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THE UNIVERSITY OF ALBERTA

ANALYSIS OF A GENETIC DISEASE IN A HUMAN ISOLATE

by

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A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

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Abstract

The presence of a rare recessive genetic trait in different sibships in a founded population suggests that the affected individuals are all autozygous for the same allele, which entered the population in one member of the founder generation. Knowledge of the original source of an allele in a population may be of some utility in a genetic counselling situation, and in estimation of the number of affected individuals one might expect to be born. We attempt to determine the ancestral source of the allele for the Bowen-Conradi syndrome , a putative autosomal recessive lethal disorder, in the Hutterite population. The Hutterites are a large Caucasian, anabaptist sect of North America. They constitute a defined population which is descended from a small number of founders, and for which extensive genealogic records exist. Sixteen cases of the Bowen-Conradi syndrome have been reported in 14 sibships in the Hutterite population. The Bowen-Conradi syndrome phenotype superficially resembles those of both trisomy 18 and a number of cases grouped together as 'pseudotrisomy' 18. Eighteen founders common to all parents of affected sibships are identified. Based on a) the average proportional contribution to the inbreeding of the affected sibships, and b) the products of the expected proportion of alleles contributed by a founder to all parents of affected sibships, one couple is chosen as most likely contributor of the allele. Estimates of the allele frequency range between 0.01 and 0.04.

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I. INTRODUCTION

The Problem

The occurrence of a simple recessive genetic trait in two related individuals where neither is ancestral to the other raises the possibility that their similar phenotypes are due to identical genotypes. The genes in question could be copies of, for instance, a gene in an ancestor common to the two individuals. It seems obvious that, depending on the degree of fitness of the trait, segregation of the gene controlling it is a more likely explanation for the trait's occurrence than is new (or recent) mutation.

In any population, a newly arising advantageous mutation has a small finite probability of establishing itself permanently in the population (Kojima & Keheller, 1962). If the population is undergoing uniform expansion, *any* newly arisen mutation, even a deleterious one, has an increased probability of survival over that in a stationary population. Only as the population size stabilises, will the number of copies of the deleterious allele begin to decline due to selection (Ewens, 1979). However, in a genetic isolate, founded by a relatively small number of individuals and subsequently experiencing rapid growth, one might expect that such a deleterious gene could reach high frequency by chance factors (founder effect and random genetic drift) and that the affected individuals are all identical by descent at the locus in question. In such a case, it may be possible to determine the most likely founder couple to have introduced the gene into the population. A more difficult problem would be to determine if a familial cluster in an isolate, of a trait with no simple mode of inheritance was, in fact, genetic.

The Bowen-Conradi syndrome is a putative single-gene autosomal recessive disorder which has been described in the Hutterites, a large Caucasian Anabaptist isolate of North America. Because the syndrome has been found in all subdivisions of the Hutterite population, it is probable that the gene for this disorder entered the population at the 'founder' generation, and is presently widespread. This project was undertaken in an attempt to answer the following questions:

1) What is the range of phenotypic variability of the Bowen-Conradi syndrome ?

2) Has the incidence of the disorder been augmented by non-random mating in the population?

3) What is the frequency of the Bowen-Conradi syndrome allele?

4) Can the most likely ancestral source of the allele be determined and can an estimate be made of the number of carriers, number of matings at high risk and number of cases to expect in the population?

Background: Studies on Isolates

A small sample of individuals from a large population may not accurately represent the frequencies of the alleles present at a given locus in their parental population. This 'founder effect' can subsequently give rise to a large drift effect in the newly established population (Cavalli-Sforza & Bodmer, 1971). Differences in fertility among the founders and their descendants, coupled with the random variation that occurs in the sampling process of passing on gametes from one generation to the next (drift) could result in an allele that occurred at low frequency in the parental population attaining a high frequency in the founded population, and vice versa. The drift effect is most pronounced when the population is small.

Endogamy (choice of a marriage partner from within one's own group), in a small population which experiences little in-migration, ultimately leads to high levels of consanguinity. (Two individuals are consanguineous if they have at least one common ancestor; the progeny of consanguineous parents are, by definition, inbred (Cavalli-Sforza & Bodmer, 1971)). Since the inbred individual is connected to the same ancestor(s) through both of his parents, he can receive two copies (one from each parent) of an allele that was carried in a single copy by that ancestor. Thus, consanguinity increases the probability of autozygosity (identity by descent) of a gene, and hence the probability of expression of a recessive gene present in a population.

If it is possible to trace to a single ancestral couple, the pedigrees of the parents of a number of sibships in which the same autosomal recessive gene is segregating, then one member of that couple was likely heterozygous for the gene in question. If, in addition, the trait is rare, it can also be assumed that this couple was the original source of the gene in the population.

Many studies have been done, in isolates, in which one goal has been to identify the ancestral source of the gene for a known genetic disorder that segregates in the

population. Two early studies of the Amish were concerned with a recessive form of dwarfism, the Ellis-van Creveld syndrome, (McKusick, *et al*. 1964) and pyruvate kinase deficiency (Bowman, *et al*. 1965). In each of these studies, the investigators were able to trace the ancestry of all parents of affected individuals back to a single immigrant ancestral couple. In addition, the parents of affected individuals were able to trace their ancestry to the relevant couple by more paths than they did to any of the other immigrant ancestral couples. Bowman, *et al*. also calculated coefficients of relevant consanguinity, F', for each affected sibship (i.e. probability of autozygosity for an allele derived from one specific ancestral couple). They found that the average F' was the equivalent of all parents being related as about second cousins (average .022961; range .001464-.050973) and that the number of ways individual parental couples were related ranged from 2 to 42. These results were considered supportive of the choice of ancestral couples, one member of which is likely to have been a carrier of the gene for these disorders.

The same method of tracing common ancestral pairs has also been used by Barbeau, *et al*. (1964), for a study of the dominant Huntington's disease, and by Laberge (1969) for recessive hereditary tyrosinemia, both in French Canadian groups. Their results were similar to those obtained in the Amish studies: in each case, parents of affected individuals could trace their ancestry back to a single immigrant ancestral couple, to whom they were apparently related in more ways than to other ancestral couples of the populations.

A recent study of the genetics of propionic acidemia in a Mennonite-Amish kindred (Kidd, et al., 1980) was, in many ways, analogous to what might be expected of an inborn error of metabolism in the Hutterite population. Kidd, *et al*. found seven individuals in four sibships with this disorder, all of whom were part of a single complex pedigree which could be traced through 11 generations to members of the founding population of the Old Order Amish in the U.S.A.. Three couples were found to be common to the ancestry of all four affected sibships. The inbreeding coefficient, F, was calculated on the entire known ancestry of each of the four affected sibships, including inbreeding through individuals who were not common to all of the affected sibships. As it was not possible to compare these F values with an average inbreeding coefficient of age-matched

children from the same community (this information was not available), the F values were calculated for each of the eight parents of these sibships. The average F for affected sibships was .01142, compared to an average of .00807 for their parental group. However, this comparison does not take into account the probability of an increase in inbreeding in each generation due to the closed nature of the population.

For each affected sibship, an F' value, defined as the probability of autozygosity for an allele derived from one specific ancestral couple, was calculated from the pedigree of each of the three ancestral couples common to all affected sibships. The F' values were used as 'probabilities', to calculate a 'relative likelihood' of each ancestral couple's being the original source of the mutant allele in the pedigree. This relative likelihood was based on the total probability over all four affected sibships, of autozygosity for an allele from each ancestral couple common to all affected sibships. This method calculates an approximation of the true likelihood of each couple being the contributor of the defective allele to the population, assuming the independent occurrence of the affected sibships. The couple chosen as most likely source of the allele was found to be about five and a half times as likely to have carried the allele as the second ancestral couple, and over 1500 times more likely than was the third couple.

Due to computational limitations, Kidd, *et al*. (1980), were unable to consider the possibility that the allele for propionic acidemia was introduced to the Amish population through more than one founder couple. This problem was approached by Thompson (1983). She presented a recursive algorithm for determining the probability that both the maternal and paternal genes at a specified locus, of a specified individual in a genealogy, derive, by descent, from a specified set of genes at that locus among the ancestors of the individual in the genealogy. Using the propionic acidemia genealogy of Kidd, *et al*. (1980), a variety of ancestries were hypothesised for each sibship, from a single gene in one of the six common founders, to six genes.

Her method gives an indication of the relative importance of certain ancestral genes in the bilateral ancestry of the affected sibships. However, the genealogy is based only on descent to affected sibships, and not to the normal descendants on whom no information is available. Thus, hypotheses of more ancestral carriers are favoured by the method, and will continue to be favoured until the point where homozygosity of the

parents is more likely than heterozygosity. In other words, without information on the normal descendants of the ancestors, the likely number of ancestral genes cannot be inferred (Thompson, 1983).

The problem of dependence between the four affected sibships, in descent from a given set of ancestors, was also considered. It was found that "... little confidence can be placed in relative likelihoods obtained by combining sibships independently". (Thompson, 1983). In general, to be considered likely, any hypothesis of ancestral source of the gene would have to be acceptable for each sibship.

Cystic fibrosis in the Ohio Amish was studied by Klinger (1983). She found a high incidence of cystic fibrosis in one group of Old Order Amish, but that a second group had had no occurrence of cystic fibrosis in children born between 1950 and 1981. The two groups reside in different counties, and represent separate Amish isolates. The counties were settled by the Amish at different times (Holmes county around 1810 and Geauga county about 1890), and their original founding groups were drawn from different populations. (Holmes County was settled by Amish immigrants to the United States; Geauga County by settlers from several Amish communities in the U.S., including some from Holmes County). Thus the most likely cause of the difference in frequency of cystic fibrosis in the two populations is founder effect.

Nineteen cases of cystic fibrosis in six Amish sibships living in Holmes county were ascertained. A frequency of 0.042 for the cystic fibrosis allele was estimated (19 cases of CF in 10816 births between 1950 and 1981) (Klinger, 1983). The parents of the affected children (obligate heterozygotes) were all found to trace their ancestry to a single common ancestral couple, who immigrated to the United States in the eighteenth century. One member of this couple has been designated the most likely original source of the cystic fibrosis allele in the population. Eleven of the twelve obligate heterozygotes can be linked in an extended pedigree at a depth of four generations (the great-grandparental level), but the closest relationship between the twelfth and any of the other parents is through a son of the couple considered most likely to have contributed the allele.

Klinger noted that the couple she identified as the most likely source of the cystic fibrosis allele were very prominent Amish immigrants, and that Amish pedigrees are often

more complete with respect to descent from this couple than for other ancestors. Since this could be a factor in the identification of the common ancestor who contributed the allele, she reconstructed the descent with respect to this couple both of the Geauga County Amish and of the spouses of the siblings of the obligate heterozygotes. It was found that the Holmes County Amish are descended from a different set of this ancestral couple's grandchildren than are those from Geauga County, and also that the descent of the spouses of the siblings of the obligate heterozygotes was different from that of the heterozygotes themselves. Both these findings lend support to the hypothesis that one member of this couple was the original carrier of the allele for cystic fibrosis in the Holmes county Amish.

The Hutterites: History

The Hutterites are a Caucasian Anabaptist sect, descendants of about 1200 people who migrated to the United States from Russia in the late 1870's. The group's history, culture and social organisation have been well documented by Hostetler (1974). The following account of their history is taken primarily from that source.

The religious origins of the Hutterite population date from the Protestant reformation in the early sixteenth century in Switzerland, where they developed as an outgrowth of the Anabaptist movement. Central to the beliefs of the Anabaptists were the separation of church and state, the baptism and church membership of adult believers only, and the practice of non-conformity to the world. They also refused to swear oaths or to participate in wars. The Anabaptists were persecuted for their beliefs, and many fled to Moravia. Among those who went to Moravia were Jacob Hutter and a group of about 200 Tyrolese Anabaptists. Under Hutter's leadership, this group established a socially cohesive communal organisation which expanded rapidly by absorbing incoming refugees. Hutter's principles form the basis of the Hutterite lifestyle today. Between 1529 and 1621, 102 Bruderhofs, or colonies, were established in Moravia, and by 1589 the Hutterite population had grown, largely through adult conversions, to an estimated twenty to thirty thousand individuals. By the late 1500's, persecution of the Hutterites was intensifying, and in 1622 they were ordered to convert to Catholicism or to leave Moravia.

Most of the approximately 2500 Hutterites who fled Moravia at this time went to Hungary, with a small group going to Transylvania. However, after a time, the persecutions resumed. The colonies in both Hungary and Transylvania were continually harassed by both the local populations and the military. They ultimately found it necessary to discontinue the practice of community of goods, and to ask to be considered as individual families. By about 1686 there were no Hutterite Bruderhofs left in Hungary, and none in Transylvania by 1695. The Transylvanian group were revitalised in the mid 1750's when migrants arrived from Carinthia (in Austria) and joined them. By 1762 the Carinthian converts had established a Bruderhof and reinstituted the community of goods. In 1767 a group of about 70 persons escaped from Transylvania to Wallachia, Romania. Three years later they moved once again, to Russia. It is estimated that about 116 members of the Hutterite sect in Hungary and Transylvania managed to get to Russia, where they had been promised land and exemption from military service by Catharine the Great, by 1784. It is this group, with the addition of some later converts, who are the biological ancestors of the modern Hutterite population (Bleibtreu, 1964).

The Hutterites lived in Russia until 1874, when their immunity from military service was revoked. Between 1874 and 1879 all the Hutterites then in Russia, with the exception of two families (1265 individuals), emigrated to the United States. Of these, about 440 settled in three colonies in the Dakota Territory and the remainder settled on individual homesteads in the same area. The Hutterites who took up individual homesteads became known as the 'Prairieleut'. Both the 'Schmiedeleut' and 'Dariusleut' subdivisions of the population had established communal living in Russia and resettled in colonies in the United States. The third group of colony Hutterites, the 'Lehrerleut', established communal living after arrival in the Dakota Territory.

With the outbreak of World War I, the Hutterites were once again persecuted because of their pacifism. Many colonies sold or abandoned their land in South Dakota and, between 1917 and 1920, established colonies in Manitoba and Alberta. After World War II, in the face of legislation restricting their land purchases, many of the Hutterite colonies reestablished daughter colonies in the United States. At the present time there are approximately 25,000 Hutterites in North America. They reside in about

300 colonies in four Canadian provinces — Manitoba, Saskatchewan, Alberta and British Columbia — and in five American states — Minnesota, North and South Dakota, Montana and Washington.

Since their migration to Russia in the late 1700's, the Hutterite population growth has been almost entirely due to natural increase. The hundred years in Russia saw an approximate ten-fold increase, from about 116 to nearly 1300 individuals, while the population of 443 who were living in colonies in the United States in 1880 had increased nearly fifty-fold, to approximately 21,500, by 1974 (Hostetler, 1974).

During the early years in North America there was some movement of families from colony to individual homestead and *vice versa*, as well as intermarriages between members of the colony and non-colony subdivisions. The movement between colony and individual homesteading had essentially ceased by the early 1900's, except for the occasional marriage of a Prairieleut woman into a colony family. The proportion of inter-leut marriages among the colony Hutterites has also declined over time, especially since World War I. At present, the majority of all marriages are between members of the same leut, although a few individuals do marry members of another subdivision (Hostetler, 1982, pers. comm.).

The Hutterites: Other Studies

The majority of the studies of the Hutterites have focussed on aspects of their social organisation, socialisation, lifestyle and culture (e.g. Bleibtreu, 1964; Hostetler and Huntington, 1967, 1968; Hostetler, 1974; Stephenson, 1979). However, the Hutterites as a group have many useful characteristics for demographic, epidemiologic and genetic studies. They constitute a defined population which is descended from a relatively few founder individuals and which has been effectively closed to migration for over 100 years. Extensive genealogic records, back to the 1700's, exist. The population has had a high rate of natural increase since it's arrival in North America in the late 1870's. At that time, three communally living subdivisions, the Schmiedeleut, Lehrerleut and Dariusleut, were established and have been maintained. The endogamy practiced by these groups, coupled with a high incidence of a sibship exchange pattern of marriage, has led to the development of a genetic isolate with a high average inbreeding

coefficient (between that of second cousins and first cousins once removed)(Steinberg, *et al.* 1967). These characteristics of the population make it particularly attractive for the study of recessive traits, which are often hard to detect and study in humans due to the outbreeding and small family sizes that are the norm in most populations.

A study of the growth of the Hutterite population, from the 443 people living in colonies at the time of the 1880 United States census, to 8542 people in 1950, was made by Eaton and Mayer (1954). They found that the growth of the population was almost entirely due to natural increase, and estimated that the Hutterite population was reproducing itself at close to the theoretical maximum level of human fertility for all but the 15 - 19 year age group. The median completed family size for Hutterite women was 10.4 liveborn children by 45 years of age. The crude birth rate (number of births per 1000 population) was estimated to be 45.9 during the period 1946 - 1950: the population was increasing by about 4% per year, leading to a doubling time of about 16 years.

In 1950, almost 51% of the population was under 15 years of age, and 2% were over 65, with an excess of males in most age groups. Contrary to what is generally observed in human populations, there was a higher death rate for females than for males in the 15 -59 age group. It was suggested that this might be the result of the large number of pregnancies experienced by most Hutterite wives causing a lowering of resistance to general morbidity in these women during the reproductive period and for about ten years after.

The demographic data analysed by Eaton and Mayer (1954) had been obtained as part of a study of mental illness in the Hutterite population. This mental health study was undertaken because the Hutterite population was thought to have essentially no mental illness, and Eaton and Weil (1955) were interested in determining the factors in the social and cultural environment of the population which might influence the frequency of appearance of various types of mental disorders. They found that the lifestyle of the Hutterites was not inhibitory to the development of severe mental illness: 199 of the 8542 Hutterites had been diagnosed as mentally ill at some point in their life. In addition, Eaton and Weil felt that some types of mental illness in the population had probably been underascertained. Although the Hutterites were found to have an unusually low rate of psychoses, the frequency of manic-depressives in this group was very high (about 74%).

The high incidence of manic-depressive disorder was attributed to cultural factors, particularly the extreme emphasis placed on communal cohesiveness by the Hutterite socialisation process.

Reproductive patterns of Hutterite women have been studied by Tietze (1957) and Sheps (1965). Tietze reported an average of 9.8 pregnancies per mother (9.6 per woman), and a very low sterility rate (2.4%), in his sample of 209 Hutterite women who had married before age 25 and were living with their husband at age 45. Both Tietze and Sheps reported a tendency for the mean interval between births to increase with birth order and increasing maternal age. Based on 562 Schmiedeleut marriages for which there were complete pregnancy records, including information on miscarriages and stillbirths, Sheps estimated that about nine percent of all pregnancies in this group had resulted in fetal loss. Mange (1964), using the same data as Sheps to examine the effect of inbreeding on fertility, reported an average of 11.2 livebirths per mother (150 families). He found no apparent effect of the value of the inbreeding coefficient of the offspring on either completed family size or on birthrate in these families. (Both completed family size and birthrate increased over all increments of mean coefficient of inbreeding of offspring except for a decrease at the last increment).

A number of analyses have been reported of various aspects of the data collected for a medical-genetic study of the entire Hutterite population, undertaken by Dr. A.G. Steinberg (Bleibtreu, 1964; Mange, 1964; Sheps, 1965; Steinberg, *et al.* 1967; Martin, 1969, 1970). The effects of colony division or splitting, a phenomenon that depends on both population size and social factors, were described by both Bleibtreu (1964) and Mange (1964). The Hutterites believe that all adult men must be charged with specific tasks. The division of a colony results from growth of the population to a point where there are a number of eligible males, but no positions of responsibility available for them. At this point, land is acquired and, once the necessary buildings are in place, the 'mother' colony is divided into two groups, partially by design and partially by lot. The division is such that each group has competent individuals for the various aspects of running a colony farm as well as approximately equal age and sex distributions. Families (not including married children) always move as a unit, and it is possible for groups of families who so wish, to remain together. The group that will move to the 'daughter'

colony is determined by lot. A man always lives in the colony in which he was born, or one of its daughter colonies, while, in an intercolony marriage, the wife always moves to the colony of her husband. One of the effects of colony division is to increase the relatedness among both the group of husbands and the group of wives within the daughter colonies. This increase in relatedness is probably the result of the tendency for a group of married brothers (or sisters) to move as a unit (Mange, 1964).

The relationship between marriage partners in the Lehrerleut was examined by Bleibtreu (1964). He found that the most frequent relationship between husbands and wives was that of second cousins (363/674 marriages or 53.9%), although most couples shared many additional relationships. Bleibtreu and Mange also noted that it is common for more than one marriage to occur between two sibships in both the Lehrerleut and the Schmiedeleut. Often one of the sibships will supply all of the husbands and the second all of the wives, but exchanges involving individuals of both sexes from each of the sibships also occur. Bleibtreu reported that over 25% of a random sample of 259 Lehrerleut marriages involved sibship exchange, while Mange's sample of 812 Schmiedeleut marriages yielded 228 (about 28%) which involved two, three or four members of one sibship all marrying members of a second sibship.

Mange (1964) attempted to estimate the maximum number of genomes present in the contemporary Hutterite population. He was able to determine that 68 individuals were sufficient to account completely for the ancestry of all Hutterites living in 1960. Due to the fact that these 68 people were not entirely unrelated to each other (pairs of individuals picked at random from the group were related, on average, as about third cousins), the maximum number of independent genomes in the Schmiedeleut was estimated to be 124.

Steinberg, *et al*. (1967), calculated inbreeding coefficients based on six generations of ancestry for all Schmiedeleut and Lehrerleut sibships whose pedigrees met a completeness criterion that the pedigree to be lacking at most one couple on either side through whom the parents could be related as second cousins. The value of the mean inbreeding coefficient for the offspring of a sample of 664 Schmiedeleut marriages was found to be F = 0.0211, and for the offspring of a sample of 618 Lehrerleut marriages F = 0.0255. The greater value of F for the Lehrerleut was felt to be due to both the fact

that the Lehrerleut subpopulation is smaller than that of the Schmiedeleut, and that the Lehrerleut have fewer remote ancestors. The inbreeding coefficients of the two subpopulations were found to be almost entirely due to random mating within the population.

Steinberg, *et al.* (1967), also determined that the 9536 Schmiedeleut and Lehrerleut individuals represented in their survey of the population could be traced to a maximum of 92 remote ancestors. The mean coefficient of consanguinity for pairs of individuals chosen at random from within this group was F = 0.0023, and it was estimated that the 92 individuals represented at most 158 independent genomes. The genetic contributions of these remote ancestors to the contemporary Lehrerleut population varied considerably, based on analysis of both the number of sibships to whom they were ancestral, and the degree of their relationship to the individual sibships.

Martin (1969; 1970) studied founder effect in the Schmiedeleut and Lehrerleut. She considered as founders only those individuals who were necessary to account for the total gene pool of the contemporary parents. These founders (i.e. the remote ancestors) did not all enter the gene pool during the same time period. Martin found that all living parents in the two leut could be traced back to 113 ancestral individuals. However, because many of these ancestors were related to each other, and some had transmitted their genes to the contemporary gene pool through only one child, the minimum number of individuals necessary to account for the gene pool of the population was not more than 91, who represented at most 150 independent genomes. Of the 91 'minimum ancestors', 67 were ancestral to the Schmiedeleut and 68 to the Lehrerleut. Fourty-four of these founders were ancestral to both leut, but their contributions to the gene pools of the two leut were different. Differential fertility on the part of the founders was considered to be, in part, the explanation for the differences in the relationships of the two leut to the set of founders which they share.

More recently, a number of studies of the Hutterite population have attempted to analyse genetic factors involved in cancer (Martin, *et al.* 1979, 1980; Simpson, *et al.* 1981). The objective of these studies has been to look for recessive gene control over oncogenesis by comparing the inbreeding levels of individuals with cancer to those of controls. Additionally, they were interested in detecting and analysing familial

aggregates of cancer in the population. It was suggested that, because all Hutterites share a relatively uniform environment and lifestyle, familial aggregates of cancer found in this population are more likely to be due to genes shared by family members, than in the general population where families differ from each other in both environmental and genetic background. With respect to the effects of inbreeding, comparison of inbreeding coefficients of cases of cancer with controls from the population, matched for age, sex and leut, showed no overall inbreeding effect, except for cases of childhood leukemia who had higher inbreeding coefficients than their matched controls.

The types of cancers found occurring in aggregates were generally those already known to show familial clustering (e.g. cancers of the breast and of the digestive system), most of which are transmitted in a pattern consistent with dominant inheritance. In particular, stomach cancer is present at elevated frequency in the male Alberta Hutterite population: several of the cases of this cancer form a familial aggregate identified in the Dariusleut (Fowlow, 1973; Gaudette, *et al.* 1978; Martin, *et al.* 1980). Although several studies have indicated an increased risk of stomach cancer in close relatives of affected individuals (Heston, 1976), it is not clear how much of this increased risk is due to common genetic *versus* common environmental factors. If a strong genetic component in the etiology of stomach cancer is proposed in this group, it is not clear what mode of transmission should be postulated. Martin, Hauch & Dreschler (1982), considering a possible autosomal recessive mode of inheritance, compared kinship coefficients of pairs of cases, cases with controls, and controls, but these showed no consistent pattern. Affected individuals occur in at least three consecutive generations, suggesting a possible autosomal dominant mode of inheritance, perhaps with incomplete penetrance. In this case the affected individuals could be either homozygotes or heterozygotes for a 'susceptibility' gene. In any case, if genetics does play a role in the incidence of this cancer, one would expect to be able to trace the pedigrees of the affected sibships back to some subset of common ancestors, as is expected for the known genetic disorders.

Organization of this Thesis

Both clinical aspects and genetic and genealogic aspects of the Bowen-Conradi syndrome in the Hutterite population are considered in this thesis.

An overview of genetic disorders in the Hutterites is presented in Chapter 2. This is followed by a general introduction to malformation syndromes, a discussion of the disorder that is the focus of this study, the Bowen-Conradi syndrome , and descriptions of several of the affected individuals. The Bowen-Conradi syndrome is compared to trisomy 18, which it superficially resembles, and to a number of cases grouped together as 'pseudotrisomy' 18.

Descriptions of the genealogical materials used in the reconstruction of the Bowen-Conradi syndrome pedigrees, and the computer programs used in the analyses are provided in Chapter 3.

Chapter 4 presents a description of the Bowen-Conradi syndrome genealogy, as used in the study. The founders to the pedigree are described and their genetic contributions to the affected sibships estimated. Inbreeding coefficients and the biological relationships of the parents and grandparents of the affected sibships are discussed. The effect on the value of the inbreeding coefficient, of the degree to which the pedigree is known, is discussed. Finally, the most likely source of the Bowen-Conradi syndrome allele and the possible allele frequency are estimated.

The concluding chapter presents some areas for further research. Some of the implications of this study with respect to genetic counselling and health care are discussed.

II. THE BOWEN-CONRADI SYNDROME IN THE HUTTERITES

Genetic Disorders in the Hutterites

A number of genetic diseases are known to occur in the Hutterites. These include cystic fibrosis, an autosomal recessive form of muscular dystrophy in the Schmiedeleut (Shokeir & Kobrinsky, 1976), an autosomal recessive 'dysequilibrium syndrome' in the Dariusleut (Schurig, *et al.* 1981), the autosomal recessive Meckel syndrome in the Dariusleut (Schurig, *et al.* 1980), and the Bowen-Conradi syndrome, also autosomal recessive, in all three leut (Bowen & Conradi, 1976; Hunter *et al.* 1979). In addition, four other autosomal recessive disorders (albinism, sensorineural deafness, methylmalonic aciduria and a new, mucolipidosis-like syndrome), four autosomal dominant disorders (spherocytosis, 5th finger brachydactyly, Dupuytren-like contractures and essential tremor), and four uncertain or polygenic disorders (diabetes, pyloric stenosis, cardiomyopathy and communicating hydrocephalus) have been described (Bowen & Lowry, 1982). It is of interest to note that the Bowen-Conradi syndrome, a lethal syndrome of skeletal and genitourinary anomalies, although only recently recognised as a distinct syndrome, has been recorded in all three subdivisions of the Hutterites (about 11 cases diagnosed since first being described in 1976). The Meckel syndrome, a lethal syndrome of occipital encephalocele, polydactyly and cystic kidneys, with other malformations, was first described by J.F. Meckel in 1822. This disorder has often been confused with other malformation syndromes, but, after delineation of its clinical and pathological features by Opitz & Howe (1969), a thorough search of the literature confirmed 49 cases occurring between 1822 and 1971 (Mecke & Passarge, 1971). The five known cases in the Hutterites are all from one of the subdivisions, the Dariusleut.

In addition to diagnostic difficulties arising from variation in the expression of many of these disorders, problems with identification of sibships segregating, in particular, the Bowen-Conradi or Meckel syndrome, may result from early lethal effects. Multiple spontaneous abortions or stillbirths appear in the reproductive histories of some of the parents of individuals with these diseases, and it is likely that some affected individuals, and their carrier parents, may never be identified due to the occurrence of these prenatal deaths.

Since disorders such as Bowen-Conradi syndrome and Meckel syndrome are rare elsewhere, it seems likely that the Hutterite individuals manifesting these disorders are autozygous for the same genes, which entered the population in a single founder couple — most likely a different couple for each of the disorders.

Congenital Malformation: Background and Terminology

Congenital malformations are morphologic abnormalities of internal or external organs that are present at birth, and that have actual or potential clinical significance. Congenital malformations are relatively common, when spontaneous abortions and stillbirths are taken into account: over 80% of aborted embryos and approximately 25% of aborted fetuses have one or more developmental abnormalities, while the incidence of congenital malformations in liveborn individuals is about 2-4% (Gerald, 1982; Poland, 1982).

Congenital malformations may be due to genetic or environmental factors. Although in most cases it is not possible to determine with certainty what factor (or factors) was responsible, it is thought that the major cause of malformation is genetic (Smith, 1982).

There are three principal genetic modes of determination for abnormal morphogenesis: polygenic, mutant genes in single or double dose, and gross genetic imbalance due to a chromosomal abnormality. The extent to which mutant mitochondrial genes contribute to congentital malformation has not been determined. It has been estimated that single mutant genes may account for about 10-15% of all congenital malformations (Moore, 1977).

A *syndrome* is a recognised pattern or aggregation of developmentally-independent malformations which has a single etiology (Pinsky, 1977). With respect to congenital malformations, syndromes are particularly likely to occur because the number of malformations found in a single individual is not random. This is due to the fact that early prenatal disturbances will often affect more than one organ of the developing embryo, leading to the presence of multiple malformations in the infant at birth. From a statistical viewpoint, the more anomalies present and the rarer each of these anomalies is in the general population, the less likely it is that they will occur together by chance in an

individual. Thus, the more likely it is that they are causally related (Cohen, 1982).

The concept of 'developmental fields' is useful in considering malformations and malformation syndromes. By definition, a *developmental field* produces characters in a sequential and organisationally hierarchical manner. The term *'developmental field complex'* (DFC) refers to a group of morphological defects which are developmentally interrelated, and which result from a single disturbance of field development. These malformations or anomalies may be confined to a single organ or region, or they may involve several contiguous or, more rarely, distant structures. The elements of a single DFC all develop at about the same time. DFC's are etiologically nonspecific: an organ or structure has a limited range of responses that it can make in response to any disturbing influence, therefore, the same anomaly may result from any one of several different causes. In addition, the same general cause may result in a greater or lesser degree of disturbance of a field, resulting in variation in the clinical severity or expressivity of the ultimate malformations.

There is a tendency to ascribe congenital malformations, especially if multiple and familial, to heredity, but this is not justified (Warkany, 1974). Ideally, demonstration of autosomal recessive inheritance requires a 25% segregation ratio, equal sex ratio, increased parental consanguinity (for rare traits) and the demonstration of a carrier state. However, for a new or obscure disorder, the presence of an affected sibling, demonstration of consanguinity between unaffected parents, and/or discovery of distant relationship between two or more affected individuals is generally considered sufficient to infer autosomal recessive inheritance (Opitz, *et al*. 1979). If the affected individuals are all male, X-linked inheritance cannot be ruled out as a possible mode of inheritance unless male-to-male transmission is observed. Dominant inheritance is suspected if transmission occurs from an affected parent to one or more offspring, however, familial occurrence in one or more generations may also have a polygenic basis.

Syndromes can be classified in two main ways — on the basis of a single discrete feature or variants thereof (e.g. syndromes with polydactyly), or on the basis of a large number of shared features (e.g. syndromes attributable to chromosomal abnormalities). This second approach is especially appropriate for malformation syndromes. Since most, if not all, of the manifestations of malformation syndromes are nonspecific,

diagnosis is usually based on loosely defined phenotype and mode of inheritance (specific biochemical tests are generally not available). For many syndromes (e.g. Down syndrome, trisomy 9p syndrome, tricho-rhino-palangeal syndrome), the resemblance of one affected individual to another, unrelated, affected individual is greater than to his/her own siblings. On the other hand, the major features of some well-defined, single gene syndromes are often not constant, either within and between affected sibships or on both sides of a single individual (e.g. the Meckel syndrome) (Opitz, *et al.* 1979; Pinsky, 1977). Autosomal recessive disorders generally show less variation in expression than do autosomal dominant ones, possibly because there is no normal gene product present to carry on the particular function. Syndromes recognised on the basis of dysmorphic features are exceptions to this generalisation, probably because the phenotype is several steps removed from the gene product. The greater variability in autosomal dominant disorders (e.g. Treacher-Collins syndrome, Holt-Oram syndrome) may be due to minor differences in the normal allele product or chance differences in ratios of normal to abnormal subunits that make up the affected molecules. Differences in genetic and environmental background may also be responsible for some of the variability observed in both dominant and recessive disorders.

Newly described syndromes generally show little phenotypic variability because the earliest examples are diagnosed on the basis of how closely they resemble the first case. The result of this selection bias is a homogeneity of phenotype which often emphasizes the most severe aspects of the syndrome (Cohen, 1982). The number of minor and/or variable features of the syndrome tends to increase as the number of patients increases, particularly as families with more than one affected member are ascertained. In such families, exclusion of the proband from the study will result in a less biased characterisation of the phenotype (Fraser and Lytwyn, 1981).

Example: The Meckel Syndrome

One autosomal recessive disorder which has been diagnosed in the Hutterites and which shows a large degree of phenotypic variability is the Meckel syndrome. Meckel (1822) reported two affected siblings, born one year apart, with occipital encephalocele, cleft palate, microcephaly, polydactyly of all four limbs, and enlarged, cystic kidneys. Since that time, there have been at least 100 individuals reported with similar findings (Norio, *et al*. 1980).

Although the defects in the Meckel syndrome are of many kinds and affect different organ systems, the 'classical triad' of occipital meningo-encephalocele, cystic kidneys and postaxial polydactyly is considered to be diagnostic. Other malformations which have often been reported are eye anomalies, cleft palate, microcephaly, micrognathia and heart defects. Cases reported with genital ambiguities may have been the Smith-Lemli-Opitz syndrome, not the Meckel syndrome (Lowry, 1983),as there is some phenotypic overlap of these two recessively inherited syndromes.

There have been a number of reviews concerned with phenotypic variability in the Meckel syndrome (Mecke and Passarge, 1971; Fraser and Lytwyn, 1981; Seller, 1981; Lowry, *et al*. 1983; Lowry, 1983). Mecke and Passarge (1971) reviewed the genetics of and summarised the clinical and pathological features of 49 cases. Seller (1981) reported a family with four affected sibs, all of whom showed the same phenotype, with only [illegible] of the major anomalies of the syndrome - encephalocele and polycystic kidneys. She noted that some 57% of the reported cases of the Meckel syndrome have all three major anomalies, 16% have encephalocele and polycystic kidneys, 15% have polycystic kidneys and polydactyly, 3% have encephalocele and polydactyly, and 9% have only one of the major features. A further review of families with more than one affected individual showed that in 53% of these families the siblings had identical phenotypes and in 47% the manifestation of the disorder, with respect to major signs, differed among the affected siblings. The expression of minor abnormalities was found to be quite variable among all cases, including sibling groups.

Fraser and Lytwyn (1981) studied the range of anomalies in the affected siblings of Meckel syndrome probands. Their rationale was that these individuals would be more representative of the true phenotypic variability of the syndrome, since they did not have

to have the 'classical' phenotype in order to be ascertained. It was found that the frequency of most of the defects was lower in the affected siblings than in the probands. All the affected siblings like the probands, had polycystic kidneys, 63% had occipital encephalocele (89% in probands), and 55% had polydactyly (85% in probands).

As a result of their review of the literature, Mecke and Passarge (1971) suggested that the presence of at least any two of the three major features of the disorder, especially if accompanied by any of the frequently associated anomalies, should be sufficient to establish the diagnosis. (However, they accepted a diagnosis of Meckel syndrome in four individuals with only one of the major features, none of whom had cystic kidneys.) More recently, Fraser and Lytwyn (1981) suggested that the 'working definition' of the Meckel syndrome should consist of cystic kidneys plus at least two of the other major defects frequently associated with the syndrome. Lowry, *et al.* (1983), do not feel that there should be an obligatory defect for the diagnosis of any syndrome, and anticipate that there will be mildly affected cases of the Meckel syndrome whose kidneys will be normal or nearly so. However, until such an individual is diagnosed (on the basis of having a sibling with 'full-blown' Meckel syndrome) the working definition of Fraser and Lytwyn is probably the best operational diagnostic criterion for the disorder.

The Meckel Syndrome in the Hutterites

The five known cases of the Meckel syndrome in the Hutterites are all from one of the population subdivisions, the Dariusleut. Two siblings who were diagnosed during life, and a third infant, diagnosed retrospectively, showed a considerable range of phenotypic variation (Schurig, *et al.* 1980). One infant showed the classical triad of cystic kidneys, occipital meningocele and postaxial polydactyly plus other malformations, while his brother, born subsequently, had no obvious external malformations. The third infant, closely related to the first two, had an occipital meningocele, hydrocephalus, cleft palate and microphthalmia, which is consistent with a diagnosis of the Meckel syndrome. It is not known if he had cystic kidneys. Two additional Dariusleut infants have been diagnosed with the Meckel syndrome (unpublished information, R.B. Lowry, P. Bowen, S. Ackroyd). Because of the extreme phenotypic variability in this disorder, the Meckel syndrome has probably been underascertained in the Hutterites. This may be the reason

why the Meckel syndrome has, so far, been found only in the Alberta Dariusleut.

The Bowen-Conradi Syndrome

The Bowen-Conradi syndrome is a lethal disorder of multiple congenital abnormalities which was recognised as a new syndrome in the Hutterites in 1976 (Bowen and Conradi, 1976). To date, 16 individuals with this syndrome have been diagnosed in 14 Hutterite sibships (See Table 2.1). The major features of the disorder, reported in essentially all patients, are intrauterine growth retardation, microcephaly, dolichocephaly, prominent nose, unusually formed antihelices, micrognathia, mild limitation of joints (fingers, hips, knees), 'rockerbottom' feet, undescended testes, normal karyotype and infant death. In addition, the infants are hypotonic at birth, have feeding difficulties and failure to thrive. Inconstant abnormalities include corneal clouding and abnormal neck or shoulder region in some patients. Because of the number of obvious features which are present in every Bowen-Conradi syndrome infant, it is unlikely that the Bowen-Conradi syndrome is presently being underascertained in Alberta, although early cases probably were missed. However, if an affected infant was born at home, it may not be ascertained, as it may not survive long enough to come to the attention of the medical geneticists, and it is not clear how it would be recorded on a death registration. On the basis of its occurrence in siblings, parental consanguinity, and the inter-relatedness of the families, the Bowen-Conradi syndrome is assumed to be an autosomal recessive disorder (Bowen & Conradi, 1976; Hunter, *et al.* 1979).

The uniformity of the clinical phenotype observed in patients with the Bowen-Conradi syndrome may be due to the fact that the description is based on relatively few cases. The range of phenotypic variation in the Bowen-Conradi syndrome, including the unpublished materials, is being reviewed (P. Bowen and R.B. Lowry, pers. comm.).

Although the Bowen-Conradi syndrome has often been misdiagnosed clinically as trisomy 18, by those who are unfamiliar with it, the phenotypic resemblance of the two disorders is only superficial. There are a number of reports in the literature of infants with the phenotype of trisomy 18 but who have normal chromosomes (e.g. Burks and Sinkford, 1964; de Grouchy, 1965; Hook and Yunis, 1965; Lazyuk, *et al.* 1980; Le Marec, *et al.* 1981; Simpson and German, 1969; Szotawa and Kowalewska, 1965; Taylor,

Table 2.1: The Bowen-Conradi Syndrome Patients

Random ID Number	Sex	Birth Year	Age at Death	Leut	Province	Included In Analysis	Comments	Source
10839	f	1982?	?	S?	?	Yes		AO & BB
18068	m	1968	16 wks	D	AB	Yes	Siblings	B&C, case 1; AGWH, IX 8
10591	m	1973	28 wks	D	AB	Yes		B&C, case 2; AGWH, IX 11
17212	m	1978?	2 wks	S	MAN	Yes		AGWH *et al.* IX 2
15286	m	1978	17 wks	S	MAN	Yes		AGWH *et al.* IX 15
12747	m	1977	34 wks	L	AB	Yes		AGWH *et al.* IX 20
17572	f	1970	6 wks	S	ND	Yes	Siblings, retro. diag.	AGWH *et al.* IX 13
13951	f	1975	2 wks	S	ND	Yes		AGWH *et al.* IX 14
17956	f	1977	6 wks	S	SD	Yes	retro. diag.	AGWH *et al.* IX21
11914	m	1987	2 wks	S	Man	Yes		AGWH *et al.* addendum
11073	f	1981	99 wks	D	AB	Yes		RBL
13132	m	1981	17 wks	D	AB	Yes		RBL
10433	f	1983	4 wks	D	AB	Yes		PB
11917	f	1979	132 wks	D	AB	Yes		PB
16722	m	1982	24 wks	L	SASK	Yes		AEC
16955	f	1967	64 wks	D	AB	No	uncertain diag.	SBF

1968). Although it is possible that some of these individuals have had a small duplication of part of chromosome 18 which was not detected, it has been suggested, on the basis of some instances of parental consanguinity and several sets of affected siblings, that these cases may comprise one or more autosomal recessive syndromes. It is not unlikely that at least some of these cases may have the Bowen-Conradi syndrome.

Twenty-eight individuals with 'pseudotrisomy' 18 have been reported in the literature since 1964. Since 1968, about 16 Hutterite infants affected with the Bowen-Conradi syndrome have been born, nine of whom have been reported in published accounts. Table 2.2 lists the major features that have been reported for trisomy 18, 'pseudotrisomy' 18 and the Bowen-Conradi syndrome, and summarises a comparison of 21 of the patients with 'pseudotrisomy' 18 and 14 of the Hutterite infants with the Bowen-Conradi syndrome. (See Appendix 1 for descriptions of individual cases of 'pseudotrisomy' 18 and the Bowen-Conradi syndrome). For each of the features the proportion (where known) of trisomy 18 patients showing the trait is given. The three conditions share several features. The affected infants have a variable degree of intrauterine growth retardation. Microcephaly, micrognathia and malformed helices ('faun's ears') are common features, as are camptodactyly and clinodactyly. It is also evident that 'pseudotrisomy' 18 and the Bowen-Conradi syndrome differ from true trisomy 18 and from each other with respect to several major features. The sex ratios of the affected infants are different in the three conditions. Over 75% of trisomy 18 infants are female, whereas only about 40% (11/28) of the reported cases of 'pseudotrisomy' 18 and 50% (8/16) of the Bowen-Conradi syndrome cases are female. A maternal age effect is evident in trisomy 18, the mean age of the mothers at the birth of an affected child being about 32 years (Taylor, 1968). However, the mothers of 'pseudotrisomy' 18 infants are about 23.5 years and those of the Bowen-Conradi syndrome infants are about 28.9 years old at the birth of their affected child. This is probably not significantly elevated as, in 1950, the mean age of Hutterite mothers at the birth of a child was about 28 years (Eaton & Mayer, 1954).

Trisomy 18 infants have an altered gestational timing: about one-third are born early and one-third are born late. The mean gestational period for 'pseudotrisomy' 18 infants is about 37 weeks — only one of 17 infants for whom length of gestation was

Table 2.2: Major Reported Features of trisomy 18, 'Pseudotrisomy' 18 and the Bowen-Conradi Syndrome

	Trisomy 18 % with trait	'Pseudotrisomy' 18	Bowen-Conradi Syndrome
sex	77% f	11/28 f	8/16 f
mother's age at birth of child (yrs)	~33	23.5	28.9
gestation (wks)	1/3↑;1/3↓	37	term
breech	—	1/21	6/14
birthweight (gms)	2340	2460	2230
birthlength (cm)	—	42.8	44.5
head circumference (cm)	—	32.5	30.6
dolichocephally	93	4/21	11/14
prominent occiput	>50	5/21	3/14
microcephally	10-50	7/21	13/14
ptosis	—	5/21	1/14
small palpebral fissures	>50	10/21	1/14
hypertelorism	81	8/21	—
epicanthus	41	2/21	2/14
small mouth	>50	7/21	1/14
micrognathia	92	14/21	13/14
palate abnormalities	—	10/21	7/14
malformed ears	88	13/21	9/14
lowset ears	88	13/21	1/14
large nose	—	8/21	7/21
prominent bridge of nose	—	—	12/14
short neck	10-50	1/21	4/14
short sternum	68	3/21	1/14
shield chest	10-50	3/21	—
distally implanted thumbs	52	5/21	—
camptodactyly &/or clinodactyly	89	17/21	11/14
hypoplastic nails	63	3/21	4/14
restricted hip &/or knee	10-50	6/21	14/14
flexion deformity, wrist	10-50	4/21	1/14
short, dorsiflexed hallux	>50	5/21	—
calcaneovalgus	52	3/21	—
clubfoot	10-50	8/21	1/14
'rockerbottom' feet	10-50	10/21	11/14
dislocated hips	<10	2/21	1/14
overlapping fingers, clenched hand	>50	16/21	5/14
cardiac anomaly	85	6/21	1/14
renal anomaly	62	5/21	1/14
cryptorchidism	100	3/14	6/7
other genital	—	4/21	1/14
hypertonic	50	6/21	1/14
hypotonic	36	5/21	—
depressed Moro & suck reflexes	—	3/21	7/14
superficially normal brain	92	—	—
feeding difficulty	96	1/21	12/14
failure to thrive	96	5/21	3/14
developmental retardation	96	5/21	4/14
respiratory distress at birth	—	9/21	3/14(?)
age at death	50% <2m, 90% <1y		

reported had a gestational period longer than 40 weeks. Most Bowen-Conradi syndrome infants have a normal gestational period. In addition, almost half (6/ 14) of the Bowen-Conradi syndrome infants were born by breech presentation, whereas only one of the 'pseudotrisomy' 18 infants was reported to be a breech presentation. The mean birthweight of trisomy 18 infants is about 2340 grams. Both 'pseudotrisomy' 18 and the Bowen-Conradi syndrome infants are small; however, the former are on the average somewhat heavier (2460 grams) and the latter lighter (2230 grams) than are trisomy 18 infants (See Table 2.3). In addition to being on average heavier at birth than are the Bowen-Conradi syndrome infants, those with 'pseudotrisomy' 18 tend to be slightly shorter (42.8 cm vs. 44.5 cm), and to have a larger head circumference (32.5 cm vs. 30.6 cm).

Epicanthus, small palpebral fissures, hypertelorism, small mouth, short sternum, distally implanted thumbs, hypoplastic nails, short dorsiflexed hallux, clubfoot, cardiac anomalies and renal anomalies are all less commonly reported in both 'pseudotrisomy' 18 and the Bowen-Conradi syndrome than they are in trisomy 18 (See Table 2.4). Malformed, lowset ears are common in trisomy 18 (88%) and in 'pseudotrisomy' 18 (13/21, 62%) infants. Sixty-four percent (9/ 14) of the Bowen-Conradi syndrome infants were reported to have poorly formed antihelices, but only one (7%) had lowset ears. Micrognathia is common in all three disorders (92% of trisomy 18, 76% (16/21) of 'pseudotrisomy' 18, 93% (13/ 14) of Bowen-Conradi syndrome). A large nose was reported in 38% (8/21) of the 'pseudotrisomy' 18 and in 50% (7/ 14) of the Bowen-Conradi syndrome infants. Some 'pseudotrisomy' 18 infants had a depressed nasal bridge, but 86% (12/ 14) of those with the Bowen-Conradi syndrome had a prominent nose, with no glabellar angle.

There are three features for which trisomy 18 and 'pseudotrisomy' 18 show a similar frequency of occurrence, which is different from that of the Bowen-Conradi syndrome. The 'trisomy 18 hand', a clenched fist with overlapping fingers, has been found in well over 50% of trisomy 18 and in 76% (16/21) of the 'pseudotrisomy' 18 cases reported. Only 36% (5/ 14) of the infants with the Bowen-Conradi syndrome were reported as having this feature. Restricted movement at the hips and/ or knees is found in less than 50% of both trisomy 18 and 'pseudotrisomy' 18 infants but in at least

Table 2.3: Gestation Period and Birthweight of Bowen-Conradi Syndrome Patients

Random ID Number	Sex	Gestation (weeks) (1)	Gestation (weeks) (2)	Birthweight (grams) (1)	Birthweight (grams) (2)
17572	f	term	—	2622	—
13951	f	term	—	2570	—
17956	f	44	—	1821	—
16955	f	—	40	—	2123
18068	m	—	40	2040	2414
10591	m	37	—	2013	2070
12747	m	42	41	2097	2102
17212	m	38	—	2210	—
15286	m	term	—	2030	—
11914	m	—	37	—	2300
11917	f	—	39	—	1975
13132	m	—	42 4/7	—	2440
11073	f	—	40+	—	2350
16722	m	—	—	—	—
10433	f	—	42	2110	2150
10839	f	term	42	2730	—

(1) published data

(2) birth registration or other

Note: if two values for gestation or birthweight were reported for a case, the average of the two was used in the calculation of the mean.

Table 2.4: Features with Different Frequencies in the three Disorders

FEATURE	Number Showing Feature		
	Trisomy 18 (%)	'Pseudotrisomy' 18	Bowen-Conradi Syndrome
epicanthus	40	2/21	2/14
small palpebral fissures	50	10/21	1/14
hypertelorism	81	8/21	—
small mouth	50	7/21	1/14
short sternum	68	3/21	1/14
distally implanted thumbs	52	5/21	—
hypoplastic nails	63	3/21	4/14
short dorsiflexed hallux	50	5/21	—
clubfoot	10-50	8/21	1/14
cardiac anomalies	85	6/21	1/14
renal anomalies	62	5/21	1/14
malformed ears	88	13/21	9/14
lowset ears	88	13/21	1/14
micrognathia	92	14/21	13/14
large nose	—	8/21	7/14
prominent nasal bridge	—	—	12/14
overlapping fingers, clenched fist	50	16/21	5/14
restricted hip &/or knee	10-50	6/21	14/14
'rockerbottom' foot	10-50	10/21	11/14
cryptorchidism	50	3/14	6/7
respiratory distress at birth	—	9/21	3/14(?)

The first 11 of these features are found more frequently in trisomy 18 than in either 'pseudotrisomy' 18 or the Bowen-Conradi syndrome , the remainder occur at different relative frequencies in the three disorders.

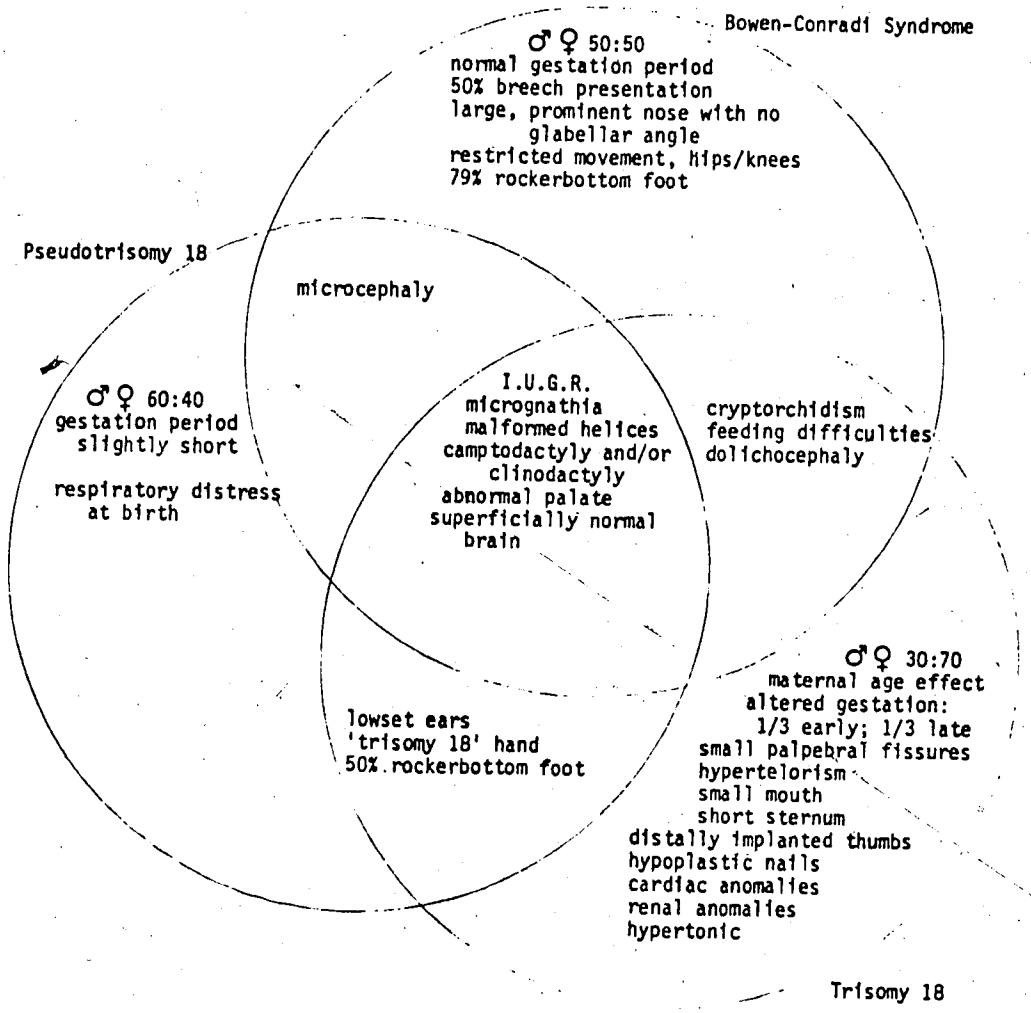
86% (12/14) of those with the Bowen-Conradi syndrome. However, a 'rockerbottom' foot deformity has been present in 79% (11/14) of the Bowen-Conradi syndrome infants but in fewer than 50% of those with either trisomy 18 or 'pseudotrisomy' 18 (10/21). Cryptorchidism is found at a high frequency in both trisomy 18 (100%) and the Bowen-Conradi syndrome (86%, 6/7), but is relatively infrequent in 'pseudotrisomy' 18 (21%, 4/14). Another feature, which has only been reported as a major trait in infants with 'pseudotrisomy' 18, is respiratory distress at birth. However, it is possible that this has been present in the Bowen-Conradi syndrome infants but not mentioned in the published reports.

Summary

Both 'pseudotrisomy' 18 and the Bowen-Conradi syndrome can be distinguished from trisomy 18 on the basis of karyotype alone. However, the cases described under the heading of 'pseudotrisomy' 18 probably comprise a heterogeneous group which may include at least some cases of the Bowen-Conradi syndrome. The similarity between 'pseudotrisomy' 18 and the Bowen-Conradi syndrome seems to lie in their superficial resemblance to trisomy 18 and in their lack of, or low frequency of, several anomalies found at high frequency in trisomy 18, rather than in their sharing, at high frequency, anomalies not found in trisomy 18 (See Figure 2.1).

As Table 2.1 demonstrates, there are many overlapping characteristics as well as some apparently differentiating features. Infants with the Bowen-Conradi syndrome tend to have a greater degree of intrauterine growth retardation, are longer and have a smaller head circumference than do those with 'pseudotrisomy' 18. Craniofacial features which are at higher frequency in the Bowen-Conradi syndrome include dolichocephaly (which may be related to a breech presentation), microcephaly and lack of glabellar angle resulting in a prominent bridge of the nose, whereas these features were either not present or were not recorded in the infants with 'pseudotrisomy' 18. In addition, males with the Bowen-Conradi syndrome have a very high incidence of cryptorchidism, and essentially all the Bowen-Conradi syndrome infants are reported to have feeding difficulties. The 'pseudotrisomy' 18 infants had a high incidence of clubfeet, they tended to have small palpebral fissure hypertelorism, a small mouth,

Figure 2.1: Overlap Between Trisomy 18, 'Pseudotrisomy' 18 and the Bowen-Conradi Syndrome. (Traits seen in >50% of affected individuals).



lowset ears, to be hypertonic and to present with extreme respiratory distress at birth.

At present, there are no well-documented cases of the Bowen-Conradi syndrome in non-Hutterite populations. This could be due to the gene for the syndrome being confined to the Hutterite population, although this seems unlikely. A more probable reason is simply that the Bowen-Conradi syndrome phenotype is relatively nonspecific, but it may be being altered somewhat by the genetic background of the Hutterite population, making diagnosis of affected individuals possible.

III. MATERIALS AND METHODS

Genealogical Materials

Much genealogical and demographic information exists for the Hutterites. The genealogies of the Schmiedeleut and Lehrerleut have been reconstructed, and computerised data bases for these leut exist in the United States (Martin, *et al.* 1980). Although the Dariusleut genealogy has not been completely reconstructed and computerised, there are many sources of information which can be used to reconstruct particular families and pedigrees as required. The available sources of genealogical and demographic information, from the laboratory of Dr. Kenneth Morgan, Department of Genetics, University of Alberta, Edmonton, included:

1. A copy of Dariusleut family records from a census taken in the 1960's by Professor A.G. Steinberg, Case Western Reserve University, and his colleagues.
2. Family reconstructions by Reverend J.K. Wipf, a Hutterite preacher in Alberta. He has reconstructed ancestral families of the Dariusleut as far back as the 1700's.
3. Family reconstructions received from Mrs. A. Burton of Calgary, Alberta. Her family records are from the period 1729-1890.
4. Kirchen Buech I, a registry containing births, baptisms, marriages and deaths from 1756-1843. An offset print of the original registry of the Hutterian Brethren, obtained from Professor John A. Hostetler.
5. Kirchen Buech II, a continuation of the register from 1844-1979, with information on a subset of the Dariusleut to 1975.

Methods

Inbreeding coefficients have been calculated for sibships with an individual affected with Bowen-Conradi syndrome (affected sibships) and for their parents. These calculations were done using a version, KUDO, of a computer program by J. MacCluer (MacCluer *et al.* 1967) which uses Kudo's method (1962). (See Appendix 2 for descriptions of all computer programs). In addition, coefficients of kinship between all pairs of affected individuals and between all pairs of their parents were calculated using

the same program. The set of all founders to the pedigree, as well as the set of founders who are common to the parents of affected sibships, were determined using the computer programs TRACEQ and PRUNE. The expected genetic contributions of these founders to the parents of affected sibships were also calculated, using the program ALLELE which computes the proportion of alleles in an individual which are attributable to a specific ancestor.

The number of Hutterite births between 1968 and 1983 was estimated from the crude birth rates for Alberta Hutterites determined by Laing (1975) from 1971 Canadian census data, and an estimate of the total population size. The average of Laing's six estimates of crude birth rate, 38.4, was used. Morgan (1983) estimated a total Hutterite population size of 20,300.

Descriptions of 14 of the Bowen-Conradi syndrome infants are provided in Appendix 1, and were used in the discussion of the disorder in Chapter 2. Most of the genetic analyses used the genealogy of ten of the affected sibships. These ten include Bowen and Conradi's original sibship, five additional sibships reported in Hunter, *et al.* (1979), (not including the sibship mentioned in their Addenda), and four unpublished sibships. The estimated genetic contributions of the founders to the affected sibships and their parents were calculated from a genealogy which contained a reconstruction of the first nine sibships identified. One of the estimates of allele frequency used the 15 sibships containing an infant with a confirmed diagnosis of the Bowen-Conradi syndrome .

Identification of Probands

Bowen and Conradi (1976) and Hunter, *et al.* (1979), reported two and nine infants, respectively, with the Bowen-Conradi syndrome (The nine infants in Hunter *et al.* include the two reported by Bowen and Conradi (1976). One of the additional infants is reported in the Addenda to the paper, and is not included in their Figure 1). Identification of the Bowen-Conradi syndrome infants in the Hunter *et al.* paper was made available to Dr. Morgan by Dr. A. Hunter, Division of Genetics, Children's Hospital of Eastern Ontario, Ottawa, with additional information provided by Dr. R.B. Lowry, Medical Genetics Clinic, Alberta Children's Hospital, Calgary. Information on the unpublished cases was made available to Dr. Morgan by Dr. P. Bowen, Division of Medical Genetics,

Department of Pediatrics, University of Alberta, Edmonton; Dr. R.B. Lowry, Medical Genetics Clinic, Alberta Children's Hospital, Calgary; Dr. A.E. Chudley, Department of Pediatrics and Child Health, Children's Hospital, Winnipeg. Additional clinical information was provided to Dr. Morgan by Dr. S. Ackroyd, Division of Medical Genetics, Department of Pediatrics, University of Alberta, Edmonton, and Dr. S.B. Fowlow, Medical Genetics Clinic, Alberta Children's Hospital, Calgary, and to Ms. Petrie by Dr. P. Bowen and Dr. S. Ackroyd.

Comparison Groups

When working with a population which forms a single pedigree, there is no true control group that can be drawn from within the population (Thompson, 1980). Because the lines of descent to the cases and controls are not independent due to the fact that both involve the same paths of descent in the same genealogy, it is difficult first to choose a control sample, and second to compare the distributions of kinship coefficients in the 'cases' versus the controls. A further major difficulty in generating any comparison group for the current study of the Bowen-Conradi syndrome in the Hutterite population was the fact that genealogical information was not available for all three subdivisions of the contemporary population. (No information was available for the contemporary Schmiedeleut population). Even so, there are a number of different types of comparison group that might be useful to improve the inferences made from an analysis of the ancestry and inbreeding coefficients of the Hutterite sibships containing an individual with the Bowen-Conradi syndrome . These include:

1 A random sample of individuals born during the same period of time as the Bowen-Conradi syndrome cases.

2 Age-, sex- and leut-matched individuals for each of the Bowen-Conradi syndrome cases.

3 Individuals affected with a different genetic disorder having the same mode of inheritance as the Bowen-Conradi syndrome .

4 Spouses of the siblings of the parents of affected individuals.

Either of the first two comparison groups would provide information on the distributions of inbreeding coefficients within the current generation of the Hutterite

population and the biological relationships between marriage partners, as well as the distribution of the estimated genetic contributions of the founders to the members of the contemporary population. Since it seems unlikely that two or more rare disorders will trace back to the same founder couple, a comparison sample of the third type, consisting of cases of another disorder, would be helpful in inferring the most likely source of the allele. A comparison group of the fourth type would provide the same information as would the first two, but in addition, because of the high frequency of sibship exchange marriages in the population, could be used to determine the existence of any marriages at high risk for producing an affected child.

In the absence of the data necessary to generate any of the above types of comparison group, the comparison data used here come from the published literature. These include the distribution of inbreeding coefficients of 667 Schmiedeleut sibships whose parents were married between about 1900 and 1960 (Mange, 1964), mean inbreeding coefficients of similar samples for all three leut (Steinberg, *et al.* 1967; Gordon and Martin, 1983), and coefficients of inbreeding of Schmiedeleut and Lehrerleut individuals ascertained with cancer, and their selected controls (Martin, *et al.* 1980a,b; Simpson, *et al.* 1981). In general, cases were grouped by sex, leut and type of cancer, controls were either all Hutterites of the same leut, sex and decade of birth as the pooled cases or, for some types of cancers, individual cases. The distributions of inbreeding coefficients derived from these data are presented in Table 3.1.

To generate the mean inbreeding coefficients shown in Table 3.1, it was necessary to determine the decades of birth of the individuals with specific cancers reported by Martin, *et al.* (1980a,b) and Simpson, *et al.* (1981). This was possible because, for many of the cancers, only a single affected individual had been reported in the population. For these cases, the control data would consist of the mean coefficient of inbreeding of all Hutterites of the same leut and sex, born within the same decade. The years of birth for many of the individual cancer cases was provided by Dr. Morgan. In this way, it was possible to estimate the mean coefficient of inbreeding of both Schmiedeleut and Lehrerleut males and females for most of the decades between 1870-1879 and 1960-1969.

Table 3.1: Estimated Mean Inbreeding Coefficients of Hutterites by Decade of Birth

A. SCHMIEDELEUT

Decade of Birth	Number of Males	Females	Total Number	Mean F (males)	Mean F (females)	Mean F (total)
1870-1879	—	8	8	—	.0137	.0137
1880-1889	56	—	56	.0096	—	.0096
1890-1899	79	55	134	.0165	.0087	.0133
1900-1909	129	225	354	.0157	.0150	.0153
1910-1919	202	192	394	.1056	.0139	.0148
1920-1929	728*	302	1030	.0195	.0176	.0189
1930-1939	467	479*	946	.0194	.0183	.0188
	"	729*	1191	"	.0200	.0198
1940-1949	—	—	—	—	—	—
1950-1959	1102*	—	1102	.0221	—	.0221

B. LEHRERLEUT

Decade of Birth	Number of Males	Females	Total Number	Mean F (males)	Mean F (females)	Mean F (total)
1880-1889	29	36	67	.0130	.0124	.0127
1890-1899	69	69	138	.0121	.0129	.0125
1900-1909	94	102	196	.0123	.0143	.0133
1910-1919	154	153	306	.0160	.0162	.0162
1920-1929	236	243	479	.0188	.0191	.0190
1930-1939	—	324	324	—	.0182	.0182
1940-1949	—	436	436	—	.0234	.0234
1950-1959	763	656	1419	.0269	.0274>	.0271
1960-1969	—	687	687	—	.0286	.0286

Derived from Martin, *et al.* (1980a,b) and Simpson, *et al.* (1981).

* There may be problems with these numbers: the 1920-1929 decade and 1950-1959 decade male sample sizes appear to be too large for these time periods. There were two possible sample sizes for the 1930-1939 females.

IV. RESULTS AND DISCUSSION

The Genealogy

The pedigrees of ten of the sibships known to have at least one individual affected with the Bowen-Conradi syndrome has been reconstructed (the six sibships in Hunter, *et al*. (1979), plus four additional sibships). The reconstruction was based on genealogic information in the possession of Dr. Morgan as of August 1983. Four of the sibships are from the Schmiedeleut, four from the Dariusleut and two from the Lehrerleut. The pedigree contains 622 persons, (including twelve affected individuals, but none of their unaffected sibs), 67 of whom are 'founders'.

Ancestor Set

Founders are defined as persons who have no known ancestors within the pedigree and thus are considered to be unrelated to each other. Table 4.1 indicates the degree of overlap in the distribution of the founders to the three leut, as represented in this pedigree. Eighteen of the founders, all born in the early 1700's, are common to all of the parents of affected sibships, and hence potential sources of the Bowen-Conradi syndrome allele. These eighteen comprise eight couples plus two wives of sons of two of these couples.

The estimated genetic contributions of the 67 founders to the parents of affected sibships were calculated using the computer program ALLELE. Individual founders contributed from 0.0% to 9.0% of the alleles of individual parents. The 18 common founders, as a group, contributed between 42% and 66% of the alleles of individual parents. Similarly, the estimated genetic contributions of the individual founders to the affected sibships were calculated. Individual founders contributed from 0.0% to 8.8% of the alleles of individual sibships. The 18 common founders as a group contributed from 46% to 62.5% of the alleles to individual sibships.

In an attempt to determine if there were any other individuals who might be a potential source of the Bowen-Conradi syndrome allele, five founders who are ancestral to all but one of the parents of the affected sibships were identified: two couples and the wife of a son of a founder. These founders are all 'excluded' on the basis of not being

Table 4.1: Distribution of Founders for the Bowen-Conradi Syndrome Pedigree

Leut	Number of Affected Sibships	Maximum Number of Founders	Number of Founders Common to all Parents of Affected Sibships
Schmiedeleut	4	57	25
Dariusleut	4	57	29
Lehrerleut	2	47	32
Combined	10	67*	18

* 39 founders are ancestral to all three leut

among the known ancestors of a parent of an affected Schmiedeleut sibship. Three of them are excluded by one Schmiedeleut mother, and two by one Schmiedeleut father. This may simply be due to the fact that, for these data, the Schmiedeleut pedigrees are less known (and less secure) than are those of the Dariusleut and Lehrerleut sibships.

The estimated mean individual allelic contributions of these five founders to those of the parents of affected sibships to whom they do make an allelic contribution ranges between 1.9% and 3.8%. Only two of these founders, one couple, have an average allelic contribution which is within the top half of the range of the contributions of the eighteen founders who are known to be common to all the parents of affected sibships. The ancestry of the parent who excluded them is 100% complete for only four generations, so it is possible that this ancestor couple may be, in fact, common to all of the parents.

Inbreeding Coefficients

The inbreeding coefficient, F, was calculated for each affected sibship and for both parents of these sibships. The values, shown in Table 4.2, were calculated on the entire known ancestry of these individuals and include inbreeding through persons who are not common ancestors to all ten sibships. The F values for the affected sibships ranged from 0.0304 to 0.0866, and for their parents from 0.0143 to 0.0721. The mean values of F for affected sibships, and for their parents, within leut, are shown in Table 4.3. This table also contains the average coefficients of kinship, ϕ_{ab}, calculated between all pairs of affected sibships, and between all pairs of parents (other than sib or first cousin pairs), by leut. Sib and first cousin pairs were excluded from the calculation to conform to the Hutterites' avoidance of marriage with individuals related as first cousins or closer. Table 4.4 shows the average kinship coefficient between sibships with an affected child, within and between leut. These indicate that, in general, the sibships with an affected child are more closely related to others within the same leut than they are to the affected sibships in the other two leut. This is not unexpected, as relatively few Hutterite marriages involve individuals from different subdivisions of the population.

Table 4.2: Inbreeding Coefficients of Bowen-Conradi Syndrome Patients and their Parents

Random ID Number of Patient	Leut	Patient	Father	Mother	Closest Degree of Relationship of Parents	Grandparents Paternal	Grandparents Maternal
17572 13951	S	.061	.043	.035	D 2 C*	1½ C	2 C
17956	S	.034	.014	.025	2 C	2½ C	3 C
18068 10591	D	.046	.030	.028	2 C	½ 2 C	½ 2 C
12747	L	.075	.042	.065	D 2 C	D 2 C	
17212	S	.054	.024	.021	2 C	3 C	3 C
15286	S	.047	.024	.072	½ 1½ C	2 C	2½ C
13132	D	.030	.058	.062	T 4 C	1½ C	2 C
11073	D	.057	.072	.039	2½ C	1½ C	3 C
16722	L	.087	.062	.042	1½ C	2 C	D 2 C
11917	D	.054	.034	.058	2 C	3 C	D 2 C

* Double second cousins; ½ — once removed
½ 1½ C — half first cousins, once removed

Table 4.3: Average Inbreeding and Kinship Coefficients of Bowen-Conradi Syndrome Affected and Parents

	Schmiedeleut (n)*		Dariusleut (n)		Lehrerleut (n)	
F_i (affected)	0.049	(4)	0.055	(4)	0.081	(2)
F_i (parents)	0.027	(8)	0.043	(8)	0.053	(4)
Φ_{ab}(affected)#	0.027	(6)	0.045	(3)	0.127	(1)
Φ_{ab}(parents)#	0.027	(23)	0.046	(12)	0.075	(2)

* number of (pairs of) comparisons
\# affected: all possible pairs except sibs
parents: all possible pairs except sibs and first cousins

F_i coefficient of inbreeding of an individual
Φ_{ab} coefficient of kinship between two individuals = F_i of their offspring

Table 4.4: Average Kinship Coefficients of Bowen-Conradi Syndrome Sibships

Overall Number of Pairwise Comparisons	Within Leut	Between Leut
.028 (36)	.043 (10	.022 (26)
.025* (35)	.033* (9)	

* Excluding Lehrerleut:Lehrerleut comparison

Kinship of Marriage Partners

As noted earlier, consanguinity increases the probability that an individual inherits alleles that are identical by descent from a common ancestor. This in turn contributes to the incidence of autosomal recessive traits in a population. The proportion of homozygous recessive individuals in a (random mating) population, produced as a result of parental consanguinity, is large when the recessive allele is rare. However, if the recessive allele is common, (allele frequency 0.1 or greater), the increased incidence of homozygotes resulting from parental consanguinity is very slight (Crow and Kimura, 1970). In an isolated population, it is possible that every member of the group will become related to everyone else; that is, all marriages will be consanguineous. In this situation, increased risk may result for the couples who are more closely related to each other than are other couples in the population (Murphy and Chase, 1975).

Coefficients of kinship have been calculated for the parents of each of the affected sibships, and for all grandparents and great-grandparents. These calculations were done using the known ancestry back to the founder generation and to only six generations for each couple. In addition, the closest biological relationship of each of these couples was determined.

The closest genetic relationship between the parents of the affected sibships were determined (See Table 4.2): one couple are first cousins once removed, one couple are half first cousins once removed, two are double second cousins, four are second cousins, and two are more distantly related. Thus, in general, the inbreeding of the affected sibships is not due to very close relationships between their parents.

The closest biological relationship between the members of each parental couple accounts for between ten and 50 percent of their total coefficient of kinship, demonstrating that there are multiple distant relationships between them. In the grandparental and great-grandparental generations, a few marriages occurred in which the closest biological relationship of a couple accounted for most of the coefficient of kinship, but in general, even in these generations, most of the kinship was due to remote relationships rather than close inbreeding.

The mean values of the coefficients of kinship, based on six-generation pedigrees, for samples of Hutterite marriages that occurred between 1900 and 1965, have been

reported by Steinberg, *et al*. (1967), for Schmiedeleut and Lehrerleut, and by Gordon and Martin (1983), for Dariusleut. For the Bowen-Conradi pedigree, the grandparental and great-grandparental marriages probably correspond to this period, and the six-generation coefficients of kinship for these couples are compared to the previous population estimates in Table 4.5. Since the number of marriages that were ascertained through infants affected with the Bowen-Conradi syndrome is small, the kinship coefficients have been averaged across the three leut. The average coefficients of kinship of the grandparental and great-grandparental couples, F = 0.025, corresponds well to the average values estimated for these generations in samples from the entire population.

This table also shows that, within the Bowen-Conradi syndrome genealogy, the average coefficient of kinship between marriage partners has increased slightly in recent generations. However, the parents of the affected sibships are on the average considerably more closely related to each other than were average Hutterite couples of the previous two generations (F=.0368 vs .0244).

Since the year of birth is not known for many of these individuals (none of the Schmiedeleut parents and grandparents), and the numbers are small, it is not feasible to calculate mean inbreeding coefficients for them by decade of birth. However, by inspection, it can be seen that the mean inbreeding coefficient of the parents of affected sibships, most of whom were probably born between 1940 and 1960, is considerably higher than that of any decade of birth for the comparsion data within that period (see Table 3.1).

Completeness of Pedigrees

It seems reasonable to assume that the calculated value of an inbreeding coefficient is in part related to the amount of information on which the calculation is based. In this context, information has two components: a) the number of generations in (or depth of) the pedigree, and b) the amount of information (or number of ancestors known) within each generation. In general, as the number of generations in the pedigree increases, the inbreeding coefficient will also increase. Increasing the amount of information within a generation will increase the accuracy of the calculation, but not necessarily the value of the inbreeding coefficient itself. Since the calculation of an

Table 4.5: Average Coefficients of Kinship (based on six-generation pedigrees)

GENERATION	
Parents	0.0368
Grandparents	0.0289
Great-grandparents	0.0218
POPULATION ESTIMATES*	
Schmiedeleut	0.0211
Dariusleut	0.0282
Lehrerleut	0.0255

* Population estimates are from the following sources:
Schmiedeleut - Steinberg, *et al.* , 1967
Dariusleut - Gordon and Martin, 1983
Lehrerleut - Steinberg, *et al.* , 1967

inbreeding coefficient is based on a restricted number of generations, the calculated value will be a minimum estimate of the true inbreeding coefficient of the individual. Thus, in comparisons of inbreeding coefficients, the amount of information on which they were calculated should also be considered.

A value called the 'percent completeness' of the pedigrees of the individuals for whom they reported inbreeding coefficients was calculated by Mange (1964), in a study of the Schmiedeleut, and Cross (1967) and Kidd, *et al.* (1980), in studies of the Old Order Amish. Mange (1964) calculated F on the basis of all known relationships of fourth cousin or closer between the parents of an individual. When the individual for whom the inbreeding coefficient is being calculated is considered to be in generation 1, this calculation uses pedigrees that are six generations deep. Each of the five ancestral generations is given a weighting of 20% — i.e. each of these generations is assumed to contribute 20% of the information on the ancestry of the sibship in question. Mange included in his analysis only those pedigrees which lacked, at most, one ancestral couple who could be the source of a second cousin relationship between the parents. This criterion ensured that the whole pedigree would be at least 74% complete. He estimated that the average percent completeness of the pedigrees of these individuals was 91%, but (apparently) made no attempt to determine whether there was any relationship between the completeness of the pedigree and the inbreeding coefficient.

Cross (1967) calculated inbreeding coefficients on the basis of the total known ancestry of the individuals in his study, using a modification of Mange's program which allowed him to use genealogical information to a depth of 12 generations. He defined the percent completeness of a pedigree to be the proportion of ancestors known compared to the maximum number of ancestors theoretically possible. The percent completeness of the pedigree of an individual was taken as the average of the percent completeness of his parents' pedigrees. For the 817 probands involved, the mean percent completeness of the pedigrees, on the father's side was 22.1%, and on the mother's side was 22.9% (giving an average completeness of 22.5% overall). There is no mean depth of pedigee reported. Cross found, especially for low values of F, that there was some correlation between the inbreeding coefficient and the percent completeness of the pedigree. The correlation coefficient was small (0.177), but it was

significant due to the large sample size. For high values of F, there was no relationship between inbreeding coefficient and pedigree completeness. Cross estimated that over 98% of the variation in the values of the inbreeding coefficients at a given degree of pedigree completeness was due to factors other than the amount of information known on ancestry.

Kidd, *et al.* (1980), calculated the completeness of the ancestry of each of the four sibships in their study of propionic acidemia in an Amish kindred. They note only that the pedigrees are over 75% complete six generations back from the probands, and that the completeness of the pedigrees decreases sharply for the earlier generations. Kidd, *et al.*, determined the 'degree to which ancestry was known' for each sibship, for each generation from the parents back, apparently, to the limits of their information: they did not determine an overall percent completeness for the pedigrees, nor did they indicate how they calculated these values.

Analysis

In an attempt to assess both the degree of completeness of the Bowen-Conradi syndrome pedigrees (amount of information), and the effect that the differences in completeness of these pedigrees might have had on the values of the inbreeding coefficients calculated, ten of the 14 sibships containing an affected individual were analysed. The inbreeding coefficients have been calculated on the total known ancestry of the individual, as well as on ancestry truncated at each generation from the fourth to the limit of the particular pedigree. The pedigree information for the affected sibships extends back ten to eleven generations, but complete ancestry is not known to that depth. The maximum depth of the pedigrees and the generation to which they are 100% complete were obtained from runs of the program KUDO, which was also used to compute the inbreeding coefficients. The number of generations involved in the calculation is given when inbreeding coefficients are computed, and, by printing out the *family lines* (identification numbers of all ancestors between the individual for whom the inbreeding coefficient is being calculated and each of the founders ancestral to him), it can be determined, by inspection, the generation in which the first 'founder' appears, and the number of ancestors who are 'unknown' in any generation. Since, by definition, a

founder is an individual whose parents are not known, the appearance of a founder in any generation indicates that information on ancestry is incomplete in the previous generation. Because the loss of information on the ancestry of the affected sibships might also affect the number of founders who are common to all the parents of these sibships and hence inference regarding potential sources of the Bowen-Conradi syndrome allele, the patterns of exclusion of founders (based on the probability of their contributing an allele to each of the parents of the affected sibships) was determined to assess whether any of the founders were excluded by only one parent, and whether these individuals, if they had been ancestral to all parents, would be a likely source of the allele for the Bowen-Conradi syndrome.

The percent completeness of the pedigrees of the affected sibships was taken to be the proportion of ancestors known compared to the maximum number of ancestors possible. (A non-inbred individual has eight ancestors at the great-grandparental generation, i.e. four sets of great-grandparents. A person whose parents are first cousins has only six ancestors at the same level; a single great-grandparental couple is ancestral to two of his grandparents. This great-grandparental couple would be counted twice when determining the number of ancestors known at that generation). These values were calculated both for the total ancestry and by generation, to the seventh generation for all affected sibships, and to the eighth generation for those sibships whose ancestry was totally known to the seventh generation.

Effects of Pedigree Depth on Inbreeding Coefficient

The inbreeding coefficients for the affected sibships were determined on the known ancestry truncated at each generation from the fourth to the limit of each pedigree. These values are presented in Figure 4.1, which shows a plot of the value of the inbreeding coefficient *versus* the number of generations of ancestry used to calculate it, for each of the ten sibships. Figure 4.2 shows the mean value of the inbreeding coefficient by level, *v* number of generations of ancestry used in the calculation. These graphs show sibships, there is an increase in the value of the inbreeding coefficient with increasing depth of pedigree information used in its calculation. By the point that nine generations of ancestry are being used in the calculation, the value of the

Figure 4.1: Inbreeding Coefficients of the Bowen-Conradi Syndrome Patients versus Number of Generations Used in the Calculation.

A. Lehrerleut

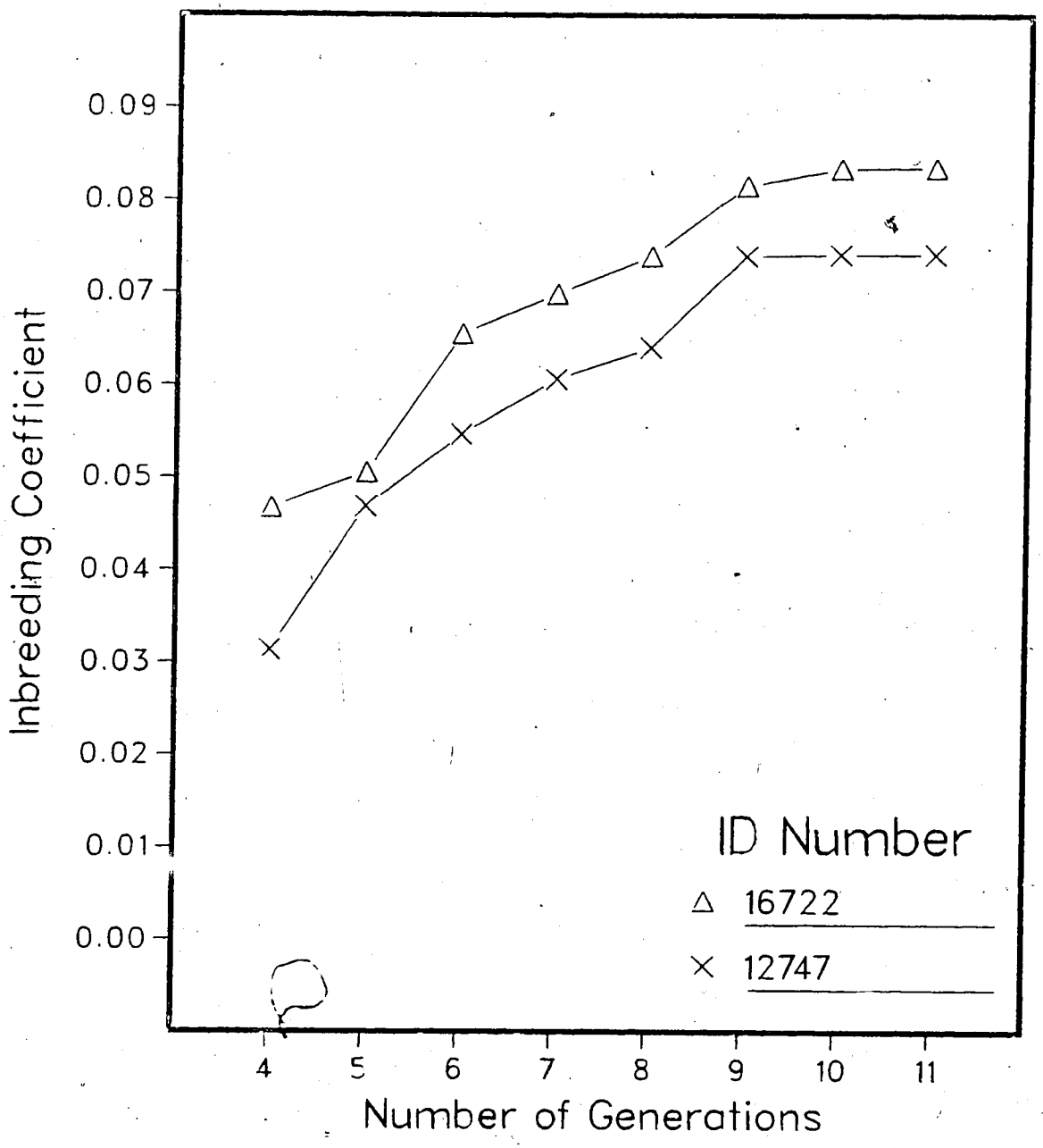


Figure 4.1: (continued)

B. Schmiedeleut

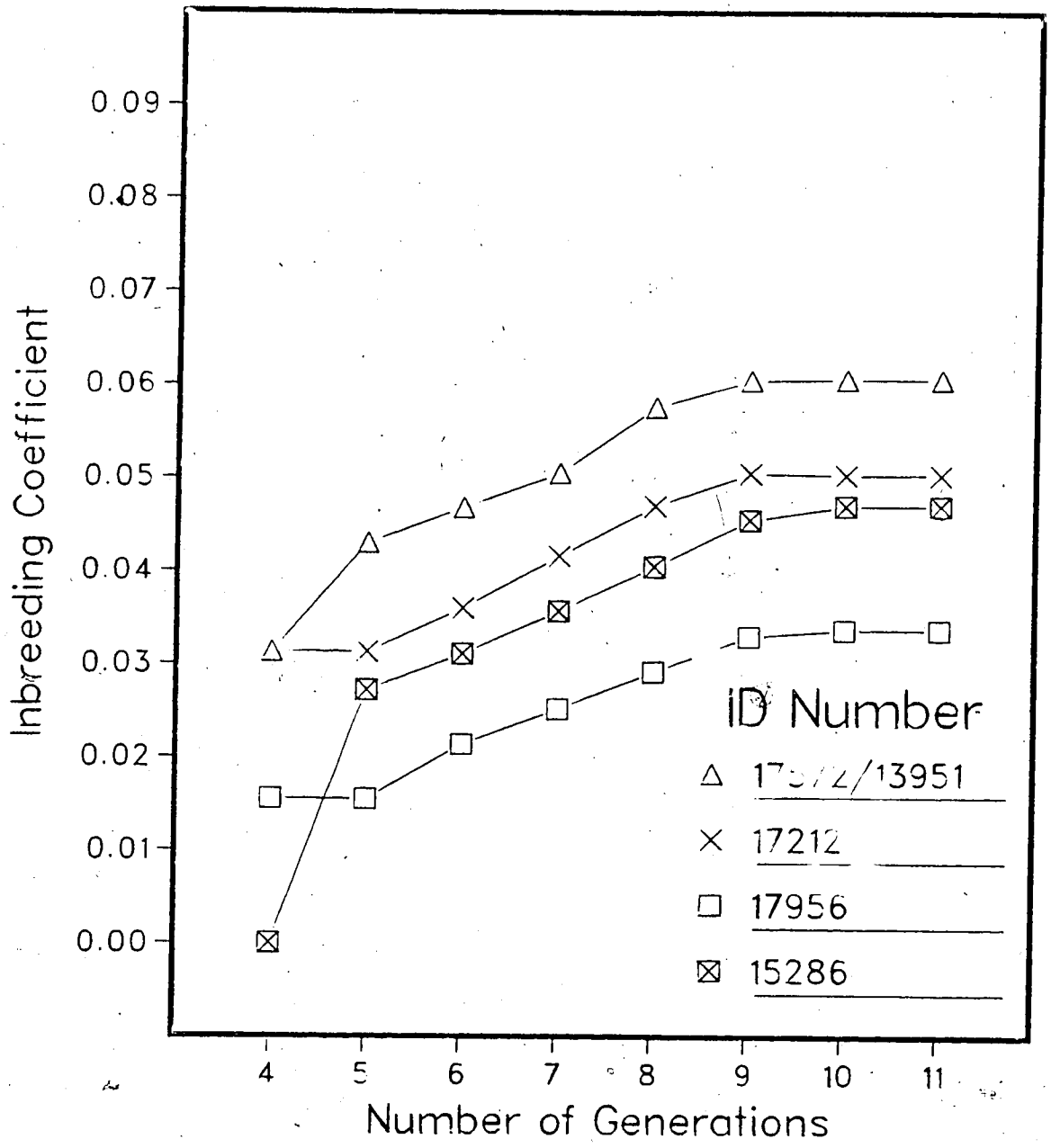


Figure 4.1: (continued)

C. Dariusleut

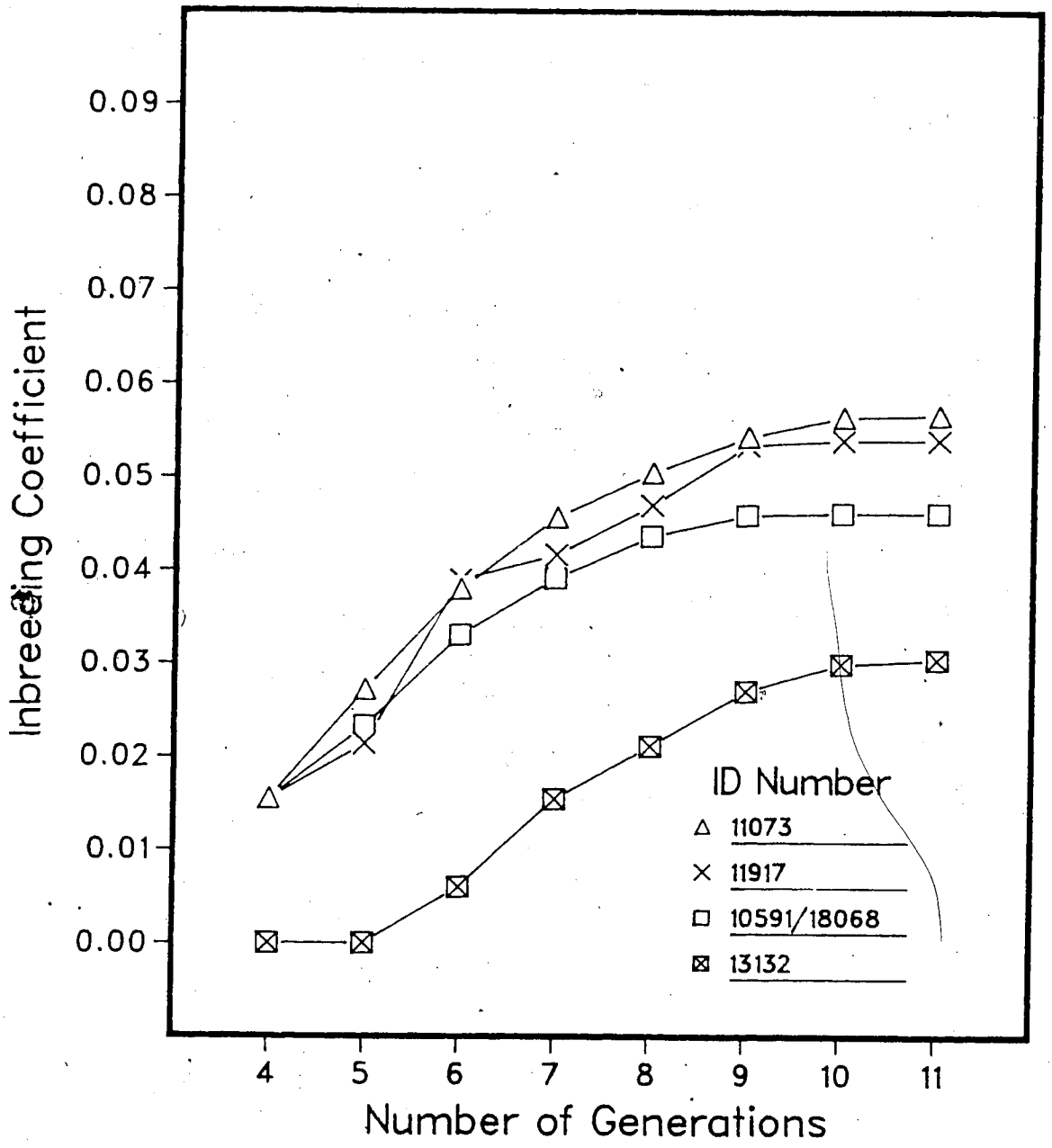
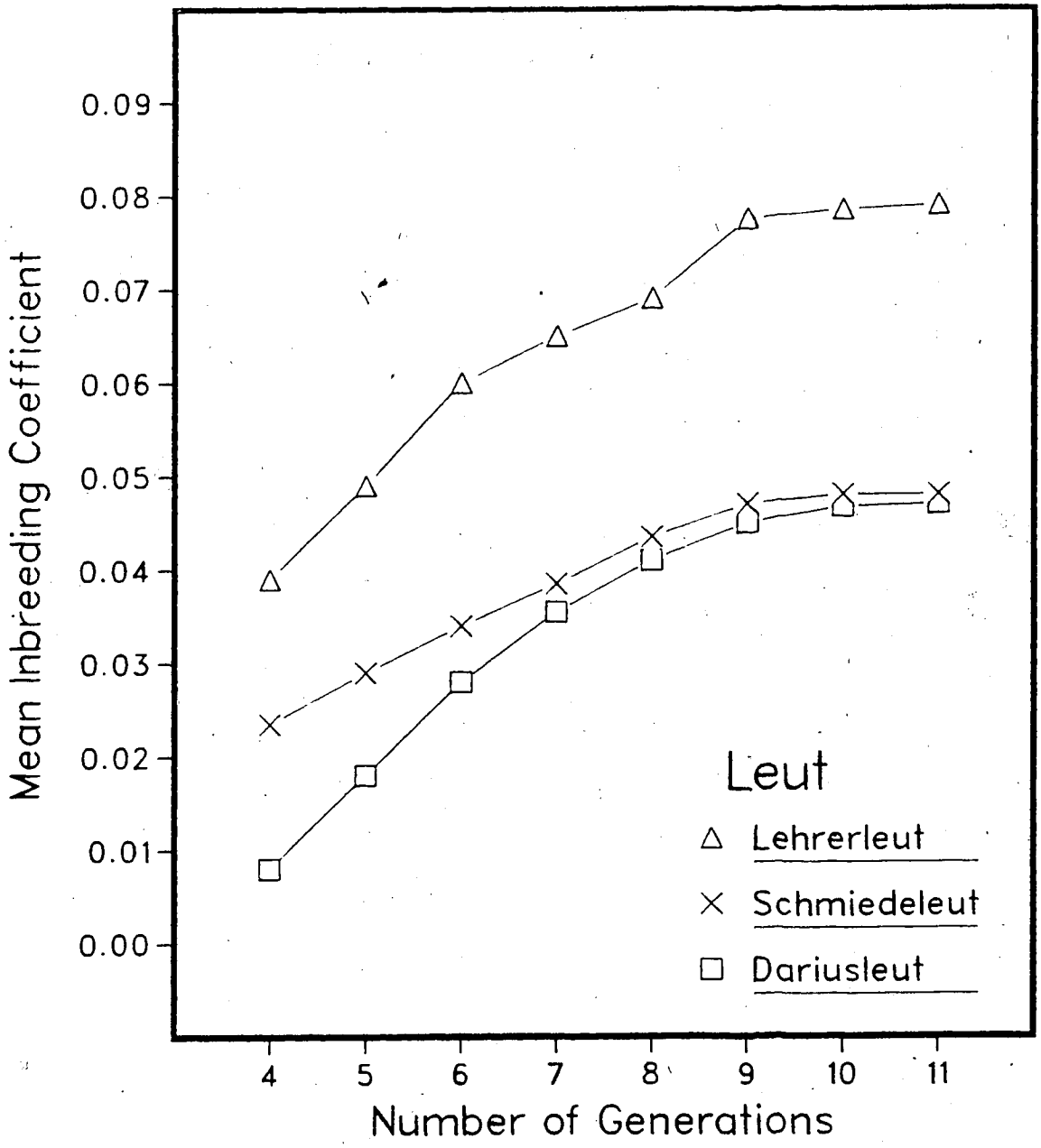


Figure 4.2: Mean Inbreeding Coefficients of the Bowen-Conradi Syndrome Patients, by Leut, versus Number of Generations Used in the Calculation.



inbreeding coefficient is between 89% and 99.9% of its ultimate value, determined when all known ancestry is used. There is a positive correlation between the values of the inbreeding coefficients at each generation from four to nine and the values of the inbreeding coefficients calculated on total known ancestry. (Kendall's tau ranges from .579 for F at four generations versus total F, to .956 for F at generation nine versus total F).

Relationship between Completeness and F

The maximum pedigree depth for the parents of the affected sibships ranges from eight to ten generations: eight to ten generations for fathers and nine to ten generations for mothers. The overall average depth and the mean depth by leut are shown in Table 4.6. It can be seen that the Dariusleut and Lehrerleut pedigrees generally have more depth and are 100% complete to a greater depth than are the Schmiedeleut pedigrees. The overall average completeness of the pedigrees of the affected sibships was 98.5% at the sixth generation and 97% at the seventh. (See Table 4.7)

The pedigrees of the affected sibships are complete for between four and seven generations: four to seven generations for paternal lines and five to seven generations for maternal lines. When the affected sibships are considered, there is no correlation between maximum pedigree depth and the value of the inbreeding coefficient calculated on the total known ancestry (Kendall's tau = 0),and the correlation between the depth to which the pedigrees are 100% complete and the inbreeding coefficient calculated on the total known ancestry is negative (Kendall's tau = -0.31). Similarly, there is a negative correlation between the percent completeness of the pedigrees of the affected sibships at both six and seven generations and the inbreeding coefficients calculated on the total known ancestry (Kendall's tau — percent completeness at six generations versus total F: -0.43; percent completeness at seven generations versus total F: -0.35. However, when the parents of the affected sibships are considered, there is a small positive correlation between both (a) maximum pedigree depth and (b) the depth to which the pedigree is 100% complete and the value of the inbreedinng coefficient when all known ancestry is used in the calculation, for both paternal and maternal lines. (Kendall's tau — maximum pedigree depth versus total F: paternal 0.58, maternal 0.29, combined 0.48;

Table 4.6: Depth of the Bowen-Conradi Syndrome Pedigrees

		Affected				Paternal			Maternal
Sibship Number	Leut	F*	Gmax+ (gen)	Gmax (gen)	100% to** (gen)	F	Gmax (gen)	100% to (gen)	F
1	D	.0301	11	10	7	.0577	10	7	.0611
2	D	.0462	10	9	6	.0295	9	6	.0282
3	D	.0566	11	10	7	.0721	9	7	.0390
4	D	.0541	10	9	7	.0338	9	7	.0583
mean	D	.0468	10.5	9.5	6.75	.0483	9.5	6.25	.0467
5	L	.0834	11	10	6	.0574	9	5	.0388
6	L	.0742	10	9	5	.0388	9	7	.0651
mean	L	.0788	10.5	9.5	5.5	.0481	9	6	.0520
7	S	.0502	10	9	4	.0142	9	6	.0212
8	S	.0338	10	9		.0143	9	6	.0254
9	S	.0469	11	10	5	.0318	9	6	.0237
10	S	.0605	10	8	5	.0354	9	5	.0431
mean	S	.0477	10.3	9	4.75	.0239	9	5.75	.0284

* F is calculated on total known ancestry
\+ maximum number of generations
** depth to which ancestry is completely known (generations)

Table 4.7: Percent Completeness of Pedigrees

Sibship Number	Generation*					% Completeness at Generation Number		
	4	5	6	7	8	6	7	8
1	100	100	100	100	91	100	100	95
2	100	100	100	95		100	98	
3	100	100	97	97		98	98	
4	100	100	100	100	87	100	100	93
5	100	100	97	95		98	94	
6	100	100	97	95		98	97	
7	100	94	94	91		98	97	
8	100	100	97	94		98	96	
9	100	100	97	92		98	95	
10	100	100	94	91		97	94	
mean	100	99	99	95		98.5	97	

Sibships are as in Table 4.6

* all pedigrees are 100% complete in generations 1 - 3

depth to which pedigree is 100% complete versus total F: paternal 0.08, maternal 0.22).

That there is no significant correlation between the value of the inbreeding coefficients of the affected sibships and a) the depth of the pedigree, b) the depth to which ancestry is completely known, and c) the percent completeness of the pedigrees, agrees with the observations of Cross (1967) in the Old Order Amish. This may be due to the fact that it is the way that the individual is related to his known ancestors rather than the *number* of known ancestors that determines the value of his inbreeding coefficient. In addition, if the major component of a (high) inbreeding coefficient is due to close consanguinity between the parents of the individual, this may mask the effect of multiple distant relationships. It is the parents' sharing of remote ancestry which would result in a correlation between increasing depth of pedigree and increasing value of inbreeding coefficient.

Most Likely Source of the Bowen-Conradi Syndrome Allele

Since knowledge of the most likely source of a deleterious autosomal recessive allele in the Hutterite population may be of value in genetic counselling and diagnosis, an attempt was made to determine the ancestor (couple) most likely to have introduced the Bowen-Conradi syndrome allele into the population. The approach used was similar to that used by Kidd, *et al.* (1980), in their analysis of propionic acidemia in the Old Order Amish. The products of the expected proportions of alleles contributed by each common founder to all parents of affected sibships (from ALLELE), and to the sibships themselves, were determined. In addition, the average proportional direct contibution of each of the common founders to the inbreeding of all affected sibships was determined (from KUDO).

When the numbers so determined are used as 'relative probabilities', both methods resulted in the same couple being most likely to have contributed the Bowen-Conradi syndrome allele to the population. This couple is about 1.5 times more likely to have done so than is the next most likely couple. However, as pointed out by Thompson (1983), this type of analysis requires information on the normal descendants of the ancestral set, and a more sophisticated computational method, neither of which was available.

Frequency of the Bowen-Conradi Syndrome Allele

A number of approaches have been used to estimate the frequency of the Bowen-Conradi syndrome allele.

Under the assumption that the sibships of the parents of the affected infants represent *all* sibships in the population which could have produced a heterozygote for the allele, the minimum number of heterozygotes in the parental generation can be determined. Since there are 29 sibships among the parents of the 15 affected sibships, and the mean completed family size of the Hutterites has been estimated at 10.4 (Eaton and Mayer, 1955), the estimated number of heterozygotes in their sibships will be 150 (29 x 10.4 x .5). Using the age and sex distribution of the Alberta Hutterite population of 1971 (Laing, 1975) as representative of the entire Hutterite population, approximately 35 percent of all Hutterites are in the 'parental' age group (20 - 49 years). Based on the population size estimate of 20,300 individuals in 1976 (Morgan, 1983), there are an estimated 7105 Hutterites in this group. Thus, the minimum frequency of heterozygotes in the population is about two percent, and of the allele frequency is 0.011.

A second estimate of the Bowen-Conradi syndrome allele frequency was obtained from the number of definite cases ascertained (15), and an estimate of the number of Hutterite births during the years spanning the births of the cases (11693). This yields an allele frequency estimate of 0.036.

The third estimate of the allele frequency, 0.027, was based on the average allelic contribution of the most likely carrier ancestor to nine of the affected sibships.

The three allele frequency estimates are presented to give an indication of the range in which the actual Bowen-Conradi syndrome allele frequency may fall.

V. CONCLUSIONS

The Bowen-Conradi syndrome is possibly the most common deleterious, autosomal recessive disorder in the Hutterite population. The fact that some parents of affected sibships are not particularly closely related implies that the allele for this disorder is widespread in the population. In addition, the Bowen-Conradi syndrome allele may be present at high frequency.

Unfortunately, the number of founders common to all parents of affected sibships is large, and it was not possible to determine, with any degree of confidence, the ancestral couple who are most likely to have contributed the Bowen-Conradi syndrome allele to the population. Thus, it is not feasible to use descent from a particular ancestor (or the most likely couple) to identify couples in the contemporary population who may be at high risk for having an affected child.

The frequency of the Bowen-Conradi syndrome allele is probably elevated in the Hutterite population, and it is likely that one or more affected infants will continue to be born each year. (Table 2.1 indicates 16 cases born between 1967 and 1982). Early diagnosis of the syndrome may be facilitated by alerting physicians who provide health care to Hutterites to the risk of this disorder in the population.

Segregation analysis was not attempted in this study because the numbers were small, and the ascertainment of cases varied. However, identification of more affected sibships may permit a segregation analysis to be done. In addition, identification of more affected sibships will allow a better estimate of the allele frequency to be made.

There are several areas in which more information on the Hutterite population would prove useful for studies of this type. There are no published data on normal Hutterite infants. Information such as average birthweight and birthlength and the incidence of congenital malformation would be useful for the discussion of phenotypic variability in a disorder such as the Bowen-Conradi syndrome . Knowledge of the distribution of relationships of marriage partners in the different subdivisions of the Hutterite population could aid in discerning whether the incidence of a genetic disorder was being augmented by non-random mating in the population.

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APPENDIX 1

Major Features of Trisomy 18, 'Pseudotrisomy' 18 and the Bowen-Conradi Syndrome

The following table is an expansion of Table 2.2. It lists the major reported features of trisomy 18, 'pseudotrisomy' 18 and the Bowen-Conradi syndrome , giving the proportion of trisomy 18 cases reported with the feature, and individual descriptions of 21 of the 'pseudotrisomy' 18 and 14 of the Bowen-Conradi syndrome patients. References to the individual cases reported are given at the end of the table.

REFERENCE		1	2	3	4	4	5	6
(case #)	Trisomy 18 % with trait				1	2		
sex	77% f	m	m	f	f	m	f	m
mother's age at birth of child (yrs)	¬33	26	24	23	18	22		
gestation (wks)			40	37		40		
breech	1/3↑ ;1/3↓							
birthweight (gms)	2340	3000	2000	2475	2380	2780		
birthlength (cm)			44		47	49.5		
head circumference (cm)					32	36		
dolichocepally	93						+	
prominent occiput	>50							
microcephally	10-50				+			
ptosis			+					
small palpebral fissures	>50			+				
hypertelorism	81						?	
epicanthus	41							
small mouth	>50		+	+				
micrognathia	92	+	+	+		+	+	+
palate (1)		A	C	C	H,A	H,A		H,A
malformed ears	88			+		+	+	
lowset ears	88	+	+	+			+	+
large nose		-					+	
prominent bridge of nose		-	-					
short neck	10-50						+	
short sternum	68				+	+	+	
shield chest	10-50				+	+	+	
distally implanted thumbs	52			+				
camptodactyly &/or clinodactyly	89			+			+	+
hypoplastic nails	63			+			+	
restricted hip &/or knee	10-50			+	+	+		+
flexion deformity, wrist	10-50					+		
short, dorsiflexed hallux	>50	+				+		
calcaneovalgus	52					+		+
clubfoot (2)	10-50	B			+	+		
'rockerbottom' feet	10-50	+		+				
dislocated hips	<10					+		
overlapping fingers, clenched hand	>50	+					+	+
cardiac anomaly	85		+	+	+	+		+
renal anomaly	62		+	+	+	+	+	
cryptorchidism	100	?	+	F	F	+	F	
other genital						+		
hypertonic	50		+	+				
hypotonic	36				+	+	+	
depressed Moro & suck reflexes					+	+	+	
superficially normal brain	92						+	
feeding difficulty	96		+					
failure to thrive	96			+			+	
developmental retardation	96			+				
respiratory distress at birth								
age at death	50% <2m, 90% <1y	5+m	5w	5m	6d	43 h	3m	

REFERENCE		7	7	7	7	7	7	7
(case #)	Trisomy 18 % with trait	1	2	3	4	5	6	7
sex	77% f	m	f	f	m	f	f	m
mother's age at birth of child (yrs)	¬33	22	25	20	21	21	26	
gestation (wks)		35	40	39	40	28	35	29
breech								
birthweight (gms)	2340	2700	2750	2850	2855	2100	2330	1680
birthlength (cm)		48	48	49	51.5	42	46	41
head circumference (cm)		31	31	32	33			28.5
dolichocepally	93							+
prominent occiput	>50							+
microcephally	10-50	+	+	+	+			+
ptosis			+	+	+			
small palpebral fissures	>50	+	+	+	+			+
hypertelorism	81		+	+	+	+	+	
epicanthus	41		+	+				
small mouth	>50		+	+				
micrognathia	92	+	+	+	+		+	+
palate (1)								
malformed ears	88	+	+	+	+			+
lowset ears	88	+	+	+	+			+
large nose					+	+	?	+
prominent bridge of nose								
short neck	10-50							
short sternum	68							
shield chest	10-50							
distally implanted thumbs	52			+	+	+		
camptodactyly & / or clinodactyly	89	+	+	+	+	+	+	+
hypoplastic nails	63							
restricted hip & / or knee	10-50							
flexion deformity, wrist	10-50	+	+				+	+
short, dorsiflexed hallux	>50			+	+			
calcaneovalgus	52					+		
clubfoot	10-50			B?	B		B	
'rockerbottom' feet	10-50	+	+	+				
dislocated hips	<10							
overlapping fingers, clenched hand	>50	+	+	+	+	+	+	+
cardiac anomaly	85			+				
renal anomaly	62							
cryptorchidism	100		F	F		F	F	?
other genital			+					
hypertonic	50	+	+	+	+			
hypotonic	36							
depressed Moro & / or suck reflexes								
superficially normal brain	92							
feeding difficulty	96							
failure to thrive	96		+	+	+			
developmental retardation	96		+	+	+			
respiratory distress at birth		+	+	+	+			
age at death	50% <2m, 90% <1y	3d	38m	4y	3y	30d	3m	10d

REFERENCE		7	7	7	7	7	7	8
(case#)	Trisomy 18 % with trait	8	9	10	11	12	13	
sex	77% f	m	m	mf	mf	m	mf	m
mother's age at birth of child (yrs)	¬33		30	29	28	28	15	21
gestation (wks)	1/3↑;1/3↓	40	40	39	34	41	37	40
breech								+
birthweight (gms)	2340	1960	3200	2500	2360	2900	2540	1380
birthlength (cm)		44				53		
head circumference (cm)		31				36.8	34	
dolichocepally	93	+						+
prominent occiput	>50	+					+	+
microcephally	10-50	+						
ptosis					+			
small palpebral fissures	>50	+	+?			+		+
hypertelorism	81	+	+		+			
epicanthus	41							
small mouth	>50	+	+				+	
micrognathia	92	+		+	+	+		+
palate (1)			C	C	C			H
malformed ears	88	+	+	+	+			+
lowset ears	88		+	+	+			
large nose		+	+					+
prominent bridge of nose								
short neck	10-50							
short sternum	68							
shield chest	10-50							
distally implanted thumbs	52							
camptodactyly & / or clinodactyly	89	+	+	+	+	+	+	+
hypoplastic nails	63							+
restricted hip & / or knee	10-50							
flexion deformity, wrist	10-50							+
short, dorsiflexed hallux	>50	+						
calcaneovalgus	52							
clubfoot (2)	10-50	B		B				
'rockerbottom' feet	10-50		+	+	+			+
dislocated hips	<10							+
overlapping fingers, clenched hand	>50	+	+	+	+	+	+	
cardiac anomaly	85							
renal anomaly	62							
cryptorchidism	100	?						+
other genital							+	+
hypertonic	50							
hypotonic	36		+?			+		
depressed Moro & suck reflexes								
superficially normal brain	92							-
feeding difficulty	96							
failure to thrive	96							
developmental retardation	96		+					
respiratory distress at birth		?	+	+	+	+		+
age at death	50% <2m, 90% <1y	1d	3m	3d	4d	6 d	4d	36h

REFERENCE		9	10	10	11	11	11	11
(case #)	Trisomy 18 % with trait		1	2	1	2	3	4
sex	77% f	f	m	m	m	m	m	f
mother's age at birth of child (yrs)	¬33	33	29	34	33	27	35	23
gestation (wks)	1/3↑ ;1/3↓	term	40	37	38	term	42	term
breech				+	+	+		+
birthweight (gms)	2340	2730	2040	2013	2210	2030	2097	2622
birthlength (cm)			42	43	46	45.5	43	
head circumference (cm)			31	30	31	30.3	30	<31
dolichocepally	93	+	+	+	+	+	?	+
prominent occiput	>50						+	
microcephally	10-50	+	+	+	+	+	+	+
ptosis							+	
small palpebral fissures	>50	+						
hypertelorism	81					?		
epicanthus	41						+	+
small mouth	>50							
micrognathia	92	+	+	+	+	+	+	+
palate (1)		C			S	S		C
malformed ears	88	+	+	+	+	+	+	+
lowset ears	88	+						
large nose		?	+?	+	+	+?	+	?
prominent bridge of nose		+	+	+	+	+	+	?
short neck	10-50						+	
short sternum	68							
shield chest	10-50							
distally implanted thumbs	52					-		
camptodactyly & / or clinodactyly	89	+	+	+	+	+	+	+
hypoplastic nails	63				+	+	+	
restricted hip & / or knee	10-50		?	+	+	+	+	+?
flexion deformity, wrist	10-50			?				
short, dorsiflexed hallux	>50							
calcaneovalgus	52							
clubfoot (2)	10-50					L		
'rockerbottom' feet	10-50		+	+	+	+	+	+
dislocated hips	<10							+
overlapping fingers, clenched hand	>50	+			+		+	+
cardiac anomaly	85	+						
renal anomaly	62			+				
cryptorchidism	100	F	+	+	+	+	-	F
other genital								
hypertonic	50	+						
hypotonic	36							
depressed Moro & / or suck reflexes			+	+		+	+	
superficially normal brain	92				+			
feeding difficulty	96		+	+?	+	+	+	+
failure to thrive	96	+	+?	+		+?	+	+?
developmental retardation	96	+				+	+	
respiratory distress at birth					+?			
age at death	50% <2m, 90% <1y		16d	6.5m	16d	4m	8m	6w

REFERENCE		11	11	11	12	13	14	15
(case #)	Trisomy 18 % with trait	5	6	7*				
sex	77% f	f	f	m	f	m	f	f
mother's age at birth of child (yrs)	¬33	28	26	28	22	25.5	30	31.5
gestation (wks)	1/3↑;1/3↓		44	37	40	42.6	42	39
breech					+	+		
birthweight (gms)	2340	2750	1821	2300	2350	2443	2150	1975
birthlength (cm)		48		44	43	46		
head circumference (cm)		31		29.5	30.5	33		
dolichocepaly	93	+	+	+	+	+	-	
prominent occiput	>50			+		+		
microcephally	10-50	+	+?	+	+	+	+	
ptosis								
small palpebral fissures	>50							
hypertelorism	81							
epicanthus	41							
small mouth	>50		+					
micrognathia	92	+	+	+	+		+	+
palate (1)				S	H,A	H	?	
malformed ears	88	?	?	+	+/		-	
lowset ears	88							
large nose		?	?	+	+			
prominent bridge of nose		?	+	+	+	+	+	+
short neck	10-50	+		+		+	-	?
short sternum	68			-	+			
shield chest	10-50							
distally implanted thumbs	52							
camptodactyly &/or clinodactyly	89	+	?	+	+	-	-	+
hypoplastic nails	63			+				
restricted hip &/or knee	10-50	+	+	+	+	+	+	+
flexion deformity, wrist	10-50	+						
short, dorsiflexed hallux	>50							
calcaneovalgus	52							
clubfoot (2)	10-50							
'rockerbottom' feet	10-50	+	?	+	+		+	+
dislocated hips	<10							
overlapping fingers, clenched hand	>50			+				
cardiac anomaly	85							
renal anomaly	62							
cryptorchidism	100	F	F	+	F	-?	F	F
other genital						+		
hypertonic	50							
hypotonic	36							
depressed Moro &/or suck reflexes			+		+	+		
superficially normal brain	92					+		
feeding difficulty	96	+	+		+	+	+	+
failure to thrive	96		+		+			
developmental retardation	96			+?				
respiratory distress at birth			+?	+				
age at death	50% <2m, 90% <1y	2w	6w	2w	93w	4m	4w	30.5 m

NOTES:

* addendum

+ present

- absent

? questionable, or from photograph

(1) Palate: A - arched, C - cleft, H - high, S - shelves

(2) Clubfoot: B - bilateral, L - left, R - right

REFERENCES:

1 de Grouchy (1965)

2 Szotawa and Kowalski (1965)

3 Hook and Yunis (1965)

4 Simpson and German (1969)

5 Taylor (1968)

6 Burks and Sinkford (1964)

7 Le Marec et al. (1981)

8 Lazyuk et al. (1980)

9 Olney and Buehler (1983)

10 Bowen and Conradi (1976)

11 Hunter et al. (1979)

12 ID# 11073

13 ID# 13132

14 ID# 10433

15 ID# 11917

APPENDIX 2

Computer Programs

CONDENSE

A FORTRAN program written by K. Morgan. CONDENSE replaces the external identification numbers of a pedigree with a packed array of subscripts. The program assigns numbers from 1 to n to the individuals in the input deck. In addition, an individual's father and mother are assigned the appropriate subscripts. Additional numbers are created if necessary: for example, founders are added if they do not appear in the input deck as individuals but only as parents of individuals in the deck.

KUDO

A FORTRAN program written by J. MacCluer (MacCluer et al., 1967), modified by K. Morgan. KUDO computes the coefficient of inbreeding for autosomal and/or X-linked genes, using the method described by A. Kudo (Am. J. Human Genetics 14:426-432, 1962) and by A. Kudo and K. Sakaguchi (Am. J. Human Genetics 15:476-480, 1963). Inbreeding coefficients, F, may be calculated for specified individuals in a pedigree or for a population, in which case F for each sibship and the mean F for the population are computed. In addition, the population may be subdivided into generations and a mean F and cumulative F computed every generation. The common ancestor, length and inbreeding coefficient of every inbreeding loop for a specified individual can be obtained. There is no restriction on the closeness of inbreeding except that selfing is not permitted. The version used in this study utilised pedigree decks that were preprocessed using the program CONDENSE.

TRACEQ

A FORTRAN program written by K. Morgan. TRACEQ determines the ancestors in a pedigree who are founders. In addition, the program determines a path (linked list) of relatives of one or more index cases. Parents preceed their offspring in the path. The pedigree deck must be preprocessed using the program CONDENSE.

PRUNE

A FORTRAN program written by K. Morgan. PRUNE determines the set of common ancestors for two or more index cases. The set of common relatives (i.e. individuals who are related to all index cases; the non-founders who are in the line of descent from a founder to an index case) is also determined. For each index case, the list of founders and a list of relatives who are non-founders is required. PRUNE removes individuals who are common founders if the founder couple had only one offspring in the pedigree, and replaces them with individuals from the common relative list. The program continues until every founder (except for individuals involved in more than one marriage) has more than one offspring in the pedigree. The founders and path of relatives for each index case is obtained from an independent run of the program TRACEQ.

ALLELE

A FORTRAN program written by K. Morgan. ALLELE calculates the contribution of an allele from each founder to the genotype of an index case. This value can be considered either the probability that an allele in the index case came from a particular founder, or the proportion of an index case's alleles that are expected to have come from the founder. The program requires the pedigree deck to be preprocessed using the program CONDENSE, and a set of founders and path of relatives for each index case, from TRACEQ.