THE INHERITANCE OF MACROCRANIA AND ITS ASSOCIATION WITH PSYCHOMOTOR IMPAIRMENT

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September, 1988

A Thesis submitted to the
Faculty of Graduate Studies and Research
in partial fulfillment of the requirements
for the degree of Master of Science

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ACKNOWLEDGEMENTS

I express my most sincere thanks to all those who have made the preparation of this thesis possible;

To the probands and their families who took the time to participate, so others could benefit from the information;

To my thesis supervisor, Dr. F. Clarke Fraser , for his expert counsel, patience, and for teaching by example, a humane approach to the study of clinical genetics, it has been a unique pleasure;

To my supervisory committee, Dr's Paige Kaplan, Michel Vekemans, and Gordon Watters, for their helpful suggestions and critical appraisal of my progress;

To all those associated with the Center for Human Genetics, especially Fran Langton and Dr's Roberta Palmour, and Leonard Pinsky, for all their behind the scenes administrative help;

To all of those who helped me in Vancouver, including the physicians who assisted with administrative aspects, and by referring their patients, Dr's Judy Hall, Barbara McGillivray, Michael Hayden, Siu Li Yong, and Paul Steinbok;

To the many others who have helped in various ways rendering this task an easier one, Marie-France, Suzanne, Danielle, Leah, Susan, Sandra, Kim, Lynn, Francine, Donna, Wendy; and to all those I haven't named;

And last, but not least, to my family, who were with me every step of the way, encouraging, supporting, and believing, I extend my deepest appreciation.

To my parents,

Ernest and Mary Louise Spickett

Abstract

Fifty probands were ascertained in order to establish inheritance patterns for macrocrania (occipito-frontal circumference (OFC) > 98th percentile), and to determine predictable variables for the increased risk for psychomotor impairment in this group. Excluded were non-caucasians, those with syndromes, born prematurely, or who are no longer macrocranic.

OFC measures of first degree relatives of the remaining study group (23 macrocranic probands, with or without psychomotor impairment) were analysed using methods suitable for quantitative data. The frequency distribution was unimodal with the mean shifted to the right, suggesting that the appearance of dominance, as previously reported, resulted from the imposition of an artificial threshold of abnormality on a polygenically determined trait.

Although the sample size was small, examination of several variables suggests that the most likely determinant of impairment was evidence of a difficult delivery, probably a result of an oversized head being delivered through a normal sized pelvis. These observations are useful for genetic counselling.

Cinquante sujets ont été examinés afin d'établir les possibilités d'hérédité en macrocéphalie (circonférence occipito-frontale (COF) supérieure à 98 pour cent), et de déterminer les variables prévisibles en matière d'augmentation des risques de troubles psychomoteurs dans ce groupe. Ces sujets étaient tous de race blanche, mais le groupe ne comprenait aucun sujet ayant des syndromes, aucun prématuré, ni aucun sujet qui n'était plus macrocéphale.

Les mesures de COF sur des parents au premier degré du groupe d'études restant (23 sujets macrocéphales, avec ou sans troubles psychomoteurs) ont été analysées avec des méthodes de données quantitatives. La distribution de fréquence a été unimodale, avec une moyenne penchant vers la droite, ce qui suggère que l'apparence de dominance, telle que déjà signalée, résultait de l'imposition d'un seuil artificiel d'anomalie sur un trait polygénique déterminé.

Bien que la taille de l'échantillon ait été réduite, l'examen de plusieurs variables suggère que la cause déterminante de trouble la plus probable était un accouchement difficile, résultant sans doute d'une tête trop grosse devant passer par un pelvis de taille normale. Ces observations sont utiles en matière de consultation en génétique.

I. INTRODUCTION

Megalencephaly, macrocephaly, and macrocrania all describe a head circumference greater than the 98th percentile. The terms do not imply pathology but simply the upper extreme end of a continuum of measurements. At this extreme end, however, there is an increase in proportion of pathological conditions, including space occupying lesions, hydrocephaly, storage disease, syndromes such as Fragile X, neurofibromatosis, achondroplasia, cerebral gigantism and many others. Non-syndromic, non-hydrocephalic, macrocrania, (considered by some to be autosomal dominant) is associated with an increased risk for psychomotor impairment To the families of affected individuals, little information regarding recurrence risks for either macrocrania or psychomotor impairment is available. To provide information for genetic counselling this study has analysed the inheritance patterns of non-syndromic macrocrania, and evaluated several variables which may give clues to the causes of the increased risk for impairment.

The human head at birth is 65% of its final size, and 90% at the age of 2 years. The size of the head is correlated closely with the size of the brain (Bray et al., 1969). The skull can be divided into two components, the neurocranium (calvaria) which supports and protects the brain, and the viscerocranium (nasofacial complex), concerned with respiration, mastication, and speech.

Evolution of man has resulted in a large calvaria relative to the viscerocranium, accompanied by a large increase in brain capacity. The calvaria is formed by the frontal, parietal, and superior occipital bones, articulating by sutures. At birth the bones are separated by fontanelles, composed of fibrous tissue (Moore, 1980). The anterior fontanel is the last to close at approximately 18 months of age. Sutural growth consists of bone deposition occurring in response to the effect of the enclosed enlarging brain. Between birth and adult life the volume of the calvaria increases four times and the maturing calvaria not only increases in circumference by sutural deposition, but also undergoes a progessive flattening, resulting in a reduction of curvature. Because the skull is a complex, precision fitted structure formed by many bones, any change in size of an individual bone results in a balanced readjustment in the adjacent bones (Sullivan, 1986). The occipitofrontal circumference is the traditional measure of the skull, and is taken to reflect the state of the underlying cerebrospinal fluid system, and the size of the brain.

Megalencephaly is described as an oversized and overweight brain that exceeds the mean by more than two standard deviations. The criterion of weight differentiates megalencephaly from megacephaly, alias macrocephaly, and macrocrania where simply a large head circumference for any cause, for example large ventricles, brain edema, or a thickened skull is implied (Warkany et

al., 1981). The literature attempts to differentiate between these clinically, but since brain weight is the major criterion distinguishing between them, it may be difficult to diagnose them accurately pre-mortem. Computerized tomography (CT), and other brain imaging studies are of assistance in this distinction. Some studies, however, have added to the confusion of the differentiation by finding that some patients have large heads associated with enlarged CSF spaces when scanned at ages below 18 months only to find resolution of the spaces at later ages and therefore an apparent diagnosis of megalencephaly (Alvarez et al., 1986). Families of individuals considered to be affected with either megalencephaly or macrocephaly have been evaluated by pedigree analysis and in both cases, autosomal dominance has been suggested to be the most likely pattern of inheritance (Alvarez et al., 1986; Demeyer 1972; Shreier et al., 1974; Asch and Meyers, 1976). For the purposes of this study, therefore, the term *macrocrania* will be used to describe a head circumference that is greater than 2SD above the mean for age and sex. The distribution of head circumference was examined in the first degree relatives of probands with the expectation that if macrocrania is determined by an autosomal dominant gene this distribution will be bimodal, whereas if it is controlled by many independant factors acting additively (multifactorial) the distribution will be unimodal (Fraser and Nora, 1986).

Over and above the pattern of inheritance there is the question of why there is an increased risk for psychomotor impairment associated with non-syndromic macrocrania. It has been reported that increased intelligence correlates with increasing head circumference between the mean and 2SD above (Lowrey, 1978). As part of the NIH Collaborative perinatal study it was found that IQ at 4 years of age increased linearly with head size, from approximately the 50th percentile to the 98th percentile where a decline occurs with increasing head circumference as seen in Figure 1.1 (Broman et al., 1976). These studies were not the first to imply that head circumference above the mean may be associated with increased intelligence. Pearl, (1909) systematically studied the association of normal intelligence and normal head size in man and found that there was a very slight positive correlation between head circumference and intelligence, attributing this to "the association between vigor and growth processes (leading to a well developed body) and vigor in mental processes would most probably be the result of the action of good conditions of nurture". After the 98th percentile, pathological processes such as hydrocephaly are presumed to exert detrimental effects influencing intelligence, accounting for the decline after the 98th percentile (Demeyer, 1987) and it has been suggested that even in the absence of obvious morbid developmental or pathologic processes that a higher prevalence of psychomotor impairment is found.

In a study of head circumference in learning disabled children it was found that 12.5% were macrocranic compared to a control group of children with average or better school performance that had only 3% macrocranic children. (Smith R.D., 1981). Further, a study of 10 megalencephalic children with normal CT scans concluded that, compared to their normal sibs, there was little difference in intelligence and language comprehension, but substantial differences were observed in motor proficiency suggesting a relationship between benign megalencephaly and developmental motor delay (Lewis et al., 1983).

It is known that many syndromes are associated with single gene effects causing macrocrania, thus it seems reasonable to asssume that a mutant gene for a disease may cause both the macrocrania and psychomotor impairment as pleiotropic, and variable additional manifestations. For example, when macrocrania is associated with enlarged CSF spaces, there may be a defect in the absorption of CSF resulting in a form of hydrocephaly that, in some individuals, is arrested early and in others exerts effects that result in psychomotor impairment (Shreier et al., 1974, Alvarez et al., 1986). Other studies dispute this stating that enlarged CSF spaces are not predictive of psychomotor delay, although they may be associated with macrocrania (Asch and Meyers, 1976; Petit et al., 1980; Day and Schutt, 1979).

Another hypothesis to be developed in this thesis, is that of a potential for birth difficulties from obstruction of the large head passing through a normal sized pelvis, (Day and Schutt, 1979) as in the case of macrosomic infants (birthweight >4000 gms) who are known to be at increased risk for birth injuries (Boyd et al., 1983).

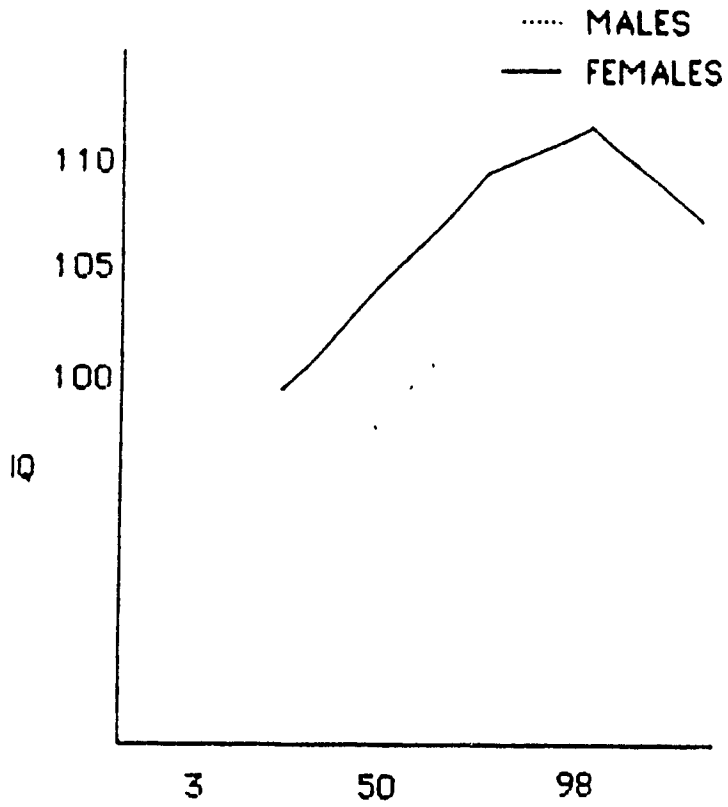
Differences in growth standards between populations are well known and accepted for measures such as height and weight, both of which are sensitive to environmental variations even though the primary determinant is genetic.

Nelhaus (1968) devised an international composite graph which compiled data for a variety of different racial and ethnic groups. Several studies since then have shown differences in head circumferences between populations substantial enough to warrant development of standards specific to specific populations (Ishikowa et al., 1987; Palti et al., 1983) Standards specific to West Indian blacks have not been developed, (McGregor, 1987) although the present study presents evidence to suggest that these may be necessary.

The main purpose of this study was to obtain information that can be used when counselling individuals and their families regarding familial macrocrania. The causes of the increased risk of psychomotor impairment will be explored in depth as will the inheritance patterns. Because of the nature of the study and the many variables involved, the thesis will be presented as a series of

distinct chapters in each of which a literature review will precede the presentation of data pertinent to that topic, followed by a discussion. A final conclusion integrating all aspects of the study will be presented in the last chapter.

FIGURE I.I



HEAD CIRCUMFERENCE AND IQ AT 4 YEARS (BROMAN 1975)

II. MATERIALS AND METHODS

The ideal method of study for a project such as this would be to ascertain macrocranic infants at birth, determine inheritance patterns, and follow them longitudinally until adolescence to determine associated risk for psychomotor impairment. Although ideal, this is not easily, or practically done. Since it has already been established that macrocranic individuals have an increased risk for learning problems, developmental delay, and motor impairment, (Broman et al., 1976; Lewis et al.,1983; Smith, 1981) it was decided that the most practical way of carrying out a study for the purpose of determining inheritance patterns, predictable variables and recurrence risks, for genetic counselling purposes, would be to ascertain known affected individuals from hospital files. The danger of this method of ascertainment is that more seriously affected individuals will be referred; also, in the genetics department cases with positive families will be more likely to be referred. Thus neither the general population risk for psychomotor impairment, nor the proportion of macrocrania that is familial will be discussed. Fifty individuals were ascertained and 23 of them were suitable for comparison of variables to determine risk factors for psychomotor impairment. Thus the study group consists of one group (12 macrocranic individuals) that have

varying degrees of psychomotor impairment, and a comparison group of 11 macrocranic individuals, that do not have psychomotor impairment but were referred for other reasons. Ascertainment of individuals will be discussed first, followed by methods of locating families, and then the investigation of variables.

II.A. Ascertainment of Probands

The first step was to establish as complete a patient list as possible from the card indexes and computer files of :
The Department of Neurology[a], The Montreal Children's Hospital;
The Department of Genetics[b], The Montreal Children's Hospital;
The Clinical Genetics Unit[c], University of British Columbia, at the Salvation Army Grace Hospital, Vancouver;B.C;
The Neurosurgery Department[d] at the British Columbia Childrens Hospital, Vancouver, B.C..

Those codes included were listings titled megalencephaly,

*Patient files were obtained under the supervision of Drs. G.V. Watters[a], F.C.Fraser[b], J. Hall[c] and P.Steinbok[d], and with the approval of the Montreal Children's Hospital Ethics Committee, and the University of British Columbia clinical screening committee for research and other studies.

macrocephaly, and macrocrania. Patient charts were obtained from medical records and inclusion criteria were that the individual must have had, the last time the head circumference was measured, a value equal to or greater than 2 standard deviations above the mean for that age and sex. Exclusion criteria were evidence of storage disease, frank hydrocephaly, space occupying lesion, and firm diagnosis of a syndrome. Also children who were not living with their parents, in foster homes or adopted, were excluded.

The preliminary list of names was established from the first two sources between October and December of 1986, and the latter two sources were utilized between January and March, 1988.

The next step was an attempt to establish contact with the families; in most cases the probands were children, therefore contact was through the parents. Telephone numbers and adresses were obtained from charts, as were the names of family doctors. If the families could not be contacted through letters, or by telephone numbers recorded on the chart, the family doctors were contacted to obtain a more current location of the family. Also, telephone books of areas surrounding Montreal were utilized. As a last resort the Régie de l'assurance automobile in Quebec City was contacted for help in locating families. Contacting families proved

to be time consuming and frustrating in the Montreal area, where telephone books were of little help since there are so many listings of the same family name, and family doctors who were contacted had in most cases also lost contact with their patients (only one patient was contacted with the help of a family doctor). The License bureau was limited in their capacity to help because it was not a matter concerning the Department of Transportation They did, however, forward a limited number of letters to families of which one responded. Contacting patients in Vancouver was mainly through the family doctors and was not difficult since many of the files were relatively recent (usually within 5 years of being seen) and most of the patients in the group were being followed consistently with one family physician. The indexes in Montreal and Vancouver contained 179 eligible candidates, and following chart review, contact was made with 57 families of which 8 decided against participation.

Contact was usually established with one parent of the proband (except in the case of adult individuals without psychomotor impairment) and consent was obtained. Following this an appointment was made to see the immediate family, in most cases at the proband's place of residence and occasionally in the Genetics Unit.

II.B. Obtaining Information

The family visit consisted of an interview with one or both parents, where a family pedigree was obtained, with particular reference to mental retardation and syndromes associated with macrocrania. Other information requested in the interview was: developmental history, medical history, and perinatal history of the proband and sibs. Measurements of first degree relatives of the proband consisted of head circumference, (obtained with unstretchable measuring tape calibrated by millimeter, placed superior to the supraorbital ridges and over the occipital protuberance, taking into consideration thickness of hair by pulling tightly, or when warranted measuring under), height, and weight. The proband's measurements consisted of those already stated plus: inner and outer canthi distances; palpebral fissure length, head length, breadth, and height; where indicated other measurements were taken. The proband was examined for signs of syndromes associated with macrocrania, (ie. hypo/ hyper-pigmented spots, large ears, large hands and feet) and dermatoglyphics and hair whorls were noted.

Medical information was corroborated and supplemented with records from hospital charts and other sources. Specific

information obtained from charts included results of neurological studies (ie. CT scans, pneumoencephalograph, ultrasound, electroencephalograph.), x-rays; amino acid, and mucopolysaccharide studies; developmental evaluation, and any other information that may have given clues as to the nature or cause of psychomotor retardation. Birth records were obtained separately when the information was not available on the hospital charts.

III. SUMMARY OF THE PRESENT STUDY

III.A. Characteristics of the Sample

Fifty macrocranic individuals from 49 families were seen. The male to female ratio was 1.7:1. This is consistent with the literature in which an excess of males has often been reported for both macrocranic and macrosomic infants. Of possible relevance to this is the theory of Y chromosome influence on growth, especially bony structure (Alvesalo et al., 1975). Of the group of 50, 11 individuals were excluded from the study group because there was sufficient evidence that their stigmata could have been syndromic in nature. This will be discussed at length in chapter VIII.

5 individuals were premature (32 to 37 weeks gestation) at delivery, all are learning disabled, and all have (or had) enlarged ventricles. Also, they all have families with large heads (average head circumference of first degree relatives is 1.08 standard deviations above the mean). One child was shunted as an infant, (MK), and it was later stated that although his cerebral ventricles were moderately enlarged, he may have simply had familial megalencephaly. He remains macrocranic, with poor coordination and learning difficulties at this time. These children were removed from the study group because of many confounding factors which

may have contributed to their psychomotor impairment, such as multiple pregnancy, (as was the case with 3 probands), respiratory distress, and simply the inherent difficulties of prematurity.

Four probands of West Indian origin were excluded early into the study when it became evident that head circumference standards specific to that population may be different from those of caucasions. Three of the four were learning disabled, one severely so with cause unknown, but the head measurements of first degree relatives were significantly greater than those of the rest of the study population. This will be discussed in greater detail in chapter IV.

Seven individuals, of which two were brothers, were ascertained originally as being macrocranic but were no longer so at the time of the study. One individual in this group has poor coordination, but the rest are functioning well. The one with poor coordination had a difficult breech vaginal delivery that was diagnosed as traumatic, with increased density seen in the area of the cerebellum on follow-up neurological studies. Early infant developmental delay was reported in 3 of these children with subsequent catch-up and no reported difficulties with learning. The first degree family measurements of this group were significantly less than those of the study population as discussed in chapter III.

The psychomotor impaired (PMI) group consists of 12

non-syndromic, non-hydrocephalic individuals (age range 2 years to adulthood with mean of 11.8 years) who have varying levels of psychomotor retardation without known cause. Five are learning disabled; 2 are mentally retarded with autistic tendencies; 2 that are under 5 years old are considerably developmentally delayed; 2 are borderline retarded (IQ's 70-75), and one is not intellectually impaired but significantly impaired in coordination.

The comparison group is made up of 11 macrocranic individuals who came to attention for reasons other than psychomotor retardation. The age group ranges from 1 year to adulthood with a mean of 8.9 years (not statistically significantly different from the group affected with psychomotor retardation). These individuals do not have reported coordination deficits or learning difficulties. A graphic summary of the macrocranic probands is shown in Figure III.1.

III.B. Parental Variables

Educational levels of all parents were compared by a scoring system (see table III.1) and it was found that out of a possible score of 8, the average for all parents of probands was 4.3. Significantly lower ($p<.05$) than the population were the parents of the premature infants with an average score of 2.4. Interestingly

the highest education score was that of the parents of the psychomotor retardation group where 72% of the mothers and fathers had at least some university education. There was no statistical difference between this group and the control group. The average levels of all groups can be seen in Table III.2 with a complete list of data in the appendix.

There was no statistical difference between groups in mean maternal or paternal ages at birth of the probands, the youngest being the parents of the premature infants and all other groups in close proximity. Maternal and paternal age distributions can be seen in Table III.3. Also no significant differences in handedness were seen between the groups of parents. Inheritance patterns of macrocrania will be discussed in chapter IV, and ethnic differences, in chapter V.

IIIC. Proband Variables

Anthropometric measures, of height; inner and outer canthal distances; cephalic indexes; birth weights; and head circumferences are compared between the PMI and the comparison groups in Table III.4. Those listed are not predictive of psychomotor impairment. Birth weight approaches significance, with birth head circumference being statistically significant

between the groups. This aspect is elaborated on in chapter VII.

It has been suggested that familial macrocrania with and without psychomotor retardation may be associated with cerebrospinal fluid space enlargement. This, therefore, is discussed in detail in chapter VI where it will be shown that although enlarged CSF spaces are present in some individuals that there is no difference between those that are psychomotor impaired and those who are not. The association of macrocrania and difficult deliveries will be elaborated on in chapter VII, with the results of the current study showing a higher number of individuals in the PMI group that have had difficult deliveries. Syndromes associated with macrocrania are presented in chart form in chapter VIII. A discussion of individuals who were excluded from the study population because they were syndromic is found in the appendix.

III.D Recurrence

Of the 12 psychomotor impaired nonsyndromic probands, it was found that there was one recurrence. This family consists of three macrocranic brothers of which two are intellectually impaired. The proband (DD), now 17, was the first born of healthy nonconsanginous (both macrocranic) parents. His delivery was a

low forcep and uneventful. No cause for the intellectual impairment, (IQ 90) has been found and he attends a special education school. The second brother is intellectually advanced as compared to his peers, but the youngest, now 10, also attends a special education class, and is reported to be "hyperactive". It is not clear if the nature of the intellectual impairment is the same in both sibs.

One sister of a male proband in the comparison group has marked speech and learning problems. The proband is the youngest of three sibs, had a normal spontaneous delivery and was referred just afer birth to neurosurgery services because his head size was greater than the 98th percentile. His oldest brother (14 years) is not macrocranic, and is also normal. The sister of interest is 10 years old, macrocranic, and was reported to have a difficult forceps delivery after presenting as a brow presentation. She had a difficult neonatal course after sufferring a pneumothorax. Her developmental milestones, including gross and fine motor skills, remained slow throughout childhood. She attends a special class and speech therapy.

In summary, of 22 sibs of macrocranic psychomotor impaired probands, 4 were macrocranic, one of which was psychomotor impaired. None of the non-macrocranic sibs of this group were impaired.

Of 13 sibs of the comparison group 3 were macrocranic, of which one has marked speech and learning difficulties (as previously discussed). Of the remaining ten non-macrocranic sibs one has learning difficulties and a head circumference at the 50th percentile. Therefore in the case that a sib is macrocranic the recurrence rate for psychomotor impairment is 2/3+4 = 28%, and 1/18+10=3% if the sib is not macrocranic. The overall recurrence rate for psychomotor impairment for all sibs combined is 8% (3/35).

Table III.1. Education Scoring Method.

Education level achieved	Score
elementary school	1
some high school	2
high school completed	3
technical school	4
some university	5
university graduate	6
graduate school	7
PhD, MD, Law.	8

Table III.2. Average Level of Education

Group	Paternal	Maternal	Signif*
Psychomotor Impaired	5.6	5.3	NS
Comparison Group	4.4	4.4	NS
Syndromic	3.8	5.1	NS
W.I.	4.5	3.0	NS
Prematures	2.4	2.4	P< 0.01*

*Education level was compared to total population average and tested with student t-test for significance.The PMI group was also tested against the comparison group averages.

Table III.3. Parental Ages at Time of Birth of Proband

Group	Paternal	Maternal	Signif*
Psychomotor Impaired	31.3	31	NS
Comparison Group	32.6	31	NS
Syndromic	32.8	28.3	NS
W.I.	33.6	30.3	NS
Prematures	26.8	25	NS

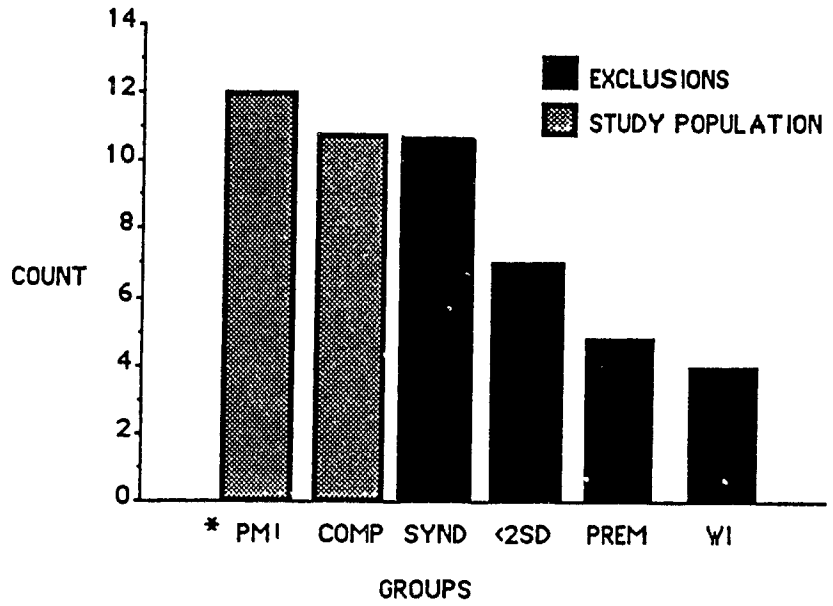
* Parental ages were compared to total population average ages and tested with student t-test for significance.The PMI group was also tested against the comparison group average ages.

Table III.4. Anthropometric Dimensions

Variable	Comp	PMI group	Signif
Head Circumference	3.10 SD	2.98 SD	NS p=.76
Height	71.9 %	63%	NS p=.26
Inner canthal distance	81.4 %	71.1%	NS p=.12
Outer cantha! distance	79 %	70.4 %	NS p=.11
Cephalic Index (W/L)	74.8 %	73.2 %	NS p=.23
Birth weight	3391 g	3616 g	NS p=.08
Birth H.C.	35.7 cms	37.5 cms	S* <.01

All dimensions were tested with the student t-test for significance.

FIGURE III.1 **TOTAL POPULATION OF MACROCRANIC INDIVIDUALS-CATEGORIES AND NUMBERS EXCLUDED FROM STUDY**



*PMI -PSYCHOMOTOR IMPAIRED
COMP-COMPARISON GROUP
SYND-SYNDROMIC
<2SD-NOT PRESENTLY MACROCRANIC
WI-WEST INDIAN

IV. GENETIC ANALYSIS OF MACROCRANIA

IV.A. Review of the Literature

IV.A.1 Inheritance of Macrocrania

Kindreds of individuals with macrocrania have been examined and autosomal dominant inheritance has been considered to be the most likely genetic determinant (Alvarez et al., 1986; Demeyer,1972; Shreier et al., 1974; Asch et al., 1976) with occasional speculation that in some cases, autosomal recessive or X-linked inheritance could be involved (McKusick, 1986). In all family studies reported, the definition of macrocrania is considered to be a head circumference greater than the 98th percentile. Day and Schutt (1979) reported that in 11 of 13 cases of children with macrocrania, one parent had a large OFC. Kindreds of macrocephalic individuals, both megalencephalic (Demeyer, 1972 and 1987) and considered to be macrocephalic with enlarged CSF spaces (Alvarez et al., 1986) and combined (evidence of some family members with enlarged CSF spaces and some without), (Shreier et al., 1974; Asch et al., 1976) demonstrate that autosomal dominant inheritance is a reasonable interpretation when utilizing the basic criteria of pedigree analysis (Fraser and Nora, 1986) where the 98th percentile is defined as the threshold of abnormality as shown in Figure IV.1.

However, macrocrania is a term used to designate the upper

2% of a continuous distribution of a quantitative character (an attribute that is measured on a continuous scale). A character such as this should not be divided into qualitative categories in the absence of discrete groups, ie. dwarfism versus normal height (Cavalli-Sforza and Bodmer, 1971).

The distinction between the genetic basis for a qualitative and a quantitative character depends on how much a Mendelian difference shifts the phenotype. At the level of DNA, all differences are discrete, therefore qualitative. For example a nucleotide substitution will code for a different amino acid (except in the case of a synonymous substitution). At the protein level qualitative differences may be distinguished by physicochemical properties revealed by techniques such as electrophoresis. Some of these differences are indistinct even at that level, and as the distinguishing character of a gene becomes further removed from the gene product the qualitative effect becomes more obscured (Cavalli-Sforza and Bodmer, 1971). Quantitative measures may distinguish qualitative characters as in autosomal recessive Tay-Sachs Disease where there is substantially reduced hexosaminidase A, measurable by enzyme assay, but two discrete populations of affected and non-affected individuals with non overlapping distributions are easily recognized even before the clinical phenotype appears. In this case testing of segregation ratios would be appropriate.

Effects of genes producing quantitative character differences are often not as clearly defined as the previous example. Among the many quantitative characters are; blood pressure, blood glucose, and growth parameters, measures which are all influenced by genetics and environment, resulting in subtle variation of characters rather than clearly defined groups that can be labelled as affected or unaffected. Therefore pedigree analysis alone is an invalid method of determining a genetic hypothesis in such cases, even though there is a natural desire for simple classification into all or none phenomena (Murphy, 1964).

> " It is possible to distribute all adult men into two alternate classes, those taller than 1.67 meters and those shorter. therefore one could easily be led to the conclusion that variability in human stature depends on a dominant gene with incomplete penetrance" (Vogel and Motulsky 1986).

Genetic analysis for measures such as this are based on models of quantitative variation that take into account the influences of environment and the joint effect of many genes. There are three basic types of quantitative variation that may be analysed in this way. The first is variation attributed to single gene differences, (ie, Hexosaminidase A, phenylalanine, pseudocholinesterase levels). These measured levels can be clearly separated into distinct distributions (non-overlapping or slightly overlapping). This type of variation may result in such distinct

qualitative differences that it could be analysed using standard techniques of Mendelian analysis.

Another category of quantitative variation is the non-Mendelian "all or none" attributes. Among these are included malformations such as neural tube defects, or cleft lip/palate. These are quantitative in the sense that their expression is the result of a continuous distribution of "liability" determined by many genes and environmental factors, with separation into discrete groups (affected and not) by a developmental threshold (Fraser and Nora, 1986). In these multifactorial disorders, the recurrence risk for sibs of unaffected parents is well under the 25% expected for a simple recessive defect.

The third category of quantitative variation includes those characters whose distributions in the population are continuous and unimodal. This would include anthropometric dimensions. This represents the sum of a large number of separate effects, genetic and environmental. Thus genetic analysis of quantitative data takes into account both the effects of environmental variation and the joint effect of many genes on a given character (Cavalli-Sforza and Bodmer, 1971).

The approach used to determine the genetic basis of a quantitative character is use of the frequency distribution, as demonstrated in the study of isoniazid degradation (Price Evans et al., 1960) and hyperlipedemia in coronary heart disease (Goldstein

et al., 1973). One would expect in the case of an autosomal dominant gene, two distinct distributions in the first degree relatives representing the two phenotypes. In the case of the present survey, this pattern would predict a distribution scattered near the 98th percentile, representing the presence of the "large head" gene and one surrounding the population mean implying the absence of the gene, resulting in a bimodal distribution. In the case that a single gene does not control these characters but a number of factors, genetic, environmental or a combination do, a normal, unimodal disribution would be expected.

Quantitative analysis using frequency distributions is not without difficulties. It is possible that there will be overlapping of distributions leading to ambiguity of classification of phenotypes giving the impression of unimodality when the means are too close together, or the variance is too large to permit distinction of the separate groups. Also the size of the population must be sufficient to demonstrate bimodality. Therefore in theory (but possibly not practice) increasing the distance between the means and reducing the variance will enhance separation of the distributions (Murphy 1964).

There are several reasons why a distribution will give the illusion of bimodality, when in reality it is not. One is nonrepresentativeness of the sample. A simple explanation of this is as follows; the present survey could result in a bimodal trend if

the sample population included children with learning disabilities with 1) large heads 2) normal sized heads. The resulting distribution would be bimodal. Another example is the age effect on blood pressures whereby combining groups of adults and children in the same study would result in the appearance of a bimodal distribution of blood pressure. Also, the illusion of bimodality may result if two observers are collecting data and each one is consistent with a specific type of measuring error. Lastly, a sample too small to represent the population may induce false bimodality (Murphy, 1964).

IV.A.2 Genetics of Growth

Genetics of growth will be discussed briefly, including the concept of heritability, because as an added point of interest in this study, correlations of midparental head circumference and average head circumference of offspring were calculated. Effects of secular changes and assortive mating will also be discussed briefly.

IV.A.3 Heritability

Heritability is the expression of the additive genetic

contribution to the trait and can be written as $h^2 = \frac{V_A}{V_P}$

where V_A is the variance of the additive genetic component and V_P is the variance of the phenotype. It is possible to determine the value of h^2 with the equation, $h^2 = \frac{r}{\sqrt{1/2}}$ where r is the mid parent correlation coefficient. A value between 0 and 1 will result, where a low value implies few contributions of additive genes to the variance of the trait and a high value suggests a large contribution.

Correlations of anthropometric measures such as stature, span, length of forearm between parents and offspring, and between sibs have been generally close to .5 demonstrating high heritability of these traits, suggesting genetic determination predominantly as a result of non-dominant genes. Epistasis or non-additive interactions between genes may lower the correlations, with assortive mating* increasing the correlations (Cavalli-Sforza and Bodmer, 1971).

*Assortive mating is the tendency for people to choose mates with similar physical or behavioural characteristics to themselves, for example a short statured man will be likely to marry a woman similar to or less in stature than himself. This increases genetic variance by increasing the proportion of individuals in the extremes of a normal population, without changing the gene frequency and should increase parent-child, and sib-sib correlations, by decreasing the amount of heterozygosity for a trait. (Cavalli-Sforza and Bodmer, 1971)

In the case that a polygenic trait is unaffected by environmental influences there should be no difference between sib-sib correlations and parent-offspring correlations of growth parameters. (This is also true of environmental conditions being held constant between generations). Secular trends of means in anthropometric measures may have an effect such that when heritability is held constant and the environment is changed between generations phenotypic correlations may be higher for sibs than for parents and children. In classical studies, such as that of Bowles (1932) where 474 father-son pairs and 79 brother-brother pairs were evaluated for several anthropometric measures, it was found that brother- brother correlations are almost always higher than father-son correlation, significantly so for height, span, and head circumference (Mueller 1986).

Longitudinal resemblances of inter or intra generation growth have been studied, which is helpful when evaluating the influence of environment and heredity, especially during periods of added vulnerability to environmental inflences. In general, parent-offspring correlations rise dramatically in the first year of life, reaching a maximum by the age of 3 years and remaining high until the age of 8 years. There is a decline in adolescent years, found in both sexes with the onset of puberty, and increasing after the age of 17 to slightly above the maximums seen between the

ages of 3 and eight. This suggests that environmental influences are exerted maximally before one year of age and during the years of adolescence (Mueller, 1986).

IV.A.4 Secular Growth Patterns

Secular growth changes are patterns of growth changes that occur in a population over time. These changes are presumably due to genetic growth potential that is influenced by secular changes in the environment. For example secular stature increases reported in London school children in a study between 1904 and 1966 demonstrated increases which were reported to have ceased between 1954 and 1959, coinciding with a decrease in pubertal age. It was suggested that even though environmental conditions were not optimal in urban London at that time a genetic threshold for growth may have been reached (Cameron, 1979). However further studies have disputed this hypothesis, and confirmed that secular increases in height have continued throughout the 1970's in the UK (from .5cms per decade in British females to 1.5cms in Scottish males) (Chinn and Rona, 1984). Also a substantial secular increase in height was seen over the past two decades in Chinese children raised in Hong Kong. This has been largely attributed to better socioeconomic conditions improving hygiene and diet. (Ling and King, 1987). One could presume that

those populations that experience the greatest changes environmentally would demonstrate the greatest secular changes in those traits that are vulnerable.

Head circumference is considered to be a trait with less environmental vulnerability than other body parts (Widowson, 1980, Balazs et al., 1986). However positive secular trends have been found in brain weight, especially in men, in a study of brain weight at autopsy between 1907 and 1977 in a British population (Miller and Corsellis, 1977). Also recent secular increases of head circumference in a British population have been reported (Ounsted et al., 1985), but recent changes in North American populations have been shown to be minimal (Roche et al., 1987). Although there were no significant secular changes in final circumference between 1928 and 1967 there is a secular trend in head circumference growth patterns, with a later, but decreased peak growth velocity (Roche et al.,1986).

IV.B RESULTS

Head circumferences were measured in first degree relatives, as described in chapter II. The study group for genetic analysis consisted of the first degree relatives of the comparison group and the PMI group. The West Indian population was excluded for reasons mentioned in the summary and discussed in detail in chapter V. The syndromic group was excluded by definition of the study. The group of individuals that are not presently macrocranic, and the families of the premature infants were also excluded for this analysis. Average head circumference of first degree relatives of each group are compared in Figure IV.2 Frequency distributions of these populations are presented in the appendix.

The results were standardized for age and sex against standards of Roche (1987) by using the standard z-method:

$$z = \frac{X - \bar{X}}{SD}$$

Values for males and females were calculated separately, and there was no statistical difference between the two ($p=0.84$), therefore the two populations were combined.

The frequency distribution is shown in figure IV.2. ($n=84$) with a mean of 1.19, median of 1.24, standard deviation of .985,

and skewness of -0.07. This distribution is unimodal but is shifted to the right significantly, ($p<.01$), as compared to the general population mean which would be at 0.

Correlations of maternal, paternal, midparental, compared to average sib head circumferences were calculated and r was found to be .324, .278, .322 respectively. Heritability was calculated using the equation $h^2 = \frac{r}{\sqrt{1/2}}$ and found to be .455.

IVC Discussion

The unimodal frequency distribution demonstrated suggests that non-syndromic head circumference (including macrocrania) is determined by multifactorial inheritance, rather than a single gene (Cavalli-Sforza and Bodmer, 1971; Murphy 1964; Vogel and Motulsky, 1986). Autosomal dominant has been previously suggested to be the most likely mode of inheritance by pedigree analysis (Alvarez et al. 1986; Demeyer, 1972; Shreier et al., 1974; Asch and Meyers 1976). In the case of a single gene effect, however, one would expect the values for first degree relatives to fall into two distibutions, one about the population mean and one about 2 standard deviations above the mean representing the two phenotypes (one macrocranic and one non-macrocranic) that would be expected with a single gene effect. This finding is consistent with other anthropometric measures such as height, which are

known to be multifactorial in origin, where the resultant character is controlled by a number of factors, genetic environmental or both. Figure IV.3 demonstrates how a "multifactorial" pedigree may appear to be autosomal dominant with the imposition of artificial threshold on a continuous trait.

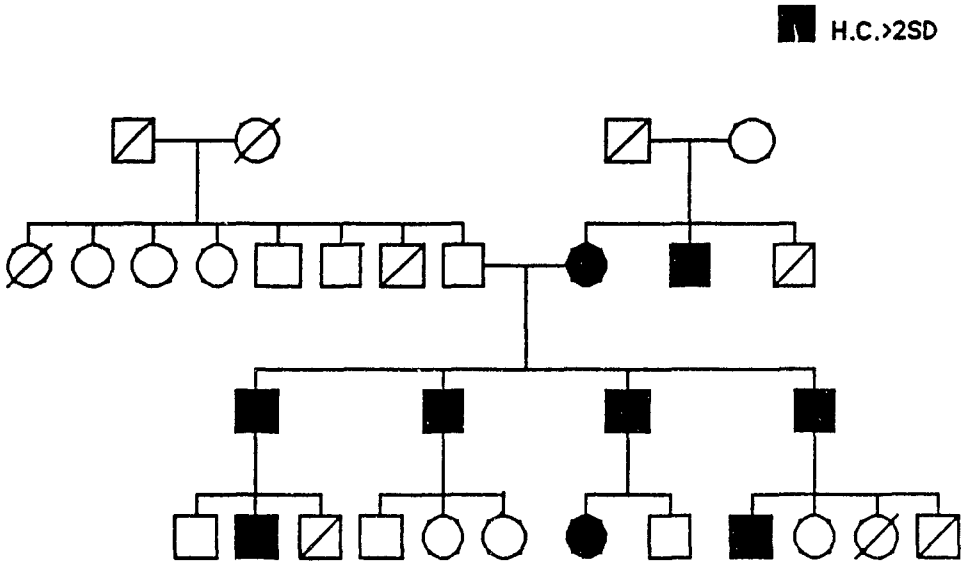
Heritability was calculated with the determination of midparental correlation (out of interest) and it was found to be .455 implying that about 50% of the variability is not accountable for by genetic factors which is consistent with previous reports of various growth parameters (Mueller, 1986), although this calculation was determined with a small sample size.

The mean head circumference of first degree relatives of each group was compared to that of the study population (comparison and PMI) results. It was of interest that degree each separate group had statistically significantly different head circumference (as determined by t-test, seen in Table IV.1) when compared to the study population, except the first degree relatives of the premature infants, suggesting that their macrocrania was not secondary to the prematurity, but rather familial in nature. Dunn et al., (1986) found in a study of 275 low birth weight children (either premature, or small for gestational age) that 6 were macrocranic. This is consistent with population expectations where two percent of any population would be expected to be macrocranic by definition (head size greater than

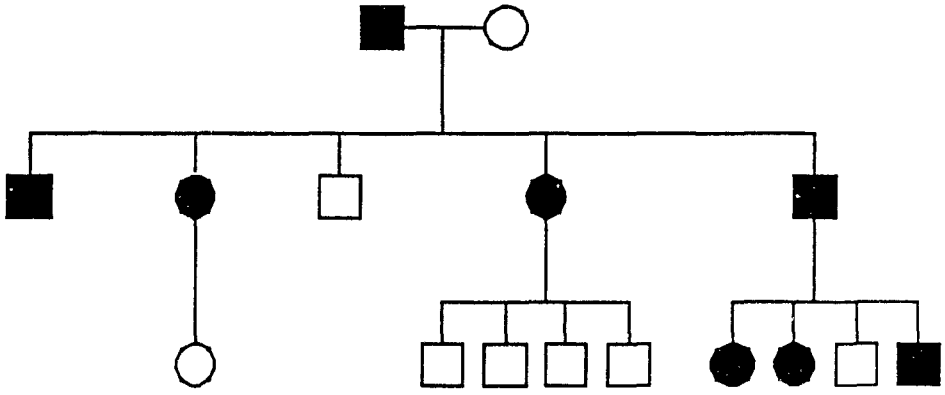
the 98th percentile for sex and age.)

In conclusion, the results of this study suggest that non-syndromic macrocrania is inherited in a multifactorial way, rather than as a single gene difference as has been previously suggested. This is important for genetic counselling. Furthermore, both the syndromic and the West Indian probands had first degree relatives with increased head circumferences, suggesting that here, also, the macrocrania of the probands may have had a genetic basis. On the other hand, the "<2SD" relatives did not differ from the general population, suggesting that their exclusion from the study population were justified. A graphic comparison of measurements of all groups is seen in Figure IV.4.

FIGURE IV.1. "DOMINANTLY" INHERITED MACROCRANIA



Asch, 1976



Demeyer, 1975

Two pedigrees reproduced from publications demonstrating the appearance of an autosomal dominant inheritance pattern.

FIGURE IV.2 DISTRIBUTION OF MEASUREMENTS OF FIRST DEGREE RELATIVES OF STUDY GROUP

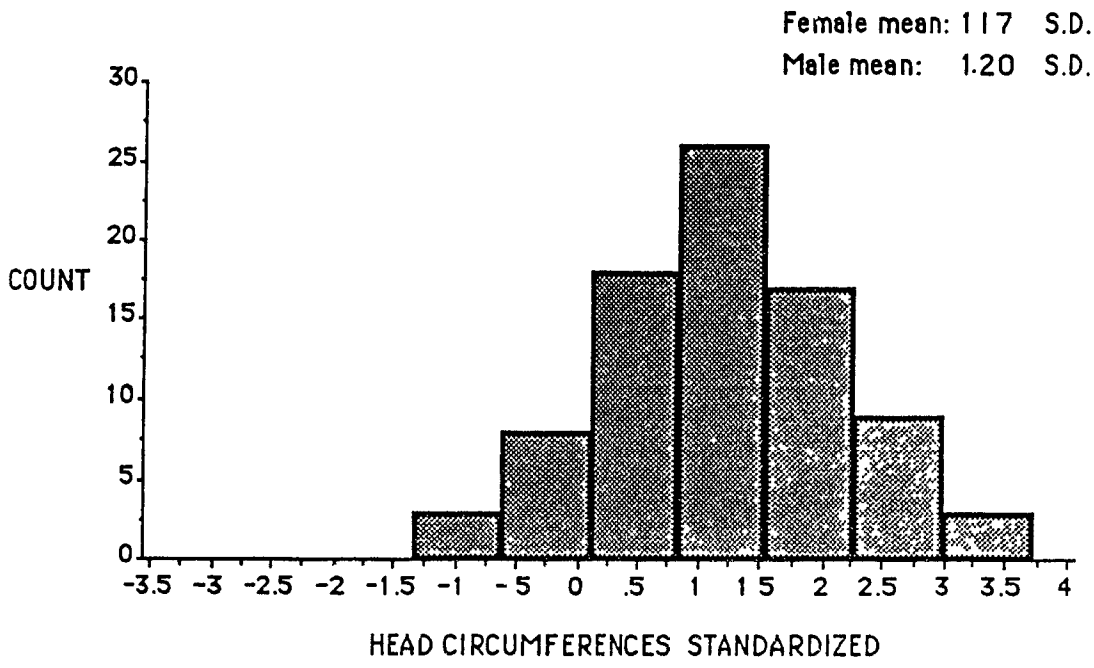
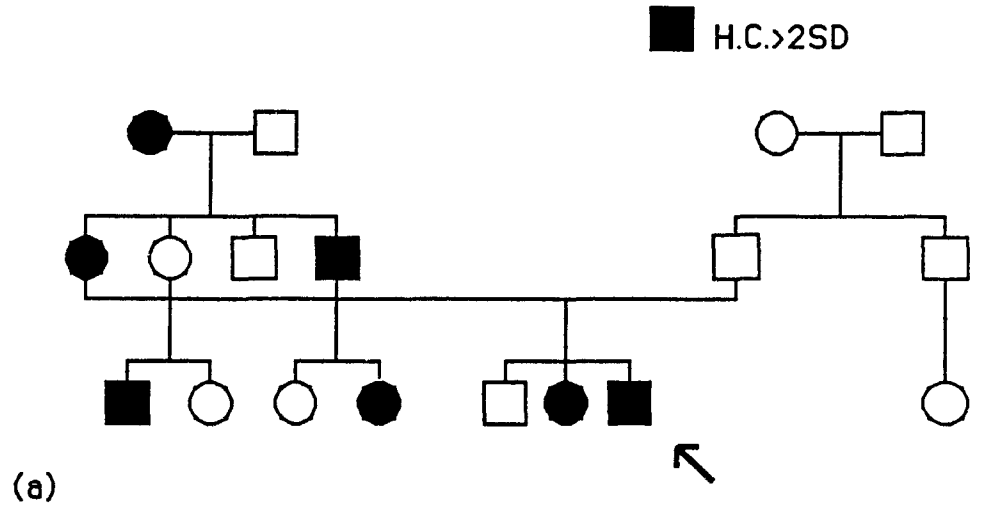
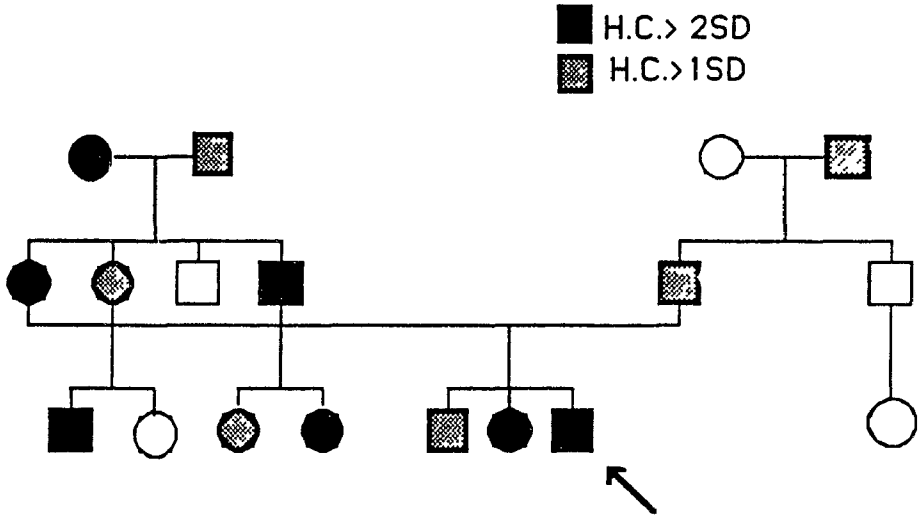


FIGURE IV.3. DOMINANT VS MULTIFACTORIAL PEDIGREES



(a)



(b)

FAMILY W

a) a "dominant" pedigree (from study population) using a head circumference of >2SD as a criterion for affected

b) same pedigree with more information, now pedigree looks "multifactorial"

FIGURE IV.4. MEAN HEAD CIRCUMFERENCE Z-SCORES OF FIRST DEGREE RELATIVES OF PROBANDS

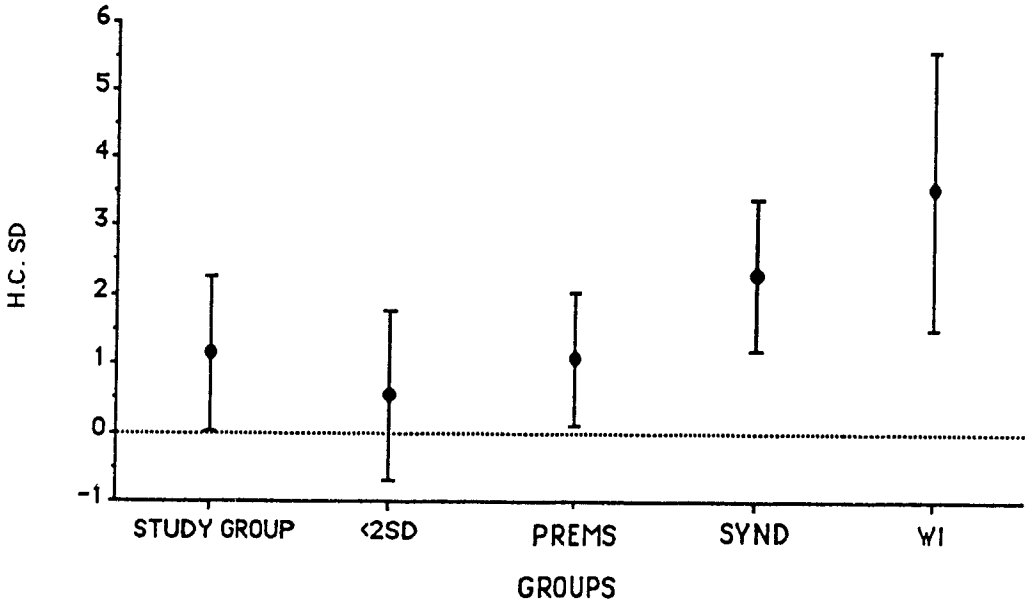


TABLE IV.1 MEAN HEAD CIRCUMFERENCES OF FIRST DEGREE RELATIVES OF PROBANDS IN THE STUDY GROUP AND OTHER CATEGORIES

	MEAN	SIGNIFICANCE *	
STUDY GROUP	1.14 SD		
<2SD	.52	p=.05	S
PREMS	1.05	p=.68	NS
SYND	2.28	p=<.01	S
WI	3.54	p=<.01	S

* All groups are compared to the study population mean with t-test for significance.

V. ETHNIC/RACIAL DIFFERENCES

V.A Review of the Literature

Population differences in body size and shape are presumably the result of differences in environmental and genetic factors and their interactions. Environmental conditions such as health and nutrition play an important role in the end state of growth, and because of this it may be difficult to determine true genetic potential, especially in groups where the environment may be poor. It has been claimed that disadvantaged children in tropical areas rarely achieve their genetic potential for growth, remaining shorter and lighter than children of higher social classes of the same ancestry (Mueller and Titcomb, 1977). South African blacks in high socioeconomic classes are taller than Europeans, but those in low socioeconomic groups of the same ethnic background show a falling off of growth in weight and length after 6 months of age, suggesting that the negative effects on growth result from poor nutrition and infectious disease (Eveleth and Tanner, 1976).

Differences in anthropometric measures between socioeconomic/geographical groups within ethnic/racial populations have been studied extensively. A demonstration of genetic potential for growth and body proportion is reported for a series of studies of Japanese children. It was found in 1957 that

Japanese born and raised in California were taller than children of the same age raised in Japan. Interestingly these differences were no longer present in 1976, implying secular changes had also occurred in Japan, over the 20 year span between the studies. An extensive analysis of these trends (Tanner et al., 1982) showed that the secular trend appeared not only for size but for body proportion and growth velocity. The main increase in size was a result of an increase in leg length as opposed to trunk length. In the past it was felt that the classical racial difference in build between Japanese and North Europeans has been the relative length of legs and trunk. It was concluded that even though the Japanese have a genetic maximal potential for height, (approximately 1 standard deviation below that of Europeans) racial differences in body proportion diminish as environmental conditions become more similar in each group. Thus some "ethnic/racial differences" may be a result of variable environmental conditions and vulnerability to those conditions.

It is generally felt that malnutrition is "head sparing" (Nelhaus, 1968; Widowson, 1980; Balazs et al., 1986) meaning that head circumference is not as environmentally vulnerable as other measures such as height and weight. There is, however, evidence that shows that brain weight reflected by head circumference may indeed be influenced by adverse conditions. (Grantham-McGregor

and Desai,1973; Balazs et al., 1986). In a study from Iran, upper income children below the age of two years were compared to those of lower income families of the same ethnic background and the same age group, for height and head circumference . It was demonstrated that the lower income group average head circumference was between the 3rd and the 10th percentile of the higher income group (Mueller, 1986).

Further evidence of this comes from a Kingston Jamaica study group of 271 infants of low socioeconomic class (Grantham-McGregor, 1973). Ninety-two percent were of black African, and 8% of mixed racial origin. These infants at birth had head circumferences close to the international standards devised by Nelhaus (1968) with early postnatal growth increasing to well beyond the 50th percentile, only to level off with time and fall slightly below it. This could be attributed to a genetic predisposition for advanced growth velocity, maximizing from birth to 4 months, and subsequently slowing, or, as the author hypothesizes, it may show a genetic potential for increased head circumference growth which is depressed as poor nutrition and conditions exert their effects. At the time of the study, malnutrition was common in Jamaica, contributing to at least 25% of all hospital admissions (Grantham-McGregor et al., 1972). The authors give further evidence that malnutrition contributes to

depression of head growth by plotting the head circumferences of 8 known malnourished infants, at the age of one year. The majority fell well below the mean and some below the 3rd percentile, demonstrating that malnutrition has had depressive effects on head growth in these children. On the other hand, a recent study of Israeli children (Palti et al., 1983) demonstrates that in the absence of poor nutrition, this population has significantly smaller heads than would be expected by international standards, which supports the knowledge that genetics does play a role in ethnic differences in head circumference growth. (See graph, Figure V.1)

Nelhaus established interracial standards for head circumferences in 1968 stating there were no significant racial, national, or geographic differences found in world wide reports published in the previous twenty years. Twelve caucasian populations, (from Britain, Switzerland, Scotland, Finland, Belgium, Czechoslavakia, and United States), 2 negro American and one Oriental population contributed to the composite international standards that even now continue to be used by medical personnel. Yet as each population is examined separately differences emerge. Interestingly, Japanese average head circumference standards at birth are on the 98th percentile of the international standards, whereas at the age of 6 months they are on the 50th percentile, and continue along or slightly below that with time. (This bears a

striking similarity to the pattern of growth seen in the Jamaican infant population (Grantham-McGregor and Desai, 1973)). Some 20 years after that paper was published a report shows that Japanese children have larger head circumferences at later ages than would be expected from the previous reports (Ishikawa et al., 1987). This is consistent with the theory previously discussed that genetic potential of head circumference may be suppressed due to adverse living conditions, and as these disappear growth potential may reach its maximum.

Since the devising of the international and interracial graphs by Nelhaus, other authors have challenged the validity of compiling all of these studies, some on the basis of claims of over representation of low socioeconomic groups (Roche et al., 1987, Grantham-McGregor and Desai, 1973) and others stating that it is an over generalization (Meredith, 1971).

Meredith objected to the over-generalization of the international composite standards and collected in excess of 70 studies (some from the 19th century) of serial measures of head circumferences of children, stating there were substantial interracial and regional differences, and claiming the standards were not valid for international use. Also, updated head circumference measures up to the age of 7 years, of a British population (Ounsted et al., 1985) shows evidence of a secular

upward trend that would invalidate the use of the international standards for this group.

Roche (1987) established head circumference charts from a study of 888 caucasian children of varied socioeconomic status ascertained during the Fels Longitudinal Study, stating that the charts derived from this study are appropriate for both U.S. black and white children, but may not be appropriate for other ethnic groups.

The updated standards demonstrate findings in the first 36 months similar to that of the National Center for Health Statistics (Hamill et al., 1979), and those of Nelhaus. However substantial positive differences are seen with increasing age, when compared to the latter study, possibly due to a more general representation of socioeconomic groups and little ethnic admixture. Therefore it is proposed by the authors that these charts represent updated, accurate standards for U.S. populations, white and black.

The current study suggests that these standards may not be valid for blacks, at least those of West Indian origin. Also, 4 studies of head circumferences of blacks from 3 American and 1 Jamaican population are shown plotted against the standards of Nelhaus (Grantham-McGregor and Desai, 1973; Wingerd et al., 1971; Verghese et al., 1969; Scott et al., 1962). This demonstrates

considerable variability with termination of 3 of the 4 studies by the age of two years (Figure V.2). The Jamaican study measures are the greatest prior to 4 months of age, with subsequent decline in velocity as has been previously discussed (Grantham-McGregor and Desai, 1973). A California study (Wingerd et al., 1971) of black infants during the first two years of life demonstrates measurements similar to standards of both Nelhaus and Roche with slightly larger sizes for the females. The one complete study of all age groups was done in the District of Columbia (Verghese 1969) between 1963 and 1965 which showed a pattern following on or lower than the 25th percentile in both males and females when compared to both the Nelhaus and Roche charts until the age of about 7 years, where measures approach the 50th percentile of those of Nelhaus. However, when compared to the standards of Roche, black males have head circumferences smaller by almost one centimeter by the age of 17 years. Of particular interest is the trend for black females to have larger heads, compared to both the Roche and Nelhaus charts. After the age of 10 years they have consistently larger heads ranging from .2 to .7 cm differences as seen in Table V.1. The present study will demonstrate a trend similar to this in female blacks of West Indian origin which challenges the interracial use of the standards set by Roche.

Table V.1

Age	Verghese U.S. 1963-1965 (black)	Roche U.S.1987 (caucasion)	Nelhaus 1968 (international)
Females			
5 yrs	49.2cms	50.68cms	50.55cms
6	50.4	51.16	50.52
7	51.1	51.6	51.46
8	51.3	52.0	51.6
9	51.9	52.27	51.87
10	53.1	52.65	52.15
11	53.5	53.05	52.64
12	53.9	53.5	53.01
13	54.1	53.96	53.7
14	54.4	54.21	54.04
15	54.7	54.31	54.4
16	55.1	54.45	54.64
17	55.3	54.6	54.78
Males			
5	50.5	51.8	51.4
6	51.2	52.2	51.4
7	51.6	52.5	52.2
8	52.0	52.8	52.3
9	52.4	53.19	52.5
10	52.7	53.6	53.1
11	52.8	53.9	53.25
12	52.9	54.1	53.71
13	53.8	54.4	54.1
14	54.3	55.0	54.59
15	54.9	55.5	54.9
16	55.4	56.0	55.4
17	55.6	56.4	55.77

V.B. RESULTS

The Canadian population consists of numerous ethnic and racial groups, of which many are represented in the current study. The macrocranic probands were predominantly caucasian, with one family of East Indian origin, and four black families who immigrated from the West Indies. Because less than half of the parents of the proband are of the same ethnic background, paternal origin was used for the analysis to determine if there were differences between ethnic groups. The families were divided into 6 groups, 1) French Canadians, 2) Europeans of Belgium, Austrian, or French descent, 3) Europeans,of Polish, Yugoslavian or Hungarian descent, 4) Individuals of English, Irish, or Scottish), 5) West Indian, 6) East Indian, and those of other origins not mentioned.

Standardized head circumferences of first degree relatives of probands were compiled for each of the groups mentioned, means and standard deviations were calculated, and each group was compared with a Student t-test to determine if the null hypothesis (there is no difference between each group and the study population) was true. The results presented in Table V.2 show that there is no difference between any of the groups and the study population average, except in the group of West Indian families. See Figure V.3 for graphic comparison.

V.C. DISCUSSION

Early in the study, the West Indian group was excluded from genetic analysis until standards specific for this population could be found. A letter from the University of the West Indies in Jamaica (McGregor, 1987) confirmed that there were no such standards available. Therefore a study was carried out by Rosemary Smith (McGill 1988, unpublished data) where it was found that West Indian adults now living in Montreal tend to have larger head circumferences than a group of 300 caucasian controls. This was statistically significant in the female population. (Summary of the results of this study can be seen in Table V.3). On the basis of these results the West Indian population was excluded from analysis.

Head circumference measurement is considered to be an integral part of the clinical examination of young children (Lowrey, 1978). The measure is related to intracranial volume (Bray et al., 1968) and therefore permits estimation of the rate of brain growth. Abnormal trends in growth give clues to the possibility of pathology such as storage diseases, hydrocephaly, and space occupying lesions. Therefore the need for accurate standards of comparison cannot be understated. It is important for practicing clinicians to be aware of those standards specific to ethnic or

racial populations especially in countries such as Canada and the United States where numerous groups coexist.

Nelhaus devised international standards that he felt could be used interracially. As presented in the literature review, several groups' head circumferences differ from those standards, as shown in the Israel, Japan, and British studies. The current study indicates that separate standards should be devised for West Indian blacks, and that further study should be done in the United States, to determine if North American blacks also have head circumferences warranting standards separate from those of the caucasion population, as suggested by Roche et al (1987). One American study on blacks, (Verghese et al., 1969) that showed head circumference sizes throughout childhood, demonstrated that females had larger average head circumferences than both the standards devised by Nelhaus and Roche. The early childhood measurements of the present study were not different from the standards stated. Therefore this may represent growth velocity of a different pattern than that seen in North American standards Also of interest was the study done in California of black and white infants in a prepaid health care system (Wingerd et al., 1971). Before the age of 12 months the black female infants demonstrated a trend to larger head size which was dismissed by the authors who felt that increased thickness of hair may have

been responsible for the larger measures.

This study cannot make any conclusions regarding the status of head circumferences of North American blacks, but preliminary results from this study and that of R. Smith strongly suggest that updated standards should be devised for the West Indian population. It is interesting that Japanese infants demonstrated a growth curve similar to that seen in blacks in Kingston, Jamaica 20 years ago. It may be that these infants have a genetic potential for larger heads that had been supressed by adverse conditions including malnutrition, as was suggested by the Jamaican authors (Grantham-McGregor and Desai, 1973). Recent studies show that Japanese do indeed have larger head circumferences than was previously demonstrated, and it may be found that West Indian blacks show the same trend with better conditions of the present day.

Table V.2

Comparisons of Z- scores of Head Circumference of First Degree Relatives of Probands of Various Ethnic Groups

Ethnic Group	Average H.C.	Significance*
French Canadian	1.23	NS
European1 (F/B/A)	.99	NS
European 2 (Y/P/H)	1.46	NS
British Isles (B/I/S)	1.35	NS
Other	.99	NS
WestIndian	3.54	p=.003

*Each group was compared to the study population mean with the student t-tests for significance

Table V.3

Unpublished data on Head Circumference of West Indian Adults in Montreal (Smith,1988)

	West Indian H.C.	Control	Significance*
Females	1.09	.27	p<.001
Males	.613	.405	NS

*Controls were white university students; each group was compared to controls for significance with student t-tests.

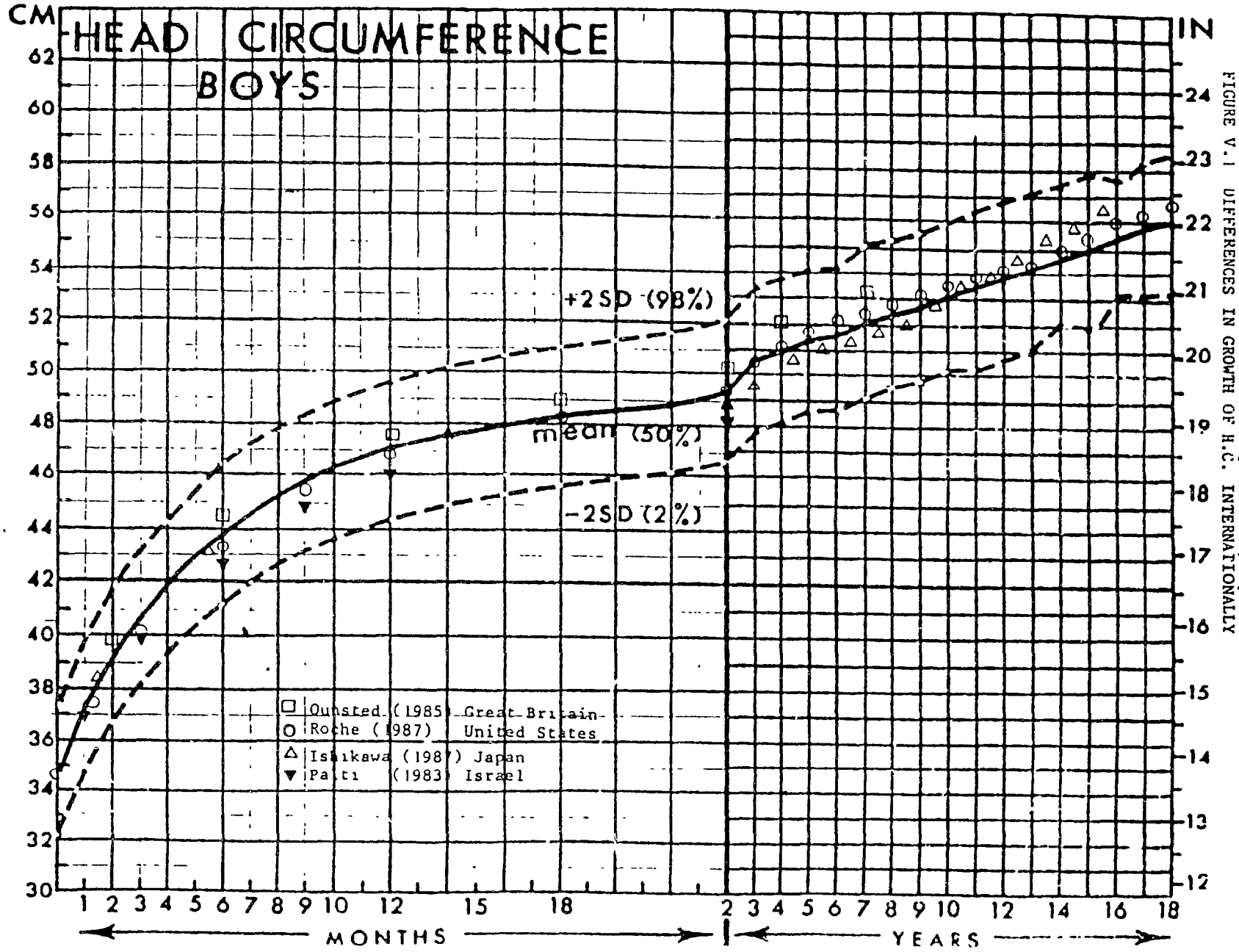


FIGURE V.1 DIFFERENCES IN GROWTH OF H.C. INTERNATIONALLY

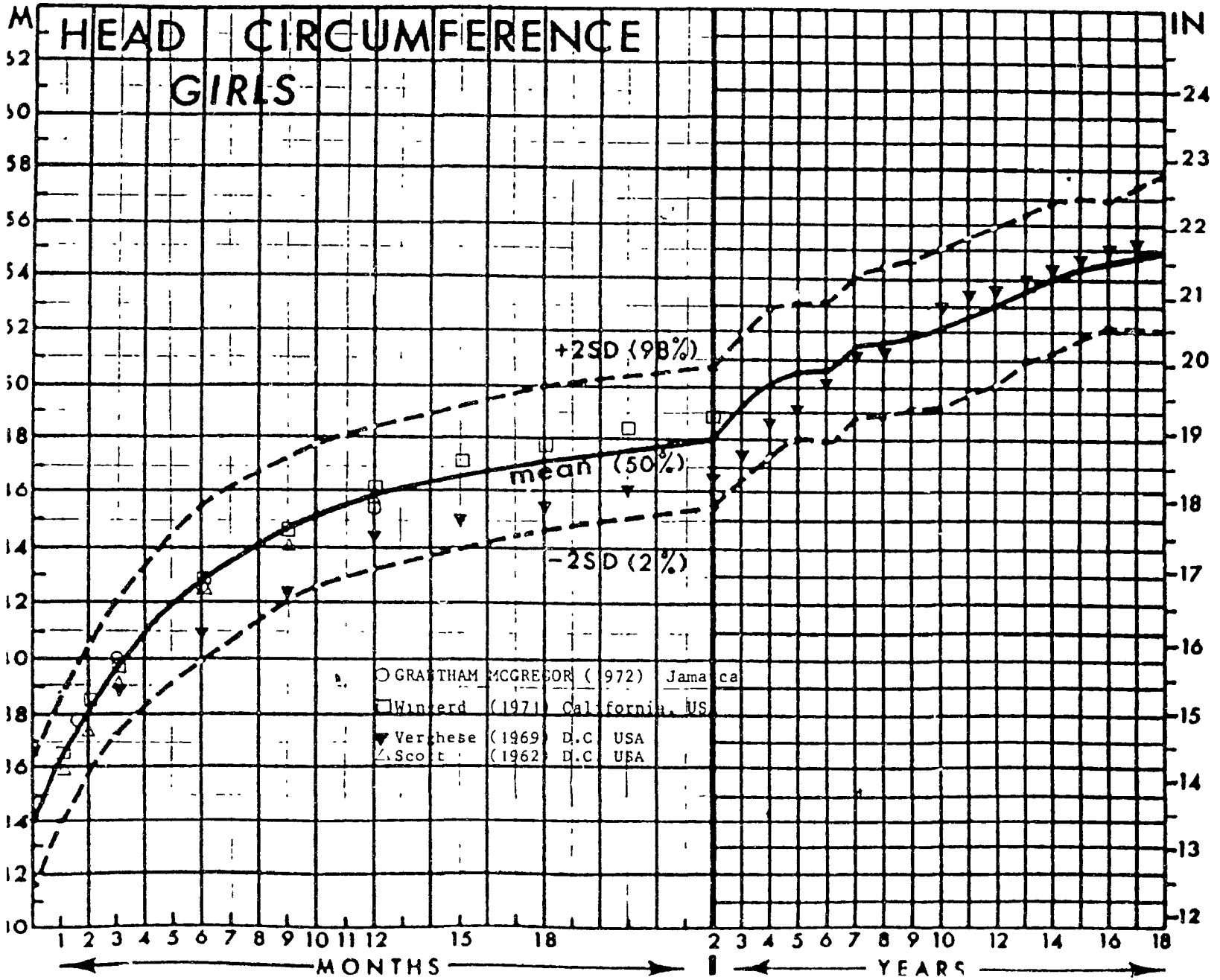
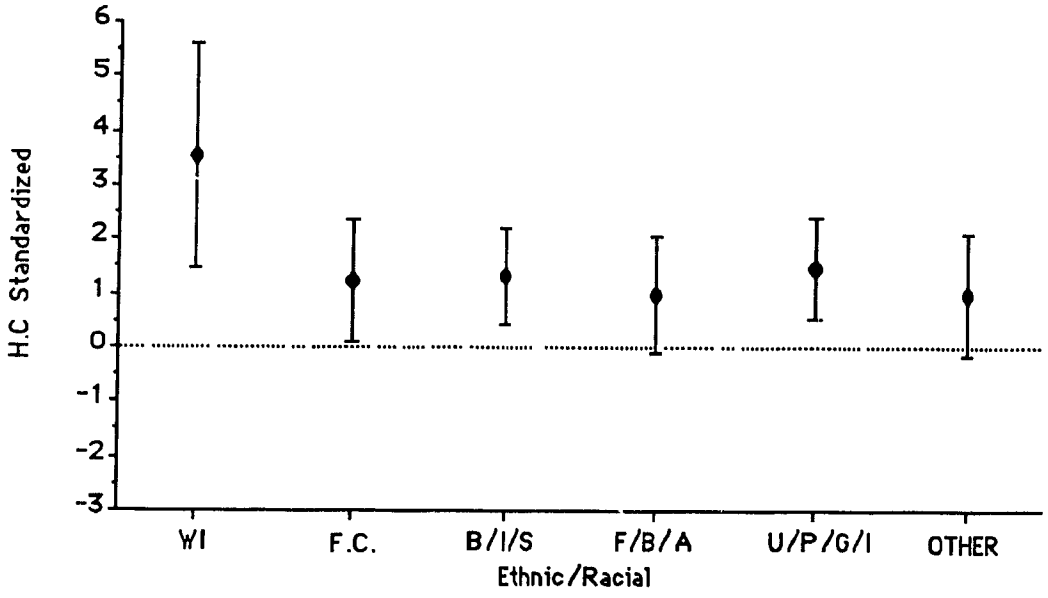


Figure V.2 COMPARISON OF 4 BLACK POPULATIONS

Figure V.3

Average Z-Scores of Head Circumference of First Degree Relatives of Various Ethnic Groups



VI. MACROCRANIA AND ENLARGED CEREBROSPINAL FLUID SPACES

VI.A. Review of Literature

That familial macrocrania is often accompanied by enlarged cerebrospinal fluid spaces is well known to clinicians and radiologists, although the basis for the relationship remains obscure. It has been postulated that a genetic defect may affect the development of the arachnoid villi, and therefore cerebrospinal fluid (CSF) absorption, linking familial macrocrania to enlarged CSF spaces (Alvarez et al., 1986).

To understand the significance of a possible relationship between familial macrocrania and impaired CSF dynamics it is necessary to review the circulation of the CSF. The main source of cerebrospinal fluid is choroid plexus, located in the roofs of the third and fourth ventricles and on the floors of the bodies and inferior horns of the lateral ventricles. The flow of CSF is from the lateral ventricles into the third ventricle via the interventricular foramina, through the cerebral aqueduct into the fourth ventricle, where it penetrates the subarachnoid space entering into the cerebellomedullary and pontine cisterns. From there CSF passes around the spinal cord and over the cerebellum, acting essentially as a "watery cushion" protecting the brain and spinal cord (Moore, 1980; Smith C., 1979).

The CSF is absorbed into venous blood mainly through the

arachnoid villi located in the dural venous sinuses. The rate of absorption is pressure dependant, with the arachnoid villi acting in a valve like manner, thus promoting absorption when CSF pressure is greater than venous pressure and preventing blood from entering the CSF when venous pressure is high.

Hydrocephaly (internal, where all or part of the ventricular system is enlarged), occurs when there is either an over production of CSF or an obstruction to its flow or absorption. A blockage in the apertures of the fourth ventricle or subarachnoid spaces will promote enlargement of all ventricles, whereas cerebral aqueduct obstruction results in enlargement of the lateral and third ventricles. Dilatation of one lateral ventricle may occur with the obstruction of one interventricular foramen. (See Figure VI.1) Communicating hydrocephaly occurs when CSF is retained within the ventricles and intraventricular pressure is increased but sagittal sinus pressure is not, resulting in a nonhydrostatic loading of parenchyma with squeezing out of venous blood, with resultant ventriculomegaly (Portnoy and Croissant, 1978).

Although enlarged CSF spaces are associated with familial macrocrania, frank hydrocephaly is only occasionally reported as being involved. A three generation kindred depicted "autosomal dominant" megalencephaly with varying levels of intelligence, and varying degrees of ventricular enlargement including two retarded

siblings with ventricular enlargement sufficient to warrant a diagnosis of communicating hydrocephalus. It was suggested that this family may have an autosomal dominant form of hydrocephaly with early arrest in most members (Shreier et al., 1974).

A subsequent study of 15 unrelated children with large heads demonstrated family histories of hydrocephaly in two of the individuals (Day and Schutt, 1979) although bona fide hydrocephaly is rarely familial. Also studies of experimental hydrocephalus show that a chronic periventricular edema of the white matter occurs when CSF pressure is increased allowing CSF to penetrate the ependymal lining (in Shreier et al., 1974). This could be a link between familial "megalencephaly" and hydrocephaly.

An association between familial macrocephaly and external hydrocephalus has also been reported. This, also termed external ventricular obstructive hydrocephaly (EVOH), is the enlargement of the subarachnoid spaces with little or no ventriculomegaly (Petit et al., 1980). These studies are summarized in Table VI.1.

Idiopathic external hydrocephalus was found to be present in 36 infants with head growth parallel to the 95th percentile (Alvarez et al., 1986). Many of these (88%) had a family history of macrocephaly, including several families with an admixture of external hydrocephalus and benign familial macrocephaly. The CT scans (computerized tomography) showed enlargement of the

subarachnoid space and frontal interhemispheric fissure and, in 10 infants, associated mild ventricular enlargement. In those infants that had repeat scans subarachnoid collections generally persisted until about 18 months of age, diminishing thereafter, and normalizing after the age of 2 years. The scans at this stage resembled those described in reports of other children with benign familial macrocephaly (Demeyer, 1972; Day and Schutt, 1979). Therefore, some macrocephalic children may have had increased subarachnoid spaces which went undetected if studies were done at an age beyond 2 years. Also of interest was the finding that 52% of the infants were developmentally delayed at 5 months, this being a transient finding, resolving by 24 months of age. The peak prevalence of reported developmental delay corresponded to the most pronounced CT abnormalities. However there was no correlation between the degree of delay, rapidity of head growth and the severity of the CT abnormalities. It was also acknowledged that it was not possible to predict long term outcome of these infants, given the higher risk for language and motor problems demonstated in children with benign megalencephaly (Lewis et al., 1983).

Other reports with similar findings are not as optimistic. The findings of enlarged CSF spaces are sometimes present in individuals with sustained developmental delay (Sahar 1978, Petit

et al., 1980). Family history of macrocrania was an occasional finding in these studies, although it was not clear how thoroughly this was investigated.

Benign subdural collections (this term is sometimes used interchangeably with external hydrocephalus) of infancy have been described in 10 macrocranic infants, all of which were developing normally (Robertson et al., 1979; Briner and Bodensteiner, 1981). CT scan results indicated not only subdural collections, which are most often seen in association with head injuries or infection, but also mildly dilated ventricles, prominent cerebral sulci, and decreased density over the convexities. CSF flow studies demonstrated a delay at the superior sagittal sinus (Briner and Bodensteiner, 1981) which is the major site of CSF drainage from subarachnoid channels over the cerebral hemispheres (Moore, 1980). This prompted the authors to postulate an impairment of CSF absorption, contributing to macrocrania. Robertson hypothesized that the impairment of CSF circulation was secondary to a mechanical block produced by the subdural collection preventing the fluid from reaching the arachnoid villi; thus the subarachnoid channels adjacent to the block would become dilated accounting for the prominent cerebral sulci, and increased CSF pressure would then be transmitted to the cerebral ventricles and result in their enlargement. No hypotheses as to the cause of

the original subdural collections were entertained nor were family histories discussed, and no genetic defect was proposed.

One report (Hood et al., 1986) linked a chromosome abnormality, 47,XY,+del(15)(pter-q15), to a mildly dysmorphic, hypotonic child, with modest ventricular enargement and prominent anterior temporal regions. CSF flow studies revealed normal flow but delayed absorption through the superior sagittal sinus. Unfortunately, whether there was a family history of macrocrania was not reported, so it is difficult to determine whether the finding of macrocrania and enlarged CSF spaces is a coincidental finding in this child or if the abnormal CSF dynamics could be attributed to chromosome abnormality.

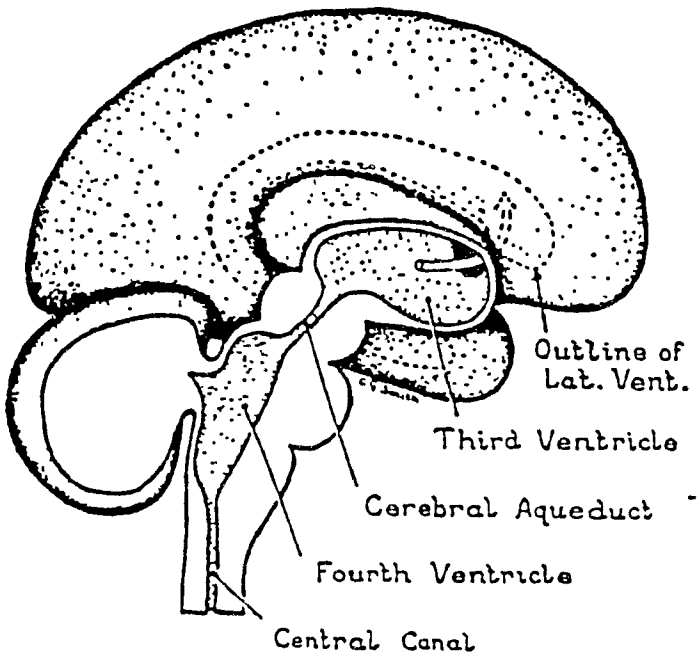
Although mechanisms have not been clearly defined for the etiology of enlarged CSF spaces, it is evident that familial macrocrania, may be associated with this phenomenon. The results of the present survey will show that no firm conclusions can be made regarding outcome in those individuals with macrocrania that have (or had) enlarged cerebrospinal fluid spaces as compared to those who do not.

Table VI.I Previous studies of abnormal intraventricular findings in children with macrocrania.

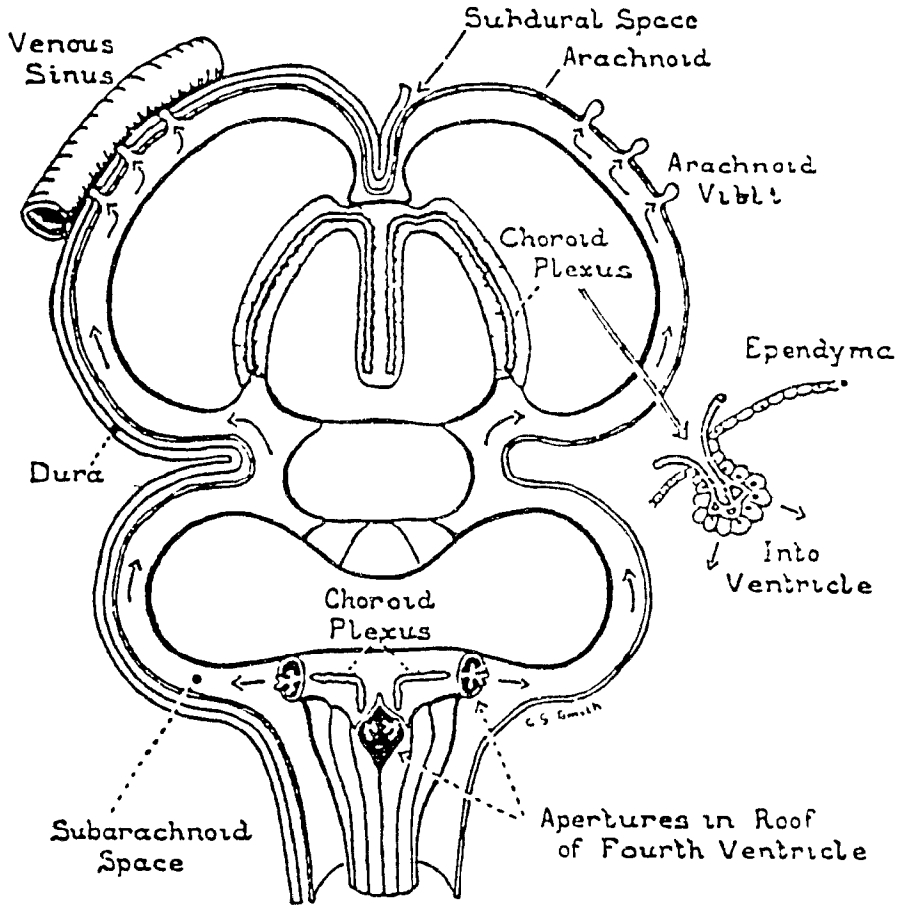
Reference	Study Group	Age	Results
Alvarez et al 1986	32 normal (14 with transient developmental delay)	infants	all had increased subarachnoid spaces with mild ventricular enlargement (resolved after 24 months)
Petit et al 1980	8 normal	infants	2 external ventricular obstructive hydrocephaly only 2 mild ventricular dilatation 2 EVOH and 2 MVD.
	7 neurological or developmental impairment	infants	1MVD 1EVOH 1 normal 4 other abnormalities.
Briner, Bodensteiner 1980	4 normal	infants	bilateral subdural collections, prominent cerebral sulci, decreased density over frontal convexities.
Robertson 1979	6 normal	infants	subdural collections, ventricular enlargement wide cerebral sulci, prominent fissures, decreased density over cerebral convexities.
Asch, Meyers 1979	5 normal (in one kindred)	1-7yrold 4 adults	3/5 enlarged 3rd and lateral ventricles.

Sahar 1978	6 intellectual or motor handicap	all<2.5 years	All had increased subarachnoid space with little or no ventricular enlargement

FIGURE VI.1



The parts of the central cavity of the brain and spinal cord as seen in a midsagittal section.



The circulation of the cerebrospinal fluid. (FROM SMITH 1979)

VI.B. RESULTS

Table VI.2 summarizes the results of cerebrospinal fluid studies as recorded in past medical records of probands in the psychomotor impaired, comparison, <2SD, and premature categories. In the PMI category 8 probands had undergone studies of this nature. of which 3 were done prior to the age of 2 years. In the comparison group, 9 probands had CSF studies of which 6 were done prior to the age of 2 years. 4 of 8 in the PMI group, 4 of 9 in the comparison group were found to have enlarged CSF spaces (not significantly different). 4 of 5 in the syndromic category, 3 of 4 in the <2SD category, and 5 of 5 in the premature group also had positive findings. These are summarized in Figures VI.3-5

Table VI.2 Pyschomotor Impaired

Patient	D.O.B.	Age at test	Test	Result
R.A.	24/02/84	3 wks	head ultrasound	Normal.
		8 mos	head ultrasound	lateral ventricles mildly dilated.
		8 mos	CT scan	as above with no evidence of progressive hydrocephaly.
		16 mos	CT scan	as above.
S.B.	07/05/84	17 mos	CT scan	Normal
		3 yrs	CT scan	Normal

P.C.	08/05/68	7yrs	echogram	Normal
L.C.*	11/03/69	7yrs 8yrs	echogram CT scan	Normal Normal
V.C.**	08/05/75		not done	
D.D.	24/12/70	9yrs 14 yrs	CT scan CT scan	Normal Normal
P.D.	23/09/62		no report	
M.G.	25/05/69		not done	
C.M.	14/04/76		no report	
R.V.	19/03/76	4 yrs	CT scan	mod enlargement of lateral and 3rd ventricles, inter-hemispheric fissure and cortical sulci are prominent.
C.S.	07/01/77	1 month	CT scan	borderline large ventricles.
E.G.***	05/02/78	9 mos	CT scan	minimal enlargement of lateral ventricles.
		15 mos	CT scan	ventricles slightly less prominent.

Comparison Group

M.I.	26/09/83	9 mos	head ultrasound	normal ventricles.
R.J.	21/04/83	11mos	head ultrasound	normal ventricles.
G.G.	28/09/81	6 wks	CT scan	mild prominence of lateral ventricles.
C.G.	07/15/81	5mos	CT scan	large prominent C.M, prominent sub-arachnoid spaces no venticular enlargement.
		14 mos	head ultrasound	
		26 mos	CT scan	CSF spaces smaller than previous scan.
W.H.			CT scan	normal
J.H.	10/02/76	2 mos	echogram	slight asymmetry of ventricles, L>R
		30 mos	CT	normal ventricles but plagiocephaly with flattening

				of right occipital and some mild flattening of left frontal area.
D.L.	03/10/84	4 mos	CT	normal
V.P.	08/06/71	6 yrs	echogram	normal
P.R.	24/06/53		not done	
A.S.	30/10/74		not done	
C.W.	31/03/87	9 mos	CT	minimal ventriculomeg no ICP
		11 mos	head ultrasound	mild bilateral ventriculomeg
Syndromic				
M.T.	11/10/74		not done	
M.A.	01/17/76		not done	
K.B.	06/11/85	12 mos	CT	large ventricles and large CSF spaces.
B.D.	23/04/86	2 mos	CT	difficult exam no gross abnormalities
		9 mos	CT	normal.
C.C.	22/04/82		CT	lissencephaly pachygyria

S.L.	22/12/22	6 mos	CT	large SAS, normal ventricles.
S.L.	26/04/79		not done	
J.T.B.	81/07/23		not done	
T. W.	70/07/23	3yrs	echogram	slight ventricular enlargement
		3yrs	pneumoenceph	slight ventricular enlargement.
D.L.			not done	

<u>≤98th percentile</u>

K.B.	02/07/82	1week	CT	normal
		5 mos	CT	normal
C.D.	17/02/80	1 week	head ultrasound	normal
S.M.	24/11/74	5 yrs	CT	large CSF spaces with minimally enlarged ventricles
A.Mi.	08/07/72		not done	
A.M.***	08/05/70	2 wks	head ultrasound	vent system normal
		9yrs	pneumoenceph	normal
		9yrs	brain scan	increased density above cerebellum (consistent with coordination difficuties)
D.S.	30/05/68	12 yrs	CT	slight asymmetry Rt>Lt ventricle.

S.S.	01/09/79	12 mos	echogram	normal
S.L.			CT	large CSF spaces normal ventricles

Premature

C.C.[1]	13/06/80	6 mos	CT	increased SAS normal ventricles.
		4 yrs	CT	normal.
M.C.[2]	05/09/81	5 mos	CT	mild ventricular dilatation
		11 mos	CT	lateral ventricles slightly enlarged
		22 mos	CT	ventricles normal
G.G.[3]	19/12/77	2 mos	CT	bilateral hypodensities in frontal parietal regions.
		3 mos	CT	increase in subarachnoid spaces paricularly in frontal region- basal cisterns and lateral ventricles enlarged.
		11 mos	CT	increased SAS around frontal lobes, frontal interhemispheric

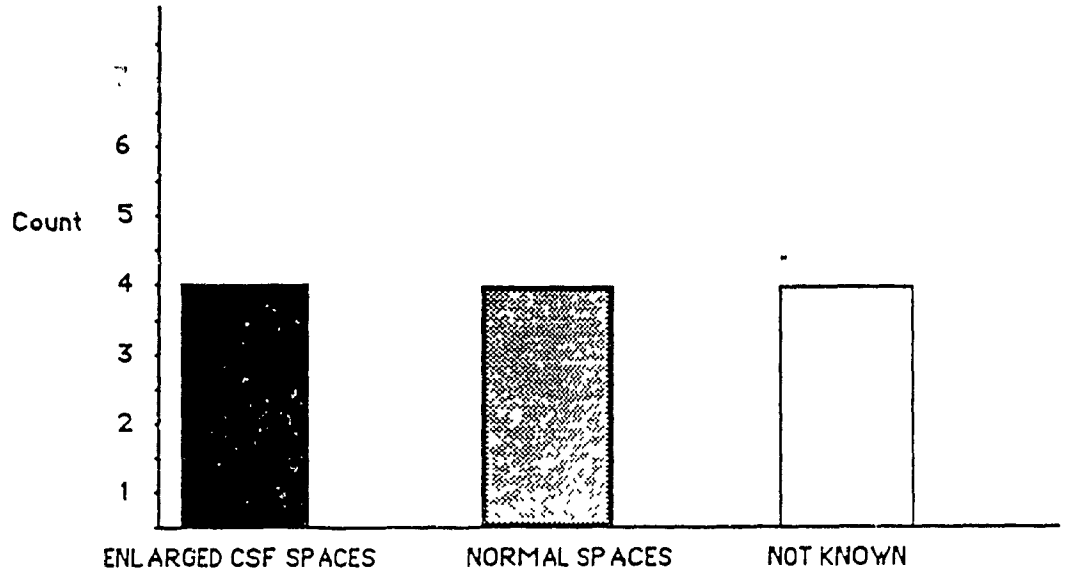
				region, basal cisterns and cerebral sulci. slight increase in lateral ventricles with asymmetry, Lt > Rt
		13 mos	CT	decrease in frontal SAS, ventricle size same.
		19 mos	CT	bilateral frontal hygroma less extensive, contour of lobes smoothed out, interhemispheric fluid less, ventricular system normal.
S. L..[4]	19/08/80	8 mos	CT	ventricular enlargement with prominent SAS.
M.K.[5]	27/02/80	4 mos	CT	mild ventricular enlargement (shunt at 4 mos)
		5 mos	CT	decrease in size
		9 mos	CT	mild enlargement of ventricles.
		5 years	CT	normal

* reported to have "arrested hydrocephaly"
** maternal aunt died as infant with hydrocephaly

***normal inellectually but severe coordination deficits
CC[1] 34 weeks gestation, 4th of quads. RDS
M.C.[2] 36 weeks gestatio, 2nd of twins
G.G.[3] 32 weeks gestation, demise of 2nd twin
S.L.[4] 34 weeks gestation, RDS, pneumothorax
M.K.[5] 37 weeks gestation, fetal distress, CAN X2, shunt at 4 mos, later evidence of primary megalencephaly with mildly dilated ventricles.

FIGURE VI.2 CSF SPACE DIFFERENCES; PSYCHOMOTOR IMPAIRMENT

N= 12



COMPARISON GROUP

N=11

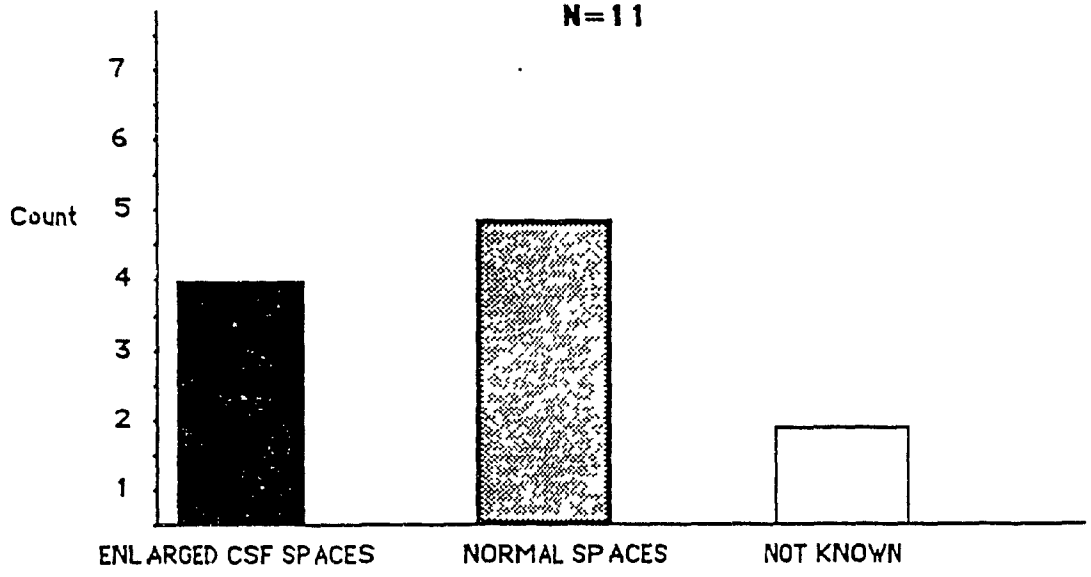
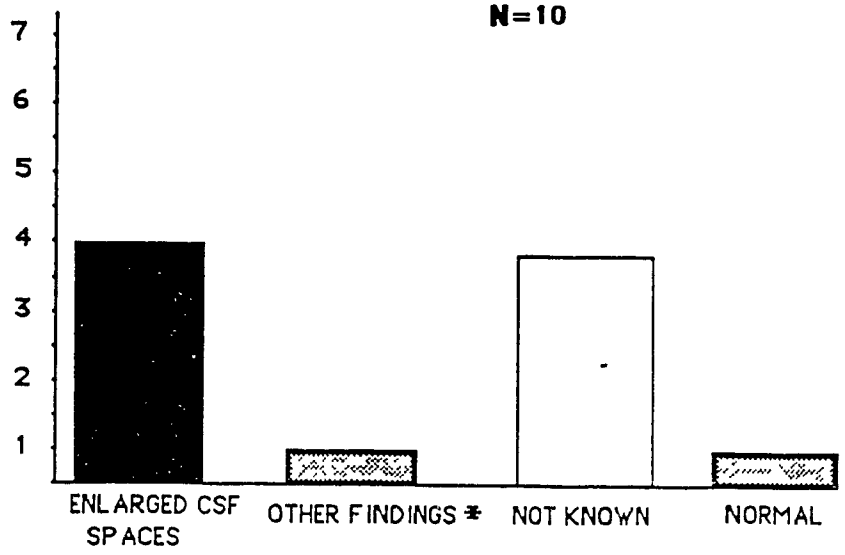


FIGURE VI.3 CSF SPACE DIFFERENCES; SYNDROMIC INDIVIDUALS

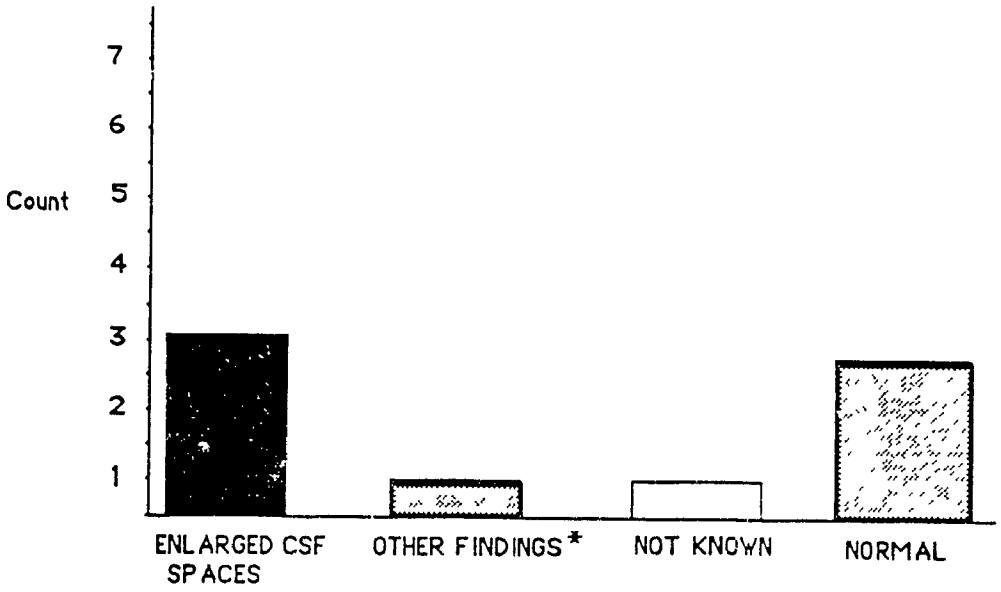
N=10



*Lissencephaly, pachygyria

< 98th PERCENTILE

N=8



*increased density over cerebellum

FIGURE VI.4 **CSF SPACE DIFFERENCES; PREMATURE N=5**

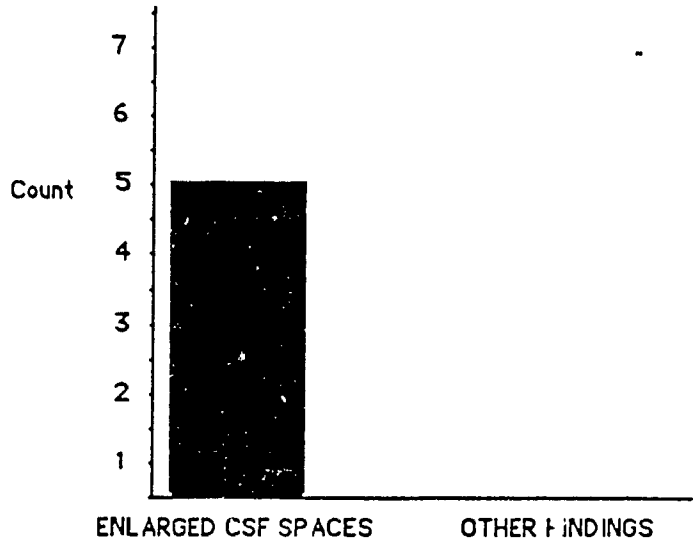
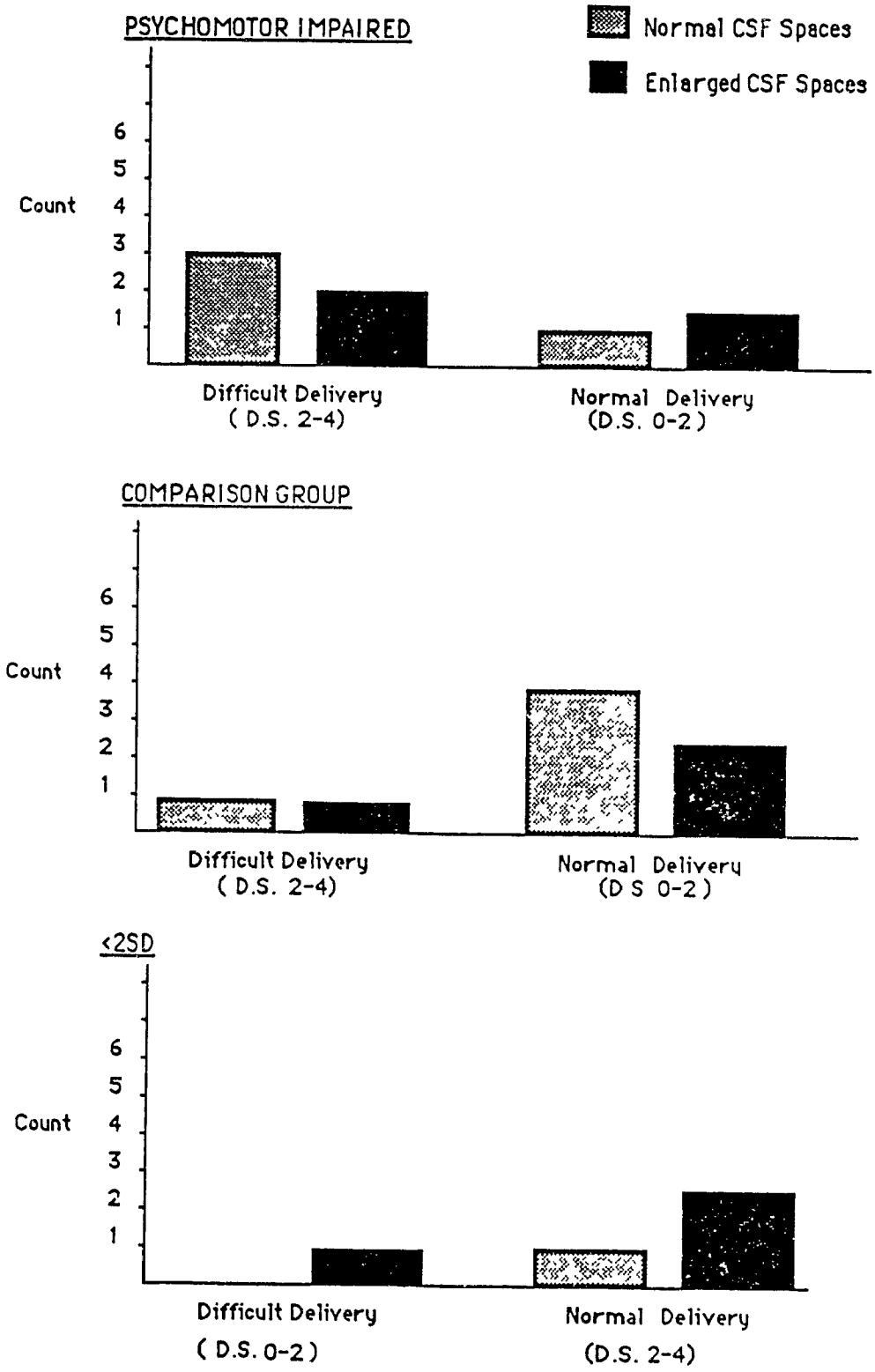


FIGURE VI.5 CSF SPACE ENLARGEMENT AND DIFFICULT DELIVERIES
(CASES IN WHICH CSF SPACES WERE STUDIED)



VI.C. DISCUSSION

The results demonstrate that for the comparison group, the PMI group and the group that are now no longer macrocranic that enlarged CSF spaces are equally as prevalent as normal sized CSF spaces and in the case of enlargement, ventricular enlargement is more common than subarachnoid space enlargement. However some individuals were not studied until after the age of 5 years, so it is not possible to know if they had enlarged spaces as infants. Two infants of the groups mentioned and three of the infants born prematurely had enlarged CSF spaces that diminished in size before the age of 18 months. This is most clearly demonstrated in the case of G.G. (prem) where studies were carried out 5 times between the ages of 2 months and 19 months. In most cases ventriculomegaly and/or enlarged subarachnoid spaces were mild, and follow-up studies were not warranted.

There was no difference in prevalence ($p=.35$, using the Fisher's exact test) or the degree of enlarged CSF spaces between the PMI group and the comparison group (Figures VI.2-.4). The numbers are small, but this is consistent with much of the literature (Petit et al., 1980; Briner and Bodensteiner, 1981; Robertson et al 1979; Asch and Meyers, 1976; Alvarez et al.,1986).

This suggests that enlarged CSF spaces are not predictive of psychomotor delay.

No relation between birth difficulty and enlarged CSF spaces is apparent in this study. (see Figure VI.5) however, it is interesting to note that all 5 of the children who were born premature had enlarged ventricles (with subsequent diminishment in at least 3). Of possible relevance is that post hemorrhagic hydrocephaly is commonly associated with prematurity, especially in those infants that have suffered birth injury . This is probably associated with a high risk for intracranial hemorrhage with prematurity. In the case that the hemorrhage is associated with the CSF circulation system, obstruction may occur causing enlargement of ventricles and subarachnoid spaces with the occurrence of subsequent hydrocephaly (Lorber and Bhatt, 1974). It is conceivable that partial obstruction could occur leading only to mild or moderate ventriculomegaly. A radiology report suggested that benign subdural effusion of infancy may be secondary to gradual subdural bleed, possibly occuring as a result of tearing of small bridging blood vessels as the head molds during labor and delivery (Helfinger and Young, 1984).

Four of the five premature children, however, continue to have macrocrania, even after ventricular size has diminished and

first degree relative measurements of this group are consistent with those found in the rest of the study implying that the primary nature of the macrocrania in these children is familial rather than secondarily associated with hydrocephaly. Dunn et al., (1986), in a study of 275 low birth weight infants found that 6/275 had head circumferences greater than 2SD above the mean at the age of 1 year (this is the expected 2% population frequency). Five were preterm appropriate for gestational age and one was small for gestational age.

Also, the infants in this group were followed closely from very early ages with a minimum of two studies of CSF spaces done on each child. Many of the children in the other groups were not studied as closely, therefore it is not possible (without bias) to comment on the prevalence of enlarged CSF spaces in these premature infants as compared to the rest of the macrocranic induviduals under study.

In conclusion, 1) Enlarged CSF spaces associated with macrocrania are of little predictive value for psychomotor impairment; 2) No conclusion can be reached regarding a genetic defect that may predispose to both altered CSF absorption and macrocrania; 3) This study does not show evidence that there is an association between enlarged CSF spaces and difficult deliveries,

although one report in the literature suggests that subtle injury occurring with molding of the head during the delivery may lead to enlarged subdural spaces; 4) the fact that all 5 premature babies had enlarged ventricles and macrocranic families suggests that the macrocrania may predispose to enlargement of the ventricles.

VII. MACROCRANIA AND DIFFICULT DELIVERIES
VII. A. Review of the Literature

The question of whether stress during labour or delivery can result in brain damage is a complex one. For one thing, it is difficult to assess whether a brain damaged infant was damaged simply by the stress of normal labour and delivery, or whether previous compromise for other reasons has made it more susceptible to these stresses.

The vast literature on the subject remains controversial and inconclusive Few papers supporting one view are left unchallenged by those with an opposing view. A recent study presented evidence that some mental retardation previously thought to be directly related to traumatic birth, appeared on autopsy not to be. In a state hospital for the mentally retarded 258 records of patients diagnosed with mental retardation secondary to birth injuries were examined (Chaney et al., 1986). The diagnosis of mental retardation as a result of birth injury in half of this series were not confirmed by subsequent diagnosis. Even though injury may have occurred at delivery, prenatal or postnatal events (toxoplasmosis, meningitis, metabolic disorders) were considered to be the primary cause of the mental retardation. One example of this was a post mortem study of a profoundly retarded, microcephalic, epileptic, 20 year old who was considered to be retarded because of a difficult forceps delivery which caused

significant bruising and a misshapen head. The study revealed that the primary cause of mental retardation was lipochondrodystrophy with generalized atrophy, and vacuolization of the basal ganglia, exemplifying the importance of thorough clinical investigation before labelling.

Mental subnormality, brain damage, and cerebral palsy have numerous and complex causes and can occur without difficult labour and perinatal hypoxia (Illingsworth, 1985). Seventy-five percent of children in whom cerebral palsy developed had normal Apgar scores at birth. (Committee on Fetus and Newborn, 1986). Defects intrinsic to the fetus may contribute substantially to morbidity, as demonstrated by evidence of IUGR, congenital abnormalities, infections and a maternal history of previous miscarriage or stillbirth in children with cerebral palsy (Illingsworth, 1985; Nelson and Ellenberg, 1986: Pharoah et al., 1987).

However, "it would be absurd to suggest that brain damage cannot occur during labour and delivery" (Illingsworth, 1985), and it should be noted that 49% of the individuals in Chaney's study were mentally retarded without any cause other than birth injury found. Therefore it is important to determine which individuals will be at increased risk and how to diminish the number of these cases. The majority of traumatic births result in a favourable outcome (Donn and Faix, 1983). Some, however, are associated with

long term sequalae of which it is estimated that 50% could be avoided (Amiel-Tison, 1974). Most traumatic births are associated with predisposing risk factors including malpresentation, pelvic dystocia, forceps-assisted deliveries, cephalopelvic disproportion, and fetal macrosomia (Donn and Faix, 1983).

A significant number of intellectually impaired children in the current study have a history of difficult deliveries; therefore of particular interest for this paper are 1) forceps assisted deliveries 2) cephalopelvic disproportion (dystocia) and 3) macrosomia, since the large head may be contributing to an obstructive delivery.

Delivery by means of forceps is indicated for both maternal and fetal reasons, in order to terminate labour faster and more safely than is possible naturally. Some of the reasons include maternal cardiac illness, intrapartum infection, exhaustion, fetal distress, and placental abruption. The risks associated with forceps assisted deliveries differ depending on the type of delivery. Low forceps delivery is defined as one in which the instruments are applied after the fetal head has reached the perineal floor (associated with low risk). High forceps deliveries are those which occur prior to engagement (vertex at the level of the ischial spines) and is discouraged from use in modern obstetrics because of substantial risk of injury to both mother and fetus. Mid forceps include the range of deliveries that occur after

engagement but prior to the head reaching the pelvic floor with a large range of associated risk reported (Pritchard et al., 1985).

Short and long term morbidity , in the form of fetal trauma, death, cerebral palsy, and decreased intelligence, has been shown to occur with the use of midforceps. In a study that compared 485 midforceps deliveries with 17 cesarean sections, where the indication for cesarean was a completely dilated cervix but failure of rotation of the head. Morbidity in the forcep group was 30% with no morbidity found in the section group. (Hughey, 1978). Consistent with this view Bowes and Bowes (1980) demonstrated 20% morbidity with the use of midforceps compared to 5% in cesarean deliveries. However, Dierker et al., (1986) while attempting to match midforceps with cesareans for indications of fetal distress or dystocia found that long term outcome of infants (developmental delay, neurological deficit) was not significantly different (5% vs 7%) between the groups, implying that indication for delivery would be a better predictor for long term sequelae since the delivery method would not alter outcome. In spite of the results this group did not advocate increasing the proportion of difficult midforceps deliveries, as opposed to cesarean sections, even though it was stated that selected midforcep delivery could be performed without greater risk of an abnormal outcome.

Macrosomic infants (birthweights greater than 4000 gms as defined in Williams) have large head circumferences proportional

to their increased body weight. Therefore, even though the average birth weight of infants in this study is that of average Canadian population standards, (see table VII.1), the head size at birth is equal to or larger than those considered to be macrosomic (see Figures VII.2 and VII.3). Thus, it is relevant to explore the literature regarding macrosomic infants and their deliveries.

Although it is reported that macrosomic infants do not experience more fetal distress, birth asphyxia, post asphyxic convulsions and cerebral signs than smaller infants there is an undisputed risk for birth injuries due to difficult deliveries implicating the delivery itself as the most dangerous time for the excessively large infant (Lazer et al., 1986; Parks and Ziel, 1978; Modanlou et al 1980; Boyd et al.,1983). The cause of the difficult delivery is a result of manipulation when the large head, and the equally large shoulders are being delivered. Dystocia may arise when an excessively large head attempts to pass through a normal pelvis. (Pritchard et al., 1985). The bones of the fetal calvaria are separated by dense connective tissue which allows for slight overlapping (molding) of the frontal, parietal, and occipital bones during labour thus facilitating passage of the fetal head through the maternal pelvis (Moore, 1980). These changes are not generally harmful to the fetus, but marked distortion (greater than 0.5 cm decrease in biparietal diameter) can lead to tentorial tears, fetal intracranial hemorrhage and cerebral injury (See Figure VII.1).

Cephalopelvic disproportion encourages medical intervention either with midforcep deliveries or C-Sections (Pritchard et al., 1985).

In a review of midforcep deliveries Cooke (1967) differentiates between difficult and easy midforcep deliveries, stating that 90% of fetal trauma was included in the group defined as difficult. It may be that a higher proportion of macrosomic infants are included in the "difficult" group. This view is supported by Boyd et al. who analysed morbidity of macrosomic infants (>4000 gms) according to type of delivery. They found that a morbidity rate of 14/1000 with spontaneous delivery and 17/1000 with low forcep, jumped almost five fold to 82/1000 with the use of midforceps.

It was interesting to note that a high rate of morbidity with C-Section was reported (40/1000). The authors concluded that a large infant may be difficult to deliver even through an abdominal incision.

Rates of congenital abnormalities are not increased in macrosomic infants (Modanlou et al., 1980; Spellacy et al., 1985) and a study of 86 oversized infants (Khwaja et al., 1986) concluded that although overall morbidity was high in the study, there was no difference between the outcome of infants of diabetic or nondiabetic mothers supporting the view that morbidity is largely due to mechanical difficulties during the

delivery and not intrinsic to the fetus in these cases.

At this time it is not clear that difficult deliveries will lead to brain damage sufficient to cause the speech and learning difficulties and mental retardation observed in the psychomotor impaired group of this study. (Dierker et al., 1986; Varner, 1983; Low et al., 1983; Kadar, 1985; Friedman, 1987). The term birth injury has been used synonymously for physical (birth trauma) and hypoxic ischemic events (Sankaran and Krishan, 1987). Therefore there is a need for further study that differentiates between the two, even though it is difficult to separate the confounding effects of disorders intrinsic to the fetus that may increase the risk for poor perinatal outcome. Interestingly, one study in which the population was chosen from the Collaborative Perinatal Study, found that four year olds that had been born weighing greater than 4100 grams (females) and 4250 grams (males) were significantly more likely, 23% vs 10.6%, to have subnormal IQ's than those of standard weights (>2500 to macrosomic criteria). No cause for this could be ascertained since there was no evidence that the macrosomic group were more likely to have congenital abnormalities or neurologic sequelae. Birth histories were not discussed and further study was recommended (Babson et al., 1969).

VII.B RESULTS

The differences between the perinatal histories of the study group (psychomotor impairment and comparison groups) will be evaluated closely, and a brief summary of the other groups will be presented.

The overall incidence of breech presentation at birth for the study was 12% which is three times as high as is found normally, (Pritchard et al., 1985) All of the PMI group were vertex presentation whereas 3 infants (16%), of the comparison group were breech presentation.

The average birth weight of the entire study population, excluding prematures, was 3250 grams and 3540 grams for females and males respectively which is not statistically different from Canadian population standards (Blidner 1984). The PMI group had a greater average birthweight than the comparison group, 3611 and 3400 grams, but this was not a statistically significant difference. Two infants in the PMI group had birth weights slightly greater than 4000, whereas the largest infant in the comparison group was 3700 grams. The average weights of all groups can be seen in Figure VII.2

Reports of head circumference at birth were obtainable in 24 of 32 individuals (excluding WI, syndromic, and prematures), and average head circumferences for both males and females were significantly greater ($p<.01$) than Canadian population standards (Blidner, 1984) as is shown graphically in Figure VII.3 The PMI

group had the largest average head circumference, significantly larger than the comparison group (37.5 vs 35.7 cms $p<.01$).

A delivery difficulty score was devised to identify those infants most likely to have been at risk for birth injury. The scoring system used can be seen in Table VII.2 where 0 signifies a non-traumatic spontaneous vaginal delivery and elective Cesarean section, and the highest score of 4 was given if there was a report of trauma at delivery. Therefore a score of 0-2 represents a reported easy, low risk delivery, and a score of 3-4 signifies a difficult, higher risk, delivery. The PMI group demonstrated a greater number of infants that experienced difficult or traumatic deliveries, however, by statistical analysis using Fisher's exact test, the level does not quite reach the 5% level of significance ($p=.06$).

In each group, there was one infant that suffered fetal distress during labour; these were removed from the study group because it is difficult to determine if the reported difficulties were related to macrocrania. One infant, (W.H.), in the comparison group, was delivered by C-section prompted by fetal heart decelerations with reported good outcome. The infant from the PMI group was delivered by spontaneous vaginal delivery, with meconium stained amniotic fluid, (signifying that there has been an episode of fetal hypoxia), and apgar scores of 4 and 7. There was evidence of cord compression, with the cord wrapped around the

neck once, and it was noted that the head circumference was 36.5. cm. Thus, although the large head size may have contributed to a prolonged delivery, the cord compression may have been equally responsible for the baby's condition.

VII.C. DISCUSSION

Breech presentation was at least three times greater in the macrocranic study population than the general population (12% vs 3-4%). Although the sample size prevents firm conclusions, this could be expected with a larger than average head circumference. It is common for a fetus to be in the breech position at the end of the second trimester with subsequent change to vertex prior to delivery. However, in the case of abnormality, such as anencephaly, hydrocephaly, oligohydramnios, and uterine anomalies such as fibroid tumors where the fetus is unable to be positioned easily in a head down position, it is more likely that it will stay in a breech presentation (Pritchard et al.,1985). Since the infants under study had larger heads than normal, it would seem reasonable that there would be a higher incidence of malpresentation. No difficulty was reported in association with these deliveries, two were delivered by elective cesarean delivery and one was an easy spontaneous delivery.

The average birth weights of the infants in the study group

are close to population standards. However head circumference is significantly greater at delivery, thus presumably contributing to a higher risk for difficult delivery. As previously stated, macrosomic infants (birthweights > 4000 grams) have proportionately large heads. The average head circumference is 36 centimeters at 4000 grams, which is just one centimeter greater than average population standards. However previous evidence demonstrates that morbidity increases in these infants as a result of difficult delivery which is in part due to a large head passing through a normal sized pelvis. Also the risk for morbidity increases with the extent of intervention required as was clearly demonstrated by Boyd (1983). Although there is evidence in the literature that macrosomia is related to increased risk for birth injury, no report to our knowledge discusses head circumference and its contribution to difficulty. The average head circumference at birth of the study population was 36 8 centimeters. This is at the 98th percentile for a 4000 gram infant. It would seem, therefore, that infants with large heads, regardless of birthweight are at increased risk for obstructive delivery.

The case of C.S. of the PMI group demonstrates this point. C.S. was the third child of healthy non-consanguinous parents. Two previous deliveries were uneventful, with the last child weighing 3500 grams. There was no warning that this infant would be at risk for a difficult delivery since it appeared to be approximately

the same size as the previous child at birth. Forceps were applied and after 13 minutes of a difficult rotation C.S. was delivered in an occiput transverse position, with apgars of 5 and 8, a weight of 3600 grams and a head circumference well over the 98th percentile at 39 centimeters. Although she was flaccid and pale resuscitation was not necessary.

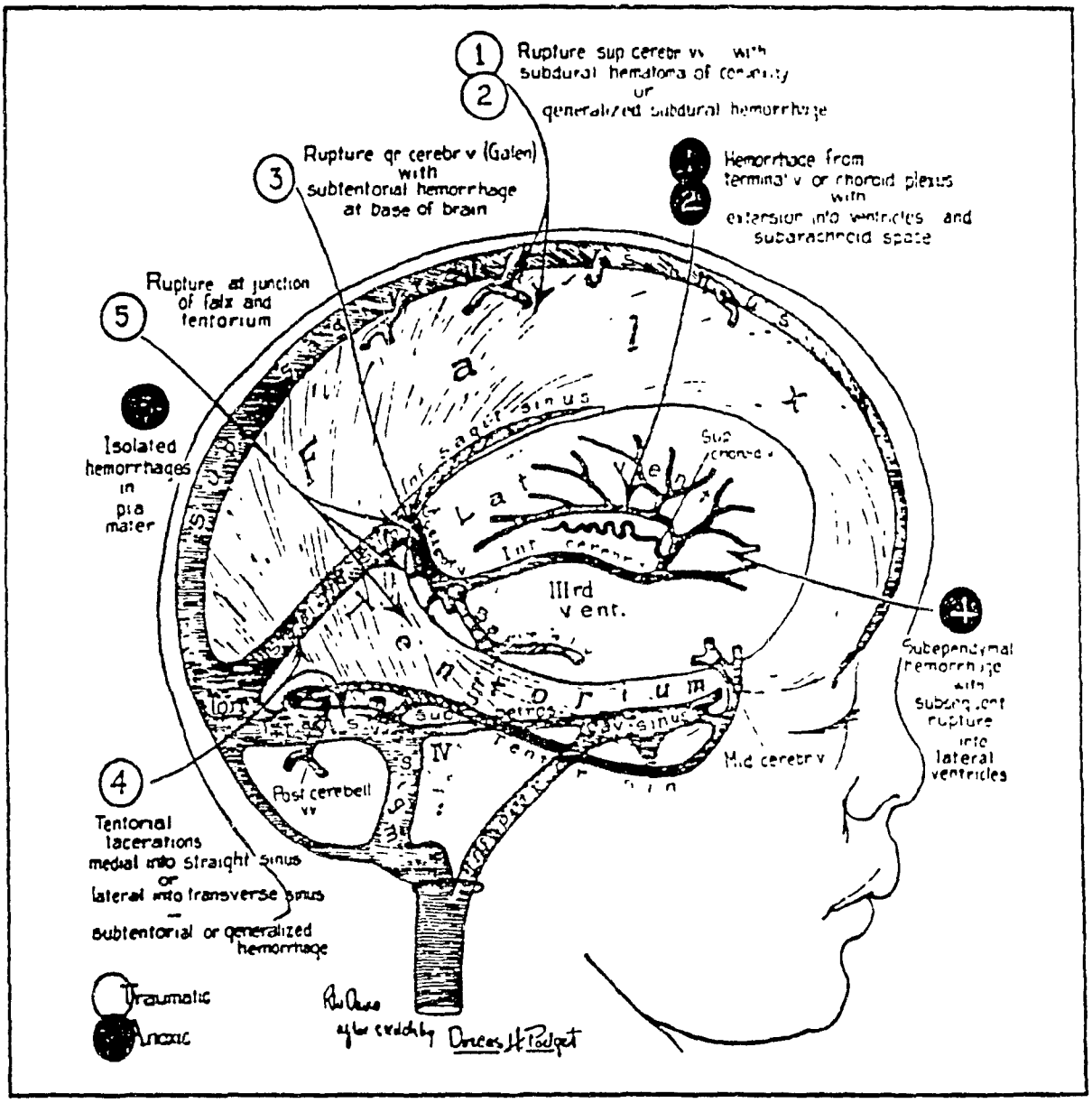
It is important to remember that not all babies with large heads will have difficult deliveries. The largest head circumference at delivery in this study was that of M.A. (PMI group) with a measurement of 40.5 centimeters. He was the fourth child of healthy parents weighing 4100 grams after an easy spontaneous vaginal delivery. This suggests that the risk for injury is also influenced by the size of the maternal pelvis.

There is little information that firmly links difficult deliveries with the long term sequelae seen in this study such as learning difficulties, mental retardation, and coordination difficulties. The main reason for this is that because it is difficult to separate causes for such sequelae that are intrinsic to the fetus versus damage at the time of delivery. In the study population there were no more congenital abnormalities, no reports of intrauterine growth retardation, no more reports of previous miscarriages or of prenatal infections in the psychomotor impaired group than in the unimpaired group. The increased frequency of difficulty in probands with psychomotor retardation,

though not quite at the 5% significant level, (p=.06) may be an indication that macrocranic babies are at increased obstetrical risk and deserves further investigation.

The degree of increased risk for difficult delivery or psychomotor impairment cannot be stated at this time. Until a prospective, long term study of macrocranic infants is done to confirm this hypothesis, guidelines can be borrowed from those of macrosomic infants. That is, the larger the head the greater the risk for morbidity associated with the delivery, taking into consideration maternal factors of course. Obstetricians have studied predisposing factors that allow clinicians to predict when a fetus is at risk for macrosomia, and thus predisposed to birth injury (Modanlou et al., 1980; Spellacy et al , 1985) This study suggests that familial macrocrania may be another factor predisposing infants to birth injury, and an awareness of this may help reduce the risks for psychomotor impairment presently seen with non-syndromic familial macrocrania.

FIGURE VII.1 SITES FOR POTENTIAL INTRACRANIAL HEMORRAHAGE WITH PERINATAL INSULT.



(Haller 1956 in Pritchard 1985)

FIGURE VII.2 **AVERAGE BIRTH WEIGHTS (EXCLUDING PREMS)**
(ONE STANDARD DEVIATION BARS)

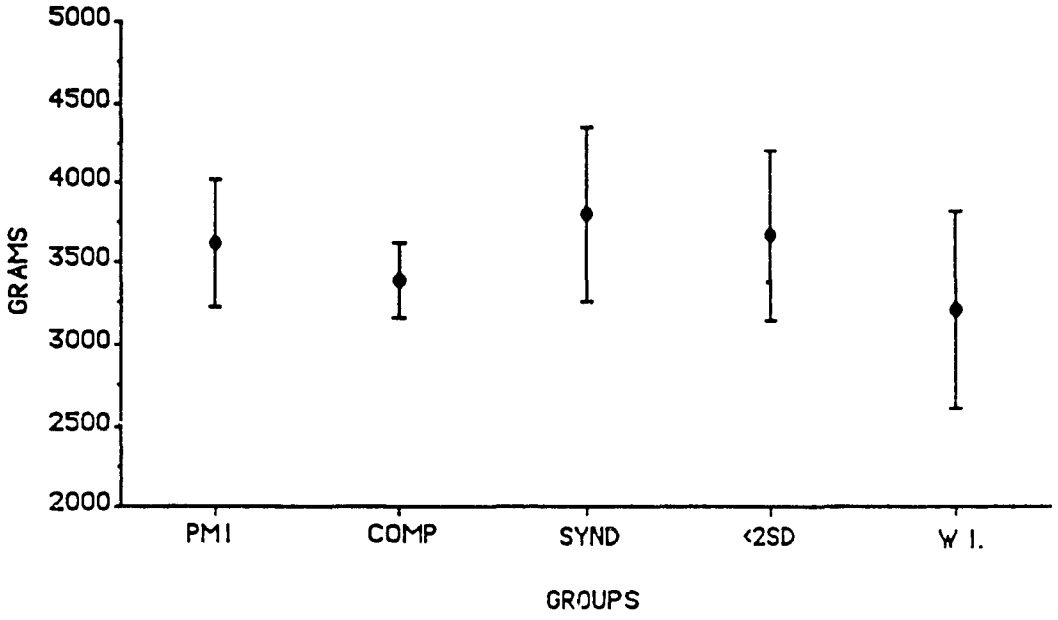
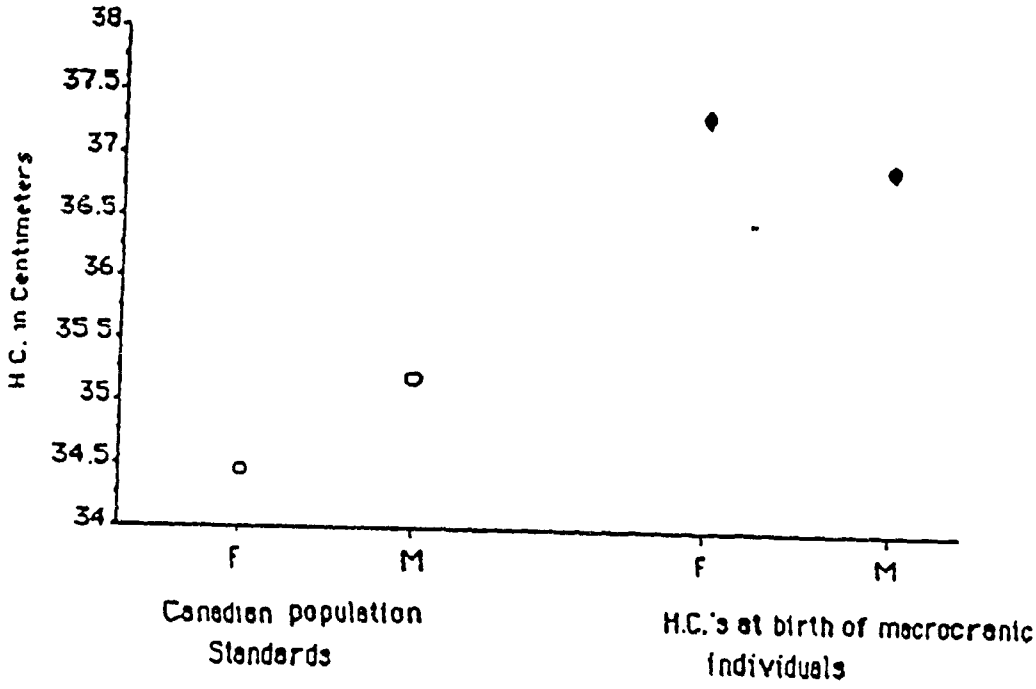


TABLE V11.1 Measurements at birth of macrocranic probands compared to Canadian standards (Blidner et al ,1984)

SEX	BIRTHWEIGHT	STANDARD*	SIGNIFICANCE
F	3442	3355	NS p= 35
M	3665	3530	NS p= 18
SEX	BIRTH H.C.	STANDARD*	SIGNIFICANCE
F	37.0 cms	34.4	S p<.01
M	36.7cms	35.2	S p<.01

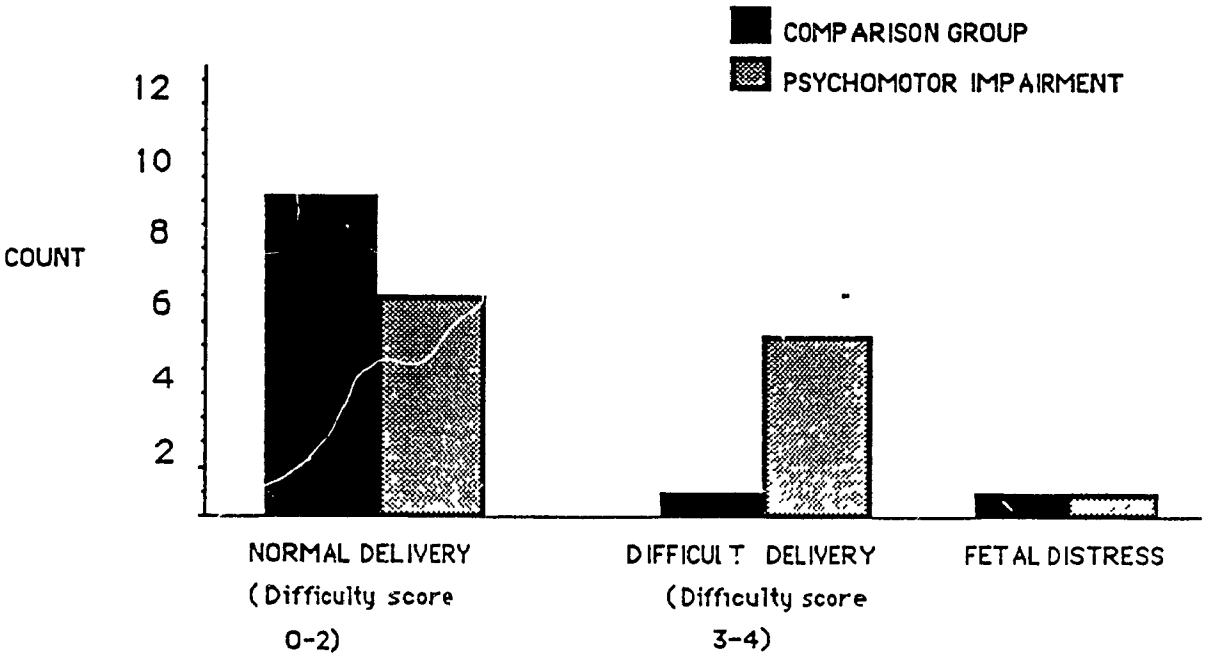
FIGURE VII.3

AVERAGE HEAD CIRCUMFERENCE AT BIRTH



Head circumferences at birth of individuals under study are significantly larger than population standards for both males and females ($P < .001$).

FIGURE VII.4 **DIFFERENCES IN PERINATAL HISTORIES BETWEEN PSYCHOMOTOR IMPAIRED AND COMPARISON GROUP PROBANDS**



Psychomotor impaired individuals are more likely to have had a difficult delivery than unaffected macrocranic individuals ($p = .06$).

TABLE VII.2

* DETERMINATION OF LEVEL OF DIFFICULTY DURING DELIVERY

SCORE	TYPE OF DELIVERY
0	SPONTANEOUS VAGINAL DELIVERY
0	ELECTIVE CESAREAN SECTION
1	LOW FORCEP DELIVERY
2	EASY MID FORCEP DELIVERY
2	CESAREAN DELIVERY AFTER LABOUR
3	CESAREAN DELIVERY AFTER TRIAL OF FORCEPS
3	DIFFICULT MID FORCEP DELIVERY
4	EVIDENCE OF TRAUMATIC DELIVERY

VIII. MACROCRANIA AND SYNDROMES

VIII.A Review of the Literature

The word syndrome is derived from the Greek words syn (together)+ dromos (running). Medically this implies a concurrence of signs and symptoms associated with a morbid process (Stedman, 1972). One of the most difficult problems a geneticist faces is to determine whether a group of dysmorphic features occurring together in an individual constitutes a syndrome, (thus associated with a single cause) or are coincidental independant findings. In the case that a syndrome can be defined by conclusive diagnostic tests, as with chromosomal aberrations, the diagnosis can be made with little difficulty, but because many dysmorphic syndromes at this time are not represented by a clear cause the diagnostician is left with the "syndrome by definition" approach which can be very subjective. This demands a knowledge of previously published cases, where features known to occur together are often named for the first person who characterized the syndrome. This is not a clear cut process because it is well known that a single cause will result in variable phenotypic expressions of the same entity (Nora and Fraser, 1974). An example of this is the simian crease associated with Down syndrome. World-wide studies of its frequency have found that it is associated with trisomy 21 in

aproximately 50% of the cases (Preus and Fraser, 1972). Prader Willi syndrome is presumably a contiguous gene syndrome caused by a deletion at 15q11. The associated features of hypotonia, hyperphagia, small hands and feet are commonly known. Fifty percent of those infants diagnosed as having the syndrome do not have a deletion detectable by current cytogenetic means and in these cases diagnosis becomes subjective (ie. can a child with hypotonic features, signs of hyperphagia, but normal sized feet be diagnosed as Prader Willi syndrome?). Sophisticated molecular techniques that will detect microscopic deletions are currently being developed and will be helpful in these cases (Schmickel, 1986) In the current study, a knowledge of phenotypic findings that would depict a "syndromic" individual was essential since in such cases both the phenotype and the family pattern would not be representative of the group under study. Intellectual deficit in these cases would likely be related to the same morbid process that caused the unusual features and would be the subject of the study of that particular syndrome.

The cause of the large head associated with syndromes is often unknown but in the case of metabolic disease is sometimes a result of accumulation of lysosomal degradation products, as in the case of mucopolysaccharidoses, which are neurologically degenerative, single gene disorders, usually autosomal recessive.

In Sanfilippo syndrome (mucopolysaccharidosis III) the large head is a result of a thickened skull (McKusick, 1983). Also, in bone dyscrasias such as osteopetrosis and sclerosteosis, the associated large head may be caused by a thickened skull. Intracranial neoplasms and calcification may be responsible for macrocrania in the phakomatoses group of disorders (neurofibromatosis, tuberous sclerosis, Sturge Weber syndrome) but may also be an incidental finding (Riccardi, 1981 and 1983).

Achondroplastic individuals have larger endocranial areas (the lining of the cranium) than normal controls (Cohen et al., 1985). Controversy surrounds the actual cause of the enlarged calvaria in achondroplasia with some authors advocating true megalencephaly (Dennis et al., 1961), and others, more convincingly demonstrating evidence of enlarged ventricles including communicating hydrocephalus which is postulated to result from CSF outlet obstruction due to a small posterior fossa, or CSF obstruction at the subarachnoid villi secondary to retrograde pressure from jugular veins (James et al., 1972, Mueller S.M., 1977).

Some of the syndromes commonly associated with macrocrania, and therefore looked for in the study population are Fragile X, cerebral gigantism (Soto's syndrome) Ruvalcaba-Myhre-Smith syndrome, Bannayan-Zonana syndrome,

tuberous sclerosis, neurofibromatosis, Weaver syndrome, the achondroplasias, and metabolic disorders (Hunter, Hurler). Features of these and other syndromes are found in Tables VIII.1 and VIII.2. These are presented in a manner that may aid in the differential diagnosis of macrocephaly syndromes by placing those with distinguishing signs that are similar to one another in close proximity in the table. For example the Marshall-Smith and the Weaver syndromes have similar characteristics (and sometimes individuals have features of both), as do the Ruvalcaba-Mhyre-Smith and the Bannayan-Zonana Syndromes. An alphabetical guide is presented in the appendix.

TABLE VIII.1 Metabolic Disorders Commonly Associated with Macrocrania

Disorder	metabolic defect	Genetics and Clinical Features
GM1 gangliosidoses	ß-galactosidase-1 deficiency	(AR) Types 1-3: Infantile, Juvenile,Adult onset, coarse features, short stature, hypotonia/hypertonia, dysostosis multiplex. (McKusick, 1983)
GM2 gangliosidosis	Hexosaminidase deficiency	(AR) Onset first year of life, neurological regression, deafness, seizures, blindness, macular-cherry red spot, death in early years. (McKusick, 1983)
Mucopolysaccharidoses MPS-1-H (Hurler)	alpha 1-iduronidase deficiency	(AR) coarse features, corneal clouding, hepatosplenomegaly, dysostosis multiplex, mental retardation, joint contractures, death usually before age 14 years.(McKusick, 1983)
MPS-2 (Hunter)	Iduronate sulphate sulphatase defect	(XR/AR) clear cornea, milder phenotype than MPS1-H, mild mental retardation or normal intelligence, survival to adulthood.(McKusick, 1983)
MPS-6 (Maroteaux-Lamy)	Arylsulphatase B deficiency	(AR) MPS-1-H phenotype but normal intelligence, joint contractures, visual loss, variable degrees of severity, may survive until third decade. (McKusick, 1983)
MPS-3 (Sanfilippo) A-D	(A) Heparan-S-Sulphaminidase (B) N-ac-alpha-	Coarse facies, dense hair, Subtypes dysostosis multiplex, progressive dementia, agression, clear

	D-glucosaminidase (C)N-acetyltrans-ferase (D)N-ac glucosaminase-6 sulphate sulphatase	cornea. Survival may be until mid adulthood. (McKusick,1983)
Cerebrohepato-renal (Zellweger)	absent peroxisomes	(AR) severe hypotonia, (Wilson G.N. 1986)
Neonatal Adrenoleuko-dystrophy	peroxisomal defect	(AR) hypotonia, seizures, developmental delay, neurologic deterioration, cataracts. (Kelley et al., 1986)

TABLE VIII.2 Syndromes Commonly Associated with Macrocrania

Name (synonyms)	Genetics	Intellectual ability	Clinical Features
Cerebral gigantism (Soto's syndrome) (1)	AD	variable mental deficiency	large span, large hands and feet, advanced bone age, prognathism, high,narrow palate, variable mental deficiency, enlarged cerebral ventricles. (Bale et al., 1985)
Bannayan-Zonana syndrome (2)	AD	speech delay, mild mental retardation	cutaneous lipomas, hemangiomas, potential for more serious tumors, poor coordination, joint hyperextensibility, occurs predominantly in males (80%), no enlargement of cerebral ventricles. (Miles et al. 1984)
Ruvalcaba-Myhre-Smith syndrome (3)	AD	variable MR (mild-severe)	intestinal polyps, pigmented macules on the penis, hypotonia, abnormal EMG, muscle biopsy shows lipid storage myopathy. (Diliberti et al., 1983)
Fragile X (Martin-Bell syndrome) (4)	X-linked	mod -severe MR , (approx 20% of male carriers are normal and approx 30% of carrier females are borderline to subnormal intelligence).	macroorchidism, large ears, prominent jaw, fragility of chromosome X-q27 site is expressed in folate deficient medium, but often not expressed in carrier females (in approx 50% of the patients). (Fryns, 1986)

Atkin-Flaitz-Patil syndrome (5)	X-linked	mild to severe mental retardation	macroorchidism, obesity, short stature, gap between upper central incisors, large square forehead, thick lower lip, ocular hypertelorism Fragile X negative.(Atkin et al.,1985)
Coffin-Lowry syndrome (6)	X-linked	mild to moderate mental retardation	small stature, hypertelorism, large ears, tapered fingers, pectus carinatum, hypotonia, pa'ulous lips, large mouth, facies may be similar to Williams syndrome. (Hunter, 1982)
New macrocephaly syndrome (7)	AD?	severe MR	short stature; large square forehead, ocular hypertelorism; low nasal bridge; coarse facies; hyperextensible joints. (Fryns, 1988)
Laxova-Brown Hogan syndrome (8)	X-linked	moderate-severe mental retardation	frontal bossing, Parkinson-like movements seizures, speech defect; no macroorchidism. (Laxova et al.,1985)
Golabi-Rosen syndrome (9)	X-linked	moderate-severe mental retardation	tall stature, coarse facies, advanced bone age, abnormal vision. (Golabi and Rosen, 1984)
Lujin-Carlin-Lubs syndrome (10)	X-linked	moderate-severe MR autistic behaviour	tall stature, Marfanoid build, long face, arachnodactyly, macrotestes, double row of teeth, absent corpus callosum. (Lujin et al., 1984)

Marshall-Smith syndrome (11)	unknown	mild MR	accelerated linear growth, advanced skeletal maturation failure to thrive in weight, (long, thin-appearance) broad forehead, flat facies, broad middle phalanges, spindle shaped fingers. (Fitch, 1985)
Weaver syndrome (12)	unknown (sporadic)		accelerated growth and maturation,similar to Marshall-Smith, camptodactyly, broad thumbs contractures and reduced joint mobility, broad splaying of femurs.(Weaver et al.,1974)
Greig Cephalo-polysyndactyly (13)	AD	normal	broad nasal root, postaxial polydacty of hands, preaxial polydactyly of feet, syndactyly of fingers and toes. (Gollop and Fontes, 1985)
Sclerosteosis (cortical hyperostosis, syndactyly) (14)	AR		bony syndactyly, hyperostosis of the skull, cranial nerve compression, enlargement of the jaw, deafness, visual loss, bone abnormalities, including clavicular. (Beighton et al., 1977)
Albers-Schonberg (infantile osteopetrosis) (15)	AR		short stature, dense thickened skull, square face, frontal bossing, visual and hearing loss, blood dyscrasia, dilated cerebral ventricles, dental abnormalities. (Khazen et al., 1986)

Osteopathia striata, cranial sclerosis. (16)	AD		dense thickened skull, facial asymmetry, cleft palate, conductive deafness, focal dermal hypoplasia, white forelock. (Winter et al., 1980)
Osteogenesis imperfecta, (types 1,3,4) (17)	1)AD 3)AR 4)AD		diffuse osteoporosis, multiple fractures, thin skin, triangular face, hearing loss, dental abnormalities, hyperextensible joints in types 1+4, blue sclera seen typically in type1 (Sillence, 1983)
Neurofibromatosis (Von Recklinghausen disease) (18)	AD	variable degrees of intellectual handicap in about 40% of patients but frank MR occurs only in about 2-5%.	cafe-au-lait spots, axillary freckling, neurofibromas, lisch nodules, CNS tumors (10-15%), seizures, cerebrovascular disorders, endocrine disorders. (Riccardi, 1981)
Proteus syndrome (19)	sporadic	usually normal	hemihypertrophy, random distribution of overgrowth, macrodactyly, exostoses, cavernous hemangiomas, lipomas, deeply rugated soles of feet, muscle atrophy in unaffected areas (Clarke et al., 1987)
Klippel-Trenaunay-Weber syndrome (Angio-osteo hypertrophy syndrome)	sporadic	usually normal	hypertrophy of one or more than one limb, including bone hypertrophy; macrodactyly; hemangiomas commonly located on legs, buttocks,

(20)			abdomen, lower trunk. (Gorlin et al.,1976)
Sturge-Weber sequence (21)	sporadic	normal-varying degrees of MR.	non-elevated, cutaneous, hemangiomata of the face and meninges; seizures, cataracts; characteristic intracranial calcification.(Gorlin et al., 1976)
Tuberous sclerosis (22)	AD	varying degrees of mental deficiency some normal	seizures; intracranial calcifications commonly in basal ganglia, or periventricular region; hypomelanotic skin macules, fibrous-angiomatous lesions, cyst-like areas in phalanges, with areas of periosteal thickening. (Riccardi, 1983)
Hypomelanosis of Ito (Incontinentia pigmenti achromians) (23)	AD?	variable mental deficiency	streaked, whorled or mottled areas of hypopigmentation, iridal heterochromia; seizures; harmartomous dental cusps. (Happle and Vakilzadeh 1982)
Acrocallosal syndrome (24)	AD?	moderate-severe MR	absent corpus callosum; pre and post axial polydactyly; hallux duplication. (Shinzel and Kaufman, 1986)
FG syndrome (25)	X-linked	usually severe MR	hypotonia; thin upper lip; tall forehead with cowlicks of hair; chronic constipation; anal

			anomalies; hyperactive behaviour; sometimes agenesis of corpus callosum. (Thompson and Baraitser 1987)
Walker-Warburg syndrome (26)	AR	severe MR	lissencephaly, characteristic brain histology, hydrocephaly, micropthalmos, cataracts. (Burton et al.,1987)
Robinow syndrome (27)	AD AR	MR in 18% of those affected	mesomelic shortening of fore-arms; frontal bossing; short upturned nose; wide palpebral fissures; long philtrum; hypoplastic genitalia. (Butler and Wadlington, 1987)
Achondroplasia* (28)	AD	normal	short tubular bones, small stature, small foramen magnum, enlarged cerebral ventricles, abnormalities of spine. (Fitzsimmons, 1985)

* Other osteochondrodysplasias commonly associated with macrocrania: achondrogenesis, asphyxiating thoracic dysplasia, campomelic dysplasia, hypochondrogenesis, Kniest dysplasia, sponastrime dysplasia.

VIII.B **RESULTS**

In the present study 10 individuals were considered to be sufficiently dysmorphic to warrant separation from the study group Of this group, two males (NA and SL) have features of Soto's, one male (TW) has features consistent with X-linked mental retardation, (Fragile X negative); one has features of Ruvalcaba-Mhyre-Smith syndrome (MV); one severely retarded male has an unknown syndrome with CT findings of lissencephaly and pachygyria and a facies similar to that of fetal hydantoin syndrome (CC); two females (BD and KB), with maternal transmission of macrocrania are hypotonic, with findings similar to that of Prader-Willi syndrome , unusual facies, and normal chromosomes; and one male (JTB) of normal stature and other anthropometric measures has a facies similar to the Ruvalcaba or the syndrome described by Hunter et al. One teenage female of high intelligence has features of a connective tissue disorder (MT), and one male with learning difficulties has several congenital anomalies (DL). The case histories of these patients will be discussed in detail in the appendix.

VIII.C DISCUSSION

The average paternal age for this group was 32.7 years and maternal age was 28.7 which is not increased over the general population. In all of these families first degree relatives, had a history of macrocrania, with average standardized head circumferences greater than that of the study population mean (2.2 vs 1.42 SD). It is difficult to determine if the macrocrania is familial, incidental to the dysmorphism, or if the macrocrania in the first degree (nonimpaired) relatives represents a form of variable expression (Fryns et al., 1988). Also, there may be some major genes segregating in this population and further subdivision according to phenotype would be necessary to establish valid inheritance patterns, given large enough samples of each group.

IX. CONCLUSION

There is an increased risk for psychomotor impairment in non-syndromic macrocranic individuals. Little information has been available regarding recurrence risks and possible causes for this. The purpose of this study is to provide information for families of macrocranic individuals. The first family that was seen in the study emphasized the need for information. The mother of S.L. had come in for genetic counselling two years previously because he was macrocranic and was markedly developmentally delayed. At the time the only information that could be given was that the macrocrania was probably dominantly inherited, there could possibly an inherited low grade form of hydrocephaly that may be related to the macrocrania, and the recurrence risk was unknown. Stephan's mother had a tubal ligation not wanting to risk having another son affected in the same way.

The present study has determined that macrocrania is inherited in a multifactorial manner (not dominantly) in the same manner as most other anthropometric measures. Also, one family of three male (all macrocranic) sibs had two that were intellectually impaired although it is not clear that the impaiment is of the same origin. Although the sample size is small, for this study there was no other evidence of recurrence and it is thought

thought that the rate is low.

22% of the individuals in the study were considered to be syndromic. Since this population was ascertained through hospital files it is presumed that this is a disproportionately high number and is not representative of the general population risk for syndromes associated with macrocrania.

Of the many variables examined, few were predictive of psychomotor delay in the nonsyndromic group of individuals. Nonhydrocephalic cerebrospinal fluid space enlargement, is often found in association with macrocrania, but this study has found no evidence that it (or its absence) is predictive of psychomotor delay. Also, parental variables did not give any clues regarding the increased risk for psychomotor impairment.

Of interest, however, is the number of individuals in the psychomotor impaired group who have had difficult midforceps delivery, including those in which trauma had been reported. A probable reason for this becomes apparent when head circumference at birth is evaluated. The head circumference not only is significantly greater than population standards but is also greater than the 98th percentile for infants who are macrosomic and therefore known to be at risk for birth trauma partly due to a large head passing through a normal sized pelvis. Besides the nonsyndromic study population, one individual who was excluded

from comparison because he is no longer macrocranic, suffers from marked coordination deficit which has been attributed to a traumatic delivery. Also one individual in the comparison group has a sister who is learning disabled and is also reported to have suffered severe birth trauma. No firm conclusions can be made based on this study because the population is so small; nonetheless based on this preliminary information it is clear that more study is warranted. If this is substantiated, the difficulties that these families must endure could potentially be prevented with the awareness by the obstetrician, of those individuals at risk that is, those families in which there is a tendency toward macrocrania.

In conclusion, psychomotor impairment occurs in every population, however the increased risk for learning disabilities and coordination deficit in this population deserves attention. This study proposes that further study should be done to determine if difficult deliveries causing subtle brain damage may contribute to this increased risk.

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APPENDIX 1

SUMMARY OF DATA

	NAME	SEX	AGE	HT %ILE	MAT HC	PAT HC	MPHC	INTELL IMPAIR	RECURR	COORD	VENT	EEG
1	WIL	F	13 0	95	•	1 89	2 58	LD	NO	MILD-M	•	•
2	GAB	M	11 6	90	5 22	1 84	3 53	MMR	NO	NORM	MLVD	ABN
3	GIE	F	17 3	20	8 00	•	•	NORM	NO	NORM	NORM	NORM
4	HOR	F	11 5	75	4 94	2 18	3 56	LD	NO	NORM	•	•
5	WAL	M	16 6	10	3 72	1 28	2 50	MR	NO	MOD-SE	MLVD	ABN
6	CAR	M	4 9	3	1 47	1 55	1 51	MR	NO	•	NORM	ABN
7	DEA	F	1 5	3	2 44	1 22	1 83	MMR	NO	•	ISAS	•
8	HES	M	7 8	98	2 20	•	•	MMR	NO	MILD-M	NORM	ABN
9	THI	M	6 0	75	1 31	2 74	2 02	MMR	NO	NORM	NORM	•
10	LAU	M	5 1	98	2 60	2 97	2 78	TD	NO	NORM	ISAS	•
11	OLB	M	16 0	30	2 59	2 12	2 35	MMR	MALE SIB	MOD-SE	NORM	ABN
12	COT	F	11 1	60	1 16	- 53	32	LD+SD	NO	MILD-M	•	ABN
13	BOY	F	2 0	98	1 30	76	1 03	MMR	NO	NORM	NORM	•
14	CAV	M	18 0	15	1 99	82	1 45	TD	NO	MILD-M	NORM	•
15	VIN	M	7 1	75	3 72	2 68	3 20	MR	NO	NORM	NORM	•
16	FAT	M	15 9	50	-1 00	1 27	24	NORM	NO	MILD-M	•	•
17	LAS	M	6 3	50	2 59	1 25	1 23	LD	NO	MILD-M	ALL	NORM
18	[illegible]	M	5 1	70	-1 60	2 40	62	NORM	NO	NORM	ISAS	•
19	[illegible]	M	10 9	50	2 59	1 81	2 21	NORM	NO	NORM	NORM	ABN
20	STA	F	12 0	50	2 25	1 84	2 05	NORM	NO	NORM	•	ABN
21	CHA	F	7 0	50	2 25	1 84	2 05	LD	NO	NORM	ISAS	•
22	HAA	M	12 0	98	2 18	1 16	1 67	NORM	NO	NORM	NORM	•
23	GAU	F	18 0	55	2 29	1 05	1 67	MR	NO	MILD-M	•	•
24	TET	F	12 0	90	2 29	1 10	1 35	NORM	NO	MOD-SE	NORM	•
25	MIZ S	M	11 9	98	3 33	1 33	2 33	NORM	NO	NORM	NORM	•
26	GRO	F	9 9	3	-1 16	1 84	34	NORM	NO	NORM	MLVD	•
27	DEL	F	7 3	50	1 09	71	90	NORM	NO	NORM	MLVD	•
28	SMI	M	7 0	80	- 41	14	- 13	NORM	NO	NORM	•	•
29	GAL	F	18 0	3	- 78	•	•	NORM	NO	NORM	MLVD	ABN
30	MAN	M	17 0	25	18	14	16	NORM	NO	MOD-SE	NORM	•
31	BRA	M	6 2	15	1 47	71	1 09	NORM	NO	NORM	NORM	NORM
32	AIK	M	4 0	50	- 54	1 24	35	MMR	NO	MILD-M	MLVD	ABN
33	LRO	M	6 6	98	1 66	1 89	1 77	LD+SD	NO	NORM	MLVD	•
34	GER	M	6 6	70	1 24	1 33	1 30	NORM	FEMALE	NORM	MLVD	NORM
35	GOW	M	9 4	70	1 09	1 40	1 25	NORM	NO	MOD-SE	MLVD	NORM
36	IVA	M	4 6	75	1 39	2 03	1 71	NORM	NO	NORM	NORM	•
37	JER	M	5 6	98	2 20	- 13	1 03	NORM	NO	NORM	NORM	•
38	KLA	M	8 1	98	1 46	1 50	1 48	LD+SD	NO	MOD-SE	MLVD	•
39	WIL	F	1 0	75	33	2 12	1 22	NORM	NO	NORM	MLVD	•
40	ATW	M	15 0	98	1 84	4 20	3 02	LD	NO	MOD-SE	•	NORM
41	CAN	M	18 0	75	1 39	48	93	MR	NO	NORM	•	•
42	DUF	F	18 0	90	2 74	1 55	2 14	MR	NO	NORM	•	•
43	DYC	F	2 0	25	2 96	57	1 76	MMR	NO	NORM	NORM	•
44	LAV	M	13 9	50	3 00	1 56	2 28	LD	NO	NORM	NORM	•
45	LYN	F	3 0	75	•	1 84	•	NORM	NO	•	NORM	NORM
46	MEY	M	11 1	98	1 91	•	•	MR	NO	•	NORM	ABN
47	PEN	M	18 0	80	1 39	2 00	1 69	NORM	FEMALE	NORM	•	•
48	VIC	M	11 1	75	2 74	1 55	1 55	LD	NO	MILD-M	MOD-VD	•
49	SKA	F	10 2	40	33	1 05	69	LD	NO	MOD-SE	NORM	•
50	MIZ A	M	15 0	98	3 33	1 33	2 33	TD	NO	NORM	•	•

	SEIZURES	GEST	MULT PREG	BIRTH ORDER	GRAMS	DELIV	PRESENTATION	LABOUR ONSET	PERI DIFF
1	NO	38	•	1/2	2530	SVD	VTX	SPONT	NO
2	GM	38	•	1/2	•	SVD	VTX	SPONT	NO
3	GM	40	•	4/5	3685	MF	VTX	SPONT	RESP
4	NO	39	•	3/3	3430	SVD	VTX	SPONT	NO
5	GM	40	•	3/3	3200	C/S-B	VTX	•	NO
6	GM	40	•	2/2	4500	C/S-B	VTX	•	NO
7	NO	40	•	2/2	3075	C/S-B	VTX	•	NO
8	NO	40	•	1\2	4400	C/S-B	BREECH	•	NO
9	NO	39	•	1/2	3280	SVD	VTX	SPONT	RESP
10	NO	42	•	1/1	4025	SVD	VTX	SPONT	RESP
11	NO	40	•	1/3	3465	LF	VTX	IND	NO
12	NO	40	•	1/2	3600	SVD	VTX	SPONT	FD
13	NO	39	•	2/2	3230	SVD	VTX	SPONT	NO
14	NO	37	•	2\3	•	MF	VTX	•	TRAUMA
15	•	38	•	1/2	3560	MF	VTX	SPONT	FD
16	NO	38	•	2/2	3120	LF	VTX	IND	NO
17	NO	34	•	2\2	2530	C/S-L	VTX	SPONT	RESP
18	NO	42	•	2/2	3340	LF	VTX	IND	NO
19	NO	38	•	4/4	3345	SVD	BREECH	SPONT	NO
20	NO	40	•	2/3	3690	SVD	VTX	SPONT	NO
21	NO	34	QUADS	5/5	2045	C/S-B	BREECH	•	RESP
22	NO	40	•	1/1	3150	C/S-L	VTX	SPONT	FD
23	•	40	•	1/1	3640	SVD	VTX	SPONT	NO
24	NO	41	•	1/2	2950	SVD	VTX	IND	NO
25	GM	39	•	2/2	4370	C/S-B	VTX	•	NO
26	NO	32	TWINS	2/3	1363	MF	VTX	SPONT	NO
27	NO	42	•	3/3	3900	SVD	VTX	SPONT	NO
28	NO	39	•	1/1	2940	LF	VTX	SPONT	NO
29	GM	42	•	1/3	3540	SVD	VTX	SPONT	NO
30	•	42	•	1/3	•	SVD	BREECH	•	RESP
31	NO	41	•	1/3	3630	SVD	VTX	•	NO
32	PM	37	•	4/5	4100	SVD	VTX	SPONT	NO
33	NO	36	TWINS	1/3	2700	V S	VTX	SPONT	NO
34	NO	40	Element 1	1/3	3690	SVD	VTX	SPONT	NO
35	NO	40	•	1/3	3741	MF	VTX	SPONT	TRAUMA
36	NO	39	•	1/2	3495	SVD	VTX	SPONT	NO
37	NO	40	•	1/2	3060	C/S-B	BREECH	•	NO
38	GM	37	•	1/4	2900	C/S-L	VTX	IND	FD
39	NO	38	•	1/1	3640	C/S-B	BREECH	•	NO
40	GM	38	•	2/2	4500	MF	VTX	IND	NO
41	•	40	•	2/3	3875	HF	VTX	SPONT	TRAUMA
42	NO	39	•	3/3	3260	SVD	VTX	SPONT	NO
43	•	43	•	2/2	3570	SVD	VTX	IND	FD
44	NO	42	•	1/1	3900	C/S-L	VTX	•	NO
45	FS	42	•	4/4	3400	SVD	VTX	SPONT	NO
46	NO	40	•	1/2	4100	•	VTX	•	TRAUMA
47	NO	40	•	1/4	3380	SVD	VTX	IND	NO
48	NO	38	•	2/2	2830	•	VTX	SPONT	NO
49	NO	38	•	3/3	3940	HF	VTX	•	TRAUMA
50	NO	37	•	1/2	4300	C/S-B	VTX	•	NO

	APGAR 1	5	DRUGS	SMOKING	ALCOHOL	CHROM DONE	II	00	HC	CI	sib 1 H C	sib 2 H C
1	9	10	VIT	0	NO	NO	60	98	3 38	74 0	2 68	•
2	•	•	VIT+OTH	0	OCCAS	NO	98	98	5 56	73 1	1 80	•
3	4	5	NO	0	OCCAS	NO	98	98	7 14	80 9	5 40	1 80
4	9	10	NO	0	NO	NO	98	98	5 45	75 6	•	•
5	8	•	•	0	NO	YES	•	•	2 28	•	1 84	2 60
6	8	•	NO	0	NO	YES	98	98	3 80	78 0	1 74	•
7	9	10	NO	0	NO	YES	75	98	2 60	•	•	•
8	7	9	OTHER	0	OCCAS	YES	75	60	5 02	80 4	•	•
9	9	10	NO	0	NO	YES	75	60	2 26	77 0	•	•
10	•	•	THYROID	0	NO	NO	3	90	1 70	73 7	•	•
11	9	•	NO	0	NO	NO	75	75	3 54	71 3	3 17	2 10
12	4	7	NO	0	OCCAS	NO	75	75	2 08	72 0	64	•
13	8	9	NO	0	OCCAS	NO	97	60	2 96	75 0	44	•
14	•	•	NO	0	NO	NO	50	50	2 68	72 0	•	•
15	7	10	GA+TH	0	NO	YES	50	65	2 90	73 0	•	•
16	•	•	NO	0	NO	NO	98	98	2 53	74 6	24	•
17	5	•	THYROID	0	NO	NO	80	80	2 60	74 2	1 25	•
18	7	9	NO	0	NO	YES	65	75	3 65	72 0	1 26	•
19	•	•	VIT	0	NO	YES	90	90	2 28	75 5	49	20
20	•	•	VIT	0	OCCAS	NO	75	75	2 66	75 0	1 59	1 70
21	8	9	OTHER	0	NO	NO	65	80	2 02	69 0	1 13	1 06
22	7	10	OTHER	0	NO	NO	98	98	5 30	82 0	•	•
23	•	•	OTHER	0	MOD	NO	50	50	2 29	76 0	1 27	1 05
24	•	•	NO	20	NO	NO	80	80	2 86	79 0	1 10	•
25	9	9	THYROID	0	NO	NO	98	98	1 92	76 0	80	•
26	8	9	VIT	0	NO	YES	25	75	1 25	77 0	37	1 70
27	9	10	NO	0	NO	NO	50	50	1 35	73 4	0	1 00
28	8	9	NO	10	NO	NO	50	98	1 16	75 0	•	•
29	•	•	•	•	OCCAS	NO	98	98	1 16	73 6	-1 16	- 42
30	•	•	NO	0	NO	NO	60	60	1 48	74 0	- 22	•
31	9	•	VIT	0	NO	NO	60	50	1 15	77 0	93	96
32	•	•	GA	15	NO	NO	97	97	4 40	72 5	50	- 77
33	•	•	GA	5	NO	NO	97	75	2 46	72 5	63	- 28
34	•	•	OTHER	20	NO	NO	97	75	2 26	71 8	2 19	1 44
35	•	•	GA	0	NO	NO	50	60	2 03	74 8	0	- 28
36	•	•	VIT	0	NO	NO	60	75	3 57	82 0	1 48	•
37	•	•	OTHER	10	OCCAS	NO	70	50	2 10	70 0	1 00	•
38	•	•	VIT	20	NO	NO	98	98	2 10	72 0	17	2 00
39	9	•	VIT	•	OCCAS	NO	98	98	5 40	73 0	•	•
40	•	•	VIT	20	OCCAS	NO	98	98	5 50	69 0	5 37	•
41	•	•	OTHER	0	OCCAS	NO	98	98	2 40	72 0	1 44	•
42	•	•	NO	20	OCCAS	YES	60	75	2 20	69 0	•	•
43	•	•	NO	5	OCCAS	YES	25	3	2 80	70 0	•	•
44	•	•	NO	•	NO	NO	97	80	2 29	72 0	•	•
45	•	•	NO	0	NO	YES	95	75	2 36	•	•	•
46	8	•	•	•	•	YES	80	60	2 30	75 0	1 60	•
47	•	•	•	•	•	NO	50	60	2 00	72 0	2 00	1 50
48	9	•	VIT	10	OCCAS	NO	50	75	3 20	74 4	69	•
49	0	2	NO	0	NO	NO	•	•	5 78	74 7	33	71
50	10	10	OTHER	•	NO	NO	•	•	81	76 0	1 92	1 92

	average sib H.C.	av offspring H.C.	BIRTH H.C	pat age	mat age	pat ethnic	mat ethnic	Category
1	2 68	3.03	•	28	26	WI	WI	W I
2	1 80	3 68	•	31	29	WI	WI	W I
3	3 60	4 18	•	•	28	WI	WI	W I
4	•	•	•	42	38	WI	WI	W I
5	2 22	2 24	•	32	26	B/I/S	B/I/S	synd
6	1 74	2 77	•	45	40	B/I/S	B/I/S	synd
7	•	•	35 0	27	19	F C	F C	synd
8	•	•	•	28	25	B/I/S	F C	synd
9	•	•	•	30	31	other	F C	synd
10	•	•	36 7	36	31	F C	B/I/S	<2SD
11	2 63	2 93	35 0	33	31	F C	F C	PMR
12	64	1 32	36 5	28	24	F C	F C	PMR
13	44	1 70	•	30	30	F C	F C	PMR
14	•	•	•	•	•	Ital	Ital	PMR
15	•	•	•	31	29	U\P\G	U\P\G	synd
16	24	1 48	•	37	34	East Ind	East Ind	control
17	1.25	1 90	•	26	23	F C	F C	prem
18	1.26	2 45	37 0	25	25	B/I/S	F C	control
19	43	90	36 5	32	24	B/I/S	B/I/S	control
20	1 65	1 98	35 0	26	26	Ital	F C	control
21	93	1 15	37 5	23	23	F C	F C	prem
22	•	•	35 0	41	37	B/I/S	U\P\G	control
23	1 16	1 53	•	37	34	F C	B/I/S	PMR
24	1 10	1 95	•	24	20	F C	B/I/S	synd
25	80	1 36	37 0	47	39	U\P\G	F\B\A\	<2SD
26	1 04	1 10	•	28	25	other	other	prem
27	50	1 17	36 5	30	30	F\B\A\	F\B\A\	<2SD
28	•	•	36 5	32	31	B/I/S	B/I/S	<2SD
29	- 79	- 14	•	22	22	F C	F C	<2SD
30	•	•	•	31	29	F\B\A\	B/I/S	<2SD
31	93	1 01	37 5	28	27	B/I/S	F\B\A\	<2SD
32	38	1 18	40 5	33	31	F\B\A\	B/I/S	PMR
33	17	93	•	36	33	B/I/S	B/I/S	prem
34	1 81	1 96	34 5	40	37	U\P\G	B/I/S	control
35	29	80	•	29	26	B/I/S	B/I/S	PMR
36	1 48	1 74	34 0	29	26	B/I/S	B/I/S	control
37	1 00	2.29	36 0	32	30	U\P\G	F C	control
38	92	1 12	39 0	21	21	other	other	prem
39	•	•	38 0	33	34	other	other	control
40	5 37	5 40	39 0	30	30	F\B\A\	F C	synd
41	1 44	1 92	37.5	32	25	B/I/S	F C	PMR
42	48	1 34	•	35	35	B/I/S	B/I/S	PMR
43	•	•	39 0	34	23	F\B\A\	F C	synd
44	•	•	•	33	30	F\B\A\	B/I/S	synd
45	•	•	•	32	37	B/I/S	other	control
46	1 60	1 96	39 0	27	25	F\B\A\	B/I/S	PMR
47	1 75	1 75	•	32	31	B/I/S	B/I/S	control
48	69	1 95	35 0	25	22	F\B\A\	F\B\A\	PMR
49	52	2.27	39 0	35	33	U\P\G	U\P\G	PMR
50	1 92	1 36	37 0	47	37	U\P\G	F\B\A\	<2SD

	Pat Education	mat education	pat-R/L	mat R/L	deliv diff	DERM	CONGENITAL ANOMALIES
1	grad school	some univ	R	R	0	0	
2	tech school	high school g	R	R	0	0	
3	tech school	grade school	R	R/L	2	0	
4	high school g	high school g	R	R	0	0	
5	univ grad	univ grad	R	R	0	0	Syndromic
6	tech school	grad school	R	R	0	6	Syndromic
7	high school g	some high s	R	R	0	•	Syndromic
8	univ grad	univ grad	R	R	0	2	Syndromic
9	univ grad	univ grad	R	R	0	0	Syndromic
10	grade school	univ grad	R	R	0	0	
11	grad school	grad school	R/L	L	2	1	
12	grad school	univ grad	R	R	3	6	
13	some univ	•	R	R	0	0	
14	grade school	grade school	R	R	4	0	
15	•	high school g	R	R	3	0	Syndromic
16	grad school	univ grad	R	R	1	0	
17	some high s	some high s	R	R	2	0	bifid uvula
18	tech school	high school g	R	R	4	0	
19	grade school	some high s	R	R	0	3	skull asymm
20	high school g	some univ	R	R	0	0	polydactyly
21	high school g	high school g	R	R	•	0	no lat incisors, strabismus
22	high school g	univ grad	R	R	2	0	small hands, obese
23	grad school	grad school	R	R	0	0	genu recurvatum
24	some high s	some high s	R	R	0	5	syndromic
25	high school g	high school g	R	R	0	•	multiple nevi
26	grade school	grade school	R	R	•	0	
27	grad school	grad school	R	R	0	0	
28	some high s	some high s	R	R	1	0	nail pitting, 9 teeth at birth
29	grade school	some high s	R	R	0	0	post auricular pit
30	some univ	high school g	R	R	4	1	
31	univ grad	some univ	R	R	•	1	hypospadias
32	univ grad	high school g	R	R	0	0	
33	high school g	high school g	R	R	2	0	
34	high school g	high school g	R	L	0	0	
35	some univ	univ grad	R	L	3	2	
36	grad school	univ grad	R	R	0	0	epicanth folds
37	high school g	high school g	R	R	0	0	
38	high school g	high school g	R	R	2	6	dysplastic test, inguin hernia,
39	univ grad	MD	R	R	0	0	epicanth folds, flat midface
40	high school g	univ grad	R	R	2	2	Syndromic
41	MD	MD	R	R	3	0	
42	univ grad	univ grad	R/L	R	0	3	cong disloc of hip
43	high school g	high school g	R	R	0	6	Syndromic
44	some high s	some high s	R	R	2	3	syndromic
45	some univ	some univ	R	R	0	•	syndactyly of 2/3 toe
46	tech school	some univ	R	R	4	3	hypopigmented spots
47	univ grad	some univ	R	R	0	0	
48	high school g	univ grad	•	•	0	0	club foot, strabis.
49	MD	univ grad	R	•	4	0	strabismus, myopia
50	high school g	high school g	R	R	0	•	

APPENDIX II

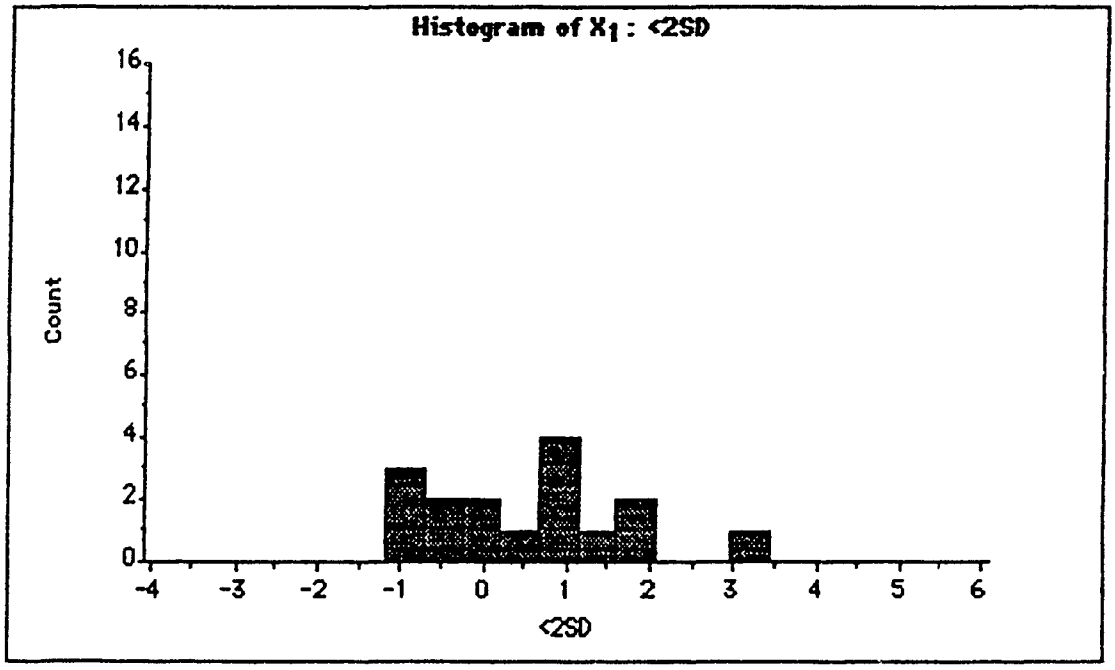
Summary of Head Circumference Measures of 1st degree relatives.

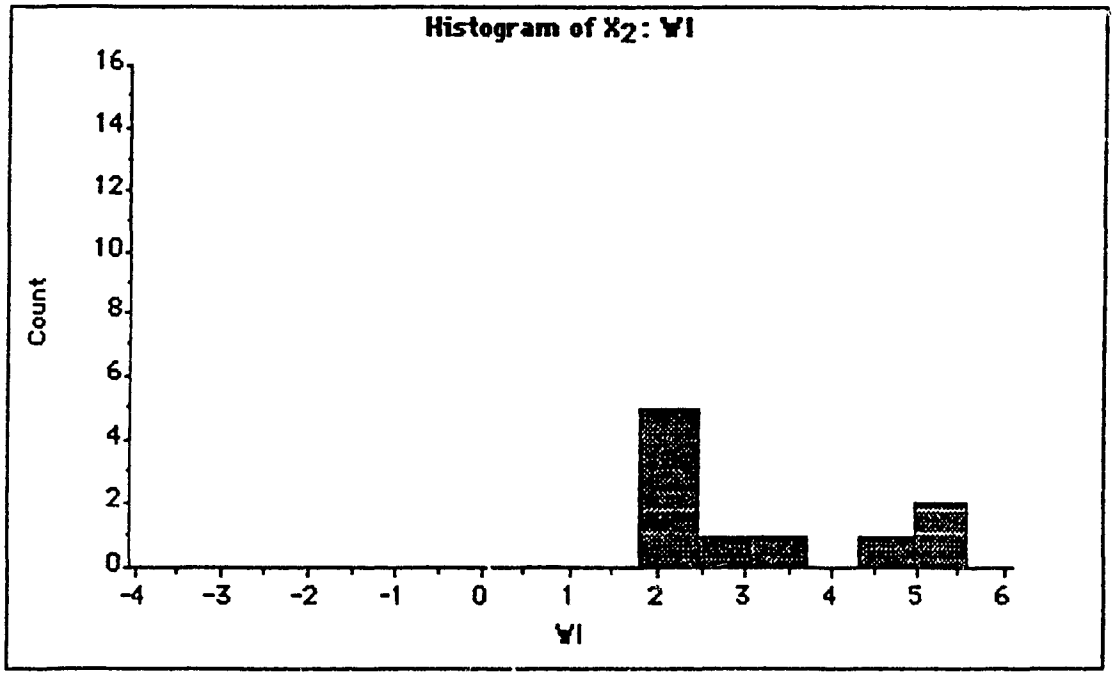
	<2SD	WI	study group 1st deg	study group female	study group male
1	.96	2.68	3.17	1.20	-.54
2	.93	1.89	2.10	1.16	.50
3	-.22	3.27	2.12	2.29	-.23
4	-1.16	1.84	2.59	2.29	2.00
5	0	5.22	.64	-.78	1.33
6	1.00	1.80	-.53	.43	1.44
7	.71	8.00	1.16	2.59	1.40
8	1.09	5.40	.44	.49	2.03
9	.14	1.80	.76	.20	-.13
10	-.41	2.18	1.30	-1.16	1.00
11	.71	4.94	3.60	2.59	2.12
12	-.42	•	.82	.64	.48
13	-.78	•	1.99	1.16	1.56
14	.80	•	.14	.44	1.55
15	1.33	•	.18	1.30	.69
16	3.33	•	-.22	3.60	3.17
17	.18	•	2.68	1.99	2.10
18	1.47	•	1.20	.18	2.12
19	.14	•	1.59	-.22	-.53
20	•	•	1.70	-.77	.76
21	•	•	1.16	1.24	.82
22	•	•	2.18	1.24	.14
23	•	•	1.10	2.19	2.68
24	•	•	.42	1.09	1.59
25	•	•	2.29	0	1.70
26	•	•	2.29	-.28	2.18
27	•	•	1.05	1.17	1.10
28	•	•	1.27	1.39	.42
29	•	•	1.05	1.48	1.05
30	•	•	1.27	2.20	1.27
31	•	•	-.78	1.46	1.05
32	•	•	.43	1.39	1.27
33	•	•	1.25	2.50	-.13
34	•	•	-.13	.48	1.25
35	•	•	2.59	3.00	.60
36	•	•	.49	1.91	1.84
37	•	•	.20	2.74	1.26
38	•	•	.60	1.50	2.40
39	•	•	1.84	2.00	1.42
40	•	•	2.59	.33	1.68
41	•	•	1.26	.33	.71
42	•	•	2.40	.33	•

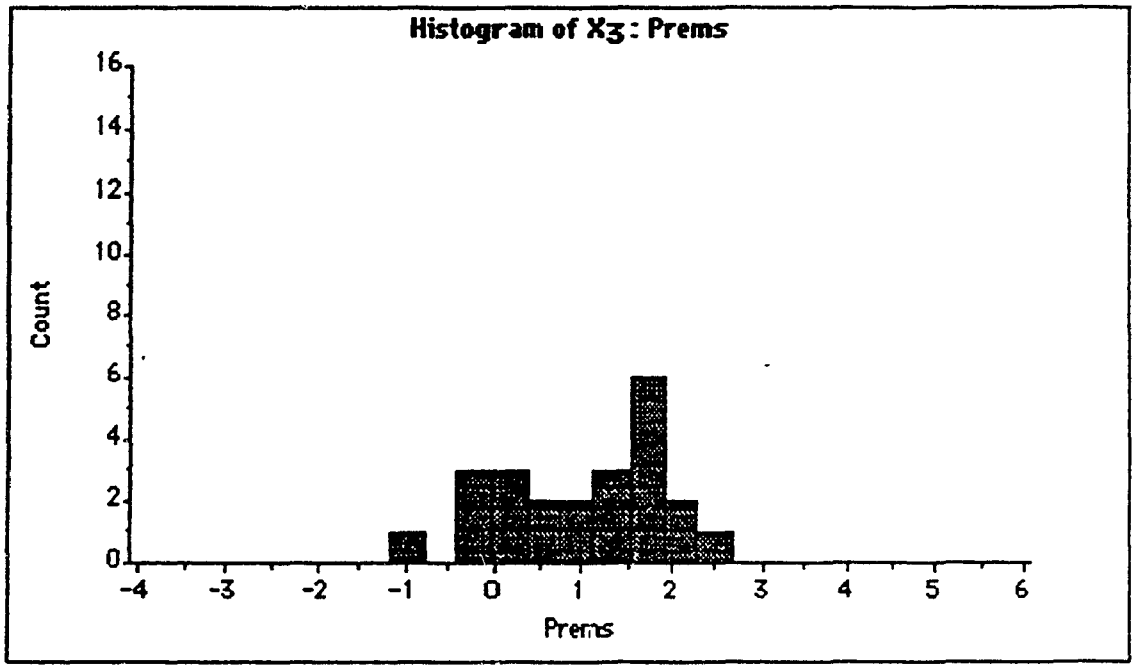
	<2SD	WI	study group 1st deg	study group female	study group male
43	•	•	-1.16	2.59 •	•
44	•	•	-.54	•	•
45	•	•	1.24	•	•
46	•	•	.50	•	•
47	•	•	-.77	•	•
48	•	•	-.23	•	•
49	•	•	2.00	•	•
50	•	•	1.33	•	•
51	•	•	1.24	•	•
52	•	•	2.19	•	•
53	•	•	1.44	•	•
54	•	•	1.40	•	•
55	•	•	1.09	•	•
56	•	•	0	•	•
57	•	•	-.28	•	•
58	•	•	1.17	•	•
59	•	•	2.03	•	•
60	•	•	1.39	•	•
61	•	•	1.48	•	•
62	•	•	-.13	•	•
63	•	•	2.20	•	•
,64	•	•	1.00	•	•
65	•	•	2.12	•	•
66	•	•	.33	•	•
67	•	•	.48	•	•
68	•	•	1.39	•	•
69	•	•	1.44	•	•
70	•	•	2.50	•	•
71	•	•	.48	•	•
72	•	•	1.56	•	•
73	•	•	3.00	•	•
74	•	•	1.91	•	•
75	•	•	1.60	•	•
76	•	•	2.00	•	•
77	•	•	1.50	•	•
78	•	•	1.55	•	•
79	•	•	2.74	•	•
80	•	•	.69	•	•
81	•	•	1.05	•	•
82	•	•	.33	•	•
83	•	•	.33	•	•
84	•	•	.71	•	•

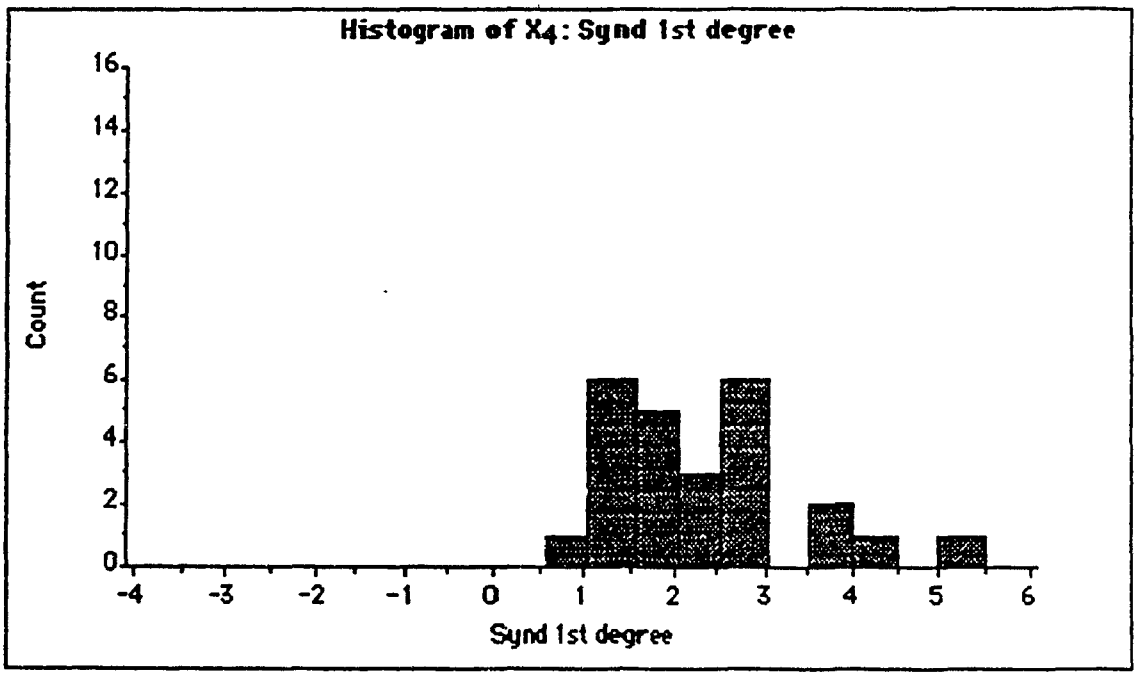
	PREMS 1ST DEGREE	SYND 1ST DEGREE
1	1.25	1.28
2	-.13	3.72
3	2.59	1.84
4	.37	2.60
5	1.70	2.97
6	1.84	2.60
7	-1.16	1.74
8	1.13	1.55
9	1.06	1.47
10	6.00E-2	1.22
11	1.62	2.44
12	1.84	2.33
13	2.25	1.31
14	1.66	2.74
15	1.89	2.20
16	.63	2.96
17	-.28	.57
18	•	•
19	•	•
20	•	•
21	•	•
22	•	•
23	•	•
24	•	•
25	•	•
26	•	•
27	•	•
28	•	•
29	•	•
30	•	•
31	•	•
32	•	•
33	•	•
34	•	•
35	•	•
36	•	•
37	•	•
38	•	•
39	•	•
40	•	•
41	•	•

Frequency distributions of H.C. measurements of 1st degree relatives divided into categories.






Histogram of X3: Prems
Count
16
14
12
10
8
6
4
2
0
-4
-3
-2
-1
0
1
2
3
4
5
6
Prems


Histogram of X4: Synd 1st degree
Count
16
14
12
10
8
6
4
2
0
-4
-3
-2
-1
0
1
2
3
4
5
6
Synd 1st degree

Appendix 1V

Alphabetical list of syndromes associated with macrocrania

Name of Syndrome	Number of listing
Achondroplasia	28
Acrocallosal	24
Albers-Schonberg	15
Atkin-Flaitz-Patil	6
Bannayan-Zonana	2
Cerebral Gigantism (Soto's)	1
Coffin-Lowry	5
FG	25
Fragile X	4
Golabi-Rosen	9
Greig-Cephalopolysyndactyly	13
Hypomelanosis of Ito	23
Klippel-Trenaunay-Weber	20
Laxova-Brown	8
Lujin-Carlin-Lubs	10
Marshall-Smith	11
Neurofibromatosis	18
"New Macrocephaly syndrome"	7
Osteogenesis imperfecta	17
Osteopathia striata	16
Proteus	19
Robinow	26
Ruvalcaba-Mhyre-Smith	3
Sclerosteosis	14
Sturge-Weber	21
Tuberous Sclerosis	22
Walker-Warburg	26
Weaver	12

APPENDIX V.

DISCUSSION OF SYNDROMIC CASES

JTB was seen at the age of 6 years, presenting with marked speech delay, learning difficulties, and poor gross motor skills. He was delivered of a 30 year old primipara whose pregnancy was complicated by mild preeclampsia. The delivery was an uneventful vertex spontaneous, with good apgars, however after delivery he developed respiratory difficulty (spontaneous pneumothorax) which warranted intensive care for ten days He also was born with a mild right club foot which was corrected with casting for three weeks. Early developmental delay was noted and he's been followed since the age of 2 1/2 years. On examination he was found to be pleasant and cooperative. The findings were as follows, H.C. 55.5cm (+2.26SD), high forehead; deep set eyes with downwardly displaced inner canthi, broad nasal root, short blunt nose, high arched palate, wide spaced teeth, mild retrognathia, elbows hyperextensible, hands appeared short and broad, (measured to be normal and normal on X-ray), and broad toes. Prophase chromosomes were found to be normal. The combination of his features gave the appearance of the Ruvalcaba syndrome, which also is similar in appearance to the syndrome of Hunter et al., and the Trichorhinophalangeal syndrome (Goodman et al 1981). Sugio and Kaji described 9 individuals of four generations with features of Ruvacalba syndrome but all of these individuals had

normal intelligence. Macrocrania has not been one of the findings in these descriptions, however the father of the proband in the paper of Hunter et al. (1977) had a head circumference of 61 cm (>2SD above the mean). The summary of the features of these syndromes is seen in Figure1 compared with the features of JTB. Whether or not he has one of these syndromes, he is sufficiently dysmorphic to be excluded from the "non-syndromic" group.

Table1

Feature	JTB	Hunter et al[1]	Ruvalcaba s[2]	Sugio et al[3]	TRP[4]
MR	+	+++	+++	-	+
Short stature	-	++	+++	++	+++
microcephaly	-	++	++	-	?
sparse hair	early	-	-	+++	+++
high forehead	+	+	-	+++	+++
palpebral downslant	-	+	+++	-	?
Nose:					
short,blunt	+	+++	-	-	-
beaked	-	-	++	+++	+
bulbous tip	+	-	-	-	+
long philtrum	50%	-	-	+++	+++
small mouth	75%	+++	+++	-	?
thin vermilion	+	+++	+++	+++	+++
retro/micro gnathia	retro	?	?	?	+++
pectus carinatum	+	-	+++	-	+++
broad hips	+	?	?	++	++
small hands	50%	+++	+++	+++	+++
small feet	-		?	+++	+++
short metacar	-	-	+++	++	?
short phalanges	-	+++	+++	+++	?
short metatarsals	-	?	++	++	++
coned epiphysis	-	+++	-	++	+++

[1]Hunter et al, 1977; [2] Hunter, 1985; [3]Sugio and Kaji 1984; [4]Goodman et al, 1981.

K. B. and B.D. were seen for the current study at the ages of 15 months and 23 months in Montreal and Vancouver, respectively. They present with similar findings, both having some features of Pradi-Willi syndrome and macrocrania that appears to be maternally derived.

K.B. is the second born child to nonconsanguiness French-Canadian parents who are both presently in good health. Mrs. B. is noticably obese with a head circumference 2.44 SD above the mean. She was followed for seizures that resolved by the age of 6 years. She had some difficulties in school and completed her studies at the level of Secondary 1.

Reduced movement was noticed during pregnancy Delivery by C-Section at 40 weeks gestation (vertex presenting) was uneventful with apgars of 9 and 10. Early feeding difficulties, developmental delay and reduced facial movements were documented at the age of 7 months Features noted on current examination are seen in table 2. The child bears a striking resemblance to her mother, but the shape of her mouth is similar to that seen in a picture of her paternal grandmother An initial CT scan at the age of 12 months showed enlarged CSF spaces "inappropriately large for familial macrocrania" and mild plagiocephaly. Follow-up studies at the age of 15 months showed a decrease in size of the CSF spaces over the convexity of the brain and a decrease in ventricular size. CT scans done on both parents

showing no abnormalities.

B.D. was first investigated for hypotonia at the age of 2 months when sweat test, CT scans, laryngoscopy, and chromosomes were all negative. She was seen by the Genetics Department of The Vancouver Grace Hospital, while she was hospitalized for investigation of recuurent respiratory infections, hypotonia and developmental delay at the age of 9 months. Investigations and results included:

1) EMG (electromyography) showing a myopathy or muscle hypoplasia of central origin.

2) ECG and echocardiography were normal (investigation of grade 1 ejection systolic murmur).

3) Immunological evaluation showing low IGA levels (16mg%)

4) Liver function tests normal (investigation of hepatomegaly of 3.0 cmsbelow the costal margin).

5) blood amino acid evaluation was normal.

B.D. is the second born child of nonconsanguineous parents of Dutch and French Canadian origin. Both parents are in good health and maternal head circumference is 2.96SD above the poplation mean. Mrs. D reports that she did not talk until after the age of 3 years but does not report any learning difficulties. Pregnancy history revealed a maternal awareness of decreased fetal movements and no teratogen intake including alcohol. The delivery

was complicated by a cord around the neck and assistance with ventilation was needed initially with subsequent observation in an isolette for 36 hours and discharge by the 5th day.

Current evaluation demonstrated progression of development whereby at the age of 23 months B.D. was just beginning to walk. Hypotonia was decreased and weight had increased markedly from the 3rd percentile at 12 months of age to beyond the 75th percentile. She also had recently had some febrile seizures treated effectively with phenobarbital. She was undergoing physiotherapy because both feet turn outward. Also of interest on current examination was an unelevated, serpiginous, red discolouration, observed in a symmetrical line distribution across outer, upperarms, lower arms, and dorsum of hand. Palpebral fissures were noted to be well below the mean Other features found on current examination are demonstrated in table 2 with a comparison of the features of Prader-Willi.

Table 2

Features	PWS *	K.B.	B.D.
Reduced intra-uterine activity	77%	yes	yes
Breech delivery	33%	no	no
Neonatal feeding difficulty	94%	yes	yes
Hypotonia	100%	mild	marked
Psychomotor retardation	98%	yes	yes
Convulsions	19%	no	febrile
Hyperphagia	86%	?	yes
Obecity	93%	yes	yes

Short stature	78%	@25%	@75%
Almond-shaped palpebral fissures	55%	?	yes
Hypogenitalism	98%	no	no
Small hands	76%	@25%	@3%
small feet		@25%	@3%

Prader-Willi syndrome occurs approximately once in every 25,000 live births but accounts for 1% of all mentally retarded individuals. Macrocrania is not a common finding and one study reported that 73% of affected individuals had head circumferences at least 1 SD below the mean (Butler and Meaney, 1987). Both of these children have features similar to those individuals with PWS (ie small hands and feet, hypotonia, obesity, psychomotor delay). Neither of these children have hypogonadism nor a facies closely similar to that usually seen in PWS They may represent a variant of PWS, and the head circumference may be part of the syndrome, dominantly inherited with variable expressivity. It is also interesting that B.D. has abnormal dermatoglyphics, an excess of arches, which was also present in her mother who is macrocranic. It is possible, however, that these children have inherited familial macrocrania and coincidentally have a PWS type syndrome.

Two individuals in the study were diagnosed as Cerebral Gigantism, a syndrome first described by Sotos in 1964, characterized by excessive growth from infancy, mental

retardation, and acromegalic changes such as large hands, feet and disproportionate sized head. C.L. and M.A., ascertained from Montreal and Vancouver were diagnosed with this syndrome based on history of birth size, (both over 4400gms) disproportionate large heads, (both > 5 S.D. above the mean) height greater than the 98th percentile, advanced bone age, and large hands and feet. Parents of these individuals were questioned regarding presence or family history of pigmented macules on the penis, and intestinal polyps, for the purpose of ruling out Ruvalcaba-Mhyre-Smith syndrome which presents with similar growth characteristics. (Halal, 1982, 1983)

S.L. presented originally with early developmental delay including some features of autism and gross motor delay. At the age of 4 $^{9}/_{12}$ he had improved markedly in most areas (perceptual, fine motor, speech) but was still approximately 2 years delayed in gross motor skills. He was seen for the current study at the age of 7 years and was functioning normally in a class appropriate for his age. His mother has a head circumference greater than the 98th percentile, and head circumference measurement could not be obtained on his father, because he lived outside the country.

M.A. was originally investigated for early developmental delay, and myoclonic seizures which were controlled with phenobarb. It was noted at the age of 15 months that he was

hypotonic and his feet were everted with a planovalgus deformity. He was seen for the present study at the age of 12 where it is reported that although he does well in school, he is followed for sustained severe, coordination defects. It is interesting to note that his father has a head circumference of 64.2 cms which is more than 3 standard deviations above the mean and a 16 year old sister has a head circumference of 62.4 cms which is approximately 6 SD above the mean and a height greater than the 98th percentile. She does not have coordination defects, nor did she have early developmental delay.

The family history makes this an unusual case since Sotos syndrome is usually sporadic, although there is a report of a family of three individuals, a mother and two daughters with features consistent with Sotos (Bale et al., 1985). Also the father of the children had a head circumference of 63 cms (Both father and mother were educated to the Master's level) The authors reviewed the literature reporting that mental retardation is now thought only to affect about 85% of cases, with a characteristic pattern of delay of expressive language and motor development in infancy followed by attainment of normal intelligence. This finding is consistent with the history of both S.L. and M.A.

D.L. was seen as part of the study at the age of 13 years. He practices competitive swimming and has a pleasant personality,

although his mother reports he has learning difficulties in all areas. He was delivered in good condition by C-Section after a prolonged labour as an only child to healthy nonconsanguineous parents. He has had several surgeries on his feet to correct a vertical talus; a skeletal survey showed that the right third rib is bifid. On current examination it was observed that he had a broad forehead, depressed nasal bridge, low set ears, flat midface, antimongoloid slant of eyes, high palate, crowding of lower teeth and some primary teeth. His right hand and foot is smaller than his left by 0.5 cms (25th to 50th%) and his left hand has a simian crease. Past clinical examinations include serum amino acids, mucopolysaccharides, and karyotype, all found to be normal. Family history demonstrated a maternal first cousin who has small hands and feet and learning difficulties, presumably due to a difficult delivery (it is not known if she is macrocranic).

D.L. does not fit into a known syndrome but because of the number of unusual features it was felt that he should not remain in the study population.

T W (now 16 years old) is the third child of healthy nonconsanguinous parents, with a maternal family history of macrocrania but no mental retardation. He was delivered by C-section, as were his two older sibs, for cephalopelvic disproportion. Early marked mental retardation was noted and he

has never been able to communicate by speaking but does use sign language. He has been treated for grand mal seizures of recent onset and also recently noted were rigid, jerky, Parkinson-like movements of his upper limbs. On examination he has a large broad forehead, prominent supraorbital ridges, thickened lips, and large low set ears. Chromosome studies including Fragile X were normal. His facies is very similar to that shown in three individuals presumably with Atkin-Flaitz-Patil syndrome, described by Baraitser and Clarke (1987). Some of his features are similar to a syndrome described by Laxova et al of an X-linked basal ganglia disorder with mental retardation although his facies is unlike the affected individuals described. Features described can be seen in Table 3, compared with the features of T.W.

Table 3

Syndrome of Laxova et al(1985)	T.W.
Macrocephaly	yes
frontal bossing	no
paresis of ocular muscle	no
seizures	yes
hypotonia	no
spasticity/rigidity	yes
movement disorder	yes
speech defect	yes.
mod to severe mental retardation	yes

It is clear that T.W. is "syndromic" and has features of known X-linked mental retardation syndromes, however it is not

certain that he fits into any particular one. This leads to a dilemma for the genetic counselling of T.W.'s sister who is now of childbearing age and also has macrocrania. It is also of interest that T.W.'s older brother has macrocrania but does not have the facial features of his brother, and is very bright. Therefore the question remains, does this syndrome include macrocrania as one of its features or is it coincidentally associated with familial macrocrania?

C.C., a severely retarded 4 year old boy born with pachygyria and lissencephaly, cortical blindness, and malrotation of the bowel. He was delivered by Cesarean Section weighing 4500 grams, to a healthy, nonconsanguineous mother and father who were 40 and 47 years old at the time of birth. He has one older healthy, bright, sister who is also macrocranic. His mother reports that his large head was detectable at 20 weeks gestation with ultrasound. He does not fit into a known syndrome, presenting with a facies very reminiscent of fetal hydantoin syndrome (although there was no exposure) and consistent with this, his dermatoglyphics consist of a high number of arches (6).

M.V., an 8 year old, with autistic tendencies, (and four toes on each foot) was delivered at 40 weeks gestation by difficult midforcep delivery, after fetal distress possibly due to cord

compression. Copious meconium was observed at the delivery although there was no report of aspiration or respiratory distress. The pregnancy was complicated by surgery at approximately the 16th week to remove an adenoma from the thyroid. A general anaesthesia was administered during this time. Following the surgery a thyroid supplement (synthroid .2g) was administered throughout pregnancy. Minimal gross motor delay was noticed at the age of 7 months. By the age of 18 months his delay was more marked and it appeared that he did respond to communication efforts by his parents. His parents are of Ashkenazi Jewish ancestry and are not consanguineous. Mucopolysaccharidosis spot test was weakly positive on first testing, but thereafter negative. Extensive laboratory testing has been negative, although in October of 1985 lactic acidosis was diagnosed at The Hospital for Sick Children. This is of interest because it has been reported that a small number of autistic children have lactic acidosis as a result of pyruvate dehydrogenase deficiency. M.V.'s PDH was found to be approximately 50% of the normal level. The significance of this was not entirely clear, but he was started on a ketogenic diet. It is also of interest that M.V. has had intestinal polyps removed surgically. He does not have pigmented penile macules, and an EMG was reported to be negative, however, the Ruvalcaba-Mhyre-Smith syndrome must be considered. This was reported and is being considered by his neurologist, with the

possibility of further pursuing the investigation with muscle biopsy. It is also interesting to note that both parents are macrocranic, and a second sib, reportedly of normal development is *micro-* cephalic.

M.T. is a 12 year old (asthmatic) female who is advanced intellectually and demonstrates this by continuing to do well in her studies after skipping a grade. She was the first born of two sibs to healthy nonconsanguineous parents. Her delivery was reported as easy and spontaneous after a long induced labour, and it was noted at birth that she had post axial polydactyly on the hands and feet At the age of 2 months it was noted that she was macrocranic, however there was no developmental delay. She since has come to attention because of poor coordination. Her height is at the 90th percentile, hand length 75%ile, third finger to hand 75%ile, upper segment to lower >1 (normal) Her joints are hyperextensible demonstrating elbow and knee extension beyond 180%. She has moderate thoracic scoliosis which is booked to be surgically treated She did not have a positive wrist and thumb signs as described by Pyeritz (1983). Her skin is soft but not noticably hyperextensible.

Although M.T. has features of joint laxity probably due to a mild connective tissue disorder, contributing to her poor coordination, she does not have features consistent (or marked enough) to be considered Marfan's syndrome. Ehlers Danlos type III, (Benign familial hypermobility), (Byers et al,1983) which is

autosomal dominant, is considered as a likely diagnosis. Neither parent report signs of being affected, but a maternal uncle has scoliosis and polydactyly.