip (p=0.011) was observed in 16% (21/131) of the "normal" category in comparison to levels of 42% (5/12) and 50% (6/12) in the FAS and Partial FAS categories respectively. Recessed midface, as judged by diagnostician's impression, was also found to be significantly different statistically between the groups (p<0.0001), 2% (3/124) of the "normal" group exhibited the trait, versus 36%(4/11) and 10% (1/10) in the FAS and partial FAS groups. With respect to growth parameters the following parameters all differed significantly between the diagnostic categories: height percentiles (p=0.0001), weight percentiles (p= 0.0001), head circumference actual measurement (p=0.0013), as well as percentiles (p= 0.0001), outer canthal distance percentiles (p= 0.0002), palpebral fissure length, actual measurement (p=0.0001) as well as percentiles (p=0.0001), and the ratio of palpebral fissure length to inner canthal distance (p= 0.0006). In general, it was those individuals with FAS, followed by those with partial FAS, who were shorter, lighter, had

smaller head sizes, had shorter outer canthal distances, shorter palpebral fissure lengths and smaller palpebral fissure length versus inner canthal distance ratios (Table 10).

When the dysmorphology data is analyzed with regards to the new diagnostic categories ("Normal", Dysmorphic (not expected to be related to alcohol exposure), Partial FAS, and FAS), using the Wilcoxon test, the results previously reported do not change. That is, the dysmorphology parameters that appear to be statistically significant based on the analysis using the original diagnostic categories based on dysmorphology assessment results, are the same parameters that appear significant in this analysis (Table 11). Similarly, analysis of the mean percentile rank scores reveals that the FAS individuals are the smallest, have shorter palpebral fissure lengths and shorter outer canthal distances. In general it is the Partial FAS group who rank second lowest, as might be expected due to the presence of alcohol in this group as well.(Table 11).

Within the "Normal" diagnostic category, 38% had been exposed to alcohol in utero. Comparisons of the exposed versus the non-exposed "normal" groups showed no statistically significant differences detected on any morphometric parameter at the $p = 0.01$ level. However, height, weight, and head circumference percentiles, appear to be borderline statistically significant, for both total exposure and graded exposure levels for the normal category (Table 12). Examination of the mean percentile rank scores indicate that the

exposed group (and high exposure group, with respect to the graded alcohol exposure analysis), are slightly (but not significantly) smaller than the low exposure and no exposure groups (Table 13).

Table 11. Results of the analysis of the dysmorphology parameters by new diagnostic categories based on dysmorphology assessment and full chart review, and the proportion of affected individuals per category (qualitative data) or mean percentile rank scores per category (quantitative data).

	Chi Sq Value	P value	Norm -al	Dys- mor- phic	Partial FAS	FAS
Qualitative Data			Proportion of Affected Individuals			
Poor Cupid's Bow	14.840	0.005	11.6%	22.2%	37.5%	50.0%
Thin Upper lip	13.486	0.009	16.0%	22.2%	62.5%	41.7%
Recessed Midface	22.238	0.000	2.4%	11.8%	14.3%	36.4%
Quantitative Data			Mean Percentile Rank			
Height Percentile	28.506	0.0001	68	64	51	22
Weight - actual measurement (kg)	11.848	0.0185	40*	34*	32*	29*
Weight - Percentile	32.542	0.0001	74	75	43	24
Head Circumference - actual measurement (cm)	25.600	0.0001	54*	54*	51*	51*
Head Circumference Percentile	34.018	0.0001	72	79	29	25
Outer Canthal Distance - actual measurement (cm)	9.5879	0.0480	8.6*	8.7*	8.3*	8.1*
Outer Canthal Distance %ile	20.036	0.0005	66	76	52	36
Palpebral Fissure Length - actual measurement (cm)	28.334	0.0001	2.68*	2.61*	2.51*	2.37*
Palpebral Fissure Length %ile	34.117	0.0001	47	38	19	11
Ratio of Palpebral fissure length to Inner canthal distance	17.556	0.0015	0.83*	0.78*	0.79*	0.74*

* denotes actual measurements, not percentile rank scores

Table 12. Comparison of exposed and non-exposed , as well as the comparison of graded level of alcohol exposure subgroups within the "Normal" Diagnostic Category, with respect to borderline statistically significant morphometric parameters.

	Chi Square and P value for Exposure to Alcohol during pregnancy	Chi Square and P value for Graded Alcohol Exposure During Pregnancy
Height Percentile	3.4398, p =0.0636	7.7788, p = 0.0205
Weight Percentile	4.0505, p = 0.0442	7.2764, p = 0.0263
Head Circumference Percentile	4.3412, p = 0.0372	6.5957, p = 0.0370

Table 13. Mean percentile rank scores corresponding to the borderline statistically significant ($0.01 \leq p \leq 0.05$) morphometric parameters idenitified during analysis of the parameters by exposure versus no expsure, and graded levels of alcohol exposure in the "Normal" diagnostic category.

	Exposure versus No Exposure to Alcohol		Graded Level of Exposure to Alcohol		
	Exposed	No Exposure	High	Low	None
Height Percentile	63	71	57	71	71
Weight Percentile	70	77	65	77	77
Head Circumference Percentile	67	76	63	72	76

3.3 Normative Data Results

Morphometric data from the "Normal" diagnostic category were used to generate the normal Native curves. The normal category was first separated and analyzed by sex. Student t-tests were performed for each of the ten morphometric parameters to determine if the data could be pooled between the sexes for analysis, or whether the means between the males and females were sufficiently different, in which case two graphs would have to be generated for each measured parameter, one for each sex. The results of the two-tailed student t-test analysis are listed in Table 14. As can be seen from the table, the only morphometric parameter that did not differ significantly between the sexes, and thus allowed for a pooled data graph to be created was the ONO angle.

Graphs for each sex were constructed for each of the following parameters: height, weight, head circumference, palpebral fissure length, philtrum length, inner canthal distance, outer canthal distance, hand length, and palm length. The ONO angle graph was created using pooled male and female normal data. The graphs and their corresponding tables are presented in Appendix E.

Each graph is comprised of two important areas. The shaded area represents the range of measurement falling between the third and ninety-seventh percentiles (except in the case of the head circumference graphs, in which the shaded area ranges from the second to ninety-eighth percentile) from the normal curves previously described in the literature, which are based

Table 14. Student t-test (two-tailed) results for comparing the means between the two sexes for each of the morphometric parameters studied.

		Male			Female		T-value	P-value
	N	Mean	Var	N	Mean	Var		
Height	74	142.847	257.23	59	134.651	230.10	3.018	0.005>p> 0.001
Weight	74	43.803	299.37	59	36.120	254.05	2.658	0.01>p> 0.005
Head Circum.	74	55.143	1.411	59	52.77	5.527	7.067	p < 0.001
Palp. Fissure Length	74	2.727	0.0291	59	2.620	0.0251	3.74	p = 0.01
Phil-trum Length	74	1.59	0.0619	59	1.48	0.0607	2.55	0.015>p> 0.01
ICD	74	3.33	0.068	59	3.19	0.118	2.59	0.01>p> 0.005
OCD	74	8.789	0.237	59	8.398	0.304	4.278	p < 0.001
Hand Length	74	15.984	3.985	59	15.207	3.396	2.328	0.02>p> 0.015
Palm Length	74	9.09	1.383	59	8.57	1.034	2.74	0.01>p> 0.005
ONO angle	74	90.86	20.502	59	91.16	20.668	0.379	0.8>p> 0.6

primarily on Caucasian populations (Nellhaus, 1968; Laestadius, 1969; Feingold and Bossert, 1974; Thomas, 1987; Hall et al, 1989). The second important aspect to each graph is the series of five lines which represent the second, sixteenth, fiftieth, eighty-fourth, and ninety-eighth percentile boundaries for the Native normal curves derived from the morphometric data collected in the Normal category of this school-aged population. In the cases of palpebral fissure lengths, philtrum lengths, inner canthal and outer canthal distances, palm and hand lengths, the same shaded area appears in both newly generated male and female Native graphs. This is due to the fact that, sex differences were not observed in the previously reported literature and thus data between the sexes could be pooled (Feingold and Bossert, 1974; Thomas, 1987, Hall et al, 1989).

Paired Student t-tests were performed on the median lines of the previously reported growth curves derived from Caucasian morphometric data, and the newly generated Native normal curves, to determine if in fact there was a significant difference between the two ethnic groups with respect to growth parameters. Data used for the statistical comparison of the medians is listed in Appendix F. The results of the paired student t-tests (Table 15) illustrate that there were statistically significant differences ($p \leq 0.01$) between the Caucasian and the Native normal curves for the following parameters for both sexes: height, weight, head circumference, hand length, inner canthal distance, outer canthal distance, and ONO angles. Females showed borderline statistical differences

($0.01 \leq p \leq 0.05$) for philtrum length and palm length with respect to comparison between the Native and Caucasian medians. No statistical differences were noted in either sex for palpebral fissure length, or for philtrum and palm lengths in males. Based on the results presented in Table 15 and in Figures 6 - 24 (found in Appendix E), it can be said that the "normal" school-aged population studied in this community are taller, heavier, have larger head circumferences, bigger hands (more precisely longer fingers), and have more widely spaced eyes as determined by increased inner and outer canthal distances than their Caucasian counterparts.

Given that statistical differences were found between the Caucasian norms and those generated in this study for the school aged Native population, comparisons of the morphometric data of the FAS (9 individuals) and partial FAS (6 individuals) groups were conducted using the newly generated curves to determine if any differences would be observed with respect to percentile ranks falling in the "abnormal ranges". Two individuals in the FAS group and one from the partial FAS group were excluded from this aspect of study, due to the fact that their age was greater than 14 years of age, and could not be accommodated on the newly generated Native normal graphs. Tables 16 - 19 present the percentile rank results obtained when each of the morphometric parameter measurements were compared on both the Caucasian standard normal curves, and the newly generated Native ones. In the majority of cases, a decrease in percentile rank was noted when the morphometric data were plotted on the

Native curves, as opposed to the previously established Caucasian curves. Table 20 provides a summary of the number of FAS and Partial FAS individuals whose percentile ranks fell into the "abnormal zone" with respect to growth retardation, telecanthus, shortened palpebral fissure size, increased philtrum, hand and palm lengths when plotted on the Native versus Caucasian curves. For example, 8 FAS individuals and 2 Partial FAS individuals were considered growth retarded with respect to height (less than the tenth percentile) on the Native curves, in comparison to 4 and 1 individual respectively, based on Caucasian percentiles. Examination of other parameters showed that when morphometric data was plotted on the Native curves : 4 additional FAS children were growth retarded with respect to weight (less than the tenth percentile), two additional cases (one FAS and one partial FAS) were microcephalic (less than the third percentile), and five more children (2 FAS and 3 partial FAS) exhibited extremely shortened palpebral fissures (less than the second percentile), than when plotted on the Caucasian standards. With respect to philtrum lengths, plotting raw data on the Native curves lead to increases in the percentile rank of many of the individuals (6/9 FAS and 5/6 Partial FAS) as compared with their previous ranks based on the Caucasian standards. The plotting of inner canthal distances on the Native versus Caucasian standards decreased the number of telecanthic cases (inner canthal distance above the ninety-eighth percentile) observed (one FAS and one Partial FAS case were removed). In many cases plotting on the Native curve decreased the inner canthal percentile rank for that

child (7/9 FAS, 5/6 Partial FAS). This general trend of, decreasing percentile ranks when Native data were plotted on the Native versus Caucasian curves, was also observed for outer canthal distance percentiles(8/9 FAS, 4/6 Partial FAS), palm (9/9 FAS, 5/6 Partial FAS) and hand lengths (7/9 FAS, 6/6 Partial FAS) for both FAS and partial FAS individuals. ONO angles did not seem to be affected uniformly in either direction when comparing the Caucasian percentile ranks to the Native ones.

Table 15. Results of the Paired Student t-test comparing the medians of the Normal Caucasian growth curves to that of the new generated Normal Native growth curves (for each sex).

	P value (Males)	P value (Females)
Height	0.0001	0.0031
Weight	0.0005	0.002
Head Circumference	0.0001	0.0004
Palpebral Fissure Length	0.5261	0.9067
Philtrum Length	0.7734	0.03
Hand Length	0.0042	0.0021
Palm Length	0.1345	0.0236
Inner Canthal Distance	0.0001	0.0001
Outer Canthal Distance	0.0001	0.0001
ONO angle	0.0049 (pooled data for both males and females)	

Table 16. Comparison of Height, Weight and Head Circumference of FAS and Partial FAS Individuals, between Caucasian and Native Normal Standard Curves.

Fetal Alcohol Syndrome Growth Parameters, Caucasian Percentiles and Native Percentiles											
ID#	Age	Sex	Height (cm)			Weight (kg)			Head Circumference (cm)		
			Value	Cauc. %ile	Nat. %ile	Value	Cauc %ile	Nat. %ile	Value	Cauc %ile	Nat. %ile
019	5 8/12	m	109	15	<2	18.2	15	2	50.5	40	5
111	5 9/12	f	109	15	<2	17.3	25	2	49.5	30	7
188	5 9/12	f	106	5	<2	22	85	35	49.2	25	5
072	6 11/12	f	119	40	2	20.1	25	16	48.4	2	5
094	8 3/4	m	136.3	80	35	19.8	<5	2	56	>98	84
051	9 9/12	m	122.2	<5	<2	23.2	<5	7	48.3	<2	<2
116	9 4/12	f	122.5	<5	<2	24.5	10	7	50.5	25	10
090	13 4/12	m	145	5	<2	32.5	<5	<2	52.5	25	<2
176	13 8/12	m	155	25	10	44.5	25	2	50.5	<5	<2
Partial Fetal Alcohol Syndrome Growth Parameters, Caucasian Percentiles, and Native Percentiles											
070	8 8/12	m	135.5	85	50	29.8	75	30	52.7	50	12
007	8 9/12	f	122.8	10	2	20.7	<5	5	49	2	5
128	8 2/12	f	121	15	<2	20	10	5	49	2	5
206	8 9/12	f	131	50	16	29.5	65	12	49.5	10	7
123	10 10/12	m	143	50	16	33.5	40	16	54.6	80	50
180	11 2/12	f	154	90	50	44.5	75	20	50.7	20	<2

Table 17. Comparison of Inner Canthal Distance, Outer Canthal Distance, and Palpebral Fissure Length of FAS and Partial FAS Individuals, between Caucasian and Native Normal Standard Curves.

Fetal Alcohol Syndrome Morphometric Measures, Caucasian Percentiles and Native Percentiles											
ID#	Age	Sex	Inner Canthal Distance (cm)			Outer Canthal Distance (cm)			Palpebral Fissure Length (cm)		
			Value	Cauc. %ile	Nat. %ile	Value	Cauc %ile	Nat. %ile	Value	Cauc %ile	Nat. %ile
019	5 8/12	m	3.4	>95	90	7.7	45	16	2.2	<5	<2
111	5 9/12	f	3.1	80	50	7.5	25	2	2.3	<5	<2
188	5 9/12	f	3.2	90	70	7.5	25	2	2	<5	<2
072	6 11/12	f	2.8	50	40	7.2	15	2	2.3	<5	2
094	8 3/4	m	4.2	>95	>98	9.4	>95	>98	2.5	15	16
051	9 9/12	m	2.8	40	2	8	25	2	2.4	5	<2
116	9 4/12	f	2.7	25	<2	8.2	40	16	2.5	15	7
090	13 4/12	m	3.3	75	35	8.4	25	7	2.3	<5	<2
176	13 8/12	m	3	40	7	8	15	<2	2.4	5	<2
Partial Fetal Alcohol Syndrome Morphometric Measures, Caucasian Percentiles, and Native Percentiles											
070	8 8/12	m	3.2	90	50	8.5	75	45	2.5	15	16
007	8 9/12	f	2.3	<5	<2	7.2	3	<2	2.4	5	<2
128	8 2/12	f	3.2	80	50	8	40	10	2.4	7	<2
206	8 9/12	f	3.2	85	45	8.3	55	20	2.4	5	<2
123	10 10/12	m	3.7	>95	84	8.2	35	10	2.7	50	40
180	11 2/12	f	3.2	80	50	9	80	84	2.6	25	16

Table 18. Comparison of Philtrum, Palm and Hand Lengths of FAS and Partial FAS Individuals, between Caucasian and Native Normal Standard Curves.

Fetal Alcohol Syndrome Morphometric Measures, Caucasian Percentiles and Native Percentiles											
ID#	Age	Sex	Philtrum Length (cm)			Palm Length (cm)			Hand Length (cm)		
			Value	Cauc. %ile	Nat. %ile	Value	Cauc %ile	Nat. %ile	Value	Cauc %ile	Nat. %ile
019	5 8/12	m	1.3	40	12	7.2	40	35	12	20	7
111	5 9/12	f	1.4	50	35	6.8	20	<2	12.4	25	7
188	5 9/12	f	1.9	60	90	7	25	2	12.5	35	7
072	6 11/12	f	1.7	55	84	7.5	30	16	13.9	55	40
094	8 3/4	m	2.1	60	>98	8.8	75	50	15.3	75	60
051	9 9/12	m	1.6	50	70	8	20	7	13.2	<3	<2
116	9 4/12	f	1.8	55	90	7.8	15	7	13.5	3	5
090	13 4/12	m	1.8	55	90	9.2	20	<2	16.2	20	<2
176	13 8/12	m	1.1	10	<2	9.6	45	<2	16.6	30	<2
Partial Fetal Alcohol Syndrome Morphometric Measures, Caucasian Percentiles, and Native Percentiles											
070	8 8/12	m	1.7	55	70	8.5	75	50	15.2	75	50
007	8 9/12	f	1.5	45	55	7.8	25	7	14.3	35	16
128	8 2/12	f	1.5	40	55	7.5	15	10	15	75	35
206	8 9/12	f	1.4	50	40	9	80	45	16	95	50
123	10 10/12	m	1.9	55	87	10	90	90	16	75	45
180	11 2/12	f	1.5	45	50	10.5	>97	84	18.7	>97	84

Table 19. Comparison of ONO angles of FAS and Partial FAS Individuals, between Caucasian and Native Normal Standard Curves.

Fetal Alcohol Syndrome ONO Angle Measurement, Caucasian Percentiles, and Native Percentiles					
ID#	Age	Sex	Value	Caucasian %ile	Native %ile
019	5 8/2	m	96	55	84
111	5 9/12	f	86	15	5
188	5 9/12	f	94.5	50	75
072	6 11/12	f	87	25	16
094	8 3/4	m	90	40	50
051	9 9/12	m	92	50	75
116	9 4/12	f	87	25	16
090	13 4/12	m	92	55	70
176	13 8/12	m	80	5	5
Partial Fetal Alcohol Syndrome ONO Angle Measurement, Caucasian Percentiles, and Native Percentiles					
070	8 8/12	m	88	30	35
007	8 9/12	f	84	15	7
128	8 2/12	f	91	45	50
206	8 9/12	f	93	55	70
123	10 10/12	m	92	60	70
180	11 2/12	f	84	20	7

Table 20. Comparison of the number of Individuals with "Abnormal" Percentile Ranks between FAS and Partial FAS data plotted on Caucasian versus Native Normal Growth Curves.

	Number of FAS and Partial FAS individuals based on Caucasian Curves	Number of FAS and Partial FAS individuals based on Native Curves
Height below 10 th percentile	4 FAS, 1 Partial FAS	8 FAS, 2 Partial FAS
Weight below 10 th percentile	3 FAS, 2 Partial FAS	7 FAS, 2 Partial FAS
Head Circumference below 3rd percentile	3 FAS, 2 Partial FAS	4 FAS, 3 Partial FAS
Inner Canthal Distance above 98th percentile	2 FAS, 1 Partial FAS	1 FAS, 0 Partial FAS
Palpebral Fissure length below 2nd percentile	5 FAS, 0 Partial FAS	7 FAS, 3 Partial FAS
Hand length below 10th percentile	2 FAS, 0 Partial FAS	7 FAS, 0 Partial FAS
Palm length below the 10th percentile	0 FAS, 0 Partial FAS	6 FAS, 1 Partial FAS
Number of individuals with one or more of the above features	9 FAS, 3 Partial FAS	9 FAS, 4 Partial FAS

4.0 Discussion

4.1 Epidemiology

4.1.1 Alcohol Abuse

Data collected in this study indicate that the overall rate of alcohol abuse during pregnancy in the study sample born in the years 1981 to 1990 was 46%. Even more alarming is the fact that 30% had been exposed to high levels of alcohol prenatally, as assessed by an affirmative answer to the question regarding alcohol as a reason for placement in the case of foster / adopted children, or scores of two or more on the TWEAK test (Russell and Bigler, 1979). These reported exposure rates are high when compared to other exposure rates reported in the literature. In a report by Dufour et al (1994) which surveyed the drinking histories and knowledge of the risks of heavy drinking during pregnancy in a group of women in the United States ranging in age from 18 to 44, the rate of risk drinking in this group of women of childbearing age was cited as 10% in 1990, where risk drinking was considered to be consumption of, on average, more than one drink per day. Similarly, Serdula et al (1991) reported on the trends of alcohol consumption in a group of pregnant women during the years 1985 to 1988. This sample of women (1712) ranged in age from 18 to 45, and represented 21 states in the U.S. According to this study, the rate of alcohol exposure declined within this four year study period from 32% in 1985 to 20% in 1988, although no significant decreases were noted in the lower age bracket, that is pregnant women under the age of 25 (Serdula et al, 1991). With respect

to levels of heavy drinking (on average two or more drinks daily), only 0.6% of pregnant women were noted to be heavy drinkers, and 2.8% were classified as binge drinkers (consuming five or more drinks on one occasion). Striessguth et al (1983) noted a 42% rate of alcohol exposure at the first prenatal visit for a sample of pregnant women in Seattle during the years 1980 to 1981. Little et al (1989) cite a heavy alcohol exposure rate of 1.4% in a group of primarily indigent women who attended prenatal clinics in Dallas, Texas, in 1987. Thus from the data presented with respect to the Manitoba study, it appears that the rates of alcohol exposure are much higher in this community than those rates found in recent reports on alcohol use in pregnant women. Particularly alarming is the rate for high levels of alcohol exposure during pregnancy. Unlike the study by Serdula et al (1991), the rate of alcohol abuse in this community does not seem to be decreasing over time. Comparisons of the alcohol exposure rate in those children born within the first half of the birth cohort versus the latter half indicate that the rate of exposure appears to be consistent (44% versus 42%).

In one of the first reports of FAS, Jones et al (1974) stated that based on the evaluation of 23 children whose mothers had histories of alcoholism, the risk of FAS among heavy drinkers was 32%. Sokol et al (1980), in a prospective cohort study, also computed a risk estimate for FAS among women who abused alcohol heavily during pregnancy. Their rate of 2.5% was considerably lower than that reported by Jones et al (1974). In Abel's update on the incidence of FAS (1995), which reviewed twenty-nine world wide prospective studies, the rate

of FAS among heavy drinkers, as defined by consumption of two or more drinks per day or five to six drinks per occasion, was cited as being 4.3%. Data presented in this thesis would indicate figures much higher than the most recent rate quoted by Abel. In this study, the rate of FAS among high alcohol exposures (as defined in the previous section) was 16.3% (8/49). If we include the number of partial FAS children who had been exposed to high levels of alcohol prenatally, the rate of having a child visibly affected by alcohol increases to 30.6% (15/49). However, it is possible, given the retrospective self-reporting method of alcohol exposure ascertainment used in this study that, the number of heavy drinkers may be an underestimate of the true figure. If we assume that all women ascertained in the study drank heavily during their pregnancies then, the rate FAS per heavy drinker would drop to 6.2% (11/178), or 10.1%(18/178) if Partial FAS cases are included. However, these decreased rates are still higher than those reported in the literature. Thus alcohol abuse among women in this community is a significant problem that has not decreased with time. This is unfortunate as it is apparently leading to increasing prevalence of FAS and partial FAS affected individuals in the community at levels much higher than those reported in the literature.

Why would such a discrepancy arise between the reported rates of drinking among women? One reason inflated rates may be observed is due to the population under study. It has been stated that women who tend to engage in long term (throughout pregnancy) risk drinking tend to be characterized as

being minorities, who are of lower educational levels and lower SES (Sokol et al, 1980; Day et al, 1993) Binge drinking patterns which lead to higher peak blood alcohol levels, and tend to affect the fetus more adversely than constant drinking, seem to be influenced by age and culture (May et al, 1983; Abel and Hannigan, 1995; Gladstone et al, 1997). For example, African and Native Americans tend to participate in binge drinking more often than their Caucasian counterparts (Abel and Hannigan, 1995). Thus if these ethnic groups are not represented in a study, it is possible that the rate of drinking would be underestimated. May et al (1983) noted drinking patterns and FAS prevalence can also vary greatly within an ethnic group. In a study of three South-Western Amerindian tribes in the United States (Plains, Pueblo, and Navajo), May et al (1983) illustrated almost a ten fold difference in the prevalence of FAS between the tribes with the highest levels being noted for the Plains tribe (19.5 per 1000) versus the Navajo and Pueblo cultures (2.5 and 2.7 per 1000 respectively). Previous studies have also illustrated that drinking patterns were highest in the Plains culture (50 - 55%) versus the Pueblo and Navajo tribes (13-23%) (Whitaker, 1962; Whitaker, 1982, Levy and Kunitz, 1974).

It is acknowledged that caution must be used when comparing rates of drinking or heavy drinking among women. It is possible that due to fears of stigmatization or punishment women may underreport the levels of alcohol consumption during pregnancy. If this is occurring, then we would expect the numbers cited in the literature to be underestimates of the true level of drinking

in women. Also, many studies use different definitions for heavy alcohol consumption. Some may report alcohol consumption by daily intake, which as Abel (1995) has stated, is not very accurate, as many people tend to drink on occasion, instead of daily. Some studies may define heavy alcohol consumption by binge drinking. Thus when comparing reported rates of heavy alcohol exposure, one must be aware that different definitions of heavy alcohol intake are used in each study and, for that reason, comparison of these rates between studies may not always be appropriate.

4.1.2 Prevalence of FAS and Partial FAS

Although epidemiological data concerning alcohol related birth defects and FAS in general are limited, the numbers in the literature illustrate one thing, that the prevalence of FAS varies not only between different countries and ethnic groups, but within them as well (Abel and Sokol, 1987; Abel and Sokol, 1991; Abel, 1995; May et al, 1983). Estimates of FAS have ranged from a world wide incidence of 1.9 per 1,000 live births in 1987 (Abel and Sokol, 1987), to a revised estimate of 0.33 cases of FAS per 1000 live births in 1991 (Abel and Sokol, 1991), to an updated figure of 0.97 per 1000 births in the general obstetric population as of 1995 (Abel, 1995). The first of these studies by Abel and Sokol was based on review of 19 prospective and retrospective worldwide studies, while the second two estimates were based solely on prospective studies. FAS incidence was twenty times higher in the U.S.A. than in Europe

(1.95 versus 0.08 per 1000), and within the United States itself a ten time higher rate is observed in areas comprised of low SES individuals of African American or Native American background, as compared to middle/upper SES Caucasian background areas (2.29 vs 0.26 per 1000) (Abel, 1995).

Relating to ethnic specific FAS epidemiology, are the studies concerning FAS in Amerindian and Canadian Aboriginal populations. Data on these particular ethnic groups are even more limited. Abel states that Native American populations were not included in the 1995 incidence estimate, due to the lack of availability of prospective data on such communities. However, studies in Canada, particularly on the West Coast, have indicated that FAS is a major problem affecting subgroups of the Canadian Aboriginal population. Wong (1983) in an unpublished study report FAS rates ten fold higher among the Native versus non-Native population of British Columbia during the years 1973 - 1980 (4.7 versus 0.4 per 1000). While the highest reported prevalence rates for FAS are those reported by Robinson et al (1987) at levels of 190 cases per 1000 livebirths, almost a 200 fold increase over the 1995 worldwide estimate. In this Manitoban study, the prevalence figures do not reach the same magnitude as Robinson et al's (1987). However, they are extremely high in comparison to the worldwide rates. The absolute minimum prevalence figure calculated using the MSB population size as 352 individuals, and assuming that no other cases of FAS would be found in the 49% of the population not studied, leads to a prevalence rate 32 fold higher than the world estimate (31 per 1000 children). If

one looks at the most likely estimate of prevalence for this study, where it is assumed that the study sample is a random sampling of the population, then the prevalence figure increases to 62 cases per 1000 children (64 fold higher than the world estimate).

This study cites the rate of FAS affected individuals to be 6.2% (11/178) of the study population, and the rate of partial FAS individuals to be 3.9% (7/178). Therefore it can be said that alcohol has adversely affected at least 10.1% (18/ 178) of the school aged population of this community. This number is not unique, and although not quite as high, is in the same order of magnitude as other previously reported rates in Canadian Aboriginal populations in British Columbia (18.5 %, Robinson et al, 1987) and the Yukon (42.5%, Asante et al, 1985).

Although the figures are high, they may still be an underestimate of the true prevalence rates in the community. Factors such as refusal to participate in the study, absence from school on the dysmorphology assessment days, and transient movement on and off reserve, may have caused researchers to "miss" some cases. Even if ascertained, given the nature by which the diagnosis is determined—primarily a qualitative opinion—there may be some individuals who have been misclassified. It was intended that, by having only one individual experienced with FAS diagnosis assesses the children that this bias and biases with respect to different criteria being used to determine FAS diagnosis could be avoided. A third bias noted in many studies is the stereotypical belief that

Natives are at increased risk for heavy drinking which may lead to the labelling of more children. Knowledge of the alcohol exposures status prior to the dysmorphology assessment of a Native child may also lead to over diagnosis. It was hoped that, by blinding each investigator to the exposure histories of the children and eliminating cases with positive dysmorphology where exposure could not be documented, biases stemming from the stigmatization centering on the stereotypical belief of higher alcohol abuse rates in Natives, would be minimized.

4.2 Dysmorphology

In examining the dysmorphology results based on diagnostic classification (both based on dysmorphology alone, and based on full chart review), it is not surprising that growth parameters such as decreased height, weight, and head circumference, and certain craniofacial landmarks—shortened palpebral fissure lengths, poorly formed Cupid's bow, thin upper lip, recessed midface, and the ratio of the palpebral fissure length to the inner canthal distance—are all statistically significant, as these are the primary items incorporated by the Dysmorphologist, when making the diagnosis of FAS. What is interesting is the identification of significant differences with respect to many of the previously listed items when one divides the study population not by diagnostic categories, but rather by positive or negative alcohol exposure histories, or by graded prenatal alcohol exposure. It is when items appear to be significantly different

between the different exposure groups that validation is given to the items used for diagnosis, as items truly reflecting the effects of alcohol on the developing fetus. In this study, the growth retardation categories, midface hypoplasia, and palpebral fissure lengths were of primary importance.

Many studies have examined indepth the different growth parameters (height, weight and head circumference) (Nellhaus, 1968; Merlob et al, 1984; Hall et al, 1989) and craniofacial landmarks associated with FAS diagnosis (short palpebral fissure length and microopthalmia, widely spaced eyes, long smooth philtrum, thin upper lip, long recessed midface, short upturned nose, flattened nasal bridge) (Hyme, 1929; Laestadius et al, 1969; Jones et al, 1978; Fuchs et al, 1980; Merlob et al, 1984; Clarren et al, 1987; Olsen et al, 1995; Astley and Clarren, 1996; Johnson et al, 1996) in populations of both affected and unaffected individuals, to determine alcohol's effect on each of the features.

Studies have consistently illustrated growth retardation as a hallmark feature of FAS, or in general alcohol exposure (Hanson et al, 1976; Little et al, 1977;Mills et al, 1984; Larroque, 1992; Day et al, 1994). Studies by Little (1977), Mills et al (1984) and Day et al (1994), report that weight (at birth and current) after correction for confounding variables (such as maternal cigarette smoking, SES, etc.) is decreased significantly with heavy alcohol consumption during pregnancy. Day et al (1994) suggest that weight is affected by alcohol exposure during one or all of the trimesters, with the highest deficits noted for exposure during the third trimester. Similarly, animal model studies have also

documented such growth retardation in mice (Middaugh et al, 1988; Middaugh and Boggan, 1991). Day et al (1994) also note alcohol exposure significantly affects height (primarily during the first and third trimester), head circumference (second and third trimester), and reduced palpebral fissure size (first and third trimester). For third trimester exposures, the reduced palpebral fissure size is probably mediated by smaller head circumference, while exposures during the first trimester alone are mediated by direct teratogenic action of alcohol on the developing eyes (Day et al, 1994).

In our study, growth retardation as documented by height and weight below the tenth percentile, and by head circumferences below the third percentile was also shown to be significantly different between those prenatally exposed to alcohol versus the unexposed segment of the school-aged population under study. Our figures for the proportion of FAS individuals expressing the characteristic hallmark features are similar to those previously reported in the literature. For example, in a study by Hanson et al (1976) in the United States, 97% of their FAS patients exhibited postnatal growth retardation, while 93% were microcephalic. Robinson et al (1987) in a study of FAS in one Canadian Aboriginal population in British Columbia noted growth retardation in 91% of FAS individuals and 91% rate of microcephaly in these affected subjects. Our Manitoba study of FAS in a Native community cites growth retardation figures of 44% for height, 33% for weight, and 33% for microcephaly when the data is plotted against the Caucasian standards. On the surface the sample in

this study does not seem to exhibit the same level of growth retardation as the previously reported data suggests. There are two possible explanations: (1) that our numerator is small in comparison to those previously reported, as this study only has one fourth and one half of the FAS patients reported in the two previously mentioned studies respectively (Hanson et al, 1976, Robinson et al, 1987); and (2) this particular population does not conform to Caucasian standard growth curves. The Caucasian and Native school-aged populations differ significantly with respect to their growth parameters. If comparisons are made based on percentile ranking against the norms for this Native population, the growth retardation rates for FAS individuals in this study would be 89% for height, 78% for weight, and 44% for microcephaly. These figures are similar to the previously established levels.

The present study is also reminiscent of previously reported literature describing characteristic facial features that are associated with alcohol exposure in utero, and used in the diagnosis of FAS. Some of these features include: microophthalmia and/or short palpebral fissures, hypertelorism, long, poorly developed philtrum, epicanthal folds, midface hypoplasia, flattened nasal bridge, and a short upturned nose (Jones and Smith, 1973; Hanson et al, 1976; Clarren and Smith, 1978). Features which were found to be significantly different between the exposed (graded) and unexposed groups in this study were: palpebral fissure length, recessed midface, and brachydactyly. Craniofacial landmarks which were considered significantly different between the

diagnostic categories included: poor cupid's bow formation, thin upper lip, recessed midface (based on the dysmorphologist's impression, not based on the ONO angle measurement), palpebral fissure length, and the ratio of palpebral fissure length to inner canthal distance. Data presented in this thesis state the rates of observance of these characteristic FAS craniofacial landmarks in the FAS diagnostic category as being: 50% poor Cupid' s bow formation, 42% thin upper lip, and 36% recessed midface. Philtrum formation was not considered significantly different between the different diagnostic categories. These figures are somewhat lower than the previously reported rates in FAS individuals, 65% for midface hypoplasia in the Hanson et al (1976) report, and 91% poor philtrum formation in the Robinson et al study (1987). With respect to shortened palpebral fissure length, comparisons against the Caucasian norms provides a rate of occurrence amongst FAS individuals in this study to be 56%, while comparison against the Native curves provides a rate of 78% in the FAS cases. The latter estimate is considered to be more in-line with the previously reported rates of 92% and 86% by Hanson et al (1976) and Robinson et al (1987) respectively. However, observed differences between the reported rates of many of these characteristic craniofacial features may be an artifact of the qualitative or descriptive nature of assessment for such features. Thus the observed differences may be a reflection of the "eye of the beholder" and not a true quantitative difference. The palpebral fissure length/inner canthal distance ratio for our FAS diagnostic category was 0.74, which falls in the middle of the

reported range by Astley and Clarren (1995) of 60-82% for FAS individuals.

Reasons why FAS established craniofacial features such as philtrum length, hypertelorism, and epicanthus do not appear to be statistically different between the diagnostic categories could be due to the fact that these items may be affected by ethnicity. In the Manitoba study, the subjects were of a single ethnic background and were not compared against an outside control group, whose ethnicity would be varied. However, in the original study of FAS by Jones and Smith (1973), eleven FAS patients were identified, six of which were of Native American origin. Thus it is perhaps possible that features such as epicanthal folds could have been considered indicative of FAS due to the fact that they appeared in this particular ethnic group, who represented roughly 50% of the study sample, and not due to its unconditional occurrence in all FAS patients irrespective of race. It is for these reasons that Striessguth et al (1988) warns against comparison made on ethnic-specific norms, which are not specific to the ethnic group understudy.

4.3 Normal Curves

Many reports in the literature have made note of the potential biases of comparing Native or other ethnic group morphometric data against normal growth curves primarily generated by data collected in Caucasian populations (Robinson et al, 1987; Streissguth et al, 1988; Bray and Anderson, 1989; Abel and Sokol, 1991; Abel, 1995). These concerns have been brought to light by the

fact that there appear to be distinct differences with respect to certain features and growth parameters between the groups. For example, African American children tend to have lower birth weights than Caucasians in the United States (Feinleib, 1989), and it is postulated that this may cause African American children to be at higher risk for FAS diagnosis based on the trait of decreased birthweight as compared to the Caucasian norms. Striessguth et al (1988) note that no growth charts specific to Natives have been generated and that given the observed differences between the birthweights of American Americans and Caucasians, it is possible that there could be substantial differences between growth parameters both at birth and postnatally for Natives and Caucasians.

Fuchs et al (1980) have also examined ethnic differences with respect to one craniofacial feature: palpebral fissure size. Statistically significant differences were noted when palpebral fissure sizes were compared between groups of African Americans, Hispanics and Caucasians. Both the African American and Hispanic populations had significantly larger palpebral fissure sizes than their Caucasian counterparts (Fuchs et al, 1980). Tennes and Blackard (1980) illustrated that epicanthal folds are more common among Natives Americans, African Americans and Hispanics. In the study of FAS among a group of Canadian Aboriginals by Robinson et al (1987), it is stated that "the presence of epicanthic folds and other anthropomorphic features of native Indians limited the comparability of these measures to standards reported from other research". Other documented differences between the "norms" in

one ethnic group versus another include: depressed nasal bridges and retroverted ears (common in African Americans) (Tennes and Blackard, 1980; Omotade, 1990), and the antimongoloid slant common in some Native Americans (Abel and Sokol, 1991).

Given that there are significant differences between ethnic groups with respect to growth parameters and certain craniofacial features, it is less useful to compare them against Caucasian normal standards. Unfortunately, the Caucasians are the only group for which standard morphometric data has been analyzed to generate many of the standard growth curves noted in the literature. Thus, if one wants to compare a group of children against norms, these are the only ones readily available with which to compare the collected data. This can be problematic, especially in the case of Native Americans "because certain features that are normal for their own reference group are atypical for whites", such as shortened palpebral fissure size and epicanthal folds (Abel and Sokol, 1991). Thus a Native American child may be at increased risk of being diagnosed as FAS, due to their subsequent "[evaluation] against a background of Caucasians" (Abel, 1995). Abel (1995) as well as Striessguth et al (1988) caution that, if appropriate race-standardized norms are not used, FAS rates in these communities may be inflated, not due to an actual increase in the number of affected individuals, but due to the impression of an increase of affected individuals, based on misattribution of some of the features used for the diagnosis of FAS as being due to alcohol exposure, and not due to normal

ethnic variation. However, it is also possible that the Native population may differ in the opposite direction from the Caucasian standards, leading potentially to missed diagnoses in the ethnic group.

The present study of FAS in a First Nations Community in Manitoba, is to our knowledge, the first of its kind to actually document statistically significant differences between the "normal" component of the Native school-age population studied, and the previously reported standard curves based on Caucasian data. This study has confirmed suspicions that the two populations differ significantly, and thus enforce warnings against the use of normal curves not specific for the ethnic group under study. Data presented indicate that the school-aged population under study are taller, heavier, have larger head circumferences, longer fingers, and more widely spaced eyes than the Caucasians used in the literature standard curves.

Data collected as part of the "Normal" diagnostic category, were used to generate the Native norms, based on the fact that all individuals included in this category do not exhibit growth retardation, characteristic facial features of FAS, or other "abnormalities". It is true however, that the "Normal" category does contain a number of individuals who have been exposed to alcohol. It is possible that inclusion of these individuals in the analysis for Native norm development, may contaminate the normal curves generated. However, statistical analysis comparing all morphometric data between the alcohol exposed "normal" group versus the nonexposed "normal" group do not support

this concern, as no statistically significant difference was observed for any of the actual morphometric measurements between these two groups. Thus, since the exposed "normal" individuals appear phenotypically normal, and do not differ statistically from their unexposed counterparts, their morphometric data has been included for the development of the Normative Native curves.

Given that the Native population under study was larger, on average, than what is reported in the Caucasian based literature, some FAS or Partial FAS children could be misclassified, due to failure to meet criteria such as growth parameters below the tenth percentile when compared to the Caucasian standards. In order to test this hypothesis, comparisons of the FAS and Partial FAS individuals against the standard curves generated using normal peer data were conducted. In general, when comparing against a group of their peers the percentile ranks of these individuals decreased. Increased number of individuals with "classic" FAS traits were observed. Some of these features included heights and weights below the tenth percentile, head circumferences below the third percentile, and shortened palpebral fissure length (less than the second percentile).

Thus the data presented in the Normative Data section of this thesis are important as they provide empirical evidence to support previous warnings against inter-racial norm comparisons. Even though these data are, we believe, the first of its kind to describe growth and craniofacial morphometric standards in a group of Aboriginal school-aged children, **caution should be used with**

respect to generalizing beyond the scope of these data. Although this was a population-based study, the numbers used to generate the curves are small, and thus a larger sample would be required to further support the trends noted here. Also, as it is true between broad ethnic groups, it is probable that the growth parameters reported here, may differ greatly with respect to different Aboriginal groups, and **thus it would not be appropriate to compare all Natives against these standards**. Given that there is much inter-tribal variation with respect to morphometric parameters, the idea of creating one single set of Normal Native curves, is most likely impossible to attain. Also, even if Native standard curves were developed for each tribe, the problem then becomes ensuring that the proper "tribal curve" is used in the appropriate population. If one applies a "tribal curve" to the morphometric parameters of a different tribe it is expected that the same effect would be observed as comparing them on a Caucasian or any other ethnic group curve, that is the potential misclassification of children, which in turn inflate or deflate the true prevalence of FAS for that particular tribe. For these reasons, it would be impractical and impossible to achieve a single Native standard curve for the morphometric parameters described in this thesis. This study, however, does provide a starting point for a relatively neglected area of research, the description of normal native morphometric parameters.

4.4 Possible biological models for increased observation of FAS among First Nations Communities.

Abel (1995) has stated that "FAS is not an equal opportunity birth defect". This appears to be true. Both data presented in this report as well as numerous other reports indicate that Native Americans and Canadian Aboriginals seem to be at increased risk of having a child with FAS. Suggestions as to why this may be so have varied. One hypothesized reason is that Native Americans and Canadian Aboriginals may have a genetic susceptibility for FAS, that is they may be lacking certain enzymes which help clear alcohol from the mother's system before it traverses the placenta and reaches the developing fetus. Some of the enzymes hypothesized in this model include: alcohol dehydrogenase (ADH), the enzyme responsible for metabolizing alcohol to acetaldehyde, and the presence of the inactive form of aldehyde dehydrogenase (ALDH2*2), which leads to accumulations of acetaldehyde in the mother's system. However, no scientific evidence exists to suggest that there is a predisposition for ceratin isoforms of ADH to be specific to Natives, nor has the scientific community found cases of ALDH2*2 in any ethnic group other than Asians (Bosron et al, 1980; Bosron et al, 1983; Faustman et al, 1992; Goedde et al, 1992; Cooper, 1993). Thus genetic predisposition based on these genes seems an unlikely model to account for the higher frequencies of FAS in these populations.

A second hypothesis has been that problem drinking is more common in the Native American and Canadian Aboriginal populations compared with the

Caucasian population. This idea also does not ring true, as the Centers for Disease Control (CDC) showed in its 1988 survey, it is women who are white, more educated, of a higher income level, married and smoke that are more likely to drink during pregnancy (CDC, 1995). Day et al (1993) also note that abstention rates are higher for women of African American, Native American and Native Canadian descent, yet, rates of heavy drinking during pregnancy are higher for Aboriginal and African American groups than for the Caucasian (Day et al, 1993; Institute of Medicine, 1996). However, in many of these studies, race has been confounded by low SES, which is thought to be the primary reason FAS is observed at higher rates in these communities rather than any genetic predisposition (Abel, 1995; Abel and Hannigan, 1995).

Abel and Hannigan have put forth a plausible model for FAS susceptibility which takes into account many of the preexisting data derived from the numerous animal model studies, and maternal risk factor studies found in the literature. They propose that, in the presence of alcohol, there are two factors, permissive factors and provocative factors that interact to put the fetus at risk for FAS. Permissive factors are defined as "predisposing behavioural, social, or environmental characteristics that produce certain biological conditions, [that]... in conjunction with heavy drinking increase fetal vulnerability to alcohol's teratogenic effects" (Abel and Hannigan, 1995). Provocative factors are " biological conditions resulting from the permissive factors which create the internal milieu responsible for the increased fetal vulnerability to alcohol at the

cellular level" (Abel and Hannigan, 1995). Permissive factors include: alcohol intake patterns, race/socioeconomic status, culture/ethnicity, and smoking. They propose that certain cultures have different patterns of alcohol intake. For example, Caucasian women are more likely to drink at a constant level during the week, while Native American women tend to drink in episodic bouts (binging consumption of 5 or more drinks on one occasion) (May et al, 1983; May et al 1989). It is those women who consume alcohol in binge fashion that have higher peak blood alcohol levels(BAL), than do women who consume alcohol steadily over time (Pierce and West, 1986; Bonthius et al, 1988; Sampson et al, 1989; Striessguth et al, 1989; Striessguth et al, 1994). Thus by this theory, it is the higher peak BAL (provocative factor) which puts Native children at higher risk for FAS, due to the cultural pattern associated with alcohol consumption (permissive factor).

Similarly, as was stated before, it is SES rather than ethnicity that seems to predispose towards development of FAS. Low SES (permissive factor) is proposed to lead to poor nutrition, increased exposure to other toxins in the environment (such as lead), cause increased psychological stress, be associated with higher parity, and increased smoking, all of which can act to exacerbate the teratogenic effects of alcohol (Abel and Hannigan, 1995). They propose that it is the biological changes (placental dysfunction, endocrine changes in the mother, and other biochemical and physiological changes) that result due to those conditions induced by low SES, which ultimately increase the

susceptibility of the fetus to the damaging effects of alcohol. Hypoxia is thought to be the primary factor induced by the interaction of the permissive and provocative factors. It initiates a cascade of cellular events leading to cell damage, inappropriate differentiation, proliferation, migration and/or regulation of cell growth as well as, free radical oxidative stress, which disrupts cellular integrity (Abel and Hannigan, 1995). Therefore, although alcohol is a necessary factor for the development of FAS, it is not sufficient as there are a whole host of other factors which also must contribute to the teratogenic effects of alcohol on the developing fetus (Abel and Hannigan, 1995).

Based on this model it is clear that Aboriginal women may be at increased risk for many of the permissive factors which tend to focus more around low SES than ethnicity. It is probably these factors related to poverty and culture, in combination with episodic, binge alcohol consumption which puts Aboriginal children at increased risk for FAS.

4.5 Significance of this body of research.

The research presented in this thesis is important for a number of reasons. Firstly, data collected and presented in the dysmorphology assessment section of the thesis support many previously established reports on the phenotypic features of individuals with FAS. These data also identify and support concerns about using craniofacial characteristics for diagnostic purposes which are normal for one ethnic group, but abnormal when compared

against Caucasian standards, or any other non-specific data. For example, African American children naturally have palpebral fissure lengths which differ from Caucasian norms (Fuchs et al, 1980), while epicanthal folds are considered normal in the Native population. Thus there may be an increased number of FAS diagnoses in these communities when these features are considered of prime importance in the diagnostic gestalt. The data presented strongly support the need for the creation of ethnic specific norms, and perhaps the development of ethnic neutral diagnostic criteria for FAS in order to prevent underestimation or overestimation of FAS due to natural ethnic diversity with respect to craniofacial features and growth parameters. However, the idea of being able to create one standard set of Native norms, is as impossible as creating one set of morphometric norms for the entire human race. Just as each ethnic group varies with respect to morphometric data, so do the various Aboriginal groups.

Finally, the presentation of the data contained in the Normative Curves section of this thesis provides empiric evidence supporting warnings such as those made by Striessguth et al (1988) concerning the inappropriate comparisons of one ethnic group against norms developed for a second race. Data presented in this study support the hypothesis that growth patterns between Natives and Caucasians differ significantly. Thus it is not appropriate to compare Natives against Caucasian norms as it will inflate or deflate the actual FAS prevalence reported, based on which parameter is being examined.

4.6 Further Research Topics

The research described in this thesis has broken ground for a number of spin off studies. It has suggested the need to develop race neutral diagnostic criteria for FAS diagnosis, such that normal ethnic variants will not be identified as an abnormality, and thus increase a child's chance of being diagnosed with FAS. To further this approach, studies into other normal Native school-aged populations would be important, to further the work initiated in the Normative curves section of the thesis. It is acknowledged that the curves were generated using a small number of individuals, further study into this area, could eventually allow for the creation of reliable Native curves **for this particular Native ethnic group** which could be used to allow for comparison of the growth of the Native children against their peers, rather than against Caucasians.

Thirdly, the epidemiology section of the thesis has unequivocally identified this community as having a problem with FAS. The question now becomes, what can be done to fix this problem? Given that the rate of alcohol exposure does not seem to be decreasing, it is possible that the situation could become worse in the community before it gets better. One way to improve the situation here, is to facilitate prevention of FAS, through intensive alcohol awareness education efforts aimed at the youth, in particular the young women. It is these individuals who have perhaps through observation of their mothers, aunts and other female relatives, acquired their drinking patterns, one of which

is drinking during pregnancy. It will become important now to stop this cycle, so that a second generation of affected children can be prevented. Perhaps this type of education can be integrated as part of an on-going course within the school's curriculum, similar to sex education or drug awareness course, or it could fall under the responsibility of local health workers as a series of special seminars within the community.

With respect to the individuals already affected by prenatal alcohol exposure, it is important that they be identified. Knowledge of the FAS or Partial FAS status of a child would allow the school to apply for extra funding needed in order to support the special education programs that will be necessary to develop in order to educate the FAS/ partial FAS individual at their appropriate level.

Many responsibilities such as control over health care and education have been transferred to some Native communities as part of a Native self-government movement in the past few years. Thus it is now important for the communities to identify and develop solutions or educative efforts to help prevent the problem.

APPENDICES

Appendix A. Consent forms used in the FAS Community Study on one First Nations Community in Manitoba.

Fetal Alcohol Syndrome / Fetal Alcohol Effect Community Study
Consent Form

Researchers from the University of Manitoba, with approval and support of the Band Council, will be conducting a study in the community over the summer and fall of 1995. The purpose of this study is to assess all school aged children in the community born between the years 1981-1990 to determine if school difficulties and behavioural problems in children can be associated with events in the pregnancy, such as exposure to alcohol or drugs before birth. By conducting this study we hope to acquire a better understanding of the effects of early alcohol exposure on academic (school), behavioural, and social performance, as well as its effects on the child's physical characteristics. This study will help identify the prevalence of Fetal Alcohol Syndrome within the community and help identify the special needs of these children.

The study will involve an interview with mothers in their homes concerning family histories, pregnancy histories, alcohol/drug use, and a rating of the child's behaviour, which will take approximately 45 minutes to one hour to complete. A rating of the child's behaviour by his/her teacher; and an assessment of the child's academic (school) abilities on a standard test by a trained person at the school will also be conducted. A partial physical examination of the child will be done by Dr. Chudley. This will take place at the school. Dr. Chudley will take a picture of the child's face as part of the examination. The picture will be kept in the child's confidential file and will not be made public in any way. Dr. Chudley will examine the child's head, neck, chest, back, abdomen, hands and feet, and will also assess the child's height and weight. The examination should take approximately 15 minutes and will involve minimal discomfort. It <u>will not</u> include blood drawing, X-rays, or any other painful tests. Following the study a written statement will be provided to you outlining the results of the study.

All information obtained as part of this study will be treated with absolute confidentiality and anonymity will be preserved. If abnormalities are found the results of your child's assessment will be discussed with you by one of the doctors, and if required, with your permission, referrals to the appropriate agencies will be provided. If the results of this study are published no individuals will be identified, nor pictures used. Your participation in this study is voluntary and you may withdraw your child from the study at any time without jeopardizing his/her present of future medical care or education.

If you agree to participate and enroll your child in the above study please sign below. We thank you for your cooperation.

I understand the purpose and nature of the Fetal Alcohol Syndrome / Fetal Alcohol Effect Community Study as explained to me by _____,

and I agree to participate and enroll _____ in the study.

_____ _____

Signature of Parent / Legal Guardian Date

_____

Witness

In the event that this study reveals that your child has FAS/FAE or other academic difficulties or physical abnormalities, this information could be used by the school to help set up special programs aimed to help your child with their difficulties. Thus in the case that an abnormality is found in your child we are asking your permission to inform the school of this information, so that they can better help your child. This information will be used strictly for academic purposes only.

If you agree with the above statement and would like us to inform the school if an abnormality is detected in your child please sign below.

I understand and agree to have_____'s individual assessment results disclosed to the school in the event that an abnormality is detected through the Fetal Alcohol Syndrome / Fetal Alcohol Effect Community Study.

_____

Signature of Parent / Legal Guardian

If you **DO NOT** agree with the above statement and **DO NOT** wish us to inform the school if an abnormality is detected in your child please sign below.

I understand the above statement, but **DO NOT** give permission for _____'s individual assessment results to be disclosed to the school in the event that an abnormality is detected through the Fetal Alcohol Syndrome / Fetal Alcohol Effect Community Study.

_____

Signature of Parent / Legal Guardian

_____ _____

Witness Date

Fetal Alcohol Syndrome / Fetal Alcohol Effect Community Study
Hospital Records Consent

One of the criteria used to diagnose FAS is growth deficiency in children. Part of the physical examination that Dr. Chudley will perform on your child will involve taking their height, weight and their head circumference. We would like to be able to compare their levels of growth, with their growth measurements at birth, to determine if children exposed to alcohol before birth continue to remain small for their age. In order to do this we require your permission to examine your child's medical files at the hospital where they were born. All information obtained from your child's file will be kept confidential and anonymity will be preserved.

If you agree to let Dr. Chudley, Dr. Moffatt and their associates have access to your child's medical records at their birth hospital for the purpose of collecting the previously mentioned information to be used in the FAS/FAE Community Study please sign below.

Thank you for your cooperation.

I, _____, understand the above statement and give permission for Dr. Chudley, Dr. Moffatt and their associates to have access to _____'s medical files at_____ hospital to obtain information for the purpose of the Fetal Alcohol Syndrome / Fetal Alcohol Effect Community Study. I acknowledge that all information obtained from the file will be treated with absolute confidentiality and that anonymity will be preserved.

_____ _____
Signature of Parent/ Legal Guardian Date

_____
Witness

Appendix B. Maternal Interview form used in the FAS study of one Manitoba First Nations Community.

Fetal Alcohol Syndrome / Fetal Alcohol Effect Community Study

Community Education and Alcohol Survey
Maternal Questionnaire

1. Student Identification __ __ __

2. Student first name
_____

3. Is _____ a
   Natural child ____
   Foster child ____
   Adopted ____

   IF Foster or Adopted
   how long has she/he been in this home?
   Years___ Months____
   Do you know whether alcohol was one of the reasons for placement? Yes___ No___
   Have you ever been told that she/he might have Fetal alcohol Syndrome or Fetal Alcohol Effects? Yes___ No___
   Does he/she originally come from this community
   _____ or from another community?
   _____ (specify)

4. How many years of school did you finish yourself? __ __

5. In the past 12 months, have there been any major stresses in your household such as divorce, separation, household move, house fire, deaths of a close relative etc, which might have affected your children's school performance?
If yes, please specify _____

6. What is the main source of income in your house?
   Salaries from work _____
   Unemployment insurance ____
   Social assistance or welfare _____

7. How many people usually live in your house? ___ ___

8. How many children live in your house (including grandchildren and children of friends or relatives)? __ __

9. How many bedrooms do you have? ___ ___

10. How much schooling does the head of the household have? ___ ___ (years)

11. If father or mother are employed please give the occupation of each.

Occupation of father _____

Occupation of mother _____

Note to the interviewer
IF this is a foster or adopted child, the interview ends here and the parents are assisted in filling out the CBCL. However, in some circumstances, where the natural mother is no longer available and the foster or adoptive parent is a relative of the natural mother, the remainder of the questions may be answered by the foster/adoptive mother.

Questions for Natural Mother

Thinking back to the time when you were pregnant with _____

a. How many liveborn children did you have before _____.
___

b. Did you have any miscarriages before _____?
0 1 2 3 4 5 or more

c. Did you have any problem getting pregnant? Yes___ No___

d. How much weight did you gain during the pregnancy?
___ ___

e. Did you have any serious accidents while pregnant? Yes__ No__

f. Did you take any prescribed drugs while pregnant? Yes__ No__
IF YES, specify_____

g. During which month did you first feel the baby move?____

h. Was _____ delivered early? ____ On time? ____ Late?____

i. Did you smoke while you were pregnant? Yes___ No___
IF YES, How many cigarettes per day? _____

j. Did you drink any alcohol? Yes____ No____
When?_____
IF YES

About how many drinks per week on average (Including beer, wine and liquor) _____

At that time, about how many drinks could you hold without falling asleep or passing out? _____

Did close friends or relatives ever worry or complain about your drinking during the time you were pregnant? Yes___ No____

Did you sometimes take a drink in the morning when you first got up? Yes___ No____

Did friends or family ever tell you about things you did or said when drinking that you could not remember? Yes____ No____

Did you ever think that you needed to cut down on your drinking during the time you were pregnant? Yes____ No____

k. Did you take any of the following drugs while you were pregnant?

marijuana Yes___ No____
LSD or acid Yes___ No____
Cocaine Yes___ No____
Talwin and Ritallin (T+R's) Yes____ No____
Other street drugs Yes___ No____
specify_____
How much?_____
When?_____

l. Did you sniff while pregnant with _____?

IF YES, what?_____ When?_____
How often?_____

What hospital was _____ born in?
_____

m. When _____ was born did s/he?

Breath right away Yes___ No____
Cry right away Yes___ No____
Need Oxygen Yes___ No____
Did you have a caesarian section ____ or a vaginal

birth____?
Did s/he come head first? Yes___ No___
Was S/he a twin or triplet? Yes___ No___
Did s/he have any major problems after birth (eg breathing problems, seizures, jaundice, feeding difficulties) Yes___ No___ IF YES specify
_____

n. Did you breast feed _____? Yes___ No___
If yes, how many months? _____

o. Was _____ difficult to feed? Yes _____ No _____
Did _____ have colic? Yes____ No _____

p. Were any malformations noted at birth Yes___ No____
IF YES specify _____

q. How many liveborn babies have you had since _____?
____
r. How many stillborn babies have you had? _____
s. How many miscarriages have you had since _____?
0 1 2 3 4 5 or more
t. Have any of your children (Live or stillborn) had any birth defects? IF YES, specify_____
u. Have any of your brothers or sisters had children who were stillborn? Yes____ No____
v. Have any of your brothers or sisters had children with birth defects? Yes_____ No_____ IF YES, specify type
_____
w. Do any of your brothers or sisters have children who have developmental delay or mental retardation Yes ____ No____
IF YES, please specify who and what type
_____

x. Do you have any brothers or sisters who have mental retardation? Yes___ No___. IF YES, do you know the cause?
_____

y. On the natural father's side are there any children with mental retardation among his brothers and sisters? Yes___ No___ IF YES, specify and if cause is known specify
_____

z. Does the natural father have any nephews or nieces who

have mental retardation or developmental delay? Yes___ No___

aa. Are you and the child's father related as cousins (blood relatives)? Yes___ No___

Now I am going to ask you to answer a questionnaire about your child's behaviour. It will take about half an hour and I will help you understand the questions if you need assistance. This questionnaire is used all over the world and it gives a very good idea of how a child is behaving in comparison to other children of the same age.

Appendix C. Hospital Records Review Form used to collect data from each child's hospital records at their hospital of birth.

FAS Community Study
Hospital Records Review Form

Name :_____ **ID #:** _____
Hospital: _____
(1) EDC _____
(2) Sex _____ (0 = female, 1 = male)
(3) Gestational age _____ weeks
(4) Route of Delivery? C/S _____ Vag _____
(5) Presentation at delivery? Vx _____ Breech _____
(6) Birth weight _____g (_____%)
(7) Birth Length _____cm (_____%)
(8) Head Circumference at birth _____cm (_____%)
(9) Apgar 1' _____
5' _____
(10) Neonatal complications ?
Jaundice _____ Hypoglycemia _____ Jitteriness _____
Others _____
_____

Nursing Database: Date of Completion _____
(11) Was alcohol used in pregnancy ? _____ (0 = no, 1 = yes)
When (trimester)? 1st _____ 2nd _____ 3rd _____ All _____
Frequency? Binge _____ Occasional _____ Heavy _____
Quantitative and Qualitative Information :_____
_____
_____

(12) Did the mother smoke cigarettes during pregnancy? _____ (0=no, 1=yes)
When (trimester)? 1st _____ 2nd _____ 3rd _____ All _____
How much (cigarettes per day)? _____
Quantitative and Qualitative Information: _____
_____
_____

(13) Were drugs used in pregnancy ? _____ (0 = no, 1 = yes)
Quantitative and Qualitative Information : _____
_____
_____

Other Chart Review:
(14) Nursing Notes (re alcohol or drugs):_____
_____
_____

(15) Physician Comments (re alcohol or drugs) : _____
_____
_____

(16) Social Work Notes (re alcohol or drugs): _____
_____

Appendix D. Physical Examination form used during the Dysmorphology Assessment aspect of the Community FAS study.

COMMUNITY STUDY FAS

PHYSICAL EXAMINATION - DYSMORPHOLOGY ASSESSMENT FORM

ID #:_____ DOB _____

EXAM DATE : _____

1. HT: _____ (_____%)
2. WT: _____ (_____%)
3. OFC: _____ (_____%)

Head----------

4. Shape : _____ (0 = Normal, 1 = Abnormal)
5. Whorl : _____ (0,1,2, 3 = Abnormal)
6. Eye Size : _____ (0 = Normal, 1 = Abnormal)
7. ICD : _____ (_____%)
8. OCD: _____ (_____%)
9. Epicanthus : _____ (0 = No, 1 = Yes)
10. Strabismus : _____ (0 = No, 1 = Yes)
11. Ptosis : _____ (0 = No, 1 = Yes)
Palpebral Fissures:
12. Slant : _____ (0=Horizontal, 1=Up, 2=Down)
13. Length: _____ (_____%)
14. Philtrum formed: _____ (0=Normal, 1=Abnormal)
15. Philtrum length: _____ (_____%)
16. Cupids bow : _____ (0=Normal, 1=Abnormal)
17.Upper lip: _____ (0=Normal, 1=Thin, 2=Cleft)
18. Palate: _____ (0=Normal, 1=High Arched, 2=Cleft)
19. Midface: _____ (0=Normal, 1=Abnormal)
20. Nose: _____ (0=Normal, 1=Short, 2=Upturned, 3=Flat Nasal Bridge, 4=Other)
21. ONO angle: _____ (_____%)
22. Ears: _____ (0=Normal, 1=Dysplastic, 2=Low set, 3=Other)
23. Chin: _____ (0=Normal, 1=Small)

Limbs----------

24. Fingers: _____ (0=Normal, 1=Abnormal)
25. Clinodactyly: _____ (0= No, 1= Yes)
26. Brachydactyly: _____ (0= No, 1= Yes)
27. Distal Hypoplasia : _____ (0= No, 1= Yes)
28. Polydactyly: _____ (0=No, 1=Yes)
29.Dermatoglyphics : _____ (0=Normal, 1= Abnormal)
30. Single Crease: _____ (0=No, 1=Yes)
31. Distal Triradii: _____ (0=No, 1= Yes)
32. Other Hand Anomalies: _____ (0=No, 1=Yes)
33. Joints: _____ (0=Normal, 1=Contractures)
34. Palm Length: _____ (_____%)
35. Hand Length: _____ (_____%)
Other----------

36. Neck: _____ (0=Normal, 1=Abnormal)
37. Hairline: _____ (0=Normal, 1=Abnormal)
38. Chest / back: _____ (0=Normal, 1=Abnormal)
39. Scoliosis: _____ (0=No, 1=Yes)
40. Pectus: _____ (0=No, 1= Yes)
41. Heart Anom.: _____ (0=No, 1= Yes)
42. Heart Murmur: _____ (0=No, 1=Yes)
43. Skin: _____ (0=Normal, 1=Abnormal)
44. Hemangioma: _____ (0=No, 1=Yes)
45. Hirsute: _____ (0=No, 1=Yes)
46. Other Anomalies: _____ (0=No, 1=Yes)

Comments:

_____

_____

_____

_____

_____

_____

_____

DX: _____ (0=Normal, 1=Dysmorphic, 2=FAS, 3=Partial FAS)

Appendix E. Normal Native curves (Figures 6 - 24) and their corresponding data tables (Tables 21 -39).

Figure 6. Normal Native Male Height Curve, derived from data collected on 74 Normal males (ages 5 - 15). The Shaded area represents the Caucasian standard graph for height (Hall et al, 1989).

Normal Height Graph
Males

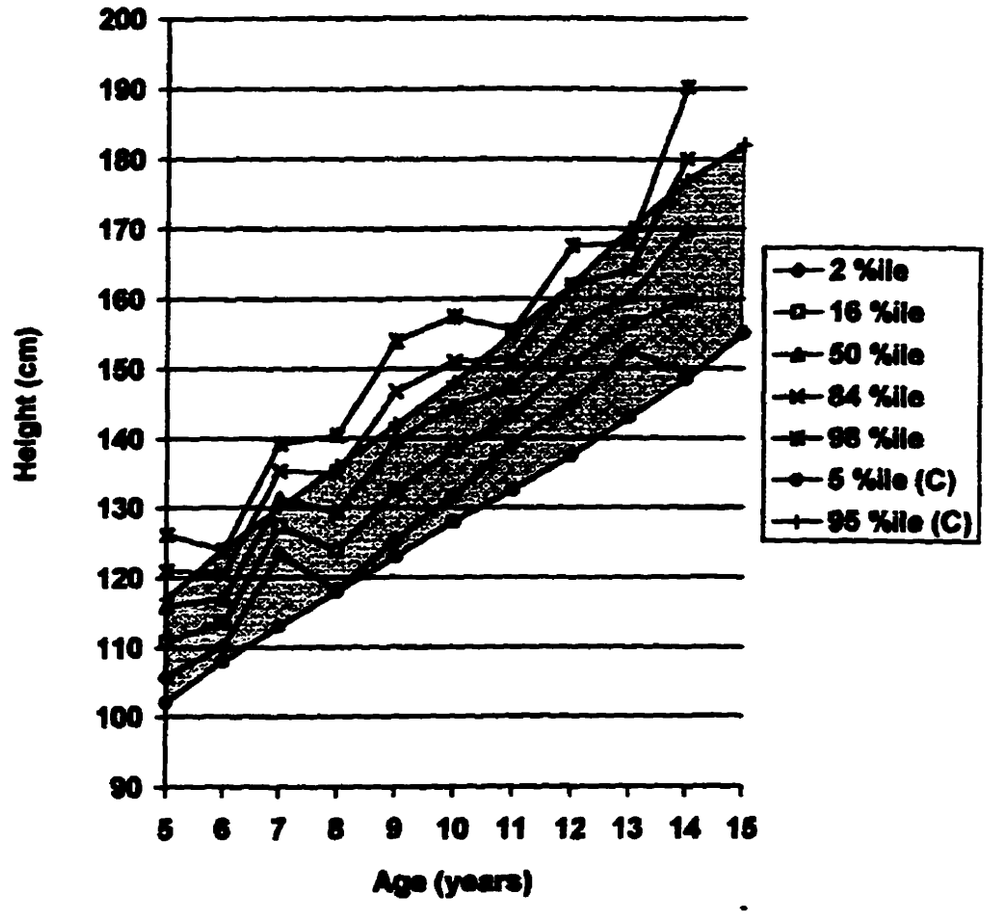


Figure 7. Normal Native Female Height Curve, derived from data collected on 59 Normal females (ages 5 -15). The Shaded area represents the Caucasian standard graph for height (Hall et al, 1989).

Normal Height Graph
Females

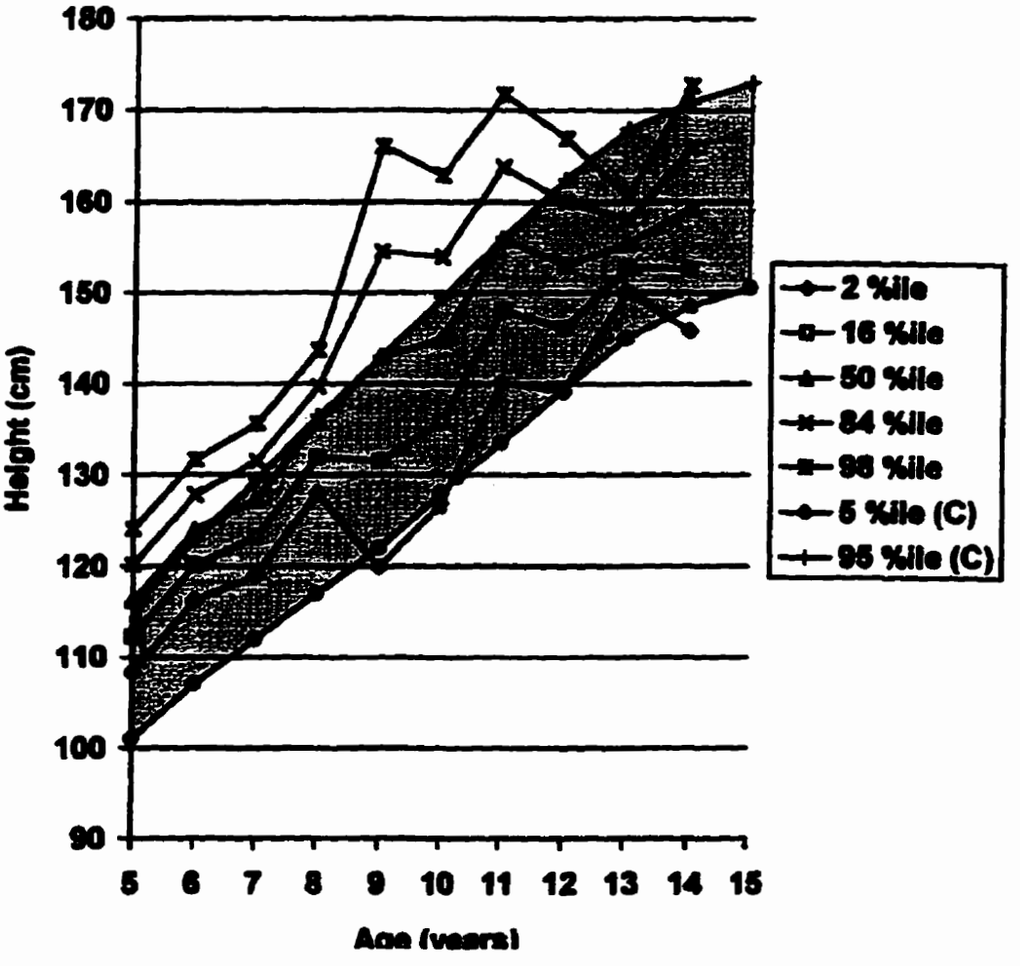


Figure 8. Normal Native Male Weight Curve, derived from data collected on 74 Normal males (ages 5 - 15). The Shaded area represents the Caucasian standard graph for weight (Reference).

Normal Weight Graph
Males

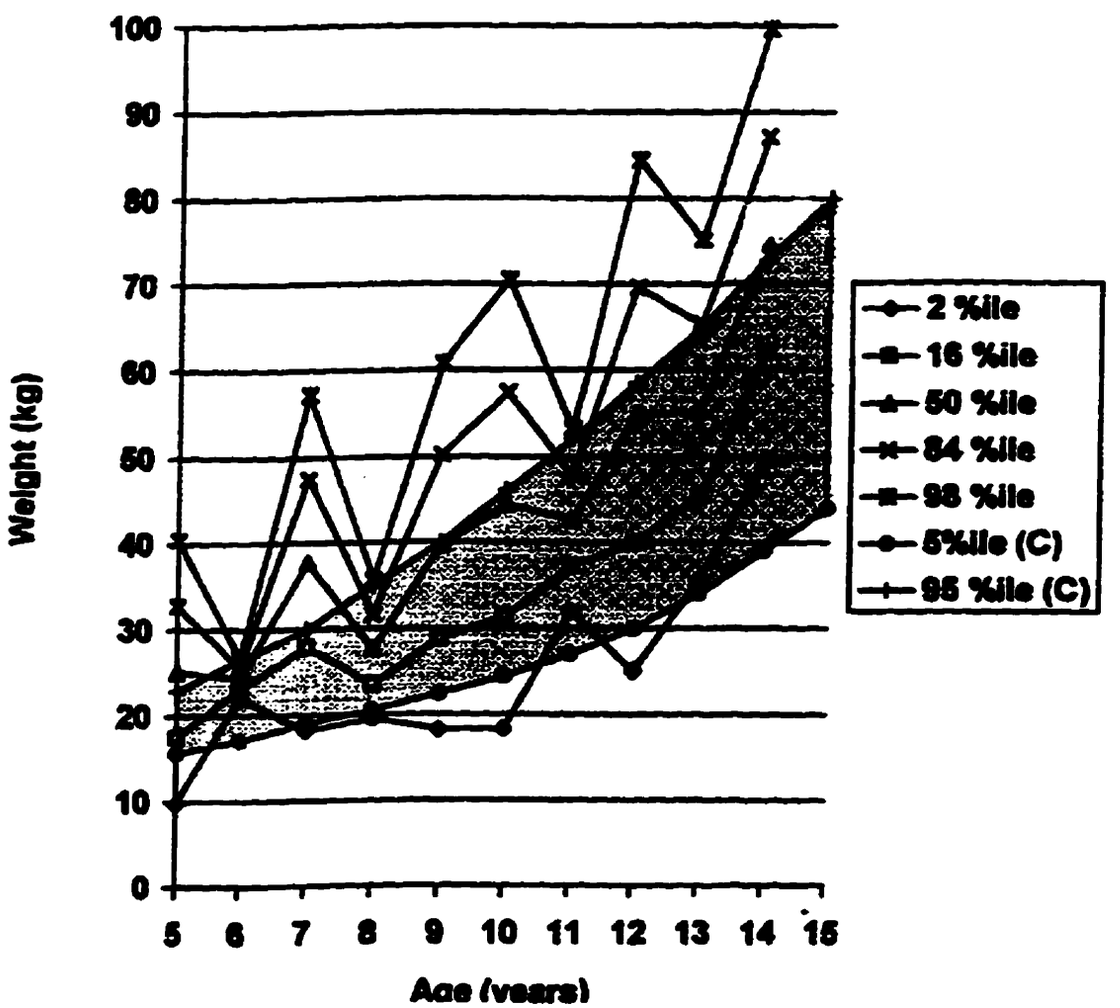


Figure 9. Normal Native Female Weight Curve, derived from data collected on 59 Normal females (ages 5 -15). The Shaded area represents the Caucasian standard graph for weight (Reference).

Normal Weight Graph
Females

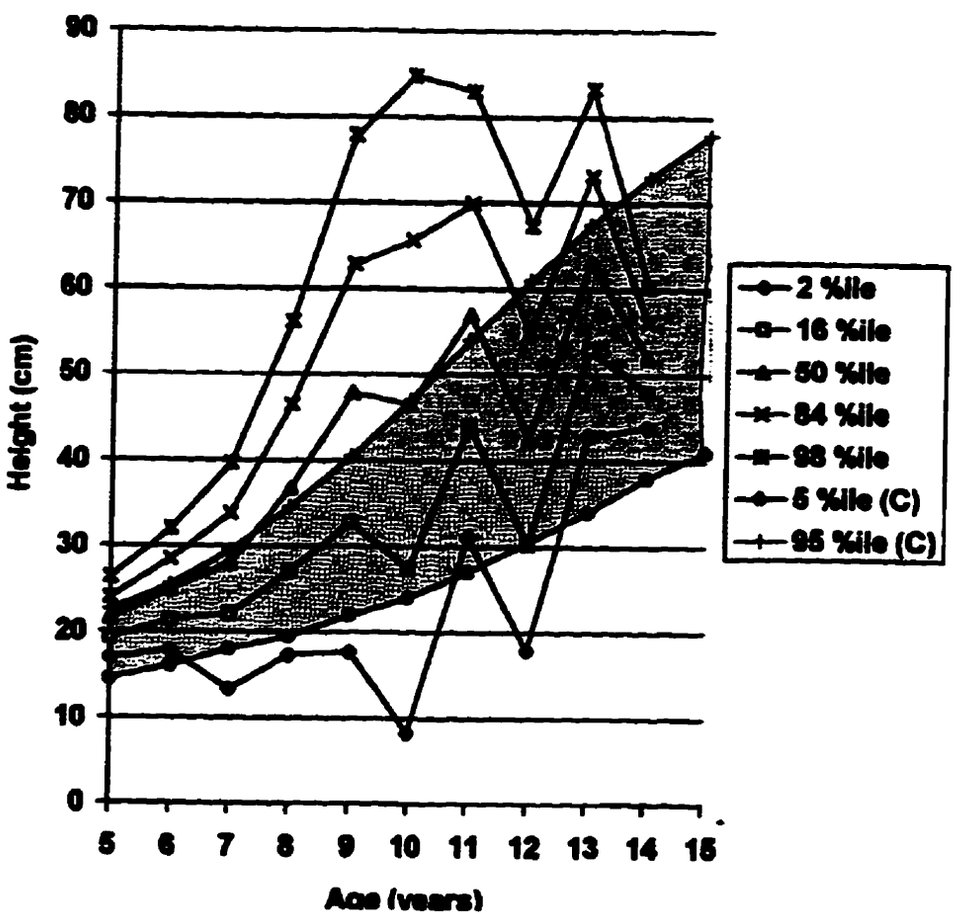


Figure 10. Normal Native Male Head Circumference Curve, derived from data collected on 74 Normal males (ages 5 - 15). The Shaded area represents the Caucasian standard graph for head circumference (Nellhaus, 1968).

Normal Head Circumference Graph
Males

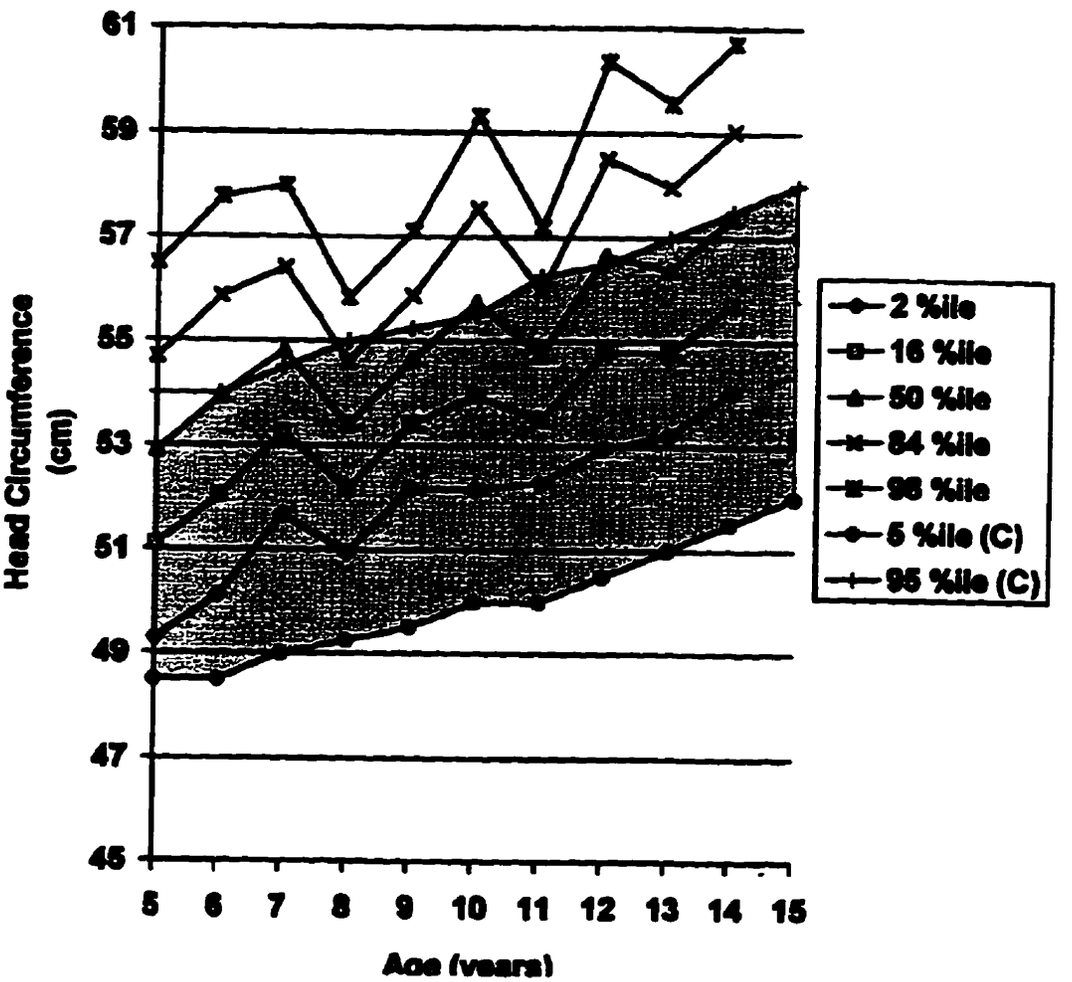


Figure 11. Normal Native Female Head Circumference Curve, derived from data collected on 59 Normal females (ages 5 -15). The Shaded area represents the Caucasian standard graph for head circumference (Nellhaus, 1968)

Normal Head Circumference Graph
Females

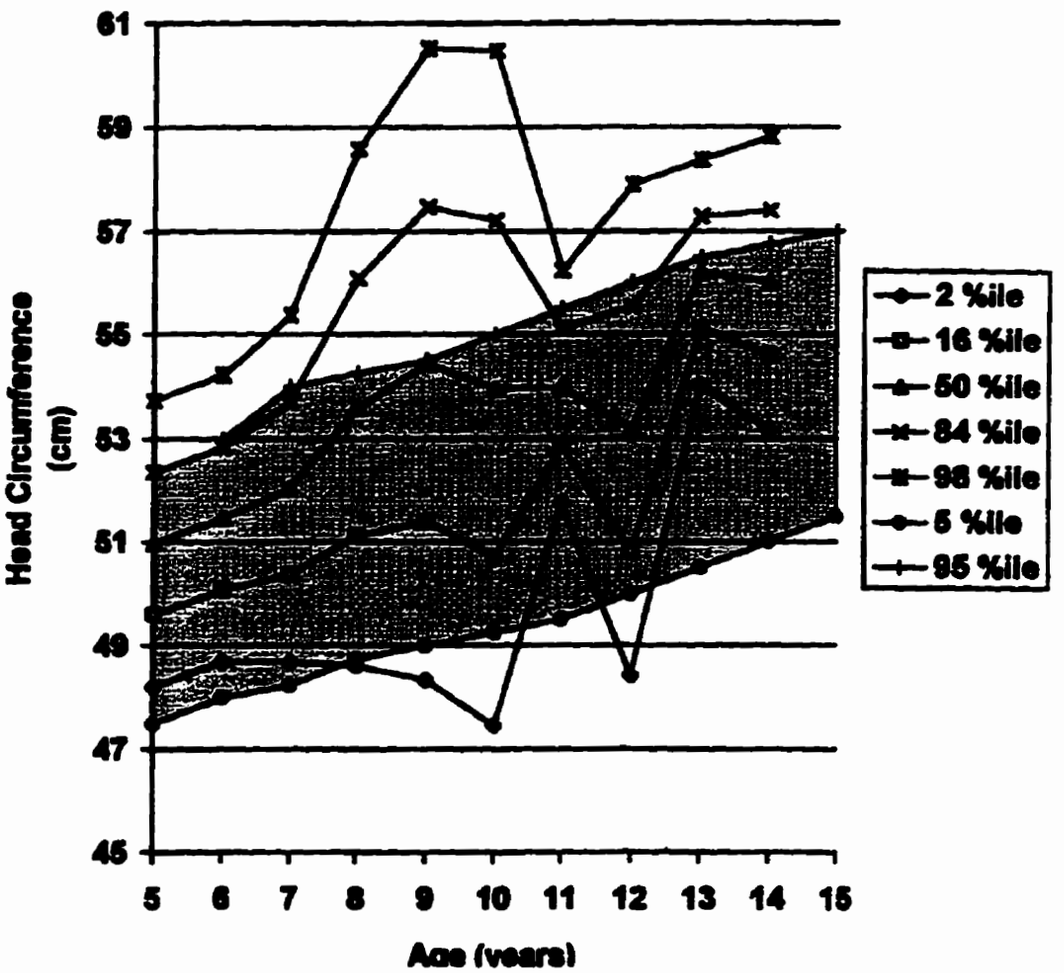


Figure 12. Normal Native Male Palpebral Fissure Length Curve, derived from data collected on 74 Normal males (age 5 - 15). The Shaded area represents the Caucasian standard graph for palpebral fissure length (pooled sex data) (Thomas et al, 1987).

Normal Palpebral Fissure Length Graph
Males

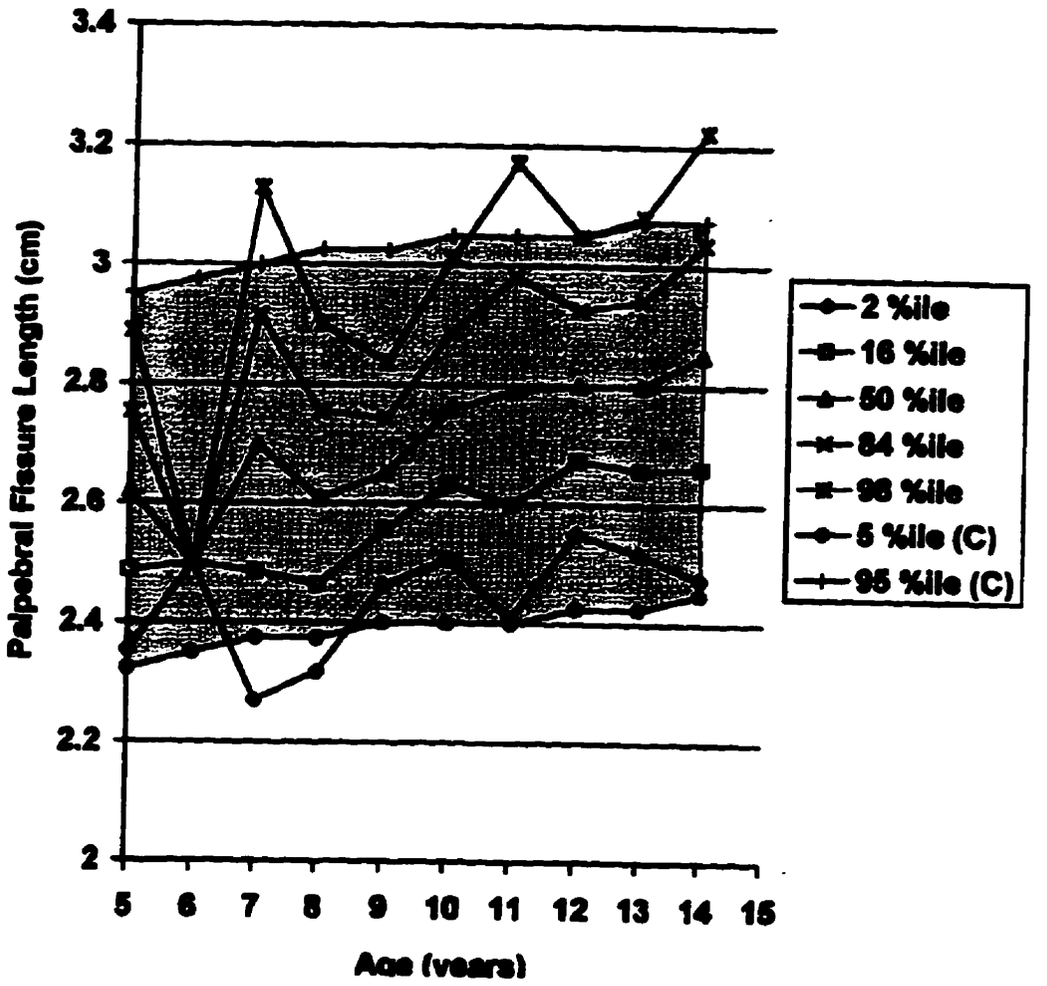


Figure 13. Normal Native Female Palpebral Fissure Length Curve, derived from data collected on 59 Normal females (age 5 - 15). The Shaded area represents the Caucasian standard graph for palpebral fissure length (pooled sex data) (Thomas et al, 1987).

Normal Palpebral Fissure Length Graph
Females

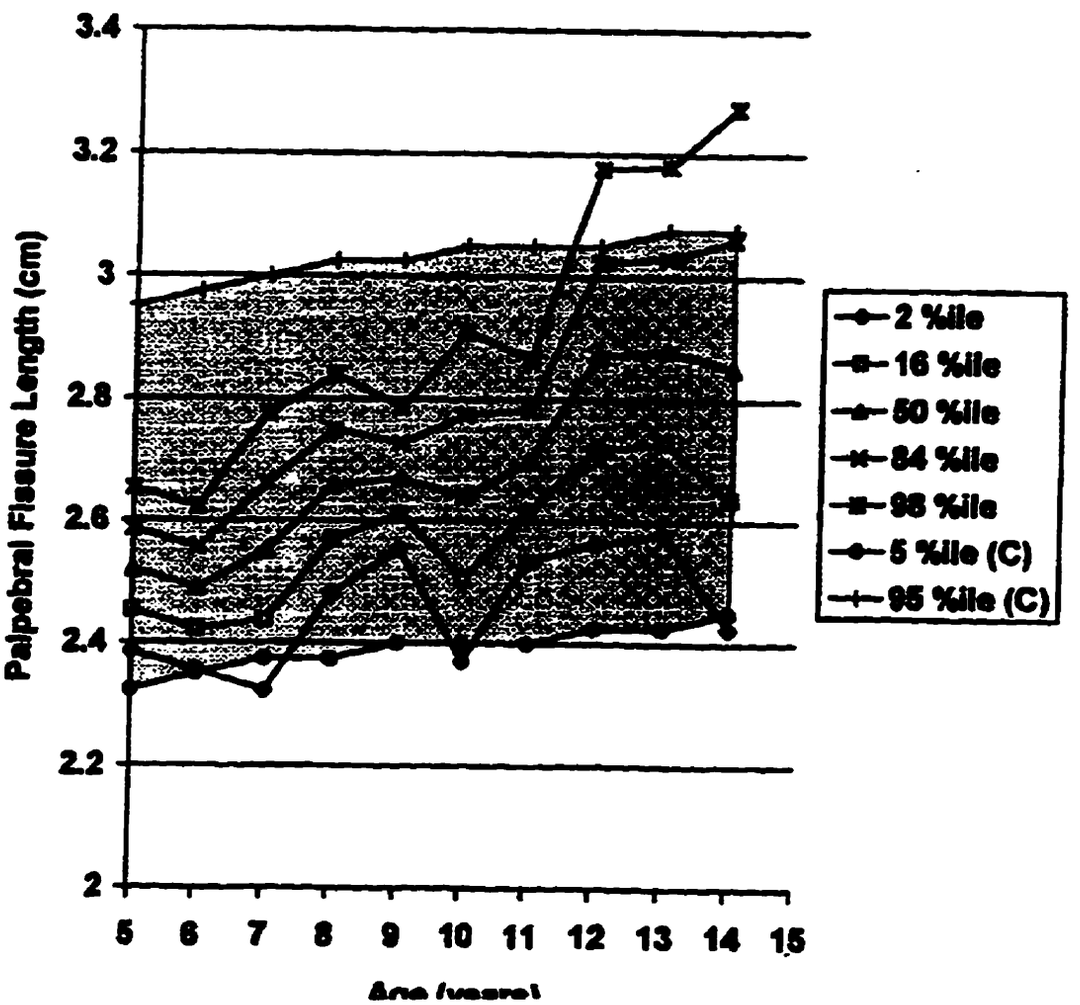


Figure 14. Normal Native Male Philtrum Length Curve, derived from data collected on 74 Normal males (age 5 - 15). The Shaded area represents the Caucasian standard graph for philtrum length (pooled sex data) (Feingold and Bossert, 1974).

Normal Philtrum Length Graph
Males

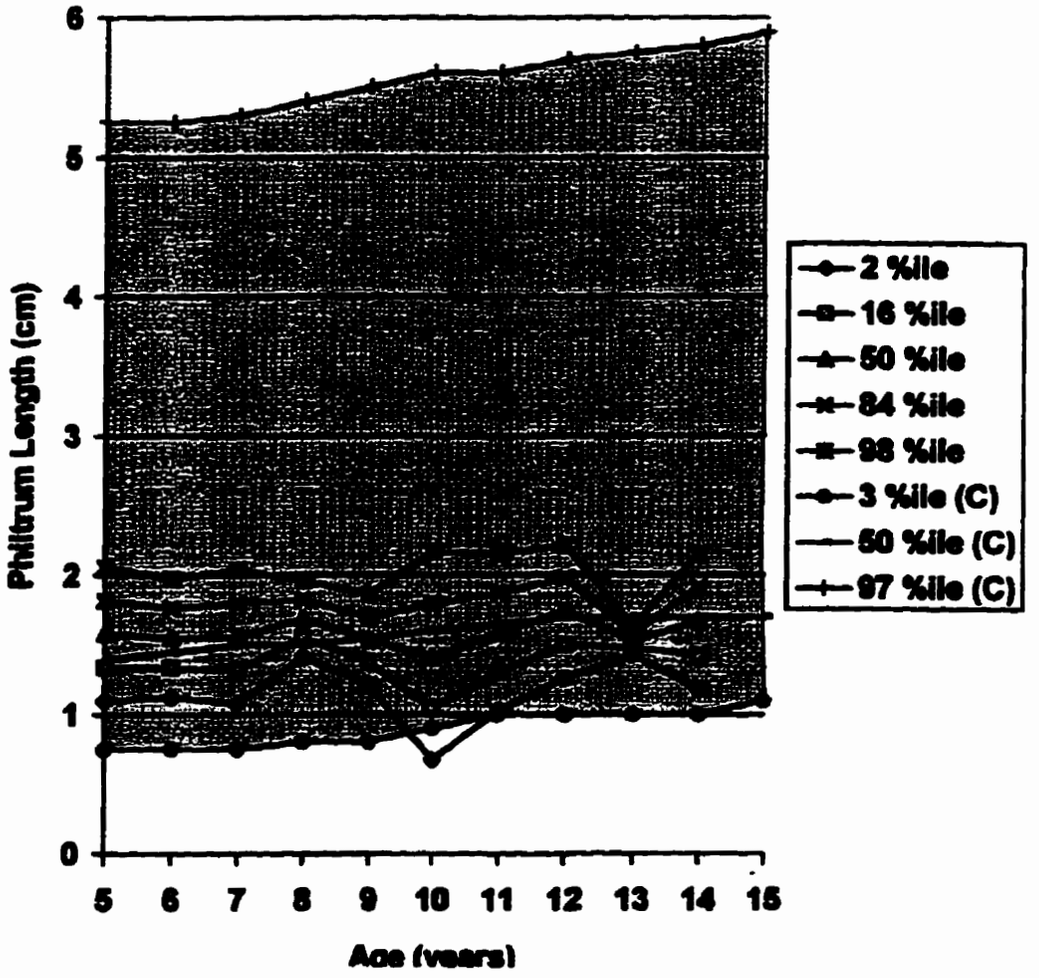


Figure 15. Normal Native Female Philtrum Length Curve, derived from data collected on 59 Normal females (age 5 - 15). The Shaded area represents the Caucasian standard graph for philtrum length (pooled sex data) (Feingold and Bossert, 1974).

Normal Philtrum Length Graph
Females

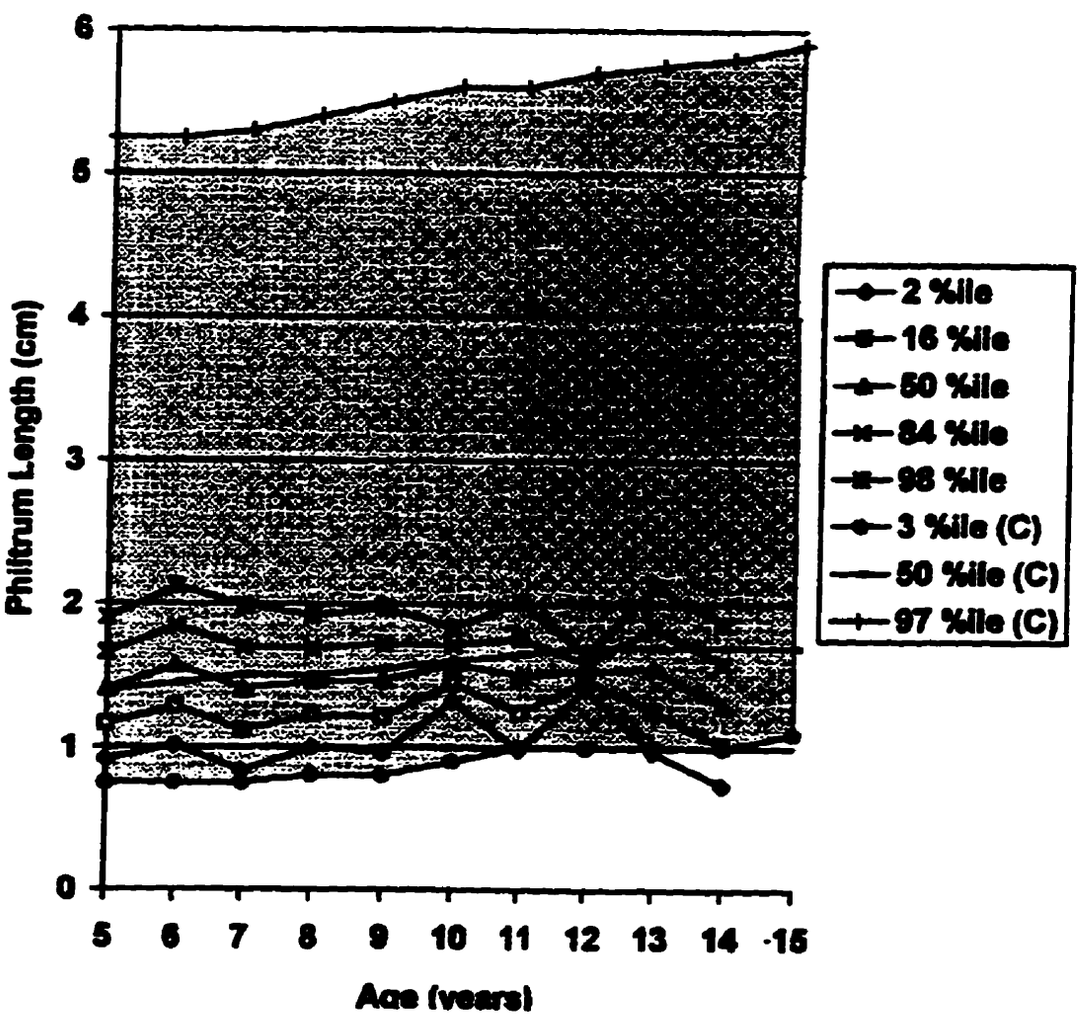


Figure 16. Normal Native Male Inner Canthal Distance Curve, derived from data collected on 74 Normal males (age 5 - 15). The Shaded area represents the Caucasian standard graph for inner canthal distance (pooled sex data) (Feingold and Bossert, 1974).

Normal Inner Canthal Distance Graph
Males

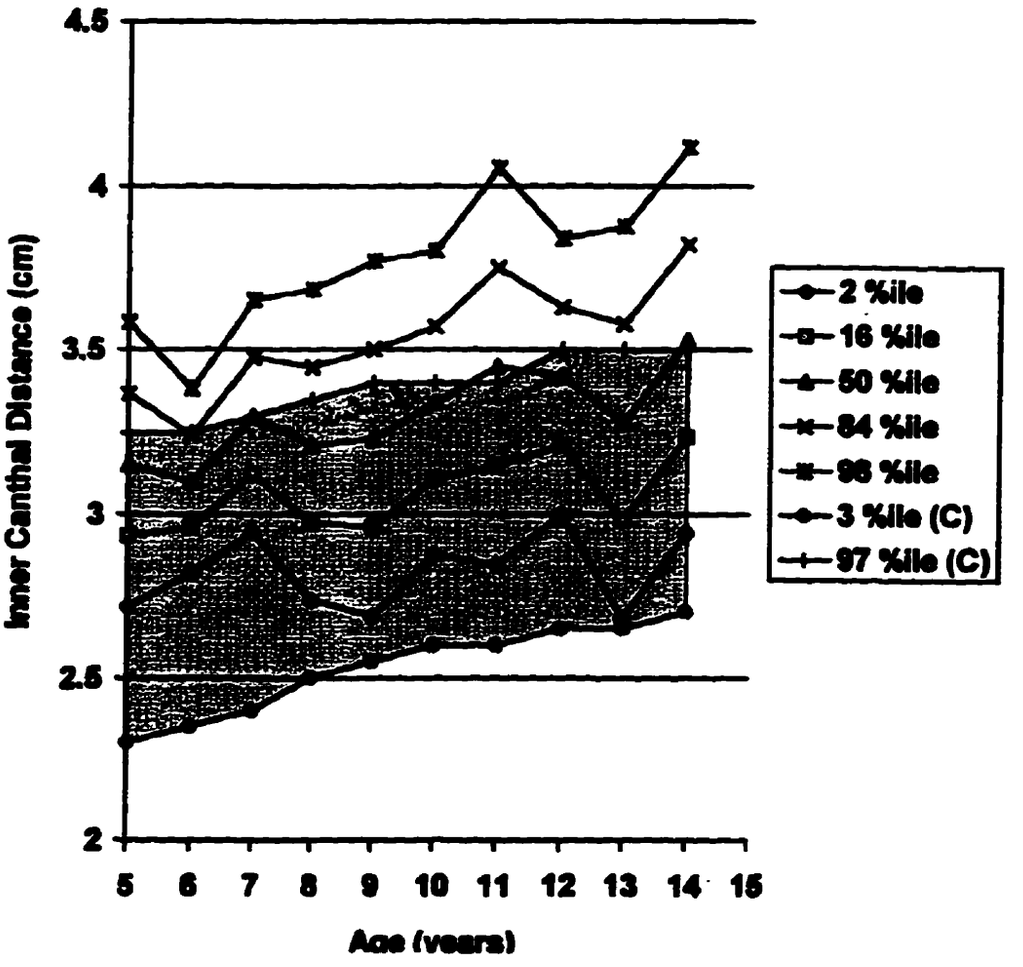


Figure 17. Normal Native Female Inner Canthal Distance Curve, derived from data collected on 59 Normal females (age 5 - 15). The Shaded area represents the Caucasian standard graph for inner canthal distance (pooled sex data) (Feingold and Bossert, 1974).

Normal Inner Canthal Distance Graph
Females

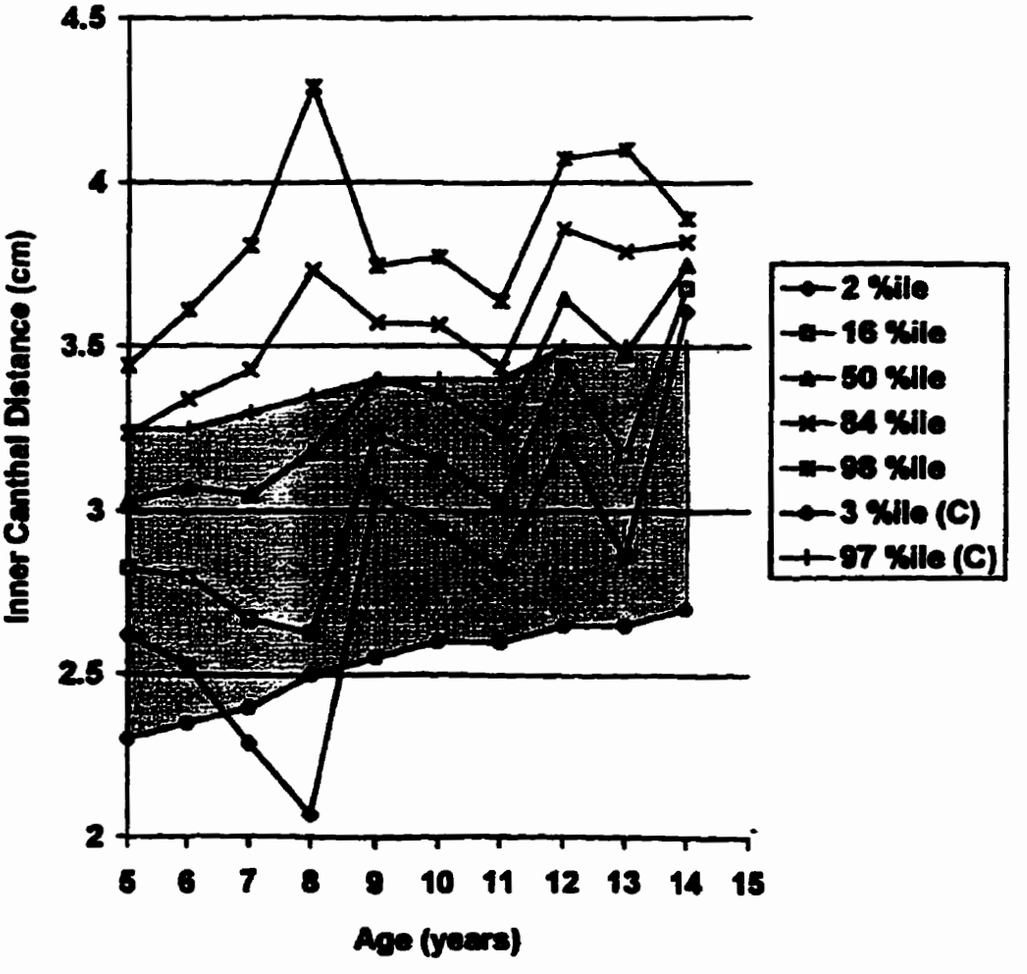


Figure 18. Normal Native Male Outer Canthal Distance Curve, derived from data collected on 74 Normal males (age 5 - 15). The Shaded area represents the Caucasian standard graph for outer canthal distance (pooled sex data) (Feingold and Bossert, 1974).

Normal Outer Canthal Distance Graph
Males

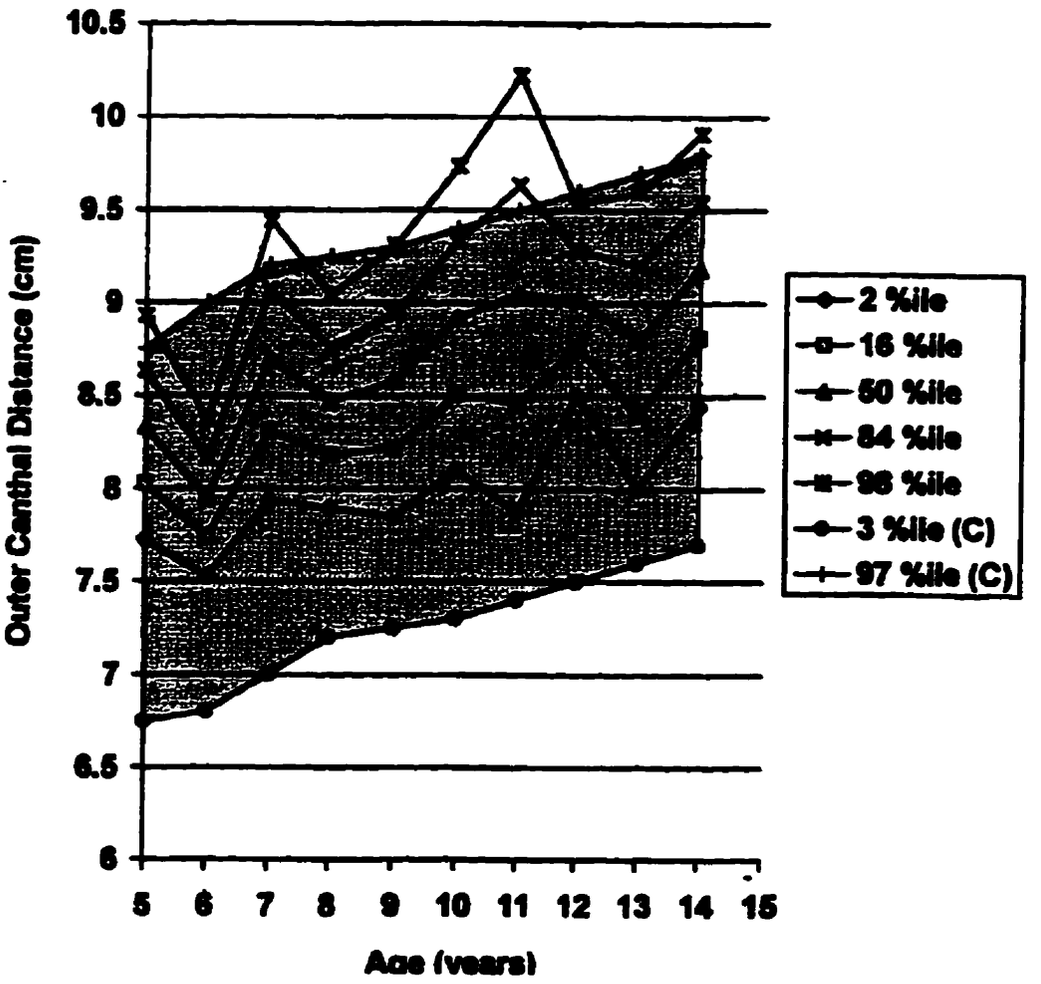


Figure 19. Normal Native Female Outer Canthal Distance Curve, derived from data collected on 59 Normal females (age 5 - 15). The Shaded area represents the Caucasian standard graph for outer canthal distance (pooled sex data) (Feingold and Bossert, 1974).

Normal Outer Canthal Distance Graph
Females

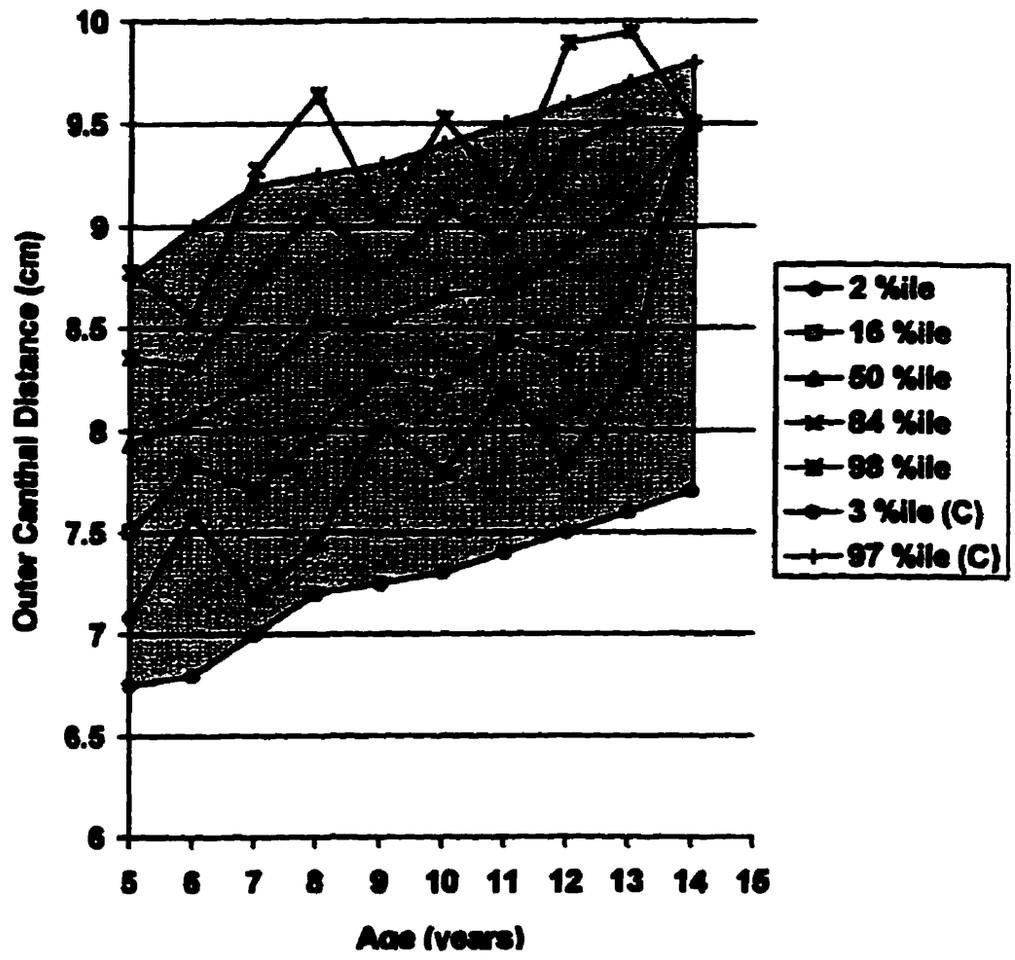


Figure 20. Normal Native Male Hand Length Curve, derived from data collected on 74 Normal males (age 5 - 15). The Shaded area represents the Caucasian standard graph for hand length (pooled sex data) (Feingold and Bossert, 1974).

Normal Hand Length Graph
Males

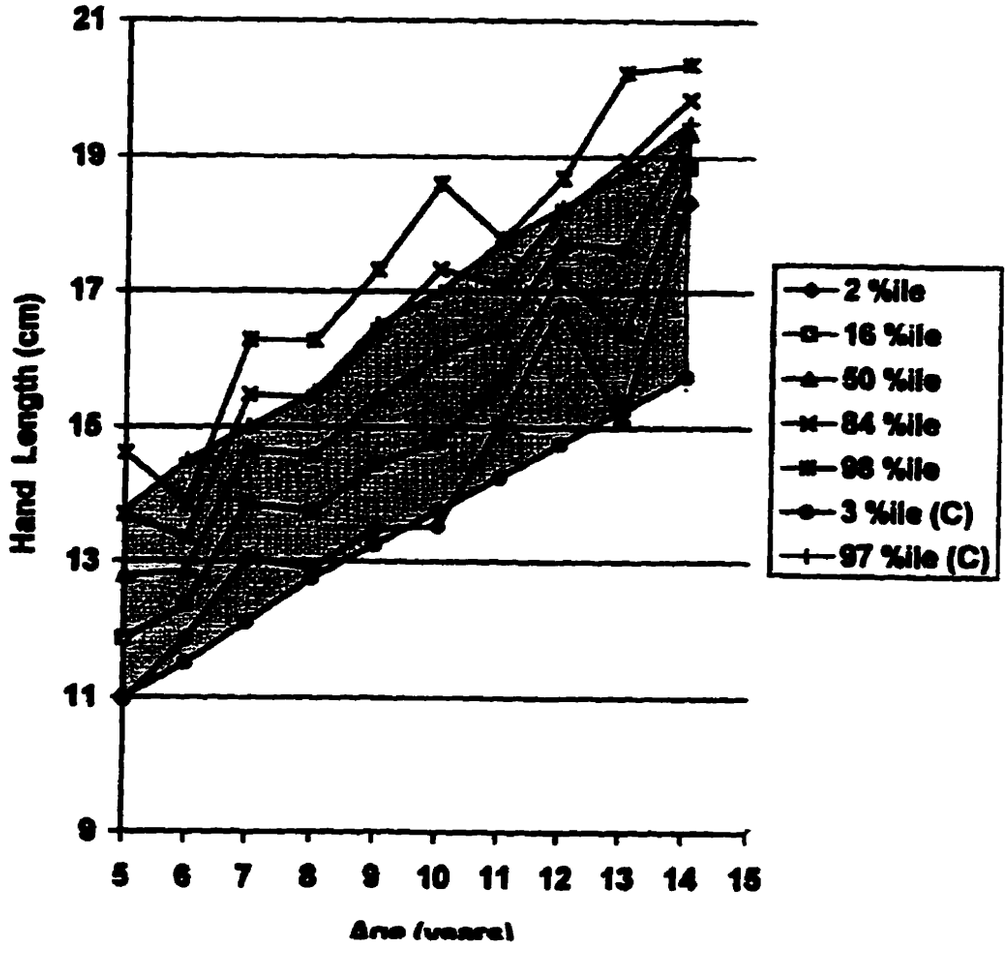


Figure 21. Normal Native Female Hand Length Curve, derived from data collected on 59 Normal females (age 5 - 15). The Shaded area represents the Caucasian standard graph for hand length (pooled sex data) (Feingold and Bossert, 1974).

Normal Hand Length Graph
Females

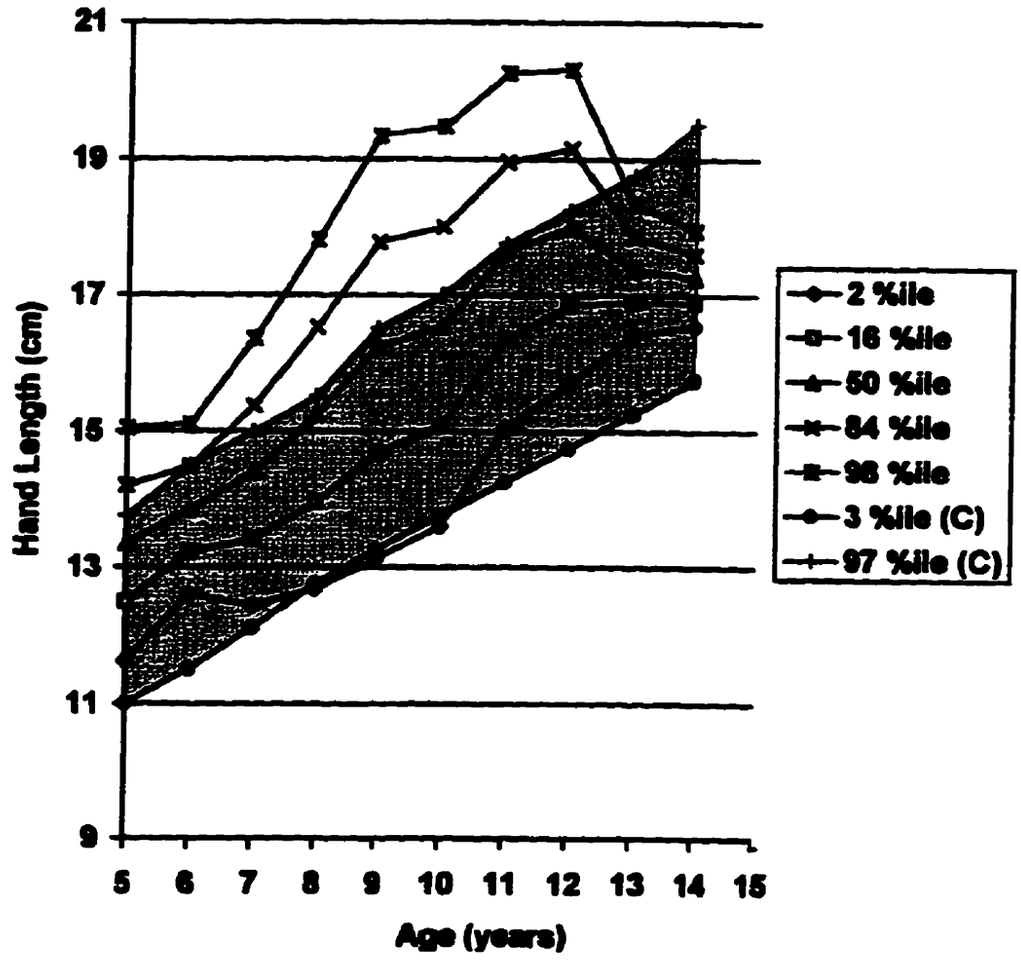


Figure 22. Normal Native Male Palm Length Curve, derived from data collected on 74 Normal males (age 5 - 15). The Shaded area represents the Caucasian standard graph for palm length (pooled sex data) (Feingold and Bossert, 1974).

Normal Palm Length Graph
Males

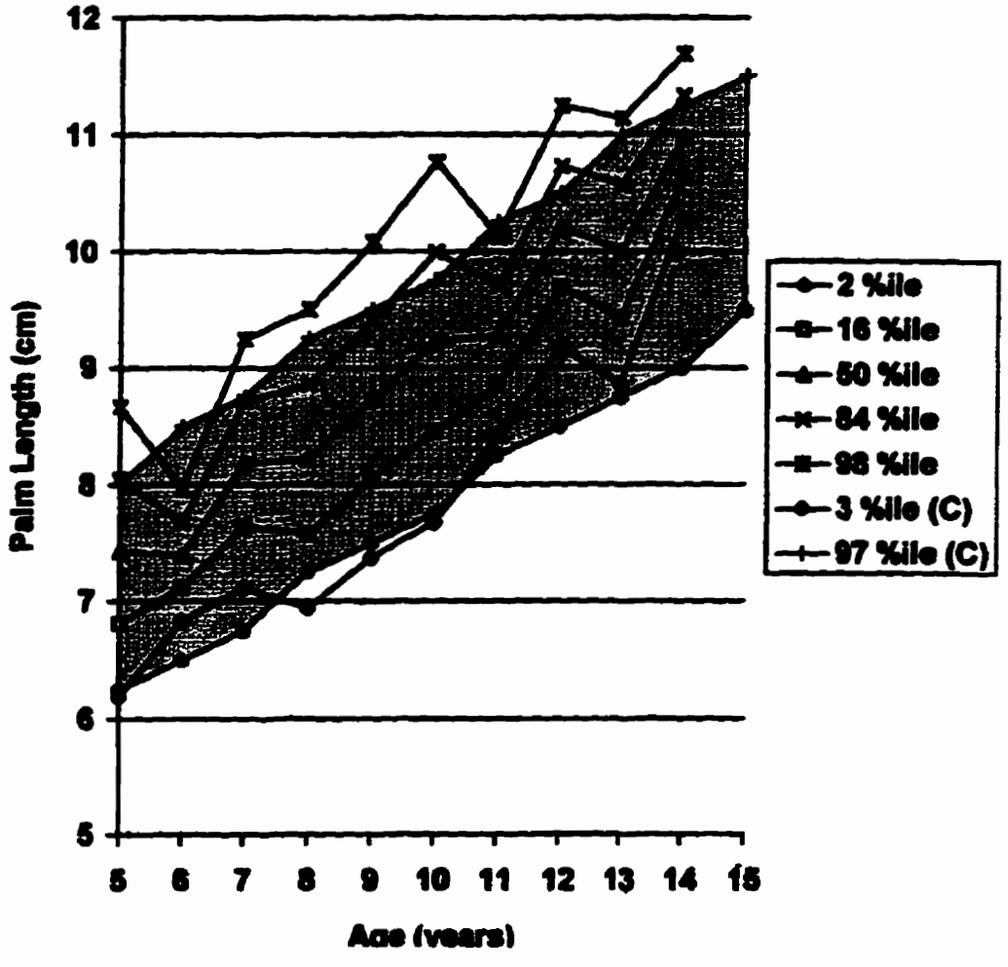


Figure 23. Normal Native Female Palm Length Curve, derived from data collected on 59 Normal females (age 5 - 15). The Shaded area represents the Caucasian standard graph for palm length (pooled sex data) (Feingold and Bossert, 1974).

Normal Palm Length Graph
Females

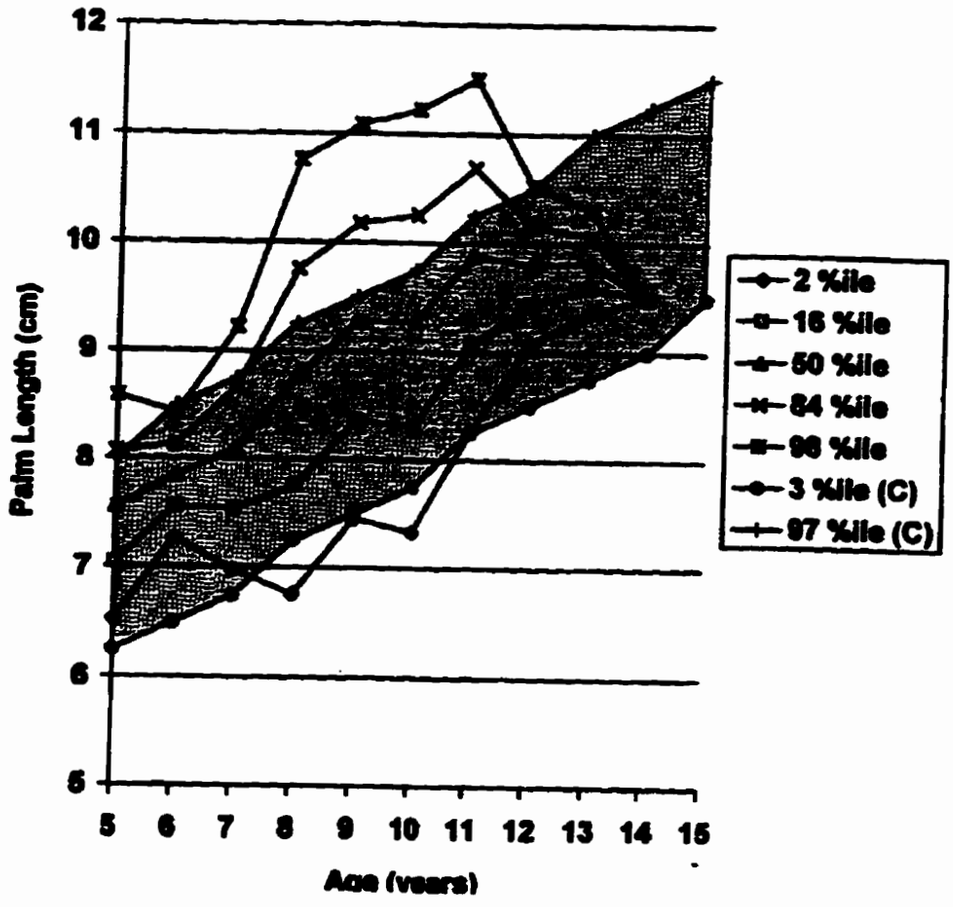


Figure 24. Normal Native ONO Angle Curve, derived from data collected on 133 Normal children (pooled sex data) (age 5 - 15). The Shaded area represents the Caucasian standard graph for ONO angles (pooled sex data) (Hall et al,, 1989).

Normal ONO Angle Graph
Males and Females
Combined

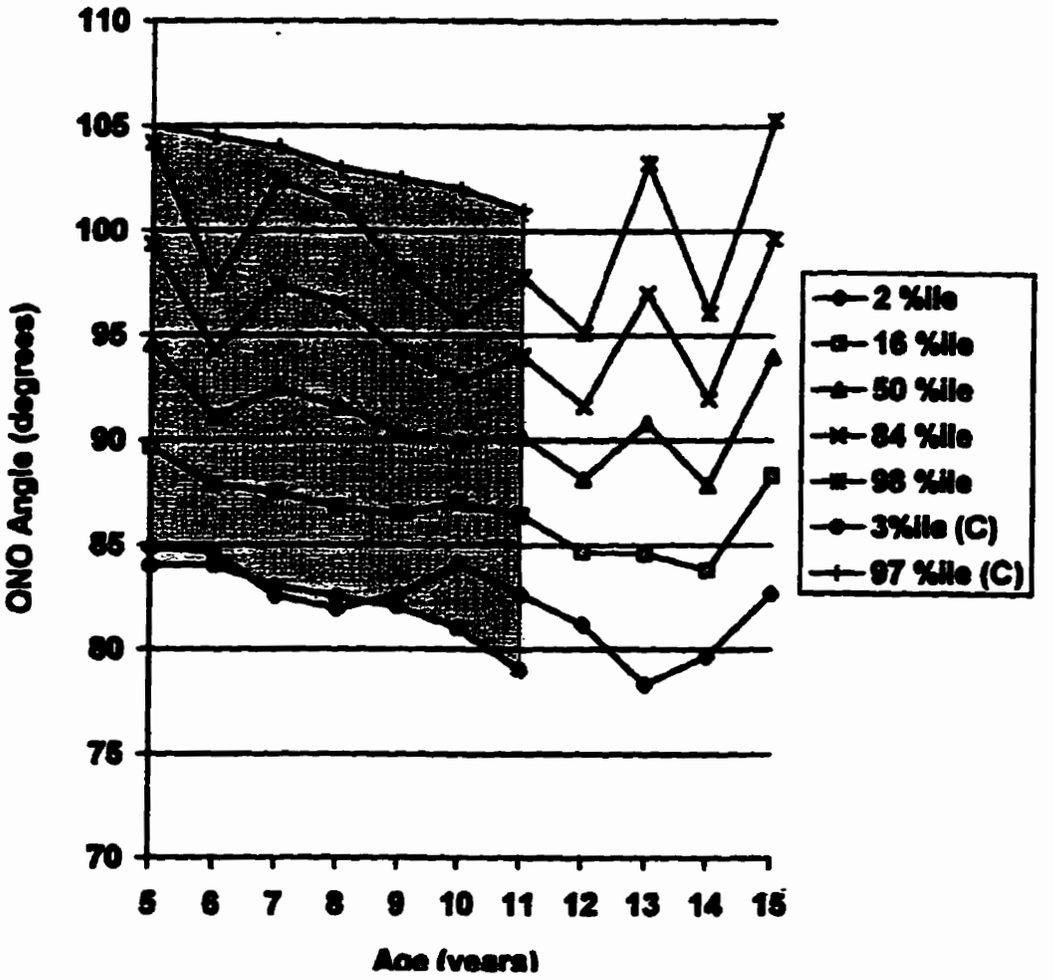


Table 21 . Normal Male Height Data

Age	Range (cm)	Mean (cm)	Standard Deviation	N
5	110 - 122	115.97	5.12	6
6	114.6 - 119.5	117.05	3.46	2
7	125.3 - 135.2	131.35	3.97	8
8	124 - 141	129.38	5.55	9
9	130.4 - 148	139.68	7.13	8
10	131 - 153	144.63	6.4	10
11	142 - 155.4	147.39	3.99	10
12	146 - 164.5	156.3	5.63	10
13	156.2 - 165.1	160.28	3.83	4
14	150.3 - 178	169.82	10.25	6

Table 22. Normal Female Height Data.

Age	Range (cm)	Mean (cm)	Standard Deviation	N
5	110 - 121	116.21	3.96	9
6	117 - 130	123.99	3.86	12
7	122 - 136	127.36	4.17	11
8	130 - 140	135.84	3.92	5
9	131 - 154	143	11.53	3
10	136 - 158	144.9	9.03	5
11	147 - 166.2	155.93	7.9	4
12	148.2 - 161	153.07	6.93	3
13	153.3 - 159.2	155.38	2.64	4
14	154.5 - 164	159.25	6.72	2

Table 23. Normal Male Weight Data

Age	Range (kg)	Mean (kg)	Standard Deviation	N
5	20 - 40	25.07	7.67	6
6	23.5 - 25.2	24.35	1.20	2
7	27.1 - 56.3	37.7	9.77	8
8	23.8 - 35.5	27.62	4.03	9
9	26.6 - 56.7	39.58	10.66	8
10	27.5 - 75.2	44.4	13.05	10
11	35.5 - 53	42.59	5.32	10
12	39 - 81.5	54.79	14.85	10
13	44.1 - 65.6	55.38	9.92	4
14	52.3 - 87	74.62	12.51	6

Table 24. Normal Female Weight Data

Age	Range (kg)	Mean (kg)	Standard Deviation	N
5	17.8 - 25.2	21.63	2.34	9
6	20 - 33.5	24.96	3.55	12
7	21.2 - 39.8	27.98	5.83	11
8	24 - 51	36.74	9.72	5
9	31 - 60	47.83	15.05	3
10	31 - 76.3	46.5	19.12	5
11	45 - 73.3	57	12.94	4
12	35 - 56.9	42.63	12.37	3
13	52.5 - 74	63.08	10.09	4
14	49.2 - 55	52.1	4.1	2

Table 25. Normal Male Head Circumference Data

Age	Range	Mean	Standard Deviation	N
5	50.5 - 54.8	52.9	1.80	6
6	52.6 - 55.3	53.95	1.91	2
7	52.1 - 57	54.83	1.58	8
8	51.4 - 55.5	53.39	1.22	9
9	53 - 56.1	54.65	1.23	8
10	53.5 - 59.2	55.75	1.79	10
11	53.5 - 56.5	54.74	1.23	10
12	55 - 60	56.66	1.85	10
13	55.1 - 58.7	56.38	1.59	4
14	55.4 - 59.2	57.38	1.67	6

Table 26. Normal Female Head Circumference Data.

Age	Range	Mean	Standard Deviation	N
5	48.2 - 52.3	50.98	1.38	9
6	50 - 54.3	51.46	1.38	12
7	50.2 - 55.8	52.04	1.67	11
8	49.3 - 55.5	53.6	2.49	5
9	51 - 56.8	54.43	3.04	3
10	49 - 58	53.96	3.25	5
11	52.5 - 55.2	54	1.12	4
12	51 - 55.7	53.17	2.37	3
13	55.5 - 57.8	56.2	1.09	4
14	55 - 57	56	1.41	2

Table 27. Normal Male Palpebral fissure length

Age	Range	Mean	Standard Deviation	N
5	2.5 - 2.8	2.62	0.133	6
6	2.5	2.5	0	2
7	2.3 - 3	2.7	0.214	8
8	2.4 - 2.8	2.61	0.145	9
9	2.5 - 2.8	2.65	0.093	8
10	2.6 - 3	2.76	0.126	10
11	2.5 - 3.2	2.79	0.191	10
12	2.6 - 3	2.8	0.125	10
13	2.7 - 3	2.8	0.141	4
14	2.7 - 3.2	2.85	0.187	6

Table 28. Normal Female Palpebral fissure length

Age	Range	Mean	Standard Deviation	N
5	2.5 - 2.7	2.52	0.067	9
6	2.3 - 2.6	2.49	0.067	12
7	2.4 - 2.7	2.55	0.113	11
8	2.5 - 2.7	2.66	0.089	5
9	2.6 - 2.7	2.67	0.058	3
10	2.5 - 2.8	2.64	0.134	5
11	2.6 - 2.8	2.7	0.082	4
12	2.7 - 3	2.87	0.153	3
13	2.7 - 3	2.88	0.15	4
14	2.7 - 3	2.85	0.212	2

Table 29. Normal Male Inner Canthal Distance

Age	Range	Mean	Standard Deviation	N
5	2.8 - 3.4	3.15	0.217	6
6	3 - 3.2	3.1	0.141	2
7	3 - 3.5	3.3	0.177	8
8	3 - 3.7	3.21	0.237	9
9	2.7 - 3.5	3.23	0.271	8
10	3 - 3.7	3.34	0.232	10
11	2.8 - 3.8	3.45	0.303	10
12	2.9 - 3.7	3.42	0.210	10
13	3 - 3.7	3.28	0.299	4
14	3.2 - 4	3.53	0.294	6

Table 30. Normal Female Inner Canthal Distance

Age	Range	Mean	Standard Deviation	N
5	2.8 - 3.5	3.03	0.206	9
6	2.7 - 3.5	3.07	0.271	12
7	2.2 - 3.5	3.05	0.380	11
8	2.3 - 3.7	3.18	0.554	5
9	3.2 - 3.5	3.4	0.173	3
10	3.1 - 3.6	3.36	0.207	5
11	3 - 3.5	3.23	0.206	4
12	3 - 3.8	3.65	0.212	3
13	3.2 - 3.9	3.48	0.310	4
14	3.7 - 3.8	3.75	0.071	2

Table 31. Normal Male Outer Canthal Distance

Age	Range	Mean	Standard Deviation	N
5	7.9 - 8.6	8.33	0.301	6
6	7.8 - 8.1	7.95	0.212	2
7	8 - 9.2	8.69	0.376	8
8	8 - 9	8.47	0.287	9
9	7.8 - 9.1	8.58	0.365	8
10	8.4 - 9.5	8.92	0.410	10
11	8 - 10	9.05	0.587	10
12	8.5 - 9.3	9.02	0.257	10
13	8.2 - 9	8.8	0.400	4
14	8.7 - 9.8	9.18	0.366	6

Table 32. Normal Female Outer Canthal Distance

Age	Range	Mean	Standard Deviation	N
5	7.6 - 9	7.93	0.424	9
6	7.8 - 8.7	8.07	0.242	12
7	7.2 - 9	8.23	0.524	11
8	7.7 - 9.2	8.54	0.550	5
9	8.3 - 8.8	8.53	0.252	3
10	8.2 - 9.2	8.66	0.434	5
11	8.5 - 9	8.68	0.236	4
12	8.3 - 9.3	8.87	0.513	3
13	8.5 - 9.5	9.1	0.424	4
14	-	9.5	0	2

Table 33. Normal Male Philtrum Length

Age	Range	Mean	Standard Deviation	N
5	1.4 - 2	1.58	0.240	6
6	1.4 - 1.7	1.55	0.212	2
7	1.2 - 2	1.56	0.239	8
8	1.5 - 2	1.69	0.136	9
9	1.3 - 1.8	1.54	0.160	8
10	0.8 - 2	1.42	0.374	10
11	1.2 - 2.2	1.59	0.281	10
12	1.3 - 2.1	1.74	0.237	10
13	1.5 - 1.6	1.53	0.050	4
14	1.3 - 2	1.67	0.242	6

Table 34. Normal Female Philtrum Length

Age	Range	Mean	Standard Deviation	N
5	1 - 1.7	1.41	0.247	9
6	1 - 2	1.57	0.277	12
7	1 - 2	1.41	0.288	11
8	1.1 - 1.7	1.46	0.230	5
9	1.2 - 1.7	1.47	0.252	3
10	1.5 - 1.8	1.58	0.130	5
11	1.2 - 1.8	1.5	0.258	4
12	1.5 - 1.6	1.53	0.058	3
13	1.2 - 1.9	1.55	0.289	4
14	1.1 - 1.5	1.3	0.283	2

Table 35. Normal Male Palm Length

Age	Range	Mean	Standard Deviation	N
5	6.5 - 8.2	7.43	0.619	6
6	7.2 - 7.6	7.4	0.283	2
7	7.5 - 9.2	8.18	0.531	8
8	7.2 - 9	8.22	0.640	9
9	8 - 9.7	8.73	0.676	8
10	7.5 - 10.5	9.22	0.771	10
11	8.5 - 9.8	9.28	0.426	10
12	9.6 - 11.5	10.21	0.520	10
13	9.3 - 10.7	10	0.572	4
14	10.5 - 11.5	10.98	0.354	6

Table 36. Normal Female Palm Length

Age	Range	Mean	Standard Deviation	N
5	7 - 8.5	7.56	0.513	9
6	7.5 - 8.4	7.85	0.288	12
7	7.2 - 9.1	8.1	0.559	11
8	8 - 10.5	8.76	1.00	5
9	8.3 - 10.1	9.27	0.907	3
10	8.2 - 10.5	9.28	0.973	5
11	8.8 - 10.5	9.88	0.810	4
12	9.5 - 10.2	9.8	0.361	3
13	9.5 - 10	9.83	0.236	4
14	-	9.5	0	2

Table 37. Normal Male Hand Length

Age	Range	Mean	Standard Deviation	N
5	11.7 - 13.8	12.78	0.915	6
6	12.5 - 13.2	12.85	0.495	2
7	13.5 - 16	14.66	0.807	8
8	13.3 - 16	14.58	0.844	9
9	14 - 16.7	15.41	0.958	8
10	13.5 - 18.5	16.06	1.269	10
11	15.5 - 17.7	16.41	0.685	10
12	16.8 - 18.3	17.72	0.483	10
13	16.5 - 19.5	17.65	1.292	4
14	18.8 - 20	19.35	0.505	6

Table 38. Normal Female Hand Length

Age	Range	Mean	Standard Deviation	N
5	12.4 - 14.7	13.34	0.856	9
6	13 - 14.9	13.85	0.626	12
7	13.1 - 16	14.39	0.980	11
8	14.5 - 17.5	15.24	1.288	5
9	14.5 - 17.5	16.23	1.553	3
10	14.9 - 18.4	16.54	1.467	5
11	15.8 - 18.7	17.65	1.303	4
12	17.1 - 19.3	18	1.153	3
13	17 - 18	17.38	0.479	4
14	17 - 17.5	17.25	0.354	2

Table 39. Normal ONO Angles (male and female combined results)

Age	Range	Mean	Standard Deviation	N
5	87 - 103	94.53	4.84	15
6	85 - 98	91.07	3.20	14
7	85 - 105	92.47	4.96	19
8	81 - 100	91.64	4.86	14
9	86 - 97	90.36	3.88	11
10	87 - 96	89.93	2.91	15
11	83 - 94	90.21	3.79	14
12	82 - 94	88.15	3.48	13
13	78 - 98	90.81	6.22	8
14	82 - 93	87.88	4.09	8
15	90 - 98	94	5.66	2

Appendix F. Data used to compare the medians of the Caucasian curves versus the newly generated Native Curves.

Age	Height - Males (cm)		Weight - Males (kg)		Head Circumference Males (cm)	
	Caucasian	Native	Caucasian	Native	Caucasian	Native
5	110	115.97	19	25.07	51.2	52.9
6	116	117.05	20.5	24.35	51.5	53.95
7	121.5	131.35	23	37.7	52.1	54.83
8	127	129.38	25.5	27.62	52.5	53.39
9	132	139.68	28	39.58	52.9	54.65
10	137.5	144.63	31.5	44.4	53.2	55.75
11	143	147.39	35.5	42.59	53.7	54.74
12	149.5	156.3	40	54.79	54	56.66
13	156.5	160.28	45.5	55.38	54.4	56.38
14	163	169.82	51	74.62	54.8	57.38

Age	Height - Females (cm)		Weight - Females (kg)		Head Circumference Females (cm)	
	Caucasian	Native	Caucasian	Native	Caucasian	Native
5	108.5	116.21	18	21.63	50.5	50.98
6	114.5	123.99	19.5	24.96	50.7	51.46
7	120.5	127.36	22	27.98	51.1	52.04
8	126	135.84	25	36.74	51.5	53.6
9	132.5	143	28.5	47.83	51.8	54.43
10	138.5	144.9	33	46.5	52	53.96
11	144.5	155.93	37	57	52.5	54
12	151	153.07	41.5	42.63	52.8	53.17
13	157	155.38	46	63.08	53.2	56.2
14	160	159.25	50.5	52.1	53.8	56

Age	Palpebral Fissure Length - Males (cm)		Palpebral Fissure Length -Females (cm)		Philtrum Length Males (cm)	
	Caucasian	Native	Caucasian	Native	Caucasian	Native
5	2.63	2.62	2.63	2.52	1.4	1.58
6	2.65	2.5	2.65	2.49	1.45	1.55
7	2.67	2.7	2.67	2.55	1.5	1.56
8	2.68	2.61	2.68	2.66	1.55	1.69
9	2.69	2.65	2.69	2.67	1.6	1.54
10	2.7	2.76	2.7	2.64	1.65	1.42
11	2.71	2.79	2.71	2.7	1.65	1.59
12	2.72	2.8	2.72	2.87	1.65	1.74
13	2.725	2.8	2.725	2.88	1.65	1.53
14	2.73	2.85	2.73	2.85	1.65	1.67

Age	Philtrum Length - Females (cm)		Hand Length - Males (cm)		Hand Length - Females (cm)	
	Caucasian	Native	Caucasian	Native	Caucasian	Native
5	1.4	1.41	12.5	12.78	12.5	13.34
6	1.45	1.57	13.1	12.85	13.1	13.85
7	1.5	1.41	13.75	14.66	13.75	14.39
8	1.55	1.46	14.25	14.58	14.25	15.24
9	1.6	1.47	14.8	15.41	14.8	16.23
10	1.65	1.58	15.5	16.06	15.5	16.54
11	1.65	1.5	16	16.41	16	17.65
12	1.65	1.53	16.5	17.72	16.5	18
13	1.65	1.55	17.1	17.65	17.1	17.38
14	1.65	1.3	17.75	19.35	17.75	17.25

Age	Palm Length - Males (cm)		Palm Length - Females (cm)		ONO angle Males + Females (degrees)	
	Caucasian	Native	Caucasian	Native	Caucasian	Native
5	7.25	7.43	7.25	7.56	95	94.53
6	7.5	7.4	7.5	7.85	94.5	91.07
7	7.8	8.18	7.8	8.1	94	92.47
8	8.1	8.22	8.1	8.76	93	91.64
9	8.5	8.73	8.5	9.27	92	90.36
10	8.75	9.22	8.75	9.28	91.5	89.93
11	9.1	9.28	9.1	9.88	91	90.21
12	9.5	10.21	9.5	9.8		
13	9.75	10	9.75	9.83		
14	10.1	10.98	10.1	9.5		

Age	Inner Canthal Distance Male (cm)		Inner Canthal Distance Female (cm)		Outer Canthal Distance Male (cm)	
	Caucasian	Native	Caucasian	Native	Caucasian	Native
5	2.75	3.15	2.75	3.03	7.75	8.33
6	2.8	3.1	2.8	3.07	7.8	7.95
7	2.85	3.3	2.85	3.05	8.0	8.69
8	2.9	3.21	2.9	3.18	8.15	8.47
9	3.0	3.23	3.0	3.4	8.25	8.58
10	3.05	3.34	3.05	3.36	8.35	8.92
11	3.1	3.45	3.1	3.23	8.45	9.05
12	3.15	3.42	3.15	3.65	8.55	9.02
13	3.15	3.28	3.15	3.48	8.65	8.8
14	3.2	3.53	3.2	3.75	8.75	9.18

Age	Outer Canthal Distance Female (cm)	
	Caucasian	Native
5	7.75	7.93
6	7.8	8.07
7	8.0	8.23
8	8.15	8.54
9	8.25	8.53
10	8.35	8.66
11	8.45	8.68
12	8.55	8.87
13	8.65	9.1
14	8.75	9.5

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