A GENETIC COMPARISON OF TWO NOVA SCOTIAN COMMUNITIES

BY

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ABSTRACT

Fifteen children of French-Acadian origin affected with Niemann-Pick disease Type D (NPD) were traced through both parents to four common ancestral couples. It is proposed that a single mutation 200-300 years ago was responsible for all known patients. Common ancestry, segregation analysis and sex ratio support the autosomal recessive inheritance hypothesis. Alstrom's and Usher's syndromes were identified in the same large kindred.

Ten of the children affected with NPD lived in the same small community (HP). Estimates of the frequency of NPD in the school age population of HP were approximately 1% homozygotes and 11-26% heterozygotes. Coefficients of inbreeding (F) were calculated for ten generations. The mean F for affected children (0.0306) was higher than that for random families in HP (0.0079) but approximately equal to the mean F value of 0.0254 in a control community WP.

Results of common ancestry calculations and the high carrier frequency estimation suggest that most parents of school age children in HP are at risk for producing children with NPD. However, advances in transportation and reduction in family size are rapidly changing the breeding patterns of both HP and WP.

SYMBOLS AND DEFINITIONS

F - Coefficient of Inbreeding, defined as the probability that any single locus is homozygous by descent.

Isonymous Marriage - marriage between individuals of the same surname.

HP - Geographical area in Yarmouth County, Nova Scotia as indicated in Figure 5 (page 22).

WP - Geographical area in Yarmouth County, Nova Scotia as indicated in Figure 5 (page 22).

ACKNOWLEDGEMENTS

This thesis would not have been possible without the assistance of Rev. C.J. d'Entremont. His extensive genealogical records, intimate knowledge of the people and willingness to spend many hours searching records are in large part responsible for the success in tracing common ancestors.

Mr. Rudolphe Doucet, School Superintendent Argyle District, Yarmouth County, made school registers available for sample selection. Mrs. I.F. Bruce assisted in collection of genealogical information.

Mr. David Bolling, Johns Hopkins University, provided the computer program. Mr. A.P. Smith and Dan Boss adapted the program for use on the Dalhousie computer.

Several members of the Medical Staffs of Yarmouth and Halifax assisted throughout the study particularly Dr. Margaret Churchill, Paediatrician, Yarmouth; Dr. E.J. Fulde, Family Physician, Tusket; Dr. J.A.R. Tibbles, Paediatric Neurologist, Halifax.

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Sincere appreciation is expressed to Dr. J. Philip Welch who supervised all aspects of the project.

CHAPTER I: INTRODUCTION

Genetic interest in the French-Canadian population of Nova Scotia was stimulated by reports of several children who suffered from an unusual lipid storage disease. The purpose of the present investigation was:

(1) to determine the mode of inheritance and the frequency of the particular disease, and

(2) to compare the families having affected children, in their breeding patterns and their frequency of other genetic conditions, with families who have similar historical origin, but do not have children affected with this condition.

An important aspect of the comparison is the amount of inbreeding and some of its consequences in these families.

Inbreeding

The terms "inbreeding" and "consanguinity" are often used interchangeably to indicate mating between individuals who are genetically related to each other. Schull and Neel (1972) distinguished between "consanguinity effects" and "inbreeding effects" on the offspring. "Consanguinity effects" refer to the effects on offspring characteristics of parents who are genetically related to each other. "Inbreeding effects" refer to the effects on offspring characteristics when one or other of the parents was the product of a consanguineous marriage. The coefficient of consanguinity or coefficient of inbreeding (F) is the probability that any single locus is homozygous by descent from a common ancestor.

Human inbreeding in Nova Scotia between 1963 and 1967 was estimated by F.M. Crawley (1971) from the frequency of isonymous marriages in 27 communities of populations less than 1000. The percentage of isonymous marriages varied over the 5 years with a range of 1.45% to 1.81%. The corresponding coefficient of inbreeding (F) values range from 0.0035 on Surette's Island, Yarmouth County, to 0.1260 in Scott's Bay, King's County. Thus, there is no doubt that detectable inbreeding does exist in Nova Scotia. Studies have been made of many inbred populations, notably the Hutterites, (Mange, 1964a), Amish (McKusick et al., 1964a and 1964b) and Japanese (Neel, et al., 1949). Perhaps one of the most relevant studies for comparison was a study of French-Canadians in Quebec by C. Laberge (1968, 1969). For a rural population he estimated an F value of 0.0958 based on church dispensation records from 1955 to 1965.

The alleged harmfulness of consanguineous marriages was discussed by Böök in 1957. His study was limited to 34 first cousin marriages and controls in the North Swedish population. He found that cousin parents tend to produce more intellectually defective and less gifted children than average control parents; and that the total genetic morbid risk for children from first cousin marriages was considerably increased, i.e. about 16% against about 4% for children from the random marriages. (For this purpose, Böök calculated genetic morbid risk on the basis of specific conditions which were known or strongly suspected to be caused by recessive genes. Stillbirths and abortions were not considered.) In a Japanese study, fetal loss and death prior

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On the other hand, the concept of an "inbreeding bot neck" implies that if the phenotype of the homozygote is deleterious inbreeding will actually cause a decline in the frequency of that ge Through close marriage over many centuries the population might redu the average number of rare recessive genes carried by each individua as compared with an outbred population.

Characteristics of the Population

Factors which suggested that the French-Acadian popula tion would be well suited for genetic studies were: availability of extensive genealogical records spanning, in some instances, thirteen generations; probability of a relatively high degree of inbreeding indicated by relatively few original settlers and a prevalence of certain surnames; relatively well-defined communities based on church

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and school boundaries; and excellent cooperation of local medical, church and school authorities.

The communities in Yarmouth County chosen for the present study are similar to the Acadian community in neighboring Digby County which was extensively studied by Hughes et al. (1960). They studied a prosperous fishing village, referred to by the code name Lavallée, from the social psychiatry viewpoint. In Lavallée, 281 individuals, of the total community population of 296, belonged to at least one of four large extended families. Hughes et al. described the family in its religious context as the most important basic social unit, regulating many economic, church centered, and social activities. The Acadians are a separate ethnic group, bound together by common language, religion, and cultural tradition. The historical background of the Acadians played a major role in the formation of this social structure.

The founding of Port Royal in 1605 marks the beginning of French settlement in Nova Scotia. Micmac Indians were already living in the area and were instrumental in helping the colony to survive. Over the next few years French families were recruited for the colonies. However, English occupation of Acadia in 1654 prevented new immigration and many Acadian families returned to France or moved to Quebec.

The colony was given back to France in 1667 and by the end of 1671, Port Royal and the neighbouring area had 68 families and a population of 373. At Cape Sable, also known under the seigneurial

name of Pobomcoup (Pubnico), belonging to the Entremont family, there were 25 persons including the two sons of Charles Latour, Jacques and Charles, who stayed with Philippe Mius d'Entremont their father's old lieutenant. Philippe had been in Acadia since 1651 when Charles Latour was named Governor of Acadia by Louis XIV.

Bona Arsenault (1966) describes the Acadian pioneers around 1700: "The fertility of the land is equivalent to the fecundity of the married couples and this was the wealth of the flourishing parishes. Large families were the rule rather than the exception and it was not unusual to have ten, fifteen, or even twenty children."

Many wars and treaties marred the life of the early Acadians. Then the expulsion of 1755 totally disrupted the colony. Exiles were spread from Massachusetts to Georgia. A few Acadian fugitives succeeded in fleeing to various points in the Maritimes seeking a living by hunting and fishing often among the friendly Indians.

Settlements in the Pubnico area where Acadians live today were all established after the return from exile about 1766 (Arsenault). Some descendants of Baron Philippe Mius d'Entremont were among those who returned from Massachusetts. At this time descendants of the Baron's sons Jacques and Abraham who married daughters of Charles Latour used the surname d'Entremont, while descendants of the third son Philippe, who married a Micmac, were known by the name Mius (d'Entremont, 1968a). Today many descendants of the d'Entremont branch of the family still live in the Pubnico area while the descendants of the Mius family tend to live in the Tusket area. Other families

currently living in Pubnico, Cape Sable, Yarmouth, and Tusket areas whose ancestors returned from the exile include Amiraults, Belliveaus, and Surettes (Arsenault).

These communities remained relatively isolated over a period of several generations. However, current widespread availability of rapid transportation, regional schools and the increasing numbers of young adults who seek employment or advanced education outside the community are rapidly changing the family structure of these previously isolated communities.

CHAPTER II: THE NOVA SCOTIA VARIETY OF NIEMANN-PICK DISEASE

Classical Niemann-Pick disease was described by Albert Niemann in 1914 and Ludwig Pick in 1933. It is characterized by serious central nervous system involvement and enlargement of the solid viscera, with a marked increase in tissue lipids, specifically sphingomyelin. Microscopically the accumulated lipid appears as large multivacuolated "foam cells". Onset occurs in infancy followed by progressive deterioration and early death.

Clinical and chemical variations in the classical picture led Crocker (1961) to divide his patients into four parts:

Type A - "Classical" Niemann-Pick disease

Type B - heavy visceral involvement but with normal central nervous system

Type C - moderate central nervous system problems with onset in late infancy

Type D - Nova Scotia Variety

Gray matter sphingomyelin increases are characteristic only for the "classical" type of infant. Crocker's other patients showed much milder abnormalities in the brain, and he concluded that the differences between groups probably were due to separate hereditary defects. Fredrickson and Sloan (1972) added type E to the Niemann-Pick disease classification to designate adults who have sphingomyelin accumulation in one or more tissues but who do not have neurological abnormalities.

The remainder of the current discussion of Niemann-Pick disease is confined to the Nova Scotia variant. At the present

time the designation of type D is reserved for patients of Nova Scotian ancestry who otherwise have a course similar in many ways to type C (Fredrickson and Sloan). However, the problem of whether type D is a separate disease entity has not been resolved. The biochemical defect in type D is currently being investigated by M.W. Spence and B.G. Rao, Departments of Paediatrics and Biochemistry, Dalhousie University.

Figure 1 illustrates the geographical distribution of all known cases of Type D Niemann-Pick disease. Type D was first described by Crocker and Farber in 1958. They described four patients who differed from the classical Niemann-Pick disease because of atypically prolonged courses with death at 12 to 20 years of age. These patients were clinically similar and were all of French-Canadian Catholic ancestry with immigration to eastern Massachusetts.

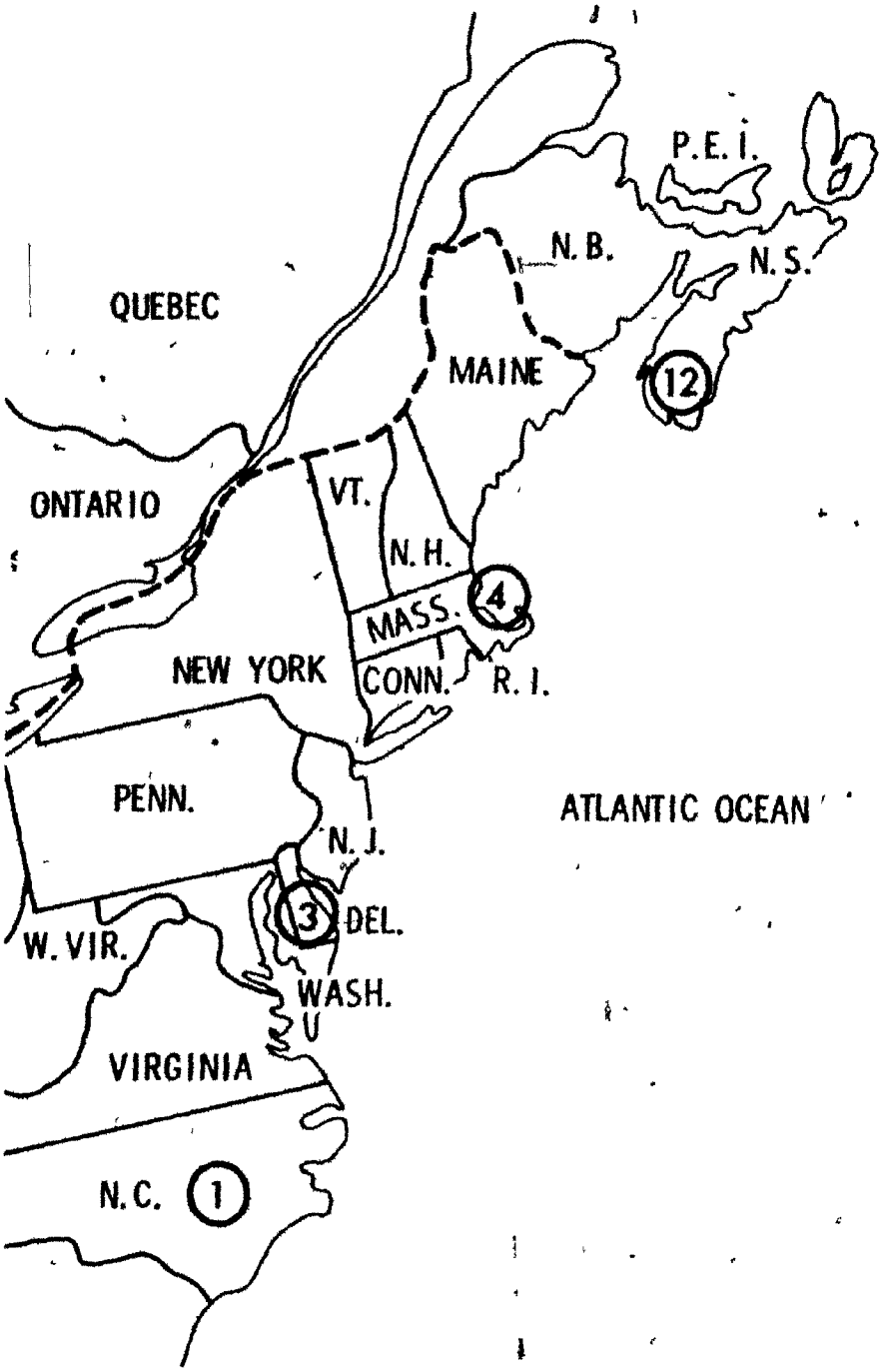
In 1966, Fredrickson reported three sibs in Delaware who were identical, in terms of their father's ethnic and geographic origin, to the patients comprising the Nova Scotian group described by Crocker and Farber. Jaundice was a prominent feature of their disease and they had a protracted course in which neurological abnormalities slowly progressed to severe disability and death.

In North Carolina, Fox and Kane (1967) described an adolescent boy of French-Canadian ancestry whose presenting symptoms resembled schizophrenia. Microscopic examination of splenic tissue (performed in Dr. Farber's laboratory) was reported as "clearly consistent with Niemann-Pick's disease".

Subsequently, twelve children were identified in

FIGURE 1

NOVA SCOTIA TYPE
NIEMANN - PICK DISEASE



Yarmouth County, Nova Scotia (Tibbles and Welch, 1972). At least five of the patients had transient jaundice in the first year of life. Intellectual development appeared normal until school age. Clumsiness and personality changes developed gradually in midchildhood. Physical and mental deterioration was progressive and no patient survived to age 20. Autopsies were performed on six patients. These all confirmed the presence of a lipid storage disease with maximal involvement of the liver, spleen, reticuloendothelial system and the brain. In the past few years, at least six children from the same community have died in childhood or early teens. In retrospect, it seems possible that some of them may have suffered from Niemann-Pick disease but no clinical details are available and they have been omitted from the current study. Inquiries were made to hospitals and physicians throughout the province of Nova Scotia but no children with a similar condition were reported in other communities.

Common Ancestors

The occurrence of a previously unknown disorder in a group of children all having a common ethnic origin, immediately suggests the possibility of autosomal recessive inheritance due to a single mutation several generations ago. If a common ancestor could be found for all affected children the recessive theory would be supported and an estimate could be made concerning how widespread the defective gene is in the present population. Crocker and Farber (1958) noticed that there was repeated occurrence of surnames in the four families they studied, but actual kinship was denied. Dr. Crocker

kindly provided us with family histories of all of his patients. Identification of Frederickson's patients was also obtained. Several unsuccessful attempts were made to trace the patient described by Fox and Kane.

The twelve Nova Scotian cases belong to nine sibships. A partial pedigree of the Niemann-Pick families was constructed by F.M. Crawley (1971) but a common ancestor was not clearly shown for all known cases. Additional information was obtained from parents, grandparents, and relatives by personal interview usually in their own home. Mrs. I.F. Bruce assisted with some of the interviews by visiting specified individuals. This was a time-consuming and often frustrating method of obtaining genealogical information. Many of the individuals did not have telephones; thus, it was often not possible to arrange in advance for interviews. In a rural area, unfamiliar to the interviewer it was often very difficult to locate an individual's home. Pedigree searching for this particular kindred was further complicated by illegitimacy, informal adoptions and occurrence of several persons with identical names. Much of the information regarding individuals born prior to the present century was obtained from Rev. C.J. d'Entremont (d'Entremont, 1967, 1968a, 1968b, 1968c). His records include all available birth, marriage and death registers as well as a great deal of unpublished material he has collected over a period of many years. A published genealogy by Brown (1888) was used with caution. In the event of discrepancies, the opinion of Father d'Entremont was accepted.

Information from all sources was integrated by means

of a card file system. When possible, the card for each individual contained the name and date of birth of the individual and the names of his parents, spouse and children. This preliminary sorting of the data was necessary in order to prepare the input for the computer calculations. Input consists of a unique code number for each individual and the code numbers of his parents. Use of nicknames, variability in spelling of names (Appendix II), and the various degrees of accuracy and completeness of the information sources contributed to the problem of assigning unique numbers. The unique number not only implies that every individual has a different number, but that every time the same individual appears in the pedigree he has the same number. The latter aspect of the coding required considerable searching and matching, especially in the case of individuals in several generations with the same name.

Calculation of the most likely common ancestor was carried out using a computer program by Mange (1964b, 1969) and adapted by Bolling (McKusick and Cross, 1968) (Appendix I). The program compares all the codes on the mother's side of the pedigree with all the codes on the father's side. All codes which appear on both sides of the pedigree may indicate a common ancestor. Since all ancestors of a common ancestor also appear on both sides of the pedigree not every match (coincidence) indicates a "real" common ancestor. The program tests for valid coincidences and tallies only those cases when the common ancestor's child on the father's side of the pedigree was different from the common ancestor's child on the mother's side.

It was possible to trace the ancestry of twelve couples (nine Yarmouth County, three in Massachusetts) for, in some instances, thirteen generations. Not included were patient E.D. of Crocker whose father is unknown and Frederickson's family whose mother was Italian. Results of the calculation of common ancestry are given in Table 1. Four couples fit the criteria for being common ancestors of both parents of the twelve sibships. The mother of Crocker's E.D. and the father of Frederickson's family can also be traced to these couples. The relationship of three of the ancestral couples to each other is shown in Figure 2. The fourth couple is not known to be directly related to these three couples.

The number of valid coincidences indicate the number of pathways between the affected individuals and these four couples (Table 1). If the mutation occurred in an individual in a remote generation, then the more pathways between that individual and his descendants, the greater the chance that the mutation was transmitted to the descendants. Of the four couples that are common ancestors, Joseph Muise (529) and his wife Marie Amirault (556) have the greatest number of valid coincidences. This seems to suggest that the mutation is more likely to have originated in one of them than the other three couples. Joseph Muise was born about 1679 and his wife Marie Amirault was born in 1684. They had five sons and eight daughters, most of whom settled in Tusket area after return from exile. According to C.J. d'Entremont (1968a) this Joseph Muise was the ancestor of all persons by the name of Muise (Appendix II) in Canada and the United States. Figure 3 is a simplified version of the pedigree showing at least one pathway to the ancestral

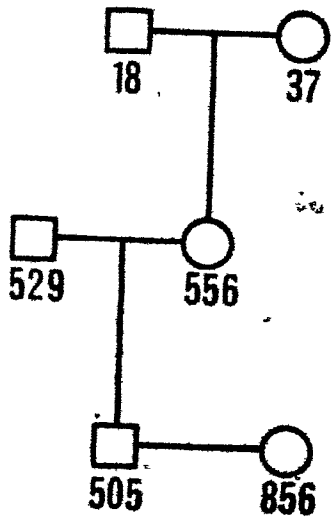
TABLE I

Common Ancestors of Children having Niemann-Pick Disease Type D

Identification Numbers	Frequency of Coincidences
529 and 556	2217
18 and 37	1353
101 and 160	343
505 and 856	184

FIGURE 2

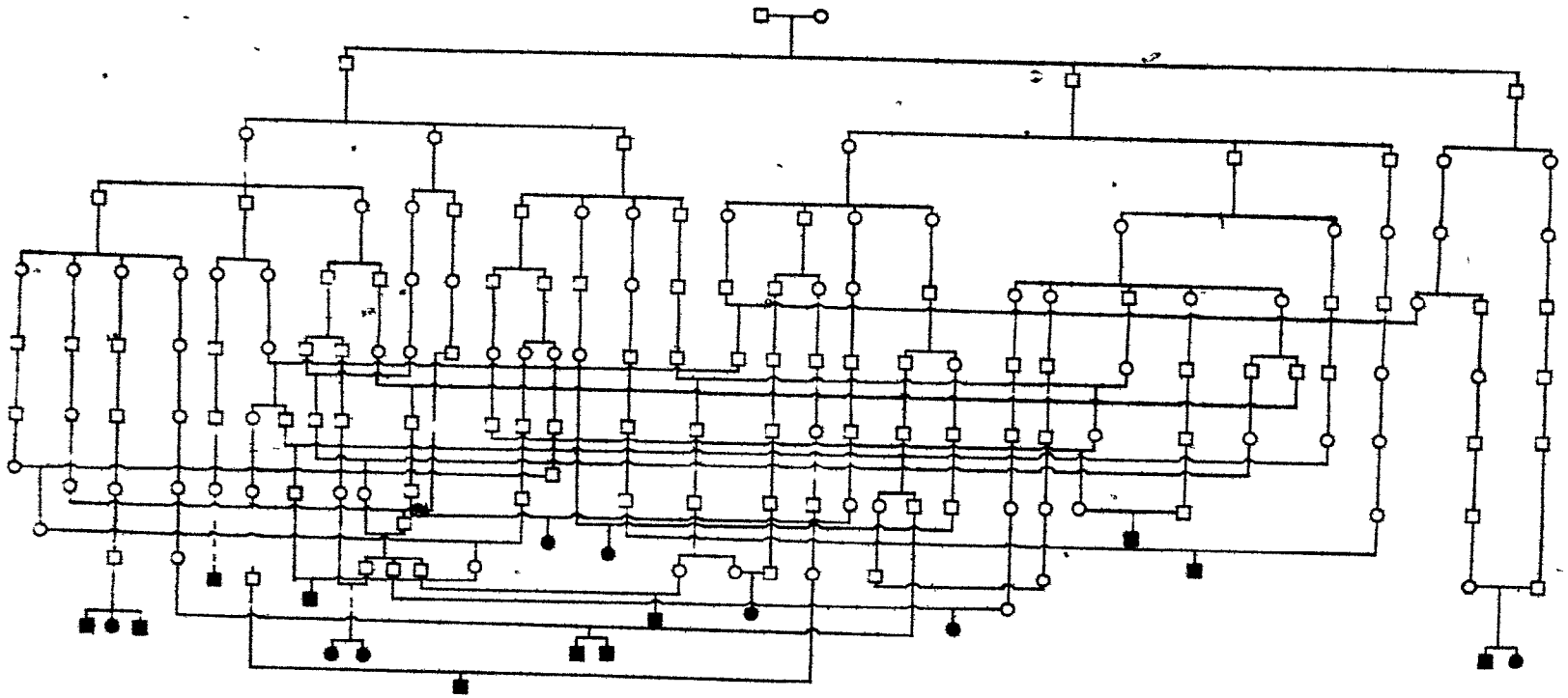
RELATIONSHIP OF COMMON ANCESTORS OF CHILDREN WITH TYPE D NIEMANN - PICK DISEASE



Numbers are identification codes

FIGURE 3

Nova Scotian Niemann–Pick Disease



couple (529 and 556) from both parents of affected children. There is no reason to believe that the pathways illustrated are the most likely pathways for transmission of the mutant gene. However, illustration of the possible 2,217 pathways was not practical.

Although it seems reasonable to propose that Joseph Muise or his wife are most likely to have transmitted the mutant gene, we cannot ignore the fact that three other couples are common ancestors of the affected children. As shown in Figure 2, couple 18 and 37 are parents of Marie Amirault (556). This relationship complicates the problem of trying to identify the origin of the mutation. If the mutation occurred in one of them (18 or 37) and was transmitted to Marie (556) but not to their other children, this could not be distinguished from the possibility that the event occurred in Marie or her husband. The same situation applies to 505 and his parents, 529 and 556.

The information now available is not sufficient to eliminate any of the four couples as a possible source of the mutation. If other patients were identified, whose parents could be traced to one of the couples but not the others, this would provide some evidence for a decision. However, due to the inbreeding, this kind of evidence seems unlikely. It is also possible that if the genealogy were more complete, other couples would fit the common ancestor criteria.

Segregation Analysis

As a further test of the recessive hypothesis, a segregation analysis was carried out for nine sibships. In all cases the parents were normal. Since heterozygote couples are not recognized

unless they have at least one affected child, allowance was made for bias of ascertainment. An attempt was made to include all cases in the community and the "a priori method" for complete ascertainment was used. The nine sibships are represented in Figure 4. Due to the late onset of the disease all children less than six years of age were omitted from the pedigree. Also children who died in early infancy or childhood were omitted. The second child in sibship H was considered affected for the purpose of analysis although she was not examined. She died at age sixteen and was described by her mother as being similar to her sister who was confirmed by tissue biopsy.

A total of thirteen observed cases was compared with 16.69 expected cases in Table II. The difference between the observed and expected numbers is less than two standard deviations and supports the recessive hypothesis.

Examination of the sex ratio of all known affected children also supports the autosomal recessive hypothesis. Of the twelve Yarmouth cases and four Boston cases, nine were male and seven were female.

Frequency

On the basis of the fact that twelve children born in Yarmouth County and three born in Massachusetts with Niemann-Pick disease type D, can all be traced through both parents to a common ancestor and that no other instances of the disease are known throughout the province of Nova Scotia, it seems reasonable to assume that the defect is due to a single mutation which occurred in one of the eight individuals who were shown to be common ancestors. Segregation

FIGURE 4

SIBSHIPS WITH ONE OR MORE CASES OF
TYPE D NIEMANN - PICK DISEASE

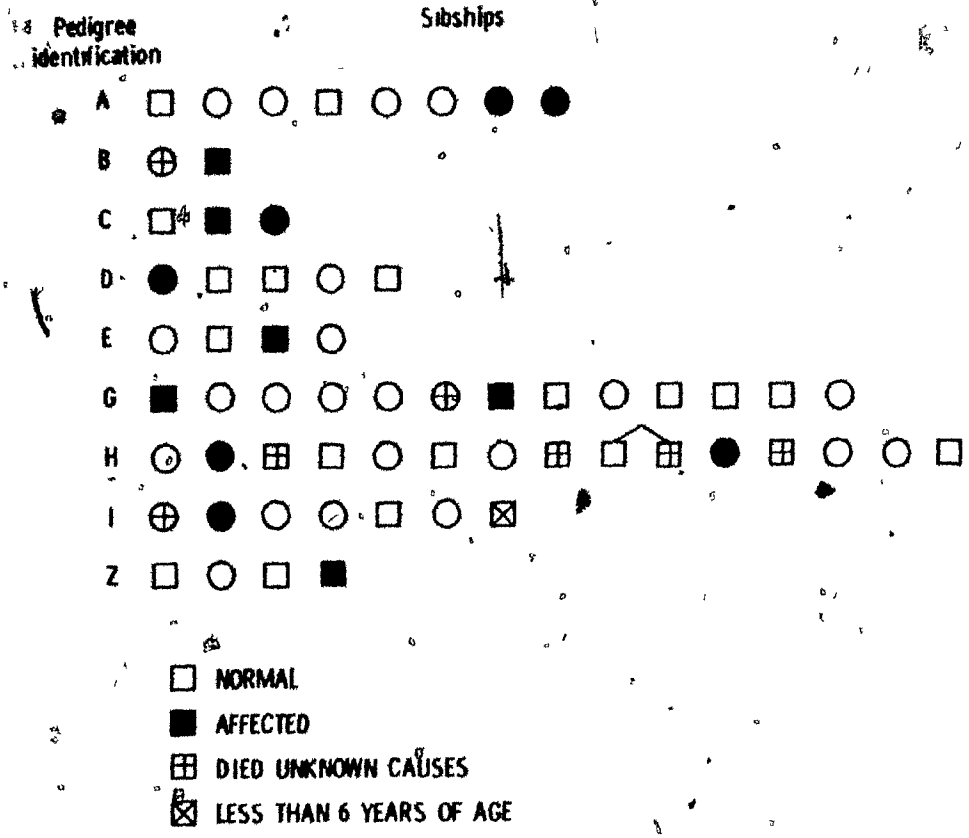


TABLE II

Segregation Analysis of Niemann-Pick Disease

Sibship Size	No. of Sibships	No. of Sibs	Number Affected Observed	Number Affected Expected*	Variance*
1	1	1	1	1.000	0.000
3	1	3	2	1.297	0.263
4	2	8	2	2.926	0.840
5	2	10	2	3.276	1.004
8	1	8	2	2.223	1.172
11	1	11	2	2.871	1.805
12	1	12	2	3.098	2.020
Total	9	53	13	16.691	7.104

S.D. 2.665

Observed - Expected =-3.691

Number of S.D. = $|3.691/2.665| = 1.385$

* From tables of L. Hogben (1946) an Introduction to Mathematical Genetics, W. W. Norton and Co., Inc. In McKusick (1969).

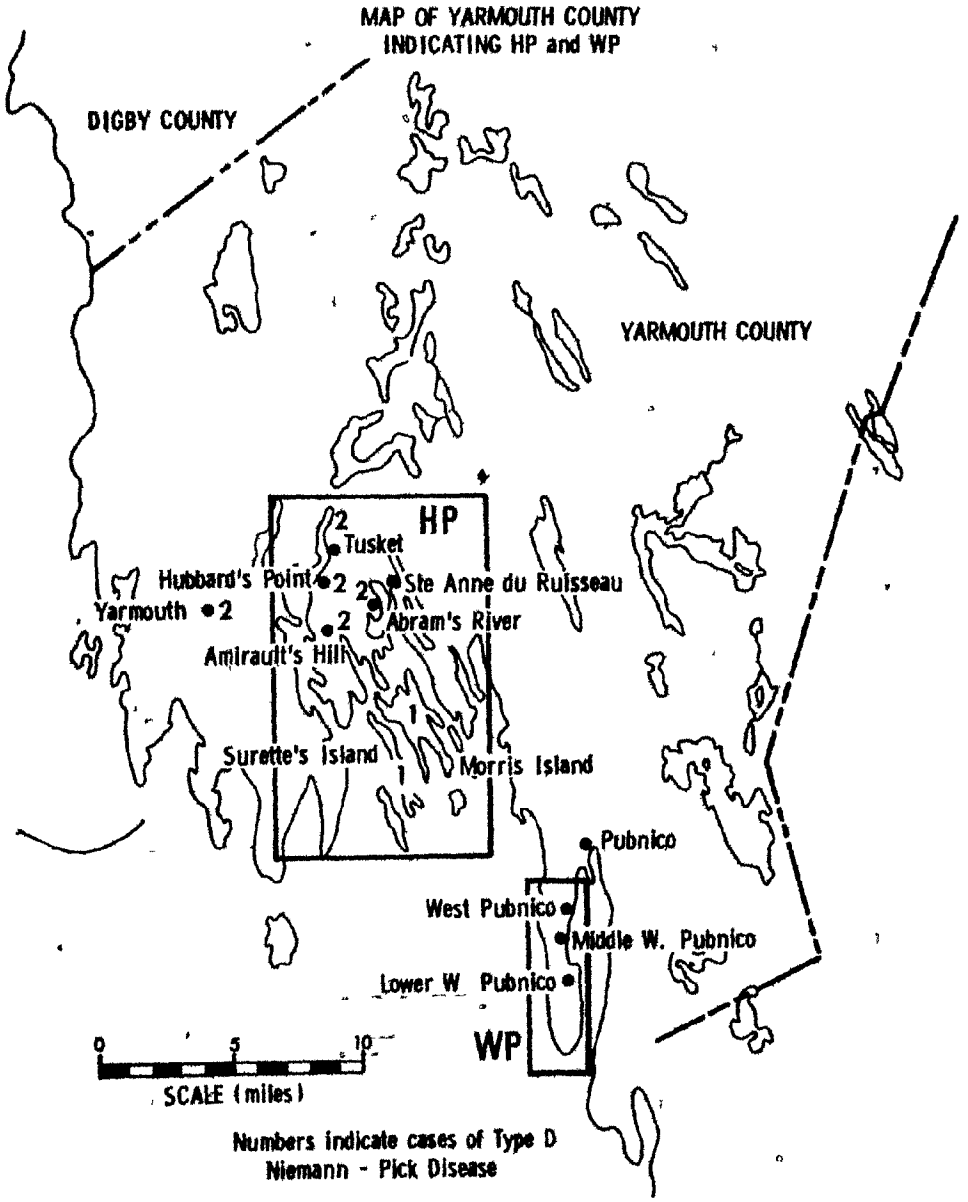
analysis and the sex ratio support the autosomal recessive inheritance theory.

Thus, based on the assumption that the disease is the result of a single mutation which occurred between two hundred and three hundred years ago and it is transmitted as an autosomal recessive gene, the following estimates of affected individuals and carriers are relevant only to a small segment of the French-Acadian population. At the present time, we know of only three living children, who are affected with Niemann-Pick disease.

Because it was impossible to trace all the descendants of the common ancestors in order to compare the total number of births with the total number of affected children, an approximation of the disease frequency was made on the basis of the current school population in the area where the majority of the affected children lived. The school population was appropriate because symptoms of the condition are usually not evident until the child is school age. The region which is served by Ste. Anne du Ruisseau and Amirault's Hill schools (HP) includes ten of the twelve cases known in Yarmouth County (Figure 5). The 1971-72 total registration for these two schools was 385. Three affected children would have been in one of these schools at the present time if they had not been affected. Thus, the frequency of affected children was estimated as 3/385 or approximately 1% (95% confidence limits 0.32-2.32).

If we assume that the affected children are homozygotes for a recessive gene, then using the Hardy-Weinberg law the heterozygotes or carrier frequency would be approximately 16%. The 95%

FIGURE 5


MAP OF YARMOUTH COUNTY
INDICATING HP and WP
DIGBY COUNTY
YARMOUTH COUNTY
HP
Tusket
Hubbard's Point
Ste Anne du Ruisseau
Yarmouth
Abram's River
Amirault's Hill
Surette's Island
Morris Island
Pubnico
West Pubnico
Middle W. Pubnico
Lower W Pubnico
WP
0
5
10
SCALE (miles)
Numbers indicate cases of Type D
Niemann - Pick Disease
HEAVY SQUARES INDICATE APPROXIMATE
GEOGRAPHICAL AREAS DESIGNATED BY
HP AND WP

confidence limits for carrier frequency would be 11% to 26% or approximately 1/9 to 1/4 of the HP school population. Use of the Hardy-Weinberg principle is based on the assumption that mating in the population is random. No human population mating is truely random but there is no evidence that matings in HP are assortative with respect to the gene for Niemann-Pick disease.

Eugenics

Most of the individuals in the HP community can be traced to at least one of the four couples shown in the previous section to be common ancestors of the Niemann-Pick children. Evidence for this comes from a random sample of ten couples. (Details of the selection of these couples are given in Chapter III). Of the ten couples, six could be traced through both husband and wife to at least one of the four common ancestors. The other four could be traced to one or more of the common ancestors through either the husband or the wife. However, for each individual that could not be traced to one of the four common ancestors the pedigree information was incomplete. An important observation was that the consanguinity is so remote in most cases that husbands and wives were not aware that they were "related" to each other or to the couples who had affected children. Thus, for practical purposes any individual with ancestors from the HP area is a possible carrier of Niemann-Pick disease. On the other hand, knowledge of the common ancestors gives reasonable assurance that an individual whose ancestors are from outside this group has practically no risk of being a carrier.

Since the biochemical defect is unknown, there is no

easy way to test for potential carriers of this disease. Characteristic "foam cells" were found in the bone marrow of patients with Niemann-Pick disease, type D, and of heterozygous carriers (Vethamany et al., 1972). However, bone marrow analysis is not a desirable or practical method of testing large numbers of individuals for carrier status.

Preliminary discussions were held with church authorities and other community members in an attempt to make the families concerned aware of the hereditary nature of the condition and to discourage their children from marrying within their own community. On the other hand, we must exercise caution in suggesting that community members be made more aware of the disease. A physician practicing in this area suggested to me that a few parents have brought healthy children for medical attention unnecessarily due to the fear of the dreaded disease. Since at the present time there is no treatment for the condition there seems to be little value in causing anxiety from the time of birth of a child until the age of onset. Detection of carriers before the production of children is obviously desirable.

CHAPTER III: COMPARISON OF TWO COMMUNITIES

Method

Two sample areas were chosen such that one (HP) included the majority of known cases of Nova Scotia variety Niemann-Pick disease and a control (WP) in which the disease was unknown (Figure 5, page 22).

West Pubnico appeared to be an ideal control community for several reasons: (1) most of the members of the community were descendants of the same early French settlers as those living in the HP area, (2) it is geographically well-defined, (3) it has approximately the same size population as HP, and (4) there were indications that the people would be willing to participate in the study.

It was not practical to obtain medical and genealogical information for every member of the two communities. Various methods of choosing a sample such as electoral boundaries, postal routes, church parishes, and school districts were considered. School registers seemed to offer a reasonable method of sample selection. These were made available by Mr. R.E. Doucet, Superintendent of Schools, Argyle Municipal School Board.

The criteria for an index family was having a school-age child and having both parents available for an interview. This method biased the sample for large families because the more children there were in a family the more likely one of the children would be chosen from the register as an index case. Two children were excluded as index children because their parents were not available

for an interview. In both cases, one of the parents was permanently confined to a hospital. Thus, selection may have biased the sample toward healthy parents.

The school districts of Ste. Anne du Ruisseau-Amirault's Hill and West Pubnico were chosen as the sample source. The total 1971-72 school enrollment for grades 1 to 8 for the former district (designated HP) was 385 and for West Pubnico (WP) was 405. Ten families were chosen from the class registers of each district using a table of random numbers. The project was discussed in advance with members of local medical, school and church groups and a letter was sent to each of the twenty families prior to a personal interview. The cooperation of all twenty families was excellent. The information requested was: (1) name, date of birth, medical and school history for each child in the index sibship, (2) names, ages, and medical problems of the father and mother, and their sibs, (3) the father's occupation, (4) names of parents, grandparents, etc. of the father and mother, and (5) whether the couple thought they were related before marriage. Information on genetic conditions known in the two communities was sought from Yarmouth physicians, interviews with the index families and medical records of the Yarmouth Regional Hospital and the Izaak Walton Killam Hospital for Children, Halifax.

Family Size

The number of live born children in each of the index families is recorded in Table III. Twins were counted as individuals for this purpose. The mother's age at the time of the interview is

TABLE III

Family Size (total live births)
for Index Families in HP and WP

	Number of children	mother's age in 1972	mother's sibship size	father's sibship size
HP 1	5	30	2	3
HP 2	6	38	10	9
HP 3	2	34	8	5
HP 4	6	43	8	10
HP 5	2	33	7	13
HP 6	6	34	3	14
HP 7	3	34	8	4
HP 8	3	30	9	14
HP 9	3	26	15	8
HP 10	5	33	5	6
Mean	4.1	33.5	7.5	8.6
WP 1	8	43	11	9
WP 2	3	36	1	5
WP 3	3	48	8	3
WP 4	5	34	13	7
WP 5	4	32	2	5
WP 6	3	28	3	9
WP 7	3	36	1	10
WP 8	3	35	9	13
WP 9	4	30	8	2
WP 10	7	39	10	6
Mean	4.3	36.1	6.6	6.9

given to indicate that families are incomplete. From this small sample there is no indication of a difference between the average family size in WP (4.3) and that in IIP (4.1). Due to the way the families were chosen they are not representative of all couples. Couples without children were not included in selection and couples with many children had a greater chance of being included in the sample than those with one or two children.

The sibship size of the father and mother was used to estimate the average family size for completed families of the previous generation (Table III). Half sibs were eliminated from this count. This information was obtained from the index couples and is subject to at least two types of error. In very large families, individuals may not recall all siblings who died or moved from the community. On the other hand, illegitimate children who were "adopted" may have been recorded as full siblings. The parental sibships are not representative of all sibships in the community of the same time period because sibships of size zero were not included. As mentioned above, the index families were biased for large families. This may mean that the parental sibships are also biased if there is a tendency for couples who have produced large families to be themselves members of large sibships. Another bias toward large families in the parental generation is that the larger the parental sibship, the more likely that one of the members married in the community and currently has offspring in school. At the 5% level of significance, there was no difference between the size of the parental sibships in

HP (8.1) and the size in WP (6.8). The mother's sibship size and the father's sibship size in each area (Table III) were combined for these estimates.

Statistical comparison of these figures with those for other populations is not justified because of the method of sample selection. However, these figures appear lower than a mean of 11.2 children reported by Mange (1964a) for completed Hutterite families. For this estimation Mange considered a complete family as one in which the father was living and the mother was age 45 or older when she died or when the data were collected. The HP and WP figures appear to be similar to the value of 7.6 children calculated by Laberge (1968, 1969) for the average completed family in the French-Canadian isolate, Isle-aux-Coudres. Completed families were those in which the mother was 45 years old or older at the time of the census (July, 1965), one parent had died before the mother was 45, or the mother had had hysterectomy or bilateral ovariectomy before the age of 45.

The most relevant observation from the data on family size is the dramatic difference between the index family size and their parents' family size. In making this comparison we must keep in mind that the size of the index families probably will increase. Yet, there seems to be little doubt that the completed families of the index couples will be smaller than their sibships. Laberge noted a recent decline in the fecundity (number of conceptions) of uncompleted families in Quebec. He suggests that it must be more a voluntary limitation of family size than the result of genetic factors because

such a sharp genetic change in so short a time is hardly possible.

Income level, education and age levels of parents, religion, ethnic origin and urbanization are all factors which affect family size (Health and Welfare Canada report on Family Planning, 1971). It was not possible to relate family size directly to income levels. In WP the fathers were all employed, seven of the ten jobs were related to the fishing industry. In HP, three were fishermen and three worked in the construction industry. One of the ten in HP was unemployed because he had a physical disability which prevented him from doing manual labor and he lacked the education and ability to do any other type of work. All of the index families in both communities are members of the Roman Catholic church. However, religion may no longer be a major determining factor in family size. In 1968, Kantner et al. reported that 62% of 396 Roman Catholic (presumably) Canadian women-at-risk were using contraceptives as compared with 76% of the total number of women-at-risk.

As a result of the decrease in family size one might predict a decrease in consanguinity for the next generation. In other words, as families become smaller each individual will have fewer cousins available to marry and hence will be more likely to seek a mate outside the family group.

Inbreeding Measurement

The coefficient of inbreeding (F) was measured by pedigree analysis for each of the ten families in the two areas. In order to code the genealogical information for the sample families

it was necessary to integrate this information with the card file established for the Niemann-Pick pedigree. This was necessary because some individuals were ancestors, not only of several families within the same community, but of families both in HP and WP. The difficulty previously mentioned resulting from several individuals having identical names was intensified. Also names were recorded differently depending on the source of information (Appendix II). In total, approximately 1700 individuals were involved in the calculations. The calculations were carried out using a computer program (Appendix I).

In addition to the coefficient of inbreeding, the "degree of completeness" of the pedigree was calculated. This measure of completeness attempts to estimate what percentage of the "true" F value is represented by the F value computed on the basis of known ancestors.

The "degree of completeness" factor must be interpreted with caution. For example, in WP, the father of index family WP 5 was born outside of Yarmouth County. His pedigree was not coded beyond his parent's generation because his ancestry was known for several generations to be non-Acadian. In this instance the "degree of completeness" for ten generations as indicated by the computer calculation was only 21.6%. Yet, we are reasonably sure that this individual is not genetically related to his wife. On the other hand, couple HP 9 also has an F value of 0.0 and relatively low (11.6%) completeness. In this case, the low completeness value is due to difficulty encountered

in obtaining information. It seems possible that if the family history of HP 9 were complete for ten generations the F value might be higher than zero. Difficulty in the interpretation of pedigree completeness was also encountered by the group at Johns Hopkins who used this program for their study of the Amish population. Bolling and Cross (Personal communication) recently altered their program so that in tracing back to a marriage that involves a person outside the Lancaster group of Amish the pedigree line is considered complete. However, the program as we used it indicated completeness only if all the ancestors were traced. Thus, one cannot distinguish between a low "degree of completeness" due to a total lack of information about the ancestors of a particular individual and a low "degree of completeness" due to discontinuance of a pedigree because it was known to extend outside the French Acadian group.

For the purpose of calculation parents are considered as first generation, grandparents second generation and great-grandparents as third generation, etc. Thus, the offspring of a first cousin marriage is expressed as consanguineous in the third generation because one set of great-grandparents on the mother's side is the same as one set on the father's side. This corresponds to an F value of 0.0625. Offspring of a second cousin marriage is indicated by an F value of 0.0156 in the fourth generation. The F values for generations one to ten and the corresponding degree of completeness of the pedigrees from which they were calculated are shown in Tables IV, V and VI for twelve children with Niemann-Pick Disease, ten randomly chosen families in HP

TABLE IV

Coefficient of Inbreeding (F) and Percent Completeness (PC) for Pedigrees of Twelve Children with Type D Niemann-Pick Disease for Ten Generations

	I		II		III		IV		V	
Proband	F	PC	F	PC	F	PC	F	PC	F	PC
457	.0000	100.0	.0000	100.0	.0000	100.0	.0000	93.8	.0000	90.0
630	.0000	100.0	.0000	100.0	.0000	100.0	.0000	100.0	.0000	97.5
305	.0000	100.0	.0000	100.0	.0000	100.0	.0000	90.6	.0156	85.0
118	.0000	100.0	.0000	100.0	.0000	100.0	.0000	100.0	.0000	95.0
288	.0000	100.0	.0000	100.0	.0000	100.0	.0000	100.0	.0000	95.0
309	.0000	100.0	.0000	100.0	.0000	100.0	.0000	100.0	.0078	100.0
327	.0000	100.0	.0000	100.0	.0000	100.0	.0000	100.0	.0000	100.0
354	.0000	100.0	.0000	100.0	.0000	83.3	.0000	75.0	.0000	70.0
436	.0000	100.0	.0000	100.0	.0000	100.0	.0000	93.8	.0000	90.0
016	.0000	100.0	.0000	100.0	.0000	100.0	.0000	100.0	.0391	95.0
126	.0000	100.0	.0000	100.0	.0000	100.0	.0156	87.5	.0156	80.0
221	.0000	100.0	.0000	100.0	.0000	100.0	.0000	100.0	.0117	97.5

	VI		VII		VIII		IX		X	
	F	PC	F	PC	F	PC	F	PC	F	PC
457	.0088	85.4	.0142	74.7	.0249	64.6	.0280	56.1	.0286	46.9
630	.0020	95.8	.0065	91.2	.0166	84.6	.0230	76.1	.0255	65.1
305	.0215	80.8	.0291	74.9	.0337	69.0	.0372	61.1	.0385	51.6
118	.0029	91.7	.0105	85.6	.0228	80.1	.0308	74.9	.0344	65.0
288	.0039	91.7	.0127	85.5	.0227	80.4	.0276	71.8	.0284	60.6
309	.0166	99.5	.0292	96.0	.0378	92.4	.0476	85.2	.0506	73.2
327	.0088	99.5	.0169	95.6	.0255	91.5	.0332	85.9	.0373	74.9
354	.0059	66.0	.0103	62.1	.0191	58.5	.0247	52.8	.0257	44.6
436	.0000	87.5	.0024	77.5	.0044	68.6	.0059	60.5	.0073	52.2
016	.0078	88.7	.0107	81.8	.0155	73.4	.0169	60.0	.0173	49.0
126	.0186	75.0	.0232	68.4	.0284	62.7	.0300	53.3	.0300	43.9
221	.0176	95.9	.0263	93.0	.0367	89.3	.0425	78.7	.0437	65.8

TABLE V

Coefficient of Inbreeding (F) and Percentage Completeness (PC) for Pedigrees of Ten Random Families in HP for Ten Generations

Identification	I		II		III		IV		V	
Code	F	PC	F	PC	F	PC	F	PC	F	PC
907	.0000	100.0	.0000	100.0	.0000	100.0	.0000	93.8	.0000	90.0
908	.0000	100.0	.0000	100.0	.0000	100.0	.0000	100.0	.0078	95.0
909	.0000	100.0	.0000	100.0	.0000	84.0	.0000	66.0	.0000	56.3
910	.0000	100.0	.0000	100.0	.0000	66.7	.0000	48.4	.0000	38.0
911	.0000	100.0	.0000	100.0	.0000	100.0	.0000	100.0	.0000	100.0
912	.0000	100.0	.0000	100.0	.0000	100.0	.0000	84.4	.0039	70.0
913	.0000	100.0	.0000	100.0	.0000	100.0	.0000	93.8	.0000	90.0
914	.0000	100.0	.0000	100.0	.0000	100.0	.0000	70.3	.0000	52.5
915	.0000	100.0	.0000	100.0	.0000	62.5	.0000	42.2	.0000	31.5
916	.0000	100.0	.0000	100.0	.0000	100.0	.0000	60.9	.0000	42.0

	VI		VII		VIII		IX		X	
	F	PC	F	PC	F	PC	F	PC	F	PC
907	.0010	87.0	.0031	82.2	.0057	73.5	.0078	64.8	.0087	54.4
908	.0078	91.7	.0114	85.6	.0138	76.8	.0158	67.4	.0172	56.4
909	.0000	49.1	.0000	43.2	.0000	37.6	.0002	32.8	.0006	27.7
910	.0000	31.3	.0000	25.6	.0000	21.3	.0000	17.7	.0000	14.7
911	.0049	100.0	.0134	96.0	.0241	92.7	.0324	87.7	.0368	76.5
912	.0059	60.1	.0083	51.2	.0096	44.5	.0103	38.1	.0106	31.8
913	.0010	84.3	.0026	76.0	.0041	65.3	.0053	56.3	.0060	46.9
914	.0000	40.4	.0000	31.8	.0000	25.9	.0000	21.6	.0000	17.8
915	.0000	25.0	.0000	20.1	.0000	16.7	.0000	13.9	.0000	11.6
916	.0000	30.7	.0000	23.5	.0000	18.8	.0000	15.3	.0000	12.6

TABLE VI

Coefficient of Inbreeding (F) and Percentage Completeness (PC) for Pedigrees of Ten Random Families in WP for Ten Generations

Identification	I		II		III		IV		V	
Code	F	PC	F	PC	F	PC	F	PC	F	PC
897	.0000	100.0	.0000	100.0	.0000	100.0	.0156	100.0	.0156	100.0
898	.0000	100.0	.0000	75.0	.0000	66.7	.0000	62.5	.0000	59.3
899	.0000	100.0	.0000	100.0	.0000	100.0	.0000	100.0	.0000	100.0
900	.0000	100.0	.0000	100.0	.0000	100.0	.0000	100.0	.0000	100.0
901	.0000	100.0	.0000	100.0	.0000	83.3	.0000	65.6	.0000	52.5
902	.0000	100.0	.0000	75.0	.0000	66.7	.0000	56.6	.0000	48.0
903	.0000	100.0	.0000	100.0	.0000	100.0	.0000	93.8	.0000	90.0
905	.0000	100.0	.0000	100.0	.0000	100.0	.0000	100.0	.0117	98.8
904	.0000	100.0	.0000	100.0	.0000	75.0	.0000	56.3	.0000	45.0
906	.0000	100.0	.0000	100.0	.0000	100.0	.0000	100.0	.0000	100.0

	VI		VII		VIII		IX		X	
	F	PC	F	PC	F	PC	F	PC	F	PC
897	.0361	100.0	.0508	95.2	.0611	86.4	.0637	73.4	.0645	60.4
898	.0020	56.5	.0026	48.5	.0037	42.0	.0047	35.9	.0054	30.2
899	.0117	100.0	.0283	95.8	.0381	87.1	.0404	73.4	.0409	60.7
900	.0029	97.9	.0064	94.2	.0135	88.2	.0192	80.8	.0230	70.0
901	.0000	43.5	.0000	36.7	.0000	31.2	.0000	26.2	.0000	21.6
902	.0000	41.9	.0015	37.8	.0031	34.0	.0040	29.5	.0046	25.1
903	.0010	87.5	.0083	83.6	.0143	76.8	.0180	67.5	.0201	56.6
905	.0254	94.8	.0337	89.6	.0422	81.9	.0458	71.8	.0469	59.8
904	.0000	37.3	.0000	31.9	.0000	27.1	.0000	23.0	.0000	18.8
906	.0156	99.5	.0303	95.6	.0447	88.8	.0483	77.9	.0489	64.3

and ten randomly chosen families in WP. It is obvious from these tables that in most cases the consanguinity is more remote than four generations. As indicated by the ten generation calculations, the effects of consanguineous marriages are cumulative. However, as the number of generations increase the contribution of each additional generation becomes very small (Table XII, Appendix I).

The F values for the tenth generation of the three groups are compared in Table VII. The mean F value of 0.0079 for index families in HP was considerably lower than the mean value of 0.0254 for index families in WP. This is perhaps not unexpected since WP is geographically and culturally more isolated than HP. However, the low mean F values for index families in HP may reflect incomplete pedigrees more than a real lack of inbreeding. In general, available genealogical records for WP tended to be more complete than those for HP. One might expect that if individuals in HP were really as inbred as the families in WP that the ancestors would be from within the community and hence be known by the informants in HP. As mentioned previously, illegitimacy frequently contributed to the difficulty in obtaining accurate pedigree information. In small rural communities it seems probable that most unidentified fathers were members of the same or nearby communities and would have contributed to the "true" F value. However, all illegitimate children were not the result of consanguineous matings. For example, in the past, according to the local rumours there were a few "Valley babies" annually. Each fall a number of young girls were transported to the Annapolis Valley to pick apples. Girls who became pregnant during this time returned to their

TABLE VII

Comparison of the Coefficient of Inbreeding (F) and Percent Completeness (PC) Calculated for Ten Generations

HP(Niemann-Pick)		HP(random)		WP(random)	
F	PC	F	PC	F	PC
.0286	46.9	.0087	54.4	.0645	60.4
.0255	65.1	.0172	56.4	.0054	30.2
.0385	51.6	.0006	27.7	.0409	60.2
.0344	65.0	.0000	14.7	.0230	70.0
.0284	60.6	.0368	76.5	.0000	21.6
.0506	73.2	.0106	31.8	.0046	25.1
.0373	74.9	.0060	46.9	.0201	56.6
.0257	44.6	.0000	17.8	.0469	59.8
.0073	52.2	.0000	11.6	.0000	18.8
.0173	49.0	.0000	12.6	.0489	64.3
.0300	43.9				
.0437	65.8				
mean					
0.0306	57.7	.0079	35.0	.0254	46.7

own community and the children were "adopted". At any rate, it seems most likely that the F values calculated from incomplete pedigrees are underestimates of the "true" F values. Thus, the real mean F value for randomly chosen families in HP is probably higher than the one calculated here (0.0079) but still lower than the mean F value for WP (0.0254).

The mean F value for Niemann-Pick families (0.0306) appears considerably higher than the value for randomly chosen HP families. It is possible that relatives of affected children were more cooperative in revealing family histories. However, it seems likely that parents of affected children really are more closely related to each other than randomly chosen couples in the same community. It is not surprising that the Niemann-Pick sibships have relatively high F values, since it was demonstrated in Chapter II that they all have at least eight common ancestors (four couples).

The estimate of the mean F value for the twelve Niemann-Pick sibships (0.0306) is considerably higher than the mean F value of 0.0097 as calculated by Crawley (1971) from two pedigrees. This discrepancy can easily be explained by the fact that the pedigree information in the present study is much more complete than that of Crawley.

The mean F value for the parents of children affected with Niemann-Pick disease (0.0306) is similar to the mean value for randomly chosen couples in WP (0.0254). This may suggest that the apparent differences in levels of inbreeding in the three groups are

due to chance and the variation in the accuracy of the estimates rather than to any real differences between the populations.

Crawley calculated F values for isolates in Yarmouth County based on the frequency of isonymous marriages (of the same surname) from 1963-1967 using the method of Crow and Mange (1965). The three isolates which she designated Yarmouth I_2 (Amirault's Hill), Yarmouth I_3 (Surette's Island) and Yarmouth I_4 (Quinan) are geographically roughly equivalent to HP of the present study. Yarmouth I_5 includes WP of the present study as well as several neighbouring villages. Estimates obtained in the two studies are given in Table VIII. The F values calculated by the two methods for the French-Canadian isolate, Isle-aux-Coudres, are also given in Table VIII. Laberge (1969) obtained his estimate of 0.0236 for the population in 1965 after 12 generations by compiling the complete genealogy, back to all migrant ancestors to Canada, of one family chosen at random on the island. All other couples were traced for five genealogical generations. He then estimated the mean F for the population by assuming that the distribution of F in generations five to twelve for all pedigrees was equal to the distribution in the one family which was traced completely.

In summary, Table VIII suggests that the coefficients of inbreeding (F) for French isolates in Nova Scotia, and Quebec range from about 0.02 to 0.05 as estimated by isonymy (Crow and Mange) or path coefficients (Wright) for 10 to 12 generations.

TABLE VIII

Comparison of Estimates of Inbreeding Coefficients (F) for Isolates in Nova Scotia and Quebec

Population	Mean F value	Method	Reference
HP	.0306	Pedigree of Niemann-Pick families (Wright, 1922)	This Study
HP	.0079	Pedigrees of Random Families (Wright, 1922)	This Study
Yarmouth I_2, I_3, I_4	.0338	Isonymous Marriages (Crow and Mange, 1965)	Crawley (1971)
WP	.0254	Pedigrees of Random Families (Wright, 1922)	This Study
Yarmouth I_5	.0498	Isonymous Marriages (Crow and Mange, 1965)	Crawley (1971)
Isle-aux-Coudres Quebec	.0236	Pedigrees (Wright, 1922)	Laberge, 1969
Isle-aux-Coudres Quebec	.0264	Isonymous Marriages (Crow and Mange, 1965)	Laberge, 1969

Surname Frequency, Isonymy and Awareness of Consanguinity

Estimates of the frequency of surnames in the two communities were made from data in the Household Directories prepared by the Federal Postal Department, 1971. The postal districts used for sampling are:

WP (Lower West Pubnico, Middle West Pubnico, and West Pubnico)

HP (Tusket R.R. 2, Tusket R.R.3, Ste. Anne du Ruisseau and Ste. Anne du Ruisseau R.R.1).

It should be noted here that WP corresponds directly with the school district previously used for sample selection. There are, however, minor discrepancies in the delineation of HP from the postal districts and the area served by schools at Ste. Anne du Ruisseau and Amirault's Hill. The problem is due, in part, to the fact that the schools chosen for sample selection use French as their first language. There is also an English speaking school near HP and families may choose which school their children will attend. Thus, families living in adjacent geographical areas may have the same postal designation but their children may attend different schools.

The percent of householders with a given surname is only a rough estimate of the number of individuals bearing a certain name. The postal listings do not differentiate between a household composed of several individuals from the listing of a person living alone. Yet, presumably the criteria for a "household" would be the same in both communities and thus percentages would be roughly proportional to the population distribution. Illegitimacy, adoptions and changes in name spelling also contribute to the error in this type of estimate.

Different forms of names which are believed to be of similar origin, such as Doucette and Doucet and Meuse and Muise were grouped for the purpose of this tally (Appendix II). The results are given in Table IX. In WP, 76.2% of the households have the surnames d'Entremont or d'Eon, while in HP, only 1.5% of the households have one or other of these names. In HP, 34.6% of the households have the surname Muise or Surette while these surnames contribute only 5.7% of the households in WP. The obvious differences in the frequency of surnames in the two communities suggests that although both populations had a common origin, they have now diverged. On the other hand, since females take the surname of their husband at marriage, migration of females between the communities would not be obvious in the examination of surname frequency.

The index couples in each community were asked whether they knew of any relationship to each other before marriage. Of the twenty index couples, only one marriage was between second cousins ($F = 0.0156$) and no closer relationships were recorded. Awareness of relationship was correlated with the occurrence of isonymous marriages and the F values which were calculated from pedigree information (Table X). The isonymous marriages and F values for the parents of 12 children affected with Niemann-Pick disease are also given for comparison. This group of parents were not systematically polled for awareness of consanguinity. However, the relationship in 11 of the 12 couples was more remote than second cousins and it seems likely that most couples were unaware of distant relationships.

TABLE IX

Surname Frequencies in WP and HP
by number of Households

Surname	WP		HP	
	Number of households	percent of total	Number of households	percent of total
d'Entremont	226	56.1	6	1.3
d'Eon	81	20.1	1	0.2
Amirault	26	6.5	22	5.0
Surette	22	5.5	70	15.8
Leblanc	10	2.5	26	5.9
Pothier	3	0.7	22	5.0
Muise	1	0.2	83	18.8
Bourque	1	0.2	49	11.1
Babin	0	0.0	18	4.1
Doucette	0	0.0	65	14.7
Hubbard	0	0.0	14	3.2
other	33	8.2	66	14.9
total	403	100.0	442	100.0

TABLE X

Isonymy, Consanguinity and Awareness of Consanguinity

	Husband and Wife Isonymous	Wife's parents Isonymous	Husband's parents Isonymous	Knowledge of relationship	F for ten generations
WP 1	no	no	no	yes	.0645
WP 2	no	no	no	yes	.0054
WP 3	yes	no	no	*	.0409
WP 4	no	yes	yes	*	.0230
WP 5	no	no	no	no	.0000
WP 6	no	no	no	no	.0046
WP 7	no	yes	no	*	.0201
WP 8	no	no	no	yes	.0469
WP 9	no	yes	no	no	.0000
WP 10	no	no	no	no	.0489
HP 1	no	no	no	no	.0087
HP 2	no	no	no	no	.0172
HP 3	no	no	no	no	.0006
HP 4	no	no	yes	no	.0000
HP 5	no	no	no	no	.0368
HP 6	no	no	no	no	.0106
HP 7	no	no	no	no	.0060
HP 8	no	no	no	no	.0000
HP 9	no	no	no	*	.0000
HP 10	no	no	no	*	.0000
NP 1	no	yes	no		.0286
NP 2	yes	no	yes		.0255
NP 3	no	no	no		.0385
NP 4	no	no	no		.0344
NP 5	no	no	no		.0284
NP 6	no	no	no		.0506
NP 7	no	no	no		.0373
NP 8	no	no	no		.0257
NP 9	no	no	no		.0073
NP 10	no	no	yes		.0173
NP 11	no	no	no		.0300
NP 12	no	no	yes		.0437

* Did not know of the exact relationship but were aware of the probability of remote consanguinity.

The data is insufficient to formulate any definite conclusions about awareness of inbreeding in the two communities. However, it appears that, in general, couples in WP are more aware of the possibility of remote consanguinity than couples in HP. This seems to be at least partly due to sense of pride and interest in ancestry which was not observed in HP. The high proportion of individuals in WP having the same surname probably also contributes to the awareness of consanguinity.

Genetic Diseases

None of the children in the index families were known to suffer from a severe genetic disease. By chance none of the index families in HP included a child with Niemann-Pick disease. However, one index father was the uncle of a child with Niemann-Pick disease and an index mother was the aunt of three girls with Alstrom's syndrome.

As mentioned in the introduction one might expect an increased incidence of rare recessive conditions in inbred communities. For example, if a recessive disease affects only four cases per million it will appear 32 times as often in the children of first cousin marriages as in the general population (Li, 1963). Three rare conditions: (1) Alstrom's syndrome, (2) Usher's syndrome, and (3) Hurler's syndrome were identified from hospital records, physicians and family interviews. These conditions are so unusual and severe that it seems likely that if additional cases existed they would have been brought to medical attention and hence would have been included in this report. It is

noteworthy, from the point of view of the genetic diversity of the two communities, that none of these conditions was present in both communities. Each condition is described separately in the following section.

Alström's Syndrome

Alström's syndrome is an autosomal recessive condition characterized by atypical retinal degeneration, obesity, diabetes mellitus and neurogenic deafness. Alström et al. (1959) first identified the condition as a distinct entity as a result of a clinical and genetic examination of a large kindred in Sweden. Their patients did not have mental retardation, polydactyly or hypogenitalism.

Weinstein, et al. (1969) described two brothers with hypogonadism, blindness, nerve deafness and metabolic abnormalities. They felt that some clinical and laboratory features of both brothers resemble those reported by Alström et al. The family was of French-Canadian origin and denied consanguinity. We have not been able to determine whether this family may have been of Nova Scotian origin.

The current report is concerned with three sisters age 26, 24, and 20 years at the time of investigation. All three were obese and totally blind. The mother reported the girls appeared normal at birth, although they were "big babies" in comparison with her other children. She recalled that as young children they could see enough to go to the nearby store unaided. Investigations at the Victoria General Hospital in 1972 revealed the girls closely resembled Alström's description of the condition (Welch, personal communication).

BM (VG72-15031) born 1948. This girl was admitted to hospital with chronic renal failure. She had been diabetic for several years and at the time of examination had bilateral cataracts, retinitis pigmentosa and a marked hearing defect. She died (age 24 years) early in 1973 and autopsy reports were not available at the time of writing.

EM (VG72-15895) born 1952. Essential features were bilateral cataracts, retinitis pigmentosa and diabetes mellitus. She had mild renal failure, possibly on the basis of her diabetes.

PM (VG72-15896) born 1946. She resembled her sisters in that she was obese, and had bilateral cataracts, retinitis pigmentosa and hearing loss. However, her glucose tolerance test was normal.

All three girls were considered to be mentally retarded, but psychological evaluations were unreliable due to the hearing and sight problems.

The family history revealed six siblings, all reputedly normal. A half-brother of the girls' father died at age 25. He was also blind and obese and probably suffered from Alstrom's syndrome although no documented medical evidence was available. His infant brother died of unknown causes.

The most common ancestral couple for the two sibships was calculated in the same manner as for the Niemann-Pick pedigree. The results are given in Table XI. These figures indicate that Francois Amirault (18) and his wife Marie Pitre (37) have the greatest number of pathways from the affected individuals. They were

TABLE XI

Common Ancestors for Alstrom's Syndrome

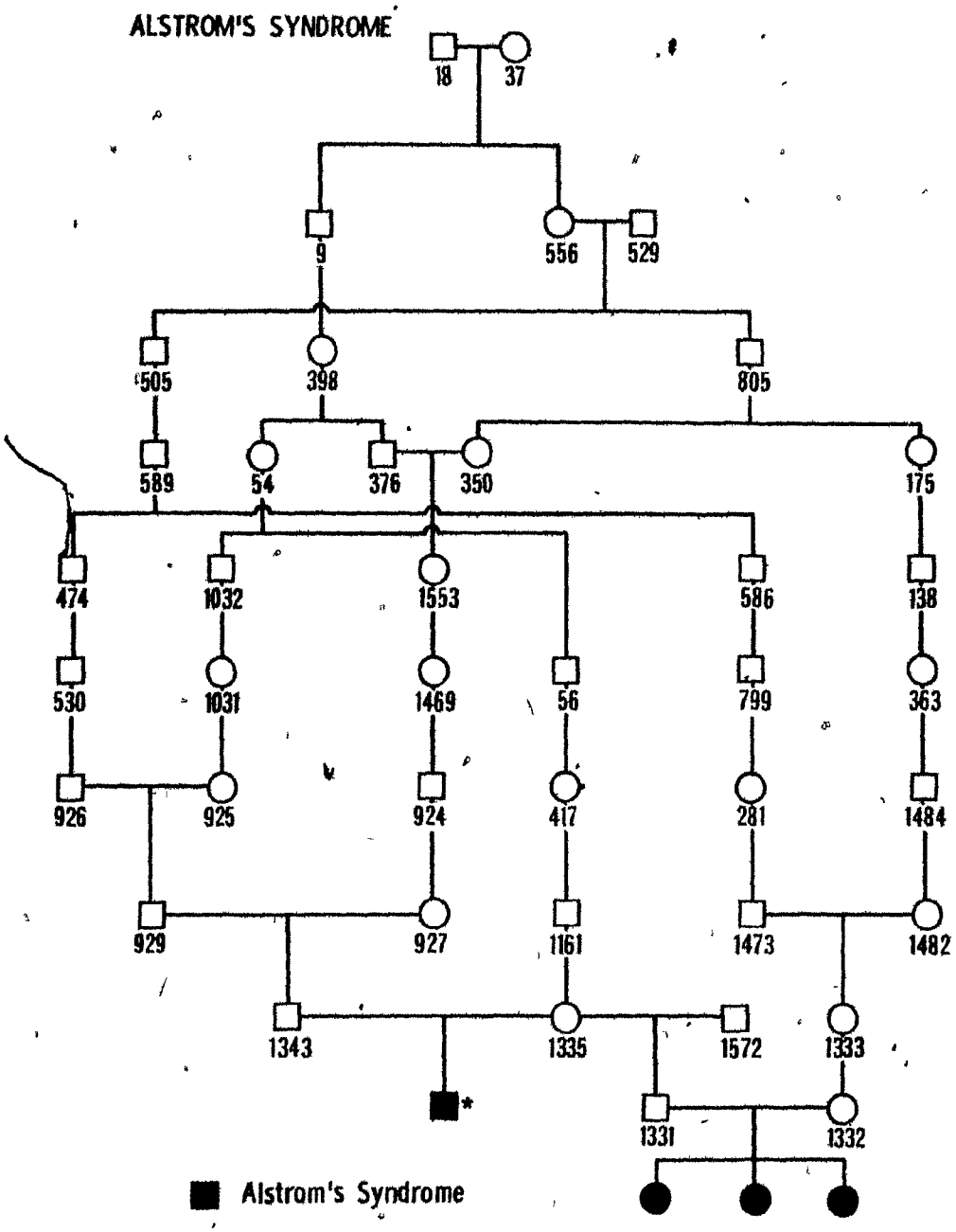
Identification Numbers	Frequency of Coincidences
18 and 37	100
529 and 556	66
409	22
398	14
652 and 659	13
101 and 160	8
485 and 571	6
505 and 856	3
113 and 136	3

married in 1683 or 1684 at Port Royal and are ancestors of many of the individuals in this study. It is interesting to note that some of the ancestors are the same as those of the Niemann-Pick pedigree. However, this appears to be due to chance rather than any real association between the two conditions.

The simplified pedigree shown in Fig. 6 traces the affected individuals to the common ancestral couple (18 and 37). As in the Niemann-Pick pedigree, only a few of the pathways are illustrated and there is no evidence concerning the most likely path of gene transmission. The parents (1331 and 1332) of the three affected girls were not aware of consanguinity. They were also unaware of any relationship to the affected boy other than the obvious link through 1335 who was the mother of the affected male and the paternal grandmother of the three affected females. It is not surprising that the families were not aware of the relationship between the affected girls' mother (1332) and the affected boy's father (1343) because the common ancestry in most cases was at least seven generations back on one side and six generations on the other.

Evidence of common ancestry and occurrence of affected males and females support the autosomal recessive inheritance theory. Based on the pedigree information there is a strong possibility that many other individuals in the community could be heterozygous for the condition. Unfortunately, at present there is no way of identifying the heterozygous state.

FIGURE 6



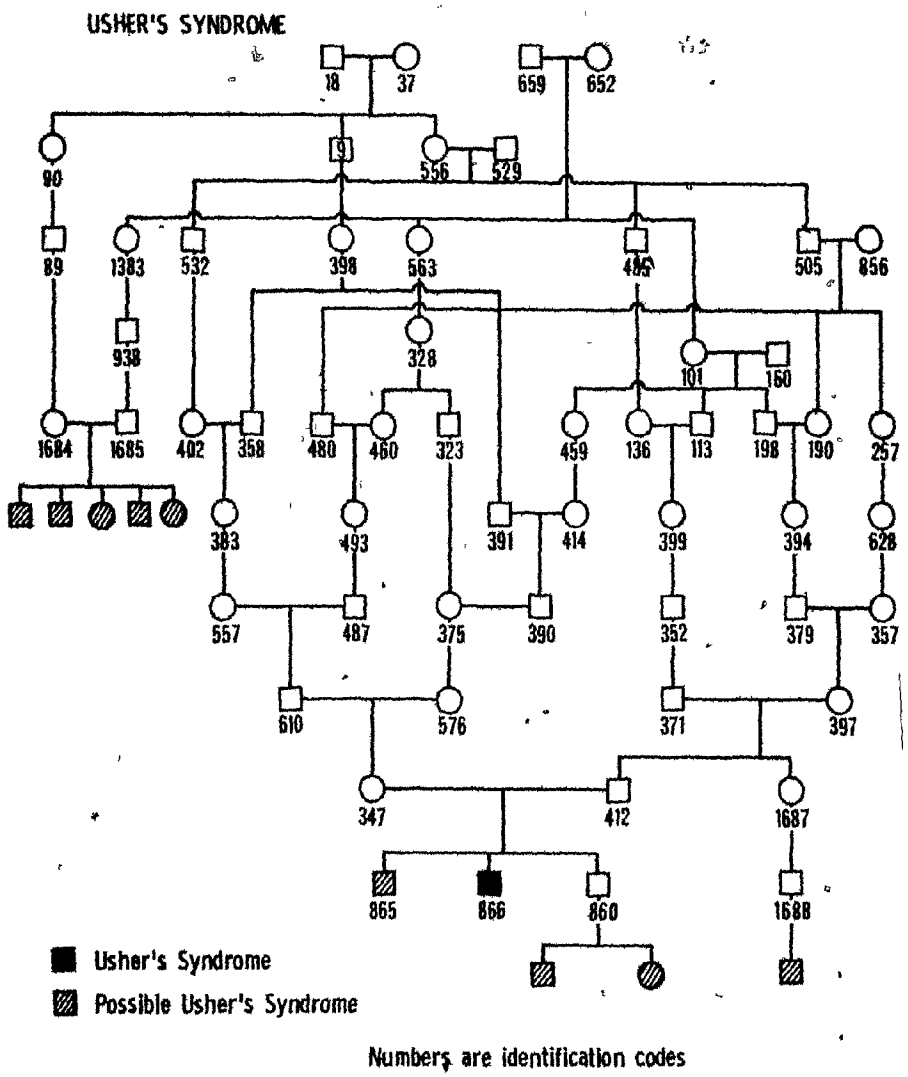
* not examined, presumed affected

Usher's Syndrome

In 1914, Usher described a syndrome involving the combination of retinitis pigmentosa and severe congenital hearing impairment, more commonly known as deaf-mutism. Kloepfer et al. (1966) studied a group of French-Acadians in Louisiana. From detailed studies of controls and of families of 44 individuals, they assumed that these individuals have a recessive gene for the syndrome. All individuals in their study group were believed to be homozygous for a single genotype. In every instance of marriage between two homozygous individuals with the syndrome, all offspring were congenitally deaf and developed the same type of eye anomaly (the number of such offspring was not specified in their report).

One man (identification code 866) living in HP was examined by Dr. J. P. Welch, and was considered to have features typical of Usher's syndrome. This man's brother (865), now deceased, reputedly was similarly affected. Medical records on three other individuals now living in the HP area indicate that they have similar clinical symptoms. In Brown's "Yarmouth, Nova Scotia, A Sequel to Campbell's History", published in 1888, five siblings were described as "deaf and dumb". These individuals, born in the early 1800's, were children of Athanase Surette (1685) and his wife Louise d'Entremont (1684). Some links between these ten individuals are indicated in the abbreviated pedigree of Figure 7. As illustrated, Pierre Surette (659), Jeanne Pellerin (652), Francois Amirault (18), Marie Pitre (37), Joseph Muise (529) and Marie Amirault (556) are common ancestors of both parents

FIGURE 7


USHER'S SYNDROME
18
37
659
652
90
556
529
89
1383
532
398
563
505
856
938
328
101
160
1684
1685
402
358
480
460
323
459
136
113
198
190
257
383
493
391
414
399
394
628
557
487
375
390
352
379
357
610
576
371
397
347
412
1687
865
866
860
1688
Usher's Syndrome
Possible Usher's Syndrome
Numbers are identification codes

of the affected brothers, 865 and 866. Computer calculations indicate that there are at least 20 additional common ancestors of the parents of these two men. Identification of the ancestors of the other three sibships is incomplete, but it seems possible that all ten affected individuals could have at least one common ancestor.

Since many Acadian exiles settled in Louisiana after the deportation of 1755, one might speculate that there is an ancestral link between the individuals in the pedigree of Figure 7 and those described by Kloepfer, et al. The data on the individuals of the HP area is insufficient to test the recessive hypothesis by segregation analysis and sex ratio, but there is no evidence for rejecting the recessive hypothesis.

Hurler's Syndrome (Mucopolysaccharidosis I)

Hurler's syndrome is a rare disorder of mucopolysaccharide metabolism. It is characterized by dwarfism, clouding of the cornea, enlargement of the liver and spleen, and mental retardation (McKusick, 1966). Patients have been described as gargoyle-like.

One child of the WP area has this condition. The diagnosis was confirmed by the presence of mucopolysaccharides in the urine and fairly classical bone changes in the spine and hand x-rays (I.W.K. UN53479). A paternal second cousin reputedly died at age 4 or 5 years in Boston due to a similar condition. However, this has not been verified by medical records. No other children in the WP or HP communities are known to suffer from this condition.

Differences in gene frequencies in HP and WP are revealed by the appearance of homozygosity for rare recessive conditions in one community but not in the other. The origin and maintenance of such genetic diversity may be attributed to genetic drift and founder effect. McKusick (1969) makes the following distinction between the two concepts: random genetic drift represents decrease in the originally existing variability because of chance gametic choices, whereas founder effect is poverty of genetic variability existing from the beginning because of chance zygotic choices.

We might suppose that the high frequency of Niemann-Pick disease in the HP area is due to founder effect. In other words, a mutation which occurred in one of the early settlers has become common after several generations due to intermarriage of the descendants of this individual.

Occurrence of the recessive conditions in HP and not in WP and vice versa may be due to drift. Under the influence of drift, village populations tend to become more and more different, even if at the beginning they were homogeneous in their composition of hereditary types (Cavalli-Sforza, 1969).

A condition which is relatively common, such as cystic fibrosis, is more likely to occur in the offspring of non-consanguineous marriages than a very rare condition. In other words, the relative increase in homozygosity due to inbreeding is less marked for common genes than for rare genes (Li, 1963). However, the risk that a carrier

will marry another carrier is higher if he marries a relative than if he marries at random. Estimates of the incidence of cystic fibrosis in the Caucasian population range from 1 in 2000 to 1 in 4000 live births with a corresponding incidence of heterozygotes of approximately 4% (Lobeck, 1972). Only one family in WP and no family in HP with affected children were known to Dr. C. T. Gillespie, Director of the Cystic Fibrosis Clinic at the I.W.K. Hospital for Children, Halifax (Gillespie, personal communication). As with the other severe conditions, if other cases existed one would expect that they would have been known to the local physicians or the Cystic Fibrosis Clinic. The two affected sibs in WP have an F value of 0.0579 for ten generations which is higher than the mean F value for randomly chosen sibships in the same community.

This account is not intended in any way to be a comprehensive investigation of all genetic or genetically influenced conditions. Congenital cleft lip and/or cleft palate were reported in several members of both communities. It was not possible to determine the frequency of these conditions since many individuals had never been treated and hence were not recorded in hospital or physician records. The inheritance of cleft lip and palate has been thoroughly studied (Fraser, 1970). Thus, investigation of the families in HP and WP did not seem to offer any significant contribution to knowledge of the genetics of this condition. Other problems such as albinism and familial mental retardation, were reported by members of both communities but were not thoroughly investigated.

SUMMARY

1. Twelve children from Yarmouth County, Nova Scotia and three of French-Acadian origin in Boston affected with Niemann-Pick disease type D were traced through both parents to four common ancestral couples. Common ancestry, segregation analysis and sex ratio support the autosomal recessive inheritance hypothesis.
2. In the community where the majority of the affected children lived (HP), the frequency of the disease in the school age population was approximately 1% with a corresponding carrier frequency that ranged from 11-26%.
3. The mean coefficient of inbreeding (F) calculated for ten generations from pedigrees of children affected with Niemann-Pick disease (0.0306) appears higher than the mean F (0.0097) of randomly chosen families in the same community (HP) but approximately equal to the mean F (0.0254) of randomly chosen families in a control community (WP).
4. Although the consanguinity of the Niemann-Pick families and the WP families over ten generations is equivalent to relationships between first (F = 0.0625) and second cousins (F = 0.0156), it is significant that the consanguinity is so remote that most couples were unaware that they were related to each other. This is important in terms of genetic counselling with regard to carriers of rare recessive conditions.
5. Comparison of current family size with the sibship size of the parents indicates a dramatic reduction in the average family size

(Summary, cont.)

in a single generation. There were no significant differences between the family sizes of the two communities.

6. In addition to Niemann-Pick disease, three rare recessive conditions were identified: Usher's and Alstrom's syndromes in HP and Hurler's in WP. This distribution suggests that two communities of common origin have become isolates over a period of approximately ten generations. Differences in the surname distribution also indicate this divergence.
7. Since the two communities compared were chosen to fit certain criteria, the conclusions regarding inbreeding and disease frequency are relevant only to the areas studied and cannot be generalized to the entire French-Acadian population.

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APPENDIX I

Computer Program for Calculating Coefficient of Inbreeding (F) and Most Likely Common Ancestors

A program called "Human Inbreeding, No Disk Storage" by Mange in 1964 was designed to calculate F by systematically searching the stored pedigree for common ancestors for six ancestral generations. The program was written in Fortran II for an IBM 1620 machine.

Extensive modifications for efficiency and expansion were made to Mange's original program by D.R. Bolling at Johns Hopkins University. The modified program was written in Fortran IV for a CDC 3300 and handles up to 11 generations.

Execution of the program on the Dalhousie University computer (CDC 6400) were carried out with the assistance of A.P. Smith and D. Boss.

Four-digit code numbers were assigned, uniquely but in no particular order, to all individuals. Data was entered on punch-cards, one for each member of the study population. On each card is the code number of the individual and the code numbers of his father and mother. For each selected individual the program will construct and print out the pedigree for eleven generations.

Search for common ancestors is carried out by comparing code numbers of all members on one side of the pedigree with all the codes on the other side. A match of the same code number on the two sides of the pedigree may indicate a common ancestor. Since all common ancestors of a common ancestor appear on both sides of the pedigree,

not every match will indicate a "real" common ancestor. A "real" common ancestor or a valid coincidence occurs when the common ancestor's child on the father's side of the pedigree is different from the common ancestor's child on the mother's side.

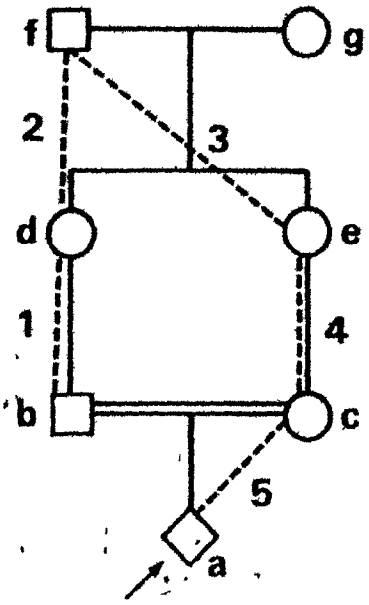
F was calculated by the method of path coefficients (Wright, 1922). The general expression for the coefficient of consanguinity is: $F = \Sigma (\frac{1}{2})^n$ where n is the number of ancestors in the path connecting one parent to the inbred offspring through a common ancestor. The values for each common ancestor are then summed. The ½ is based on the assumption that if an individual has a certain gene that there is a 50% chance that he will pass this gene to his offspring. If one of the common ancestors is himself inbred, then the expression becomes: $F = \Sigma (\frac{1}{2})^n (1 + F_A)$ where F_A is the coefficient of inbreeding for the common ancestor.

For example, (Figure 8) offspring of a first cousin marriage could be homozygous be descent for a gene from their great-grandfather (f) or their great-grandmother (g). There are five steps in the pathway from the father (b) to the offspring (a) through the common ancestor (f) as illustrated. Similarly, there are five steps in the pathway from (b) to (a) through the common ancestor (g). Thus for a first cousin marriage: $F = (\frac{1}{2})^5 + (\frac{1}{2})^5 = 1/16$ or 0.0625.

If the great-grandmother or great-grandfather were inbred their F value would be calculated independently and substituted for F_A in the expression: $F = \Sigma (\frac{1}{2})^n (1 + F_A)$

FIGURE 8

CALCULATION OF COEFFICIENT OF INBREEDING (F) FOR OFFSPRING OF A FIRST COUSIN MARRIAGE



a - Offspring of first cousin mating

-------- Pathway for calculation of F

The computer keeps score, by generation, of the increasingly incremented F value. Thus, F values are dependent on the number of generations included in the pedigree.

The program as adapted by Bolling is limited to eleven generations. In a few cases our data extends beyond this limit. However, expansion of the program appeared to present major difficulties with regard to computer storage facilities. However, the contribution of more remote generations to the total F value appears to be so small that it was ignored. Table XII indicates the relative contribution of consanguineous marriages to the total F value.

The program also calculates a measure of "degree of completeness" which attempts to estimate what percentage of the "true" F value is represented by the F computed on the basis of the known ancestors. This measure of completeness is the fraction of coincidences which is knowable. It is equal to the product of the fraction of the father's pedigree that is known by the fraction of the mother's pedigree that is known. These fractions are based on the concept of area. Figure 9 illustrates the principle. For four generations the area on each side of the pedigree is 32 units, where a unit is the size of a rectangle occupied by an ancestor in the fourth generation.

For example, suppose the pedigree on the father's side is known except for two members of generation IV (2/32 of the area) and on the mother's side only the mother's parents are known (16/32 of the area). Then, the percent completeness of the four generation pedigree is: $\frac{32-2}{32} \times \frac{32-16}{32} \times 100 = 46.9\%$

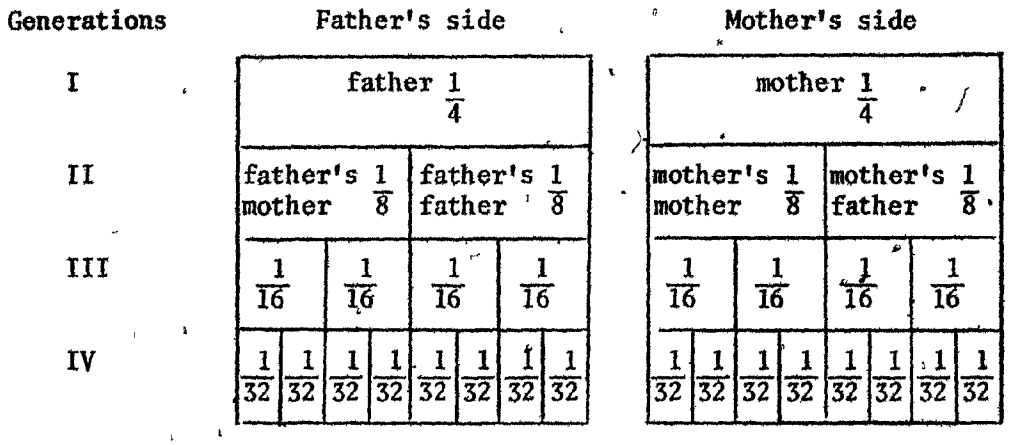
TABLE XII

Contribution of a consanguineous marriage to the total F value relative to the number of generations from the index case

Number of Generations	Contribution to F value
3	$(\frac{1}{2})^4 = 6.25 \times 10^{-2}$
4	$(\frac{1}{2})^6 = 1.56 \times 10^{-2}$
5	$(\frac{1}{2})^8 = 3.91 \times 10^{-3}$
6	$(\frac{1}{2})^{10} = 9.77 \times 10^{-4}$
7	$(\frac{1}{2})^{12} = 2.44 \times 10^{-4}$
8	$(\frac{1}{2})^{14} = 6.10 \times 10^{-5}$
9	$(\frac{1}{2})^{16} = 1.53 \times 10^{-5}$
10	$(\frac{1}{2})^{18} = 3.81 \times 10^{-6}$
11	$(\frac{1}{2})^{20} = 9.54 \times 10^{-7}$
12	$(\frac{1}{2})^{22} = 2.38 \times 10^{-7}$
13	$(\frac{1}{2})^{24} = 5.96 \times 10^{-8}$
14	$(\frac{1}{2})^{26} = 1.49 \times 10^{-8}$
15	$(\frac{1}{2})^{28} = 3.70 \times 10^{-9}$

FIGURE 9

Area Representation of Four Generations
for Calculation of Pedigree Completeness



The relative sizes of the rectangles represent the fraction of completeness for each side of the pedigree when the person in that position is known.

(modified from Mange, 1969)

APPENDIX II

Variations in Spelling of Surnames which were considered as Equivalent in this Study

Amirault - Amero

Bouchier - Boutier, Bouchie

Bourque - Burke

Clement - Clermont

d'Eon - Duon

Doucette - Doucet

Dulong - Dulain, Dulin

Frotten - Frontain

Hubbard - O'Bird, Hebert

Lefave - Lefevre

Muise - Emieuse, Meuse, Mieurs, Mieus, Mieuss, Mieusse, Miousse, Mius, Muis (d'Entremont, 1968a)

Pothier - Pottier

Surette - Suret