INVESTIGATION OF FAMILIES WITH TWO OR MORE MENTALLY RETARDED SIBLINGS: A PROPOSED SIBLING EVALUATION METHOD

Thesis for the Degree of M. S.

MICHIGAN STATE UNIVERSITY

ROBERT JOHN PANDOLFI

1973

College of Natural Science

, 1973

Robert J Landolfi

ABSTRACT

INVESTIGATION OF FAMILIES WITH TWO OR MORE MENTALLY RETARDED SIBLINGS: A PROPOSED SIBLING EVALUATION METHOD

By

Robert John Pandolfi

Forty-nine families were identified in which two or more siblings were mentally retarded and residents of Lapeer State Home and Training School. For each such family, data on age, I.Q., diagnosis, maternal and paternal age and mental status, numbers of normal and retarded siblings, physical and biochemical characteristics, birth weight, parturition, early development, socio-economic status, family history and cytogenetic findings were collected. The data were collectively analyzed to obtain a range of variables which exist in a population which has produced an excess of retarded individuals. After analyzing the various data a "sibling evaluation method" was devised to facilitate a rapid identification of those families within the retarded population that have an increased chance of displaying a previously undescribed biochemical defect or syndrome.

INVESTIGATION OF FAMILIES WITH TWO OR MORE MENTALLY RETARDED SIBLINGS: A PROPOSED SIBLING EVALUATION METHOD

By

Robert John Pandolfi

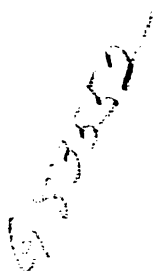
A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

MASTER OF SCIENCE

Department of Zoology

1973



To My Parents and Family

ACKNOWLEDGMENTS

It is a pleasure to acknowledge help and encouragement received during the development of this thesis.

The author especially wishes to express his gratitude and admiration to Dr. James V. Higgins for his guidance and patience during the course of this study.

I wish to thank Drs. Emanual Hackel and John Shaver for serving on my guidance committee and offering their advice and criticisms.

I also wish to thank Dr. Herman Slatis for his advice during the initial development of this thesis.

This study could not have materialized without the co-operation of the staff and administration of Lapeer State Home and Training School. Special thanks to Mrs. Cora Crow and her staff in Resident Records and Mr. John Sting, Director of Resident Affairs.

I wish to thank my fellow graduate students Mike Abruzzo, Sally Cullen, Habib Fakhrai, Dan Friderici, Terry Hassold, Gary Marsiglia, Kathy Blight, Sue Reimer, Lou Betty Richardson and Carola Wilson for their friendship and encouragement during the past three years.

Thanks to my good friends John Brissette and Tom Adair for their help in the preparation of charts and tables.

Last, but not least, I wish to express my deepest appreciation to my parents for their concern, encouragement and support throughout the course of my education.

TABLE OF CONTENTS

	Page
DEDICATION	ii
ACKNOWLEDGMENTS	iii
LIST OF TABLES	vi
LIST OF FIGURES	viii
LIST OF APPENDICES	ix
INTRODUCTION	1
LITERATURE REVIEW	3
METHODS	17
RESULTS	20
Intellectual Status	20
Age	23
Sex Distribution	25
Diagnoses	27
Position in Family Birth Order	28
Maternal and Paternal Age at Time of Retardate's Birth	28
Maternal and Paternal Mental Status	30
Number of Retarded Siblings Excluding Probands	33
Birth Weight	33
Parturition	33
Early Development	35
Socio-Economic Status	37
Abnormal Physical Characteristics	40
Sibling Evaluation Method	46
DISCUSSION	57
SUMMARY	67
APPENDICIES	70
REFERENCES	87

LIST OF TABLES

Table		Page
1.	Levels of Mental Retardation	5
2.	Sex Distribution of 230 Siblings According to Intellectual Status	21
3.	Distribution of Families According to Family Size and Numbers of Retarded Siblings	24
4.	Age Distribution of Retarded Sibling Group Individuals	25
5.	Sex Distribution of 230 Siblings According to Intellectual Status	26
6.	Sex Distribution of 49 Mentally Retarded Sibling Groups	26
7.	Diagnoses of 104 Siblings in 49 Families	28
8.	Frequency of Birth Order Position of 105 Mentally Retarded Siblings from 49 Families	29
9.	Parental Mental Status of 49 Retarded Sibling Groups	32
10.	Intellectual Status of the Offspring of 22 Not Retarded, Retarded, Questionably Retarded, Mentally Ill and Questionably Mentally Ill Parents	32
11.	Summary of the Parturition Process of 114 Retarded Siblings in 49 Families	35
12.	Explanation of 23 Abnormal Births of 114 Retarded Siblings in 49 Families	36
13.	Summary of Early Development of 114 Siblings in 49 Families	38
14.	Explanation of the Abnormal Early Development of 25 Siblings	38

Table Page

15. Socio-Economic Status of 49 Families Containing 114 Retarded Siblings 39

16. Comparison of I.Q. Levels of Retarded Siblings from Dependent and Non-Dependent Families . . 39

17. Key of Physical Data Code 41

18. Frequency of Specific Abnormalities in 89 Retarded Siblings 43

19. Abnormal Physical Characteristics Common in 89 Retarded Siblings 44

20. A Sibling Evaluation Method 47

21. Comparison of the Distribution of Retardation Between the Present Study and Studies by Wright *et al.* (1959) and Priest *et al.* (1961). 58

22. The Frequency of Mental Retardation within 49 Families that Contain Two or More Retarded Siblings (after removal of 98 probands) . . . 63

LIST OF FIGURES

Figure		Page
1.	Intellectual Status of 243 Siblings in 49 Families.	22
2.	Age Distributions of Parents of 49 Retarded Sibling Groups.	31
3.	Distribution by Birth Weight of Sex of 90 Individuals in 49 Sibling Groups.	34

LIST OF APPENDICES

Appendix		Page
A.	Code	71
B.	Abnormal Physical Characteristics in the Siblings at Lapeer State Home	81

INTRODUCTION

Mental retardation is a condition which afflicts 3 percent of the population; for 65 to 70 percent of these people the retardation is of unknown etiology. The remaining 30 to 35 percent have a known etiology and fall into over one hundred well defined syndromes. Before prevention or treatment of mental retardation can be realized, the causative factors must be elucidated; this has been shown most clearly in the classic example of phenylketonuria. Although all retardates included in the "unknown cause" group do not have inherited defects, there exists a probability that a number of syndromes with a genetic basis have yet to be discovered. Thus, the problem is reduced to finding a population of individuals who have an increased risk of having inherited defects which are manifested as mental retardation. Criteria for selection of this population will be examined in this study.

There are various methods of organizing screening procedures to identify these high risk individuals. Wright et al. (1959) was the first to examine only retarded siblings in the hopes of identifying new syndromes. The present study will take the same approach of examining only those families which contain two or more retarded siblings. The

investigation has a two-fold purpose: (1) to identify for further study those families in which there appears to be a good probability of having a previously unidentified genetic defect, and (2) to set up criteria, based upon the findings of this and other studies, which will facilitate a more rapid identification of these high-probability families from the retarded population.

LITERATURE REVIEW

"Mental Retardation refers to subaverage general intellectual functioning which originates during the developmental period and is associated with impairment in adaptive behavior" (Heber, 1959). This is the official definition which was adopted by the American Association on Mental Deficiency in 1959. The term mental retardation incorporates all of the meanings that have been historically ascribed to such concepts as amentia, feeblemindedness, mental deficiency, mental subnormality, idiocy, imbecility, moronity, etc. Choice of the term was made since it appears to be the most preferred term of professional personnel of all disciplines concerned (Heber 1959). "Subaverage," in the context of Heber's definition, refers to performance, which is more than one standard deviation below the population mean of the age group involved, on measures of general intellectual functioning. "General Intellectual Functioning" is assessed by performance on various standardized tests that have been developed for that purpose. The upper age limit of the "developmental period" has been regarded, for practical purposes, as approximately sixteen years. "Impairment in adaptive behavior," as used in the definition, refers to the individual's inability to adapt to the natural and social demands of his environment (Heber, 1959).

Intellectual functioning is measured by intellectual quotient, or I.Q., which is defined as the quotient (multiplied by 100) of the mental age of the individual, as defined by the standardized test, and his chronological age. These tests assign a score of 100 as the mean value of the population and are constructed so that higher and lower scores are distributed approximately in a normal curve (Stern, 1960). This results in a decreasing number of individuals achieving scores which have a increasing deviation from the mean. The official classification of the American Association on Mental Deficiency uses intelligence test scores as the basis for categorizing the degrees or levels of mental retardation. Table 1 is adapted from the Association's manual. It is pointed out that conversion of I.Q. scores according to standard deviation values will vary slightly depending on the particular test utilized.

Jaederholm, in collaboration with Pearson, carried out one of the first quantitative studies on mental retardation (Pearson and Jaederholm, 1914). They tested and analyzed 301 children attending "help classes" in Stockholm as well as a control group. The test scores were continuously distributed and gave a good approximation to a Gaussian curve. They also showed that the children in the "help classes" formed part of this distribution; the fit was three times better if they were included. Pearson and Jaederholm stated that it was clear that very low grade

TABLE 1.--Levels of Mental Retardation.*

Level of Deviation in Measured Intelligence	Range of Level in Standard Deviation Units	Descriptive Term	Conversion of I.Q. Scores to Standard Deviation Scores		
			A**	B	C
-1	-1.01 to -2.00	Borderline	83-67	83-68	84-70
-2	-2.01 to -3.00	Mild	66-50	67-52	69-55
-3	-3.01 to -4.00	Moderate	49-33	51-36	54-40
-4	-4.01 to -5.00	Severe	32-16	35-20	
-5	Less than -5.00	Profound	Less than 16	Less than 20	

*Adapted from Heber, 1958.

**A=Arthur Point Scale of Performance Tests, Form I.
B=Revised Stanford Binet Tests of Intelligence, Forms L. and M.
C=Wechsler-Bellevue Intelligence Scale, Forms I and II. Wechsler Intelligence Scale for Children. Wechsler Adult Intelligence Scale.

defectives could not be accommodated in the normal curve. They also found an excess in the moderate and mild retarded groups. They concluded that the causation of defect for low grade defectives was pathological, whereas most of those in the "help classes" represented the negative tail of the normal distribution. This paper was largely overlooked, for it wasn't until 1918 when Fisher provided the basis for the genetic treatment of continuous variation, could Pearson and Jaederholm's paper be understood in the context of then current Mendelian thought. A more detailed examination of the negative tail of the normal curve was undertaken by Roberts, Norman and Griffiths (1938), and summarized by Roberts (1950). The conclusions reached were that at the extreme negative tail there is an excess of very low values, representing deviations due to definite pathological causes, either an abnormal gene or an accident in development. The proportion of these extreme deviates was estimated as four per thousand. Some of the single causes may produce no more than moderate retardation, but the indications are that their contribution to the sum total of high grade mental deficiency is relatively small. The great bulk of high grade mental deficiency is multiple in causation and the genetic element is multifactorial. Doll, on the other hand, questions the concept of mental retardation in terms of continuous variation. He claims there is something innate about a high grade institutionalized defective which differentiates him

from non-institutionalized individuals of equal I.Q. who are not defectives (Doll, 1947). This may be genetic, but it has not been demonstrated. Masland believes that the factor of brain damage operates throughout the whole range of intelligence and that minor degrees of damage are much more common than those which are severe and overt (Masland et al. 1958).

It is generally agreed that about three percent of the general population will demonstrate difficulties in environmental adjustment that is associated with subnormal intelligence in sufficient degree to result in their being identified as retarded (Eastham and Jancer, 1958, Reed and Reed, 1965). This estimate represents the number of persons who may be identified as retarded at some point in their lives and does not reflect the number who will be identified and will require special services at any given point in time. Practically all previous investigators have reported the highest frequency of mental retardation to occur during the school years, with a peak at 10 to 12 years [Mayer-Gross (1948), Dahlberg (1951), Essen-Moller (1954) and Goodman et al. (1956)]. The usual explanation presented is that at this age the schools impose their highest standards of adaptive behavior with a focus on abstract verbal performance. These authors agree that many persons who are indistinguishable from their age peers in the preschool years fail to meet minimum requirements in school and are

identified as retarded. Upon termination of schooling, they merge into society, make an adequate adjustment, and therefore can no longer be viewed as retarded. Lemkay and Imre (1966) believe that opportunities are presented to evaluate the intelligence of the entire population only through the school years. Instead of relying, as previous surveys had done, upon schools and community clinics for identification of retardates, these investigators evaluated every household in the sample area. Unlike the previous studies, they did not find a decrement in prevalence at postschool ages, nor did they find as sharp an increment in prevalence from preschool to school entry.

Various studies have indicated that there are a greater number of male than female retardates. Penrose (1938) found that 56.5 percent of his probands were male; Askesson (1961) found 53.8 percent males in his study of mental retardation in Southern Sweden. Birch (1970) found that in the eight to ten year old category 56 percent of the retardates were male, even though the number of males and females in his population was almost equal (51 percent males). Reed and Reed (1965), on the other hand, had a lesser number of male probands in their study: 47.7 percent males.

There are clear differences in the mean I.Q.'s of various socio-economic groups. This will give rise to substantial differences in the prevalence of I.Q.'s falling

into the mentally retarded range. It has been shown by Halperin (1945), Buch et al. (1970) and Heber (1970) that the lower the socio-economic status of the family, the higher the incidence of mental retardation. This has been shown most clearly for borderline and mild retardation. The incidence of very severe retardation appears to be independent of the socio-economic status of the home. These findings remain similar regardless of whether the groups are defined in terms of family income, quality of housing, parental education or parental occupation (Heber, 1970).

Reed and Reed (1965) have found that five-sixths of the retardates in their study are either first or second degree relatives of another retarded person. They point out that this data is of great significance because it demonstrates the large extent to which transmission is involved in the etiology of mental retardation. This is supported by a table compiled by Brugger (1939), indicating the nature of the increasing risks of mental retardation with one or more parents involved. Levitan and Montagu (1971) also state that the normal children of defective parents are likely to have a lowered intelligence as a consequence of the inheritance of some of the defective genes from a defective parent or parents.

Maternal age is a well known factor in the etiology of certain conditions. Down's syndrome is more frequent in children of older mothers; so is hydrocephalus, spina bifida

and anencephaly (Crome and Stern, 1967). They claim that the estimated excess in the incidence of various malformations in children of mothers aged 40 years or more was approximately two to three times that found in younger mothers. There is also a considerably increased risk for very young mothers, those under 15 years (Hendricks, 1955). The father's age appears to be much less important, but according to Blank (1960), there is a slight correlation of acrocephalosyndactyly (Apert's syndrome) with advanced paternal age. Higher paternal age may also be significant in the incidence of the 21/22 translocation form of Down's syndrome (Penrose, 1963).

The risk of being congenitally malformed and mentally retarded is not the same for all members of a sibship. All firstborns and the younger children in large families seem to run a greater risk; the additional hazards are, however, not very high (Penrose, 1963), and pathogenic mechanisms are uncertain. Since it is known that first births tend to be more difficult than later ones, some of the danger in the case of firstborn children may be from birth injury (Crome and Stern, 1967). However, primogeniture is also a factor in the etiology of conditions which cannot be attributed to birth injury, e.g. anencephaly and spina bifida (Pitt, 1962; Penrose, 1963).

The season of birth has been shown to be related to the incidence of certain congenital malformations. Anencephaly, hairlip and congenital dislocation of the hip occur

with a slightly increased frequency in children born in the winter (Edwards, 1961). The mortality rate of infants with congenital malformations has been shown by Buck (1955) in Canada to be higher between November and March than at other times of the year. Pintner and Forlano (1943) found that children born in the winter were more frequently retarded. This agrees with the findings of Knoblock and Pasamanick (1958) and thus suggests that the significant factor may be the hot weather during the early organogenic stage of gestation. The heat, according to this argument, could upset metabolism in certain vulnerable individuals.

The etiology of mental retardation has been divided into various groups but approximately 60 to 70 percent of all cases still must be placed in the unknown category (Wright et al., 1959; Eastham and Jancar, 1968). About 20 percent of cases are thought to be due to exogenous causes (e.g. birth injuries, etc.), 5 percent are caused by known metabolic disorders and 5 percent are caused by recognized chromosomal anomalies (Eastham and Jancar, 1968). Reviews of the causes of mental retardation are numerous. They include Wright et al. (1958), Hirschhorn and Cooper (1961), Anderson (1964), Oster (1964), Eastham and Jancar (1968) and Heber (1970).

Several investigators have directed their research toward siblings in an attempt to delineate new syndromes (Wright et al., 1959; Priest et al., 1961; Karlsson et al.,

1961). Wright et al., studied 61 families clinically and made careful examinations of urine, blood, and buccal smears of 110 siblings in a search for previously unidentified biochemical or chromosomal anomalies, but failed to find any. They suggested that the sampling procedure would be improved by using only cases of severe retardation (I.Q. under 50) and without significant environmental factors. They further stated that some biochemical defects might cause death at an early age, with the result being that such diseases would be under-represented in an institutional population. It is their belief that a study of cerebrospinal fluid may be more revealing than an analysis of blood or urine.

Priest et al. (1961) analyzed data from 83 families with two or more retarded siblings, examining relationships between parental mental status, sibling mental status and family size. Priest found that 90 percent of the families studied had non-specific diagnoses.

Karlsson et al. (1961) examined the urine of siblings in 50 unrelated families for excretion of nitrogenous compounds. In each case where a high excretor was found, it was noted that the excretor's sibling was also a high excretor or in the high norm group. Since this occurred in nine families they suspect that a common gene basis exists between the sibs in a given family. Their observations, however, only show a kidney absorption defect which may be multicausal.

The theoretical justification for sib studies was provided by Fisher (1918) and reviewed by Roberts (1964). It has been shown that siblings hold one-half of their genes in common. Thus, the likelihood seems high that within families with two or more retarded siblings, there are some persons with an inherited defect. Many genetically determined biochemical abnormalities associated with mental retardation have first been described in siblings. As Wright (1959) points out, there were two defective brothers among the first group of patients with phenylketonuria described by Folling; Baron and his co-workers described Hartnup disease in two sibs in one family; Allen described aminoaciduria with mental retardation in a brother and sister; "maple syrup" urine disease was first noted in four siblings from one family and Bigler described an abnormality of lipoproteins in two defective sibs.

Renpenning et al., in 1962, described a large family in which mental retardation appears to be inherited as a sex-linked recessive; the mean I.Q. is approximately 30, with a great preponderance of I.Q.'s in the 20 to 35 range. The retardation has made its appearance in three successive generations resulting in 21 retarded males. The striking feature of this condition is the lack of any physical, or detectable biochemical or chromosomal anomalies; Renpenning claims that the men are well built, physically strong and have no definite abnormal features apart from somewhat prominent ears.

As Smith and Bostian (1964) point out, congenital anomalies of structure are indicators of abnormal prenatal development. These anomalies are arbitrarily divided into those which are of major concern and those which are of minor concern. Defects which cause a medical or cosmetic problem are termed major, and those which are not a direct consequence to the patient are termed minor defects. Since minor anomalies are by definition not a management problem, they may be overlooked and their potential significance as indicators of altered embryonic differentiation not appreciated (Smith and Bostian, 1964). Opitz (1969) states that it is of paramount importance to search for minor anomalies associated with mental retardation. He points out that minor anomalies may indicate the presence of a major anomaly. The study by Marden et al. (1964) of several thousand newborn infants showed that some 15 percent of them had one minor anomaly, 0.76 percent had two, and about one in 2000 had three or more. Of the last group, over 90 percent also had a major anomaly. More importantly, claims Opitz, several minor anomalies are frequently found in individuals with idiopathic mental retardation. The study by Smith and Bostian (1964) showed that some 42 percent of children with idiopathic mental retardation had three or more anomalies, 80 percent which were minor. At the present time it is impossible to state which individual or particular combination of minor anomalies observed in the neonatal period

are most frequently associated with later mental retardation. Opitz believes that the risk of mental retardation increases directly with the number and severity of the anomalies in the patient. He also believes that the presence of three or more minor and/or major anomalies in an individual with mental retardation may indicate more than a developmental relationship between the retardation and the dysmorphogenetic syndrome; there may be a common cause for the malformation and the retardation. Since at the present time it is probably impossible to prepare a comprehensive list of all minor anomalies detectable on a surface examination, Opitz considers that it is more important to be aware of normal structure and then to be alert and to note any obvious variation from this "normal" pattern during the examination of a particular patient. He further recognizes that the practical assessment of minor anomalies is further complicated by the fact that most of them have not yet been quantitated; thus it is frequently difficult to evaluate the validity of published claims that a particular patient had certain minor anomalies, especially if these observations are not documented. Opitz suggests that collaborative studies begin in order to find objective anthropometric criteria that can be used to describe minor variations of normal development in quantitative terms. He also points out that some anomalies may change with age, that some traits may differ in incidence and/or severity in one or the other sex, that there probably

exists no obligatory anomalies in a given syndrome, that the severity of given anomalies will vary from person to person in a given syndrome and that not all anomalies have the same penetrance. He summarizes by stating: "the greater the total number of anomalies identified in a given syndrome, and the greater the mean penetrance of the component anomalies, the greater will be the mean number of anomalies per patient and the greater is the chance that a reliable diagnosis can be made."

METHODS

This study was carried out at Lapeer State Home and Training School, a Michigan State Home for the mentally retarded. Among a population of about 2,500 residents, 49 families were identified in whom two or more retarded siblings were, at the time of this study, residents of Lapeer State Home. Identification of these families were made by Lapeer personnel from Resident Records.

Each resident's folder was examined in detail and the following data collected:

1. age
2. sex
3. I.Q.
4. specific diagnosis
5. birth order
6. maternal age at time of resident's birth
7. maternal mental status
8. paternal age at time of resident's birth
9. paternal mental status
10. number of normal siblings
11. number of retarded siblings, excluding probands
12. birth weight (lbs, oz.)
13. parturition difficulties
14. resident's early development
15. socio-economic status of resident's family.

The genetic laboratory records at Lapeer State Home were also examined; urine is routinely screened for pH, glucose, blood protein, ketones, reducing substances, phenylalanine, ketoacids, sulfhydryl groups, mucopolysaccharides, indican and hydrindic acid. Urinary chromotography is also

performed and stained with ninhydrin, Ehrlich's and Pauly's reagents. In addition, blood chromatographic studies are done in order to determine aminoacidemias or aminoacidurias; any abnormal findings are noted. Karyotypes were available for selected residents; this information was examined and the results incorporated.

The family history of all sibling groups was examined to determine the extent of mental retardation in each family. Information was available in the medical and family history records at the institution. Additional information, when required, was obtained directly through the family or guardians of the resident by questionnaires.

Each resident included in the study was given a surface physical examination to record major and/or minor anomalies of development; also reported were any physical characteristic not commonly found in the population. These data were coded by a numbering method adapted from Meditel, a computerized diagnostic aid for the practicing physician. A key to this code may be found in the results section.

All data obtained were collectively analyzed and compared to previous studies. Each sibling set was then individually analyzed on the basis of data collected and a determination was made if the family seemed to warrant further, detailed biochemical examination. After analysis, certain criteria were derived from this data and that of

previous studies to develop a sibling evaluation method to facilitate a more rapid screening procedure.

RESULTS

In presenting the results, a "sibling group" will refer to all children of a family that contains two or more retarded sibs; a "retarded sibling group" will refer only to the defective siblings within the family. Table 2 and Figure 1 represent in tabular and graphic form data on number and intellectual status of all sibs in the 49 families. The identification of families in the text refers to the number assigned to the family in Figure 1.

Intellectual Status

As can be seen from Table 2 and Figure 1, there are 243 children in 49 families; 103 children are considered not retarded and are indicated on the chart by the open symbols. These are persons about whom statements appeared in Lapeer Resident Record folders that they are of normal intelligence or are doing satifactorily in school or adequately in employment. Twenty-three persons are designated in the category "unknown" because of lack of adequate information. Some are persons for whom no reliable information could be obtained from records or questionnaires (family no. 14, 15, 21, 22, 31 and 34); others are placed in this category if death occurred before intellectual status could be determined (family no. 4, 7 and 35). Also included in this category

TABLE 2.--Sex Distribution of 230 Siblings According to Intellectual Status.

Intellectual Status	Males		Females	
Normal	52	(39.7%)	48	(57.8%)
Retarded	79	(60.3%	35	(42.2%)
Unknown	12		4	
Total	143		87	
		230		
	Unknown	13		
		243		

are three children who were classified in Table 2 as "questionably retarded" (family no. 3 and 21), and are indicated as half-shaded symbols in Figure 1. This is an arbitrary group of siblings about whom the Resident Record folders contained such statements as "slow," "dull," or "subnormal." These siblings have not been formally tested for intellectual status and are thus placed in the "unknown" category in Figure 1.

Nine siblings are listed as "retarded, I.Q. unknown." They include four siblings who are still at home (family no. 19, 28 and 39), three in other institutions (family no. 47), and two who are dead (family no. 15 and 36). There was definite evidence that the I.Q.'s of all of these children were in the retarded range, i.e. less than 70, but these tests had been done at outside facilities.

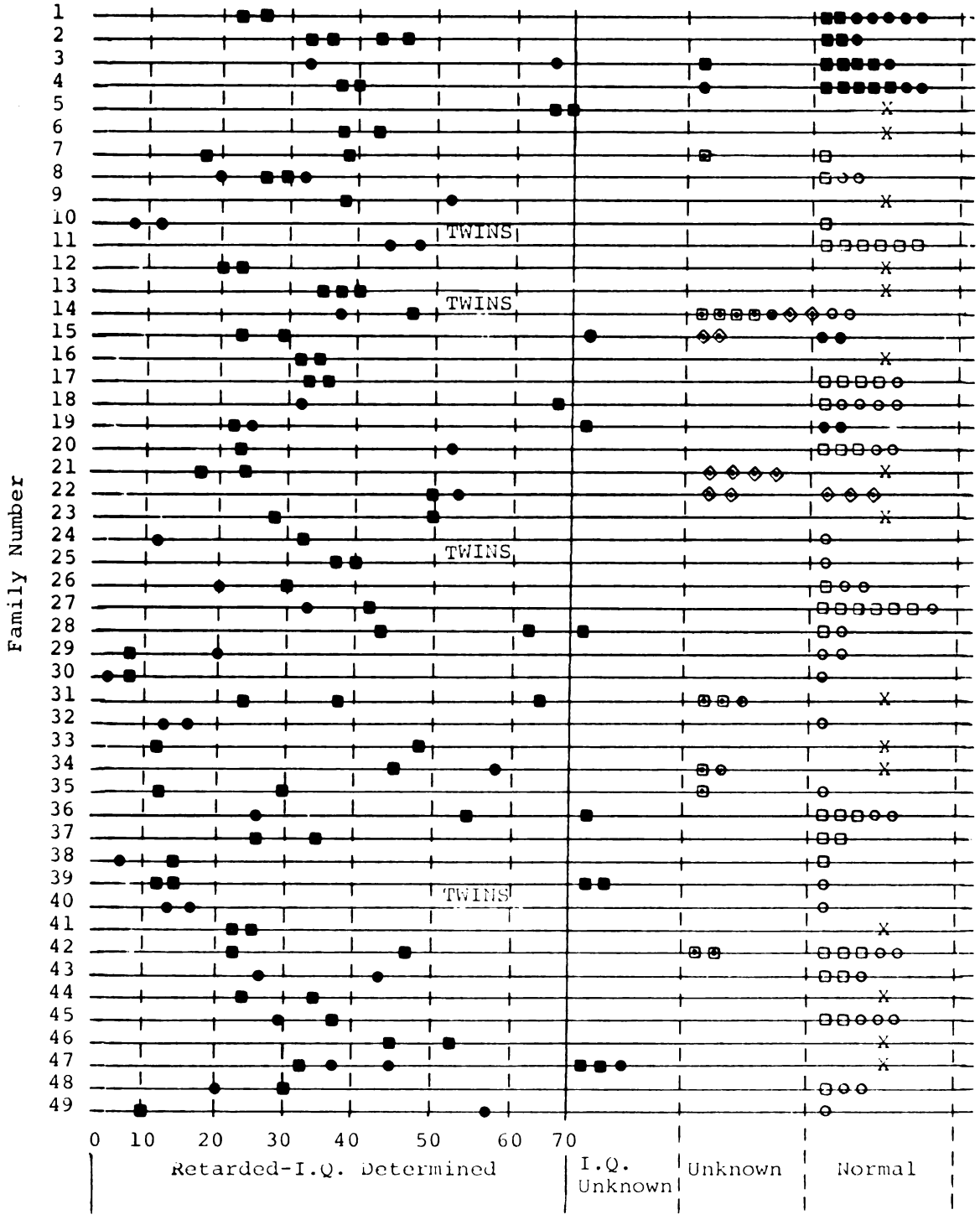


Figure 1.--Intellectual Status of 243 Siblings in 49 Families.

The 114 siblings who were in Lapeer State Home and who comprise the "retarded, I.Q. determined" group are indicated in the chart according to the highest known I.Q. of the retarded sib within the family. The most recent determination of I.Q. is presented in the chart.

Table 3 presents the distribution of the 49 families according to the number of children in the family and the number of defective siblings among them. The size of the sibling groups range from 2 to 11, and the number of retarded children in the groups from two to six. The 49 families are arranged according to this scheme, from 10 families with only two siblings, both retarded to one family with 11 siblings with two known retarded persons (family no. 14).

Age

Age data, determined as the number of whole years between the year of birth and 1972, were collected for 107 of the 114 retardates. For seven retardates data could neither be obtained through records or questionnaires (one sib of family 15, two sibs of family 39 and three sibs of family 47); one member of retarded sibling group no. 39 died at four years. Table 4 is a tabulation of age data. The mean age for the 107 retardates was 29.6 years with a range of 5 to 72 years.

TABLE 3.--Distribution of Families According to Family Size and Numbers of Retarded Siblings.

No. Children in Family	No. Such Families	Total No. Children	Total Retarded Siblings	Distribution of Families According to Number of Retarded Sibs				
				1	3	4	5	6
2	10	20	20	10				
3	9	27	19	8	1			
4	5	20	10	5				
5	6	30	16	3	2	1		
6	3	18	11	1	1			
7	8	56	21	5	1	2		
8	3	24	7	2	1			
9	3	27	6	3				
10	1	10	2	1				
11	1	11	2	1				
Total	49	243	114			49		

TABLE 4.--Age Distribution of Retarded Sibling Group Individuals.

Age Range (Years)	No. of Retardates	Percent of Total
1 - 10	4	3.7
11 - 20	38	35.5
21 - 30	25	23.4
31 - 40	13	12.1
41 - 50	13	12.1
Above 50	14	13.1
Total	107	100.0

Sex Distribution

The sex distribution of 230 siblings according to intellectual status is given in Table 5. The sex of 13 siblings from four families could not be determined from the records or through questionnaires; these sibs were excluded from Table 5. There were 143 males, of whom 79, or 60.3 percent were retarded, and 87 females, of whom 35, or 42.4 percent were retarded.

The sex distribution of the 49 families is given in Table 6. In 24 of the 49 families only males were retarded. In six families females alone are affected (two families were the result of identical twins) and in 19 families there are both male and female retarded siblings. The data was analyzed by comparing the number of families expected to contain male retardates only to that observed. For families which contain, for example, two retarded sibs, we would

TABLE 5.--Sex Distribution of 230 Siblings According to Intellectual Status.

Intellectual Status	Males		Females	
Normal	52	(39.7%)	48	(57.8%)
Retarded	79	(60.3%)	35	(42.2%)
Unknown	12		4	
Total	143		87	
		230		
	Unknown	13		
		243		

TABLE 6.--Sex Distribution of 49 Mentally Retarded Sibling Groups.

Sex of Retarded Siblings	No. of Families (%)
All Male	24 (49)
All Female	6 (12)
Mixed (Males and Females)	19 (39)

expect p^2 of those families to contain males only; $1-p^2$ would represent the expected proportion of families which do not contain only male retardates. For p = .54 (the frequency of males in Lapeer State Home), chi-square was calculated to be 10.98, which shows, at a confidence level of .001, that there is an excess of families which contain only male retardates. To determine if this observed excess was due to an overall excess of males within our sample, the probands (the two retarded sibs with the lowest I.Q. from each family in Figure 1) were removed, and an expected number of males were calculated and compared to number observed. Chi-square was .1818, indicating that it was not a disproportionate number of males that was responsible for the excess of families with only males retarded. One may therefore speculate that this excess of families with only male retardates may be due to sex linkage, sex influence and/or sex limitation.

Diagnoses

One hundred and four of the 114 retardates in the 49 retarded sibling groups were examined by the medical staff at Lapeer State Home; diagnoses were made and appear in the Appendix. Table 7 summarizes the data collected. Non-specific diagnoses were made in 85, or 81.7 percent of the cases. Nineteen specific diagnoses were made, and these appear in Table 7; each diagnosis is based upon clinical

TABLE 7.--Diagnoses of 104 Siblings in 49 Families.

Diagnosis	No. of Siblings	Percent
Non-specific	85	81.7
Specific	19	18.3
Down's Syndrome (Tri-G)	6	
Phenylketonuria	6	
Down's Syndrome (G-G Trans.)	2	
Kernicterus	2	
Tay-Sach's Disease	1	
Bielschowsky's Disease	1	
Congenital Lipodosis	1	

examination, laboratory analysis, and cytogenetic procedures where applicable.

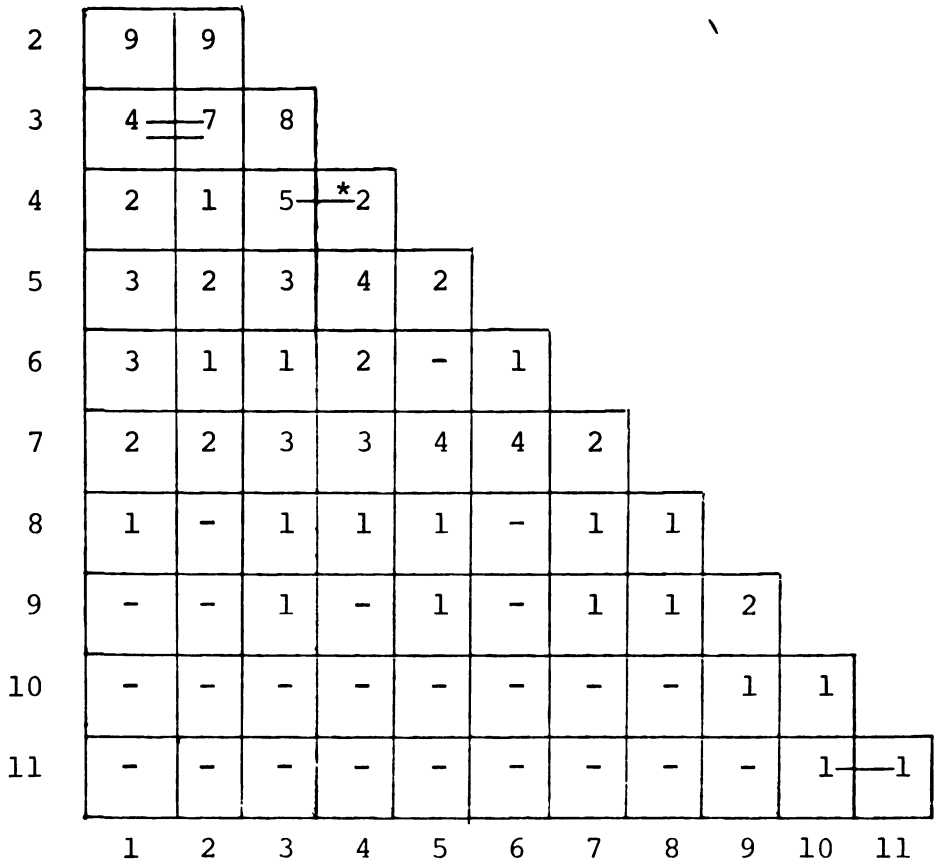
Position in Family Birth Order

These data are reproduced in the Appendix and summarized in Table 8; this table gives the relative frequency of position in birth order of 105 retardates with respect to their sibship size. The quantity of data collected was too small to be validated by non-parametric methods.

Maternal and Paternal Age at Time of Retardate's Birth

The maternal and paternal age at the time of the retarded child's birth were determined from the records; in 96 of 114 cases, this information was available. The mean maternal age of these 96 children was 27.1 years with a standard deviation of 6.8 years; the father's mean age at

TABLE 8.--Frequency of Birth Order Position of 105 Mentally Retarded Siblings from 49 Families.



*Note: A dashed line between adjacent birth positions indicate the occurrence of twins.

the time of the retardate's birth was 31.3 years with a standard deviation of 8.6 years. Figure 2 shows the distribution of parental ages. Maternal age is skewed while the paternal age is randomly scattered from 20 to 59 years.

Maternal and Paternal Mental Status

Table 9 presents this data using the following terminology:

Retarded: I.Q. known to be less than 70, or adequate evidence of retardation by history.

Questionable Retarded: I.Q. unknown but questionably retardation by evidence in the history as indicated by such terms as "slow" or "dull."

Not Retarded: I.Q. known to be 90 or above or evidence by history of normal mental function as indicated by terms such as "normal," "average" or "bright."

Mentally Ill: Evidence by history of confinement in a mental hospital or documented psychiatric reports.

Questionably Mentally Ill: Questionably evidence of emotional or mental instability in the history as consistently indicated by such terms as "unstable," "mental insecurity" or "nervous temperment."

Unknown: No reliable information of any kind available with respect to mental functioning.

Table 10 presents the intellectual status of the offspring of these parents. The number within the parenthesis following each category represent the total number of parents within that category.

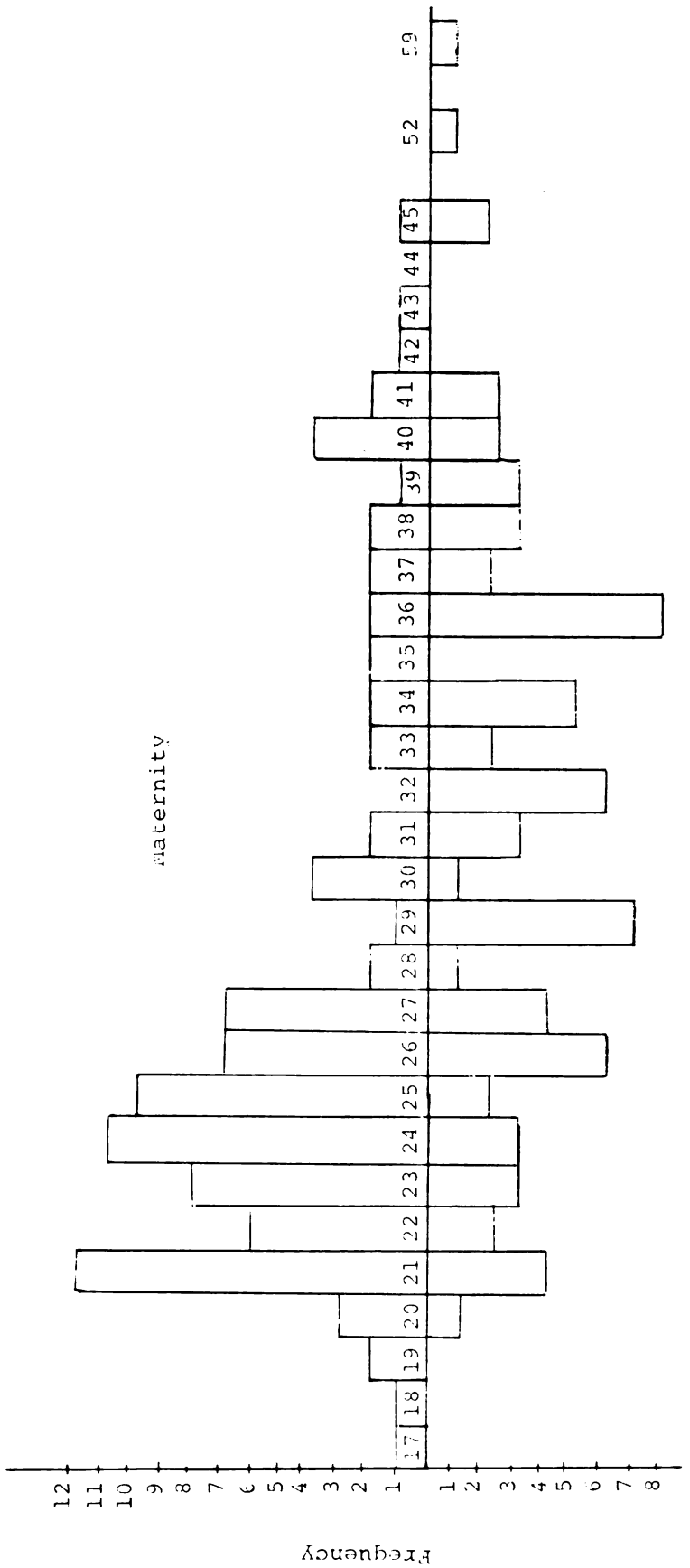


Figure 2.--Age Distributions of Parents of 49 Retarded Sibling Groups.

TABLE 9.--Parental Mental Status of 49 Retarded Sibling Groups.

Mental Status	No. of Mothers	No. of Fathers
Not Retarded	33	37
Retarded	3	0
Questionably Retarded	6	5
Mentally Ill	3	1
Questionably Mentally Ill	1	3
Unknown	3	3
Total	49	49

TABLE 10.--Intellectual Status of the Offspring of 22 Not Retarded, Retarded, Questionably Retarded, Mentally Ill and Questionably Mentally Ill Parents.

		No. of Retarded Offspring I.Q.			
		Below 20	20-50	Above 50	Total
Maternity (No. Affected)	Not Retarded (33)	16	47	6	69
	Retarded (3)	2	5	1	8
	Questionably Retarded (6)	1	12	2	15
	Mentally Ill (3)	2	1	2	5
	Questionably Mentally Ill (1)	0	1	1	2
Paternity (No. Affected)	Not Retarded (37)	14	55	9	78
	Retarded (0)	0	0	0	0
	Questionably Retarded (5)	2	8	1	11
	Mentally Ill (1)	2	0	0	2
	Questionably Mentally Ill (3)	2	3	1	6

Number of Retarded Siblings Excluding Probands

There are a total of 114 retardates in the 49 families. Excluding the probands and the 26 persons in the mentally unknown category (including three in the questionably retarded group) there remains 16 retarded siblings and 119 total siblings, which is 13.4 percent. If the 26 whose mentality is unknown are included in the total sibling group the percentage of retarded sibs drops to 11.0 percent. Three of 26, or 11.5 percent, of the children in the unknown group exhibit questionable evidence of retardation.

Birth Weight

Birth weights were available for 90 retarded members of the 49 families; the range was 4.12 to 9.50 pounds with a mean of 7.02 pounds and a standard deviation of 1.34 pounds. The mean weight for males was 7.25 pounds with a standard deviation of 1.33 pounds; for females the mean weight was 6.51 pounds with a standard deviation of 1.25 pounds. The distribution is represented in Figure 3.

Parturition

Information was available about the births of 95 siblings. Table 11 summarizes the parturition process and events which could cause cranial injury at birth (use of instruments, etc.). The following terminology is used:

Apparently Normal: Reports from hospital records, physician's reports and maternal information indicates that no injury or condition which could lead to mental retardation was noted at birth.

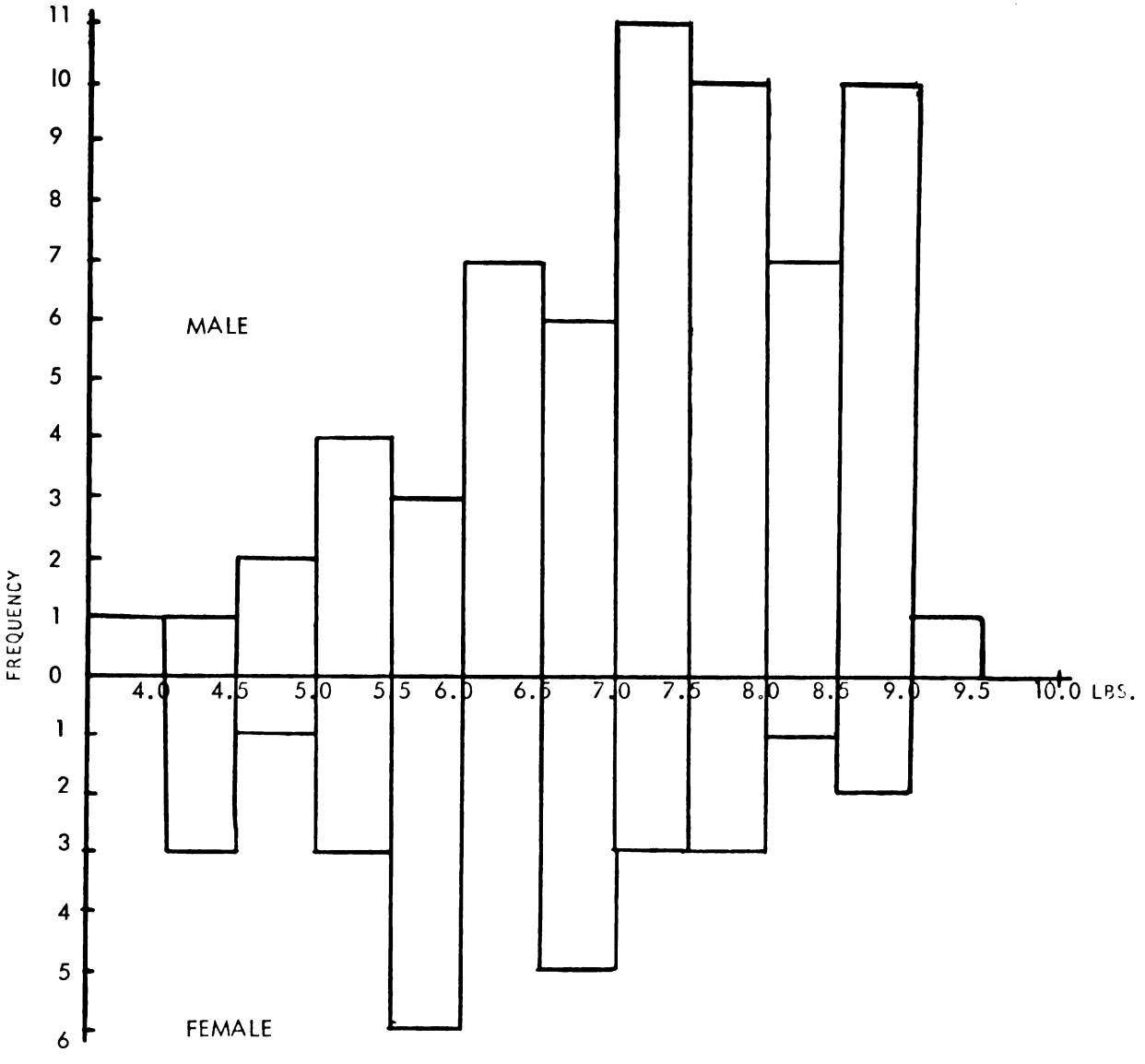


Figure 3.--Distribution by Birth Weight of Sex of 90 Individuals in 49 Sibling Groups.

TABLE 11.--Summary of the Parturition Process of 114 Retarded Siblings in 49 Families.

Classification	No. of Births (percent)
Apparently Normal	71 (62.3)
Abnormal	23 (20.2)
Unknown	20 (17.5)
Total	114 (100.0)

Abnormal: Abnormal birth process which may have resulted in cranial injury at birth.

Unknown: No reliable information about the retardate's birth is available.

Table 12 subdivides the 23 abnormal births as to their cause. Information was obtained from hospital and physician reports; information from the mother was only accepted if no conflicting reports from hospitals or medical personnel was found. The numbers and letters following each specific cause refers to the retarded sibling group and the specific retarded sib.

Early Development

Early development refers to childhood diseases, injuries, metabolic defects or pre-natal brain damage which might relate to, or be manifested as mental retardation. Data were collected from Lapeer State Home clinical and resident records and supplemented by personal questionnaires. Terminology for

TABLE 12.--Explanation of 23 Abnormal Births of 114 Retarded Siblings in 49 Families.

Cause	No. of Times	Retardate Designation
Abnormally Long and Difficult Labor	7	4B; 7A,B; 8C; 16A,B; 30B;
Cranial Injury at Birth (Natural or Instruments)	4	18A; 24B; 30A; 40A;
Caesarian Birth	4	26A,B; 32A,B;
Prematurity	3	24B; 29A,B;
Prematurity and Cranial Injury	2	25A,B;
Severe Respiratory Problems	2	34B; 40B;
Mild Erythroblastosis Fetalis	1	5B;

Table 13, as well as the data found in the Appendix, is as follows:

Apparently Normal: Evidence through reports from parents, physicians and hospitals indicating neither disease or injuries in early childhood which may have resulted in retardation.

Abnormal: Abnormal early development as reported parents, physicians and hospital records.

Unknown: No reliable information available on early development.

Table 14 gives data as to the type of abnormality in early development. Post-natal cranial injury refers to those children about whom evidence has been presented that physical injury has resulted due to a fall or accident. In both cases there is no conclusive evidence that these injuries were the

TABLE 13.--Summary of Early Development of 114 Siblings in 49 Families.

Classification	No. of Retardates (percent)
Normal	69 (60.5)
Abnormal	25 (21.9)
Unknown	20 (17.6)
Total	114 (100.0)

TABLE 14.--Explanation of the Abnormal Early Development of 25 Siblings.

Condition	No. of Times	Retardate Designation
Seizures and Convulsions	14	13A,C; 16A; 19A; 22A,B; 23A,B; 27B; 34B; 40A, B; 44B; 47C
Post-Natal Diseases	9	5A; 14A,B; 18B; 19C; 28A; 31B; 45A; 48A
Post-Natal Cranial Injuries	2	1A; 8B
Total	25	

causative factor of the retardation; they are included since the possibility exists. "Post-natal diseases" refer to those children in whom severe diseases, often accompanied with high fever, existed in early childhood. Although the records indicate that in many cases the onset of noticeable retardation occurred soon after the illness, there is no conclusive proof that the post-natal disease was the causative factor. The occurrence of seizures and convulsions in the early development of the retardates is indicative of abnormal brain functioning, and is thus included; the relationship of seizures and convulsions to mental retardation is obscure.

Socio-Economic Status

The socio-economic classification of the 49 families was based upon reports from state social agencies and records at Lapeer State Home, and is summarized in Table 15. Terminology used in Table 15 is as follows:

Comfortable: Middle-class or above; self-supporting.

Marginal: Lower middle-class; some public assistance (food stamps, medicare, etc.), but substantially self-supporting.

Dependent: Poor; usually not employed; on welfare, not self-supporting.

Unknown: No reliable information available.

Table 16 compares the I.Q. levels of retarded siblings from dependent and non-dependent (comfortable and marginal) families. The table illustrates a shift of dependent families toward the dull normal range.

TABLE 15.--Socio-Economic Status of 49 Families Containing 114 Retarded Siblings.

Socio-Economic Status	No. of Families (percent)
Comfortable	16 (32.6)
Marginal	19 (38.8)
Dependent	10 (20.4)
Unknown	4 (8.2)
Total	49 (100.0)

TABLE 16.--Comparison of I.Q. Levels of Retarded Siblings from Dependent and Non-Dependent Families.

	No. of Siblings (percent of total sibs)	
I.Q. Level	Non-Dependent	Dependent
Below or equal to 30	34 (48.6)	7 (29.1)
31-50	31 (44.3)	12 (50.0)
51-70	5 (7.1)	5 (20.9)
Total	70 (100.0)	24 (100.0)

Abnormal Physical Characteristics

Ninty-one retarded siblings were examined and unusual physical characteristics or anomalies were noted; these were coded and placed in groups corresponding to body regions. The code key is given in Table 17; the Appendix describes, using this code, all positive findings for the 91 retardates. Table 18 describes the number of times, and relative percentages, that each characteristic appeared in the 91 siblings. The table shows that 56 of the 91 retardates, or 61.5 percent, displayed dentition abnormalities (code no. 81) while only one retardate (from Appendix, sib 7A) had a porwine stain (code no. 17). The characteristics most frequently noted were dentition abnormalities (61.5%), guttural, abnormal speech (44.0%), below normal physical stature (27.5%), high-arched or narrow palate (26.4%), aphrasia (26.4%), extended ears (25.3%) and squat nost (20.9%). Other characteristics that were observed more than 10 percent of the time included narrow, pointed tongue (19.8%), abnormally large or prominent ears (18.7%), dry, rough skin (14.3%), dull, expressionless faces (12.1%), thick or protruding lips (11.0%) spasticity or hypertonia (11.0%). Table 19 shows those characteristics which are found in two or more retarded siblings from the same family. The table shows that both sibs in family no. 6 display 10 similar abnormal characteristics. These are: stature below normal, dry, rough skin, dry and fragile hair, mongoloid

TABLE 17.--Key of Physical Data Code.

Number	Physical Characteristic
General	
1	Dull, expressionless faces
2	General physical retardation
3	Obesity
4	Self-mutilation
5	Stature below normal
Skin	
11	Red blotches, dispersed
12	Dry, crusty patches, localized
13	Dry areas, localized, with patches of dark hair
14	Dry, rough skin, general
15	Malar flush
16	Pox marks
17	Port-wine stain
Hair	
21	Dry and fragile
22	Hirsutism
23	Sparse or absent
Head and Face	
31	Asymmetry
32	Frontal bossing
33	Macrocephaly
34	Enlarged mandible
35	Microcephaly
36	Prominent maxillae
Eyes	
41	Blue scleae
42	Defective vision
43	Discolored scleae
44	Epicanthal fold
45	Eyelids--antimongoloid slant of
46	Eyelids--mongoloid slant of
47	Exopthalmus
48	Nystagmus
49	Ocular hypertolorism
50	Skin folds above eye
51	Strabismus
52	Sunken eyes
Nose	
61	Abnormally large
62	Beaked
63	Broad-saddle shaped
64	Depressed bridge
65	Squant nose

TABLE 17.--Continued.

Number	Physical Characteristic
Ears	
71	Asymmetry
72	Deafness or hearing loss
73	Extended
74	Hairy pinna
75	Large or prominent ears, abnormal
76	Low set ears
77	Small ears, abnormal
78	Telangiectasia
Mouth and Pharynx	
81	Dentition abnormality
82	Guttural, abnormal speech
83	Lips, abnormally thin
84	Lips, thick or protruding
85	Aphrasia
86	Palate, high-arched or narrow
87	Palate, low
88	Tongue, large or flabby
89	Tongue, narrow, pointed
Neck and Torso	
91	Abdomen, distended
92	Short neck
Genitalia	
101	Cryptorchid
102	Infantile penis
103	Testicular atrophy
Extremities	
111	Clinodactyly
112	Equinovarus
113	Fallen arches
114	Generalized foot deformity
115	Generalized hand deformity
116	Hands, broad and flabby
117	Joints of hands, enlarged
118	Short thumb
119	Simian crease
120	Thumb and toe deformity, generalized
121	Thumb or great toe, broad
122	Toes, overlapping
Muscular and Nervous Systems	
131	Abnormal or absent reflexes
132	EEG abnormality
133	Hyperreflexia
134	Limited range of joint movements
135	Rigidity, muscle
136	Seizures
137	Spasticity, hypertonia

TABLE 18.--Frequency of Specific Abnormalities in 89 Retarded Siblings.

Abnormality (code no.)	No. of Times	Percent	Abnormality (code no.)	No. of Times	Percent
1	11	12.1	72	4	4.4
2	7	7.7	73	23	25.3
3	2	2.2	74	7	7.7
4	6	6.6	75	17	18.7
5	25	27.5	76	7	7.7
11	1	1.1	77	13	14.3
12	3	3.3	78	2	2.2
13	2	2.2	81	56	61.5
14	13	14.3	82	40	44.0
15	1	1.1	83	8	8.8
16	1	1.1	84	10	11.0
17	1	1.1	85	23	25.3
21	8	8.8	86	24	26.4
22	3	3.3	87	1	1.1
23	2	2.2	88	8	8.8
31	3	3.3	89	18	19.8
32	3	3.3	91	1	1.1
33	1	1.1	92	1	1.1
34	3	3.3	101	3	3.3
35	2	2.2	102	1	1.1
36	1	1.1	103	1	1.1
41	1	1.1	111	4	4.4
42	1	1.1	112	3	3.3
43	1	1.1	113	5	5.5
44	2	2.2	114	8	8.8
45	3	3.3	115	2	2.2
46	6	6.6	116	2	2.2
47	3	3.3	117	2	2.2
48	2	2.2	118	1	1.1
49	2	2.2	119	2	2.2
50	2	2.2	120	2	2.2
51	4	4.4	121	2	2.2
52	8	8.8	122	1	1.1
61	8	8.8	131	1	1.1
62	7	7.7	132	2	2.2
63	4	4.4	133	2	2.2
64	4	4.4	134	3	3.3
65	19	20.9	135	1	1.1
71	2	2.2	136	3	3.3
			137	10	11.0

TABLE 19.--Abnormal Physical Characteristics Common in 89 Retarded Siblings.

Family No.--Characteristics in Common (coded)	
1	26--81, 89, 137
2	27--5, 81, 113
3--81	28--81
4--73, 82	29--1, 85
5--82	30--5, 85
6--5, 14, 21, 46, 47, 65, 73, 77, 81, 82	31
7--4	32
8--2sibs: 65; 3sibs: 81, 82	33--82, 89
9--72, 82	34
10	35--4, 65, 81
11	36
12--85	37--1, 73
13--2sibs: 81, 136	38
14	39
15	40
16--61, 75, 81, 82	41
17	42
18	43--5, 46, 65, 81, 82, 86, 88
19--2 sibs: 2, 35, 65, 84, 85	44--5, 81, 82, 86
20	45--5, 85, 119
21--73, 74, 81	46
22--81, 89	47
23--21, 73, 75, 81	48
24	49
25--77	

slant of the eyelids, exopthalmus, squat nose, extended ears, abnormally small ears, dentition abnormality and guttural, abnormal speech. A karyotype of these retardates has confirmed a diagnosis of G-G translocation Down's syndrome. Seven similar characteristics in both siblings are noted in family no. 43, in which both retardates have been confirmed by karyotypes as non-disjunction type Down's syndrome. Two of the three retarded siblings in family 19 were available for examination. Five abnormal characteristics were noted in both sibs. They were general physical retardation, microcephaly, squat nose, thick or protruding lips and aphrasia. It seems significant that of the 91 retardates examined these siblings were the only two to display microcephaly and were among only seven to present generalized physical retardation. Other notable similarities include the occurrence of self-mutilation in both siblings of families no. 7 and 35; these two families account for four of only six cases where self-mutilation occurs. Both sibs in family no. 9 were noted to have bilateral hearing loss; this was noted only four times in the children of the 49 families. Two of the three sibs in family no. 13 have seizures and they are among only three retardates of the 91 examined to have this problem. The two male sibs of family no. 21 are among only seven retardates to display hairy pinnas. Both sibs of family no. 27 display fallen arches, a characteristic noted in only five retardates in

this study. The only retardates who display a simian crease are the two siblings from family no. 45; they have been confirmed by karyotype to have Down's syndrome. Similarities other than those noted above have been deemed insignificant because of the large number of unrelated retardates that display these characteristics.

Sibling Evaluation Method

By analyzing the various data from the 49 families, it was possible to arrive at criteria which will help facilitate a more rapid identification of those families in whom there may exist a previously undescribed biochemical defect. A sibling evaluation method is therefore proposed and is presented in Table 20. Families with two or more siblings institutionalized, could be initially analyzed on the basis of their institutional folder. A determination could be made, using the sibling evaluation method, as to whether a given family showed sufficient promise of displaying a new genetic defect to warrant an intensive biochemical investigation. To use the sibling evaluation method a criteria class is chosen, based upon the number of retarded probands within the family. For purposes of this method, identical twins are considered one person with an I.Q. that is the average of the two individual I.Q. scores. If the retarded sibship is made up of only identical twins they are removed from further consideration. There are seven steps in the screening method and each step imposes restrictions on the

TABLE 20.--A Sibling Evaluation Method.

If there are 2 mentally retarded siblings as probands--use criteria A.
If there are 3 mentally retarded siblings as probands--use criteria B.
If there are 4 mentally retarded siblings as probands--use criteria C.
If there are 5 mentally retarded siblings as probands--use criteria D.
If there are more than 5 mentally retarded siblings as probands--choose 5 probands with the lowest I.Q. scores and use criteria D.

Step 1--I.Q. level of siblings (sum of individual sibling I.Q. scores)

Criteria A. If sum total is less than, or equal to 50, with no individual score above 35, proceed to step 7, criteria A. If not, proceed to step 2, criteria A.

B. If sum total is less than, or equal to 100, with no individual score above 45, proceed to step 7, criteria B. If not, proceed to step 2, criteria B.

C. If sum total is less than, or equal to 160, with no individual score above 55, proceed to step 7, criteria C. If not, proceed to step 2, criteria C.

D. If sum total is less than, or equal to 250, with no individual score above 70, proceed to step 7, criteria D. If not, proceed to step 2, criteria D.

Step 2--Continuation of I.Q. level consideration.

Criteria A. If sibling's total score is between 51 and 100, with no individual score above 57, proceed to step 3, criteria A. If not, remove sibling group from further consideration.

B. If sibling's total score is between 101 and 150, with no individual score above 66, proceed to step 3, criteria B. If not, remove sibling group from further consideration.

C. If sibling's total score is between 161 and 220, with no individual score above 66, proceed to step 3, criteria C. If not, remove sibling group from further consideration.

D. If sibling's total score is between 251 and 275, with no individual score above 70, proceed to step 3, criteria D. If not, remove sibling group from further consideration.

TABLE 20.--Continued.

Step 3--Age of retarded siblings (sum of individual sibling ages).

Criteria A. If sibling's total age is less than, or equal to 40 years, with no individual age greater than 25 years, proceed to step 7, criteria A. If not, proceed to step 4, criteria A.

B. If sibling's total age is less than, or equal to 70 years, with no individual age greater than 25 years, proceed to step 7, criteria B. If not, proceed to step 4, criteria B.

C. If sibling's total age is less than, or equal to 95 years, with no individual age greater than 28 years, proceed to step 7, criteria C. If not, proceed to step 4, criteria C.

D. If sibling's total age is less than, or equal to 125 years, with no individual age greater than 30 years, proceed to step 7, criteria D. If not, proceed to step 4, criteria D.

Step 4--Continuation of age consideration.

Criteria A. If total age is less than, or equal to 60 years, with no individual age greater than 35 years, proceed to step 5. If not, remove sibling group from further consideration.

B. If total age is less than, or equal to 95 years, with no individual age greater than 35 years, proceed to step 5. If not, remove sibling group from further consideration.

C. If total age is less than, or equal to 125 years, with no individual age greater than 35 years, proceed to step 5. If not, remove sibling group from further consideration.

D. If total sibling age is less than, or equal to 155 years, with no individual age greater than 35 years, proceed to step 5. If not, remove sibling group from further consideration.

Step 5

Criteria A,B,C,D.
Presence of similar major physical anomalies in 2 (or more) of the retarded probands. If similarities are noted proceed to step 7, criteria A, B, C or D for 2, 3, 4 or 5 or more probands, respectively. If no similarities are detected, proceed to step 6.

TABLE 20.--Continued.

Step 6

Criteria A,B,C,D.
If evidence in the family history indicates the presence of retarded siblings (not previously considered), parents, grandparents, aunts or uncles, proceed to step 7, criteria A, B, C or D for 2, 3, 4 or 5 or more probands, respectively. If not, remove sibling group for further consideration.

Step 7--Diagnosis.

Criteria A. If a specific diagnosis has been made for one or both siblings, remove the sibling group from further consideration.

B. If a specific diagnosis has been made for 2 or more siblings, remove the sibling group from further consideration. If a confirmed diagnosis has been made for one sibling of the group, omit that sibling and return to step 1, criteria A. If no diagnoses have been made, the sibling group will be considered for biochemical evaluation.

C. If a specific diagnosis has been made for 3 or more siblings, remove the sibling group from further consideration. If a diagnosis was made for 2 siblings of the group, omit these siblings and return to step 1, criteria A. If a diagnosis was made for only one sibling of the group, omit that sibling and return to step 1, criteria B. If no diagnoses were made, the sibling group will be considered for biochemical evaluation.

D. If specific diagnoses have been made for 4 or more siblings, remove the sibling group from further consideration. If a confirmed diagnosis has been made for 3, 2 or 1 sibling(s), omit that (those) sibling(s) and return to step 1, criteria A, B or C respectively. If no diagnosis has been made, the sibling group will be considered for biochemical evaluation.

various criteria classes. Instruction at each step will direct, based on the retarded sibling group data, the investigator to another step or indicate removal of the family from further consideration. Those families not removed in any of the steps shall be considered for biochemical evaluation.

Using this method to analyze the 49 families containing retarded siblings at Lapeer State Home, 16 were selected for biochemical evaluation. Each of these families is described below.

Family no. 2: Of a sibship of seven, four males are mentally retarded, two males are normal and one female is normal. The retardate's ages are 25, 27, 28 and 33 with respective I.Q.'s of 37, 37, 46 and 49. The parents are both mentally normal and the family is socio-economically comfortable. Both and early development of all four retardates were reported to be normal; there are no outstanding physical anomalies or characteristics. One of two maternal uncles was institutionalized at Lapeer for retardation.

Family no. 7: The sibship consisted of four males, the two retarded probands, one normal male and one who died at about two years of age of pneumonia. The I.Q. scores of the retarded sibs, ages 15 and 25 are 19 and 39 respectively. Both retarded boys are self-mutilating; both appear small for their age. The parents and relatives are described as mentally normal and the family is socio-economically comfortable.

Family no. 8: The retarded sibship consists of two males, ages 20 and 27 with I.Q.'s of 30 and 28 respectively and two females, ages 20 and 23 with respective I.Q.'s of 20 and 32. There are three normal children in the sibship, one male and two females. The parents are both mentally normal with no other relative reported as mentally defective; the socio-economic status of the family is marginal. Three of the four retarded siblings display dentition abnormalities and guttural, abnormal speech; two of the four have an abnormally squat nose.

Family no. 9: The two retardates, a male, age 18 with an I.Q. of 39, and a female, age 20, with an I.Q. of 52, are the only offspring of two mentally normal parents. The sibs both suffer from hearing loss and have guttoral, abnormal speech. The socio-economic status of the family is described as marginal.

Family no. 10: This retarded sibship consists of two females ages 56 and 59 with I.Q.'s of 12 and 9 respectively. Both parents are reported as mentally normal and there was one mentally normal brother who died of heart trouble at age 18; the socio-economic status of the family is marginal. There is no other history of retardation in the family.

Family no. 13: The only offspring of this family are three retarded males, ages 37, 38 and 40 with I.Q.'s of 42, 6 and 21 respectively. The mother is reported as mentally retarded with mental illness; the father is reported as

questionably retarded. Both parents were treated for syhillus in 1930, two years before the birth of their first son. Both the 38 and 40 year old sibs have had seizures and the 37 and 38 year old both display dentition abnormalities. The maternal grandmother was described as "insane."

Family no. 19: This sibship consists of two normal females and three retarded sibs. One male, age 10 with an I.Q. of 21 and one female, age 15 with an I.Q. of 24 are residents of Lapeer State Home. There is another retarded male, age 13 at home, I.Q. unknown. The two siblings at Lapeer were noted to have certain physical characteristics in common. They are: general physical retardation with skeletal abnormalities, microcephaly, squat nose, thick, protruding lips and aphrasia. The parents are mentally normal and there is no knowledge of other retardation in the family; since the father was adopted, relatively little is known about the paternal side of the family. Analysis of urine shows a positive indican reaction in the female of this retarded sibship. The socio-economic status of the family is described as comfortable.

Family no. 25: This retarded sibship consists of a 27 year old male with an I.Q. of 30, and a 40 year old female with an I.Q. of 20. There is a set of normal female twins and a normal male within the sibship; the parents are described as mentally normal. Both retarded sibs display hypertonia, spastcity, dentition abnormalities and a narrow,

pointed tongue. Both children were Caesarian births; the socio-economic status of the family is described as marginal. One paternal uncle was institutionalized at Lapeer; there are three normal paternal aunts and three normal paternal uncles.

Family no. 29: This retarded sibship consists of a male, age 16, with an I.Q. of eight, and a 14 year old female with an I.Q. of 20. The parents are reported to be mentally normal and there are two normal females at home; the mother has had three miscarrages. The institutional records stated that both retardates were premature, the male's birthweight was 3 pounds, 14½ ounces and the female's birthweight was 4 pounds, 8 ounces. Both sibs display dull, expressionless faces and aphrasia.

Family no. 31: In this retarded sibship there are three males, ages 14, 15 and 18 with I.Q.'s of 25, 38 and 66 respectively. There is one normal sib at home and three sibs of unknown mental status. The two older retarded sibs were seen and both are small for their age. The parents are reported to be mentally normal and the family's socio-economic status is described as dependent. The births of the retardates were reported as normal and the early development of the 14 and 18 year old were reported as normal. The 15 year old sib was reported to have a "flu with a 106 degree temperature" during infancy.

Family no. 32: This sibship consists of two females, ages 19 and 20, with respective I.Q.'s of 17 and 11, and one normal female. The mother was evaluated at Lafayette clinic and was diagnosed chronic schizophrenia paranoid type. The father was also characterized by the clinic as "very disturbed." The maternal age at birth of the retarded sibs was 39 and 40; both deliveries were caesarian. There are no outstanding physical anomalies present in the sibs. The socio-economic status is described as marginal.

Family no. 35: This sibship consists of two retarded males, ages 14 and 17 with I.Q.'s of 30 and 13 respectively, one normal male and one male who died at eight months of heart disease. Both parents are reported as mentally normal and their socio-economic status is reported as marginal. Both retarded sibs are self-mutilating, display a squat nose and aphrasia. Both sibs are abnormally small and underdeveloped for their age. Birth and early development of both retarded sibs were reported as normal.

Family no. 39: This sibship consists of four retarded males and one normal female. Two retarded sibs are at Lapeer, ages 17 and 19 with respective I.Q.'s of 11 and 15. The mother's mental status is reported as normal and the father is questionably psychotic. The maternal age at the time of the sibs birth was 40 and 42. The socio-economic status of the family is marginal. The 19 year old sibling has elevated

methionine and ornithine in his urine and low cystine and leucine in his serum. The 17 year old sibling was reported to be normal by chromatographic screening.

Family no. 47: This sibship consists of six retarded children, three males and three females. Two females, ages 29 and 33 with I.Q.'s of 38 and 44 respectively, and one male, age 38 with an I.Q. of 32 were at Lapeer at the time of this study. The father was reported as mentally normal and the mother is questionably retarded. The family's socio-economic status is reported as dependent. The retarded sibs are wards of the court and hence, there is a dearth of family background. It appears as if deliveries were normal for the sibs at Lapeer.

Family no. 48: The retarded sibship consists of a female, age 13 with an I.Q. of 20, and a male, age 11, with an I.Q. of 30 (estimated). Both parents, two sisters and a brother are reported as mentally normal. The mother claims that the female suffered cranial birth injury and had "high fever" before 3 months old. Family is described as socio-economically marginal. Little is known about the family background.

Family no. 49: The retarded siblings consist of a male, age 18 with an I.Q. of 10, and a female, age 13, with an I.Q. of 57. The parents and a sister are reported as mentally normal. There are no outstanding physical characteristics shared by the retarded sibs. Birth and early

development of both are reported as normal. The socio-economic status of the family is described as apparently comfortable. There is no other report of mental retardation within this family.

(All data presented may be found in tabular form in the Appendix.)

DISCUSSION

Table 21 compares the distribution in the present study to that found by Wright et al. (1959) and Priest's et al. (1961). As can be seen in the table, the 42.4 percent normal siblings in the present study is higher than the 33.5 percent reported by Wright or the 24.8 percent reported by Priest. The percentage of siblings in the questionable retarded category is lower in the present study than in either the Wright or Priest study. The present study had 9.5 percent of its siblings in the unknown category while Wright reported 7.2 percent and Priest 20.5 percent. Agreement was good when considering the percentage of retarded siblings within the families; the present study found 46.9 percent of the siblings retarded which compares well to 48.0 percent found in the two previous studies.

The retarded population in this study had a smaller percentage of retarded parents than did the previous studies by Wright and Priest. If a population with many borderline retardates were studied, we would expect a greater number of retarded parents. Upon examination of Wright's data, however, it becomes clear that there is no preponderance of borderline retardates born to the retarded parents; thus, this cannot serve as a suitable explanation for the differences

TABLE 21.--Comparison of the Distribution of Retardation Between the Present Study and Studies by Wright et al. (1959) and Priest et al. (1961).

	Present Study		Wright et al.		Priest et al.	
	No.	%	No.	%	No.	%
Siblings						
Total No. of Siblings	243	100.0	319	100.0	443	100.0
Retarded	114	46.9	153	48.0	210	48.0
Questionably Retarded	3	1.2	28	8.8	32	7.2
Not Retarded	103	42.4	107	33.5	110	24.8
Unknown	23	9.5	23	7.2	91	20.5
Parents						
Total No. of Parents	98	100.0	122	100.0	166	100.0
Retarded	3	3.1	16	13.1	36	21.7
Questionably Retarded	19	19.4	49	40.2	30	18.1
Not Retarded	70	71.4	53	43.4	82	49.4
Unknown	6	6.1	4	3.3	18	10.8

between the percent of retarded parents within the two studies. The questionably retarded parents (including mentally ill and questionably mentally ill) made up 19.4 percent of the parental population in this study and compares favorably to the 18.1 percent value arrived at by Priest in 1961. Both values are significantly lower than Wright's value of 40.2 percent, but this may be because Wright has chosen to include in this category parents who display alcoholism, incest, brutality, promiscuity, disertion, eccentricity or epilepsy. These

conditions are not included in Priest's or this study's classification of questionably retarded.

As can be seen in Table 4 age distribution ranges from 5 to 72 years, although 59 percent of the retarded population are between 11 and 30 years; similarly, 57.1 percent of Wright's population was also between 11 and 30 years. This may be due to, as Goodman et al. (1956) suggest, the fact that in preschool years some retardates may be indistinguishable from their nonretarded peers. As school requirements increase in difficulty, the retardate is more likely to be identified. Some conditions might cause an early death, thus explaining the sudden drop and leveling off of the number of retardates after age 30.

Seventy-nine, or 69.3 percent of the 114 retarded siblings from the 49 families were male: this agrees closely with Wright's data in which there were found 67.0 percent males. Of the three studies, Priest had the lowest number of males as probands, 59 percent.

The present study found that 24 of the 49 families, or 49 percent, contained only male retardates; Wright found that 42.6 percent of his families contained only male retardates and Priest found 34.9 percent to contain retarded males only. It is tempting to consider sex-linkage, sex influence and sex limitation as factors to account for the predominance of families with only males affected. Renpenning et al. (1962) has presented two large families in which mental

retardation seems to be transmitted as a sex-linked recessive; the outstanding feature in this syndrome is the lack of abnormal physical or biochemical characteristics. In the present study, family no. 2 appears to fit the requirements for Renpenning's syndrome. Four of six males in the sibship are retarded, the degree of each within the moderate range; there is one normal sister. One of two maternal uncles was institutionalized because of retardation. All the retarded individuals are well built, physically strong and have no outstanding physical characteristics except for somewhat prominent ears. In six families, or 12 percent, of the 49 families studied, only females were affected (in two families the female sibs were identical twins). Wright found 9.8 percent and Priest found 18.1 percent of their families to contain only females.

Penrose found in his 1953 study that firstborns and the younger children in large families run a slightly higher risk of being retarded. Although a statistical significance could not be shown in the present study, there appears to be a skewing of the distribution toward the younger members (see Table 8).

Crome and Stern (1967) have estimated a two to three fold increase in incidence of Down's syndrome to mothers forty years old or older. In this study, the mean age of mothers who have produced retarded offspring, excluding the mothers who have had children with non-disjunctal Down's

syndrome was found to be 26.0 years with a standard deviation of 6.7 years. There were eight children with Down's syndrome in this study, six of which were of the non-disjunctal type; the mean maternal age for the mothers of these six children at the time of the children's birth was 39.2 years. This approaches two standard deviations above the mean; thus it appears that this data is in agreement with Crome and Stern.

The lack for specific diagnoses became apparent in this investigation; 81.7 percent of the siblings studies had no specific diagnosis. Priest et al. (1961) similarly found that 90 percent of their retarded siblings were without diagnoses and Wright et al. (1959) had found that 77 percent of their retardates had no diagnoses. In all three studies, the lack of diagnoses within families with two or more retarded siblings is higher than the 67 percent found by Berg in 1961 in his study of 800 retardates admitted over a 10 year period to the Fountain Hospital in England. One possible explanation is that retarded siblings may contain a higher percentage of rare genetic disorders that have not been elucidated. Support of this idea can be found by comparison of this study to data collected by Higgins et al. (1970) from Lapeer State Home. As part of their investigation, 2989 unrelated retardates were screened for phenylketonuria; 28, or .93 percent of the total population was positive. In this study six retardates, or 5.3 percent of a population of 114 were found to have PKU, a five-fold increase over the

previous study; the occurrance of PKU in siblings is found to be significantly higher than the overall retarded population. The study by Higgins also found six of the 2989, or .20 percent positive for indican; the present study identified one retardate of a population of 114 who was indican positive. This is .87 percent, a four-fold increase over the Higgins study. It should be noted that this retardate was selected by the proposed sibling evaluation method for further biochemical evaluation.

The frequency of mental retardation within families with two or more affected siblings is examined in Table 22. The table compares the data found in this study with that collected by Wright in 1959 and Priest in 1961. These figures are calculated by dividing the number of retardates within these families (after removal of the 98 probands) by the number of all siblings (minus probands) within the families. Two calculations are made: one excluding those siblings whose mental status is uncertain, and one including those siblings. In the three studies, it becomes clear that the percentage of retardates in these families is well above the frequency of 3 percent found in the general population. This seems indicative of the potential value of sibling groups in searching for previously undescribed genetic defects. The elevated frequencies, however, may be due, in part, to environmental stimuli which has acted upon these sibling groups. At the present time, it is impossible to infer

TABLE 22.--The Frequency of Mental Retardation within 49 Families that Contain Two or More Retarded Siblings (after removal of 98 probands).

Precent of Retarded Siblings	Present Study	Wright et al. (1959)	Priest et al. (1961)
Case 1*	13.4	28.6	28.5
Case 2**	11.0	19.9	15.9

*Case 1--Excluding siblings with uncertain mental status (unknown and questionably retarded categories).

**Case 2--Including siblings with uncertain mental status.

from the data, the relative contribution of each component in elevating the frequencies.

Table 16 shows that non-dependent socio-economic families produce a greater percent of retardates with severe retardation than do dependent families. It is well known that the majority of high-grade retardates are to be found in the lower socio-economic classes (Reed and Reed, 1965). Wright, in his 1959 study, also found that families where the afflicted sibs were more severely deficient were more often of average or above socio-economic status and less frequently on relief; he, however, did not quantify his data.

This study found 94.5 percent of the 91 retardates available for surface examination to have at least one minor anomaly or abnormal characteristic not generally found in the normal population. It was also found that 83.5 percent

of the probands had three or more of the anomalies listed in Table 17. The specific findings for each patient can be found in the Appendix. Smith and Bostian (1964) have found that of 50 children with non-specific retardation, 78 percent of them have one or more abnormal physical anomaly; in 42 percent of their cases, the retardate was found to display three or more anomalies. If those 19 retardates in the present study with confirmed diagnoses are excluded from consideration 57 of 72, or 79.2 percent are found to have three or more anomalies; this is still a much higher percentage than found by Smith and Bostian. The differences in observing or classifying characteristics which are abnormal may contribute to the difference in estimates. As Opitz (1969) points out, the need for quantification of physical anomalies is necessary before the worth of this kind of data can be estimated.

Wright et al., in 1959 and Priest et al. in 1960 identified families in which there existed two or more retarded siblings, for the purpose of delineating individuals for further study. Wright et al. then biochemically screened all 61 families he had identified in the hopes of finding a new biochemical defect; unfortunately he found none. The only positive findings within the 61 families were four sibships of PKU and one retarded sibship with gargoylism. The proposed sibling evaluation method was applied to Wright's data and resulted in the elimination of

40 families from his biochemical screening population. It is significant to note that among the 21 families selected by the sibling evaluation method, three of the four PKU families were included in addition to the retarded sibship afflicted with gargoylism. One sibship with PKU was eliminated by the evaluation method because one sib had an abnormally high I.Q. This proposed sibling evaluation method has the advantage of allowing an investigator to quickly and conveniently select a population of retarded individuals which have a relatively high probability of containing undescribed biochemical defects. Instead of biochemically screening large numbers of individuals, this method will identify certain families based on information readily available in the resident's institutional folder. This shall save time and money that would be expended in proforming a screening procedure on all retarded siblings.

The sibling evaluation method is so designed as to concentrate on younger individuals who are afflected with severe retardation. Wright (1961) points out, after his failure to identify a new biochemical defect, that further studies might be more successful if carried out with younger, more severely retarded individuals. Since retarded individuals with I.Q.'s of 50 or greater are usually accepted as representing the negative tail of the Gausian curve, it is desirable to remove them when searching for a biochemical defect. Younger individuals, as suggested by Wright, are

desirable since biochemical defects may be modified with time, as in diseases such as idiopathic hypoglycemia, phenylketonuria, Hartnup disease and idiopathtic hypercalcemia. These biochemical defects may cause an early death, and thus be under-represented in an older population. The sibling evaluation method also takes into consideration the incidence of mental retardation within the family and physical similarities between retarded siblings. It is hoped that this method will be used in other institutions to arrive at a fairly large population of individuals to be screened for new biochemical defects. It should be noted, that the proposed evaluation method does not claim to identify all families who will display a biochemical defect. It was designed, so that, an investigator, given limited time and money, would have a higher probability of identifying a genetic defect. Since the purpose of future research will be identification of previously undescribed genetic defects, and not classification of retardates into known syndromes this evaluation method may prove to be a valuable tool.

SUMMARY

This study investigated 49 families, in which two or more siblings from each family were classified as mentally retarded and were residents of Lapeer State Home. The purpose was to examine various data about these families in order to determine their individual worth for further biochemical examination. The 49 families were first analyzed collectively in order to get a generalized picture of variables within a population which has produced an excess of mentally retarded individuals. It was noted that:

1. The greatest percent of retardates in this study were between the ages of 11 and 30 years (58.9); 35.5 percent of all retarded siblings were between 11 and 20 years.

2. A larger proportion of males were found in the retarded population (69.3 percent).

3. Twenty-four of 49 families contained only male retardates.

4. Non-specific diagnoses were made for 81.7 percent of the retarded individuals.

5. Fifty percent of the retarded sibships excluding identical twins contained males only; 8.6 percent contained females only.

6. The mean maternal age for mothers of children with non-disjunction Down's syndrome approached two standard deviations above the population mean.

7. Families who were non-dependent socio-economically produced a greater percent of retardates in the severe and moderate range than did dependent families.

8. Certain abnormal physical characteristics occur frequently in a retarded population.

9. 79.2 percent of the retardates with non-specific diagnoses were found to have three or more abnormal physical characteristics.

10. In 8 of 16 families selected by the sibling evaluation method, the siblings had at least one abnormal physical characteristic in common and in two of these families the retarded sibs exhibited three or more abnormal characteristics in common.

A sibling evaluation method was then devised, in order to facilitate a rapid identification of those families who would have a relatively high probability of displaying a new biochemical defect previously undefined. The criteria set up in the evaluation method was somewhat arbitrary, but was designed to remove from consideration those families deemed unworthy of further investigation. As designed, the method removed 33 families, or 67.3 percent of the 49 families from further consideration. The 16 families that remain, in

addition to other families which will be identified using the proposed evaluation method, shall comprise a population which will be biochemically analyzed, searching for new biochemical defects or syndromes previously undescribed.

APPENDICES

APPENDIX A

CODE

CODE

1. Sibling designation

2. Age

3. I.Q. (most recent)

4. Diagnosis: Kern. = kernicterus; PKU - phenylketonurla; Biels. = Bielschowsky's disease; C. Lipo. = Congenital lipoidosis

5. MA = maternal age

6. MMS = maternal mental status

7. PA = paternal age

8. PMS = paternal mental status

9. PBO = position in birth order; position of sib/total no. siblings

10. No. NS = number of normal siblings within the family, excluding siblings of unknown mental status

11. No. RS = number of retarded siblings within the family excluding the propositus

12. BW = birth weight

13. B = birth; N = normal; U = unknown; AB-. = abnormal; DL = difficult labor; EF = erythrobastosis fetalis, mild; CI = cranial injury; P = prematurity; C = caesarian birth; RP = severe respiratory problems

14. ED = early development; N = normal; U = unknown; AB-. = abnormal; PI = post-natal injury; PD = post-natal disease; S = seizures;

15. SEG = socio-economic group; C = comfortable; M = marginal; D = dependent;

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Sib	Age	I.Q.	Diagnosis	MA	MMS	PA	PMS	PBO	No.NS	No.RS	BW	B	ED	SEG
1A	29	29	NS	38	OR	52	NR	8/9	7	1	8-9.5	N	^B-PI	M
1B	22	24	Down's	45	"	59	"	9/9	"	"	U	N	N	"
2A	27	37	NS	25	OR	26	NR	4/7	3	3	7-8	N	N	C
2B	28	46	NS	24	"	25	"	3/7	"	"	5-8	"	"	"
2C	33	49	NS	19	"	20	"	1/7	"	"	8-12	"	"	"
2D	25	37	NS	27	"	28	"	5/7	"	"	7-4	"	"	"
3A	18	68	NS	25	U	26	U	1/8	6	1	U	U	U	U
3B	10	33	Kern.	33	"	34	"	7/8	"	"	"	"	"	"
4A	29	40	NS	33	NR	36	NR	9/10	7	1	8-6	N	N	C
4B	26	39	NS	36	"	39	"	10/10	"	"	8-13	AB-DL	N	"
5A	22	79	NS	23	NR	30	NR	2/2	0	1	5-8	N	AB-PD	C
5B	21	80	Kern.	24	"	31	"	1/2	"	"	5-8	^B-EF	N	"
6A	23	38	Down's	25	NR	33	NR	1/2	0	1	6-1.5	N	N	C
6B	20	45	Down,s	28	"	36	"	2/2	"	"	6-1.5	N	N	"
7A	15	19	NS	30	NR	32	NR	1/4	1	1	7-4	AB-DL	N	C
7B	25	39	NS	20	"	22	"	3/4	"	"	6-8	AB-DL	N	"
8A	23	32	NS	24	NR	26	NR	4/7	3	3	7-8	N	N	M
8B	22	20	NS	25	"	27	"	5/7	"	"	8-10	N	^B-PI	"
8C	27	28	NS	20	"	22	"	1/7	"	"	U	AB-DL	U	"
8D	20	31	NS	27	"	29	"	6/7	"	"	8-2	N	N	"
9A	20	52	NS	23	NR	23	NR	1/2	0	1	7-7.5	N	N	M
9B	18	39	NS	25	"	25	"	2/2	"	"	7-7	N	N	"
10A	56	12	NS	24	NR	24	NR	3/3	1	1	7-0	N	N	M
10B	59	9	NS	21	"	21	"	2/3	"	"	U	N	N	"
11A	20	47	NS	21	NR	26	NR	3-4/8	6	1	5-10.5	N	N	C
11B	20	45	NS	"	"	"	"	"	"	"	5-8	N	N	"
12A	20	23	PKU	27	NR	27	OR	2/2	0	1	8-10.5	N	N	C
12B	26	20	PKU	21	"	21	"	1/2	"	"	6-13	N	N	"

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
13A	38	6	NS	23	R	28	OR	2/3	0	2	U	N	AB-S	M
13B	37	42	NS	24	"	29	"	3/3	"	"	6-2	N	N	"
13C	40	21	U	21	"	26	"	1/3	"	"	6-0	N	AB-S	M
14A	39	46	NS	43	R	55	NR	9-10/10	2	1	7-2	N	AB-PD	M
14B	39	39	NS	"	"	"	"	"	"	"	6-0	N	AB-PD	"
15A	67	30	NS	U	U	U	U	6/7	2	2	8-0	N	N	U
15B	64	23	NS	"	"	"	"	7/7	"	"	U	U	U	"
16A	50	36	Tay-Sachs	24	NR	29	NR	2/2	0	1	9-0	AB-DI	AB-S	M
16B	47	31	NS	27	"	32	"	1/2	"	"	8-8	AB-DI	N	"
17A	52	33	NS	22	NR	26	NR	2/7	5	1	7-4	N	N	M
17B	45	39	NS	29	"	33	"	5/7	"	"	7-4	N	N	"
18A	22	31	NS	23	QMI	26	NR	3/7	5	1	7-0	AB-CI	N	M
18B	18	73	NS	27	"	30	"	6/7	"	"	7-5	N	N	"
19A	15	24	NS	21	NR	25	NR	1/5	2	2	5-9.25	N	AB-S	C
19B	10	21	NS	26	"	30	"	3/5	"	"	7-15	N	N	"
20A	41	51	NS	U	R	U	QMI	6/7	5	1	U	U	N	D
20B	45	22	NS	"	"	"	"	4/7	"	"	"	"	N	"
21A	57	18	NS	18	NR	23	NR	1/6	4	1	8-0	N	U	M
21B	54	23	NS	21	"	26	"	2/6	"	"	9-0	N	U	"
22A	18	54	NS	23	OR	28	OR	2/7	3	1	8-4	N	AB-S	U
22B	16	50	NS	25	"	30	"	3/7	"	"	8-3	N	AB-S	"
23A	45	50	NS	22	NR	27	NR	2/2	0	1	6-8	N	AB-S	M
23B	47	29	NS	20	"	25	"	1/2	"	"	7-0	N	AB-S	"
24A	44	36	NS	37	NR	40	NR	3/3	1	1	8-0	N	N	M
24B	47	14	Down's	34	"	37	"	2/3	"	"	4-2	AB-P	N	"
25A	16	38	NS	31	NR	31	NR	1-2/3	1	1	4-14	AB-PCI	N	C
25B	16	40	NS	31	"	31	"	"	"	"	4-12	"	N	"

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
26A	27	30	NS	35	NR	43	NR	5/5	3	1	9-8	AB-C	N	M
26B	40	20	NS	22	"	30	"	1/5	"	"	7-12	AB-C	N	"
27A	33	41	NS	41	NR	50	NR	9/9	7	1	8-0	N	N	M
27B	48	36	NS	24	"	35	"	3/9	"	"	7-0	U	AB-S	"
28A	20	62	NS	20	NR	21	NR	2/5	2	?	8-1.5	N	AB-PD	C
28B	17	42	NS	23	"	24	"	4/4	"	"	8-12	N	N	"
29A	16	18	NS	22	NR	24	NR	3/4	2	1	3-14.5	AB-P	N	U
29B	14	20	NS	24	"	26	"	4/4	"	"	4-8	AB-P	N	"
30A	28	5	PKU	25	NR	33	NR	2/3	1	1	8-0	AB-CI	N	C
30B	23	1	PKU	40	"	48	"	3/3	"	"	6-13	AB-DL	N	"
31A	14	25	NS	22	NR	25	NR	4/6	1	2	7-13.5	N	N	D
31B	15	38	NS	21	"	24	"	3/6	"	"	6-1	N	AB-PD	"
31C	18	66	NS	17	"	20	"	1/6	"	"	8-12	N	N	"
32A	20	11	NS	39	MI	28	MI	2/3	1	1	5-12	AB-C	N	M
32B	19	17	NS	40	"	29	"	3/3	"	"	5-15	AB-C	N	"
33A	60	49	NS	U	QR	U	QR	U	U	U	U	U	U	C
33B	57	11	NS	"	"	"	"	"	"	"	"	"	"	"
34A	15	57	NS	36	MI	50	NR	3-4/4	1	1	6-4	N	N	D
34B	15	44	NS	"	"	"	"	"	"	"	4-0	AB-RP	AB-S	"
35A	14	30	NS	24	NR	24	NR	3/4	1	1	6-14	N	N	M
35B	17	13	NS	21	"	21	"	1/4	"	"	6-8	N	N	"
36A	47	55	NS	25	NR	41	NR	5/8	5	1	U	N	N	M
36B	42	27	NS	30	"	46	"	8/8	"	"	8-0	N	N	M
37A	21	27	PKU	24	NR	32	NR	3/4	2	1	8-8	N	N	M
37B	23	35	PKU	22	"	30	"	2/4	"	"	8-0	N	N	"
38A	17	15	Biels.	28	NR	30	NR	2/3	1	1	7-2	N	N	C
38B	15	7	C.Lipo.	30	"	32	"	3/3	"	"	6-9	N	N	C

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
39A	17	11	NS	42	NR	34	QMI	5/5	1	3	8-6	N	N	M
39B	19	15	NS	40	"	32	"	4/5	"	"	9-0	N	N	"
40A	34	15	NS	25	NR	36	NR	1-2/3	1	1	5-7.5	AB-CI	AB-S	C
40B	34	19	NS	"	"	"	"	"	"	"	4-3	AB-RP	AB-S	"
41A	50	23	NS	21	NR	23	NR	1/2	0	1	6-0	N	N	D
41B	52	23	NS	19	"	21	"	2/2	"	"	7-8	N	N	"
42A	72	49	NS	24	U	34	U	5/9	2	1	U	U	U	D
42B	63	21	NS	35	"	45	"	7/9	"	"	"	"	"	"
43A	12	42	Down's	41	NR	40	NR	4/5	3	1	5-8	N	N	D
43B	26	27	Down's	37	"	36	"	3/5	"	"	4-2	N	N	"
44A	42	24	NS	23	NR	26	QMI	2/2	0	1	8-0	N	N	D
44B	34	34	NS	21	"	24	"	1/2	"	"	7-8	N	AB-S	"
45A	5	30	Down's	40	NR	41	NR	7/7	5	1	5-12	N	AB-PD	C
45B	7	39	Down's	38	"	39	"	5/7	"	"	5-7	N	N	"
46A	23	45	NS	21	MI	29	NR	1/2	0	1	5-15	N	N	D
46B	21	56	NS	23	"	31	"	2/2	"	"	6-1	N	N	"
47A	29	38	NS	34	QR	36	NR	6/6	0	6	7-8	N	N	D
47B	33	44	NS	30	"	32	"	4/6	"	"	U	N	U	"
47C	38	32	NS	27	"	29	"	1/6	"	"	8-0	N	AB-S	"
48A	13	20	NS	27	NR	29	NR	3/5	3	1	7-0	N	AB-PD	M
48B	11	30	NS	25	"	27	"	4/5	"	"	U	U	U	"
49A	13	57	NS	31	NR	37	NR	3/3	1	1	8-10	N	N	C
49B	18	10	NS	26	"	32	"	1/3	"	"	8-14	N	N	"

APPENDIX B

ABNORMAL PHYSICAL CHARACTERISTICS IN THE SIBLINGS AT LAPEER STATE HOME

Abnormal Physical Characteristics in the Siblings at Lapeer State Home

AN = No abnormal characteristics noted; U = Unavailable for examination

Sibling Designation	Findings, Coded (refer to key, table 16)
1A	U
1B	U
2A	75, 81
2B	75, 81, 82, 89
2C	U
2D	U
3A	81
3B	2, 11, 14, 65, 81, 85, 86, 134
4A	73, 82, 132
4B	73, 82
5A	3, 82, 132
5B	14, 49, 65, 81, 82, 77, 117
6A	5,14, 21, 46, 47, 65, 73, 77 81, 82, 84, 89
6B	5,14, 21 46, 47, 65, 73, 77, 81, 82, 83, 111
7A	4, 17, 76, 81, 85, 137
7B	2, 4,62, 73, 82 ,31, 101, 117, 118, 121, 131
8A	82
8B	5, 65, 74, 81, 136, 137
8C	14, 48, 50, 65, 81, 83, 89, 101
8D	51, 61 73, 75, 81, 82
9A	51, 72, 82
9B	72, 81, 82, 86
10A	1, 14, 61, 85, 135, 137
10B	62, 78, 81, 82, 83
11A	U
11B	U
12A	15, 23, 78, 85, 86
12B	4, 22, 34 81, 85, 87 112
13A	5, 21, 65, 73, 81, 91, 121, 136
13B	23, 42, 64, 76, 81, 82, 85, 89, 136
14A	5, 73, 81, 82, 120
14B	U
15A	U
15B	U
15C	U
16A	5, 61, 75, 81, 82
16B	50, 61, 62, 73, 75, 76, 81, 82, 83
17A	51, 62, 74, 81, 82
17B	1, 5, 74, 81, 82, 89
18B	75
19A	1, 2, 12, 35, 44, 65, 75, 84, 85, 88
19B	2, 28,35, 65, 76, 81, 84, 85, 86, 112
19C	U
20A	64
20B	5, 75, 81, 82, 86
21A	61, 73, 74, 75, 76, 81, 85, 86
21B	73, 74, 75, 81, 82, 89

22A	1, 81, 82, 84, 89
22B	81, 89
23A	21, 73, 75, 81, 82, 86, 88
23B	2, 21, 71, 73, 75, 81, 85
24A	73, 75, 76, 83, 86, 89,122
24B	3, 46, 65, 77, 82, 88
25A	77, 82
25B	5, 65, 73, 77,81
26A	13, 34, 81 82, 89, 114, 137
26B	21,71, 81, 86, 89, 137
27A	5, 8, 65, 77, 82, 89, 113, 114, 115
27B	5, 81, 102, 103, 111, 113
28A	52, 81, 88
28B	81, 82, 86
28C	U
29A	1, 2, 31, 32, 33, 63, 77, 81, 84, 85, 101
29B	1, 85, 112
30A	5, 41, 47, 83, 85
30B	5, 16, 52, 62 84, 85, 137
31A	85
31B	U
31C	31, 77, 81, 82
32A	5, 65, 81, 85, 86
32B	1
33A	32, 48, 82, 89
33B	62, 82, 89
34A	AN
34B	AN
35A	4, 45, 65, 81, 82, 84, 86, 113, 133, 137
35B	4, 65, 73, 81 85
36A	52, 61, 73, 81, 82, 86, 89
36B	AN
36C	U
37A	1, 5, 73, 76
37B	1, 22, 52, 73, 77, 81
38A	14, 21, 34, 36, 64, 77
38B	1, 2, 81, 82 85, 133, 134
39A	1, 4,72, 85, 86, 89
39B	45, 52, 83
40A	5, 12, 13, 14, 51, 52, 63, 81, 120
40B	5, 12, 13,52,63, 81, 89
41A	74, 81, 82, 86
41B	74, 81, 82, 86, 89
42A	AN
42B	71, 75, 81
43A	5, 46, 65, 81, 82, 86, 88
43B	5, 46, 65, 81, 82, 86, 88, 111, 114
44A	5, 73, 75, 81, 82, 86, 88, 113, 115
44B	5, 14, 21, 81, 82, 86.
45A	5, 14, 46, 63, 85, 114, 119
45B	5, 32, 44,65, 73, 77, 81, 85, 86, 114, 116
46A	52, 77, 88
46B	AN
47A	U
47B	U
47C	45, 64, 73, 75, 81, 82, 83, 86 113, 114, 116

48A	49, 61, 65, 84, 92, 111, 114
48B	5, 14, 75, 81, 85, 124, 127
49A	U
498	5, 14, 62, 81, 84, 85, 86, 137

REFERENCES

REFERENCES

Akesson, H. O. Epidemiology and Genetics of Mental Deficiency in a Southern Swedish Population. Uppsala: Admqvist and Wilsells, 1961.

Anderson, E. V. Mental Retardation; A Review of Research. Edited by H. A. Stevens, and R. Heber. Chicago: University of Chicago Press, 1964.

Benda, C. E.; Squires, N. D., Ogonik, M. J.; and Wise, R. "Personality Factors in Mild Mental Retardation." American Journal of Mental Deficiency, 68, 24, 1963.

Berg, J. M. Second International Congress on Mental Retardation, Part I. Basel: Karger, Vienna, 1961.

Birch, H. G.; Richardson, S. A.; Baird, D.; Borobin, G.; and Illsley, R. Mental Subnormality in the Community. A Clinical and Epidemiologic Study. Baltimore: The Williams and Wilkins Company, 1970.

Blank, C. E. Apert's syndrome (a type of acrocephalosyndactyly). Annals of Human Genetics, 24, 151, 1960.

Brugger, C. Handbook of Heredity. Edited by G. Just, K. H. Bauer, E. Hanhart, and J. Lange. Berlin: Julius Springer, 1939.

Buch, C. "Exposure to Virus Disease in Early Pregnancy and Congenital Malformations." Canadian Medical Association Journal, 72, 744, 1955.

Crome, L., and Stern, J. The Pathology of Mental Retardation. Boston: Little, Brown and Company, 1967.

Dahlberg, G. Mental Deficiency Acta Genetica, 2, 55, 1951.

Doll, E. A. "Feeble-Mindedness and Intellectual Retardation." American Journal of Mental Deficiency, 51, 456, 1947.

Eastham, R. D., and Jancar, J. Clinical Pathology in Mental Retardation. Baltimore: The Williams and Wilkins Company, 1968.

Edwards, J. H. "Seasonal Incidence of Congenital Disease in Birmingham." Annals of Human Genetics, 25, 89, 1961.

Essen-Möller, E. "Individual Traits and Morbidity in a Swedish Rural Population." Acta Psychiatrica, Supplement 100, 1954.

Fisher, R. A. "The Correlation Between Relatives on the Supposition of Mendelian Inheritance." Trans Royal Society of Edinburough, 52, 399, 1918.

Goodman, M. B.; Gruenberg, E. M.; Dorwing, J. J.; and Rogot, E. "Prevalence Study of Mental Retardation in a Metropolitan Area." American Journal of Public Health, 46, 122, 1956.

Halperin, S. L. "A Clinico-Genetical Study of Mental Defect." American Journal of Mental Deficiency, 50, 8, 1945.

Hendricks, C. H. "Congenital Malformations; Analysis of the Ohio Records." Obstetrics and Gynecology, 6, 592, 1955.

Heber, R., ed. "A Manual on Terminology and Classification in Mental Retardation." Monograph Supplement. American Journal of Mental Deficiency, 64, No. 2, 1958.

Higgins, J. V.; Scott-Emuakpor, A.; and Berker, I. O. "A Screening Program for Metabolic Errors Among the Mentally Retarded." Michigan Mental Health Research Bulletin, 4, No. 3, 1970.

Hirschhorn, K., and Cooper, H. L. "Chromosomal Abberations in Human Disease." A review of the status of cytogenetics in medicine. American Journal of Medicine, 31, 442, 1961.

Karlsson, J. L.; Kihara, H.; Grant, J.; and Nelson, T. L. "Metabolic Disorders Leading to Mental Deficiency." I. Screening for excessive urinary excretion of nitrogenous compounds. Journal of Mental Deficiency Research, 5, 17, 1961.

Knoblock, H., and Pasamanick, B. "Seasonal Variations in the Births of the Mentally Deficient." American Journal of Public Health, 48, 1201, 1958.

Levitan, M., and Montagu, A. Textbook of Human Genetics. New York: Oxford University Press, 1971.

Marden, P. M.; Smith, D. W.; and McDonald, J. J. "Congenital Anomalies in the Newborn Infant Including Minor Variations." Journal of Pediatrics, 64, 357, 1964.

Masland, R. L.; Sarason, S. B.; and Gladwin, T. Mental Subnormality. New York: Basic Books Incorporated, 1958.

Mayer-Gross, W. "Mental Health Survey in a Rural Area." Eugenics Review, 40, 18, 1948.

Oster, J., ed. International Copenhagen Congress on the Scientific Study of Mental Retardation, I. Copenhagen: Det Berlingske Bogtrykkeri, 1964.

Pearson, S., and Jaderholm, L. Mendelism and the Problem of Mental Defect. On the Continuity of Mental Defect. Cambridge: Cambridge University Press, 1914.

Penrose, L. S. A Clinical and Genetic Study of 1280 Cases of Mental Defect. London: His Majesty's Stationary Office, 1938.

_____. The Biology of Mental Defect. London: Sidgwick and Jackson, 1963.

Pinter, R., and Forlano, G. "Season of Birth and Mental Differences." Psychological Bulletin, 40, 25, 1943.

Pitt, D. B. "A Study of Congenital Malformations." Australian Journal of Obstetrics and Gynecology, 2, 23, 1962.

Priest, J. H.; Thuline, H. C.; LaVeck, G. D.; and Jarvis, D. B. "An Approach to Genetic Factors in Mental Retardation." Studies of Families containing at least two siblings admitted to a state institution for the retarded. American Journal of Mental Deficiency, 66, 42, 1961.

Reed, E. W., and Reed S. C. Mental Retardation: A Family Study. Philadelphia and London: W. B. Saunders Company, 1965.

Renpenning, H.; Gerrard, J. W.; Zaleski, W. A.; and Tabata, T. "Familial Sex-Linked Mental Retardation." Canadian Medical Association Journal, 87, 954, 1962.

Roberts, J. A. F. "The Genetics of Ologophrenia." Proceedings ler Congressional Mondial de Psychiatrie, Paris, 6, 55, 1950.

Roberts, R. G.; Norman, R. M.; and Griffiths, R. "Studies on a Child Population." IV. The form of the lower end of the frequency distribution of Stanford-Binet Intelligence quotients and the fall of low intelligence quotients with advancing age. Annals Eugenics, London, 8, 319, 1938.

Smith, D. W., and Bostian, K. E. "Congenital Anomalies Associated with Idiopathic Mental Retardation." Journal of Pediatrics, 65, 189, 1964.

Stern, C. Principles of Human Genetics. 2nd ed. San Francisco and London: W. H. Freeman and Company, 1960.

Wright, S. W.; Tarjan, G.; Lippman, R. W.; and Perry, T. L. "Etio Logic Factors in Mental Deficiency: Errors of Metabolism that may Lead to Mental Deficiency." American Journal of Diseases of Children, 97, 445, 1959.

Wright, S. W.; Tarjan, G.; and Eyer, L. "Investigation of Families with Two or more Defective Siblings-Clinical Observations." American Journal of Diseases of Children, 97, 445, 1959.

Wright, S. W.; Shaw, K. N. F.; Roth, P.; Traub, J.; and Johnson, A. "Families with Two or more Defective Sibs." American Journal of Diseases of Children, 102, 302, 1961.