Quebec Cooperative Study of
Friedreich's Ataxia

Genetic and Family Studies in Friedreich's Ataxia

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SUMMARY: *This study consists of two parts: 1. A detailed genetic analysis of 35 sibships in which 58 individuals were affected with Friedreich's ataxia; and 2. Clinical and laboratory examinations of parents and siblings, in an attempt at carrier detection and diagnosis of the pre-clinical state.*

The increased parental consanguinity, the lack of affected individuals in other generations, and the lack of significance of extrinsic etiological variables, all suggested an autosomal recessive mode of inheritance, and this was confirmed by formal genetic analyses, employing several different methods.

Associated abnormalities in our series of 58 patients included cardiomyopathy (51.7%), diabetes mellitus (19.0%), optic atrophy (5.2%), nerve deafness (5.2%) and congenital malformations (6.9%). The incidence of diabetes mellitus, congenital malformations, and epilepsy and/or febrile convulsions was elevated in first degree relatives of patients with Friedreich's ataxia.

Examinations in first degree relatives revealed an increased frequency of neurological and skeletal abnormalities (26.3%), but no abnormalities on neuro-ophthalmological examination. Frequent EMG abnormalities were noted in parents (56.3%), but not in siblings; and these could usually be attributed to extrinsic causes. There was an increased incidence of ECG abnormalities in both parents (50.0%) and siblings (25.0%, and some of these abnormalities may represent cardiomyopathy. An increased frequency of EEG abnormalities was also recorded in parents (14.3%) and siblings (27.2%), but these were not specific. None of these examinations resulted in a practicable method of carrier detection or preclinical diagnosis.

Since carrier detection is still not feasible, genetic counselling remains the only possible means of prevention of Friedreich's ataxia.

RÉSUMÉ: *La présente étude comprend deux parties: 1. Une analyse génétique détaillée de 35 familles dont 58 individus sont atteints d'Ataxie de Friedreich. 2. Une étude clinique et d'examens de laboratoire des parents et de la fratrie dans le but de définir si possible la détection des porteurs et le diagnostic de l'état pré-clinique.*

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INTRODUCTION

The hereditary nature of Friedreich's ataxia was recognized by Friedreich in the same year as the original description of the disease (Friedreich, 1863). However, the exact mode of inheritance was disputed and the hereditary factor was believed to be dominant by some and recessive by others. Brain (1925) concluded that the inheritance of the disease could not be explained by a single Mendelian character, and postulated that the disease depends on the presence of two Mendelian characters, one dominant and the other recessive, the recessive character acting as a modifying gene. Hanhart (1923) analyzed a series of 46 Friedreich's ataxia patients in Switzerland, and found that the proportion of affected siblings approached the 25 per cent expected for a recessive mode of inheritance.

Bell and Carmichael (1939), in a classical monograph, collected all the pedigrees with more than one case of Friedreich's ataxia which had been published to that date. Of 136 pedigrees, 124 were considered to represent probably recessive inheritance, while 12 were considered to be probably dominant. The mean age of onset was 12 years in the recessive group, and 20 years in the dominant group. In their own clinical material of 30 sibships collected in England, Bell and Carmichael found no instance of dominant inheritance, and the proportion of affected siblings was approximately 25%.

Sjögren (1943), in a clinical and genetic study in Sweden of 188 patients with heredo-ataxia in 118 families, found 84 cases of Friedreich's ataxia, and concluded that these had a very high probabil-

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ity of autosomal recessive inheritance.

Boyer et al (1962), in a series of 26 sibships with Friedreich's ataxia studied in the United States, found recessive inheritance in 24 sibships, and dominant inheritance in two sibships.

Pedigrees with hereditary ataxia showing partial sex-linkage have been reported (Schut, 1950), but in these families several clinical forms have occurred. Sex-linked recessive inheritance has also been reported (van Bogaert and Moreau, 1939).

The genetic studies of Friedreich's ataxia have recently been reviewed by Pratt (1967) and Tyrer(1975). Pratt (1967) concluded that the mode of inheritance in Friedreich's ataxia appears to be usually recessive, and that the smaller group with dominant inheritance may contain atypical examples of other forms of heredo-ataxia.

Despite these various studies, a uniform mode of inheritance for classical Friedreich's ataxia has not been confirmed, and there is considerable confusion regarding the genetic transmission of the disorder, probably because of the inclusion of atypical or mixed forms, which may have different modes of inheritance. Accurate determination of the mode of inheritance of classical Friedreich's ataxia is important, since genetic counselling is still the only means of prevention of the disease.

A number of authors have noted occasional partial manifestations of the features of Friedreich's ataxia in relatives who do not themselves develop the full-blown disease (Bell and Carmichael, 1939). However, in the absence of a known biochemical defect, carrier detection and diagnosis of the pre-clinical state are not yet feasible.

The present study was undertaken with the following objectives:

1. To obtain a large number of pedigrees of patients with a diagnosis of classical Friedreich's ataxia.
2. To determine the mode of inheritance of the disorder in these families by formal genetic analysis, and to rule out the significance of other factors in the etiology of the disease.
3. To determine the incidence of various associated abnormalities, eg. cardiomyopathy, diabetes mellitus, scoliosis, and optic atrophy, in patients and relatives.
4. To carry out various clinical and laboratory studies in parents and siblings of patients with Friedreich's ataxia in an attempt to find a means of carrier detection and early diagnosis.

CLINICAL MATERIAL AND METHODS

The clinical material consisted of fifty-eight patients in thirty-five sibships, in which one or more individuals were affected with Friedreich's ataxia (Table I). This group of patients and families is different from the series of fifty patients investigated in the other studies reported in this volume, and there was no overlap between the two groups. The families were found in the files of the following hospitals: Montreal Neurological Hospital — 15; Montreal Children's Hospital — 7; Hôpital Sacré-Coeur — 5; Hôtel Dieu de Montréal — 4; Hôpital Ste. Justine — 3; and the Shriner's Hospital for Crippled Children — 1. Many of the patients had been investigated at several of these hospitals.

The diagnostic criteria employed in ascertaining our patients are outlined in another paper. Care was taken to confirm the diagnoses in patients who had died or who were not available for examination, and only patients whose records were sufficiently detailed and complete to enable unequivocal diagnosis of Friedreich's ataxia were included. Of the 58 patients included in the series, 55 (94.8%) had detailed clinical examinations, and only three were confirmed by history alone, when one or more of their siblings had a definite diagnosis of Friedreich's ataxia. 53 of the patients (91.4%) had complete neurological investigations as inpatients: 16 (27.6%) had EMG studies; two had both an EMG and sural nerve biopsy; 5 (8.6%) had cardiac catheterization; and 2 patients were autopsied.

Detailed family and pregnancy histories were obtained from each of the families. The family histories included information on ethnic and geographic origin, consanguinity, state of health and causes of death of family members, and detailed pedigrees, tracing the families back as far as possible. The genealogical studies on these families are included with those on the fifty patients reported elsewhere in this survey. The pregnancy histories included such factors as: drug ingestion, radiation exposure, exposure to contagious disease, and maternal illness or operations during pregnancy; type of delivery; and birth weight. This information was recorded for all pregnancies including those which resulted in unaffected siblings, as well as for those terminating in abortion or stillbirth.

Following the initial interviews, detailed neurological and functional examinations, including the Mayo Clinic Scale and the Northwestern Functional Scale, were carried out on patients, parents, and siblings. These individuals were also encouraged to have electromyographic, electrocardiographic and electroencephalographic examinations, as well as detailed neuro-ophthalmological assessments. Several of the families also participated in the studies of pyruvate metabolism reported elsewhere in this survey. Although the patients themselves were encouraged to come in for these examinations in order to confirm the diagnoses as well as to follow the progress of their disease, the main emphasis of the clinical portion of this study was on the unaffected parents and siblings.

The electromyographic studies included the following: Motor and sensory conduction velocities and latencies; evoked potentials; "H" reflex; "M" waves; "F" wave conduction velocities; refractory period studies, and EMG needle studies of muscle. These studies were carried out in the EMG laboratory of the Montreal Neurological Hospital, under the supervision of Dr. Andrew Eisen. The electrocardiographic studies consisted of routine ECG recordings performed in the ECG

laboratory of the Royal Victoria Hospital. The records were reviewed by Drs. David Stubington and André Pasternac of the Cardiology Department of the Royal Victoria Hospital. The electroencephalographic studies consisted of routine 8- or 16-channel recordings performed in the EEG Department of the Montreal Neurological Hospital. The only provocative techniques used were hyperventilation and intermittent photic stimulation. The records were reviewed, and some of the findings in the family studies have been reported in the paper dealing with electroencephalography in Friedreich's ataxia. The neuro-opthalmological assessments included visual acuity, visual fields, fundoscopy, range of ocular movements, optokinetic responses, testing with colour plates, and measurement of intraocular pressures. These were performed by Dr. Trevor Kirkham at the Montreal Neurological Hospital.

The number of patients and relatives who underwent each of these studies is summarized in Table II.

RESULTS

The clinical and genetic date on each of the 35 sibships studied is summarized in Table I. Before proceeding to a formal genetic analysis of the data, a number of variables on which information was obtained from the family and pregnancy histories were analyzed.

Ethnic origin

The ethnic and geographic origin of the grandparents in the 35 sibships is summarized in Table III. Twenty-two of the thirty-five families (62.8%) were of French-Canadian origin and five families (14.2%) were Anglo-Saxon. There were two families from Europe — Greek and Italian respectively — and one from Syria. The remaining five families represented mixtures of the above ethnic groups, as well as one mixed French-Canadian and North American Indian family. When the ethnic origins of the 140 grandparents are considered individually, 96 or 68.5% were French-Canadian and 27 or 19.3% Anglo-Saxon, with the remaining 17 grandparents (12.2%) being of European, Asian and North American Indian descent.

The distribution of ethnic origins found in the Friedreich's ataxia group corresponds very closely to that of the general population of the Montreal area, and would thus seem to indicate that there is no ethnic predilection for the disease. The absence of Jewish cases should be noted, since Jews comprise about 5% of the population of the Montreal area. However, this may represent a sampling error due to the relatively small number of families studied.

The birthplaces of the French-Canadian grandparents, were in a radius of about 100 miles from Montreal, and the remainder came from almost all areas of the Province of Quebec. There would seem to be no evidence for a concentration of grandparental birthplaces in certain areas. This may be influenced by the method of ascertainment of our families, since detailed family histories and clinical studies on relatives could be done much more easily on families residing in the greater Montreal area.

Consanguinity

The consanguinous marriages in parents and grandparents are listed in Table IV. There was close parental consanguinity in three families (8.6%), and in two further families the grandparents were first cousins. The rate of first cousin marriages in the parents (5.7%) is elevated 4- to 6-fold over that in the general population, but is not as high as that seen in rare recessive disorders. On the other hand, some of the French-Canadian parents may be distantly related without their knowledge, since the founding French population in Quebec was relatively small, and many French-Canadians can be traced back to a common ancestral couple or couples. The fathers in sibships GFA 12 and GFA 25 are brothers, as are the fathers in sibships GFA 15 and GFA 23. The mothers in sibships GFA 12 and GFA 25 are second cousins whereas the mothers in sibships GFA 12 and GFA 23 have the same maiden names, and are distantly related. Thus it may be possible to link up many of the French-Canadian sibships with Friedreich's ataxia, and this has been attempted in the section on genealogy in this survey.

Pregnancy order

The pregnancy order of the affected individuals was distributed, as shown in Table V. The observed number of affected individuals for each birth rank was compared with the expected number by the Greenwood-Yule method (Greenwood and Yule, 1914). All pregnancies including abortions and stillbirths, were used in this calculation, because this method is more accurate than the birth order, where only liveborn children are included (Metrakos and Metrakos, 1963). The single sibship with sibship size 1 was excluded because it did not contribute anything to the calculation. The results indicate that the pregnancy order of the affected individuals is entirely random ($X^2_5 = 1.158$; $P > 0.90$) (Table V). A similar calculation for birth order, omitting abortions and stillbirths, also revealed a random distribution ($X^2_5 = 4.795$; $0.30 < P < 0.50$).

Maternal and paternal ages at time of birth of the patients

The mean maternal age at the time of birth of 52 of the Friedreich's ataxia patients on whom the information was available was 29.5 ± 0.92 years. The comparable values for two control groups were 28.6 (N=99) and 28.7 (N = 112), respectively. These control groups were selected from a class of university students at McGill University, and from a random group of patients at the Montreal Children's Hospital, respectively. Thus the maternal age at the time of birth of the Friedreich's ataxia patients does not seem to differ significantly from that in the general population.

Similarly, the mean paternal age at the time of birth of 51 of the Friedreich's ataxia patients was 32.5 ± 2.03. The comparable figures for the two control groups described above

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were 32.8 (N=93) and 31.6 (N=112), respectively, and the differences were again not significant.

Sex distribution

The sex distribution of the Friedreich's ataxia patients is shown in Table VI. Of the 58 patients, 26 were males (44.8%) and 32 females (55.2%). Although there is a slight preponderance of female patients, the difference is not statistically significant ($X^2_1 = 0.31$; $0.5 < P < 0.7$).

Pregnancy and delivery

A number of factors during pregnancy and delivery were compared for pregnancies resulting in patients with Friedreich's ataxia with those resulting in unaffected siblings. Since the latter pregnancies shared a common maternal environment, as well as many common genetic features, they served as useful internal controls. Some of the factors compared were maternal radiation during pregnancy, exposure of mother to infectious disease, prematurity, breech delivery, forceps delivery, placenta praevia, and foetal asphyxia due to cord around the neck. It should be pointed out that this retrospective information can only be considered as approximate, since most of the patients were born several decades ago, and the birth records could not be verified in most cases.

In 4 of 52 pregnancies resulting in Friedreich's ataxia patients (9.6%), the mother was exposed to pelvic or abdominal radiation, whereas the corresponding figure for sibling pregnancies was 2 of 98 (2.0%). The difference was not statistically significant, particularly when the Yates correction was employed ($X^2_1 = 1.55$; $0.20 < P < 0.30$). Furthermore, it was difficult to determine retrospectively during which trimester of pregnancy these x-rays were taken. In none of the patient pregnancies were the mothers exposed to infectious diseases, whereas in two of the sibling pregnancies, the mother was exposed to whooping cough.

Information on birth history was available for 45 patients and 86 unaffected siblings. 4 of 45 patients (8.9%) were reported to be asphyxiated with the umbilical cord around the neck, as compared to 2 of 86 siblings (2.3%), but this difference was not statistically significant. Two of the patients were breech presentations (4.4%), as compared to one of the siblings (1.1%). Only one of the patients was born prematurely (2.2%) following less than eight months' gestation, as compared to four of the siblings (4.7%). The mean birth weight of the patients was 7.29 pounds, as compared with 7.14 pounds for their unaffected siblings. None of these differences was statistically significant.

Outcome of pregnancy

The outcome of all the pregnancies of Friedreich's ataxia patients in our study is summarized in Table VII. Of 187 total births, 169 (90.%) resulted in liveborn offspring. There were 16 spontaneous abortions and 2 stillbirths. If the latter are expressed as percentage of livebirths, the figures are 9.5 and 1.2% respectively, and these are not elevated as compared to the general population (Warburton and Fraser, 1961).

Two of the pregnancies resulted in twins (1.1%), and this corresponds exactly to the rate of twinning reported for the general population (1 in 88). One of the 58 patients (1.7%) was a twin (GFA 31), while her twin brother was unaffected. The other twin pregnancy resulted in non-identical unaffected males (GFA 7).

34.3% of all liveborn individuals in the sibships developed Friedreich's ataxia, whereas 65.7% were unaffected siblings. These data will be analyzed in detail subsequently.

GENETIC ANALYSIS

From the above analyses, it is seen that Friedreich's ataxia does not seem to show any pregnancy or birth order effect. Furthermore, the mean maternal and paternal ages, and various factors during pregnancy and delivery do not differ from those in the general population, or from corresponding factors in the pregnancies of unaffected siblings. Thus environmental factors do not seem to be significant in the etiology of Friedreich's ataxia.

Furthermore, the increased parental consanguinity, the tendency for affected individuals to occur in sibships, and the lack of affected individuals in other generations, all suggest autosomal recessive inheritance.

In view of this, a formal genetic analysis was carried out in order to assess the mode of inheritance in these families.

Distribution of affected individuals

The distribution of affected individuals in the 35 sibships is shown in Table VIII. Here the sibship size includes only liveborn individuals. There was one affected individual in 19 sibships (54.2%), two affected in 10 sibships (28.6%), three affected in 5 sibships (14.3%) and four affected in 1 sibship (2.9%). Table VIII also shows that the majority of sibships had between two and five liveborn offspring (71.3%), the most frequent being three (28.5%).

Sibling analysis

58 out of 169 liveborn siblings (34.3%) were affected with Friedreich's ataxia (Table IX). This proportion lies between those expected for autosomal recessive and autosomal dominant inheritance, respectively.

The proportions of affected and unaffected individuals were then calculated, assuming complete, single, and multiple incomplete ascertainment, respectively (Stern, 1960; Thompson and Thompson, 1966 (Table IX)). In these methods, probands are omitted from the calculations. The proportion of affected siblings was calculated to be 22.7%, assuming complete ascertainment, and 17.2%, assuming single ascertainment. Multiple incomplete ascertainment yielded an intermediate value of 19.6%. These values are all slightly below the 25% value expected for autosomal recessive inheritance. When Li's method (Li, 1964) was employed, counting only siblings after the first affected, the proportion of affected indivuals was 24.5%, in agreement with that seen in autosomal recessive inheritance.

A priori method

Finally, tests of significance were

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carried out, assuming complete truncate ascertainment, using the a priori method (Stern, 1960).

Table X shows the test of significance, assuming autosomal recessive inheritance. The observed number of affected individuals was 58, as compared with a calculated expected value of 57.55, and the results were in excellent agreement with the hypothesis of autosomal recessive inheritance ($X^2_9 = 2.55$; $P > 0.90$).

A similar test of significance was carried out, assuming autosomal dominant inheritance. The expected number of affected individuals in this case was calculated to be 124.83, and the difference between observed and expected was almost significant at the 5% level ($X^2_9 = 15.98$; $0.05 < P < 0.10$).

The results of all the tests employed above indicate that the findings in the Friedreich's ataxia families ascertained in our study are in excellent agreement with those expected for an autosomal recessive mode of inheritance.

CLINICAL DATA

The 58 patients in our study were ascertained, employing the criteria outlined in Materials and Methods. It should be emphasized that these patients are entirely distinct from the 50 patients described in the other chapters of this survey.

Since our group of patients fulfilled the neurological criteria for the diagnosis of Friedreich's ataxia, the specific neurological findings will not be detailed here. However, before proceeding to the family studies, certain temporal characteristics of the disease which can only be discerned from a retrospective survey will be presented, and associated abnormalities in patients and their families will be compared.

The temporal characteristics of the disease in our patients are presented in Table XI.

Age of onset

The age of onset of the disease was taken to be the age at which symptoms were first noted by the patient or by his family. The age of onset in 50 patients on whom information was available ranged from 4 to 17 years, with a mean of 9.0±0.6 years (Table XI). The age of onset in our patients is somewhat younger than that found by Bell and Carmichael (1939) (11.75±0.35) and by Sjögren (1943) (13.0±0.7).

The variability of the age of onset calculated for 21 sib pairs for which the information was available gave a mean difference of 1.9±0.6 years.

When the age of onset in the younger sibling was subtracted from that in the older sibling for the same sib pairs, the mean difference was −1.2 years, indicating that the onset was younger in the older siblings. This is in contrast to the findings of Bell and Carmichael (1939), who obtained a comparable mean value of —0.65 years, based on 230 cases.

Age at death

15 of the 58 patients (25.9%) had died at the onset of this study. One girl died at age 4½ years, within several months of the onset of her disease, of intercurrent infection. The age at death of the 14 remaining patients ranged from 17-40 years, with a mean of 30.6 ± 1.3 years (Table XI). In Bell and Carmichael's study, the mean age at death for 72 patients was 26.46±1.41 years.

Duration of disease

The duration of the disease in the 14 patients who died ranged from 6 - 32 years, with a mean of 20.8 ± 1.9 years (Table XI). The comparable value in Bell and Carmichael's study (1939) was 15.99±1.19 years, based on 66 patients.

The duration of the disease in 35 living patients on whom the information was available ranged from 2 - 38 years with a mean of 15.1±2.1 years (Table XI). This compares with 11.47 ± 0.51 years in Bell and Carmichael's study.

Associated abnormalities

The associated abnormalities in patients and relatives are summarized in Table XII. The data in Table XII were obtained from the family histories, as well as from review of hospital charts, and do not include the findings of the family studies, which will be reported later in this paper.

30 of the 58 patients (51.7%) had a history of cardiomyopathy (Table XII), documented by clinical and ECG evidence in all patients, and by cardiac catheterization in five (16.7%). This figure probably represents an underestimate, since all the patients did not have a cardiological investigation, particularly those born several decades ago. There was no family history of cardiomyopathy. However, some of the parents and siblings have ECG findings suggestive of cardiomyopathy, as will be shown in the section on family studies.

Eleven of the patients (19.0%) had a history of diabetes mellitus, as did four of the parents (5.7%), and two siblings (1.8%) (Table XII). One of the siblings had juvenile diabetes mellitus. A history of diabetes mellitus was obtained in second degree relatives (aunts and uncles and grandparents) in 13 families (37.1%). At least 9 of the 140 grandparents (6.4%) had diabetes mellitus. In five of the families (14.3%), there was a strong family history of diabetes, with a large number of relatives affected. In four of these, this occurred on the paternal side. Thus, there seems to be a somewhat increased frequency of diabetes mellitus in relatives of Friedreich's ataxia patients.

Three patients in different sibships (5.2%) had optic atrophy with markedly decreased visual acuity, and at least one other patient was found to have optic atrophy on examination. No history of optic atrophy was obtained in unaffected relatives.

Three of the patients (5.2%) had nerve deafness, and one of these also had optic atrophy. One of the mothers, as well as several of her siblings, had a history of hearing loss and renal calculi, and may have been affected with Alport's syndrome.

Four of the patients (6.9%) had documented congenital malformations (cleft palate, C3-C4 fusion, congenital megacolon, a prolapsing mitral valve leaflet syndrome, respectively) (Table XII). The first two patients also had a history of

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congenital heart disease, as did another patient, but these were not well documented, and were difficult to distinguish retrospectively from the cardiomyopathy of Friedreich's ataxia. Two of the parents (2.9%) had a history of congenital malformations (club feet in one father, familial malformation of the ear canal in one mother). Four siblings (3.6%) also had congenital malformations (congenital heart disease, bifid ureter, cervical rib, and anal atresia). Congenital malformations were reported in more distant relatives in 7 families (20%). These included club feet, congenital malformation of the ear canal, spina bifida with multiple congenital anomalies, malformed arm, and Down's syndrome. Although the frequency of major congenital malformations appears to be somewhat elevated in patients and first degree relatives, no consistent pattern of malformation is noted, with the possible exception of an increased frequency of congenital heart disease in the patients which is, however, not well documented.

Four of the patients (6.9%) had a history of seizures, and one of these had chronic epilepsy (Table XII). Three parents (4.3%) had epilepsy or a history of convulsions in infancy, whereas three siblings were epileptic (2.7%). Epilepsy was reported in more distant relatives in two families (5.7%). The incidence of epilepsy and/or a history of convulsions is elevated in patients and first degree relatives, as compared to the general population.

Four of the patients (6.9%) had urinary tract disease. This included nephrotic syndrome in two siblings; and cystitis and pyelitis, and membranous trigonitis, respectively, in two other siblings. Two mothers had pyelonephritis, and one of these had a nephrectomy. Another mother had familial hearing loss associated with renal calculi.

Arteriosclerotic heart disease, frequently associated with a history of myocardial infarction, was reported in 7 fathers (10% of parents; 20% of fathers) and four siblings (3.6%). Arteriosclerotic heart disease was reported in second degree relatives (aunts and uncles and grandparents) in 7 families (20%). In 6 of these families, there was a strong family history of arteriosclerotic heart disease on the paternal side, with several affected family members. In some of these families, there was also a strong family history of diabetes mellitus.

Scoliosis was present in the majority of the patients at some time in their disease. However, since many of the patients were only investigated at the onset of their illness, when the scoliosis was not yet apparent, a definite frequency cannot be given. A history of scoliosis was obtained in two parents (2.9%) and one sibling (0.9%). In one of the parents, the scoliosis was treated surgically.

In one family, the father and a paternal uncle, and possibly the paternal grandmother as well, had a form of spino-cerebellar degeneration with ataxia and diminished or absent deep tendon reflexes, with onset in the fifth decade.

Mortality in patients

Fifteen of 58 Friedreich's ataxia patients (25.8%) died before the onset of this study. The causes of death in 14 of these patients were obtained as follows: cardiomyopathy — 5; bronchopneumonia and pulmonary oedema — 2: viral pneumonia — 1; bronchitis — 1; intestinal obstruction and cardiac failure — 1; cerebrovascular accident — 1; abdominal aortic aneurysm — 1; diabetic coma — 1; and diabetes mellitus — 1. 12 of the patients who died (80%) had cardiomyopathy, and 7 had diabetes mellitus (46.7%). This includes 6 patients (40%) who had both cardiomyopathy and diabetes mellitus. These two frequently associated conditions appear to be important factors in determining the mortality of Friedreich's ataxia.

Mortality in siblings

In contrast to the patients themselves, only 6 of 111 liveborn siblings (5.4%) had died at the onset of this study. The causes of death were, as follows: pneumonia — 2; diphtheria — 1; pulmonary congestion — 1; drowning secondary to epilepsy — 1; and myocardial infarction — 1. Four of the siblings died in infancy and childhood.

FAMILY STUDIES

Clinical and laboratory studies were carried out in patients and first degree relatives (parents and siblings), as outlined in Materials and Methods. The findings are summarized in Table XIII. The data were initially analyzed separately according to sex, but since no significant sex differences were found in the frequency of abnormalities noted, the results were combined. The examinations listed in Table XIII for the patients themselves included those carried out prior to the onset of this study. However, all the parents and siblings were examined during the course of the study.

Siblings were divided into two groups, according to age (Table XIII). They were considered to be above the age of onset for Friedreich's ataxia if they were two or more years older than the oldest age of onset in their affected siblings. This classification was based on the fact that the mean variability in the age of onset between siblings was found to be 1.9 ± 0.6 years (Table XI).

Complete neurological examinations

Fifty-five patients had complete neurological examinations, 19 during the course of this study. All of the patients showed the characteristic features of Friedreich's ataxia.

At least one first degree relative was examined in 13 of the 35 families (37.1%). Seven out of 20 parents (35%) showed some neurological or skeletal abnormalities (Table XIII). These included hypoactive ankle jerks in three parents (15%), one of whom also had mild kyphosis; scoliosis in two parents (10%); depressed knee jerks and absent ankle jerks with decreased sensation in the digits in one father who had diabetes mellitus; and generalized hyporeplexia or areflexia associated with ataxia in a father who had late-onset spinocerebellar degeneration. This man's brother showed the same

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physical findings. Two of the parents had heart murmurs.

Of 14 siblings above the age of onset of the disease, one brother had spondylolisthesis of the lower lumbar spine, but no abnormalities on neurological examination. A sister had a heart murmur and possible paroxysmal atrial tachycardia.

Of 4 siblings below the age of onset of the disease, one sister had generalized hyporeflexia, congenital weakness of the sixth cranial nerve, and nystagmus; another sister had scoliosis, but an otherwise normal neurological examination.

Thus, of 38 first degree relatives examined, 10 or 26.3% were found to have neurological or skeletal abnormalities.

Neuro-ophthalmological examinations

Complete neuro-ophthalmological examinations as outlined in Materials and Methods were performed on severe Friedreich's ataxia patients during the course of this study. Six other patients had had previous ophthalmological evaluations, usually due to visual problems. All the patients showed some abnormalities. Three patients had optic atrophy with decreased visual acuity, and in one of these there was associated pendular nystagmus and constriction of visual fields. A fourth patient also had optic atrophy, but was less severely affected. The remaining nine patients all showed a specific dysmetric ocular motor defect, characterized by hypometria on moving the eyes away from the midline, and hypermetria with overshoot on return of the eyes to the midline. Several of the patients had variable degrees of myopia and astigmatism, and one patient also had retinal folds over both maculae.

Fourteen first degree relatives in 8 families underwent complete neuro-ophthalmological examinations, and none showed evidence of optic atrophy or the characteristic ocular motor defect described above (Table XIII).

Electromyography

Sixteen patients in 13 sibships had EMG examinations, 10 in the course of this study. All showed the characteristic abnormalities of Friedreich's ataxia: absent or markedly diminished sensory potentials; absent "H" reflex; slowing of "F" wave conduction velocities, with normal distal motor conduction velocities; and prolonged silent periods, all compatible with involvement of the dorsal root entry zone. Some patients also showed variable degrees of neurogenic changes on EMG needle studies.

EMG studies were carried out on 26 first degree relatives in 11 families, 17 of whom had measurements of "F" wave conduction velocities. These studies yielded some abnormality in 5 out of 7 fathers (71.4%), and in 4 out of 9 mothers (44.4%) (Table XIII). One of the fathers had marked slowing of proximal conduction as measured by "F" wave conduction velocities, but this could probably be attributed to disc disease. The father with late-onset spinocerebellar degeneration and areflexia showed marked abnormalities, involving primary sensory conduction, but with some slowing of the motor conduction in the legs. These findings were compatible with dorsal root entry zone diseases, as well as peripheral segmental demyelination. Three other fathers showed only mild sensory changes, which could be attributed to a specific etiology in each case — diabetes mellitus, trauma, and old age, respectively. One mother had marked slowing of proximal conduction in the posterior tibial nerve, while three other mothers had mild slowing of proximal conduction, which was within normal limits. These findings were considered to be related to disc disease, although no clinical history of this was obtained. Thus all the abnormalities seen in the parents could probably be attributed to factors unrelated to their heterozygous state.

Ten unaffected siblings had EMG examinations, including 7 siblings above and 3 siblings below the age of onset. All of the examinations were normal.

Electrocardiography

ECG examinations were available for 32 of the 58 patients (55.2%) Twenty-four of the 32 patients (75%) had ECG findings compatible with cardiomyopathy (Table XIII). These included ST-T wave changes, evidence for right atrial and ventricular hypertrophy, conduction defects, and atrial fibrillation.

ECG examinations were obtained in 44 first degree relatives in 18 families. Seven out of 9 fathers (77.8%) had some abnormality in the ECG, as compared to 5 of 15 mothers (33.3%), with a total frequency of abnormalities in parents of 50.0% (Table XIII). The abnormalities consisted of ST-T wave changes compatible with ischemia or cardiomyopathy in 6 parents, left axis deviation in two parents, conduction defects in two parents, and an abnormal QRS complex in one father with a possible history of myocardial infarction.

Five out of 16 siblings above the age of onset (31.3%) showed some ECG abnormalities (Table XIII). These included ST-T wave changes in three, right axis deviation suggestive of right ventricular hypertrophy in one, and minor nonspecific interventricular conduction defect in one. Four siblings below the age of onset of the disease had normal ECG examinations.

Electroencephalography

EEG examinations were available for 18 of the 58 patients in the study (31.0%). Eight of the 18 patients had normal EEG examinations (44.4%). Three patients had mild dysrhythmia, and two had posterior slow waves which were considered excessive for the age. The remaining five patients (27.8%) had definite abnormalities, consisting of diffuse or focal slow wave abnormalities. with frequent paroxysmal features. Only one patient had a potentially epileptiform abnormality in the right temporal lobe.

EEG examinations were performed on 32 first degree relatives in 16 families. Three of 21 parents (14.3%) had a mild to moderate intermittent disturbance over the left temporal region, as well as a diffuse paroxysmal disturbance of cerebral activity. In two of these parents, the

abnormality was potentially epileptiform. Six other parents had minimal diffuse slow or fast dysrhythmias, but the records were considered to be within normal limits.

EEG examinations in 11 unaffected siblings above the age of onset of the disease resulted in three abnormal records (27.7%). These showed a mild intermittent disturbance over the left temporal region, a projected slow wave abnormality over the posterior quadrant, and an excessive response to intermittent photic stimulation, respectively. Two other siblings had minimal slow and fast dysrhythmias, but their records were considered to be within normal limits.

Thus 6 out of 32 first degree relatives (18.8%) had a definite EEG abnormality (Table XIII).

DISCUSSION

The classical genetic studies of Friedreich's ataxia were carried out in Europe several decades ago (Hanhart, 1923; Bell and Carmichael, 1939; Sjögren, 1943). Although pedigrees of various forms of hereditary ataxia have appeared in the literature, some of which include cases of Friedreich's ataxia and/or mixed forms (Spillane, 1940; Schut, 1950; Woodworth, 1959), a formal genetic analysis of classical Friedreich's ataxia in a North American population has not been carried out.

Saucier (1948) published a pedigree of a French Canadian family from the Montreal area, which included eight cases of classical Friedreich's ataxia in three different generations. He commented on the fact that Friedreich's ataxia appears to be relatively infrequent in the United States, whereas 2 or 3 new cases were seen by him every year. Due to the occurrence of affected cases in several generations, Saucier postulated a dominant mode of inheritance in his family, despite a first-cousin marriage in the parents of one affected sibship.

Boyer et al. (1962) reported 26 sibships with Friedreich's ataxia seen at the Johns Hopkins Hospital between 1935 and 1957, in two of which there was an apparently dominant mode of inheritance.

We have analyzed the data on 58 patients with Friedreich's ataxia in 35 sibships living in the Montreal area, and this group is entirely distinct from the 50 patients in 32 sibships from various parts of the Province of Quebec, who have been included in the prospective collaborative study, and are described in detail in the other papers of this survey.

From this study, we have seen that there appears to be no specific ethnic predilection for the disease, since the distribution of ethnic origins of the grandparents corresponds very well to that of the general population of the Montreal area. Furthermore, the birthplaces of the grandparents do not appear to be concentrated in a specific geographic area of the Province of Quebec. This is in contrast to what we have found for several autosomal recessive disorders prevalent in the French Canadian population of Quebec, namely Tay-Sachs disease and Sandhoff's disease (Andermann et al., 1973, 1976); agenesis of the corpus callosum with sensorimotor neuronopathy (Andermann et al., 1972, 1975); and collagen vascular disease with spasticity and mental retardation (Leppik et al., 1975).

None of the factors studied during pregnancy and delivery appeared to be significant in the etiology of Friedreich's ataxia. The pregnancy order of the affected individuals was randomly distributed, and the mean maternal and paternal ages at the time of birth of the probands did not differ from those found in the general population.

The rate of first-cousin marriage in the parents (5.7%) was elevated as compared with the general population, but not as high as those found by Hanhart (1923) (17%), by Bell and Carmichael (1939) in their personal series (12.7%), and by Sjögren (1943) (12.5%), indicating that the gene frequency of Friedreich's ataxia in the population group under study may be higher than the corresponding frequencies in Switzerland, England and Sweden. In the series of Boyer et al. (1962), only one out of 24 affected sibships had first cousin parents (4.2%).

The sex distribution of Friedreich's ataxia patients revealed a slight excess of affected females, but did not differ significantly from a 1.1 ratio. Although seven of the nine cases originally reported by Friedreich were females, none of the studies since that time have shown any significant sex differences (Boyer et al., 1962).

The increased parental consanguinity, the tendency for affected individuals to occur in sibships, the lack of affected individuals in other generations, and the insignificance of environmental factors, such as birth order, in the etiology of Friedreich's ataxia, all suggested an autosomal recessive mode of inheritance. Formal genetic analysis, assuming various modes of ascertainment, all gave values close to the 25% figure expected in autosomal recessive inheritance. The slightly lower values obtained by some of these methods may be due to the fact that some of the asymptomatic siblings below the age of onset may still develop the disease. Since many of our cases were ascertained retrospectively, the vast majority of the sibships have been completed, as the mothers are now beyond the child-bearing age. Genetic analysis employing the a priori method and assuming complete truncate ascertainment resulted in excellent agreement with the hypothesis of autosomal recessive inheritance.

The mean age of onset of the disease in 50 of our patients (9.0±0.6 years) is somewhat lower than the corresponding values found by Bell and Carmichael (1939) and by Sjögren (1943), but is higher than that found by Boyer et al. (1962) (7.6 years). The mean age at death and duration of disease in both living and deceased patients were about four years older in our series as compared to the series reported by Bell and Carmichael, and this can probably be attributed to the improved therapeutic measures for infectious, cardiac, and diabetic complications of the disease in the past four decades.

Associated abnormalities in our series of 58 patients included cardiomyopathy (51.7%), diabetes mellitus (19.0%), optic atrophy (5.2%), and nerve deafness (5.2%).

The frequency of cardiomyopathy in our series corresponds to that found by Boyer et al. (1962) (55%), but in both series, this probably represents an underestimate. Although none of the parents or unaffected siblings had clinical evidence for cardiomyopathy, a number showed ECG changes compatible with this condition.

The incidence of diabetes mellitus in our series of patients (19%) corresponds very closely to that found by Thorén (1962) in Sweden (18%), but is higher than that found by Hewer and Robinson (1968) (8%). As for cardiomyopathy, the 19% incidence in our study probably represents an underestimate, since this information was obtained by history alone, and many of the patients did not have metabolic investigations. The incidence of diabetes mellitus in parents and grandparents of Friedreich's ataxia patients appears to be elevated 3 to 6 fold, as compared with the general population. A history of diabetes mellitus was obtained for one or more second-degree relatives in 37.1% of the families, and this would also appear to be excessive.

Optic atrophy and nerve deafness, respectively, were each found in 5.2% of patients, but not in their relatives.

Congenital malformations and epilepsy and/or febrile convulsions were 3 to 6 times as frequent in Friedreich's ataxia patients as compared with the general population. The frequencies of these abnormalities were also elevated, but to a lesser extent, in first degree relatives.

Arteriosclerotic heart disease does not appear more frequently in the relatives of Friedreich's ataxia patients than in the general population, although in several families there is a strong family history of this on the paternal side. The presence of arteriosclerotic heart disease in the patients themselves is difficult to distinguish from the car-

TABLE I

Clinical Material

Kindred Number	Sibship	Ethnic and Geographic Origin	Parental Consanguinity	Comments
GFA 1	F+ M M F F M 1 2 3 4 5 6	French Canadian	No	No. 1 - d. 6 yrs. of pneumonia No. 4 - cystitis and pyelitis, poss. mild diabetes No. 5 - membranous trigonitis
GFA 2	F M M F 1 2 3 4	English and English Canadian	No	No. 1 - epilepsy and peptic ulcer Father and three of his siblings are diabetic
GFA 3	F+ M M 1 2 3	Greek	No	No. 1 - d. 39 yrs. Father has ECG consistent with cardiomyopathy
GFA 4	F M M+ a F a M 1 2 3 4 5 6 7	French Canadian	No	No. 1 - cervical rib No. 3 - d. 26 yrs. of cardiomyopathy No. 5 - congenital heart malformation
GFA 5	M M a M a 1 2 3 4 5	Syrian	First Cousins	No. 1 - bilateral optic atrophy and profound sensori-neural deafness; marked scoliosis; also has thyroid carcinoma. Father and three of his brothers have arteriosclerotic heart disease.
GFA 6	M F F F F 1 2 3 4 5	German; English Canadian; English and French American	No	No. 3 - prolapsing mitral valve leaflet syndrome No. 4- scoliosis No. 5 - strabismus, decreased deep tendon reflexes. Father - myocardial infarction and cardiac arrest at age 51
GFA 7	M+ M M M M 1 2 3 4 5	French Canadian	First cousins once removed	No. 1 - d. 28 yrs. intestinal obstruction and cardiomyopathy
GFA 8	M F+ 1 2	Irish Canadian; Scottish Canadian; and French Canadian	No	No. 1 - benign hyperglycemia No. 2 - d. 39 yrs. bronchopneumonia and congestive heart failure. Had diabetes and cardiomyopathy. Autopsy revealed myocardial degeneration and fibrosis. Father died age 57 of cerebrovascular disease.
GFA 9	M M M+ 1 2 3	English Canadian	No	No. 3 - bilateral optic atrophy; marked scoliosis; cardiomyopathy; diabetes mellitus. Died age 23 of broncho-pneumonia and pulmonary oedema. Autopsy revealed massive cardiac hypertrophy and dilatation with diffuse interstitial myocardial fibrosis.
GFA 10	M F	French Canadian	No	
GFA 11	M+ F M+ M M M M M 1 2 3 4 5 6 7 8	French Canadian	No	No. 1 - d. 2 yrs. gastroenteritis No. 3 - d. 34 yrs. cardiomyopathy
GFA 12	F+ F M F M M M M 1 2 3 4 5 6 7 8	French Canadian	No	No. 1 - diabetes and cardiomyopathy. Died 37 years of cerebrovascular accident No. 2 - ECG shows nonspecific ST-T wave changes. Father died of arterio-sclerotic heart disease. Three paternal first cousins also had Friedreich's ataxia (GFA 25). These patients are also distantly related to GFA 23 through both maternal sides. One female maternal second cousin possibly affected.
GFA 13	F F+ F+ F F 1 2 3 4 5	French Canadian	No	No. 1 - early diabetes No. 2 - severe diabetes and cardio-myopathy. Died age 30 in diabetic coma. No. 3 - diabetes and cardiomyopathy; physical and mental retardation; amenorrhoea. Died age 17 in diabetic coma. No. 4 - diabetes and cardiomyopathy; hearing loss. No. 5 - bifid ureter; non-specific ST-T wave changes in ECG. Father and two of his siblings, as well as paternal grandmother, have diabetes and arterio-sclerotic heart disease.
GFA 14	a M F M M F M 1 2 3 4 5 6 7	French Canadian and ? German	No	No. 4 - repaired cleft palate No. 4 & No. 6 - probable cardiomyopathy Father - bilateral club feet
GFA 15	F M 1 2	French Canadian	No	No. 1 - cardiomyopathy with right ventricular hypertrophy and dilatation demonstrated on cardiac catheterization. Father operated for scoliosis; also had peripheral neuropathy. Paternal first cousin has Friedreich's ataxia (GFA 23)
GFA 16	M	French Canadian	No	Maternal half-brother died at age 17 of muscular dystrophy
GFA 17	M F 1 2	French Canadian	No	No. 1 - heart murmur No. 2 - cardiomyopathy confirmed by cardiac catheterization. Mother, maternal grandfather and two maternal aunts and uncles have congenital malformation of ear canal. Mother had nephrectomy for pyelonephritis. Strong history of diabetes in maternal grandmother's family.
GFA 18	M a F a M F 1 2 3 4 5 6	Italian; French Canadian	No	No. 3 - cardiomyopathy No. 5 - nephrotic syndrome, cardio-myopathy, and epilepsy No. 6 - febrile convulsions in first 2-3 yrs.; cardiomyopathy; onset nephrotic syndrome age 13. Mother and maternal first cousin are epileptic.
GFA 19	F M F M 1 2 3 4	Scottish, English and English Canadian	No	No. 1 - juvenile diabetes mellitus

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diomyopathy of Friedreich's ataxia, and the two may often be associated.

The increased incidence of diabetes mellitus, congenital malformations and epilepsy in patients and first degree relatives may be explained either by the pleiotropic effect of the Friedreich ataxia gene, but this would also be expected on the basis of multifactorial inheritance (Falconer, 1965).

The family in which the father and paternal uncle were affected with late-onset spinocerebellar degeneration associated with hypo- or areflexia is interesting, but probably represents a fortuitous association of two different diseases in one family, rather than indicating autosomal dominant inheritance.

An analysis of the mortality of Friedreich's ataxia patients indicated that the majority of patients who died had cardiomyopathy and/or diabetes mellitus. The mortality in patients was increased five-fold as compared to that of their unaffected siblings.

The clinical and laboratory studies performed in an attempt to find methods of carrier detection and early diagnosis showed an apparent increase in the incidence of abnormalities on neurological (26.3%), EMG (34.6%), ECG (38.6%), and EEG (18.8%) examinations in unaffected first degree relatives. The hyporeflexia and scoliosis seen in the parents and siblings may represent a partial expression of the gene. The neuro-ophthalmological examinations in relatives did not reveal any abnormalities.

56.3% of parents had abnormal EMG's, some with slowing of proximal conduction as measured by "F" wave determinations. However, in most cases, this could be explained by external factors, such as disc disease, trauma, and metabolic disorders. All of the siblings tested had normal EMG examinations. Thus, it does not appear to be possible to detect heterozygous carriers of Friedreich's ataxia by present EMG techniques.

50.0% of the parents and 25.0% of the siblings had ECG abnormalities, and some of these may be consistent with cardiomyopathy. It is planned

TABLE 1 (continued)

Clinical Material

Kindred Number	Sibship	Ethnic and Geographic Origin	Parental Consanguinity	Comments
GFA 20	F F M 1 2 3	French Canadian	No	No. 3 - epilepsy; possible Friedreich's ataxia. Mother - scoliosis
GFA 21	F F F 1 2 3	French Canadian	No	Mother's ECG shows sinus bradycardia and first degree heart block. Maternal grandparents are first cousins.
GFA 22	F F F M F M M F 1 2 3 4 5 6 7 8	French Canadian	No	Father had seizures in infancy
GFA 23	F M M	French Canadian	No	No. 3 - possibly affected. Paternal first cousin has Friedreich's ataxia (GFA 15). Distantly related to GFA 12 on maternal side.
GFA 25	M F a M+ M F F F a 1 2 3 4 5 6 7 8 9 M+ F 10 11	French Canadian	No	No. 4 - d. 29 yrs. abdominal aneurysm; gangrene (L.) leg. Also had diabetes and cardiomyopathy. No. 8 - diabetes and cardiomyopathy No. 10 - d. 30 yrs. of viral pneumonia. Had diabetes and cardiomyopathy. Two paternal first cousins also affected with Friedreich's ataxia (GFA 12).
GFA 26	F M + F F a F 1 2 3 4 5 6	French Canadian	First Cousins	No. 2 - Post-traumatic epilepsy. Drowned at age 21. Maternal uncle has epilepsy. Paternal uncle - club feet.
GFA 28	M F M+ M + F M + F 1 2 3 4 5 6 7 M M F + M M M a F M M 8 9 10 11 12 13 14 15 16 17	French Canadian	No	No. 3 - convulsions in infancy. Cardiomyopathy with cardiac hypertrophy d. age 37 yrs. No. 4 - d. 22 mos. of pneumonia No. 6 - d. 58 yrs. of myocardial infarction. No. 8 - myocardial infarction at 54 yrs. No. 10 - severe convulsions as a baby; diabetes mellitus. Died age 30 yrs. No. 12, No. 15 - arteriosclerotic heart disease No. 5, No. 16 - hypercholesterolemia treated with diet. Mother and several paternal aunts and uncles died of diabetes and heart disease.
GFA 29	M M F 1 2 3	French Canadian	No	No. 1 - cardiomyopathy with intermittent auricular fibrillation; myocardial infarction at age 20, bilateral optic atrophy; severe scoliosis. No. 3 - Hypertrophic cardiomyopathy confirmed by cardiac catheterization. Father died of diabetes and heart disease at 54 years. Strong family history of diabetes and heart disease on paternal side.
GFA 30	M M F 1 2 3	French Canadian	No	
GFA 31	F F M+ a F M M a a 1 2 3 4 5 6 7 8 9 M F M M M+ 10 11 12 13 14	Canadian Indian and French Canadian	No	No. 1 - deafness left ear. No. 3 - d. diptheria age 4 yrs. No. 6 - married, no children No. 11 - strabismus operated No. 14 - d. pulmonary congestion age 3 yrs Father, four paternal uncles, and both paternal grandparents died of heart disease and alcoholism. Paternal grandparents were first degree cousins. Mother and several of her siblings have hearing problems and renal calculi.
GFA 32	M M F a M F 1 2 3 4 5 6	French Canadian and American	No	No. 2 - probable cardiomyopathy. No. 3 - cardiomyopathy confirmed by cardiac catheterization. Married with two children.
GFA 33	M F+ F+ F+ a a M F 1 2 3 4 5 6 7 8	French Canadian	No	No. 2 - d. 18 yrs. cardiomyopathy No. 3 - premie 7 mos. Died 6 hrs. deformed. No. 4 - probably affected. Congenital megacolon. Died at 4½ yrs. following bronchitis. No. 7 - anal atresia operated at 7 yrs. Spondylolisthesis. Father and paternal uncle both have form of spinocerebellar degeneration with onset in early 40's. Paternal grandmother possibly had same disease.
GFA 34	F M M 1 2 3	Italian	No	No. 2 - probably cardiomyopathy. Father mild nonspecific ST-T wave changes
GFA 35	F M M F 1 2 3 4	French Canadian	No	No. 2 & No. 3 - both probably have cardiomyopathy. Father hypertensive; ECG shows mild nonspecific T wave flattening. Maternal grandmother had coronary thrombosis age 62. Paternal grandmother diabetic.
GFA 36	F F M M F F F 1 2 3 4 5 6 7	English Canadian	No	No. 5 & No. 6 - evidence for cardiomyopathy.
GFA 37	F+ F M M 1 2 3 4	Scottish, English and Irish	No	No. 1 - stillborn female premie - 8 months gestation - not malformed. No. 4 - cardiomyopathy; psychiatric problems. One male nephew, son of No. 3 died at 5 wks. - spina bifida and multiple congenital malformations

\+ deceased
= proband
— secondary index case
M Male
F Female
a abortion
∧ twins
Numbers indicate order of birth.

to study these individuals further, employing the techniques of echocardiography and vectocardiography.

Finally, abnormal EEG'S were recorded in 14.3% of the parents and 27.2% of the siblings, consisting mainly of focal and diffuse slow waves with paroxysmal features. In several family members, these abnormalities were potentially epileptiform. EEG abnormalities were more frequent in siblings than in parents, and this agrees with studies on the genetics of epilepsy (Metrakos and Metrakos, 1961; Andermann and Metrakos, 1968), since most EEG abnormalities are age-dependent.

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Table II

GENETIC AND FAMILY STUDIES IN FRIEDREICH'S ATAXIA

Patients and relatives examined in present study

Examination performed	Number of individuals examined				
	Patients	Relatives			Total
		Parents	Siblings	Total	
Complete neurological examination	19 (53)	20	18	38	57 (91)
Neuro-ophthalmological examination	7 (13)	5	9	14	21 (27)
EMG	10 (16)	16	10	26	36 (42)
ECG	10 (32)	24	20	44	54 (76)
EEG	5 (18)	21	11	32	37 (50)

The numbers in brackets include examinations on the Friedreich's ataxia patients prior to the onset of this study.

Table III

GENETIC AND FAMILY STUDIES IN FRIEDREICH'S ATAXIA

Ethnic and geographic origin of grandparents

Ethnic and geographic origin	Families		Grandparents	
	Number	%	Number	%
French-Canadian	22	62.8	96	68.5
Anglo-Saxon	5	14.2	27	19.3
European	2	5.7	11	7.9
Asian	1	2.9	4	2.9
North American Indian	--	---	2	1.4
French-Canadian and Anglo-Saxon	2	5.7	--	---
Anglo-Saxon and European	1	2.9	--	---
French-Canadian and European	1	2.9	--	---
French-Canadian and North American Indian	1	2.9	--	---
TOTAL	35	100.0	140	100.0

Table IV

GENETIC AND FAMILY STUDIES IN FRIEDREICH'S ATAXIA

Consanguineous marriages in parents and grandparents

Consanguineous marriages	Degree of consanguinity	Number	%
Parents	First cousins	2	5.7
	First cousins once removed	1	2.9
		3	8.6
Maternal grandparents	First cousins	1	2.9
Paternal grandparents	First cousins	1	2.9
TOTAL		5	14.4

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Table V

GENETIC AND FAMILY STUDIES IN FRIEDREICH'S ATAXIA

Pregnancy order effect

Sibship size	Pregnancy order 1	2	3	4	5	6 - 17	Total
2	2	2					4
3	4	4	2				10
4	1	2	2	1			6
5	1	1	2	1			5
6-17	2	3	6	5	6	10	32
Observed	10	12	12	7	6	10	57
Expected	11.92	11.92	9.92	6.59	5.09	11.62	57
$\frac{(o-e)^2}{e}$	0.309	0.001	0.436	0.026	0.163	0.223	1.158

$\chi^2_5 = 1.158$ $P > 0.90$

Table VI

GENETIC AND FAMILY STUDIES IN FRIEDREICH'S ATAXIA

Sex distribution of patients

	Male	Female	Total
Observed	26	32	58
Expected	29	29	58
% $\frac{\text{observed}}{\text{total}}$	44.8	55.2	100.0

$\chi^2_1 = 0.31$ $0.5 < P < 0.7$

TABLE VII

GENETIC AND FAMILY STUDIES IN FRIEDREICH'S ATAXIA

Outcome of pregnancy in 35 sibships

	Number*	% of total births	% of live births
Liveborn	169	90.4	100.0
Affected	58	31.0	34.3
Unaffected	111	59.4	65.7
Spontaneous abortions	16	8.5	9.5
Stillborn	2	1.1	1.2
Total Births	187	100.0	—

*Twin pregnancies are counted as 2 individuals for the purposes of the calculations.

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Table VIII

GENETIC AND FAMILY STUDIES IN FRIEDREICH'S ATAXIA

Distribution of affected individuals in 35 sibships

Sibship size	Number of sibships: Number of affected individuals per sibship 1	2	3	4	Total	%
1	1				1	2.9
2	4				4	11.4
3	8	2			10	28.5
4	2	1	1		4	11.4
5	4	2	1		7	20.0
6		1	1		2	5.7
7		1			1	2.9
8		2	1		3	8.5
9			1		1	2.9
11				1	1	2.9
16		1			1	2.9
Total	19	10	5	1	35	
%	54.2	28.6	14.3	2.9		100.0

Table IX

GENETIC AND FAMILY STUDIES IN FRIEDREICH'S ATAXIA

Sibling analysis assuming various methods of ascertainment

Method of Ascertainment	Affected	Unaffected	Total	% Affected
Raw data	58	111	169	34.3
Complete	62	211	273	22.7
Single	23	111	134	17.2
Multiple incomplete	42	172	214	19.6
Li's method	23	71	94	24.5

Table X

GENETIC AND FAMILY STUDIES IN FRIEDREICH'S ATAXIA

Test of significance for an autosomal recessive mode of inheritance, assuming complete truncate ascertainment

Sibship size	Number of sibships	Number of affected individuals: Observed	Expected	$\frac{(o-e)^2}{e}$
1	1	1	1.00	0.00
2	4	4	4.57	0.07
3	10	12	12.97	0.07
4	4	7	5.85	0.23
5	7	11	11.48	0.04
6	2	5	3.65	0.50
7	1	2	2.02	0.00
8	3	7	6.67	0.02
9	1	3	2.43	0.13
11	1	4	2.87	0.45
16	1	2	4.04	1.04
	35	58	57.55	2.55

$\chi^2_9 = 2.55$ $P > 0.90$

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TABLE XI

GENETIC AND FAMILY STUDIES IN FRIEDREICH'S ATAXIA

Temporal characteristics of the disease

Characteristic	N	Range	Age in years: Mean ± S.E.	Median	Mode
Age of onset	50	4 - 17	9.0 ± 0.6	8	5
Variability of age of onset	21	0 - 10	1.9 ± 0.6	1	0
Age at death	14	17 - 40	30.6 ± 1.3	30	28
Duration of disease					
Patients who died	14	6 - 32	20.8 ± 1.9	21	21
Living patients	35	2 - 38	15.1 ± 2.1	14	15.5

Table XII

GENETIC AND FAMILY STUDIES IN FRIEDREICH'S ATAXIA

Associated abnormalities in patients and relatives

			Relationship to patients: Parents (N=70)		Siblings (N=111)		Other Relatives** (N=35)	
	Patients* (N=58)							
Associated abnormalities	No.	%	No.	%	No.	%	No.	%
Cardiomyopathy	30	51.7	—	—†	—	—†	0	0.0
Diabetes mellitus	11	19.0	4	5.7	2	1.8	13	37.1
Optic atrophy	3	5.2	0	0.0	0	0.0	0	0.0
Nerve deafness	3	5.2	1	1.4	0	0.0	1	2.9
Congenital malformations	4	6.9	2	2.9	4	3.6	7	20.0
Epilepsy and/or febrile convulsions	4	6.9	3	4.3	3	2.7	2	5.7
Urinary tract disease	4	6.9	3	4.3	0	0.0	1	2.9
Scoliosis	—	—†	2	2.9	1	0.9	0	0.0
Arteriosclerotic heart disease	—	—†	7	10.0	4	3.6	7	20.0
Late-onset spinocerebellar degeneration with areflexia	—	—†	1	1.4	0	0.0	1	2.9

*The patients in this study were ascertained in a retrospective manner, and represent a different group from the 50 patients described in the other papers of this survey.

**Here the number of families in which a particular abnormality was found in family members outside of first degree relatives is stated. † For explanations, see text.

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Table XIII

GENETIC AND FAMILY STUDIES IN FRIEDREICH'S ATAXIA

Clinical and laboratory examinations in patients and relatives

	Complete neurological examination		Neuro-ophthalmological examination		EMG		ECG		EEG	
Individuals examined	N	% Abn.	N	% Abn.	N	% Abn.	N	% Abn.	N	% Abn.
Patients *	55	100.0	13	100.00	16	100.0	32	75.0	18	61.1
Parents	20	35.0	5	0.0	16	56.3	24	50.0	21	14.3
Siblings above age of onset	14	7.1	8	0.0	7	0.0	16	31.3	11	27.2
Siblings below age of onset	4	50.0	1	0.0	3	0.0	4	0.0	0	0.0
Total first degree relatives	38	26.3	14	0.0	26	34.6	44	38.6	32	18.8

* The investigations on patients include those performed prior to the onset of this study.

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