File No. N. H. and W. R604-5-25

DEPARTMENT OF NATIONAL HEALTH AND WELFARE

	NAME OF CORRESPONDENT OR PURPORT OF COMMUNICATION	CROSS REFERENCES
R604-5-25	QUEBEC - PROGRESS REPORT MENTAL HEALTH GRANT STUDY OF GENETICS OF EPILEPSY (McGILL UNIVERSITY)	604-5-25

DATE	P.A. OR B.F.	REFERENCE	REFERRED TO	FOR REMARKS (If purpose for which referred cannot be expressed on one line, add minute to file and enter here "With Minute")	INITIALS	DATE
1-8-62	—	VS	MH	Request	GRL	27/7/62
AUG 17 1962						
16/8/62	—	J.E.	Mental Health	Copy	JC	15-8-62

N.H. & W. 12C

Date	P.A. or B.F.	Initials	Referred to	FOR REMARKS	Initials	Date
				(If purpose for which referred cannot be expressed on one line, add minute to file and enter here "With Minute")		

R 604-5-25

OTTAWA, April 21, 1955.

J.W. Boyes, Esq., M.D.,
Chairman,
Department of Genetics,
McGill University,
MONTREAL, Quebec.

Re: Project "Study of Genetics of Epilepsy"

Dear Dr. Boyes:

Thank you for your letter of April 7th and for the two copies of the final report on this project which came along from Dr. Gregoire.

The report has been passed along to Dr. Roberts for his perusal. We understand he is at present out of the city and will not return for about a month. However, on his return he will let you know if a supplement to the present data is required.

Yours very truly,

Gordon E. Wride, M.D., D.P.H.,
Principal Medical Officer,
National Health Grants.

GEW/jg

30 June 55

DEPARTMENT OF

NATIONAL HEALTH AND WELFARE

Memorandum: Dr. Roberts

I have not acknowledged this letter as I thought you might want to make some comments on the report.

M.V.

001029

McGILL UNIVERSITY
MONTREAL

April 7th, 1955.

Dr. Gordon E. Wride, D.P.H.,
Principal Medical Officer,
National Health Grants,
Ottawa, Canada.

re: 604-5-25 - Study of Genetics of Epilepsy

Dear Dr. Wride,

This is to let you know that I have forwarded to you, through Dr. Jean Grégoire, two copies of our final report on the Study of Genetics of Epilepsy - Project No. 604-5-25.

I regret that we were unable to forward this to you promptly as of March 31st and hope that the slight delay will not be of any inconvenience to you.

In presenting most of the data we have used to a considerable extent histograms combined with pertinent data. We feel that this method of presentation is the clearest, but appreciate that you may desire to have a more detailed presentation of the actual data used in the preparation of these histograms for use in statistical analyses. If this is your wish, we will of course prepare a supplement setting forth in more detail the data and their analyses.

With very best personal regards, I remain,

Yours very sincerely,

J. W. Boyes

J. W. Boyes, Chairman,
Department of Genetics.

JWB:mm

Report not yet received as of April 19th 1955 [illegible]

R 604-5-25

OTTAWA, April 15, 1955.

Jean Gregoire, Esq., M.D., D.P.H.,
Deputy Minister,
Ministry of Health for the
Province of Quebec,
QUEBEC, Quebec.

ATTENTION: Dr. J.C. Beaudet

Re: Project "Study of Genetics of Epilepsy (McGill University")

Dear Dr. Gregoire:

This will acknowledge, with thanks, receipt of your letter of April 7th forwarding two copies of a final report on the above mentioned project.

Yours very truly,

Gordon E. Wride, M.D., D.P.H.,
Principal Medical Officer,
National Health Grants.

/jg

1 copy to Library

PROVINCE OF QUEBEC
MINISTRY OF HEALTH
DEPUTY MINISTER'S OFFICE

Quebec, April 7, 1955.

Doctor G.E. Wride,
Principal Medical Officer,
Health Insurance Studies,
Department of National Health & Welfare,
Ottawa, Ont.

Re: 604-5-25-Study of Genetics of Epilepsy.

Dear Doctor Wride:

With reference to your letter of March 16th I am enclosing herewith two copies of a final report on the above mentioned project.

Yours very truly,

Jean Gregoire, M.D.,
Deputy Minister.

JCB/dm
encl.

STUDY OF
GENETICS OF EPILEPSY
PROJECT No. 604-5-25
FINAL REPORT

Project No. 604-5-25
Final Report
March 31, 1955.

- STUDY OF GENETICS OF EPILEPSY -

I. INTRODUCTION

1-13

Throughout the history of epilepsy various investigators have suggested that the frequency of convulsive disorders among the relatives of epileptics may be several times higher than among the relatives of non-epileptics. However, the earlier estimates were based mainly on the presence or absence of a positive family history, and often without regard to the genetic relationship of the affected individuals to the proband. Consequently, because of the wide distribution of the epileptic symptom-complex throughout the population, reports of eighty percent or more of positive family histories were not uncommon. It was not until comparatively recent years that the statistical approach has been employed, using the correlation, contingency and twin study methods.

The chief contribution in support of an hereditary factor in the etiology of epilepsy has been made by Lennox[9], who analyzed the medical histories of 20,000 near relatives, i.e., the parents, siblings and children, of 4231 epileptics. He divided the index cases into two groups: 1) those with antecedent brain injury which he terms "symptomatic", and 2) those with no apparent history of antecedent brain injury which he terms "essential" or asymptomatic. Using the incidence of epilepsy among the United States of America draftees of World War I and II (0.515%), Lennox finds a significantly higher incidence of epilepsy among the relatives of both the symptomatic (3.6 times as high) and the essential (7.2 times as high) groups.

Lennox's evidence for a hereditary predisposition to epilepsy is supported further by the longitudinal study of 173 twin pairs made by Lennox and Jolly[14]. Among the monozygotic twins of this series approximately 60% were concordant whereas approximately 10% were concordant among the dizygotic twins. Furthermore, the concordance rate was considerably higher (84%) when monozygotic twins without prior brain damage were considered separately. This high degree of concordance among the monozygotic twins without antecedent brain damage was present also in the type of seizure and in the pattern of the electroencephalographic epileptiform discharge.

Recently, Alstrom[15], a Swedish investigator, has challenged the "evidence" for a hereditary factor in the etiology of epilepsy, reporting that the overall incidence of 1.5% which he found among the near relatives of 897 epileptic probands was not significantly higher than the frequency of epilepsy in the same control group used by Lennox[9]. Furthermore, when Alstrom divided his epileptics into three distinct groups, namely those with unknown, probable, and known etiology to account for their seizures, he found no significant difference in the incidence of epilepsy in the near relatives of these three groups. (It must be pointed out, however, that the incidence of 1.7%, 1.2% and 1.1% for the "unknown", "probable" and "known" groups was in the direction expected from Lennox's study).

The schism between these two diametrically opposite points of view becomes even more pronounced when it is considered that the massive and painstakingly collected data of both Lennox and Alstrom is subject to and has received considerable criticism. For example, some of Lennox's material may have been biased by the fact that about one-third of his index cases were referred to him by other neurologists who knew that he was

interested in familial cases. It is our opinion and experience[16] that such a procedure is more likely to produce a case with a positive family history than a sporadic one, thus causing the incidence of epilepsy in the relatives of the index cases to appear unduly high. The twin data collected by Lennox and Jolly[14] may also be biased since the proportion of monozygotic to dizygotic pairs far exceeds the one-to-two ratio which is found in an unselected population[17]. Unless epilepsy occurs more frequently in monozygotic than in dizygotic twins -- a supposition not supported by other twin series[5,15,18] -- then this excess would suggest that the twins were not selected on the sole basis that one of the pair had epilepsy. Whenever twin pairs are selected by criteria other than that one of the pair has epilepsy, then it becomes highly probable that concordant pairs would be selected more frequently than discordant ones[17].

The incidence of epilepsy in the control population used by Lennox[9] was based on the proportion of draftees (0.515%) in the United States rejected because of epilepsy. Comparing the incidence of epilepsy in the near relatives of the index cases with this type of control group is not justified for no account is taken of the sex and age distribution and of other dissimilarities which make the two groups not comparable.

With regard to Alstrom's methods, Steinberg[19] has pointed out that biases of a different nature may have occurred in his selection of index cases. More important, Steinberg has shown that in Alstrom's data the incidence of epilepsy in the siblings of index cases is higher if one parent is affected than if both parents are normal; a fact not pointed out by Alstrom but which nevertheless suggests that genetic factors may be in operation. Davidson[20] has pointed out that the lower frequency of epilepsy among the near relatives of Alstrom's epileptic probands may be due to the later

age of onset of seizures among Alstrom's patients as compared to Lennox's patients for in both groups the age of onset seems to be correlated with the frequency of epilepsy that is found among the relatives.

It has already been pointed out that although there was no significant difference between Alstrom's three groups of epileptics, nevertheless the figures are in the same direction as Lennox's. Unfortunately, Alstrom, like Lennox, has no adequate control group.

In 1940 Lennox et al[21] published data suggesting that the cortical dysrhythmia underlying the epileptic diathesis is inherited as a Mendelian dominant factor. Although his later publications do not fit his theory as well as the earlier ones did, nevertheless the idea of an inherited cortical dysrhythmia and the idea that cortical dysrhythmia might be the predisposing factor to seizures have been suggested by so many investigators[21-27] that they merit further investigation.

II. PROPOSED RESEARCH

In view of the two diametrically conflicting opinions regarding the role of heredity as an etiological factor in convulsive disorders it was deemed necessary that an independent group be organized to reinvestigate the question of heredity in epilepsy.

The results of earlier and current investigators suggest that if a hereditary factor is involved in the production of epilepsy, then the group in which this factor is most likely to be demonstrated is in the so-called "idiopathic" form. However, neither the term "idiopathic" nor its many synonyms -- familial, cryptogenic, essential, petit-mal, hereditary, metabolic, asymptomatic, genetic, genuine, intrinsic, etc., -- none of these terms describe adequately and objectively, the type of

epilepsy under investigation.

Recently Penfield and Jasper[28] have formulated a system of classification which places seizures into three main groups, namely localized, unlocalized and centrencephalic, depending upon the origin of the epileptic discharge within the central nervous system. The chief advantage of this classification is that it attempts to correlate the type of clinical seizures with the pattern of the electroencephalogram, or, as it was mentioned above, the origin of the epileptic discharge within the central nervous system.

Centrencephalic Probands: For the reasons outlined above, this investigation was begun by taking epileptic probands from the Neurology Service of The Montreal Children's Hospital who have:-

1) a history of recurrent petit-mal and/or grand mal seizures;

2) no obvious neuropathology to account for their seizures; and

3) a centrencephalic type of electroencephalogram, i.e., either a typical paroxysmal bilaterally synchronous 3/sec. wave-and-spike (Fig.1-A) or an atypical epileptiform discharge originating from the centrencephalic areas of the higher brain stem.

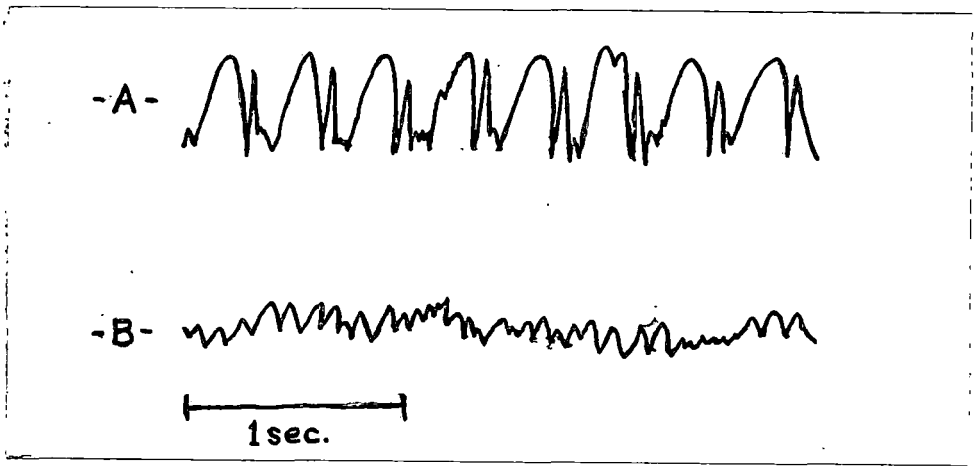

FIG. 1-A) Typical centrencephalic 3/sec. wave-and-spike EEG; and B) Normal EEG for child 6 yrs. old.

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In actual practice, the medical records of all patients who come to the Neurology Service with a history of seizures are examined and if there is no obvious neuropathology to account for the seizures and if the EEG pattern is of the centrencephalic type (Fig. 1-A) then the patient becomes an index case and family studies as outlined below are undertaken. Obtaining epileptic probands by these specific and objective criteria and then investigating their families ensures a reasonable uniformity in the group and was considered the most efficient and quickest way to arrive at an answer to the question of whether epilepsy and/or cortical dysrhythmia are abnormally frequent in the relatives of patients with a clearly defined type of epilepsy. A brief medical history of such a centrencephalic proband and which illustrates some of the problems that must be dealt with in handling epileptics is given below:-

Case [redacted] born [redacted] who at the age of [redacted] years began to have typical petit mal seizures. At first the seizures would occur quite frequently for a two-to-three-day period followed by a two-to-four-day period when there were relatively few seizure episodes. The seizure episodes had been observed by the parents and the teacher. It is stated that each episode would last from 5 to 30 seconds. She was first seen at the MCH in April 1951 at which time it was learned that her birth and early development were normal and that she never had any serious accidents or illnesses. She has never had a generalized convulsion. Physical examination, including a detailed central nervous system investigation, were within normal limits. Her skull X-ray is normal. In June 1951 her EEG showed typical 3/sec. wave-and-spike complexes consistent with centrencephalic epilepsy (Fig. 2). Her full scale I.Q. is 101. She was placed on

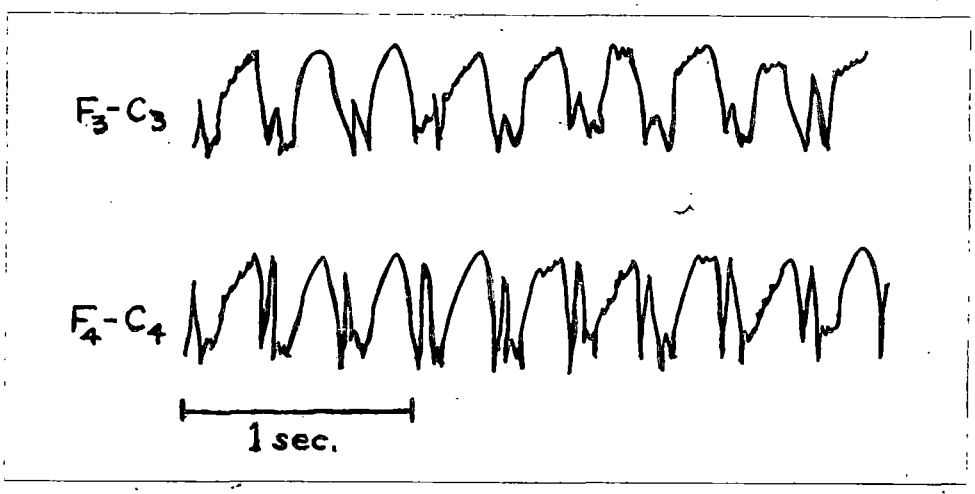


Fig.2. Centrencephalic EEG of a [redacted] year old girl with petit mal epilepsy.

a daily dose of phenobarbital when first seen and her seizures ceased and she was reported to be doing quite well both in respect to seizures and school work. The family is pleased with her progress and have not found it necessary to tell relatives and friends about the patient's condition, however, they have been warned to exercise caution where heights, swimming and bicycling are concerned. A repeat EEG in August 1954 showed no typical wave-and-spike activity but there were some 3/sec. paroxysmal waves suggestive of a centrencephalic disorder. In February 1954 the parents complained that at times she acted as if she was hard of hearing and that questions and commands had to be repeated before she would respond. It is difficult to state whether these were episodes of hidden seizures; however, because of the rapid growth of the patient, the continued EEG abnormality, plus the fact that she had been on very small amounts of anti-convulsant drugs, it was felt advisable to increase her medication and thereby ward off any recurrence of seizures. She is now on phenobarbital and paradione. She was last seen in December 1954 and has been doing very well with no further suggestions of hidden seizures. Her hemogram is within normal limits. She is to be seen three to four times a year and have a repeat EEG in September 1955. Since the patient began coming here for diagnosis, research, treatment, and follow-up, there have been more than twenty-five visits plus numerous telephone conversations with the mother. Prognosis must still be guarded.

Control Probands: Selecting an adequate control group to compare with the centrencephalic group is a difficult task but also of paramount importance in interpreting the data collected. The epileptic and control probands must be as comparable as possible in order to control the experiment and get rid of variable factors other than those to be studied. For example, the two groups must be similar for 1) age and sex of proband, 2) parental age, 3) size of proband's and parents' sibship, 4) ethnic origin, 5) miscarriage and stillborn rate of mother and paternal and maternal grandmother, 6) intelligence quotient of probands, 7) birth order of proband, father and mother, 8) parental consaguinity, 9) frequency of twinning, 10) socio-economic status, and for many other variables, unless, of course, one of these factors is correlated with the presence or absence of epilepsy.

For reasons of comparison, therefore, the control probands are drawn at random from the same hospital population to which the epileptics belong. And again, in actual practice, the medical record of every fifth admission is examined and if there is no history of convulsions and if the patient

is not in the Infant Ward (for technical reasons, it is difficult to obtain electroencephalograms from infants) the child becomes a potential control proband. An EEG is ordered (providing, of course, that the child's illness is not neuropathological) and if the pattern is found to be within normal limits, the patient is accepted as a control proband. (Potential probands who have no history of seizures and no neuropathology but whose EEG is not within the normal limits are not accepted in the present control group, but are now being used in a projected study which was begun recently.)

Following is a brief medical history of a typical control proband:

Case born . who has never had any seizures. She came into the control series when she was admitted to the hospital for a tonsillectomy. Physical and CNS examinations were normal. Birth was said to be normal and early developmental milestones were within normal limits. She never had a serious illness or an accident. Her EEG was within normal limits for her age group (Fig. 3) and her full scale I.Q. is 100.

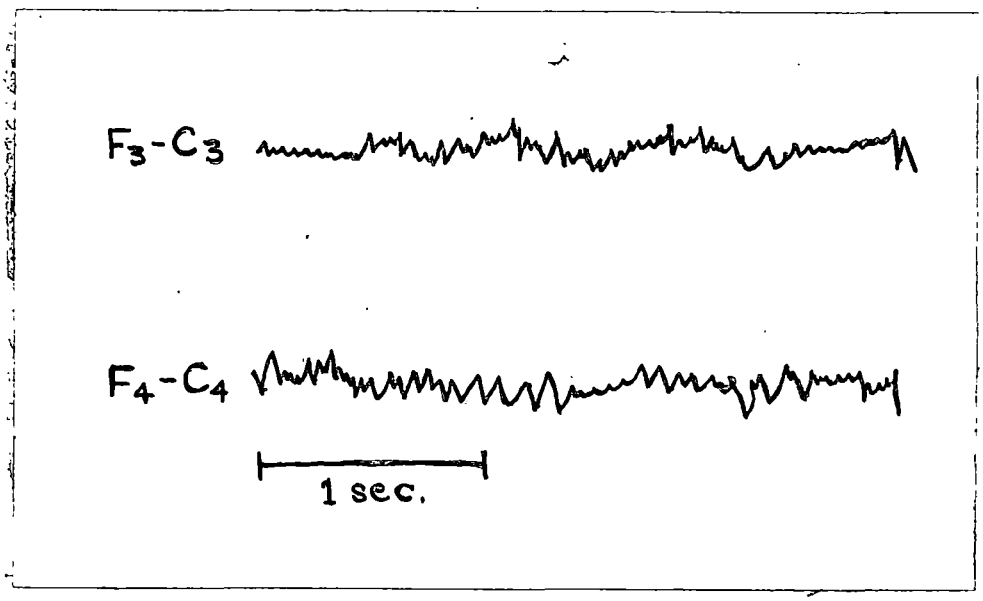


Fig. 3. Normal EEG of a year old girl who has no history of epilepsy.

Family-Studies: When a suitable proband is found, centrencephalic or control, a family and medical history is taken by interviewing the parents, and in some cases, one or more of the grandparents. In the family history information is obtained about the siblings, parents, grandparents, aunts, uncles and cousins of the probands (Fig. 4).

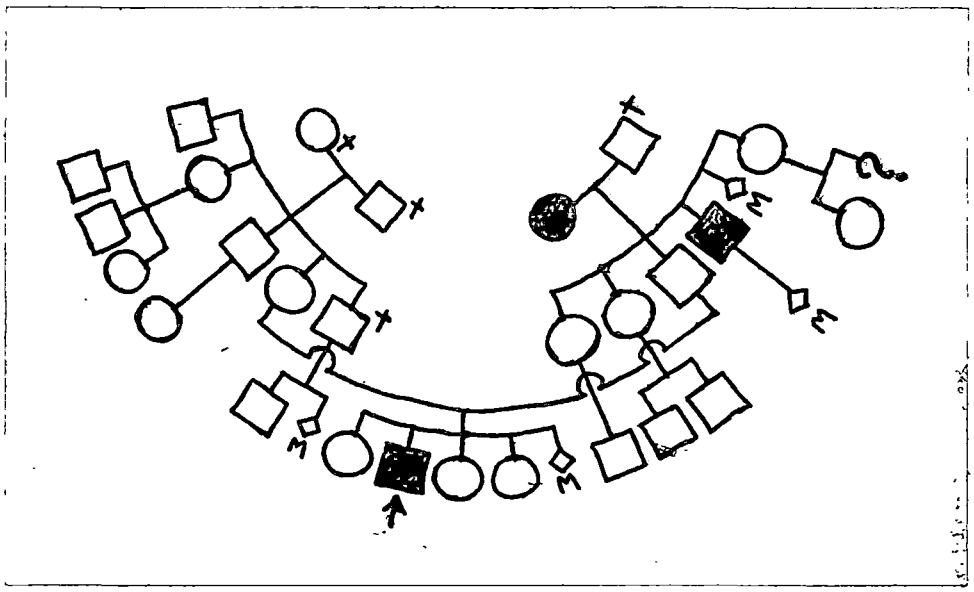


Fig. 4. Pedigree illustrating all near relatives of proband who is here indicated by an arrow.

Other near relatives, such as children of siblings of the proband, may also enter the pedigree but they are not included in the present analyses. A detailed investigation, including a neurological and electroencephalographic examination of the parents and siblings is made. Psychometric studies are done on the probands of both the epileptic and control groups in order to ascertain whether persons with centrencephalic epilepsy suffer any mental deterioration.

Whenever a history of a convulsive disorder in anyone within the limits of the pedigree is obtained an effort is made to substantiate all such reports by seeing the individual and/or by writing to the hospital or physician concerned. (Recently this project has received additional financial support and it has become possible to employ a Social Worker who contacts persons with a history of convulsions and directs them to the neurologist of the project (K.D.M.) for further questioning and examination.)

At this point, two things must be emphasized: firstly that the same procedures are undertaken in investigating the families of centrencephalic and control probands; and secondly, that centrencephalic or control probands are used only to identify the centrencephalic or control families but are not included in "frequency" or "incidence-of-the-condition" analyses[29].

III. PILOT STUDY

Before the above plan of procedure was put into effect, one of us (F.C.F.) attended the epilepsy clinic of the Montreal Neurological Institute and collected a number of pedigrees of epileptic patients. This was done in order to get an idea of the problems involved in a study such as the one which eventually was undertaken.

Although pedigrees collected only by interview of a single family member are unreliable for genetic analysis of diseases as capricious as epilepsy, the experience gained was most helpful in designing the present program in such a way as to avoid some of the pitfalls of ascertainment[30] which previous workers have fallen into.

Eight twin pairs where at least one member has epilepsy had been located and studied by one of us (J.D.M.) before the present project was undertaken. It is believed that the zygosity and concordance or discordance of these twins have been adequately established. The investigation of all twins that come into the centrencephalic or control series is continued and as soon as an adequate series is available the twin study method of analysis will be made[31].

IV. RESULTS

Employing the methods outlined above 55 centrencephalic (35 typical and 20 atypical) and 52 control families have been studied. This represents the results of the present investigation up to September 30, 1954.

Sex of Probands: Table 1 shows the sex distribution among the 55 centrencephalic and 52 control probands. This is compared with the sex distribution found among 259 patients of Wards D and E, the source of most of the control probands.

TABLE 1.

SEX OF 55 CENTRENCEPHALIC, 52 CONTROL AND 259 WARD D AND E PROBANDS.

SEX	CENTRENCEPHALIC	CONTROL	WARD D & E
FEMALE	30	19	102
MALE	25	33	157
TOTAL	55	52	259

The sex distribution of 30♀♀ and 25♂♂ in the centrencephalic group is not

statistically significant (X^2=3.49; P=.10) from the 19♀♀ and 33♂♂ in the control nor from the 102♀♀ and 157♂♂ in the Ward D and E control (X^2=4.28; P=.05). There is no indication, therefore, from the present series that centrencephalic epilepsy is more common among girls than among boys for the 30:25 ratio is not significantly different from a 1:1 ratio nor from the two control ratios 19:33 and 102:157 which are predominantly male. In Alstrom's[15] epileptics, those with unknown etiology, i.e., the group most comparable with the present series, there were 300♀♀ and 306♂♂, a ratio obviously not significantly different from 1:1.

Age of Probands, Mothers and Fathers: In Table 2 are listed the mean age in months of the probands and the mean age in years of the mothers and fathers. The mean age of the "centrencephalic" mothers (26.98±0.80yrs.) and of the "control" mothers (26.58±0.73 yrs.) and also the mean age of the "centrencephalic" fathers (29.95±0.71 yrs.) and of the "control" fathers (30.48±0.78 yrs.) are very similar in the two groups.

TABLE 2.

MEAN AGE OF PROBANDS, MOTHERS AND FATHERS.

	CENTREN-CEPHALIC	CONTROL	P
PROBANDS	94.54±7.17 mos.	80.02±5.59 mos.	.20
MOTHERS	26.98±0.80 yrs.	26.58±0.73 yrs.	.80
FATHERS	29.95±0.71 yrs.	30.48±0.78 yrs.	.70

The mean age of the centrencephalic probands (94.54±7.17 mos.) is approximately 14 mos. more than the mean age of the control probands (80.02±5.59 mos.). However, this difference is not statistically significant (P=.20) and it must be pointed out that the mean age of the centrencephalic

probands that is given here is the age at which the centrencephalic patients were first seen by the project neurologist (K.D.M.) and not the age at which they had their first seizures, nor the age at which they were first seen at the Neurology Clinic.

Ethnic Origin: The majority of the patients of the Montreal Children's Hospital are more or less equally divided between French and English. The remainder, which constitute about 10%, are Jewish, Negroes or of some other ethnic origin. In Table 3 the probands are divided among French, English, Jewish and other ethnic origins and the distribution among the centrencephalic and control is compared. It is quite apparent from the figures that there is no statistically significant difference between the two groups (P=.60)

TABLE 3.

ETHNIC ORIGIN.

	CENTREN-CEPHALIC	CONTROL	TOTAL
FRENCH	47%	48%	48%
ENGLISH	44%	35%	39%
JEWISH	5%	6%	6%
OTHER	4%	11%	7%
TOTAL	100%	100%	100%

Pregnancy History: In order to find out if there are any differences in the number and type of pregnancies between the centrencephalic and control groups, the pregnancy histories of the mother, maternal and paternal grandmothers of the two groups were compared. In these comparisons the proband, mother, and father are included among the pregnancies of the mother, maternal and paternal grandmothers, respectively.

In Table 4 the number of liveborn pregnancies are compared and no significant differences are found. The higher number of pregnancies (6-7) that the grandmothers have than the mothers (3-4) is partly due to the fact that the grandmothers' families are, for the most part, complete whereas most of the maternal ones are incomplete.

TABLE 4.

LIVEBORN PREGNANCIES OF MOTHERS AND OF MATERNAL AND PATERNAL GRANDMOTHERS

	CENTREN-CEPHALIC	CONTROL	P
MOTHERS	3.31 ± 0.25	3.60 ± 0.28	.50
MATERNAL GMS	6.20 ± 0.57	6.79 ± 0.48	.50
PATERNAL GMS	5.71 ± 0.38	6.40 ± 0.64	.40

In Table 5 the same type of analysis as in Table 4 is undertaken only here the miscarriages and stillborn are considered. Again there is no significant difference between the centrencephalic and control mothers and grandmothers.

TABLE 5.

MISCARRIAGE AND STILLBORN PREGNANCIES OF MOTHERS AND OF MATERNAL AND PATERNAL GRANDMOTHERS

	CENTREN-CEPHALIC	CONTROL	P
MOTHERS	0.60 ± 0.15	0.37 ± 0.08	.20
MATERNAL GMS	0.71 ± 0.16	0.69 ± 0.19	.90
PATERNAL GMS	0.31 ± 0.13	0.29 ± 0.01	.90

In Table 6 the total number of pregnancies of the mothers and grandmothers of the two groups are compared. As anticipated from Tables 4 and 5 no significant difference was found.

TABLE 6.

TOTAL NUMBER OF PREGNANCIES OF MOTHERS AND OF MATERNAL AND PATERNAL GRANDMOTHERS

	CENTREN-CEPHALIC	CONTROL	P
MOTHERS	3.91 ± 0.32	3.96 ± 0.31	.90
MATERNAL GMS	6.91 ± 0.59	7.48 ± 0.54	.50
PATERNAL GMS	6.02 ± 0.41	6.69 ± 0.66	.40

There is no indication whatsoever from Tables 4, 5 and 6 that there is any significant difference between the centrencephalic and control groups as to number or type of pregnancies of the mothers and grandmothers.

Birth Order: It has been suggested by many that birth order may be a factor in epilepsy. If first born are more subject to birth trauma then one would expect birth order to be one of the factors in focal epilepsy. However, the question here is whether birth order is a factor in epileptics with no demonstrable cerebral injury. Nielsen and Butler[32] have suggested that "birth primacy" is a cause of idiopathic epilepsy. On the other hand, however, Orr and Risch[33] have suggested that "epilepsy occurred more frequently in people approaching the end of the line of birth rather than in those holding the position of first born".

In Table 7 the birth order of the 55 centrencephalic, 52 control and of the 259 Ward D & E patients referred to in Table 1 is compared. The centrencephalic group does not differ significantly from either of the two controls (P=.30 and .40).

TABLE 7.

BIRTH ORDER

BIRTH ORDER	CENTRENCEPHALIC No.	%	CONTROL No.	%	WARD D & E No.	%
1	23	42%	17	33%	105	41%
2	13	24%	11	21%	67	26%
3	10	18%	11	21%	39	15%
4	6	11%	4	8%	26	10%
5	1	2%	4	8%	8	3%
6-13	2	4%	5	10%	14	5%
TOTAL	55	101%	52	101%	259	100%

Parental Consanguinity: The significance of parental consanguinity in the family history has been amply demonstrated by Fraser[34,35] and many others. In the 107 families of the present series only in one were the parents related. This was a centrencephalic family and the parents were second cousins (Fig. 5). This single case of parental consanguinity

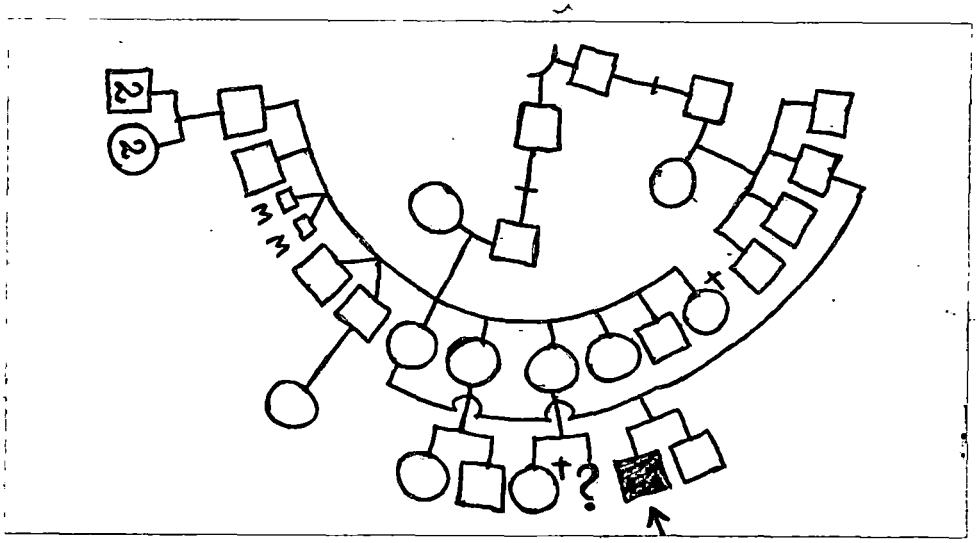


Fig. 5. Case D.M.; parental consanguinity in a centrencephalic family.

in 55 centrencephalic families is not significantly higher than the one per cent estimate that is given by Stern[36] as the incidence in the general population.

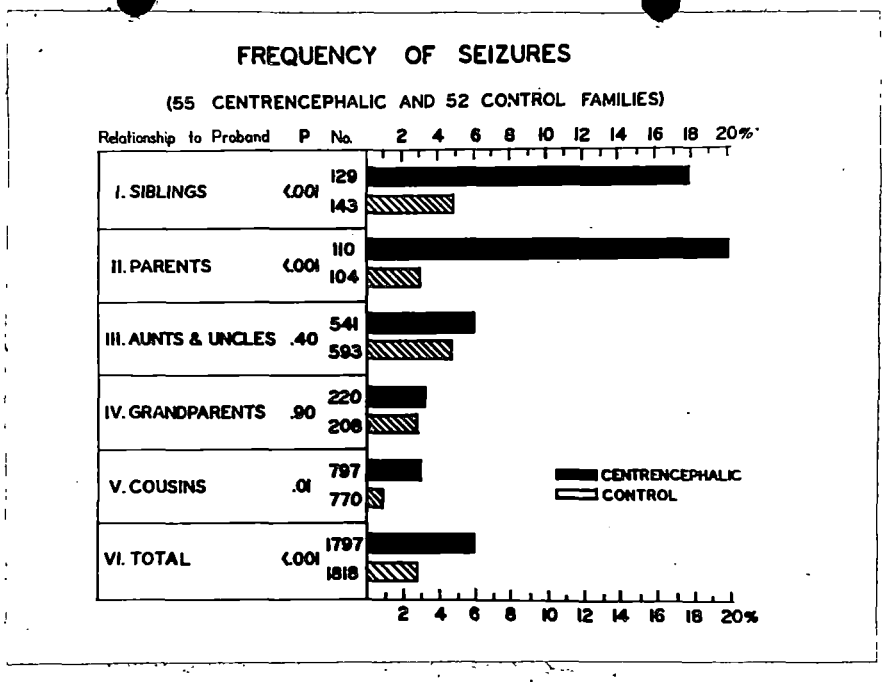
Psychometric Examinations: As has been stated previously a psychometric examination of both centrencephalic and control probands is undertaken. This examination includes a) an intelligence quotient based on verbal and non-verbal tests; b) a social quotient; c) a visuo-motor acuity test, and other tests as deemed necessary. Separate point values are assigned to the various tests and then an overall Intelligence Quotient is recommended by the psychologist who has conducted the tests as being representative of the child's overall mental capabilities. There was no significant difference found (P=.50) when this overall Intelligence Quotient of 41 centrencephalic probands (93.9±3.0) was compared with that of 22 control probands (94.3±4.5). However, it is important to point out that four of the centrencephalic probands have shown deterioration in their full scale I.Q., having deteriorated from the normal average range of 85-100 to the mental defective but presumably educable range of 60-70.

Frequency of Seizures: In the frequency of seizures and electroencephalographic abnormalities no sex difference was obtained, hence, for simplicity in the analyses which follow the figures for the two sexes have been combined.

In each sibship only full siblings have been included. So that, for example, half-brothers or maternal half-uncles have been omitted.

In Table 8 the frequency of seizures in the near relatives of the 55 centrencephalic and 52 control families is compared.

TABLE 8



An individual is classified as affected if his seizures are not attributed to metabolic disorders, hysteria, syncope or carotid sinus syndrome. Individuals with vague and unsubstantiated history of seizures are omitted from this analysis. It must be clearly stated that individuals who are classed as affected cannot be regarded as belonging exclusively to the centrencephalic class. On the other hand, of all the affected relatives, approximately 88% had three or more epileptic episodes and in addition many of these were on drug therapy and could be classed as chronic epileptics.

The total number of relatives investigated in each group is shown at the base of each histogram. In all there were 1797 relatives in the centrencephalic and 1818 in the control group.

In summary the following observations may be made from this table:-

1) As the genetic distance between the relative studied and the proband increases, the frequency of epileptic seizures tends to decrease (from approximately 20% to 3%) in the case of the centrencephalic group, but tends to fluctuate within fairly narrow limits around 3% in the control group.

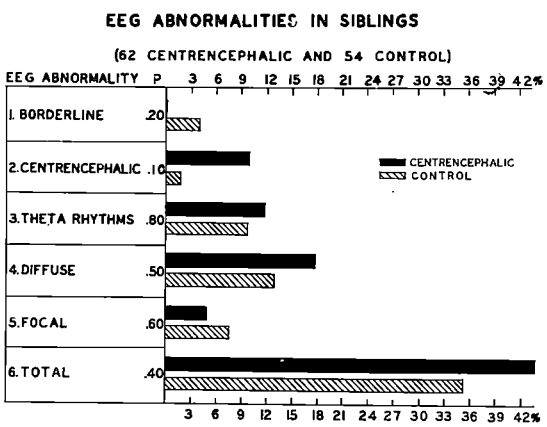
2) The frequency of seizures among the siblings (17.8%), parents (20.0%) and cousins (2.9%) of the centrencephalic probands is significantly higher than the comparable frequencies (4.9%, 2.9%, and 0.9%) of the control probands. The aunts and uncles group would also be significant save for a single control family in which eight of the ten maternal aunts and uncles presented a definite history of seizures.

3) The frequency of seizures among the parents of the centrencephalic probands (20%) is comparable with that among the siblings (17.8%). (The possible genetic significance of this observation will be discussed in a later section.)

4) When all the near relatives are considered together, the frequency of seizures in the centrencephalic group (6.0%) is more than two times and significantly higher (P=.001) than in the control group (2.8%).

EEG Abnormalities: In Table 9 the EEG abnormalities of 62 centrencephalic and 54 control siblings are considered separately under five main classes of EEG abnormalities[28], and also all together.

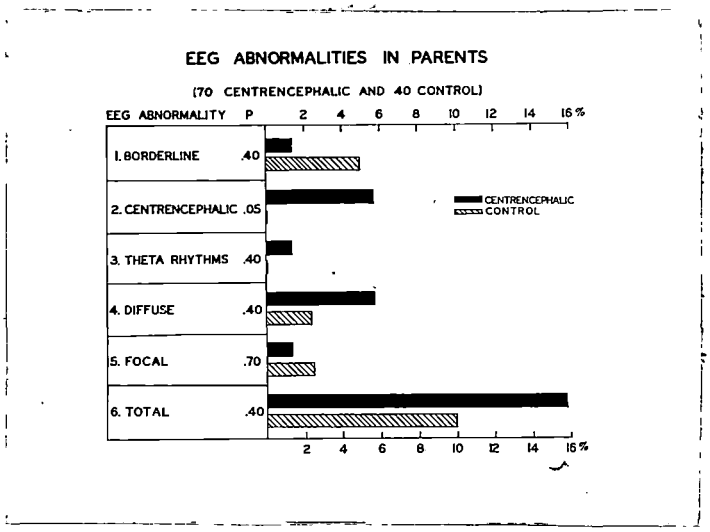
TABLE 9.



Contrary to all expectations and to the amazement of the electroencephalographers, the total number of EEG abnormalities in the centrencephalic group (43.6%) although numerically greater was not significantly higher (P=.40) than in the control group (35.2%). Nor were there any statistical differences obtained when the abnormalities were considered separately under Borderline, Centrencephalic, Theta Rhythms, Diffuse, or Focal. It should be pointed out, however, that the lowest P value (.10) was obtained for the centrencephalic type of EEG abnormality where six centrencephalic and one control siblings had the abnormality.

In Table 10 the same comparisons are made for 70 centrencephalic and 40 control parents. Again the total number of EEG abnormalities

TABLE 10.

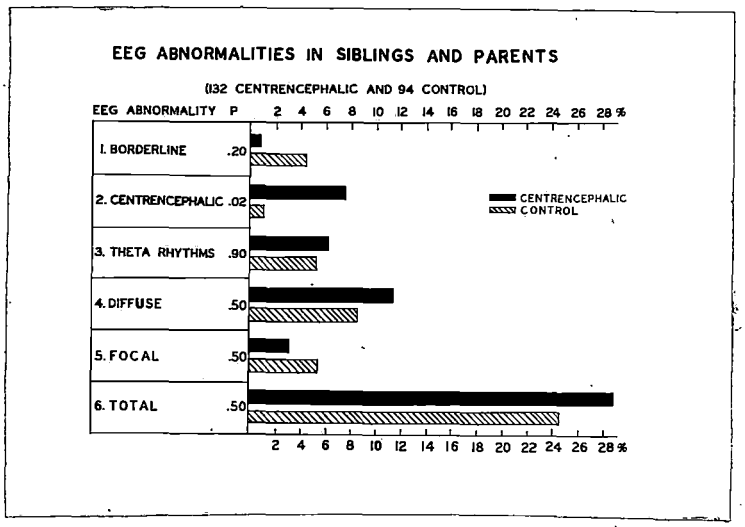


in the centrencaphalic group (15.7%) is numerically greater but not significantly higher (P=.40) than in the control group (10.0%). And again the lowest and only P value (.05) approaching significance was for the centrencephalic group of EEG abnormalities. There were four parents in

the centrencephalic and none in the control that had a centrencephalic type of EEG abnormality.

Table 11 combines the data of the last two tables and considers siblings and parents together. 132 siblings and parents of the centrencephalic group are compared with 94 of the control. As anticipated

TABLE 11.



from the last two tables, there are no strongly significant differences either for the total or for any of the individual abnormalities. The ten centrencephalic EEG abnormalities of the centrencephalic group are significantly more numerous at the 2% level than the single case in the control.

In summary, therefore, the electroencephalographic studies of the present investigation do not reveal any positive evidence that cerebral dysrhythmias of the type other than the centrencephalic are more likely to be obtained in the near relatives of centrencephalic than in control patients. That the centrencephalic type of EEG abnormality is correlated with the presence of seizures is supported by the fact that of the ten parents and siblings with a centrencephalic type of EEG seven also

had clinical seizures.

Mode of inheritance: Of the 55 centrencephalic probands 35 had no affected parent with regard to clinical seizures, 18 had one affected parent (11 mothers and 7 fathers) and two had both parents affected. Table 12 shows that the frequency of seizures among the siblings of the 18 centrencephalic probands who had one parent affected (19.5%) is not significantly higher (P=.50) than in the siblings of the 35 "unaffected parent" families (17.1%).

In pedigrees such as those shown in Figs. 6 and 7 one is struck by the suggestion that seizures tend to be grouped among members of one side of the family and not be distributed randomly through both sides of the family.

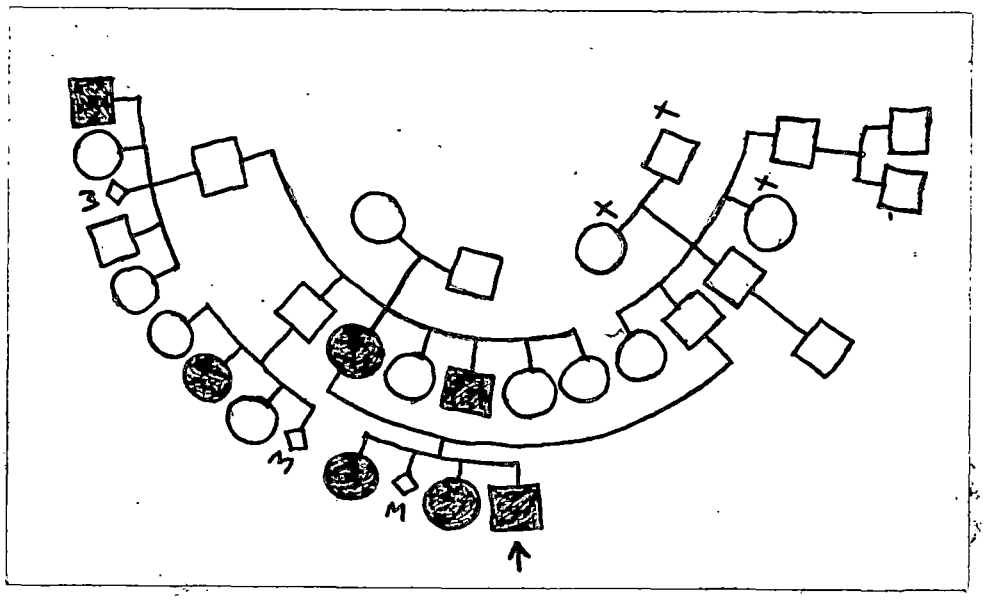


Fig. 6. Pedigree with four affected members on the maternal side.

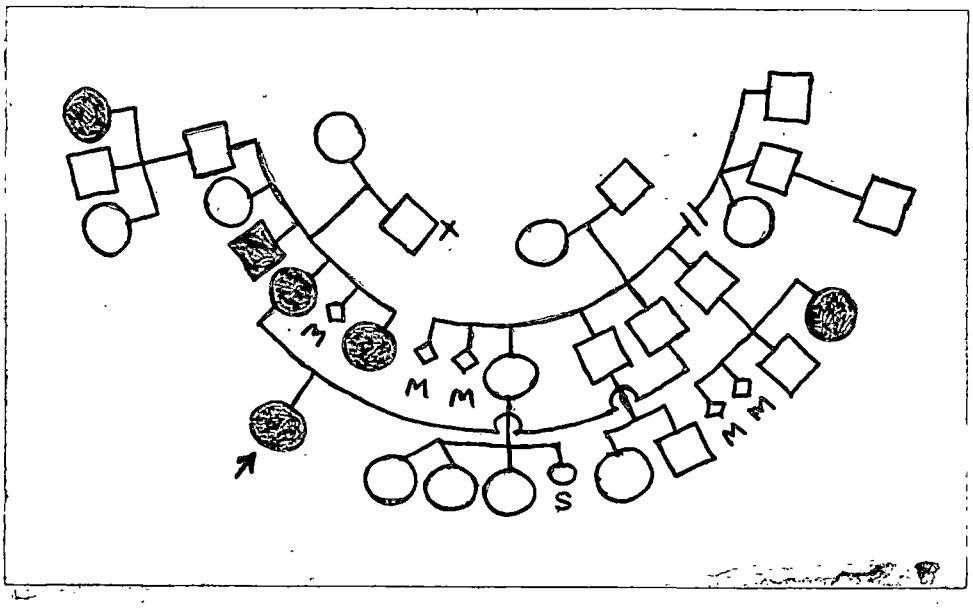
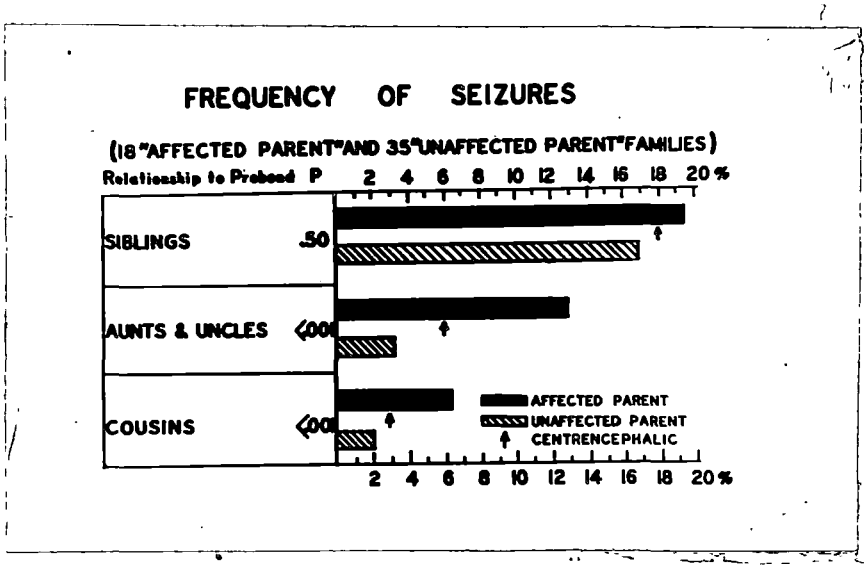


Fig. 7. Pedigree with four affected members on the maternal side and one on the paternal side.

To test whether seizures tended to be confined to individuals on the "affected parent" side of the family, the following analysis was made. The frequency of seizures among the aunts and uncles of the "affected parent" side of the family -- in other words the siblings of the affected parent -- was compared with the frequency of the same relatives of the unaffected side of the family. The same thing was done with the cousins of the proband, i.e. the nephews and nieces of the affected and unaffected parent.

Table 12 clearly demonstrates the following two points:-

TABLE 12



1) The 3% frequency of seizures among the aunts and uncles and among the cousins of the "unaffected parent" families is comparable with that found for the same relatives of the control group; and

2) There is conclusive evidence that seizures tend to appear significantly more often (P=.001) in the "affected parent" side of the family than in the "unaffected parent" side, for the frequency among the aunts and uncles (12.8%) and among the cousins (6.2%) of the "affected parent" families is three to five times higher than in the same relatives of the "unaffected parent" side of the family (2.9% and 2.0% respectively).

These findings are compatible with a dominant mode of inheritance[30].

Clinical Aspects: In an investigation such as this one, it is impossible to separate completely the research aspects from the clinical aspects, for the two go side by side. As has been pointed out before, when a child comes to the Montreal Children's Hospital with a history of seizures, a medical examination, patch test, and blood Wasserman are done and then the child is referred to the Neurology Clinic for further investigation and treatment. If the EEG is centrencephalic and the case meets the research criteria then the patient becomes an index case and is followed by the neurologist of the project (K.D.M.) at a special neurology clinic which comes under the direct supervision of the Chief of Neurology Service. However, referral to this special clinic does not mean for research purposes only but for the entire management of the case and the family. If, for example, a condition is found in the patient or in a relative of the patient which requires medical supervision, then this is done either by the special neurology clinic personnel or by referring the person to the correct clinic or physician.

Thus an attempt has been made to integrate all phases of medical care under one physician's supervision. Needless to say that when research and clinical treatment are conducted simultaneously, the research team is assured of better cooperation from the patient, parents, hospital staff and referring physician.

When a child first comes to the special neurology clinic, discussions with the parents regarding general management are begun. The main purpose of these discussions is to get the parents to accept that their child has epilepsy, for once this is achieved complete cooperation in following the neurologist's directions becomes more or less automatic.

During these talks with the parents, advice is given regarding 1) emergency care during a convulsion; 2) a good regime with special reference to rest, healthy diet, vitamin supplement and outdoor activities and 3) need for epileptic child to lead as normal a life as possible with no severe curtailment of activities. Later when the confidence and cooperation of the parents has been obtained, treatment and prognosis are discussed in greater detail.

In these cases chemotherapy is, of course, the keystone to treatment. The more commonly used drugs are phenobarbital, dilantin, paradione, tridione, trimedone, mesantoin, mysoline, milontin, pheunurone, thiantoin, bromides, and mebarol[37-42]. These may be used alone or in various combinations. It seems best as a general rule to begin with phenobarbital, then following a trial period, if results are unsatisfactory, to add dilantin and/or tridione. If hyperactivity or behaviour problems are complicating factors, then benadryl, dexedrine, benzedrine, serpasil, or

largactil (chloropromazine) may be used.

In order to evaluate the progress being made by an individual patient, he must be followed regularly watching for toxic effects, blood changes, and changes in the electroencephalogram. It is felt that the patient should be free from seizures while on medication for at least two years before a gradual decrease in medication is attempted.

Social service is active in most of these cases for their help is necessary in evaluating the family, arranging for schooling and camps, and for eventual rehabilitation and vocational guidance.

There are, too, many emotional problems which must be met. The parents have many anxieties and fears and may soon become "worn out" by their child's condition unless proper guidance and frank attitudes are forthcoming from the physician, the social worker, and from everyone else concerned with the case. The comforting, moral support that is given by the physician to the parents ranks high as a factor in total treatment.

Finally it must be stated that in our experience about 80-90% of childhood epileptics are fairly easily handled and come under control quickly. The other 10-20%, however, are very difficult to handle and no matter how much or type of medicine is given, they still have many seizures and may eventually deteriorate and become behaviour problems. At this time it is not possible to give scientific and objective criteria to enable one to predict how a given case will react. It is only by clinical impressions and after several months of close observation that the neurologist can venture any prognosis. As a general rule, it seems

that if the seizures began before one year of age, the prognosis is poorer than if they began at two to four years of age. If the seizures begin between eight and twelve years of age, a guarded prognosis must be given as to the possibility of adult epilepsy.

V. PROJECTED STUDY.

This investigation is being continued and has expanded to include a) epileptics with dysrhythmias other than the centrencephalic type; and b) controls with electroencephalograms other than normal.

VI. CONCLUSIONS.

In conclusion, this investigation has suggested:

1. That the frequency of convulsive disorders among the parents and siblings of probands with centrencephalic seizures and centrencephalic EEG abnormalities is four to five times higher (4.59X) than in the parents and siblings of probands with no history of seizures and with a normal EEG.

2. That there is at the present time no evidence that cerebral dysrhythmias other than of the centrencephalic type are more frequent in the parents and siblings of centrencephalic probands than in the same relatives of the control probands. This does not necessarily preclude the possibility that such dysrhythmias may have a familial distribution.

3. That since the frequency of seizures among the siblings is essentially the same whether one parent is affected or not, and since seizures tend to appear more frequently in one side of the family, dominant inheritance is a likely mode of transmission.

4. That the simplest mode of inheritance that is compatible with the data is an autosomal dominant with approximately 35% penetrance. This is the simplest explanation but not necessarily the correct one.

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R604-5-25

OTTAWA, March 16, 1955.

Jean Gregoire, Esq., M.D., D.P.H.,
Deputy Minister,
Ministry of Health for the
Province of Quebec,
QUEBEC, Que.

ATTENTION: Dr. J.C. Beaudet

Re: Project "Study of Genetics of Epilepsy (McGill University)"

Dear Dr. Gregoire:

May we refer to our letter of September 20th last in which we requested that a final report on this project should be submitted by March 31st, 1955.

We are writing to inquire if Dr. Boyes has completed his report yet and when we may expect to receive the two copies required.

Yours very truly,

Gordon E. Wride, M.D., D.P.H.,
Principal Medical Officer,
National Health Grants.

MV/jg

DEPARTMENT OF NATIONAL HEALTH AND WELFARE

INTRADEPARTMENTAL CORRESPONDENCE

TO: The Director,
Health Insurance Studies.

OUR FILE NO. R604-5-25
REF. YOUR FILE NO.
DATED

FROM: Dr. C.A. Roberts.

DATE: 20 September, 1954.

SUBJECT: STUDY OF GENETICS OF EPILEPSY (MCGILL UNIVERSITY)

It is recommended that the attached letter be forwarded to the province of Quebec regarding this project.

C.A. Roberts

R 604-5-25

20 September, 1954.

Dr. Jean Gregoire,
Deputy Minister,
Ministry of Health for the Province of Quebec,
Quebec, Quebec.

Dear Dr. Gregoire, Attention: Dr. J.C. Beaudet
STUDY OF GENETICS OF EPILEPSY
(MCGILL UNIVERSITY)

This project began in 1952 and was officially terminated at the end of the fiscal year 1953-54. During that period $14,385 were expended. At the request of the director a non-expended residue of $1,300 from the fiscal year 1953-54 was authorized for the present fiscal year. It is requested that Dr. Boyes be informed that we should appreciate receiving a final report on this study by March 31st next and that the progress report for the present fiscal year may be incorporated in that final report.

Yours very truly,

DX
15/3/5

F.W. Jackson, M.D.,
Director,
Health Insurance Studies.

CAR/B

DEPARTMENT OF NATIONAL HEALTH AND WELFARE

INTRADEPARTMENTAL CORRESPONDENCE

TO: Dr. C.A. Roberts, Chief,
Mental Health Division

OUR FILE NO. R 604-5-25

REF. YOUR FILE NO. DATED

FROM: Dr. J.W. Fisher

DATE: September 17, 1954.

SUBJECT: RE: FINAL REPORT: GENETICS OF EPILEPSY, McGILL

This project began in 1952 and will terminate March 31/55.

The Subcommittee on Research under the Mental Health Grant did not recommend support for 1954-55. From 1952/53 to 1953/54, $14,385 were expended. At March 31/54 an unexpended residue of $1,300 was at hand which Dr. Boyes asked to use during the present fiscal year. His request was granted.

It is recommended that Dr. Boyes be informed that we should appreciate receiving a final report on this study by March 31st next, and that the progress report for present fiscal year may be incorporated in it.

J.W. Fisher.

FILE No. R604-5-25

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Jackson	BF	15	3	55	[illegible]	18	3	5	
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Wade	B.F.	19	4	5	[illegible]	22	4	5	
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PROJECT NO. 604-5-25

STUDY OF GENETICS OF EPILEPSY

PROGRESS REPORT (JAN. - NOV. 1953)

I. INTRODUCTION

During the past ten months data on additional epileptic and control families have been collected employing the same methods which have been outlined in detail in a previous report (Oct. 1952) and which are stated briefly below. This report is brought up to date by including tables of the cumulative data.

II. METHODS

In order to evaluate the genetic role in the etiology of idiopathic epilepsy, the near relatives (parents, siblings, uncles, aunts, cousins and grandparents) of two groups of patients of the Children's Memorial Hospital were compared. The probands of the two groups are ascertained in the following manner: -

Idiopathic Probands - These are patients who come to the neurology service and who:

a) have a history of recurrent petit mal and/or grand mal seizures;

b) have no obvious neuropathology; and

c) whose electroencephalogram pattern is of the paroxysmal, bilaterally synchronous 3/sec. spike and wave type.

Control Probands - The paramount importance of an adequate control goup has been stressed in earlier reports (e.g. Oct. 1952). An attempt has been made to randomize the control sample by selecting every fifth admission to the hospital, and investigating the relatives provided the patient satisfies the following conditions: -

a) no history of seizures

b) no obvious neuropathology; and

c) electroencephalogram within normal limits.

When a suitable proband (idiopathic or control) is found, a family and medical history is taken. A detailed study, including neurological and EEG examinations of the parents and siblings, is made. A psychometric evaluation of all probands (idiopathic and control) is done by the Department of Psychiatry.

III. DATA

Frequency of Seizures - In Table 1 below the relative frequency of seizures in the near relatives of 45 idiopathic and 37 control families is compared. An individual is classified as affected if, as far as is possible to ascertain, his seizures are not attributed to metabolic disorders, hysteria, syncope, or carotid sinus syndrome. Individuals with vague or unsubstantial history of seizures are omitted from this analysis.

- TABLE 1 -

Frequency of Seizures in Families of Idiopathic and Control Probands

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	IDIOPATHIC	CONTROL	P
Siblings	22.8% (21/92)	4.8% (4/83)	.001
Parents	16.3% (14/86)	2.8% (2/72)	.01
Uncles and Aunts	4.7% (20/425)	3.9% (15/388)	.70
Grandparents	1.2% (2/172)	0.0% (0/141)	.30+
Cousins	2.5% (15/603)	0.2% (1/481)	.01
Total	5.2% (72/1378)	1.9% (22/1166)	.001

+Employing Fisher's exact method.

It is to be noted from Table 1 that the frequency of seizures among the siblings (22.8%), parents (16.3%), and cousins (2.5%) of the idiopathic probands is significantly higher than the comparable frequencies (4.8%, 2.8%, and 0.2%) of the control probands. Further-

more, when all the near relatives are considered together, the frequency of seizures in the idiopathic group (5.2%) is significantly higher than in the control group (1.9%).

It is important to note, too, that as the genetic distance between the relative studied and the proband increases, the frequency of epileptic seizures tends to decrease (from approximately 23% to 2%) in the case of the idiopathic group, but tends to fluctuate within fairly narrow limits (between 4.8% and 0.0%) in the control group.

Frequency of EEG Abnormalities - In Table 2 the frequency of EEG abnormalities in the siblings and parents of idiopathic and control probands is compared. The EEG abnormalities are divided into a) "idiopathic" (paroxysmal, bilaterally synchronous, 3/sec. spike and wave), and "symptomatic" (all other EEG abnormalities). "Borderline normals" and "borderline abnormals" are omitted from the analysis.

- TABLE 2 -

Frequencies of EEG Abnormalities in Parents and Siblings of Idiopathic (I) and Control (C) probands.

	NUMBER (I)	NUMBER (C)	"IDIOPATHIC" (I)	"IDIOPATHIC" (C)	"SYMPTOMATIC" (I)	"SYMPTOMATIC" (C)	BOTH (I)	BOTH (C)
Parents	58	20	2/36 5.6%	0.0%	3/36 8.3%	1/15 6.7%	5/36 13.9%	6.7%
Siblings	60	22	12/42 28.6%	0.0%	10/42 23.8%	2/11 18.2%	22/42 52.4%	2/11 18.2%
TOTAL	118	42	14/78 17.9%	0.0%	13/78 16.7%	3/26 11.5%	27/78 34.6%	3/26 11.5%

Table 2 clearly shows that the frequency of EEG abnormalities ("idiopathic" or "symptomatic") is higher in the idiopathic than in the control group. Two observations may be stressed at this time: -

a) 28.6% (12/42) of the siblings and 5.6% (2/36) of the parents of idiopathic probands had an idiopathic EEG tracing but none of the siblings and parents of the control probands.

b) The frequency of EEG abnormalities (idiopathic or symptomatic) among the siblings of idiopathic probands (52.4%) is significantly higher than among the siblings of the control probands (18.2%).

Other Comparisons - As has been reported in earlier reports, no significant differences have been found in 1) birth order, 2) maternal age, 3) left handedness, and 4) intelligence quotient between the idiopathic and control probands.

Atypical Idiopathics - These are patients who come to the neurology service with a clinical picture identical with that of the typical idiopathics and who are placed on and respond to identical medication. However, the EEG pattern of these patients is not of the typical 3/sec. spike and wave but the frequency may vary from 2-6/sec. In these patients the discharge is bilaterally synchronous and there is no other background abnormality in the EEG pattern. To see if this group might be worthy of more extensive research, the families of a few of these atypical idiopathic probands have been studied and compared with the same control group mentioned above.

Table 3 shows the frequency of seizures in the near relatives of 16 atypical idiopathic families, and is compared with the frequencies given in Table 1.

- TABLE 3 -

Frequency of Seizures in Families of Atypical Idiopathic, Idiopathic and Control Probands

	ATYPICAL		TYPICAL	CONTROL	
Siblings	11.4% (5/44)	(21/92)	22.8%	4.8%	4/83
Parents **	16.7% (5/30)	(14/86)	16.3%	2.8%	2/72
Uncles and Aunts	5.3% (8/151)	(20/425)	4.7%	3.9%	15/388
Grandparents	3.3% (2/60)	(2/172)	1.2%	0.0%	0/141
Cousins	1.2% (3/243)	(15/603)	2.5%	0.2%	1/481
TOTAL **	4.4% (23/528)	(72/1378)	5.2%	1.9%	22/1166

It is to be noted here that, on the whole, the frequency of seizures in the various groups of relatives of atypical idiopathic probands is quite comparable to that found in the same relatives of typical idiopathic probands. There is no statistical significance between "atypical" and "typical" for any of the six groups, i.e. siblings, parents, uncles and aunts, grandparents, cousins and total.

Table 4 compares the frequency of EEG abnormalities in the atypical (A.I.) and typical (T.I.) idiopathic groups. Again, on the whole, the frequency of EEG abnormalities is quite comparable

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Frequency of EEG Abnormalities in Atypical (A.I.) and Typical (T.I.) Idiopathic Groups.

	NUMBER (A.I.)	(T.I.)	"IDIOPATHIC" (A.I.)	(T.I.)	"SYMPTOMATIC" (A.I.)	(T.I.)	BOTH (A.I.)	(T.I.)
Parents	11	58	2/11 18.2%	2/36 5.6%	1/11 9.1%	3/36 8.3%	3/11 27.3%	5/36 13.9%
Siblings	9	60	2/9 22.2%	17/42 28.6%	2/9 22.2%	10/42 23.8%	4/9 44.4%	22/42 52.4%
TOTAL	~~30~~ 20	118	4/20 20.0%	14/78 17.9%	3/20 15.0%	13/78 16.7%	7/20 35.0%	27/78 34.6%

See letter of Dec 11/53 for the questions

between the two idiopathic groups. None of the differences are statistically significant. The implication is that the two groups have a common etiological basis. Further work is needed to prove whether or not this important relationship is true.

IV. CONCLUSIONS

1. In previous reports it was suggested that the data indicated hereditary factors in the etiology of "idiopathic" epilepsy. The analysis of the cumulative data up to the present time strongly supports this contention, for the incidence of epilepsy in the siblings, parents and cousins of idiopathic probands is significantly higher than in the comparable groups of the control probands. The overall frequency of seizures in the idiopathic group (5.2%) is significantly higher ($p = .001$) than in the control group (1.9%). (See Table 1).

2. Genetic factors seem to be in operation also in the production of EEG abnormalities, for these abnormalities are more frequently generally in the idiopathic group than in the control. (See Table 2).

3. There is a suggestion that hereditary factors may also be involved in atypical idiopathic epilepsy both as to frequency of seizures and EEG abnormalities. (See Tables 3 and 4).

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Julius D Metrakos

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Katherine Metrakos M.D.

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PROJECT NO. 604-5-25

STUDY OF GENETICS OF EPILEPSY

PROGRESS REPORT (JAN. - NOV. 1953)

SUMMARY

The frequency of seizures (5.2%) among the near relatives (siblings, parents, grandparents, uncles, aunts and cousins) of idiopathic probands is found to be significantly higher ($p = .001$) than in the same relatives of control probands. When the siblings and parents are considered together, the frequency of seizures is 6.5 times as high in the idiopathic (20.2%) than in the control (3.9%).

The electroencephalographic abnormalities are more frequent in the parents and siblings of idiopathic (34.6%) than of control (11.5%) probands. The frequency of EEG abnormalities in the siblings of idiopathic probands (52.4%) is 2.9 times as high as in the control 18.2%. Considering only EEG abnormalities of the "idiopathic" type, the difference is even more striking - 28.6% in the siblings of idiopathic probands and 0.0% in the siblings of control probands.

A comparison between typical and "atypical" idiopathic groups indicates that the two may be comparable and that the same differences may exist between atypical idiopathics and controls as between typical idiopathics and controls.

B604-5-25

PROJECT NO. 604-5-25

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a) have a history of recurrent petit mal and/or grand mal seizures;
b) have no obvious neuropathology; and
c) whose electroencephalogram pattern is of the paroxysmal, bilaterally synchronous 3/sec. spike and wave type.

See page 2 of 1952-53 progress report "referrals" is more likely to include cases c family history than sporadic cases

Control Probands - The paramount importance of an adequate control group has been stressed in earlier reports (e.g. Oct. 1952). An attempt has been made to randomize the control sample by selecting every fifth admission to the hospital, and investigating the relatives provided the patient satisfies the following conditions: -

a) no history of seizures
b) no obvious neuropathology; and
c) electroencephalogram within normal limits.

Personnell for 1952-53
Metrakos, K.; B.A. MD 3700 Full time 44 h week
Part Time sec
" psych

When a suitable proband (idiopathic or control) is found, a family and medical history is taken. A detailed study, including neurological and EEG examinations of the parents and siblings, is made. A psychometric evaluation of all probands (idiopathic and control) is done by the Department of Psychiatry.

III. DATA

Frequency of Seizures - In Table 1 below the relative frequency of seizures in the near relatives of 45 idiopathic and 37 control families is compared. An individual is classified as affected if, as far as is possible to ascertain, his seizures are not attributed to metabolic disorders, hysteria, syncope, or carotid sinus syndrome. Individuals with vague or unsubstantial history of seizures are omitted from this analysis.

- TABLE 1 -

Frequency of Seizures in Families of Idiopathic and Control Probands

	IDIOPATHIC	CONTROL	P
Siblings	22.8% (21/92)	4.8% (4/83)	.001
Parents	16.3% (14/86)	2.8% (2/72)	.01
Uncles and Aunts	4.7% (20/425)	3.9% (15/388)	.70
Grandparents	1.2% (2/172)	0.0% (0/141)	.30+
Cousins	2.5% (15/603)	0.2% (1/481)	.01
Total	5.2% (72/1378)	1.9% (22/1166)	.001

+Employing Fisher's exact method.

It is to be noted from Table 1 that the frequency of seizures among the siblings (22.8%), parents (16.3%), and cousins (2.5%) of the idiopathic probands is significantly higher than the comparable frequencies (4.8%, 2.8%, and 0.2%) of the control probands. Further-

	ab		ab	
g	27	34	5-1	78
c	3	11.5	23	26
	30		74	104

$$\chi^2 = \frac{\left[(27 \times 23) - (3 \times 51) - \frac{1}{2}(104)\right]^2}{30 \times 74 \times 26 \times 78}$$

$$= \frac{[621 - 153 - 52]^2}{X} = 416^2$$

$$= \frac{173056}{4502160} = < 3.84 \quad (05)$$

$\bar{c}$ 1 D.f

DEPARTMENT OF

NATIONAL HEALTH AND WELFARE

Memorandum:

more, when all the near relatives are considered together, the frequency of seizures in the idiopathic group (5.2%) is significantly higher than in the control group (1.9%).

It is important to note, too, that as the genetic distance between the relative studied and the proband increases, the frequency of epileptic seizures tends to decrease (from approximately 23% to 2%) in the case of the idiopathic group, but tends to fluctuate within fairly narrow limits (between 4.8% and 0.0%) in the control group.

Frequency of EEG Abnormalities - In Table 2 the frequency of EEG abnormalities in the siblings and parents of idiopathic and control probands is compared. The EEG abnormalities are divided into a) "idiopathic" (paroxysmal, bilaterally synchronous, 3/sec. spike and wave), and "symptomatic" (all other EEG abnormalities). "Borderline normals" and "borderline abnormals" are omitted from the analysis.

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Frequencies of EEG Abnormalities in Parents and Siblings of Idiopathic (I) and Control (C) probands.

	NUMBER (I)	(C)	"IDIOPATHIC" (I)	(C)	"SYMPTOMATIC" (I)	(C)	BOTH (I)	(C)
Parents	58	20	5.6%	0.0%	8.3%	6.7%	13.9%	6.7%
Siblings	60	22	28.6%	0.0%	23.8%	18.2%	52.4%	18.2%
TOTAL	118	42	17.9%	0.0%	16.7%	11.5%	34.6%	11.5%

Table 2 clearly shows that the frequency of EEG abnormalities ("idiopathic" or "symptomatic") is higher in the idiopathic than in the control group. Two observations may be stressed at this time: -

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Table 3 shows the frequency of seizures in the near relatives of 16 atypical idiopathic families, and is compared with the frequencies given in Table 1.

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TOTAL	4.4% (23/528)	5.2%	1.9%

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Parents	11	58	18.2%	5.6%	9.1%	8.3%	27.3%	13.9%
Siblings	9	60	22.2%	28.6%	22.2%	23.8%	44.4%	52.4%
TOTAL	20 (30)	118	20.0%	17.9%	15.0%	16.7%	35.0%	34.6%

between the two idiopathic groups. None of the differences are statistically significant. The implication is that the two groups have a common etiological basis. Further work is needed to prove whether or not this important relationship is true.

IV. CONCLUSIONS

1. In previous reports it was suggested that the data indicated hereditary factors in the etiology of "idiopathic" epilepsy. The analysis of the cumulative data up to the present time strongly supports this contention, for the incidence of epilepsy in the siblings, parents and cousins of idiopathic probands is significantly higher than in the comparable groups of the control probands. The overall frequency of seizures in the idiopathic group (5.2%) is significantly higher ($p = .001$) than in the control group (1.9%). (See Table 1).

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R604-5-25

PROJECT NO. 604-5-25

STUDY OF GENETICS OF EPILEPSY

PROGRESS REPORT (JAN. - NOV. 1953)

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B 604-5-25

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R 604-5-25

PROJECT NO. 604-5-25

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- TABLE 2 -

Frequencies of EEG Abnormalities in Parents and Siblings of Idiopathic (I) and Control (C) probands.

	NUMBER		"IDIOPATHIC"		"SYMPTOMATIC"		BOTH	
	(I)	(C)	(I)	(C)	(I)	(C)	(I)	(C)
Parents	58	20	5.6%	0.0%	8.3%	6.7%	13.9%	6.7%
Siblings	60	22	28.6%	0.0%	23.8%	18.2%	52.4%	18.2%
TOTAL	118	42	17.9%	0.0%	16.7%	11.5%	34.6%	11.5%

Table 2 clearly shows that the frequency of EEG abnormalities ("idiopathic" or "symptomatic") is higher in the idiopathic than in the control group. Two observations may be stressed at this time: -

a) 28.6% (12/42) of the siblings and 5.6% (2/36) of the parents of idiopathic probands had an idiopathic EEG tracing but none of the siblings and parents of the control probands.

b) The frequency of EEG abnormalities (idiopathic or symptomatic) among the siblings of idiopathic probands (52.4%) is significantly higher than among the siblings of the control probands (18.2%).

Other Comparisons - As has been reported in earlier reports, no significant differences have been found in 1) birth order, 2) maternal age, 3) left handedness, and 4) intelligence quotient between the idiopathic and control probands.

Atypical Idiopathics - These are patients who come to the neurology service with a clinical picture identical with that of the typical idiopathics and who are placed on and respond to identical medication. However, the EEG pattern of these patients is not of the typical 3/sec. spike and wave but the frequency may vary from 2-6/sec. In these patients the discharge is bilaterally synchronous and there is no other background abnormality in the EEG pattern. To see if this group might be worthy of more extensive research, the families of a few of these atypical idiopathic probands have been studied and compared with the same control group mentioned above.

Table 3 shows the frequency of seizures in the near relatives of 16 atypical idiopathic families, and is compared with the frequencies given in Table 1.

- TABLE 3 -

Frequency of Seizures in Families of Atypical Idiopathic, Idiopathic and Control Probands

	ATYPICAL	TYPICAL	CONTROL
Siblings	11.4% (5/44)	22.8%	4.8%
Parents	16.7% (5/30)	16.3%	2.8%
Uncles and Aunts	5.3% (8/151)	4.7%	3.9%
Grandparents	3.3% (2/60)	1.2%	0.0%
Cousins	1.2% (3/243)	2.5%	0.2%
TOTAL	4.4% (23/528)	5.2%	1.9%

It is to be noted here that, on the whole, the frequency of seizures in the various groups of relatives of atypical idiopathic probands is quite comparable to that found in the same relatives of typical idiopathic probands. There is no statistical significance between "atypical" and "typical" for any of the six groups, i.e. siblings, parents, uncles and aunts, grandparents, cousins and total.

Table 4 compares the frequency of EEG abnormalities in the atypical (A.I.) and typical (T.I.) idiopathic groups. Again, on the whole, the frequency of EEG abnormalities is quite comparable

- TABLE 4 -

Frequency of EEG Abnormalities in Atypical (A.I.) and Typical (T.I.) Idiopathic Groups.

	NUMBER (A.I.)	(T.I.)	"IDIOPATHIC" (A.I.)	(T.I.)	"SYMPTOMATIC" (A.I.)	(T.I.)	BOTH (A.I.)	(T.I.)
Parents	11	58	18.2%	5.6%	9.1%	8.3%	27.3%	13.9%
Siblings	9	60	22.2%	28.6%	22.2%	23.8%	44.4%	52.4%
TOTAL	30	118	20.0%	17.9%	15.0%	16.7%	35.0%	34.6%

between the two idiopathic groups. None of the differences are statistically significant. The implication is that the two groups have a common etiological basis. Further work is needed to prove whether or not this important relationship is true.

IV. CONCLUSIONS

1. In previous reports it was suggested that the data indicated hereditary factors in the etiology of "idiopathic" epilepsy. The analysis of the cumulative data up to the present time strongly supports this contention, for the incidence of epilepsy in the siblings, parents and cousins of idiopathic probands is significantly higher than in the comparable groups of the control probands. The overall frequency of seizures in the idiopathic group (5.2%) is significantly higher ($p = .001$) than in the control group (1.9%). (See Table 1).

2. Genetic factors seem to be in operation also in the production of EEG abnormalities, for these abnormalities are more frequent generally in the idiopathic group than in the control. (See Table 2).

3. There is a suggestion that hereditary factors may also be involved in atypical idiopathic epilepsy both as to frequency of seizures and EEG abnormalities. (See Tables 3 and 4).

Respectfully submitted,

Julius D. Metrakos

Julius D. Metrakos, Ph.D.

Katherine Metrakos M.D.

Katherine Metrakos, M.D.

B604-5-25

PROJECT NO. 604-5-25

STUDY OF GENETICS OF EPILEPSY

PROGRESS REPORT (JAN. - NOV. 1953)

SUMMARY

The frequency of seizures (5.2%) among the near relatives (siblings, parents, grandparents, uncles, aunts and cousins) of idiopathic probands is found to be significantly higher (p = .001) than in the same relatives of control probands. When the siblings and parents are considered together, the frequency of seizures is 6.5 times as high in the idiopathic (20.2%) than in the control (3.9%).

The electroencephalographic abnormalities are more frequent in the parents and siblings of idiopathic (34.6%) than of control (11.5%) probands. The frequency of EEG abnormalities in the siblings of idiopathic probands (52.4%) is 2.9 times as high as in the control 18.2%. Considering only EEG abnormalities of the "idiopathic" type, the difference is even more striking - 28.6% in the siblings of idiopathic probands and 0.0% in the siblings of control probands.

A comparison between typical and "atypical" idiopathic groups indicates that the two may be comparable and that the same differences may exist between atypical idiopathics and controls as between typical idiopathics and controls.

R604-5-25

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A comparison between typical and "atypical" idiopathic groups indicates that the two may be comparable and that the same differences may exist between atypical idiopathics and controls as between typical idiopathics and controls.

Second Report
For 1952-1953
Sent in response to request for more data!

Project No. 604 - 5 - 25

STUDY OF GENETICS OF EPILEPSY

PURPOSE

In view of conflicting reports regarding the importance of heredity in epilepsy, the applicants have begun an investigation in order to prove whether or not the parents and siblings of patients (from The Children's Memorial Hospital) with "idiopathic" epilepsy are more likely to have convulsive disorders and/or cortical dysrhythmias than the immediate relatives of patients with no history of convulsions and whose electroencephalograms are normal.

PREVIOUS WORK

Throughout the history of epilepsy various investigators have suggested that the frequency of convulsive disorders among the relatives of epileptics may be several times higher than among the relatives of non-epileptics. The earlier estimates were based mainly on the presence or absence of a positive family history, and often without regard to the genetic relationship of the affected individuals to the proband. Consequently, because of the wide distribution of the epileptic symptom-complex throughout the population, reports of eighty percent or more of positive family histories were not uncommon. It was not until comparatively recent years that the statistical approach has been employed using the parent-sibling and twin study methods.

The chief contribution in support of an hereditary factor in the etiology of epilepsy has been made by Lennox (1951) who analyzed the medical histories of 20,000 near relatives i.e. the parents, siblings, and children of over 4,000 epileptics. He found the overall incidence of epilepsy in this

group to be 6-7 times higher than in a control group. When he divided the group into those with and those without antecedant brain damage, the incidence of epilepsy was twice as great in the group without brain damage, but the frequency of both groups remained significantly higher than the frequency in the control group.

Lennox's evidence for a hereditary predisposition to epilepsy is supported further by his studies on 122 pairs of twins, for of the 69 monozygotic twins 61% were concordant (i.e. both had epilepsy), whereas of the 53 dizygotic twins only 9% were concordant.

Recently, Alstrom (1950), a Swedish investigator, has challenged the "evidence" for a hereditary factor in the etiology of epilepsy, reporting that the overall incidence of 1.5% which he found among the near relatives of some 900 epileptics was not significantly higher than the frequency of epilepsy in the same control group used by Lennox. Furthermore, when Alstrom divided his epileptics into three distinct groups, namely, those with unknown, those with probably, and those with known etiology, he found no significant difference in the incidency of epilepsy in the near relatives of these three groups.

The schism between these two diametrically opposite points of view becomes even more pronounced when it is considered that the massive and painstakingly collected data of both these investigators is subject to and has received considerable criticism. For example, some of Lennox's material may have been biased by the fact that about one-third of his index cases were referred to him by other neurologists who knew that he was interested in familial cases. It is our opinion and experience that such a procedure is more likely to include cases with a positive family history than sporadic cases, thus causing the incidence of epilepsy in the relatives of the index

cases to appear unduly high. The twin data collected by Lennox may also be biased, since the proportion of monozygotic to dizygotic pairs far exceeds the 1:2 ratio which is found in a normal population. Unless epilepsy occurs more frequently in monozygotic than in dizygotic twins - a supposition not supported by other twin series - then Lennox's excess of monozygotics would suggest that the twins were not selected on the sole basis that one of the pair had epilepsy. Whenever twin pairs are selected by criteria other than that one of the pair has epilepsy then it becomes highly probable that concordant pairs would be selected more frequently than discordant pairs.

The incidency of epilepsy in the "control" population used by Lennox was based on the portion of draftees (0.515%) in the United States rejected because of epilepsy during World War I. Comparing the incidence of epilepsy in the near relatives of the index cases with this control group is not justified for no account is taken of the age distribution and of other dissimilarities which make the two groups not comparable.

With regard to Alstrom's methods, Steinberg (1951) has pointed out that biases of a different nature may have occurred in his selection of index cases. More important, Steinberg has shown that in Alstrom's data the incidence of epilepsy in the siblings of index cases is higher if one parent is affected than if both parents are normal; a fact not pointed out by Alstrom but which nevertheless suggests that genetic factors may be in operation.

Although there was no significant difference between Alstrom's three groups of epileptics, nevertheless the figures (1.7%, 1.2% and 1.1%

for unknown; probable and known etiology respectively) are in the same direction as Lennox's. Unfortunately, Alstrom, like Lennox, has no adequate control group.

PROPOSED RESEARCH

In view of the two diametrically conflicting opinions regarding the role of heredity as an etiological factor in convulsive disorders, Dr. J. Preston Robb, Registrar of the Montreal Neurological Institute and Director of Neurology of the Children's Memorial Hospital, suggested to Dr. Clarke Fraser, who is the Director of the Department of Medical Genetics, at the same hospital, that it might be possible to organize an independent group to reinvestigate the question of heredity in epilepsy. (All research activities of the latter hospital department are the responsibility of the Department of Genetics at McGill, and under the supervision of its Chairman.) The program of investigation outlined below was then initiated.

1. Selection of Epileptic Probands. It was felt from an examination of both Lennox's and Alstrom's studies that if a hereditary factor is involved in the production of epilepsy, then the group in which this factor is most likely to be demonstrated is in the so-called "idiopathic" or "cryptogenic" type. Consequently, it was proposed that the investigation begin with probands from the Neurology Service of the Children's Memorial Hospital who : -

(a) have a history of recurrent petit mal and/or grand mal seizures;

(b) have no obvious neuropathology; and

(c) whose electroencephalogram pattern is of the paroxysmal bilaterally synchronous 3/second spike and wave type.

The medical records of all patients who come to the Neurology Service with a history of convulsions are examined and if there is no obvious neuropathology to account for the seizures and if the EEG pattern is of the 3/sec. spike and wave type, then the patient becomes an index case and family studies, as outlined below are undertaken. Obtaining epileptic probands by these specific and objective criteria, and then investigating their families was considered the most efficient and quickest way to arrive at an answer to the question of whether epilepsy and/or cortical dysrhythmia are abnormally frequent in the relatives of patients with a clearly defined type of epilepsy.

2. Selection of Control Probands. Selecting an adequate control group to compare with the idiopathic group is a difficult task but also of paramount importance in interpreting the data collected. The epileptic and control probands must be as comparable as possible (re age, birth order, number of siblings, age and racial origin of parents, economic status, etc. etc.) in order to control the experiment and get rid of variable factors other than those to be studied. For this reason the control probands are drawn at random from the same hospital population to which the epileptics belong. The medical record of every fifth admission is examined and if there is no history of convulsions and if the patient is not in the Infant Ward (EEG's are difficult to do on infants) the child becomes a potential control proband. An EEG is ordered (providing of course, that the child's illness is not neuropathological) and if the pattern is found to be within normal limits, the patient is accepted as a control proband. (Potential probands who have no history of seizures and no neuropathology but whose electroencephalogram is not within the normal limits are not accepted in the present control group, but will be used later in the projected study.)

3. Family-studies. When a suitable proband is found, both idiopathic or control, a family and medical history is taken by interviewing the father and mother. In the family history information is obtained about the (I) grandparents, (II) the paternal and maternal uncles and aunts, (III) the paternal and maternal cousins, and (IV) the siblings and nieces and nephews of the probands.

A detailed study including a neurological examination and electroencephalographic study of the parents and all available siblings is made. An effort is made to substantiate all reports of history of convulsive disorders by writing to the hospitals or physicians concerned.

It is to be noted that the same procedures are undertaken with the family of epileptics as with the family of non-epileptic hospital patients, and that there are no biases of selection.

4. Psychiatric Studies. The Psychiatry Department under the direction of Dr. Taylor Statten, is conducting psychometric studies on both the epileptic and control probands. This portion of the investigation will help to answer the question of whether epileptics of the idiopathic type suffer any mental deterioration.

5. EEG studies. The electroencephalographic tracings are read by Dr. H. H. Jasper, Professor of Experimental Neurology, Montreal Neurological Institute, without any previous knowledge as to the patient's family or neurological history.

WORK DONE BEFORE GRANT WAS OBTAINED

Before this grant was obtained, Dr. F. C. Fraser attended the epilepsy clinic of the Montreal Neurological Institute and collected a number of pedigrees of epileptic patients. This was done in order to get an idea of the problems involved in a study such as the one which eventually was under-

taken. Although pedigrees collected only by interview of a single family member are unreliable for genetic analysis of diseases as capricious as epilepsy, the experience gained was most helpful in designing the present program in such a way as to avoid some of the pitfalls into which previous workers have fallen.

Dr. J. D. Metrakos located and studied eight pairs of twins where at least one member has epilepsy. The zygosity and concordance or discordance of these twins have been adequately established. Dr. Metrakos is continuing to investigate all twins that come into the idiopathic or control series outlined above.

RESULTS

A progress report for April to the end of September 1952 has been submitted separately. Portions of this report are repeated here with some additional notes.

1. History of Seizures in Parents and Siblings. Table I shows the relative frequency of seizures in the parents and siblings of twenty-eight idiopathic and nine control families. An individual is classified as affected if his seizures are not attributed to metabolic disorders, hysteria, syncope or carotid sinus syndrome. Individuals with vague and unsubstantiated history of seizures are omitted from this analysis.

- TABLE I -

Frequency of Seizures in Parents and Siblings.

	IDIOPATHIC	CONTROL	χ^2	P
Parents	16% (9/56)	6% (1/18)	1.29	.30-.20
Siblings	18% (11/59)	4% (1/24)	2.89	.10-.05
Total	17% (20/115)	5% (2/42)	4.07	.05-.02

In the idiopathic group, nine (5 fathers and 4 mothers) or 16% of the parents gave a definite history of seizures. In the control group only one mother or 6% of the parents gave a substantiated history of seizures.

On the basis of a Chi-Square test (2 x 2 table) the increased frequency of seizures among the parents and siblings of idiopathic probands over that found among the parents and siblings of the control probands is not significant when parents and siblings are considered separately. However, when the parents and siblings are considered together the incidence of seizures in the idiopathic group (17%) is significantly higher ($p = .05-.02$) than that in the control group (5%).

2. History of Seizures in Distant Relatives. Table 2 shows the relative frequency of seizures (as obtained by interview with the parents of the proband) in the grandparents, uncles and aunts, and cousins of the 37 probands mentioned above. So far, some affected grandparents (2/106 plus 6 others with a vague history) and cousins (13/342) have been found among the

- TABLE 2 -

Frequency of Seizures in Distant Relatives

	IDIOPATHIC	CONTROL	χ^2	P
Grandparents	1.9% (2/106)	0.0% (0/36)	-	-
Uncles and Aunts	3.2% (8/249)	11.0% (9/82)	7.63	.01-.001
Cousins	3.8% (13/342)	0.0% (0/91)	-	-
Total	3.3% (23/697)	4.3% (9/209)	0.48	.50-.30

idiopathic group but not among the control group. Because the "Affected-Control" class in these two groups is zero, the standard χ^2-square test is not valid, but it seems obvious that the differences are not statistically significant.

The frequency of seizures in the uncles and aunts of the control group (11.0%) is significantly higher ($p = .01-.001$) than in the idiopathic group (3.2%). This entire difference was brought about by the fact that in one of the nine control families, seven out of the nine maternal uncles and aunts presented a definite history of seizures. However, even with this family included, the relative frequency of seizures in the idiopathic (3.3%) and control group (4.3%) is not significantly different ($p = .50-.30$) when the three groups of relatives are considered together.

3. <u>EEG Abnormalities in Parents and Siblings.</u> Table 3 shows the relative frequency of EEG abnormalities found among the parents and siblings of the idiopathic and control families. Borderline normals and borderline abnormals were not included in this analysis. Far too few EEG's of the control group have been done to date and consequently the two groups cannot be compared adequately. However, it is of interest to note at this time the high frequency (55%) of EEG abnormalities exhibited by the siblings of idiopathic probands. (As the four control siblings that were tested were all normal, the standard χ^2-square test was not done.) When the parents and siblings are considered together, the frequency of EEG abnormalities in the idiopathic group (31%) is 2.2 times as high as in the control group (14%); however, this difference is not a statistically significant one ($p = .50-.30$).

- TABLE 3 -

Frequency of EEG Abnormalities in Parents and Siblings

	IDIOPATHIC	CONTROL	X^2	P
Parents	16% (5/32)	33% (1/3)	0.61	.50-.30
Siblings	55% (11/20)	0% (0/4)	-	-
Total	31% (16/52)	14% (1/7)	0.82	.50-.30

PROPOSED ANALYSIS OF FUTURE DATA

At the present time the data collected are too few for suitable breakdown and statistical analysis. Percentages and a simple X^2 test were used above on pooled data in order to see what trends if any, are indicated. When more data are collected the following breakdowns and analyses will be done in order to answer questions relative to :-

1) Sex Distribution :- male and female probands, fathers and mothers, brothers and sisters, etc., will be considered separately in order to determine whether there is any difference in the sex distribution of epilepsy and whether or not there are any sex-linked factors involved.

2) Family Size and Birth Order :- the mean family size and the birth order of the control and idiopathic probands will be compared in order to see if birth-rank is an important environmental factor in producing epilepsy.

3) Antenatal, Natal and Neonatal Histories :- detailed information is being collected on the antenatal, natal and neonatal histories

of all probands and their siblings. This data will be analysed and the idiopathic and control groups compared in order to see if there are any significant antenatal, natal or neonatal factors.

4) Psychometric Testing :- both the idiopathic and control probands are tested by the Psychiatry Department and their Intelligence, Social and Total Quotients are obtained. A comparison between the two groups will contribute some information on the question of whether any mental deterioration or whether any behaviour problems accompany epilepsy in children.

5) Heredity of Cortical Dysrhythmia :- Lennox, Gibbs and Gibbs, (1945) have published data suggesting that the cortical dysrhythmia underlying the epileptic diathesis is inherited as a Mendelian dominant factor. Although in later publications of these investigators, the Mendelian dominant theory is not supported nevertheless the idea of an inherited cortical dysrhythmia merits further investigation.

6) Genetic Factors :- this is the main aspect of the project and when sufficient data have been collected, the question regarding the importance of heredity in idiopathic epilepsy will be answered for if a) the frequency of seizures is statistically higher in the idiopathic than in the control group, then genetic factors are involved; if however, b) the frequency of seizures is not significantly different in the two groups then it must be concluded that epilepsy affects individuals at random and that no hereditary factors are involved.

To analyse the data here the standard sibship genetic formulae (Weinberg, Fisher, Hogben, Haldane, and others) will be used as it becomes necessary. The Sequential Analysis method, by comparing paired individuals from the idiopathic and control groups, is also

under consideration as a possible analytical tool; however at the present time there are too few individuals in each category to attempt such an analysis.

INDICATIONS FROM WORK SO FAR

At the present time it appears that a hereditary factor (or factors) in the etiology of "idiopathic" epilepsy is indicated for : 1) the incidence of seizures among the parents and siblings of idiopathic probands is 3.4 times as high as in the control group, (statistically significant at the 5% level); and 2) the incidence of EEG abnormalities in the parents and siblings of idiopathic probands is 2.2 times as high as in the control group (not statistically significant).

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1st Report for 1952-5-3.

Project No. 604-5-25 - Study of Genetics of Epilepsy
Report for April to the end of September 1952

1st Report

(A) ACTIVITIES:

The first month of this study was devoted mainly to organizational problems. There were consultations with the Department of Electroencephalography, Radiology, Neurology and Psychiatry, in order to coordinate the various aspects of the investigation. Up until the end of September the following activities have been conducted:-

1. Medical Genetics:

(a) Family histories: Forty-eight families have been interviewed and a medical history has been obtained on the siblings of the proband, his parents and grandparents, his maternal and paternal uncles and aunts, and on his maternal and paternal cousins.

(b) Physical examinations: One hundred and thirty-two physical examinations have been carried out; fifty-eight on probands, thirty-eight on parents and thirty-six on siblings.

(c) Analysis of data: The data are tabulated daily as they are collected and an analysis made whenever required. A preliminary report was presented to the American Human Genetics Society at Cornell University, Ithaca, New York. This report (brought up to-date) is summarized in section B.

2. Electroencephalography: One hundred and twenty-four EEG's have been done on probands and on parents and siblings of probands.

Idiopathic and control probands	38
Individuals unsuitable as probands	18
Parents and siblings of probands	63
Repeated EEG's	5
	124

3. Psychiatry: Forty-nine psychometrics (Intelligence and Social quotients) have been done; forty-five on probands, and four on twin siblings of probands.

4. Radiology: Thirty-six skull X-rays have been done.

Continued.....

Summary of above activities:

Family histories	48
Physical examinations	132
Preliminary reports	1
Electroencephalograms	124
Psychometrics	49
Skull X-rays	36

(B) ANALYSIS of DATA:

(a) History of seizures: Table 1 shows the relative frequency of seizures (not attributed to metabolic disorders, syncope or carotid sinus syndrome) that was found in twenty-eight idiopathic and nine suitable control families.

TABLE 1

	SEIZURES	
	Idiopathic	Control
Parents	16% (9/56)	6% (1/18)
Siblings	18% (11/59)	4% (1/24)
Total	17% (20/115)	5% (2/42)

(b) Electroencephalographic abnormalities: Table 2 shows the relative frequency of EEG abnormalities (borderline abnormalities are not included) found in the parents and siblings tested so far in the twenty-eight idiopathic and nine control families mentioned above.

TABLE 2

	ELECTROENCEPHALOGRAMS	
	Idiopathic	Control
Parents	16% (5/32)	33% (1/3)
Siblings	55% (11/20)	0% (0/4)
Total	31% (16/52)	14% (1/7)

Continued.....

(c) CONCLUSIONS:

At the present time the numbers are too small to arrive at any definite conclusions, however, certain trends are indicated because:

(a) 16% of the parents of idiopathic probands have definite histories of seizures as compared with 6% of parents of control probands;

(b) 18% of the siblings of idiopathic probands have definite, substantiated histories of seizures as compared with 4% of siblings of control probands;

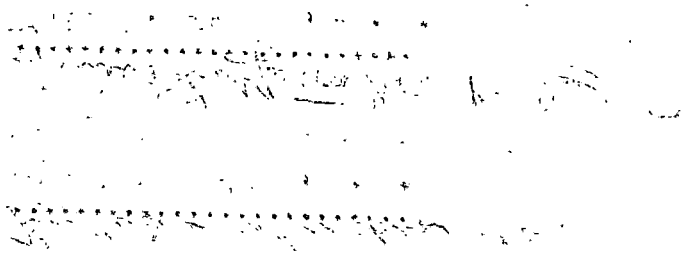
(c) 55% of the siblings of idiopathic probands show electroencephalographic abnormalities. (Too few EEG's have been done on parents and siblings of control probands; and therefore, the percent abnormalities found in the idiopathic group cannot be adequately compared).

At the present time, therefore, it appears that a hereditary factor in the etiology of "idiopathic" epilepsy is indicated for: 1) the incidence of seizures among the parents and siblings of idiopathic probands is at least three times as high as in the control group; and 2) the incidence of electroencephalographic abnormalities in the parents and siblings of idiopathic probands is at least two times as high as in the control group.

Respectfully submitted,

Katherine Metrakos M.D.
Katherine Metrakos, M. D.

Julius D. Metrakos Ph.D.
Julius D. Metrakos, Ph. D.



Dental 10-11

for 1952-1953

Project No. 604 - 5 - 25

STUDY OF GENETICS OF EPILEPSY

1952 - 53

PURPOSE

In view of conflicting reports regarding the importance of heredity in epilepsy, the applicants have begun an investigation in order to prove whether or not the parents and siblings of patients (from The Children's Memorial Hospital) with "idiopathic" epilepsy are more likely to have convulsive disorders and/or cortical dis-rhythmias than the immediate relatives of patients with no history of convulsions and whose electroencephalograms are normal.

PREVIOUS WORK

Throughout the history of epilepsy various investigators have suggested that the frequency of convulsive disorders among the relatives of epileptics may be several times higher than among the relatives of non-epileptics. The earlier estimates were based mainly on the presence or absence of a positive family history, and often without regard to the genetic relationship of the affected individuals to the proband. Consequently, because of the wide distribution of the epileptic symptom-complex throughout the population, reports of eighty percent or more of positive family histories were not uncommon. It was not until comparatively recent years that the statistical approach has been employed using the parent-sibling and twin study methods.

The chief contribution in support of an hereditary factor in the etiology of epilepsy has been made by Lennox (1951) who analyzed the medical histories of 20,000 near relatives i.e. the parents, siblings, and children of over 4,000 epileptics. He found the overall incidence of epilepsy in this

group to be 6-7 times higher than in a control group. When he divided the group into those with and those without antecedant brain damage, the incidence of epilepsy was twice as great in the group without brain damage, but the frequency of both groups remained significantly higher than the frequency in the control group.

Lennox's evidence for a hereditary predisposition to epilepsy is supported further by his studies on 122 pairs of twins, for of the 69 monozygotic twins 61% were concordant (i.e. both had epilepsy), whereas of the 53 dizygotic twins only 9% were concordant.

Recently, Alstrom (1950), a Swedish investigator, has challenged the "evidence" for a hereditary factor in the etiology of epilepsy, reporting that the overall incidence of 1.5% which he found among the near relatives of some 900 epileptics was not significantly higher than the frequency of epilepsy in the same control group used by Lennox. Furthermore, when Alstrom divided his epileptics into three distinct groups, namely, those with unknown, those with probably, and those with known etiology, he found no significant difference in the incidency of epilepsy in the near relatives of these three groups.

The schism between these two diametrically opposite points of view becomes even more pronounced when it is considered that the massive and painstakingly collected data of both these investigators is subject to and has received considerable criticism. For example, some of Lennox's material may have been biased by the fact that about one-third of his index cases were referred to him by other neurologists who knew that he was interested in familial cases. It is our opinion and experience that such a procedure is more likely to include cases with a positive family history than sporadic cases, thus causing the incidence of epilepsy in the relatives of the index

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On the basis of a Chi-Square test (2 x 2 table) the increased frequency of seizures among the parents and siblings of idiopathic probands over that found among the parents and siblings of the control probands is not significant when parents and siblings are considered separately. However, when the parents and siblings are considered together the incidence of seizures in the idiopathic group (17%) is significantly higher ($p = .05-.02$) than that in the control group (5%).

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Frequency of EEG Abnormalities in Parents and Siblings

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PROPOSED ANALYSIS OF FUTURE DATA

At the present time the data collected are too few for suitable breakdown and statistical analysis. Percentages and a simple χ^2 test were used above on pooled data in order to see what trends if any, are indicated. When more data are collected the following breakdowns and analyses will be done in order to answer questions relative to :-

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of all probands and their siblings. This data will be analysed and the idiopathic and control groups compared in order to see if there are any significant antenatal, natal or neonatal factors.

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Project No. 604 - 5 - 25

1952-53

STUDY OF GENETICS OF EPILEPSY

2nd Report

PURPOSE

In view of conflicting reports regarding the importance of heredity in epilepsy, the applicants have begun an investigation in order to prove whether or not the parents and siblings of patients (from The Children's Memorial Hospital) with "idiopathic" epilepsy are more likely to have convulsive disorders and/or cortical dysrhythmias than the immediate relatives of patients with no history of convulsions and whose electroencephalograms are normal.

PREVIOUS WORK

Throughout the history of epilepsy various investigators have suggested that the frequency of convulsive disorders among the relatives of epileptics may be several times higher than among the relatives of non-epileptics. The earlier estimates were based mainly on the presence or absence of a positive family history, and often without regard to the genetic relationship of the affected individuals to the proband. Consequently, because of the wide distribution of the epileptic symptom-complex throughout the population, reports of eighty percent or more of positive family histories were not uncommon. It was not until comparatively recent years that the statistical approach has been employed using the parent-sibling and twin study methods.

The chief contribution in support of an hereditary factor in the etiology of epilepsy has been made by Lennox (1951) who analyzed the medical histories of 20,000 near relatives i.e. the parents, siblings, and children of over 4,000 epileptics. He found the overall incidence of epilepsy in this

group to be 6-7 times higher than in a control group. When he divided the group into those with and those without antecedant brain damage, the incidence of epilepsy was twice as great in the group without brain damage, but the frequency of both groups remained significantly higher than the frequency in the control group.

Lennox's evidence for a hereditary predisposition to epilepsy is supported further by his studies on 122 pairs of twins, for of the 69 monozygotic twins 61% were concordant (i.e. both had epilepsy), whereas of the 53 dizygotic twins only 9% were concordant.

Recently, Alstrom (1950), a Swedish investigator, has challenged the "evidence" for a hereditary factor in the etiology of epilepsy, reporting that the overall incidence of 1.5% which he found among the near relatives of some 900 epileptics was not significantly higher than the frequency of epilepsy in the same control group used by Lennox. Furthermore, when Alstrom divided his epileptics into three distinct groups, namely, those with unknown, those with probably, and those with known etiology, he found no significant difference in the incidency of epilepsy in the near relatives of these three groups.

The schism between these two diametrically opposite points of view becomes even more pronounced when it is considered that the massive and painstakingly collected data of both these investigators is subject to and has received considerable criticism. For example, some of Lennox's material may have been biased by the fact that about one-third of his index cases were referred to him by other neurologists who knew that he was interested in familial cases. It is our opinion and experience that such a procedure is more likely to include cases with a positive family history than sporadic cases, thus causing the incidence of epilepsy in the relatives of the index

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2nd Report

PURPOSE

In view of conflicting reports regarding the importance of heredity in epilepsy, the applicants have begun an investigation in order to prove whether or not the parents and siblings of patients (from The Children's Memorial Hospital) with "idiopathic" epilepsy are more likely to have convulsive disorders and/or cortical dysrhythmias than the immediate relatives of patients with no history of convulsions and whose electroencephalograms are normal.

PREVIOUS WORK

Throughout the history of epilepsy various investigators have suggested that the frequency of convulsive disorders among the relatives of epileptics may be several times higher than among the relatives of non-epileptics. The earlier estimates were based mainly on the presence or absence of a positive family history, and often without regard to the genetic relationship of the affected individuals to the proband. Consequently, because of the wide distribution of the epileptic symptom-complex throughout the population, reports of eighty percent or more of positive family histories were not uncommon. It was not until comparatively recent years that the statistical approach has been employed using the parent-sibling and twin study methods.

The chief contribution in support of an hereditary factor in the etiology of epilepsy has been made by Lennox (1951) who analyzed the medical histories of 20,000 near relatives i.e. the parents, siblings, and children of over 4,000 epileptics. He found the overall incidence of epilepsy in this

group to be 6-7 times higher than in a control group. When he divided the group into those with and those without antecedant brain damage, the incidence of epilepsy was twice as great in the group without brain damage, but the frequency of both groups remained significantly higher than the frequency in the control group.

Lennox's evidence for a hereditary predisposition to epilepsy is supported further by his studies on 122 pairs of twins, for of the 69 monozygotic twins 61% were concordant (i.e. both had epilepsy), whereas of the 53 dizygotic twins only 9% were concordant.

Recently, Alstrom (1950), a Swedish investigator, has challenged the "evidence" for a hereditary factor in the etiology of epilepsy, reporting that the overall incidence of 1.5% which he found among the near relatives of some 900 epileptics was not significantly higher than the frequency of epilepsy in the same control group used by Lennox. Furthermore, when Alstrom divided his epileptics into three distinct groups, namely, those with unknown, those with probably, and those with known etiology, he found no significant difference in the incidency of epilepsy in the near relatives of these three groups.

The schism between these two diametrically opposite points of view becomes even more pronounced when it is considered that the massive and painstakingly collected data of both these investigators is subject to and has received considerable criticism. For example, some of Lennox's material may have been biased by the fact that about one-third of his index cases were referred to him by other neurologists who knew that he was interested in familial cases. It is our opinion and experience that such a procedure is more likely to include cases with a positive family history than sporadic cases, thus causing the incidence of epilepsy in the relatives of the index

cases to appear unduly high. The twin data collected by Lennox may also be biased, since the proportion of monozygotic to dizygotic pairs far exceeds the 1:2 ratio which is found in a normal population. Unless epilepsy occurs more frequently in monozygotic than in dizygotic twins - a supposition not supported by other twin series - then Lennox's excess of monozygotics would suggest that the twins were not selected on the sole basis that one of the pair had epilepsy. Whenever twin pairs are selected by criteria other than that one of the pair has epilepsy then it becomes highly probable that concordant pairs would be selected more frequently than discordant pairs.

The incidency of epilepsy in the "control" population used by Lennox was based on the portion of draftees (0.515%) in the United States rejected because of epilepsy during World War I. Comparing the incidence of epilepsy in the near relatives of the index cases with this control group is not justified for no account is taken of the age distribution and of other dissimilarities which make the two groups not comparable.

With regard to Alstrom's methods, Steinberg (1951) has pointed out that biases of a different nature may have occurred in his selection of index cases. More important, Steinberg has shown that in Alstrom's data the incidence of epilepsy in the siblings of index cases is higher if one parent is affected than if both parents are normal; a fact not pointed out by Alstrom but which nevertheless suggests that genetic factors may be in operation.

Although there was no significant difference between Alstrom's three groups of epileptics, nevertheless the figures (1.7%, 1.2% and 1.1%

for unknown; probable and known etiology respectively) are in the same direction as Lennox's. Unfortunately, Alstrom, like Lennox, has no adequate control group.

PROPOSED RESEARCH

In view of the two diametrically conflicting opinions regarding the role of heredity as an etiological factor in convulsive disorders, Dr. J. Preston Robb, Registrar of the Montreal Neurological Institute and Director of Neurology of the Children's Memorial Hospital, suggested to Dr. Clarke Fraser, who is the Director of the Department of Medical Genetics, at the same hospital, that it might be possible to organize an independent group to reinvestigate the question of heredity in epilepsy. (All research activities of the latter hospital department are the responsibility of the Department of Genetics at McGill, and under the supervision of its Chairman.) The progrom of investigation outlined below was then initiated.

1. Selection of Epileptic Probands. It was felt from an examination of both Lennox's and Alstrom's studies that if a hereditary factor is involved in the production of epilepsy, then the group in which this factor is most likely to be demonstrated is in the so-called "idiopathic" or "cryptogenic" type. Consequently, it was proposed that the investigation begin with probands from the Neurology Service of the Children's Memorial Hospital who : -

(a) have a history of recurrent petit mal and/or grand mal seizures;

(b) have no obvious neuropathology; and

(c) whose electroencephalogram pattern is of the paroxysmal bilaterally synchronous 3/second spike and wave type.

The medical records of all patients who come to the Neurology Service with a history of convulsions are examined and if there is no obvious neuropathology to account for the seizures and if the EEG pattern is of the 3/sec. spike and wave type, then the patient becomes an index case and family studies, as outlined below are undertaken. Obtaining epileptic probands by these specific and objective criteria, and then investigating their families was considered the most efficient and quickest way to arrive at an answer to the question of whether epilepsy and/or cortical dysrhythmia are abnormally frequent in the relatives of patients with a clearly defined type of epilepsy.

2. Selection of Control Probands. Selecting an adequate control group to compare with the idiopathic group is a difficult task but also of paramount importance in interpreting the data collected. The epileptic and control probands must be as comparable as possible (re age, birth order, number of siblings, age and racial origin of parents, economic status, etc. etc.) in order to control the experiment and get rid of variable factors other than those to be studied. For this reason the control probands are drawn at random from the same hospital population to which the epileptics belong. The medical record of every fifth admission is examined and if there is no history of convulsions and if the patient is not in the Infant Ward (EEG's are difficult to do on infants) the child becomes a potential control proband. An EEG is ordered (providing of course, that the child's illness is not neuropathological) and if the pattern is found to be within normal limits, the patient is accepted as a control proband. (Potential probands who have no history of seizures and no neuropathology but whose electroencephalogram is not within the normal limits are not accepted in the present control group, but will be used later in the projected study.)

3. Family-studies. When a suitable proband is found, both idiopathic or control, a family and medical history is taken by interviewing the father and mother. In the family history information is obtained about the (I) grandparents, (II) the paternal and maternal uncles and aunts, (III) the paternal and maternal cousins, and (IV) the siblings and nieces and nephews of the probands.

A detailed study including a neurological examination and electroencephalographic study of the parents and all available siblings is made. An effort is made to substantiate all reports of history of convulsive disorders by writing to the hospitals or physicians concerned.

It is to be noted that the same procedures are undertaken with the family of epileptics as with the family of non-epileptic hospital patients, and that there are no biases of selection.

4. Psychiatric Studies. The Psychiatry Department under the direction of Dr. Taylor Statten, is conducting psychometric studies on both the epileptic and control probands. This portion of the investigation will help to answer the question of whether epileptics of the idiopathic type suffer any mental deterioration.

5. EEG studies. The electroencephalographic tracings are read by Dr. H. H. Jasper, Professor of Experimental Neurology, Montreal Neurological Institute, without any previous knowledge as to the patient's family or neurological history.

WORK DONE BEFORE GRANT WAS OBTAINED

Before this grant was obtained, Dr. F. C. Fraser attended the epilepsy clinic of the Montreal Neurological Institute and collected a number of pedigrees of epileptic patients. This was done in order to get an idea of the problems involved in a study such as the one which eventually was under-

taken. Although pedigrees collected only by interview of a single family member are unreliable for genetic analysis of diseases as capricious as epilepsy, the experience gained was most helpful in designing the present program in such a way as to avoid some of the pitfalls into which previous workers have fallen.

Dr. J. D. Metrakos located and studied eight pairs of twins where at least one member has epilepsy. The zygosity and concordance or discordance of these twins have been adequately established. Dr. Metrakos is continuing to investigate all twins that come into the idiopathic or control series outlined above.

RESULTS

A progress report for April to the end of September 1952 has been submitted separately. Portions of this report are repeated here with some additional notes.

1. History of Seizures in Parents and Siblings. Table I shows the relative frequency of seizures in the parents and siblings of twenty-eight idiopathic and nine control families. An individual is classified as affected if his seizures are not attributed to metabolic disorders, hysteria, syncope or carotid sinus syndrome. Individuals with vague and unsubstantiated history of seizures are omitted from this analysis.

- TABLE I -

Frequency of Seizures in Parents and Siblings.

	IDIOPATHIC	CONTROL	χ^2	P	
Parents	16% (9/56)	6% (1/18)	1.29	.30-.20	not sig
Siblings	18% (11/59)	4% (1/24)	2.69	.10-.05	not sig
Total	17% (20/115)	5% (2/42)	4.07	.05-.02	

In the idiopathic group, nine (5 fathers and 4 mothers) or 16% of the parents gave a definite history of seizures. In the control group only one mother or 6% of the parents gave a substantiated history of seizures.

On the basis of a Chi-Square test (2 x 2 table) the increased frequency of seizures among the parents and siblings of idiopathic probands over that found among the parents and siblings of the control probands is not significant when parents and siblings are considered separately. However, when the parents and siblings are considered together the incidence of seizures in the idiopathic group (17%) is significantly higher ($p = .05-.02$) than that in the control group (5%).

2. History of Seizures in Distant Relatives. Table 2 shows the relative frequency of seizures (as obtained by interview with the parents of the proband) in the grandparents, uncles and aunts, and cousins of the 37 probands mentioned above. So far, some affected grandparents (2/106 plus 6 others with a vague history) and cousins (13/342) have been found among the

- TABLE 2 -

Frequency of Seizures in Distant Relatives

	IDIOPATHIC	CONTROL	X^2	P
Grandparents	1.9% (2/106)	0.0% (0/36)	-	-
Uncles and Aunts	3.2% (8/249)	11.0% (9/82)	7.63	.01-.001
Cousins	3.8% (13/342)	0.0% (0/91)	-	-
Total	3.3% (23/697)	4.3% (9/209)	0.48	.50-.30

idiopathic group but not among the control group. Because the "Affected-Control" class in these two groups is zero, the standard χ^2-square test is not valid, but it seems obvious that the differences are not statistically significant.

The frequency of seizures in the uncles and aunts of the control group (11.0%) is significantly higher ($p = .01-.001$) than in the idiopathic group (3.2%). This entire difference was brought about by the fact that in one of the nine control families, seven out of the nine maternal uncles and aunts presented a definite history of seizures. However, even with this family included, the relative frequency of seizures in the idiopathic (3.3%) and control group (4.3%) is not significantly different ($p = .50-.30$) when the three groups of relatives are considered together.

3. EEG Abnormalities in Parents and Siblings. Table 3 shows the relative frequency of EEG abnormalities found among the parents and siblings of the idiopathic and control families. Borderline normals and borderline abnormals were not included in this analysis. Far too few EEG's of the control group have been done to date and consequently the two groups cannot be compared adequately. However, it is of interest to note at this time the high frequency (55%) of EEG abnormalities exhibited by the siblings of idiopathic probands. (As the four control siblings that were tested were all normal, the standard χ^2-square test was not done.) When the parents and siblings are considered together, the frequency of EEG abnormalities in the idiopathic group (31%) is 2.2 times as high as in the control group (14%); however, this difference is not a statistically significant one ($p = .50-.30$).

- TABLE 3 -

Frequency of EEG Abnormalities in Parents and Siblings

	IDIOPATHIC	CONTROL	X^2	P
Parents	16% (5/32)	33% (1/3)	0.61	.50-.30
Siblings	55% (11/20)	0% (0/4)	-	-
Total	31% (16/52)	14% (1/7)	0.82	.50-.30

PROPOSED ANALYSIS OF FUTURE DATA

At the present time the data collected are too few for suitable breakdown and statistical analysis. Percentages and a simple X^2 test were used above on pooled data in order to see what trends if any, are indicated. When more data are collected the following breakdowns and analyses will be done in order to answer questions relative to :-

1) Sex Distribution :- male and female probands, fathers and mothers, brothers and sisters, etc., will be considered separately in order to determine whether there is any difference in the sex distribution of epilepsy and whether or not there are any sex-linked factors involved.

2) Family Size and Birth Order :- the mean family size and the birth order of the control and idiopathic probands will be compared in order to see if birth-rank is an important environmental factor in producing epilepsy.

3) Antenatal, Natal and Neonatal Histories :- detailed information is being collected on the antenatal, natal and neonatal histories

of all probands and their siblings. This data will be analysed and the idiopathic and control groups compared in order to see if there are any significant antenatal, natal or neonatal factors.

4) Psychometric Testing :- both the idiopathic and control probands are tested by the Psychiatry Department and their Intelligence, Social and Total Quotients are obtained. A comparison between the two groups will contribute some information on the question of whether any mental deterioration or whether any behaviour problems accompany epilepsy in children.

5) Heredity of Cortical Dysrhythmia :- Lennox, Gibbs and Gibbs, (1945) have published data suggesting that the cortical dysrhythmia underlying the epileptic diathesis is inherited as a Mendelian dominant factor. Although in later publications of these investigators, the Mendelian dominant theory is not supported nevertheless the idea of an inherited cortical dysrhythmia merits further investigation.

6) Genetic Factors :- this is the main aspect of the project and when sufficient data have been collected, the question regarding the importance of heredity in idiopathic epilepsy will be answered for if a) the frequency of seizures is statistically higher in the idiopathic than in the control group, then genetic factors are involved; if however, b) the frequency of seizures is not significantly different in the two groups then it must be concluded that epilepsy affects individuals at random and that no hereditary factors are involved.

To analyse the data here the standard sibship genetic formulae (Weinberg, Fisher, Hogben, Haldane, and others) will be used as it becomes necessary. The Sequential Analysis method, comparing paired individuals from the idiopathic and control groups, is also

under consideration as a possible analytical tool; however at the present time there are too few individuals in each category to attempt such an analysis.

INDICATIONS FROM WORK SO FAR

At the present time it appears that a hereditary factor (or factors) in the etiology of "idiopathic" epilepsy is indicated for : 1) the incidence of seizures among the parents and siblings of idiopathic probands is 3.4 times as high as in the control group, (statistically significant at the 5% level); and 2) the incidence of EEG abnormalities in the parents and siblings of idiopathic probands is 2.2 times as high as in the control group (not statistically significant).

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Project No. 604-5-25 - Study of Genetics of Epilepsy
Report for April to the end of September 1952

1 ST Report

(A) ACTIVITIES:

The first month of this study was devoted mainly to organizational problems. There were consultations with the Department of Electroencephalography, Radiology, Neurology and Psychiatry, in order to coordinate the various aspects of the investigation. Up until the end of September the following activities have been conducted: -

1. Medical Genetics:

(a) Family histories: Forty-eight families have been interviewed and a medical history has been obtained on the siblings of the proband, his parents and grandparents, his maternal and paternal uncles and aunts, and on his maternal and paternal cousins.

(b) Physical examinations: One hundred and thirty-two physical examinations have been carried out; fifty-eight on probands, thirty-eight on parents and thirty-six on siblings.

(c) Analysis of data: The data are tabulated daily as they are collected and an analysis made whenever required. A preliminary report was presented to the American Human Genetics Society at Cornell University, Ithaca, New York. This report (brought up to-date) is summarized in section B.

2. Electroencephalography: One hundred and twenty-four EEG's have been done on probands and on parents and siblings of probands.

Idiopathic and control probands	38
Individuals unsuitable as probands	18
Parents and siblings of probands	63
Repeated EEG's	5
	124

3. Psychiatry: Forty-nine psychometrics (Intelligence and Social quotients) have been done; forty-five on probands, and four on twin siblings of probands.

4. Radiology: Thirty-six skull X-rays have been done.

Received from Dr. Boyce at an interview with him on Nov. 6/52. JWG

Continued .....

Summary of above activities:

Family histories	48
Physical examinations	132
Preliminary reports	1
Electroencephalograms	124
Psychometrics	49
Skull X-rays	36

(B) ANALYSIS OF DATA:

(a) History of seizures: Table 1 shows the relative frequency of seizures (not attributed to metabolic disorders, syncope or carotid sinus syndrome) that was found in twenty-eight idiopathic and nine suitable control families.

TABLE 1

	SEIZURES	
	Idiopathic %	Control %
Parents	16% (9/56)	6% (1/18) 3/56
Siblings	18% (11/59)	4% (1/24) 2/48
Total	17% (20/115)	5% (2/42)

(b) Electroencephalographic abnormalities: Table 2 shows the relative frequency of EEG abnormalities (borderline abnormalities are not included) found in the parents and siblings tested so far in the twenty-eight idiopathic and nine control families mentioned above.

TABLE 2

	ELECTROENCEPHALOGRAMS	
	Idiopathic	Control
Parents	16% (5/32)	33% (1/3)
Siblings	55% (11/20)	0% (0/4)
Total	31% (16/52)	14% (1/7)

Continued .....

(c) CONCLUSIONS:

At the present time the numbers are too small to arrive at any definite conclusions, however, certain trends are indicated because:

(a) 16% of the parents of idiopathic probands have definite histories of seizures as compared with 6% of parents of control probands;

(b) 18% of the siblings of idiopathic probands have definite, substantiated histories of seizures as compared with 4% of siblings of control probands;

(c) 55% of the siblings of idiopathic probands show electroencephalographic abnormalities. (Too few EEG's have been done on parents and siblings of control probands; and therefore, the percent abnormalities found in the idiopathic group cannot be adequately compared).

At the present time, therefore, it appears that a hereditary factor in the etiology of "idiopathic" epilepsy is indicated for: 1) the incidence of seizures among the parents and siblings of idiopathic probands is at least three times as high as in the control group; and 2) the incidence of electroencephalographic abnormalities in the parents and siblings of idiopathic probands is at least two times as high as in the control group.

Respectfully submitted,

Katherine Metrakos, M.D.

Julius D. Metrakos, Ph.D.

Project No. 604-5-25 - Study of Genetics of Epilepsy
Report for April to the end of September 1952

1st Report

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1. Medical Genetics:

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One hundred and twenty-four EEG's have been done on probands and on parents and siblings of probands.

Idiopathic and control probands	38
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Forty-nine psychometrics (Intelligence and Social quotients) have been done; forty-five on probands, and four on twin siblings of probands.

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Thirty-six skull X-rays have been done.

Continued .....

Summary of above activities:

Family histories	48
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Preliminary reports	1
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(a) History of seizures: Table 1 shows the relative frequency of seizures (not attributed to metabolic disorders, syncope or carotid sinus syndrome) that was found in twenty-eight idiopathic and nine suitable control families.

TABLE 1

	SEIZURES	
	Idiopathic	Control
Parents	16% (9/56)	6% (1/18)
Siblings 18.6 = 19%	18% (11/59)	4% (1/24)
Total	17% (20/115)	5% (2/42) 4.76%

(b) Electroencephalographic abnormalities: Table 2 shows the relative frequency of EEG abnormalities (borderline abnormalities are not included) found in the parents and siblings tested so far in the twenty-eight idiopathic and nine control families mentioned above.

TABLE 2

	ELECTROENCEPHALOGRAMS	
	Idiopathic	Control
Parents 15.6	16% (5/32)	33% (1/3)
Siblings	55% (11/20)	0% (0/4)
Total 30.7	31% (16/52)	14% (1/7)

Continued .....

(c) CONCLUSIONS:

At the present time the numbers are too small to arrive at any definite conclusions, however, certain trends are indicated because:

(a) 16% of the parents of idiopathic probands have definite histories of seizures as compared with 6% of parents of control probands;

(b) 18% of the siblings of idiopathic probands have definite, substantiated histories of seizures as compared with 4% of siblings of control probands;

(c) 55% of the siblings of idiopathic probands show electroencephalographic abnormalities. (Too few EEG's have been done on parents and siblings of control probands; and therefore, the percent abnormalities found in the idiopathic group cannot be adequately compared).

At the present time, therefore, it appears that a hereditary factor in the etiology of "idiopathic" epilepsy is indicated for: 1) the incidence of seizures among the parents and siblings of idiopathic probands is at least three times as high as in the control group; and 2) the incidence of electroencephalographic abnormalities in the parents and siblings of idiopathic probands is at least two times as high as in the control group.

Respectfully submitted,

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Katherine Metrakos, M.D.

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Julius D. Metrakos, Ph.D.

Director, Health Insurance Studies 604-5-25

From: Mental Health Division Feb. 6/52

Quebec Project: Study of Genetics of Epilepsy (McGill University) - Technical Evaluation.

A Progress Report received on this project has been reviewed by competent appraisers and considered by the Subcommittee on Research. This project appears to be of value in the mental health field but epilepsy has already had considerable investigation in respect to the heredity factor. Even if the present study were to solve the problems referred to by the investigators it is doubtful that this would have applied clinical significance. There is, however, a great need for genetic work in the field of psychiatry and as there are very few geneticists in the country and as it is necessary for these geneticists to become familiar with the field of psychiatry it would probably be helpful for them to start this project with the hope that they would later be able to study psychiatric problems of much greater significance. The following comments are made on their submission: It is possible that the study as outlined by the grantee will have the same defects as the studies which they have discussed in their submission. It is suggested that they should use the following procedure: (1) Sample at random children in the specified age-group living in Montreal; (2) classify the children sampled as epileptic or non-epileptic; (3) Sub-sample at random the non-epileptics at a sampling rate that will produce a group approximately equal in size to the epileptic group; (4) examine the relatives of the epileptic and non-epileptic groups in accordance with the stipulated procedure.

It will also be necessary for the plan of analysis of data to be clearly outlined so that it will be possible to estimate the amount of data which must be collected.

In this type of project it appears that the statistical analysis of data is at least as important as the collection of the medical data and it is recommended that the grantees should intimately involve a qualified statistician in the Department of Mathematics (e.g., Dr. R. A. Bradley) of McGill University. Provided that these matters are brought to the attention of the grantees the Committee recommends that this project be approved.

C. A. Roberts, M.D.

CAR/KM

A STUDY OF THE GENETICS OF EPILEPSY.

Children's Memorial Hospital and McGill University, Montreal.

Purpose. To decide whether or not the immediate relatives of patients with "idiopathic" epilepsy are more likely to have epilepsy or cortical dysrhythmias than the immediate relatives of persons without epilepsy or cortical dysrhythmia chosen from an otherwise comparable population.

Previous work.

For many years Lennox (4) has been the outstanding authority on the inheritance of epilepsy. His results show a higher - than - normal incidence of epilepsy in the relatives of epileptics, that this excess is greatest in the families of patients with "idiopathic" epilepsy, but is still significantly greater than normal in the families of patients with "symptomatic" epilepsy. His figures are based on a very large number of patients, and his estimate of the incidence of epilepsy in the 'normal' population is based on the figures of the U.S. draft in 1917 and 1942. This evidence for a hereditary predisposition to epilepsy is supported by studies on 122 twin pairs in which it is shown that the concordance rate for monozygotic pairs is higher than that for dizygotic pairs.

Unfortunately Lennox's data are open to some criticism. About one third of his patients were referred to him by other neurologists, who knew he was interested in "familial" cases. This procedure is very liable to bias the data, since it is our experience that cases with a

positive family history are much more likely to be referred than 'sporadic' cases. Thus the incidence of epilepsy in the relatives of the index cases is liable to appear unduly high. The picture is further confused by some uncertainty as to the criteria by which a diagnosis of epilepsy can be made. The twin data may also be biassed, since the proportion of monozygotic to dizygotic pairs is far higher than that which occurs in the normal population. This suggests that the twins were selected by some criterion other than that one of the pair had epilepsy. If so, it is possible that concordant pairs may have been more likely to be selected than discordant pairs. Furthermore, the data can be criticized because they did not take into account the age distribution of the relatives, and since the incidence of epilepsy varies with age it is not fair to compare the incidence in relatives of epileptics with the U.S. draft figure, based on persons with a different age distribution.

Lennox has also published data suggesting that the cortical dysrhythmia underlying the epileptic diathesis is inherited as a Mendelian dominant factor. Although his later publications do not fit his theory as well as the earlier ones did, the idea of an inherited cortical dysrhythmia seems sufficiently well substantiated to merit further investigation.

Recently Alström (1) has challenged Lennox's position by publishing data, based on a large number of Swedish patients, purporting to show that the incidence of epilepsy is the same in the relatives of

persons with "idiopathic" epilepsy, with "symptomatic" epilepsy, or with no epilepsy at all. This view, if true, would necessitate a major reorientation of medical thought on this subject. However, it seems that there are some possible weaknesses to this study as well. Steinberg (5) has pointed out that some bias may have occurred due to the fact that not all the patients originally selected as index cases were followed up. This, in our opinion, does not constitute as great a bias as that in Lennox's series, but may be important, nevertheless. Furthermore it has been shown (ibid) that the incidence of epilepsy in the sibs of index cases is higher if one parent is epileptic than if both parents are normal, a fact not pointed out by Alström, and suggesting that genetic factors do play a part in the etiology of epilepsy.

The existence of two directly conflicting opinions, both supported by massive data, on a subject of such great medical importance, renders it desirable to have the question reinvestigated by an independent group. In Montreal there exists a world-renowned neurological centre, a children's hospital treating a large group of epileptics and a medical geneticist. Such a fortunate combination of circumstances provides a unique opportunity for us to contribute to the understanding of the genetics of epilepsy.

Plan of Research.

1. Selection of probands. It is proposed to begin our investigation by choosing for probands patients with recurrent petit mal or grand mal seizures and the spike-wave E E G pattern characteristic of "idiopathic" epilepsy, with no obvious neuropathology. This is the group most widely accepted as showing a hereditary tendency, and it is felt that choosing

probands by these specific and objective criteria is the most efficient and quickest way to get a positive answer to the question of whether epilepsy and/or cortical dysrhythmia are abnormally frequent in the relatives of patients with "idiopathic" epilepsy. An adequate group of such patients is available at the Neurology Clinic of the Children's Memorial Hospital.

2. Family-study. All the available siblings and both parents of each proband will be visited, and data will be collected on the medical history relevant to seizures, migraine and allergy. In addition an E E G will be done on each member of the family (as defined above) using hyperventilation and photic stimulation. Psychometric tests will be done on all epileptics and individuals showing cortical dysrhythmias. Other observations will also be recorded relative to physical characteristics such as body build, hair color and eyecolor, to look for possible constitutional factors related to the "epileptic diathesis".

3. Controls. The same procedures will be undertaken with the relatives of a group of non-epileptic hospital patients without cortical dysrhythmias, of a similar age group. This is the most difficult, but also the most critical way to control the experiment and gets rid of the age-distribution difficulty.

4. Results. Let us assume that the E E G set-up could handle 600 E E G's in two years for this project. If these were equally distributed among the epileptic and control families, and allowing 5 members per family this would mean 60 families for each group in two years. With this number,

the following results could be obtained.

a. Lennox's theory of the inheritance of cortical dysrhythmia could be checked. If the control incidence is 10%, and the incidence in sibs of epileptics approaches 50%, and the incidence in at least one parent approaches 100% as Lennox claims, a group this size could positively support or deny this claim.

b. If the control incidence of seizures is 0.5% and the incidence in the sibs of epileptics is 5%, one would expect to find in the above group 1 or 2 epileptics (60 x 4 x 0.5%) in the families of the controls, and 12 epileptics (60 x 4 x 5%) in the families of the epileptics. Although this is an inadequate number for proving anything about the inheritance of seizures, it should give a good indication of how a larger series would turn out.

c. Any well defined constitutional differences between epileptics and otherwise comparable non-epileptics should be detectable in the estimated sample.

It is estimated, therefore, that certain positive results could be obtained in two years of study, but that it would probably take about five years, with the existing facilities, to answer

completely the question asked. If the results of our study and circumstances are favorable, the programme might be expanded to include other types of epilepsy and other age-groups.

5. Personnel. J. Preston Robb, M.D., C.M., M.Sc., Director of the Department of Neurology of the Children's Memorial Hospital, Registrar, Montreal Neurological Institute and Director of Neurology at the Queen Mary Veterans Hospital will supervise the neurological aspects of the work.

F. Clarke Fraser, Ph.D., M.D., Director of the Department of Medical Genetics of the Children's Memorial Hospital and McGill University, and Assistant Professor, Department of Genetics at McGill, will supervise the genetic aspects of the work.

Katherine Metrakos, M.D., is working as a Research Fellow on the programme and will undertake the main responsibility for contacting and examining patients and coordinating the activities of the neurology clinic, E E G department and psychology department. She will handle some of the medical aspects of the cases, prescribing medications, etc.

Julius Metrakos, Ph.D., who is studying the occurrence of various diseases in twins will investigate any twins discovered during the study, and will assist Dr. Katherine Metrakos with the genetic aspects of her work.

K. Tukel, M.D., Supervisor of the E E G department, Children's Memorial Hospital, will undertake the recording and

interpreting of the E E G's.

7. Work already done.

Dr. Fraser has attended the epilepsy clinic of the Montreal Neurological Institute regularly during the past year, and has collected a number of pedigrees of epileptic patients. This was done in order to get an idea of what problems may be encountered in a study such as the one proposed here. Although pedigrees collected only by interview of a single family member are unreliable for genetic analysis of diseases as capricious as this, the experience gained may be helpful in designing the present program in such a way as to avoid some of the pitfalls which previous workers have fallen into.

Dr. J. Metrakos has already located and is studying 8 epileptic twins, and hopes to obtain more cases during the proposed study. All adequately studied cases of twins selected because at least one of them is epileptic are of great value in assessing the role of heredity in the etiology of epilepsy.

Dr. K. Metrakos has surveyed the records of the Children's Memorial Hospital, has found fifty cases of convulsions which comply with the criteria outlined above, and has begun taking the Family Histories of some of those cases.

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20/9/54	PA	J.D.	Dr. Fisher - Reg.	SEP 21 1954	GW	31/8/4
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26/10/54	PA		Dr. Roberts - Reg		GW	25/10/4
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16 May	BF		Dr Roberts (1)			19/4/5
21/4/5	PA	JS	Miss Van Dusen	APR 22 1955		21 Apr
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