THE GENETICS OF CONVULSIVE DISORDERS IN THE FAMILIES OF HEMIPLEGICS

by

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I. INTRODUCTION

> "The disease [epilepsy] begins in the mother's womb where it takes root, it is implanted in the children and grows with them- - - The disease is not always immediately manifest, because the root is not always strong enough or large enough to show its noxious quality, but it does grow and does become stronger so that seventy years later it may be recognized - - - Sometimes the disease appears after a shock, but the shock is not the cause."
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> Philip Theophrastus Bombast von Hoenheim (1493-1541). Zilboorg translation, 1941, page 144.

A. Review of the Literature.

Epilepsy, from the earliest times, has been branded 'hereditary', and marriage and children for those "possessed" by this ailment was frowned upon. To Hippocrates and Galen (115) idiopathic epilepsy was that type which developed in the brain directly and was assumed to have a hereditary basis. Burton (84) in his "Anatomy of Melancholy", claims that the ancient Scots "instantly gelded" any man with falling sickness, and if a woman "were found to be with child, she with her brood were buried alive and this was done for the common good, lest the whole nation should be injured or corrupted". There is a law in Sweden prohibiting the marriage of epileptics which dates back to the seventeenth century (5), and, indeed, even today the laws of many of the states of the United States of America forbid the marriage of an epileptic and even threaten fine or imprisonment for any who assist.

These strict eugenic laws restricting the lives of epileptics originated in the old belief that the convulsive

disorders were a homogenous group that had a very strong genetic factor in its aetiology. At the turn of this century, Gowers (84) studied a series of several thousand epileptics and concluded that in at least fifty percent of all cases of epilepsy, the malady was "ultimately the result of neurotic inheritance". Davenport and Weeks (21) in 1911, concluded that epilepsy was due to a simple recessive gene and proposed that "The most effective mode of preventing the increase of epileptics that society would probably countenance is the segregation during the reproductive period of all epileptics". However, in the last few decades it has become increasingly evident that epilepsy does not act as a "unit defect" (21), and being a symptom of disease rather than a disease proper, is heterogenous both clinically and genetically. Support for this belief can be found both in animal and human studies.

1) Animal Studies:- Evidence for constitutional factors in the aetiology of convulsive disorders is well documented in animal studies. The fact that convulsions, spontaneous or induced, are more common in some species of animals than in others is a demonstration of constitutional differences (57, 145). There are intra- as well as inter-specific differences in susceptibility. For example, audiogenic seizures can be induced more readily in domestic rats than in wild Norway and Alexandrine rats and in grey Norway than in Wistar Albino rats (43).

Other investigations have indicated that convulsive disorders in animals may originate as a result of specific genetic factors. Dice (26) discovered, following an

outcross, that epilepsy appeared in a waltzing stock of Peromyscus maniculatus and was apparently due to the effect of a single recessive gene. Nachtsheim (57) studied the white "Viennese" variety of rabbit and observed typical convulsions only in certain families. He concluded that it was due to a specific recessive gene with seventy per-cent penetrance and allelic to the pigment determining factor. Antonitis (7) studied the susceptibility to convulsions of 73 rabbits subjected to intense auditory stimulation and his observations supported Nachtsheim's interpretation of monohybrid inheritance. Thus the potential capacity for convulsive disorders in animals is at least partially controlled by specific mutant genes.

2) Human Studies:- In the attempts to demonstrate that hereditary factors play a role in the aetiology of convulsive disorders in humans, various investigative procedures have been used. In the majority of the studies carried out in the earlier part of this century, and in some of the recent ones, an attempt was made to assess the relative importance of heredity in the causation of epilepsy by comparing the proportion of epileptics with a positive family history of seizures with that of a control group. For example, of the 200 epileptics, of all types, which Brain (14) studied, 28 percent had a family history of seizures as opposed to 10 percent of the control group. Stein (148) found a positive family history in 18.1 percent

of a group of institutionalized epileptics and in only 4.6 percent of his control group. Himler (48) separated his patients into "idiopathic" and "symptomatic" epileptics and found that 15.6 percent of the former and 8.8 percent of the latter had one or more relatives with a convulsive disorder. Forty-five percent of the children with febrile convulsions had one or more relatives with a history of convulsions in Lennox's study (75) opposed to only 3 percent of children who did not have convulsions with fever. Livingston (93) and Fridericksen and Melchior (32) also studied children with febrile convulsions and found 8.9 percent and 4.2 percent respectively with positive family histories. Ounsted (107) obtained a positive family history in 39 percent of children with convulsions, Peterman (130) in over 50 percent of patients with "genetic epilepsy", and Lennox (84) in 29.3 percent of his epileptic group. The great variation in the results of the authors cited above is mainly due to the faults inherent in the "positive family history" method of investigation. Counting simply the number of positive family histories does not take into account the number of affected individuals within each family, or the degree of relationship of the affected individual to the proband. Thus a family with many affected relatives carries the same weight as a family with only one affected relative, and a family with an affected distant relative is scored the same way as a fam-

ily with an affected near relative. In addition, depending on where the limits are set in obtaining the family history, the proportion of patients with positive family histories will vary, for if one goes far enough along the branches of the family tree, everyone will be found to have a relative with a history of a convulsive disorder.

A much better method is the "contingency method of statistical prediction". Here one measures the frequency of affected individuals in each class of relatives separately. However, in presenting their final data, many authors group these various classes of relatives together. In a study of institutionalized epileptics, Stein (148) found that 3.7 percent of 6572 parents, sibs and children of epileptics had a history of seizures, while only 1.3 percent of a control group were subject to convulsions. Conrad (47) estimated that among the children of epileptic parents 6 percent were epileptic, but he counted dreamy states and endogenous depressions as epileptic. Himler (48) obtained a history of epilepsy in 1.9 percent of the near relatives (parents, siblings and offspring) of "idiopathic" epileptics. Lennox has collected family data on a series of epileptics of all types and his latest figures (84) show that of 20,000 near relatives of his 4231 patients, 3.2 percent had a history of seizures. In the subgroup without a history of antecedent brain damage 3.6 percent of the near relatives had a convulsion at sometime in their

life. Unfortunately, he did not collect a control group but compared these prevalences with an estimate of 0.5 percent for the general population - - - an estimate obtained from a study of U.S.A. army draftees. Harvald (47) estimated the morbidity risk for the near relatives (parents, siblings, and offspring) of patients with "cryptogenic" epilepsy to be 4.2 percent. He found this was significantly higher than Fremming's estimate of 0.46 percent for the prevalence of epilepsy in the general population. Ounsted (109) studied a group of children with convulsive disorders and calculated that the risk of developing convulsions of any type was 17 - 25 percent for each sib depending on whether the proband had epilepsy or simple febrile convulsions. Kimball (61) ascertained his cases by choosing only those epileptics with at least one parent affected, and observed that 11.8 percent of their sibs had a history of epilepsy. Eisner et al (27, 28) estimated that 6.53 percent of the relatives of their idiopathic epilepsy group had a history of convulsions of all types as compared to 2.78 percent of the relatives of a control group.

Metrakos and Metrakos (98) measured the prevalence of individuals with a history of having had at least one convulsion among the sibs, parents, uncles and aunts, grandparents and cousins of patients of a pediatric hospital who had a history of convulsions, irrespective of cause,

and found that it was significantly higher than that for the near relatives of nonconvulsant patients drawn from the same hospital population. When all near relatives (parents, siblings, uncles, aunts, grandparents and cousins) were considered together the prevalence for those of the convulsant group was 3.79 $\pm$ 0.45% and significantly higher than that for the control group (1.31 $\pm$ 0.15 percent). The prevalence among the near relatives of patients with centrencephalic epilepsy was 3.93 $\pm$ 0.22 percent, a figure significantly higher than that of the control group (1.79 $\pm$ 0.22 percent).

Most of the results quoted above and the results of many other similar studies demonstrate a significantly higher prevalence of individuals with convulsive disorders among the relatives of epileptics than among the relatives of non-epileptics. However, it must be added that some investigators do not agree with these conclusions. Stein (148) in 1933, in spite of a three-fold increase in the prevalence of epilepsy in the near relatives of epileptics as compared to the prevalence in a control group, decided that "the results of this study do not justify the conclusion that the symptom complex known as epilepsy is an inherited condition;" that is, he agreed with the findings, but did not think that one could interpret them as meaning inheritance. Bridge (16) claimed that heredity does not play a role in 57 percent of epileptics and is pronounced in only 15 percent. However, his

method of assessing the relative importance of genetic factors in the individual case leaves much to be desired in the eyes of a geneticist.

Böök (12) studied a Swedish population and did not find a significantly higher prevalence of convulsive disorders (grand mal seizures) among the siblings of epileptics. Alstrom (5) estimated that the frequency of epilepsy among the 5847 relatives of his epileptic group was only 1.5 percent and not significantly higher than for his control group. Lennox (84) claimed that, since the familial tendency decreases with increasing age of onset, the reason Alstrom obtained this low prevalence was the late age of onset of seizures in his patients. (This concept will be discussed in another part of this review).

It is apparent, therefore, that even the contingency method of statistical analysis does not produce uniformly consistent results. Most of these inconsistencies are the result of the difficulties inherent in any study of human genetics. These difficulties will be discussed later.

3) Electroencephalographic Studies: The development of the electroencephalogram opened a new dimension in the study of hereditary factors in convulsive disorders for it now became possible to correlate the type and frequency of clinical seizure with the type and localization of cerebral dysrhythmia. Furthermore, the electroencephalogram made it possible to identify individuals without clinical

seizures but who had a subclinical abnormality manifested by an abnormal EEG. When this new aid became available various investigators studied the records of relatives of their epileptic patients with the anticipation of finding similarities in their EEG records. Gottlober (41) did not find a significant similarity of records within families, but Lowenbach (94) observed abnormal tracings in 17 out of 37 relatives of epileptic patients. Straus et al. (149) obtained abnormal recordings in 4 (26.9 percent) of 13 non-epileptic relatives, and Robinson(135) studied the EEGs of 36 non-epileptic relatives of 31 epileptic patients and found that 36 percent were abnormal and 27 percent questionably abnormal. Such findings led Lowenbach (94) to conclude: "The dysrhythmias in the relatives of epileptic persons are the expression of an inherited non-specific functional instability of the nervous system and additional unknown factors must be present to make up clinical epilepsy."

Lennox, Gibbs and Gibbs (81) examined the EEGs of the near relatives of their epileptic patients and found that 60 percent of them were abnormal. When recordings were obtained of a control group only 10% of them were found to contain dysrhythmias. They concluded that "the dysrhythmia of epilepsy is inheritable and such a dysrhythmia when demonstrable may represent a predisposition to epilepsy or some allied disorder". They demonstrated the great value of the EEG in ascertaining subclinically affected

individuals by calculating that persons with this predisposition outnumber actual epileptic subjects by twenty-five to one.

Lennox, Gibbs and Gibbs (82) and Lennox (71, 75) extended their observations to 470 near relatives and observed some degree of abnormality in 50% as compared to 16% of a control group. EEGs were performed on both parents of 140 epileptic patients and in only 19% did both parents have normal recordings. They concluded that "the EEG is a hereditary trait and brain wave tracings, properly made and interpreted, may be of positive value in visualizing a transmitted quality which, with the possible help of acquired pathology or pathophysiology, may eventuate in epilepsy. The practical value of this evidence is limited. Because cortical electrical activity is a fluid trait, dysrhythmia cannot always be demonstrated in patients and tracings of relatives may display only minor deviations from normal. Therefore, negative EEG evidence may not be significant".

Many other authors have since used the EEG in their studies on genetic factors in epilepsy, and have obtained similar results. Kennard and Willner (59) obtained abnormal tracings in 57% of the siblings of patients with central nervous system disease, largely epilepsy. Greenstein (42) found that the proportion of epileptics with normal EEGs was greater in those without a family history of epilepsy

than in those epileptics with near relatives suffering from a convulsive disorder. Harvald (46, 47), in an extensive study of the families of epileptics, analyzed the EEGs of 547 near relatives and compared them with the tracings of a control group composed of 693 male applicants for aviation training. Unfortunately, he discarded the records of patients with only childhood convulsions as well as those of all relatives under the age of sixteen. Due to the fact that seizure discharges are most common at this age, if persons below the age of sixteen had been included, the positive results would have been far more striking. Nevertheless, he found that 55.7% of the near relatives had normal EEGs as compared to 80% of the control group.

In spite of the numerous inconsistencies, chiefly stemming from the variable interpretation of what constitutes a cerebral dysrhythmia, the EEG has added further evidence that hereditary factors do contribute to the aetiology of convulsive disorders.

4) Twin Studies: The "Twin study method", in which the concordance among individuals with identical inheritance (MZ twins), is compared with that of individuals with non-identical genotypes (DZ twins), is a most effective genetic procedure if it is applied to statistically representative samples. When combined with an ordinary sibling study, the twin study method assumes particular significance (56). This method has been used extensively in studies on the herediatry factors in epilepsy with respect to both clinical seizures

and EEG tracings. The earliest twin studies which dealt with numbers of monozygotic and dizygotic pairs adequate for comparison were those of Rosanoff, Handy and Rosanoff (1934) (139) and Conrad (1935) (84). The former studied 107 twin pairs of which one, at least, had epilepsy. Among the 23 MZ pairs there was 61% concordance, while only 24% of the 84 DZ pairs were concordant with respect to convulsions. Conrad included 157 pairs of twins in his investigation. He divided his cases into "essential" and "symptomatic" epilepsy and found that in the essential group 86% of the MZ as compared to 4% of the DZ pairs were concordant. On the other hand, in the case of the symptomatic group only 12% of the MZ and 0% of the DZ were concordant. In a series of 264 pairs, containing twins with essential and some with symptomatic epilepsy, Lennox (84) found that the MZ pairs were concordant in 70% of the cases, while the DZ pairs displayed only 14% concordance. In 1960 he reported on his collection of 225 twin pairs and for those with "metabolic" (idiopathic) epilepsy there was 84.5% concordance among the MZ twins as opposed to 15.9% concordance in the DZ pairs. He concluded that "The high degree of concordance in one-egg twins without brain injury leaves no doubt that heredity is very important in the aetiology of epilepsy" (84).

One finds even more convincing evidence for the relative importance of heredity in epilepsy when the EEGs of twins are compared. Davis and Davis (24) obtained tracings of nine pairs of normal identical twins. Lennox (84) combined their

results with the EEGs of six pairs with cortical dysrhythmia and found that in each of these fifteen pairs, whether normal or abnormal, the tracings of the co-twins were remarkably similar. Lennox has since obtained EEG records of a large series of twins and has published his results in a number of reports (75, 77, 81, 83). As early as 1950 he observed that: "In MZ twins with no acquired brain injury almost invariably both of them not only have seizures, but the same type of seizure and the same abnormal pattern of the EEG" (76). By 1960 he had a series of 225 twin pairs. Of the 121 pairs with "metabolic" epilepsy, for 3 per second spike-wave discharges, there was 84.3% concordance in MZ twins and 0% concordance among the DZ twin pairs. When he combined all of the abnormal discharges he found the concordance among MZ twins to be 70% and among DZ twins 2.2% (84).

When only one of MZ twins has epilepsy plus cortical dysrhythmia, the EEG of the "normal" co-twin is almost always abnormal and the epileptic one almost always has evidence of having experienced an acquired brain lesion (71). Lamy et al (63) obtained similar results in their twin studies. This similarity of the EEG tracings of identical twins led Lennox (71) to conclude that "The pattern of the waves, their frequency, voltage and wave configuration is a hereditary trait". Twin studies have demonstrated high concordance among MZ twins not only for the presence or absence of seizures, but also for the type and age of onset of clinical seizure,

the type of cerebral dysrhythmia, and the details of the EEG tracings.

5) Sex Distribution: Directly and indirectly, most of the studies mentioned revealed several discrepancies on the influence of sex and age on the familial prevalence of convulsive disorders. Most investigators have found a preponderance of males in their series of epileptics (5, 67, 92, 108), but in some studies females outnumber males (73, 84). Ounsted (108) claimed that this preponderance of males compares with that of unaffected siblings in his study, and that there is probably no significant sex preponderance in idiopathic epilepsy. The greater liability of males to acquire epilepsy through cerebral trauma undoubtedly accounts for part, if not all, of this small overall preponderance of males.

Lennox (84) calculated that the genetic factor (as measured by the number of epileptic relatives) is greater when the index case is a female than when it is a male. For the total group of epileptics, the average prevalence of affected relatives of male patients was 3.6%, and of female patients 4.1%. However, Lennox himself points out that this difference is probably not significant. In a group of mentally abnormal epileptics, the same author found that female patients had twice as many epileptic relatives as male patients (69).

Ounsted (108) estimated that of children with convulsive disorders and positive family histories, the positive history

was found two and one-half times as frequently on the maternal side of the family than on the paternal side. Himler (48) claimed that in his series there was a "slightly higher hereditary incidence among females". Lennox, Gibbs and Gibbs (81) obtained abnormal EEG tracings more frequently among relatives of female patients than among relatives of male patients. Furthermore, the EEG abnormalities were more prevalent among female than male relatives. However, these findings of increased hereditary influence in females are not all statistically significant, nor are they consistently found by all investigators. Metrakos and Metrakos (98) have reported no such sex influence in their series of children with convulsions.

6) Age of Onset:- Lennox (71, 75, 76, 84) has consistently found that the earlier symptoms appeared the greater was the hereditary factor. This was particularly so when there was no evidence for an acquired injury to the brain occurring early in life. In the group of epileptics without antecedent brain damage, if the convulsions began in infancy, 6.4% of the relatives were affected as against only 1.5% if the epilepsy started after the age of thirty. He claims that this is to be expected since conditions which are predominantly genetic in origin tend to manifest themselves early in life. But many conditions, which have a large genetic factor in their aetiology (e.g. Huntington's Chorea, diabetes, etc.) have their onset relatively late in life.

Ounsted (109) discarded the patients with seizures due to cerebral infection and those with an age of onset after eight years and divided the remainder into three groups depending on the age of onset of convulsions -- group A- 0 - 1 year; group B - 1 - 3 1/2 years; and group C - 3 1/2 - 8 years. His calculations showed that the risks of the siblings of patients of Group B were the highest, thus concluding that "seizures in this age period have a powerful genetic determination", and theorized that "the inherited factor operates through some transient imbalance of electrochemical maturation which may be corrected with advancing age".

However, it may not be the age of onset, per se, but the different types of epilepsy that are more prevalent in certain age groups, that are related to the degree of genetic influence.

7) Birth Order and Other Perinatal Factors:- Brain (14) and Nielsen (106) discovered that a high proportion of their epileptics were first-born and suggested that the increased liability of first-born children to receive cerebral injury at birth may be an explanation of their disability. Nielsen found that 39.12% of his "idiopathic" epileptics were first-born; but Metrakos (97) has pointed out that in a population with average mean family size, 35-40% of all individuals are first-born and thus Nielsen's findings in epileptics may well be comparable to that of the general population.

Lilienfeld and Parkhurst (87) after investigating the

neonatal histories of cerebral palsy patients, proposed that "there exists a continuum of reproductive casuality composed of a lethal component consisting of stillbirths, neonatal deaths and a sublethal component consisting of cerebral palsy". Lilienfeld and Pasamanick (88) performed a similar study on epileptics and suggested that epilepsy be included in the sublethal component and that cerebral palsy was just a more severe form of brain damage than epilepsy. They proposed that the finding of a familial aggregation in epilepsy was merely a manifestation of a familial aggregation of various meternal and fetal factors. These conclusions were based on their observations of a higher proportion of pregnancy and neonatal complications among epileptics than among the control group. These conclusions cannot be extended to epilepsy in general, especially the idiopathic group, since they are based partly on cases of symptomatic epilepsy. Thirty-five percent of the white epileptics had associated defects, which is certainly higher than one would find in a randomly selected group of people with a history of convulsions. They included neonatal convulsions as one of their criteria of "neonatal difficulty" and thus it is not surprising that they were found more commonly among the epileptic group. Although there most certainly is an association of perinatal injury in some forms of epilepsy, one cannot conclude from their results that all the epilepsies, idiopathic or symptomatic, are due to perinatal injury.

Eisner et al. (27) found a familial aggregation of convulsive disorders, but in view of the heterogeneity of this group of disorders, concluded that: "The causes of epilepsy may well be multiple and present knowledge does not, in our opinion, allow one to rule out any of the possible causes".

8) Interaction of Heredity and Environment in Acquired Epilepsy: In discussions on the relative effects of nature and nurture, one finds statements claiming that since there is definite evidence of an environmental cause of a disorder, hereditary factors play no role. But heredity and environment are not mutually exclusive, and all one can attempt is the assessment of the relative importance of these two interacting factors in the aetiology of any disease. In many papers on acquired epilepsy one finds statements discrediting hereditary factors simply because there is evidence of cerebral pathology. Many authors, although cognizant of the interacting roles of heredity and environment in the aetiology of many diseases, nevertheless arrive at the conclusion that inheritance plays no part in acquired epilepsy. Penfield (113, 115) has repeatedly refuted the claims of hereditary factors in traumatic epilepsy, stating that: "Inheritance of a tendency to fits, so far as my observations go, seems to play little or no role in the probability of onset of attacks in such cases". Other authors have arrived at similar conclusions (91, 133, 153, 164).

Ounsted (109) conducted a study of childhood convulsive disorders and found that in patients with epilepsy due to infections of the brain, or other insults, the risk to their siblings of developing any convulsive disorder was 6.47%. He claimed that these risks are barely, if at all, in excess of general risks and quotes Thom's (150) figure of 6% for the prevalence of seizures in children. He concluded that: "When febrile convulsions are produced by slight insults genetic endowment seems to play a major aetiological role, but where gross insults evoked the seizure, genetic endowment played a negligible part". He also studied patients with temporal lobe epilepsy with focal discharges in their EEGs (presumably acquired epilepsy) and calculated that the risk for their sibs of developing seizures was 15%. After analyzing all his results he arrived at the opinion that:"Acquired epileptic foci may require an appropriate genetic background for their expression". Similar conclusions have been reached by others (156, 158).

Lennox, since his earliest investigations, has been a staunch supporter of the view that genetic factors play a large role in acquired epilepsy. In 1940, Lennox, Gibbs and Gibbs (81) arrived at the conclusion that the sharp separation of sympatomatic and essential epilepsy was unjustified since they found that the symptomatic group of epileptic patients had three times as many near relatives with seizures as had persons in the general population. They also observed

that of twenty-seven parents and sibs with symptomatic epilepsy, 60% had abnormal EEGs. This is the same prevalence which they recorded for the near relatives of patients with essential epilepsy.

In 1942, (82) they recorded the EEGs of seven pairs of monozygous twins of which only one member was epileptic, and in six there was definite evidence of brain injury. They observed that in all seven pairs both members had pronounced dysrhythmias. From these results they concluded: "Probably the great majority of patients who have traumatic epilepsy had a pre-existing hereditary dysrhythmia. The acquired injury or defect of the brain, which is not consistently epileptogenic, may act on an already present asymptomatic dysrhythmia and make it appear externally as epilepsy". In his later twin studies, Lennox (74, 84) found that in the twins that had at least one member with antecedent brain damage, the concordance rate among MZ twins was twice that found among DZ twins, and concluded that: "As a cause of epilepsy in this group of patients heredity is twice as important as an acquired brain lesion".

In his investigations on the prevalence of convulsive disorders in the near relatives of epileptics, Lennox (69, 75, 77, 84) separated his patients into those with and those without evidence of antecedent brain damage. He consistently observed that the prevalence of convulsive disorders among the near relatives of the brain damaged group lay in between that of the near relatives of the "metabolic" epileptics and

his estimate of 1% for the prevalence of convulsive disorders in the general population. Of the total 4231 patients, the prevalence of affected relatives was 3.2%. Among the relatives of the epileptics without brain damage the prevalence was 3.6%, and among the relatives of those with brain damage it was 1.8%. He concluded that: "If the metabolic and organic groups were mutually exclusive and epilepsy in the brain damaged group were due solely to the acquired condition, the affected relatives of this group should not exceed the number in the general population. This nearly twofold increase reflects the fact that in many patients both genetic and acquired conditions are at work". Although there is much evidence pointing towards the operation of hereditary factors in the aetiology of organic epilepsy, it is not as strong as that for idiopathic epilepsy, and more well-controlled studies are needed in this area.

9) Mode of Inheritance: The literature which has been reviewed has, according to Lennox (84), established the fact that heredity is an important factor in the aetiology of epilepsy, in "at least that form which is not complicated by evidence of an acquired brain lesion". This mass of evidence has not so far clearly established the mode of inheritance, although many theories have been proposed.

Davenport and Weeks (21), 1911, claimed that epilepsy acted as a unit defect and spoke of simple recessive inheritance. In 1940, Lennox, Gibbs and Gibbs (81) proposed that not epilepsy per se, but cerebral dysrhythmia, is a hereditary

trait and thought that it might prove to be due to a dominant gene. Lamy (63) reviewed Lennox's data and claimed that there was solid evidence that the dysrhythmia is transmitted as a dominant. Whitteridge (146) speculated that it was really an incomplete dominant which caused cerebral dysrhythmia in the heterozygote and clinical epilepsy in the homozygote. Kimball and Hersh (61) thought that they had definite evidence that epilepsy was due to a simple autosomal dominant gene with about 65% penetrance, and that a potential epileptic (only cerebral dysrhythmia) was also a heterozygote. Fraser and Metrakos (31), on the basis of a detailed study of a group of centrencephalic epileptics, theorized that the simplest mode of inheritance for centrencephalic epilepsy, compatible with their data, was a simple autosomal dominant gene with approximately 35% penetrance. However, they hastened to point out that although this may be the simplest explanation compatible with the data, it may not be the correct one. In 1953 Lennox and Jolly (83) changed their views on the mode of inheritance when, on the basis of their twin studies, they claimed that the genetic factor in epilepsy was probably recessive in type.

Much doubt has been expressed concerning the validity of the single gene hypothesis. Conrad (84) and Kallmann (56, 57) were in favour of a multifactorial mode of inheritance. According to Harvald (47) the inheritance is, in most cases, polymeric with additive gene action. Ounsted (109) proposed a concept involving a quantitative seizure threshold, but stated that a single gene pair would fill the requirements for it would

be progressively and quantitatively modified by the action of other genes. Eisner et al. (28) after analyzing their data concluded that they could not rule out or prove the multiple gene hypothesis or that of a single gene with low penetrance. Although many theories have been proposed, no definitive statement can be made as to the mode of inheritance of cerebral dysrhythmias or clinical epilepsy.

10) Mechanisms of Gene Action:- The mechanisms by which the genes involved in the inheritance of convulsive disorders operate are also in dispute. Some authors claim that all forms of epilepsy and dysrhythmia are controlled by the same set of genetic factors, while others believe that several independent factors are involved. Livingston (93) suggested that there may be a significant difference between the hereditary factors which predispose to chronic epilepsy and those which predispose to childhood convulsions. Tizard (151) proposed that in families with febrile fits, rather than a predisposition towards epilepsy, the hereditary factor may be a peculiar reaction to high fever -- "a specific hereditary reactivity to fever, which reactivity would cause a fit in anyone in whom it was present".

Williams (156) proposed a dual inheritance of the state of epilepsy -- the "epileptic factor" (a tendency to attacks) and the "limiting" or "antiepileptic factor" (preventing the spread of the epileptic state). Harvald (47) speculated that the tendency toward paroxysmal dis-

charges and the tendency for such to pass into generalized seizures depended on mutually independent hereditary factors, and that this second factor involved the transition of even inconsiderable paroxsyms into generalized epileptic seizures. Ounsted (107, 109) proposed a concept in which the inherited factors operated through some transient imbalance of electrochemical maturation, which may be corrected with advancing age.

11) Convulsive Threshold Concept:- Reference has already been made to the evidence of many workers (69, 75, 77, 81, 82, 84, 109, 156, 158) that even in cases of epilepsy associated with brain damage, there is an elevated prevalence of convulsions among the relatives. The most reasonable explanation for this fact is that there is a genetically influenced threshold for convulsions. Patients with a low threshold are likely to have convulsions following brain damage. Their relatives have an increased probability of inheriting a low threshold and will therefore also be predisposed to convulsions.

Throughout the literature on epilepsy one finds many references to such a constitutional predisposition (4, 10, 14, 22, 45, 47, 57, 62, 67, 70, 71, 73, 75, 76, 80, 81, 82, 84, 90, 102, 106, 112, 129, 130, 132, 136, 137, 138, 145, 148, 151, 154, 155, 156, 157). Some authors, however, have firmly denied its existence (25, 49, 140, 141, 143, 153).

Humans vary widely in their ability to react to a convulsant stimulus by manifesting an EEG dysrhythmia or a clinical seizure. Many lesions of the nervous system will produce convulsions in one patient and will not in another. Ajmone Marsen and Ralston (4) administered metrazol to many

patients and then recorded their EEGs. They observed that in some people EEG changes occurred after minimal doses while in others they did not occur at all or only with relatively high doses. Sal Y Rosas (136) also found differences in the convulsive threshold to metrazol. Electrical stimulation has also revealed marked differences in threshold of excitability between individuals. Gastaut (33) investigated the relatives of epileptics and found evidence for a hereditary predisposition in their lowered threshold for convulsions produced by photic stimulation.

Nielsen and Courville (106) postulated that the absence of seizures following cerebral anoxia may depend on varying degrees of susceptibility to convulsions in different persons. They contradicted Lilienfeld and Pasamanick's (88) theory of a continuum of reproductive casuality, claiming, that birth trauma could not by itself produce seizures, for these could be precipitated only in a predisposed individual. This threshold concept has been extended to febrile convulsions and many authors (67, 102, 129, 130) believe that febrile convulsions occur only in children who have a hereditary predisposition to seizures. Evidence for a constitutional predisposition has also been found in convulsions due to anaesthesia (112, 157), delirium tremens (137), and toxemia of pregnancy (138).

A great controversy still exists as to whether a hereditary predisposition is involved in the development of seizures in cases of cerebral trauma and neoplasms. Some authors (22, 84, 155) claim that a pre-existing predisposition

or low threshold determines their ability to react with seizures, while Penfield (115), Denny Brown (25), and Russell (140, 141), among others, do not believe that hereditary predisposition is an underlying factor in these cases. According to Lennox, Gibbs and Gibbs (80, 81, 82), the cerebral dysrhythmia is often evidence of this hereditary predisposition and in people without the dysrhythmia, brain injuries would have to be much more serious in order to give rise to seizures.

When one considers all the evidence and arguments for and against hereditary predisposition as an aetiological factor in convulsive disorders, one cannot escape the conclusion that the sum total of the evidence is overwhelmingly in favour of genetic factors. However, one must also conclude that little if anything is yet known about the mechanisms of action of these genetic factors. Many consider that this predisposition involves the activation of a cerebral dysrhythmia, but Gastaut (84) has remarked "Predisposition is not a problem of the origin of the epileptic discharge, but of its propagation". MacKay (95) has suggested that "all epilepsy is one" and that a common underlying predisposition will be found, irrespective of the precipitating factor.

A brief summary of the convulsive threshold concept has been given by Tizard (151), who writes that: "Any individual given an adequate stimulus will have a fit, but

the nature and degree of the precipitating agent varies from person to person. At one end of the scale are those who will only convulse in response to a severe electrical shock, or an injection of insulin or leptazol. While at the other end are those in whom fits occur spontaneously, i.e. the precipitating factors are not detectable. In between these extremes one would place those individuals who convulse in response to conditions such as high fever, brain injury and cerebral tumor, conditions which might not cause fits in others with a higher convulsive threshold". Thus the problem appears to concern the relative effects of nature and nurture. It is once more stressed that these forces are not mutually exclusive and do not operate independently. The major factor in one individual may be his inherent predisposition, while in another it may be the external stress to which he is subjected.

B. BASIS FOR PRESENT STUDY

1) Difficulties of Genetic Study of Epilepsy:- This review of the literature has revealed several conflicting views, not only as to whether hereditary factors do or do not play a role in convulsive disorders, but as to how much of a role they play, how they operate, and in which forms of epilepsy they act. The influence of hereditary factors is estimated to be high by those who study children (15, 99, 109), low by those who work with adults (5);

high by those who use twin material (63, 74, 82, 83), low by those attempting general geographical ascertainment (5, 12); high by those who use EEG evidence (80, 81, 82, 98, 99), lower by those relying on clinical evidence alone (5).

Many of these discrepancies are due to difficulties inherent in any study of human heredity. One of the major difficulties is in defining the terms "affected" and "not affected" so that there is a clear-cut dichotomy between them. Throughout the older literature one finds reports of a positive family history in as high as 80% of the cases, for these studies include as "affected" all individuals with conditions suggesting cerebral and emotional instability, and ranging from syphilis to hysteria. Stein (148) reviewed the older literature and was of the opinion that the majority of it was not significant for a variety of reasons, e.g. paucity of data, lack of controls, introduction of clinical entities like alcoholism, hypertension and insanity, into the affected group, etc., etc. Even in the more recent literature there appears to be no agreement as to what constitutes an "affected" individual. Some authors will call an individual affected only if he is a chronic epileptic, others set one convulsive episode as their baseline, and still others will count a person as affected if he has an abnormal EEG even though he has never had any seizures.

Another cause for disagreement is the problem of classification of the convulsive disorders. Since these

constitute a highly heterogeneous group of disorders, and since there are often no clear-cut lines of demarcation, what one author classifies as homogenous may fall into several distinct groups when considered by another investigator. Some classify their cases clinically (Ounsted) (107, 109), others by means of their medical histories (Lennox) (84), some by their family histories (Kimball) (60, 61), and still others by means of their EEGs (Metrakos) (98, 99).

Different methods of ascertainment also tend to confuse the issue. Some ascertain their cases from homes for chronic epileptics (14) while others (98) will accept as probands any child with as few as one single isolated convulsive episode.

In comparing the prevalence of affected relatives of the epileptics with that of affected individuals in a control group one runs into two more sources of confusion. First, is the definition of the pedigree limits. Only parents and sibs may be included by some authors (60, 84) while others include collateral relatives such as cousins, aunts and uncles (98). The second is in obtaining a comparable control figure. Many authors have used the figure of 0.5% for the prevalence of epilepsy in the general population. This figure and those of Ledeboer (0.5%) (156), Kurland (0.38%) (62), Book (0.39%) (12), and Fremming (0.35%) (46) are based on the prevalence of chronic epilepsy, and one should use these figures for comparison only when the term

"affected" applies to chronic epileptics. When one includes all convulsive disorders, irrespective of cause and severity, the figure becomes much higher. Lennox (84) has estimated that the prevalence of individuals with a history of only one or two seizures is about 1%. When populations of children were investigated, the estimates were found to be much higher than this. Thom (150) calculated that the prevalence of infantile convulsions was about 7%. Peterman (128) estimated that under 2% of children admitted to a large hospital were subject to convulsions. The Metrakoses (98) estimated, from sample of 1000 consecutive admissions to a children's hospital, that the prevalence of patients with a history of having had at least one convulsion was 11.5%. This was reduced to 8.76% when patients admitted because of a convulsion were excluded. The true value presumably lies somewhere between these figures.

The estimates for the prevalence of convulsions in a normal group depends on how the sample is ascertained and on the definition of the term "affected". The most reliable method of obtaining this baseline is to estimate the prevalence of affected individuals among the relatives of a control group drawn from the same population as the test group. Eisner et al. (27, 28) and the Metrakoses (98, 99) have both used this method to advantage in their carefully controlled studies.

The convulsive disorders are a group which is hetero-

geneous, both clinically and genetically. Kallmann (57) claimed that one should be able to distinguish genetically between : (a) the innate capacity for reacting convulsively to drastically stimulating agents; (b) the inherited capacity to develop convulsive disease without unusual stimulation; and (c) the inheritance of special genes producing specific cerebral lesions which may be incidentally associated with convulsions.

The Metrakoses (98) considered the genes that may contribute to an individual's resistance or susceptibility to convulsions in three major categories: 1. Epilepsy genes -- Are there specific genes for epilepsy per se? 2. Cerebral disease genes -- There are many known genes for specific cerebral diseases (tuberose sclerosis, myoclonus epilepsy, infantile amaurotic idiocy) in which convulsions may be one of the associated signs and symptoms; 3. Threshold genes -- Genes which determine the convulsive threshold of an individual. The genes responsible for these three major genetic categories are probably closely interrelated.

2) Thesis of Present Study:- The group in which there is most controversy as to the role of hereditary factors is the acquired or symptomatic epilepsies. Any genetic factor involved here would most probably involve the "threshold genes" and/or the "cerebral disease genes". Since a familial tendency was demonstrated in epileptics with general brain damage (84), it was thought that it would be of value to

investigate the role of heredity in epileptic probands with some definite neuropathology. Patients with hemiplegia, a condition in which interference with the control of one side of the body arises as a result of lesions of the brain, were chosen for this investigation as they are believed to have close to uniform neuropathology, in the spatial sense at least. The prevalence of hemiplegics with convulsions ranges, in the literature, from 35 - 68%, with a mean of about 50%. Why do only one-half of these patients with approximately the same neuropathology have convulsions? Is it due to chance alone, to variations in the severity of the neuropathology, or to an inherited low threshold to seizures? This project was undertaken humbly in an effort to unravel this complex problem. The basic question underlying the premise is the following: Is the prevalence of individuals with convulsions and/or cerebral dysrhythmias among the near relatives of hemiplegics with convulsions significantly higher than that among the near relatives of hemiplegics without convulsions?

II. MATERIALS AND METHODS

A. Definitions: A clear and precise definition of terms is essential to any study of human heredity. To avoid confusion, it was thought that it would be profitable to commence by defining some of the terms which will be used throughout this thesis.

Cerebral Palsy: "All those conditions in which interference with the motor system arises as a result of lesions within the brain " (9).

Hemiplegia: A subclass of cerebral palsy in which one side of the body is affected. It is usually spastic and is due to neuropathology in the contralateral cortex (103).

Individual with convulsions: Any person with a history of one or more convulsions occurring at any time during his life.

Hemiplegia with convulsions: An individual with hemiplegia who has had one or more convulsions at any time during his life.

Hemiplegia with convulsions before onset: A hemiplegic with convulsions whose first convulsion preceded the onset of the motor disability.

Hemiplegia with convulsions at or after onset: A hemiplegic with convulsions whose first seizure occurred during the same week or postdated the onset of the motor disability.

Serial control group: Individuals chosen at random from the same hospital population as the hemiplegics but who do not have a history of convulsions or of any other neurological disorder.

Intermediate control group: Those individuals of the serial control group whose electroencephalogram is not normal.

Absolute control group: Those individuals of the serial control group who have been found to have a normal electroencephalogram, usually on a single examination.

B. Ascertainment of Probands: The hemiplegic probands were ascertained by examining the medical records of the patients registered with the Cerebral Palsy Rehabilitation Centre and the Physiotherapy department of the Montreal Children's Hospital, as well as some private patients of Dr. J.P. Robb, Director of the Neurology Service of the hospital. These patients were divided into two main groups on the basis of their medical histories: (a) "Hemiplegia With Convulsions", and (b) "Hemiplegia Without Convulsions." The former was further divided into two groups, "Hemiplegia With Convulsions Before Onset" and "Hemiplegia With Convulsions At Or After Onset", depending on whether their first convulsion occurred before, at, or after the onset of their motor disorder. (See definitions above). Sometimes a hemiparesis is noted during an acute illness or with a

convulsive episode, but it does not persist. Such cases were not included in this sample.

In selecting an appropriate control group, the control and test groups should be drawn from the same or a similar population and be comparable in all factors other than those being studied, unless, of course, the variables are associated with the presence or absence of the abnormalities in question. These variables include such things as age, sex, ethnic origin, and birth order of the proband; size of sibship of proband and of parents; maternal and paternal age; and many others.

In an attempt to randomize or eliminate these variables, the control probands were drawn from the same hospital population to which the hemiplegics belong. The medical record of every twentieth admission was examined, and, if there was no history of convulsions or any other neurological disorder, the child was accepted into the "Serial Control Group".

C. Associated Characteristics of Hemiplegic Probands: Information was obtained about many characteristics of the probands, e.g. severity of neuropathology, laterality of involvement, time of onset of neuropathology, intelligence, birth weight, birth order, associated defects, etc. The severity of the motor disorder was used as an indirect guide to the severity of the neuropathology. Employing a scheme devised by Dr. Robb and under his direction, the

author conducted a neurological examination of hemiplegic and control probands. The severity of the motor disability was classified as mild, moderate or severe, according to the following criteria: (a) "Mild" - if the hand carried out useful activity; (b) "Moderate" - if the hand served as a helping hand; and (c) "Severe" - if the hand served no useful purpose. It was realized that this classification serves only as a very rough indicator of the degree of neuropathology, but it was felt that any error would be randomized among the various groups of hemiplegics.

In so far as this series of patients was collected over a number of years, the age of the proband recorded was the child's age when first seen by a member of the Department of Medical Genetics.

"Laterality of Involvement" refers to the side of the patient's body which is affected by the motor disorder.

The medical records divided the time of onset of neuropathology in five groups: prenatal, natal, congenital unknown, postnatal, and unknown. Here a distinction has been made between "natal" and "congenital unknown" because the term "congenital" simply means "present at birth" but does not pinpoint the onset. Since the distinction between prenatal and natal is usually a matter of subjective impression, the first three classes were grouped together. In this thesis, time of onset of neuropathology was classified into three groups: "Congenital", "Postnatal" and "Unknown".

The majority of the hemiplegic probands had already been examined by the Psychology Department of The Montreal Children's Hospital as part of their routine workup. Copies of these test results were obtained and an effort was made to have psychometrics performed on any proband, hemiplegic or control, who had never been interviewed by a psychologist. The psychometric testing was performed by psychologists experienced in testing handicapped children. The child was given the benefit of the doubt when there was any possibility of the handicap lowering the test results. The psychologists used one of three tests depending on, among other things, the age of the child. The tests used were: the Cattell Infant Intelligence Scale, the Stanford Binet Intelligence Test, and the Wechsler Intelligence Scale for Children. A Bender Visuomotor Gestalt Test was given to some of the patients. If the child had been tested more than once, the score of what was considered the most reliable test was included in the analysis. This was usually the most recent test, since testing was repeated if the previous results were considered inadequate.

The birth weight and "birth order" of the probands were also recorded. In this study birth order refers to gravidity since a miscarriage is given the same weight as a livebirth.

Information about various associated defects of the probands including speech, hearing and visual difficulties,

congenital malformations, and behaviour problems was obtained from the medical records of the patient and from the interview with the near relatives.

D. Classification of Probands: The hemiplegic and control probands were classified further according to their EEG pattern. Most of the hemiplegic patients had already had one or more EEGs recorded as part of their routine workup. Copies of these were obtained, and if they were not available or if the patient had never had an EEG, he was referred to the EEG department of the Montreal Children's Hospital. In order to minimize differences of interpretation all the EEGs were reviewed and coded by one electroencephalographer, Dr. Katherine Metrakos, according to a master code (Appendix A). The probands of each of the three groups of hemiplegics mentioned above were classified into nine subgroups on the basis of their EEG code (Fig. 1). If the records of more than one EEG were available for any patient, all the various diagnoses were combined to reach the final code number. If epileptiform activity was recognized in at least one of the patient's tracings, he was put in the epileptiform group. If at least one of the records showed bilateral abnormalities, he was admitted into the bilateral group. For example, if the records of four EEGs were available for a patient and they were coded as normal, borderline, diffuse epileptiform, and focal non-epileptiform, he would be classed as "bilateral epileptiform". The patients with only unilateral EEG abnor-

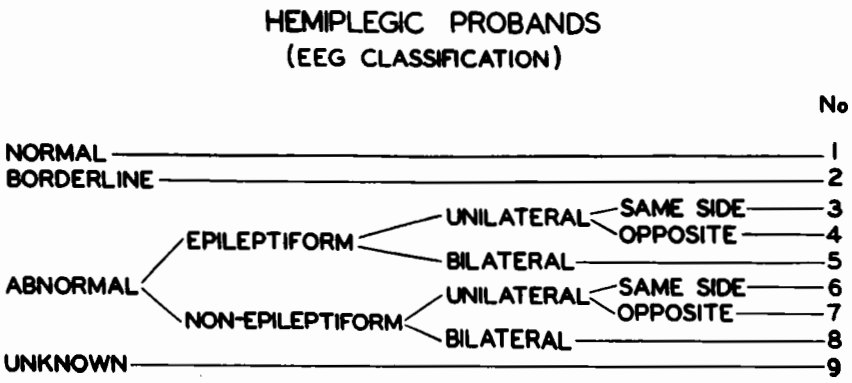
HEMIPLEGIC PROBANDS
(EEG CLASSIFICATION)
No
NORMAL
1
BORDERLINE
2
ABNORMAL
EPILEPTIFORM
UNILATERAL
SAME SIDE
3
OPPOSITE
4
BILATERAL
5
NON-EPILEPTIFORM
UNILATERAL
SAME SIDE
6
OPPOSITE
7
BILATERAL
8
UNKNOWN
9

FIGURE 1.

malities were separated into two groups: (a) EEG abnormality on the same side as the motor disability, and (b) EEG abnormality on the side opposite the motor disorder. By this method, twenty-seven groups of hemiplegic patients were obtained (Fig. 2).

As stated above, probands of the "Serial Control Group" were also classified according to their EEG. The records were reviewed and coded by the same electroencephalographer. If the pattern was within the normal limits for the age group of the child, he was classed as a member of the "Absolute Control Group". If the tracing was not normal, the child was placed in the "Intermediate Control Group". The EEGs were classified into normal, borderline, and abnormal, and four subgroups of control patients were obtained (Fig. 3).

E. Family and Medical Histories: When a suitable proband, hemiplegic or control, was obtained, the mother and/or father, and perhaps one or more of the other relatives, were interviewed and a medical and family history were recorded. Information was obtained about the proband's age, sex, birth weight, birth order, about maternal and paternal age, number of miscarriages, stillbirths, livebirths, twins in each sibship, and many other details. In the family history information was obtained about the siblings, parents, uncles, aunts, grandparents and first cousins of the proband. Other relatives (half-sibs of the proband or parents, second

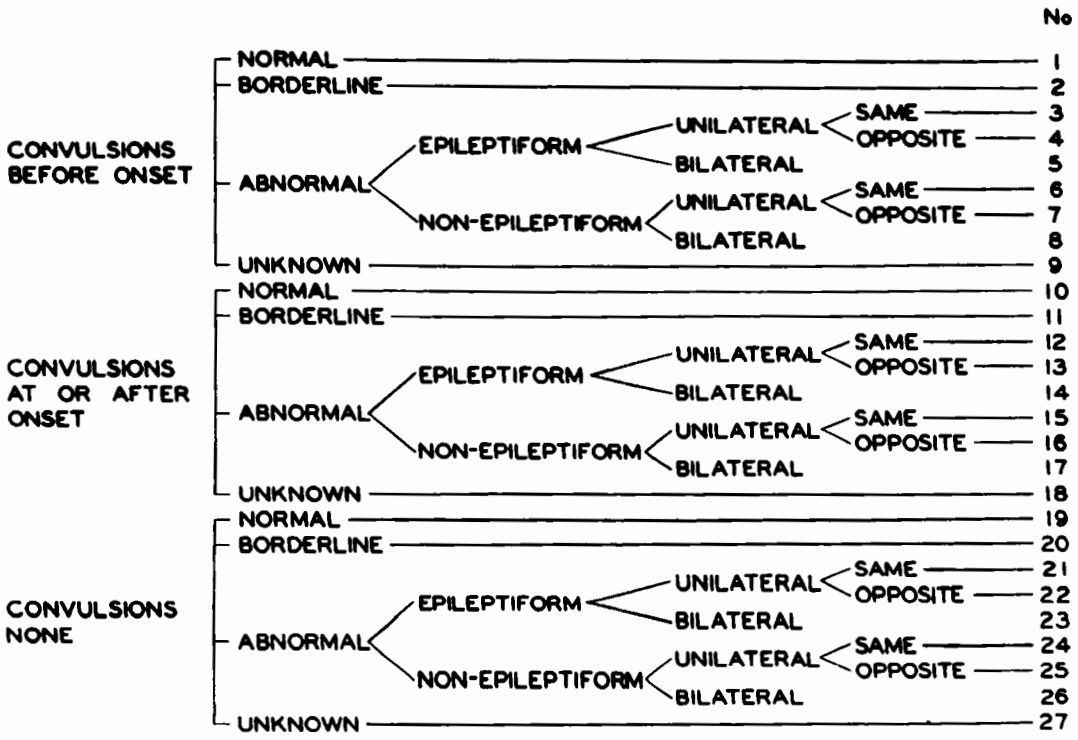
HEMIPLEGIC PROBANDS
(CLINICAL & EEG CLASSIFICATION)
No
CONVULSIONS BEFORE ONSET
NORMAL 1
BORDERLINE 2
ABNORMAL
EPILEPTIFORM
UNILATERAL
SAME 3
OPPOSITE 4
BILATERAL 5
NON-EPILEPTIFORM
UNILATERAL
SAME 6
OPPOSITE 7
BILATERAL 8
UNKNOWN 9
CONVULSIONS AT OR AFTER ONSET
NORMAL 10
BORDERLINE 11
ABNORMAL
EPILEPTIFORM
UNILATERAL
SAME 12
OPPOSITE 13
BILATERAL 14
NON-EPILEPTIFORM
UNILATERAL
SAME 15
OPPOSITE 16
BILATERAL 17
UNKNOWN 18
CONVULSIONS NONE
NORMAL 19
BORDERLINE 20
ABNORMAL
EPILEPTIFORM
UNILATERAL
SAME 21
OPPOSITE 22
BILATERAL 23
NON-EPILEPTIFORM
UNILATERAL
SAME 24
OPPOSITE 25
BILATERAL 26
UNKNOWN 27

FIGURE 2

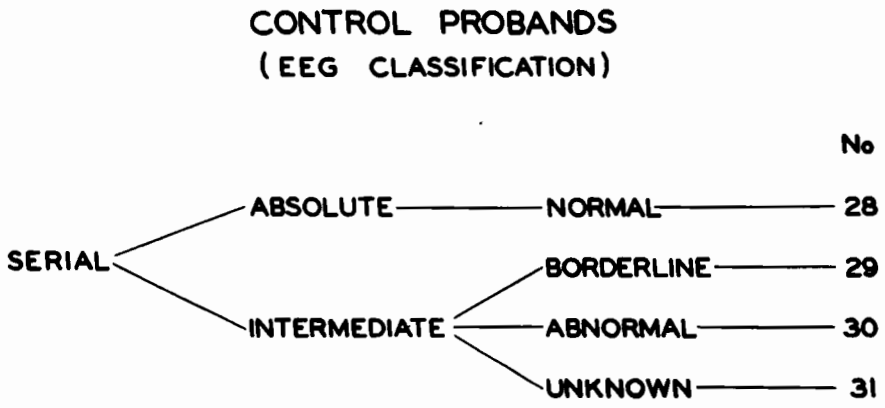
CONTROL PROBANDS
(EEG CLASSIFICATION)
No
SERIAL
ABSOLUTE
NORMAL
28
INTERMEDIATE
BORDERLINE
29
ABNORMAL
30
UNKNOWN
31

FIGURE 3

cousins, etc.) may have been discussed but were not included in the data that was analyzed. Since the probands came from a pediatric age group they had no offspring.

Since the number of informants was limited, the reliability of the information was not the same for all the individuals in the pedigree and it was probably quite inexact when the genetic distance between the informant and the individual in question was great. In order to improve upon the accuracy of this information, several further steps were taken. Whenever a history of convulsions was obtained for an individual within the pedigree limits, the individual was interviewed or the physician or hospital concerned was contacted to substantiate the report. A Field Worker from the Department of Social Service of the Montreal Children's Hospital contacted certain relatives when additional information was required.

F. Classification of Near Relatives: Wherever possible, electroencephalographic studies were carried out on all available parents and siblings of hemiplegic and control probands. If a parent, sibling or other near relative had an EEG in the past, an effort was made to obtain a copy of this record. These tracings were reviewed and coded by the same electroencephalographer. On the basis of this coding, the parents and siblings were classified into seven groups (Fig. 4). Total abnormalities refers to the summation of all the groups except normal and borderline. Another class-

PARENTS & SIBLINGS
(EEG CLASSIFICATION)

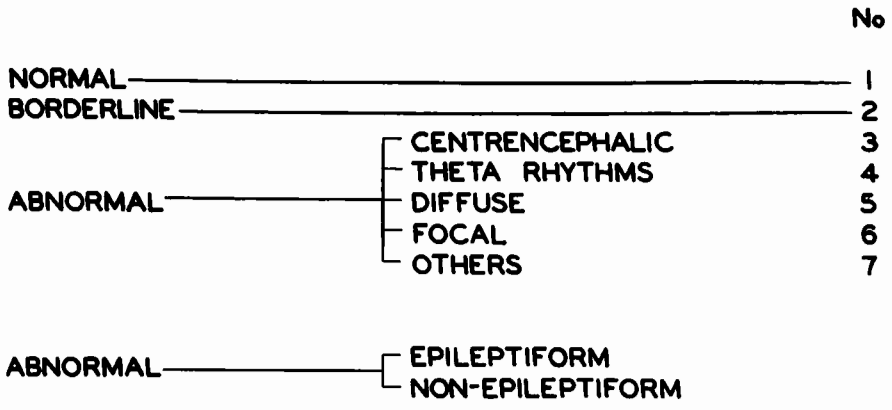

FIGURE 4

ification of the parents and siblings was devised on the basis of whether or not there was epileptiform activity in the EEG. Thus those relatives with abnormal EEGs, could be classed as "abnormal,""epileptiform" or "abnormal nonepileptiform". In this way, the near relatives of the probands could be classified as affected on the basis of three separate criteria: 1. Clinical convulsions; 2. EEG abnormality; and 3. Epileptiform activity in the EEG.

III. RESULTS

With the methods outlined above, a total of 158 hemiplegics and 270 control probands and their families were investigated.

A. Hemiplegic Probands:- The 158 hemiplegic probands were classified into two groups on the basis of whether or not they had ever experienced at least one convulsive episode during their lifetime. Ninety-eight, or approximately 62%, had such a history of convulsions, and sixty, or approximately 38%, did not (Table 1).

TABLE 1

Hemiplegic Probands With and Without Convulsions

Group	+/T	% Affected
Hemiplegia with convulsions	98/158	62.0 ± 3.9
Hemiplegia without convulsions	60/158	38.0 ± 3.9

Of the 98 hemiplegics with convulsions, only six had their first seizure before the onset of their motor disabilities, while in 92, the first seizure occurred during the same week or postdated the onset of the motor disorder. In Table 2, this group of probands is classified according to the number of convulsions that had occurred by the time of the initial interview by a member of the Department of Medical Genetics. Approximately 11% had

TABLE 2

Number of Convulsions Among the Hemiplegics With Convulsions

Number of Convulsions	+/T	% Affected
1	11/98	11.2
2	5.98	5.1
3-5	13/98	13.3
6-9	6/98	6.1
10 or more	63/98	64.3

experienced only one convulsion, whereas 64.3% had a history of ten or more such convulsive episodes.

The probands with a history of seizures were further classified into four groups on the basis of the clinical characteristics of their convulsions. Focal seizures refer to those in which only a limited part of the body is involved in the convulsive movements, and is contrasted from generalized seizures which involve both sides of the body. The "Others" group includes such forms of seizures as petit mal, akinetic, minor motor, psychomotor, etc. This group comprises approximately 7% of all cases. The rest are more or less equally divided among the Focal, Generalized, and Focal and Generalized groups (Table 3).

TABLE 3

A Classification of

The Hemiplegics on the Basis of Seizure Type

Type of Convulsion	+/T	% Affected
Focal	28/98	28.6
Generalized	34/98	34.7
Focal and Generalized	29/98	29.6
Others	7/98	7.1

The most likely cause of the neuropathology was stated in the medical records of 156 of the hemiplegic probands. These causes were classified into four main groups - "Prenatal", "Natal", "Congenital Unknown", and "Postnatal". The distribution of the probands among these categories is shown in Table 4.

While the various diagnoses are all presumptive, Table 4 gives one an insight into the many aetiological factors involved in the production of hemiplegia, and an estimate of their relative importance. The cases classed as prenatal were presumably due to hereditary or developmental factors (e.g., Sturge Weber syndrome). In this series of hemiplegics, birth trauma was the most important single aetiological factor for it was believed to be the major factor in 44 or 27.9% of all the cases and in 44.4% of the congenital hemiplegics. Among the postnatal causes,

TABLE 4

The Presumptive Aetiology of the Hemiplegia of 158 Probands

Group		+/T	% Affected
Prenatal		4/158	2.5
Natal	a. Prematurity	16/158	10.1
	b. Birth Trauma	44/158	27.9
	c. Anoxia	6/158	3.8
	d. Haemorrhage	1/158	0.6
	Total	67/158	42.4
Congenital Unknown		28/158	17.7
Total Congenital		99/158	62.7
Postnatal	a. Trauma	8/158	5.1
	b. Infection	17/158	10.8
	c. Vascular	30/158	19.0
	d. Neoplasm	1/158	0.6
	e. Not Known	1/158	0.6
	Total	57/158	36.1
Not Known		2/158	1.3

vascular difficulties were the most prevalent, and were believed to be responsible for 52.6% of the postnatal hemiplegias. These include such things as venous thrombosis (inflammatory and noninflammatory), arterial embolus and cerebral haemorrhage.

B. Convulsers vs. Non-Convulsers:- The two main groups of hemiplegics, those with and those without convulsions, have been compared for a large number of things with a view to ascertaining which of these factors may be aetiologically associated with whether a particular hemiplegic does or does not develop convulsions.

(1) Sex:- The distribution of males and females among the two groups of hemiplegics is shown in Table 5. The percent males among the convulsers (48.0%) is not significantly different (P=0.80) from that found among the nonconvulsers (45.0%).

TABLE 5

Sex Distribution Among the Hemiplegic Probands

Sex	With Convulsions +/T	With Convulsions % Affected	Without Convulsions +/T	Without Convulsions % Affected
Male	47/98	48.0 ± 5.0	27/60	45.0 ± 6.4
Female	51/98	52.0 ± 5.0	33/60	55.0 ± 6.4

2. Laterality of Involvement:- The probands were classed as Right or Left Hemiplegics depending on which side of the body was affected by the motor disorder. As seen

from Table 6, 62.2% of the hemiplegics with convulsions had a right-sided hemiplegia as compared to 60.0% of the hemiplegics without convulsions. The difference is not statistically significant (P=0.80).

TABLE 6

Distribution of Right and Left Hemiplegia

Side of Body Involved	With Convulsions		Without Convulsions	
	+/T	% Affected	+/T	% Affected
Right	61/98	62.2 ± 4.9	36/60	60.0 ± 6.3
Left	37/98	37.8 ± 4.9	24/60	40.0 ± 6.3

3. Severity of Neuropathology:- The severity of the motor disability was used as a rough index of the degree of neuropathology. The probands were classed as "Mild", "Moderate" or "Severe" according to the criteria outlined in section II C (Table 7). The hemiplegics without convulsions had, on the average, less severe motor disability than the hemiplegics with convulsions. However, a goodness of fit test demonstrated that the difference was not statistically significant (P=0.10).

TABLE 7

Distribution of the Three Degrees of Severity of Motor Defect

Degree of Severity	With Convulsions		Without Convulsions	
	+/T	% Affected	+/T	% Affected
Mild	35/98	35.7	31/60	51.7
Moderate	51/98	52.0	27/60	45.0
Severe	12/98	12.2	2/60	3.3

4. Onset of Neuropathology:- The hemiplegic probands were divided into two groups depending on whether the neuropathology was of congenital or postnatal origin. It was impossible to state this with any degree of certainty about two of the probands and they were consequently omitted from this particular analysis. Table 8 demonstrates the distribution of the age of onset of neuropathology among the two groups of hemiplegic probands.

TABLE 8

Frequency of Congenital and Postnatal Factors in Hemiplegia

Time of Onset	With Convulsions +/T	% Affected	Without Convulsions +/T	% Affected
Congenital	54/96	56.3 ± 5.1	45/60	75.0 ± 5.6
Postnatal	42/96	43.8 ± 5.1	15/60	25.0 ± 5.6

The proportion of probands who acquired their neuropathology postnatally was higher among the hemiplegics with convulsions (43.8%) than among the hemiplegics without convulsions (25.0%). This difference was statistically significant (P=0.02).

5. Intelligence:- The hemiplegic probands were divided into a "Mentally Retarded" group (those with a psychometric score of 65 or less) and a "Not Mentally Retarded" group. Table 9 demonstrates the distribution of mental retardation among the two groups of hemiplegics. This information was available for only 148 of the hemi-

plegics.

TABLE 9

The Frequency of "Mental Retardation"

Among the Hemiplegic Probands

Group	With Convulsions +/T	With Convulsions % Affected	Without Convulsions +/T	Without Convulsions % Affected
Mentally Retarded	38/91	41.8 ± 5.2	14/57	24.6 ± 5.7
Not Mentally Retarded	53/91	58.4 ± 5.2	43/57	75.4 ± 5.7

The frequency of mental retardation among the hemiplegics with convulsions (41.8%) was significantly higher than the frequency of 24.6% among the hemiplegics without convulsions (P=0.01).

The mean psychometric score of the hemiplegics with convulsions was calculated as 69.16 ± 5.44 and that of the hemiplegics without convulsions as 80.51 ± 7.43. These figures are based on the psychometric scores of 126 hemiplegics (75 with and 51 without convulsions) who were given an actual psychometric score. To test the hypothesis that the mean psychometric score of the hemiplegics without convulsions is higher than that of the hemiplegics with convulsions, Welch's test was performed (44). The difference is indeed a highly significant one for Welch's t=3.329.

The 126 hemiplegic probands were divided into five groups on the basis of their psychometric scores (Table 10, Fig. 5).

PSYCHOMETRIC SCORES of HEMIPLEGICS

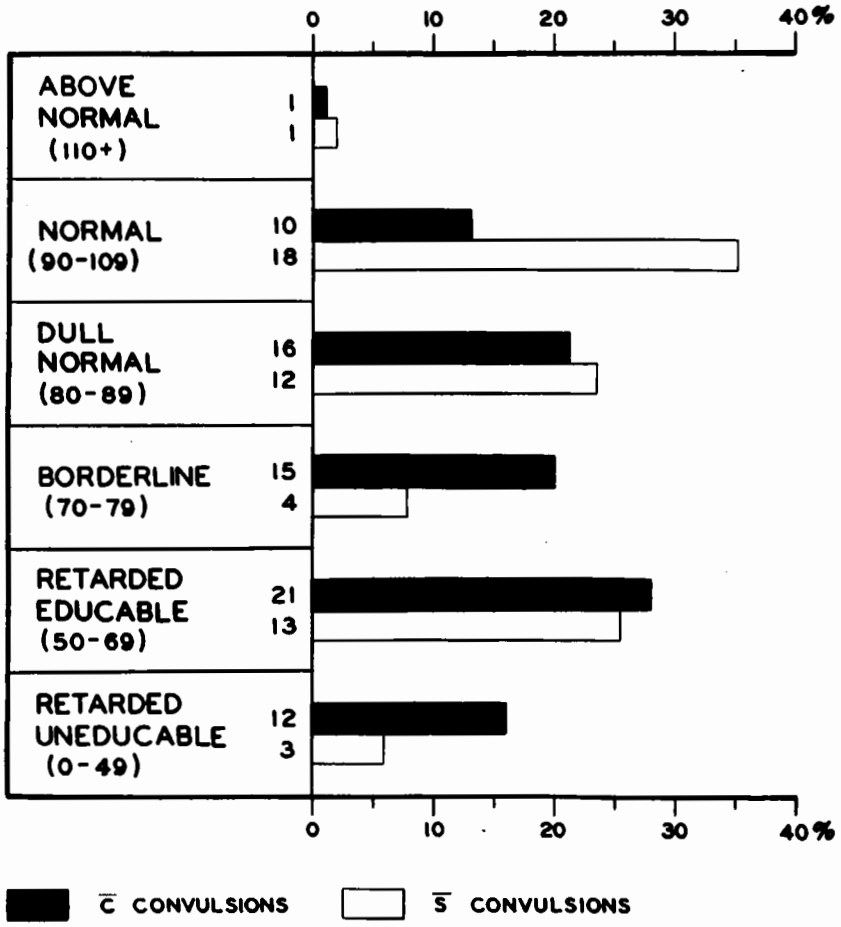

FIGURE 5

TABLE 10

A Classification of

the Hemiplegic Probands by Psychometric Score

Group	Score	With Convulsions +/T	With Convulsions % Affected	Without Convulsions +/T	Without Convulsions % Affected
Above Normal	110+	1/75	1.3	1/51	2.0
Normal	90-109	10/75	13.3	18/51	35.3
Dull Normal	80-89	16/75	21.3	12/51	23.5
Borderline	70-79	15/75	20.0	4/51	7.8
Retarded educable	50-69	21/75	28.0	13/51	25.5
Retarded Uneducable	0-49	12/75	16.0	3/51	5.9

Note: Welch's t=3.329 i.e. highly significant.

As seen in Table 10 and Fig. 5, one of the modal frequencies of the hemiplegics without convulsions lies in the normal range (90-109) while that of the hemiplegics with convulsions lies in the retarded educable range (50-69). There is a higher proportion of hemiplegics without convulsions with psychometric scores above 80 than of hemiplegics with convulsions. This shift of the convulsive group to a lower range of intelligence than the nonconvulsive group was demonstrated by all the methods of analysis attempted.

Not all the patients interviewed by a psychologist received a Bender Visuomotor Test. The frequency of visuomotor problems, as calculated by counting those probands whose psychometric reports state that such a problem exists, would certainly be an underestimate. Of those patients

who received a psychometric test, 32 of 75 (42.7 ± 5.7%) hemiplegics with convulsions were reported as having visuo-motor problems as opposed to 13 of 51 (25.5 ± 6.1%) hemiplegics without convulsions. However, this difference was not significant (P=0.05).

6. Birth Weight:- As it has been noted above, in the majority of the hemiplegic patients (99/158 or 62.7%) the presumptive aetiology was congenital. Birth trauma was found to be a major cause of congenital hemiplegia (Table 3). Since birth trauma is believed by some (87, 88) to be related to birth weight, the mean birth weights of the congenital hemiplegics, with and without convulsions, were calculated. They were found to be 6.64 lbs. and 6.56 lbs. respectively, a difference which is certainly not a significant one.

The 99 congenital hemiplegics were divided into three groups on the basis of their birth weights: "Premature" (5 lbs., 8 ozs. or less), "Normal" (5 lbs., 9 ozs. to 7 lbs., 15 ozs.) and "Heavy" (8 lbs. or more). The distribution of these three groups among the hemiplegics with and without convulsions is shown in Table 11.

TABLE 11

A Classification of Congenital Hemiplegics by Birth Weight

Group	Weight	With Convulsions +/T	% Affected	Without Convulsions +/T	% Affected
Premature	5 lbs. 8 oz. or less	14/54	25.9	12/45	26.7
Normal	5 lbs. 9 ozs. - 7 lbs.15 ozs.	26/54	48.2	20/45	44.4
Heavy	8 lbs. or more	14/54	25.9	13/45	28.9

For all three groups, the distribution of birth weights among the congenital hemiplegics with convulsions is comparable to that of the congenital hemiplegics without convulsions.

7. Birth Order:- The ninety-nine probands whose hemiplegia was due to congenital factors were classified into four groups on the basis of their parity order (Table 12).

TABLE 12

A Classification of

Congenital Hemiplegics by Birth (parity) Order

Birth Order	With Convulsions +/T	% Affected	Without Convulsions +/T	% Affected
First	21/54	38.9	16/45	35.6
Second	12/54	22.2	8/45	17.8
Third	6/54	11.1	3/45	6.7
Fourth or more	15/54	27.8	18/45	40.0

The distribution of birth order among the congenital hemiplegics with and without convulsions can be seen to be comparable.

8. Associated Defects:- Information concerning defects of speech, hearing and vision, congenital malformations and behavior problems was recorded by examining the medical records of the 158 hemiplegic patients. Since a patient may have one or more of these problems without it being recorded in his medical record, the frequencies of these

disorders listed in Table 13 are probably underestimates.

TABLE 13

The Frequencies of Various

Associated Defects Among the Hemiplegics

Type of Problem	With Convulsions +/T	With Convulsions % Affected	Without Convulsions +/T	Without Convulsions % Affected
Speech	40/98	40.8 ± 5.0	20/60	33.3 ± 6.1
Hearing	4/98	4.1 ± 2.0	3/60	5.0 ± 2.8
Vision	15/98	16.3 ± 3.6	7/60	11.7 ± 4.1
Congenital Malformations	16/98	16.3 ± 3.7	9/60	15.0 ± 4.6
Behavior Problems	36/98	36.7 ± 4.9	11/60	18.3 ± 5.0

The frequencies of speech, hearing and visual defects as well as congenital malformations are comparable among the two groups of hemiplegics. The frequency of behavior problems among the hemiplegics with convulsions was found to be 36.7%, which was significantly higher than the frequency of 18.3% for the hemiplegics without convulsions (P=0.01).

C. EEG Classification of Probands:- At least one EEG tracing was obtained for 141 of the 158 hemiplegic probands. (As is usually the case, most of these patients have EEGs as part of the follow-up procedure). The EEGs of these 141 patients were coded and the patients were classified according to the scheme presented in Fig. 1. The distribution

of the probands among these classes and combinations of these classes is presented in Table 14.

TABLE 14.

An Electroencephalographic Classification of the Hemiplegic Probands

Group Number		Group	+/T	% Affected
1		Normal	9/141	6.4
2		Borderline	6/141	4.3
3	Epileptiform	Unilateral - same	3/141	2.1
4	Epileptiform	Unilateral - opposite	36/141	25.5
5	Epileptiform	Bilateral	45/141	31.9
6	Non-Epileptiform	Unilateral - same	3/141	2.1
7	Non-Epileptiform	Unilateral - opposite	21/141	14.9
8	Non-Epileptiform	Bilateral	18/141	12.8
3,4,5		Total Epileptiform	84/141	59.6
3,4,5,6,7,8		Total Abnormal	126/141	89.4
3,4,6,7		Total Unilateral	63/141	44.7
5,8		Total Bilateral	63/141	44.7
3,6		Total Unilateral - same	6/ 141	4.3

Of the 141 patients, 9 (6.4%) had unequivocally normal EEG tracings, while 15 (10.6%) never displayed anything more serious than a borderline cerebral dysrhythmia. There was a definite abnormality, of one type or another, in at

least one tracing, in 126 of the 141 hemiplegics (89.4%). The abnormality was of the epileptiform type in 84 (59.6%) of the probands. Abnormalities of this type were found in the hemiplegics without convulsions as well as among the hemiplegics with a history of seizures.

Of the 126 probands with some definite EEG abnormality, 63 displayed an abnormality on only one side, while it was bilateral in the other 63. Thus in exactly 50% of the patients with an EEG dysrhythmia, the abnormality was recorded from both sides of the brain, even though their motor disorder was strictly unilateral. An unexpected observation was that 6 (4.3%) probands displayed EEG abnormalities only on the same side as their motor disorder.

The hemiplegic probands were divided into twenty-seven groups in accordance with the classification presented in Fig. 2. The distribution of the probands among these twenty-seven categories is shown in Table 15.

All types of EEG abnormalities were found in the hemiplegics without convulsions as well as among those with a history of convulsions. By combining groups 21, 22 and 23 it can be seen that 27 of the 60 hemiplegics who had never experienced a convulsive episode displayed epileptiform abnormalities in their EEG tracings.

Of the 270 probands in the serial control group, 163 had EEGs. The EEGs of these were coded and the patients were classified in accordance with the scheme presented in Fig. 3. The distribution of the probands among the various control groups is given in Table 16.

TABLE 15

A Clinical and Electroencephalographic Classification of the Hemiplegics

Convulsions	EEG		Group number	+/T	% Affected
Before Onset		Normal	1.	0/158	0.0
		Borderline	2.	0/158	0.0
	Epileptiform	Unilateral-same	3.	0/158	0.0
		Unilateral-opposite	4.	2/158	1.3
		Bilateral	5.	1/158	0.6
	Nonepileptiform	Unilateral-same	6.	0/158	0.0
		Unilateral-opposite	7.	1/158	0.6
		Bilateral	8.	0/158	0.0
		Not Known	9.	2/158	1.3
At or After Onset		Normal	10.	3/158	1.9
		Borderline	11.	3/158	1.9
	Epileptiform	Unilateral-same	12.	2/158	1.3
		Unilateral-opposite	13.	22/158	13.9
		Bilateral	14.	30/158	19.0
	Nonepileptiform	Unilateral-same	15.	1/158	0.6
		Unilateral-opposite	16.	13/158	8.2
		Bilateral	17.	9/158	5.7
		Not Known	18.	9/158	5.7
None		Normal	19.	6/158	3.8
		Borderline	20.	3/158	1.9
	Epileptiform	Unilateral-same	21.	1/158	0.6
		Unilateral-opposite	22.	1/158	0.6
		Bilateral	23.	14/158	8.9
	Nonepileptiform	Unilateral-same	24.	2/158	1.3
		Unilateral-opposite	25.	7/158	4.4
		Bilateral	26.	9/158	4.7
		Not Known	27.	6/158	3.8

TABLE 16

An Electroencephalographic

Classification of the Control Group

Group	EEG	+/T	
Absolute	Normal	84/163	
Intermediate	Borderline	26/163	79/163
	Abnormal	53/163	

Thus 84 of the 163 (51.5%) control patients who had EEGs recorded were found to have normal tracings as opposed to only 6.4% of the hemiplegic patients.

D. General Comparison of Hemiplegics and Controls:- The hemiplegic probands and their families were compared with a random sample of the control probands and their families with respect to certain variables, such as sex, age first seen at the Department of Medical Genetics, maternal and paternal ages at the time of birth of the proband, parity order of the proband, and the prevalence of livebirths, abortions, stillbirths, and multiple births among the sibships of the proband, of his mother and of his father.

The hemiplegic and control groups were found to be comparable in all of the factors studied other than sex. Among the hemiplegic probands approximately one-half were male (47.5%) while among the controls approximately two-thirds were male (65.2%). (Numerically, this difference

TABLE 17

A Comparison Between the Hemiplegics and Control Probands and Their Families

		Hemiplegic		Control	
a. Sex	Male	75/158	47.5%	73/112	65.2%
	Female	83/158	52.5%	39/112	34.8%
b. Age	proband	7.72 years		6.06 years	
	maternal	29.04 years		27.27 years	
	paternal	31.85 years		30.98 years	
c. Parity order mean -		2.80		2.96	
	First born	37.4%		36.6%	
d. Proband's Sibship					
	No. of pregnancies	638		510	
	livebirths	522/638	81.8%	447/510	87.7%
	abortions	105/638	16.5%	60/510	11.8%
	stillbirths	11/638	1.7%	3/510	0.6%
	multiple births	9/638	1.4%	21/510	4.2%
e. Mother's Sibship					
	No. of pregnancies	930		861	
	livebirths	847/930	91.1%	799/861	92.8%
	abortions	72/930	7.7%	55/861	6.4%
	stillbirths	11/930	1.2%	7/861	0.8%
	multiple births	15/930	1.6%	9/861	1.1%
f. Father's Sibship					
	No. of pregnancies	1051		793	
	livebirths	990/1051	94.2%	756/793	95.3%
	abortions	36/1051	3.4%	31/793	3.9%
	stillbirths	25/1051	2.4%	6/793	0.8%
	multiple births	19/1051	1.8%	12/793	1.5%

is a highly significant one (P=0.001), however it is of no biological significance as will be seen in section IV E.

E. The Prevalence of Individuals with Convulsions Among the Near Relatives of the Probands:- The following analyses were performed using the data obtained from the family histories of 157 hemiplegic probands and 270 control probands. The family history of one hemiplegic proband was considered to be quite unreliable and it was excluded from the analysis. The prevalence of convulsions among the parents, siblings, uncles and aunts, grandparents, and cousins of the twenty-seven groups of hemiplegic probands is shown in Tables 18, 19 and 20.

Since the group of hemiplegics with convulsions before the onset did not have their first convulsions precipitated by or postdating the onset of this definite neuropathology, the question arose as to whether they could be included in the large group of hemiplegics with convulsions. The prevalence of individuals with a history of seizures among the near relatives of "Hemiplegics With Convulsions Before The Onset" was 1.67 $\pm$ 0.95% (Table 18) as compared to 2.06 $\pm$ 0.22% (Table 19) for the near relatives of "Hemiplegics With Convulsions At Or After The Onset". This difference is not statistically significant (P=0.69) and it was thus felt that the combination of these two groups was justifiable. In all further analyses the term "hemiplegics With Convulsions" will refer to all hemiplegics with a history

TABLE 18

The Prevalence of Individuals With Convulsions among the Near Relatives of 6 Hemiplegics With Convulsions Before Onset

Proband's EEG		Number	Parents +/T	Siblings +/T	Aunts and Uncles +/T	Grandparents +/T	Cousins +/T	Total +/T	% Affected
	Normal	1.	0/0	0/0	0/0	0/0	0/0	0/0	0
	Borderline	2.	0/0	0/0	0/0	0/0	0/0	0/0	0
Epileptiform	Unilateral-same	3.	0/0	0/0	0/0	0/0	0/0	0/0	0
	Uni-opposite	4.	0.4	0.4	0.22	0.8	1/26	0/64	1.56
	Bilateral	5.	0/2	1/3	1/10	0/4	0/18	2/37	5.41
Non-epileptiform	Unilateral-same	6.	0/0	0/0	0/0	0/0	0/0	0/0	0
	Uni-opposite	7.	0/2	0/7	0/4	0/4	0/5	0/22	0
	Bilateral	8.	0/0	0/0	0/0	0/0	0/0	0/0	0
	Not Known	9.	0/4	0/7	0 /15	0/8	0/23	0/57	0
	TOTAL		0/12 (0%)	1/21 (4.76%)	1/51 (1.96%)	0/24 (0%)	1/72 (1.39%)	3/180	1.67 ± 0.95

TABLE 19

The Prevalence of Individuals With Convulsions Among The Near Relatives of 92 Hemiplegics With Convulsions At or After Onset

Proband's EEG		Number	Parents +/T	Siblings +/T	Aunts and Uncles +/T	Grand-parents +/T	Cousins +/T	Total +/T	% Affected
	Normal	10.	0/6	0/5	0/30	0/12	0/19	0/72	0
	Borderline	11.	1/6	0/8	2/28	0/12	1/42	4/96	4.17
Epileptiform	Unilateral-same	12.	0/4	0/2	2/29	0/8	1/18	3/61	4.92
	Uni-opposite	13.	2/43	2/58	10/240	1/86	1/330	16/757	2.11
	Bilateral	14.	2/59	5/59	12/352	2/118	4/634	25/1222	2.05
Non-epileptiform	Unilateral-same	15.	0/2	0/1	1/14	0/4	0/21	1/42	2.38
	Uni-opposite	16.	0/26	0/27	5/142	2/52	0/298	7/545	1.28
	Bilateral	17.	0/18	5/28	3/98	0/36	1/216	9/396	2.27
	Not Known	18.	0/16	0/22	6/86	2/32	1/249	9/405	2.22
	TOTAL		5/180 (2.78%)	12/210 (5.71%)	41/1019 (4.02%)	7/360 (1.94%)	9/1827 (0.49%)	74/3596	2.06±0.22

TABLE 20

The Prevalence of Individuals With Convulsions Among The Near Relatives of 60 'Hemiplegics Without Convulsions'

Proband's EEG		Number	Parents +/T	Siblings +/T	Aunts and Uncles +/T	Grandparents +/T	Cousins +/T	+/T	Total % Affected
	Normal	19.	0/12	1/22	1/77	0/24	1/114	3/249	1.20
	Borderline	20.	0/6	0/8	0/47	0/12	0/72	0/145	0
Epileptiform	Unilateral-same	21.	0/2	0/0	0/2	0/4	0/3	0/11	0
	Uni-opposite	22.	0/23	0/17	1/118	0/48	1/184	2/390	0.51
	Bilateral	23.	1/28	2/26	4/140	0/54	1/258	8/506	1.58
Non-epileptiform	Unilateral-same	24.	0/4	0/9	0/23	0/8	0/64	0/108	0
	Uni-opposite	25.	1/14	0/15	2/77	0/28	0/98	3/232	1.29
	Bilateral	26.	0/18	2/25	1/71	1/32	0/113	4/259	1.54
	Not Known	27.	0/12	0/11	0/35	0/24	0/56	0/138	0
	TOTAL		2/119 (1.68%)	5/133 (3.76%)	42/1070 (1.53%)	1/243 (0.43%)	3/962 (0.31%)	20/2038	1.02±0.22

of one or more seizures whether their first convulsion occurred before, at or after the onset of their motor disorders.

The prevalence of near relatives with convulsions in the group of hemiplegic probands whose EEG abnormalities occurred only on the same side as their motor disorders was 1.80 $\pm$ 0.84% as compared to 1.44 $\pm$ 0.26% in the near relatives of hemiplegics whose EEG abnormalities were only on the opposite side of their motor disorders. This difference is not statistically significant (P=0.70). The two groups were therefore combined.

The hemiplegics with bilateral EEG abnormalities were analysed to see if they are comparable to the hemiplegics with unilateral EEG abnormalities. The prevalence of individuals with convulsions among the near relatives of the bilateral group is 1.98 $\pm$ 0.28% and that of the unilateral group is 1.48 $\pm$ 0.26%. This difference is not significant (P=0.20) and the two groups are thus considered comparable.

A comparison was made between the prevalence of individuals with convulsions among the near relatives of hemiplegics with convulsions and the near relatives of hemiplegics without convulsions (Table 21 and Fig. 6). The prevalence was found to be consistently higher among all classes of relatives of the hemiplegics with convulsions than among the similar classes of relatives of the hemiplegics without convulsions, (Parents=2.60% and 1.68%; Siblings=

TABLE 21

The Prevalence of Individuals With Convulsions Among the Near Relatives of Hemiplegics With Convulsions v.s. Hemiplegics Without Convulsions

Relationship to Proband	With Convulsions +/T	% Affected	Without Convulsions +/T	% Affected	P
Parents	5/192	2.60 ± 1.14	2/119	1.68 ± 1.14	0.28
Siblings	13/231	5.63 ± 1.52	5/133	3.76 ± 1.61	0.20
Parents and Siblings	18/423	4.26 ± 0.95	7/252	2.78 ± 1.00	0.14
Aunts and Uncles	42/1070	3.93 ± 0.59	9/590	1.53 ± 0.45	0.001**
Grandparents	7/384	1.82 ± 0.63	1/234	0.43 ± 0.32	0.024
Cousins	10/1899	0.53 ± 0.17	3/962	0.31 ± 0.18	0.19
Total	77/3776	2.04 ± 0.22	20/2038	1.02 ± 0.22	0.001**

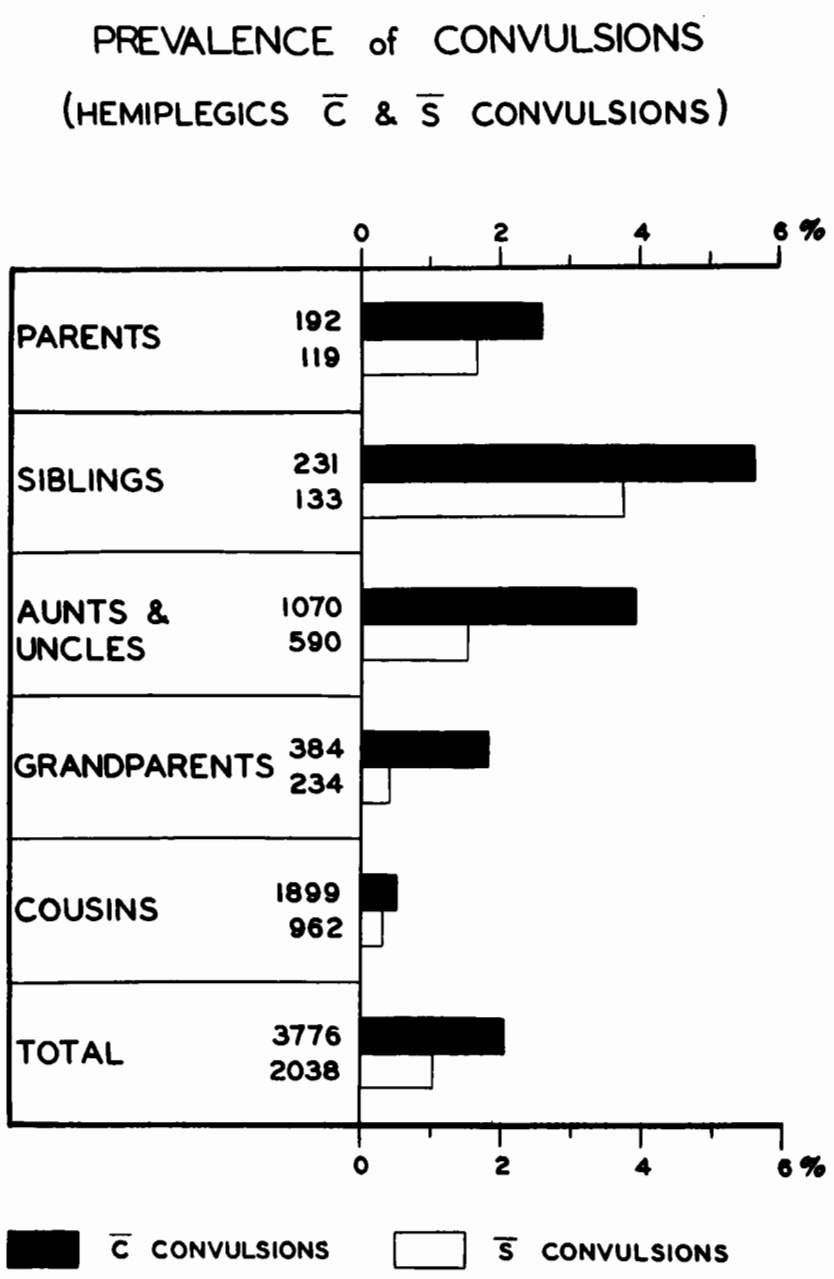
PREVALENCE of CONVULSIONS
(HEMIPLEGICS C̄ & S̄ CONVULSIONS)
0
2
4
6 %
PARENTS
192
119
SIBLINGS
231
133
AUNTS & UNCLES
1070
590
GRANDPARENTS
384
234
COUSINS
1899
962
TOTAL
3776
2038
C̄ CONVULSIONS
S̄ CONVULSIONS

FIGURE 6

5.63% and 3.76%; Aunts and Uncles=3.93% and 1.53%; Grandparents= 1.82% and 0.43%; and Cousins=0.53% and 0.31%). However, the only individual difference that is statistically significant is that between the aunts and uncles. When one considers all of the classes of near relatives together, the prevalence among those of hemiplegics with convulsions is 2.04 ± 0.22% as compared to 1.02 ± 0.22% among the near relatives of hemiplegics without convulsions. This difference is highly significant (P=0.001).

The prevalence of individuals with convulsions among the various classes of near relatives of the three groups of control probands is shown in Table 22. The prevalence of individuals with a history of seizures is 2.08 ± 0.30% among the near relatives of the intermediate control probands (i.e., "controls" who have abnormal EEGs) and 1.72 ± 0.22% among the near relatives of the absolute control probands (normal EEGs). This difference is not statistically significant (P=0.17). The values for the serial control groups obviously do not differ from those of the absolute control group.

A comparison between the prevalence rates of the hemiplegics without convulsions and the serial control group is made in Table 23. The prevalence of individuals with convulsions among the five classes of near relatives of the serial control probands is consistently higher than among the similar classes of relatives of the hemiplegics without

TABLE 22

The Prevalence of Individuals With Convulsions Among the Near Relatives of:

The Control Probands

Relationship To Proband	Serial Control Group		Absolute Control Group		Intermediate Control Group	
	+/T	% Affected	+/T	% Affected	+/T	% Affected
Parents	16/540	2.96 ± 0.71	3/168	1.79 ± 1.00	6/106	5.66 ± 2.24
Siblings	39/721	5.41 ± 2.60	12/215	5.58 ± 1.50	13/161	8.07 ± 2.14
Aunts and Uncles	68/2754	2.47 ± 0.28	23/860	2.67 ± 0.55	15/561	2.67 ± 0.63
Grandparents	9/1080	0.83 ± 0.27	3/336	0.89 ± 0.45	5/212	2.36 ± 1.00
Cousins	27/4242	0.64 ± 0.10	8/1263	0.63 ± 0.20	5/1073	0.47 ± 0.20
Total	159/9337	1.70 ± 0.10	49/2842	1.72 ± 0.22	44/2113	2.08 ± 0.30

TABLE 23

The Prevalence of Individuals With Convulsions Among the Near Relatives of: 'Hemiplegics Without Convulsions' and 'Serial Controls'.

Relationship To Proband	Hemiplegics Without Convulsions		Serial Controls		
	+/T	% Affected	+/T	% Affected	P
Parents	2/119	1.68 ± 1.14	16/540	2.96 ± 0.71	
Siblings	5/133	3.76 ± 1.61	39/721	5.41 ± 2.60	
Aunts and Uncles	42/1070	1.53 ± 0.59	68/2754	2.47 ± 0.28	
Grandparents	1/234	0.43 ± 0.32	9/1080	0.83 ± 0.27	
Cousins	3/962	0.31 ± 0.18	27/4242	0.64 ± 0.10	
Total	20/2038	1.02 ± 0.22	159/9337	1.70 ± 0.10	0.002**

convulsions (Parents - 2.96% and 1.68%; Siblings - 5.41% and 3.76%; Aunts and Uncles - 2.47% and 1.53%; Grandparents - 0.83% and 0.43%; and Cousins - 0.64% and 0.31%). The prevalence among all of the near relatives of the probands of the serial control group is 1.70 $\pm$ 0.10% and significantly higher than the prevalence of 1.02 $\pm$ 0.22% among the near relatives of hemiplegics without convulsions (P=0.002).

A similar comparison was made between the relatives of the hemiplegics with convulsions and those of the serial control probands (Table 24). The prevalence of individuals with convulsions among the siblings (5.63%), aunts and uncles (3.93%) and grandparents (1.82%) of the hemiplegics with convulsions was higher than the prevalence among the siblings (5.41%), aunts and uncles (2.47%) and grandparents (0.83%) of the serial control probands. However, the inverse relationship was found in the prevalences among parents (2.60% and 2.96%) and cousins (0.53% and 0.64%). The prevalence among all of the near relatives of the hemiplegics with convulsions was 2.04 $\pm$ 0.22% and higher than the prevalence among the near relatives of the serial control probands (1.70 $\pm$ 0.10%). However, this difference is not statistically significant (P=0.08).

Fig. 7 demonstrates the relationship of the prevalence of individuals with convulsions among the various classes of near relatives of hemiplegics with convulsions, serial control probands, and hemiplegics without convulsions. Except for parents and cousins, the control group lies between the two groups of hemiplegics.

TABLE 24

The Prevalence of Individuals With Convulsions Among the Near Relatives of: 'Hemiplegics With Convulsions' and 'Serial Controls'.

Relationship To Proband	Hemiplegics With Convulsions		Serial Controls		
	+/T	% Affected	+/T	% Affected	P
Parents	5/192	2.60 ± 1.14	16/540	2.96 ± 0.71	
Siblings	13/231	5.63 ± 1.52	39/721	5.41 ± 2.60	
Aunts and Uncles	42/1070	3.93 ± 0.59	68/2754	2.47 ± 0.28	
Grandparents	7/384	1.82 ± 0.63	9/1080	0.83 ± 0.27	
Cousins	10/1899	0.53 ± 0.17	27/4242	0.64 ± 0.10	
Total	77/3776	2.04 ± 0.22	159/9337	1.70 ± 0.10	0.08

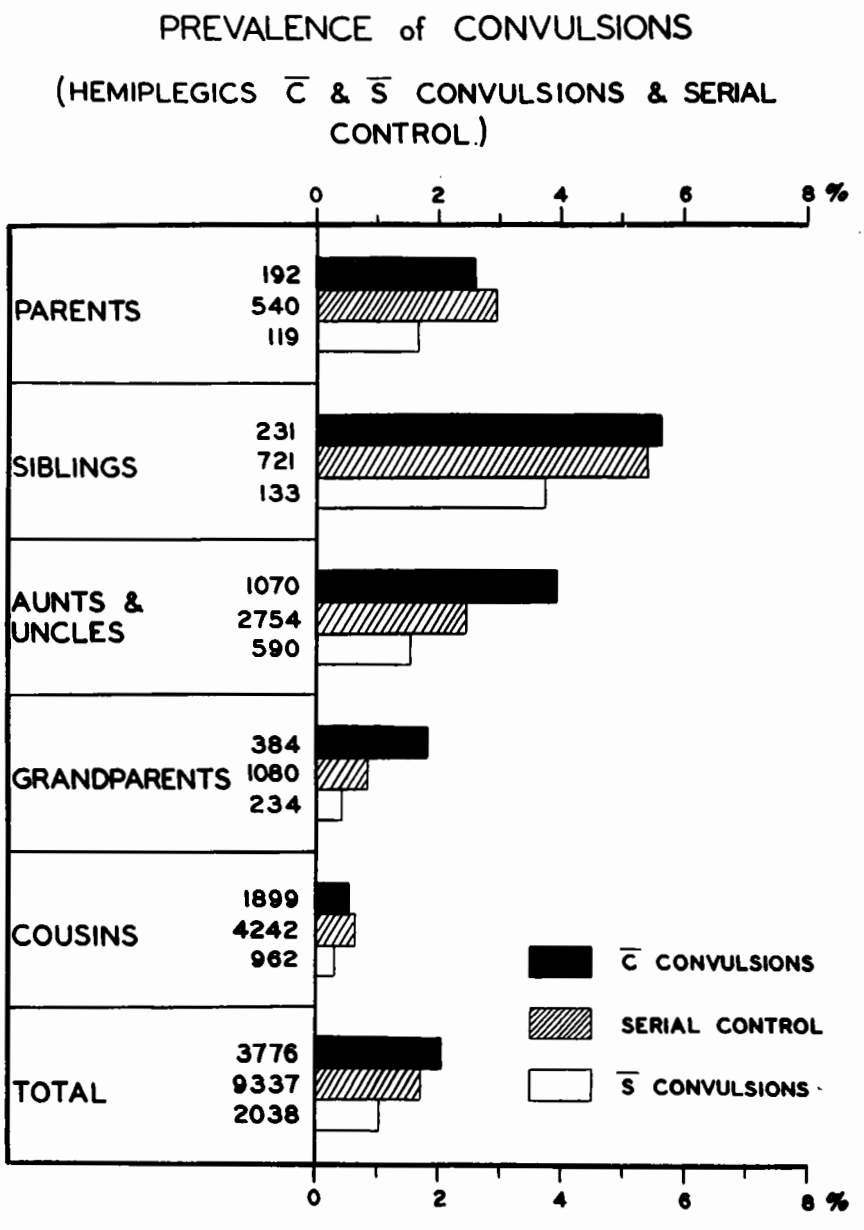
PREVALENCE of CONVULSIONS
(HEMIPLEGICS C̄ & S̄ CONVULSIONS & SERIAL CONTROL.)
0
2
4
6
8 %
PARENTS
192
540
119
SIBLINGS
231
721
133
AUNTS & UNCLES
1070
2754
590
GRANDPARENTS
384
1080
234
COUSINS
1899
4242
962
TOTAL
3776
9337
2038
C̄ CONVULSIONS
SERIAL CONTROL
S̄ CONVULSIONS

FIGURE 7

Since the EEG is a fluid trait, a proband with a history of one or more convulsions may be found to have a non-epileptiform EEG tracing. However, on the basis of our neurophysiological interpretations, we must assume that at some time this patient must have had some epileptiform dysrhythmia. Conversely, among the 60 hemiplegics who have never had a seizure, 27 have epileptiform disturbances in their EEGs and may be thought of as potential convulsors. It was thought that these two groups - hemiplegics with convulsions and hemiplegics without convulsions but with an epileptiform EEG -- formed a natural group since they all had, at one time or another, an epileptiform dysrhythmia. Similarly hemiplegics without convulsions and with a non-epileptiform EEG form another natural group that may be compared with this first group (Table 25, Fig. 8).

The prevalence of individuals with a history of convulsions among each class of relative of the hemiplegics with convulsions and/or an epileptiform EEG is consistently higher than the prevalence among similar relatives of the hemiplegics without convulsions and a non-epileptiform EEG. (Parents=2.45% and 1.85%; Siblings=5.47% and 3.80%; Aunts and Uncles=3.53% and 1.36%; Grandparents=1.43% and 0.96%; and Cousins=0.51% and 0.22%; (Table 25)). Although all of these did however go in the same direction, the only one that is significant is that among uncles and aunts (P=0.003). The prevalence of individuals with convulsions

TABLE 25

The Prevalence of Individuals With Convulsions Among the Near Relatives of Hemiplegics With Convulsions and/or an Epileptiform EEG and Hemiplegics Without Convulsions and a Nonepileptiform EEG.

Relationship To Proband	Convulsions and/or Epileptiform EEG		No Convulsions and a Nonepileptiform EEG		
	+/T	% Affected	+/T	% Affected	P
Parents	6/245	2.45 ± 0.95	1/54	1.85 ± 1.82	0.39
Siblings	15/274	5.47 ± 1.38	3/79	3.80 ± 2.86	0.30
Aunts and Uncles	47/1330	3.53 ± 0.50	4/295	1.36 ± 0.63	0.003**
Grandparents	7/490	1.43 ± 0.45	1/104	0.96 ± 0.95	0.33
Cousins	12/2334	0.51 ± 0.15	1/461	0.22 ± 0.22	0.14
Total	87/4683	1.86 ± 0.20	10/993	1.01 ± 0.32	0.01**

PREVALENCE of CONVULSIONS

(HEMIPLEGICS $\overline{C}$ CONVULSIONS &/or EPILEPTIFORM EEGs
HEMIPLEGICS $\overline{S}$ CONVULSIONS & NONEPILEPTIFORM EEGs)

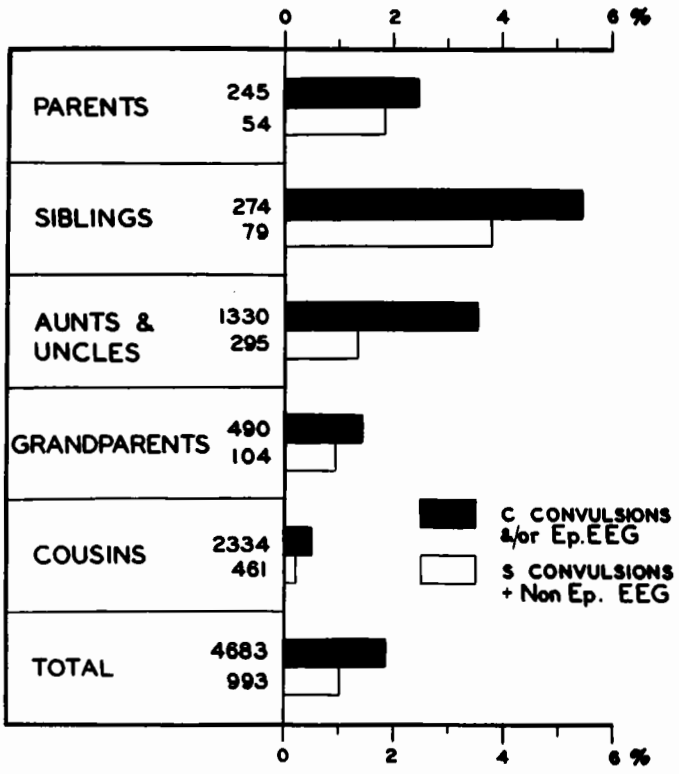

FIGURE 8

among all of the near relatives of the hemiplegics with convulsions and/or an epileptiform EEG is 1.86 $\pm$ 0.20% and significantly higher than the prevalence of 1.01 $\pm$ 0.32% among the near relatives of hemiplegics without convulsions and with a non epileptiform EEG (P=0.01).

Fig. 9 demonstrates the relationship of the various groups of hemiplegic and control probands with respect to the prevalence of individuals with a history of convulsions among their near relatives. Among all of the near relatives the prevalence is greatest for the intermediate (not normal EEG) control group (2.08 $\pm$ 0.30%), less for the hemiplegics with convulsions and/or an epileptiform EEG (1.86 $\pm$ 0.20%), still less for the absolute (normal EEG) control group (1.72 $\pm$ 0.22%), and least for the hemiplegics without convulsions and with a non-epileptiform EEG (1.01 $\pm$ 0.32%).

F. <u>EEG Patterns of Near Relatives</u>:- The EEG patterns of the near relatives were classified into seven groups - normal, borderline, centrencephalic, theta rhythm, diffuse dysrhythmia, focal dysrhythmia, and other abnormalities. The prevalences of these seven classes of EEG patterns among the parents and siblings of the twenty-seven groups of hemiplegic probands is shown in Tables 26-34. Total abnormalities refers to all of the groups exclusive of normal and borderline, i.e., centrencephalic, theta, diffuse, focal and other. The relatives with abnormal EEG patterns were divided into those with epileptiform and non-epileptiform abnormalities. Total epileptiform refers to the prevalence

PREVALENCE of CONVULSIONS

(HEMIPLEGICS $\overline{C}$ CONVULSIONS &/or EPILEPTIFORM EEGs, HEMIPLEGICS $\overline{S}$ CONVULSIONS & NONEPILEPTIFORM EEGs, CONTROLS with ABNORMAL EEGs & CONTROLS with NORMAL EEGs.)

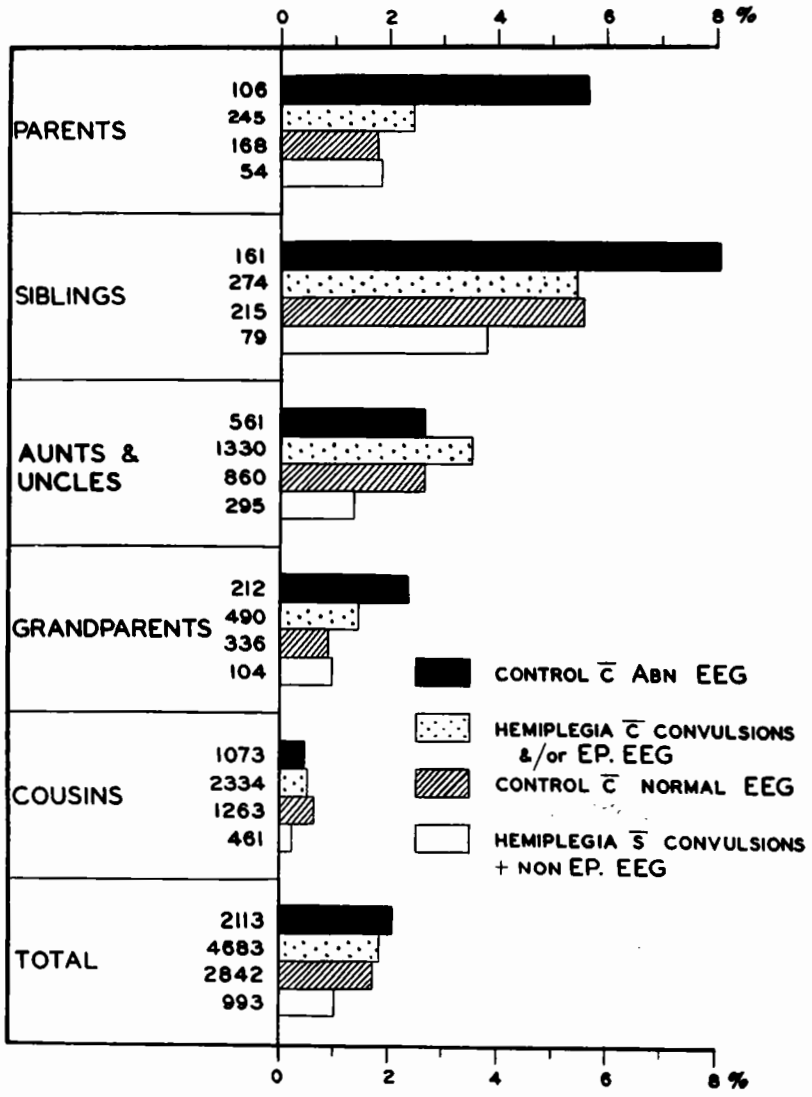

FIGURE 9

TABLE 26

The Prevalence of Eelectroencephalographic Patterns Among the Parents of 'Hemiplegics with Convulsions Before Onset'.

Proband's EEG		No.	Normal +/T	Borderline +/T	Centrencephalic +/T	Theta +/T	Diffuse +/T	Focal +/T	Other +/T	Total Abnormal +/T	% Affected	Total Epileptiform +/T	% Affected
	Normal	1.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Borderline	2.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
Epileptiform	Uni-same	3.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Uni-opposite	4.	2/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0	0/2	0
	Bilateral	5.	0/1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0	0/1	0
Non-Epileptiform	Uni-same	6.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Uni-opposite	7.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Bilateral	8.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Not Known	9.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Total		2/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3	0	0/3	0

TABLE 27

The Prevalence of Electroencephalographic Patterns Among the Siblings of 'Hemiplegics with Convulsions Before Onset'

Proband's EEG		Number	Normal	Borderline	Centrencephalic	Theta	Diffuse	Focal	Other	Total Abnormal		Total Epileptiform	
			+/T	+/T	+/T	+/T	+/T	+/T	+/T	+/T	% Affected	+/T	% Affected
	Normal	1.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Borderline	2.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
Epileptiform	Uni-same	3.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Uni-opposite	4.	0/2	0/2	1/2	0/2	1/2	0/2	0/2	2/2	100.0	1/2	50.0
	Bilateral	5.	2/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0	0/2	0
Non-epileptiform	Uni-same	6.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Uni-opposite	7.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Bilateral	8.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Not Known	9.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	TOTAL		2/4	0/4	1/4	0/4	1/4	0/4	0/4	2/4	50.0	1/4	25.0

TABLE 28

The Prevalence of Electroencephalographic Patterns Among the Parents and Siblings of 'Hemiplegics with Convulsions Before Onset'

Proband's EEG		Number	Normal	Borderline	Centrencephalic	Theta	Diffuse	Focal	Other	Total Abnormal		Total Epileptiform	
			+/T	+/T	+/T	+/T	+/T	+/T	+/T	+/T	% Affected	+/T	% Affected
	Normal	1.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Borderline	2.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
Epileptiform	Uni-same	3.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Uni-opposite	4.	2/4	0/4	1/4	0/4	1/4	0/4	0/4	2/4	50.0	1/4	25.0
	Bilateral	5.	2/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3	0	0/3	0
Non-epileptiform	Uni-same	6.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Uni-opposite	7.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Bilateral	8.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Not Known	9.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	TOTAL		4/7	1/7	1/7	0/7	1/7	0/7	0/7	2/7	28.57	1/7	14.29

TABLE 29

The Prevalence of Electroencephalographic Patterns Among the Parents of 'Hemiplegics with Convulsions At or After the Onset'

Proband's EEG		Number	Normal	Borderline	Centrencephalic	Theta	Diffuse	Focal	Other	Total Abnormal		Total Epileptiform	
			+/T	+/T	+/T	+/T	+/T	+/T	+/T	+/T	% Affected	+/T	% Affected
	Normal	10.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Borderline	11.	0/1	0/1	1/1	0/1	0/1	0/1	0/1	1/1	100.0	1/1	100.0
Epileptiform	Uni-same	12.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Uni-opposite	13.	7/10	2/10	0/10	0/10	1/10	0/10	0/10	1/10	10.0	1/10	10.0
	Bilateral	14.	6/8	1/8	1/8	0/8	0/8	0/8	0/8	1/8	12.5	1/8	12.5
Non-epileptiform	Uni-same	15.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Uni-opposite	16.	4/7	1/7	1/7	0/7	1/7	0/7	0/7	2/7	28.57	1/7	14.29
	Bilateral	17.	2/3	0/3	0/3	0/3	1/3	0/3	0/3	1/3	33.33	0/3	0
	Not Known	18.	1/2	0/2	0/2	0/2	1/2	0/2	0/2	1/2	50.0	1/2	50.0
	TOTAL		20/31	4/31	3/31	0/31	4/31	0/31	0/31	7/31	22.58	5/31	16.13

TABLE 30

The Prevalence of Electroencephalographic Patterns Among the Siblings of 'Hemiplegics With Convulsions At or After the Onset'

Proband's EEG		Number	Normal	Borderline	Centrencephalic	Theta	Diffuse	Focal	Other	Total Abnormal		Total Epileptiform	
			+/T	+/T	+/T	+/T	+/T	+/T	+/T	+/T	% Affected	+/T	% Affected
	Normal	10.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Borderline	11.	0/2	0/2	2/2	0/2	0/2	0/2	0/2	2/2	100.0	2/2	100.0
Epileptiform	Uni-same	12.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Uni-opposite	13.	4/11	0/11	5/11	0/11	1/11	1/11	0/11	7/11	63.64	5/11	45.45
	Bilateral	14.	4/10	1/10	3/10	0/10	2/10	0/10	0/10	5/10	50.0	3/10	30.0
Non-epileptiform	Uni-same	15.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Uni-opposite	16.	5/7	0/7	0/7	0/7	2/7	0/7	0/7	2/7	28.57	0/7	0
	Bilateral	17.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Not Known	18.	1/3	1/3	0/3	0/3	1/3	0/3	0/3	1/3	33.33	0/3	0
	TOTAL		14/33	2/33	10/33	0/33	6/33	1/33	0/33	17/33	51.52	10/33	30.30

TABLE 31

The Prevalence of Electroencephalographic Patterns Among the Parents and Siblings of 'Hemiplegics with Convulsions At or After the Onset'

Proband's EEG		Number	Normal	Borderline	Centrencephalic	Theta	Diffuse	Focal	Other	Total Abnormal		Total Epileptiform	
			+/T	+/T	+/T	+/T	+/T	+/T	+/T	+/T	% Affected	+/T	% Affected
	Normal	10.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Borderline	11.	0/3	0/3	3/3	0/3	0/3	0/3	0/3	3/3	100.0	3/3	100.0
Epileptiform	Uni-same	12.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
	Uni-opposite	13.	11/21	2/21	5/21	0/21	2/21	1/21	0/21	8/21	38.10	6/21	28.57
	Bilateral	14.	10/18	2/18	4/18	0/18	2/18	0/18	0/18	6/18	33.33	4/18	22.22
Uni	Uni-same	15.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
Non-epileptiform	Uni-opposite	16.	9/14	1/14	1/14	0/14	3/14	0/14	0/14	4/14	28.57	1/14	7.14
	Bilateral	17.	2/3	0/3	0/3	0/3	1/3	0/3	0/3	1/3	33.33	0/3	0
	Not Known	18.	2/5	1/5	0/5	0/5	2/5	0/5	0/5	2/5	40.0	1/5	20.0
	TOTAL		34/64	6/64	13/64	0/64	10/64	1/64	0/64	24/64	37.50	15/64	23.44

TABLE 32

The Prevalence of Electroencephalographic Patterns Among the Parents of 'Hemiplegics Without Convulsions'

Proband's EEG		Number	Normal	Borderline	Centrencephalic	Theta	Diffuse	Focal	Other	Total Abnormal		Total Epileptiform	
			+/T	+/T	+/T	+/T	+/T	+/T	+/T	+/T	% Affected	+/T	% Affected
	Normal	19.	2/4	2/4	0/4	0/4	0/4	0/4	0/4	0/4	0	0/4	0
	Borderline	20.	0/1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0	0/1	0
Epileptiform	Uni-same	21.	2/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0	0/2	0
	Uni-opposite	22.	4/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0	0/4	0
	Bilateral	23.	6/10	0/10	0/10	0/10	3/10	1/10	0/10	4/10	40.00	1/10	10.0
Non-epileptiform	Uni-same	24.	2/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0	0/2	0
	Uni-opposite	25.	5/6	1/6	0/6	0/6	0/6	0/6	0/6	0/6	0	0/6	0
	Bilateral	26.	1/3	2/3	0/3	0/3	0/3	0/3	0/3	0/3	0	0/3	0
	Not Known	27.	2/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3	0	0/3	0
	TOTAL		24/35	7/35	0/35	0/35	3/35	1/35	0/35	4/35	11.43	1/35	2.86

TABLE 33

The Prevalence of Electroencephalographic Patterns Among the Siblings of 'Hemiplegics Without Convulsions'

Proband's EEG		Number	Normal	Borderline	Centrencephalic	Theta	Diffuse	Focal	Other	Total Abnormal		Total Epileptiform	
			+/T	+/T	+/T	+/T	+/T	+/T	+/T	+/T	% Affected	+/T	% Affected
	Normal	19.	3/4	1/4	0/4	0/4	0/4	0/4	0/4	0/4	0	0/4	0
	Borderline	20.	2/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0	0/2	0
Epileptiform	Uni-same	21.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	0/0	0
Epileptiform	Uni-opposite	22.	0/2	1/2	0/2	0/2	1/2	0/2	0/2	1/2	50.0	0/2	0
Epileptiform	Bilateral	23.	0/5	1/5	1/5	0/5	2/5	1/5	0/5	4/5	80.0	2/5	40.0
Non-epileptiform	Uni-same	24.	2/3	0/3	1/3	0/3	0/3	0/3	0/3	1/3	33.33	1/3	33.33
Non-epileptiform	Uni-opposite	25.	4/5	1/5	0/5	0/5	0/5	0/5	0/5	0/5	0	0/5	0
Non-epileptiform	Bilateral	26.	1/7	3/7	0/7	0/7	3/7	0/7	0/7	3/7	42.86	1/7	14.29
	Not Known	27.	0/2	0/2	2/2	0/2	0/2	0/2	0/2	2/2	100.0	1/2	50.0
	TOTAL		12/30	7/30	4/30	0/30	6/30	1/30	0/30	11/30	36.67	5/30	16.67

TABLE 34

The Prevalence of Electroencephalographic Patterns Among the Parents and Siblings of 'Hemiplegics Without Convulsions'

Proband's EEG		Number	Normal	Borderline	Centrencephalic	Theta	Diffuse	Focal	Other	Total Abnormal		Total Epileptiform	
			+/T	+/T	+/T	+/T	+/T	+/T	+/T	+/T	% Affected	+/T	% Affected
	Normal	19.	5/8	3/8	0/8	0/8	0/8	0/8	0/8	0/8	0	0/8	0
	Borderline	20.	2/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3	0	0/3	0
Epileptiform	Uni-same	21.	2/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0	0/2	0
	Uni-opposite	22.	4/6	1/6	0/6	0/6	1/6	0/6	0/6	1/6	16.67	0/6	0
	Bilateral	23.	6/15	1/15	1/15	0/15	5/15	2/15	0/15	8/15	53.33	3/15	20.0
Non-epileptiform	Uni-same	24.	4/5	0/5	1/5	0/5	0/5	0/5	0/5	1/5	20.0	1/5	20.0
	Uni-opposite	25.	9/11	2/11	0/11	0/11	0/11	0/11	0/11	0/11	0	0/11	0
	Bilateral	26.	2/10	5/10	0/10	0/10	3/10	0/10	0/10	3/10	30.0	1/10	10.0
	Not Known	27.	2/5	1/5	2/5	0/5	0/5	0/5	0/5	2/5	40.0	1/5	20.0
	TOTAL		36/65	14/65	4/65	0/65	9/65	2/65	0/65	15/65	23.08	6/65	9.23

of individuals with epileptiform dysrhythmias.

The prevalence of individuals with epileptiform EEGs among the parents and siblings of "Hemiplegics With Convulsions Before the Onset," was 14.29%, and of total abnormalities 28.57% (Table 28). The prevalences among the parents and siblings of "Hemiplegics With Convulsions At Or After The Onset" were 23.44% and 37.50% respectively (Table 31). These two differences are not significant and the grouping of these two classes of hemiplegics together was considered justifiable, at least for the present.

The parents and siblings of the hemiplegics with convulsions were compared with those of the hemiplegics without convulsions with regard to the prevalence of individuals with epileptiform dysrhythmias (Table 35, Fig. 10). The prevalence was higher among both the parents ($14.71 \pm 6.07\%$) and siblings ($29.73 \pm 7.52\%$) of the hemiplegics with convulsions than among the parents ($2.86 \pm 2.81\%$) and siblings ($16.76 \pm 6.80\%$) of the hemiplegics without convulsions. These differences are not significant ($P=0.038$ and $=0.098$ respectively). However by combining the parents and siblings one obtains a prevalence of $22.54 \pm 4.95\%$ for the hemiplegics with convulsions, which is significantly higher ($P=0.015$) than the prevalence of $9.23 \pm 3.58\%$ for the hemiplegics without convulsions.

The prevalence of total EEG abnormalities among the parents ($20.59 \pm 6.93\%$) and siblings ($51.35 \pm 8.22\%$) of

TABLE 35

The Prevalence of Individuals With Epileptiform EEGs Among the Parents and Siblings of 'Hemiplegics With Convulsions' and 'Hemiplegics Without Convulsions'.

Relationship To Proband	Hemiplegics With Convulsions +/T	% Affected	Hemiplegics Without Convulsions +/T	% Affected	P
Parents	5/34	14.71 ± 6.07	1/35	2.86 ± 2.81	0.038
Siblings	11/37	29.73 ± 7.52	5/30	16.67 ± 6.80	0.098
Parents and Siblings	16/71	22.54 ± 4.95	6/65	9.23 ± 3.58	0.015**

PREVALENCE of EPILEPTIFORM EEGs

(HEMIPLEGICS $\overline{C}$ & $\overline{S}$ CONVULSIONS)

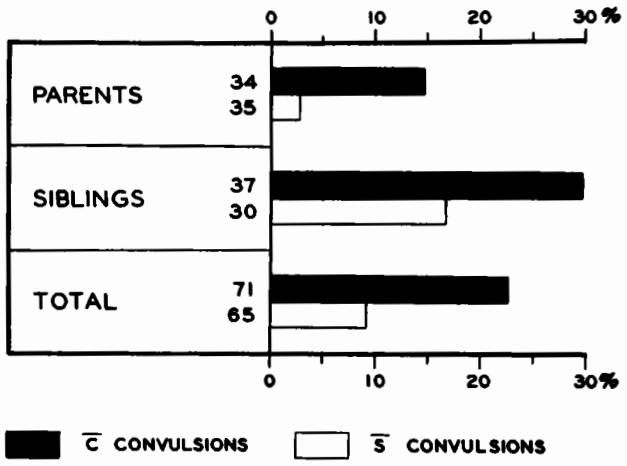

FIGURE 10

hemiplegics with convulsions was higher than that among the parents (11.43 ± 5.38%) and siblings (36.67 ± 8.80%) of the hemiplegics without convulsions (Table 36 and Fig. 11). These differences are not significant (P=0.15 and 0.11) and significance is not obtained (P=0.04) when parents and siblings are combined (36.62 ± 5.71% and 23.08 ± 5.23%).

Centrencephalic dysrhythmias were found in the EEG tracings of 18 parents and siblings of the hemiplegic probands. It is worthy of note that fourteen of these were related to hemiplegics with convulsions. Of the four hemiplegics without convulsions who had relatives with centrencephalic EEGs, one had an epileptiform EEG, one had a non epileptiform EEG and the EEGs of two were unknown (Tables 28, 31 and 34). Thus 15 of the 18 parents and sibs with centrencephalic EEGs were the relatives of hemiplegics with convulsions and/or epileptiform EEGs while only one was related to a hemiplegic without convulsions and with a non epileptiform EEG.

The prevalences of the various classes of EEG patterns among the parents and siblings of the control probands is shown in Tables 37, 38 and 39. The prevalence of epileptiform EEGs (16.67 ± 4.06%) and total abnormalities (23.81 ± 4.64%) among the parents and siblings of the intermediate (not normal EEGs) control probands was higher than the prevalences of epileptiform dysrhythmias (7.94 ± 2.41%) and total EEG abnormalities (18.25 ± 3.44%) among the parents and siblings

TABLE 36

The Prevalence of Abnormal EEGs Among the Parents and Siblings of: 'Hemiplegics With Convulsions' and 'Hemiplegics Without Convulsions.

Relationship To Proband	Hemiplegics With Convulsions +/T	% Affected	Hemiplegics Without Convulsions +/T	% Affected	P
Parents	7/34	20.59 ± 6.93	4/35	11.43 ± 5.38	0.15
Siblings	19/37	51.35 ± 8.22	11/30	36.67 ± 8.80	0.11
Parents and Siblings	26/71	36.62 ± 5.71	15/65	23.08 ± 5.23	0.04

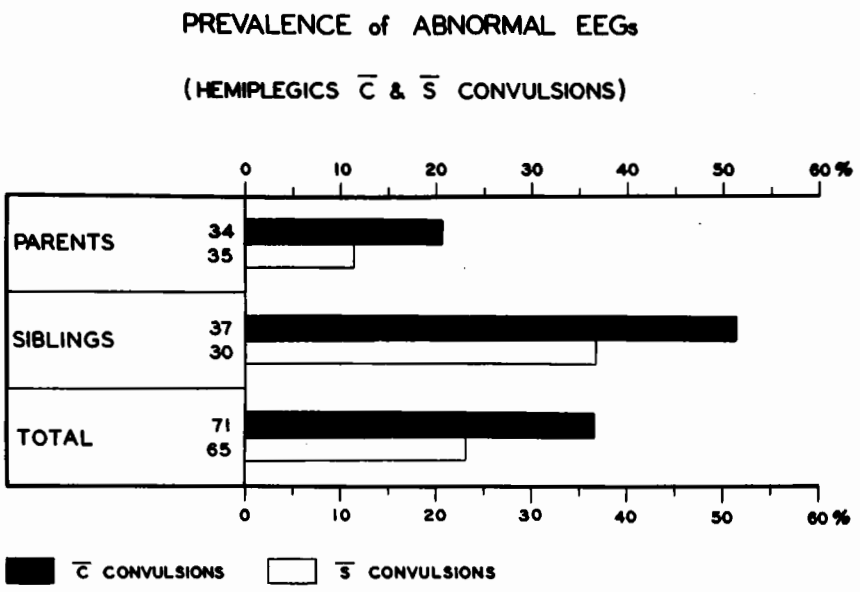
PREVALENCE of ABNORMAL EEGs
(HEMIPLEGICS C̄ & S̄ CONVULSIONS)
0
10
20
30
40
50
60 %
PARENTS
34
35
SIBLINGS
37
30
TOTAL
71
65
C̄ CONVULSIONS
S̄ CONVULSIONS

FIGURE 11

TABLE 37

The Prevalence of EEG Patterns Among the Parents of the Control Probands

Parent's EEG	Serial Control Group +/T	% Affected	Absolute Control Group +/T	% Affected	Intermediate Control Group +/T	% Affected
Normal	81/116	69.83	49/61	80.33	20/30	66.67
Borderline	14/116	12.07	5/61	8.19	6/30	20.00
Centrencephalic	6/116	5.17	2/61	3.28	2/30	6.67
Theta	2/116	1.72	0/61	0.00	1/30	3.33
Diffuse	6/116	5.17	2/61	3.28	0/30	0.00
Focal	6/116	5.17	3/61	4.92	1/30	3.33
Other Abnormalities	1/116	0.86	0/61	0.00	0/30	0.00
Total Abnormal	21/116	18.10 $\pm$ 3.56	7/61	11.48 $\pm$ 4.06	4/30	13.33 $\pm$ 6.20
Total Epileptiform	11/116	9.48 $\pm$ 2.70	3/61	4.92 $\pm$ 2.76	4/30	13.33 $\pm$ 6.20

TABLE 38

The Prevalence of EEG Patterns Among the Siblings of the Control Probands

Sibling's EEG	Serial Control Group +/T	% Affected	Absolute Control Group +/T	% Affected	Intermediate Control Group +/T	% Affected
Normal	74/153	48.37	32/65	49.23	28/54	51.85
Borderline	35/153	22.88	17/65	26.15	10/54	18.52
Centrencephalic	14/153	9.15	3/65	4.62	6/54	11.11
Theta	2/153	1.31	1/65	1.54	0/54	0.00
Diffuse	16/153	10.46	8/65	12.31	5/54	9.26
Focal	9/153	5.88	3/65	4.62	5/54	7.41
Other Abnormalities	3/153	1.96	1/65	1.54	1/54	1.85
Total Abnormal	44/153	28.76 ± 3.65	16/65	24.63 ± 5.34	16/54	29.63 ± 6.21
Total Epileptiform	25/153	16.34 ± 2.98	7/65	10.77 ± 3.85	10/54	18.52 ± 5.28

TABLE 39

The Prevalence of EEG Patterns Among the Parents and Siblings of the Control Probands

Parent's and Sibling's EEG	Serial Control Group +/T	% Affected	Absolute Control Group +/T	% Affected	Intermediate Control Group +/T	% Affected
Normal	155/269	57.62	81/126	64.29	48/84	57.14
Borderline	49/269	18.22	22/126	17.46	16/84	19.05
Centrencephalic	20/269	7.43	5/126	3.97	8/84	9.52
Theta	4/269	1.49	1/126	0.79	1/84	1.19
Diffuse	22/269	8.18	10/126	7.94	5/84	5.95
Focal	15/269	5.58	6/126	4.76	5/84	5.95
Other Abnormalities	4/269	1.49	1/126	0.79	1/84	1.19
Total Abnormal	65/269	24.16 ± 2.61	23/126	18.25 ± 3.44	20/84	23.81 ± 4.64
Total Epileptiform	36/269	13.38 ± 2.07	10/126	7.94 ± 2.41	14/84	16.67 ± 4.06

of the absolute (normal EEGs) control probands. However, this difference was not statistically significant (P=0.03).

The relationship of the prevalences of epileptiform dysrhythmias and total EEG abnormalities among the parents and siblings of the hemiplegics with convulsions, the serial control probands and the hemiplegics without convulsions is shown in Figs. 12 and 13. The prevalences among the parents and among the parents and siblings combined decrease as one passes from hemiplegics with convulsions to control to hemiplegics without convulsions. However this relationship does not hold true for the siblings.

The hemiplegic probands were again classified into the two groups - hemiplegics with convulsions and/or epileptiform EEGs and hemiplegics without convulsions and non epileptiform EEG. The prevalences of individuals with epileptiform dysrhythmias among the parents (12.00 $\pm$ 4.59%) and siblings (29.55 $\pm$ 6.88%) of the former were higher than the prevalences among the parents (0.00%) and siblings (9.52 $\pm$ 6.40%) of the latter probands (Table 40 and Fig. 14). The difference between the parents was not significant (P=0.085), but that between the siblings was significant (P=0.018). Among the parents and siblings combined, the difference in prevalence between the two groups was 14.80% (20.21% - 5.41%) and highly significant (P=0.004).

The prevalences of abnormal EEGs among the parents (22.00 $\pm$ 5.86%), siblings (54.55 $\pm$ 7.50%) and parents and

TABLE 40

The Prevalence of Individuals With Epileptiform EEGs Among the Parents and Siblings of: 'Hemiplegics With Convulsions and/or An Epileptiform EEG' and 'Hemiplegics Without Convulsions and a Nonepileptiform EEG'.

Relationship to Proband	Convulsions and/or Epileptiform EEG +/T	% Affected	No Convulsions and a Nonepileptiform EEG +/T	% Affected	P
Parents	6/50	12.00 ± 4.59	0/16	0	0.085
Siblings	13/44	29.55 ± 6.88	2/21	9.52 ± 6.40	0.018**
Parents and Siblings	19/94	20.21 ± 4.14	2/37	5.41 ± 3.71	0.004***

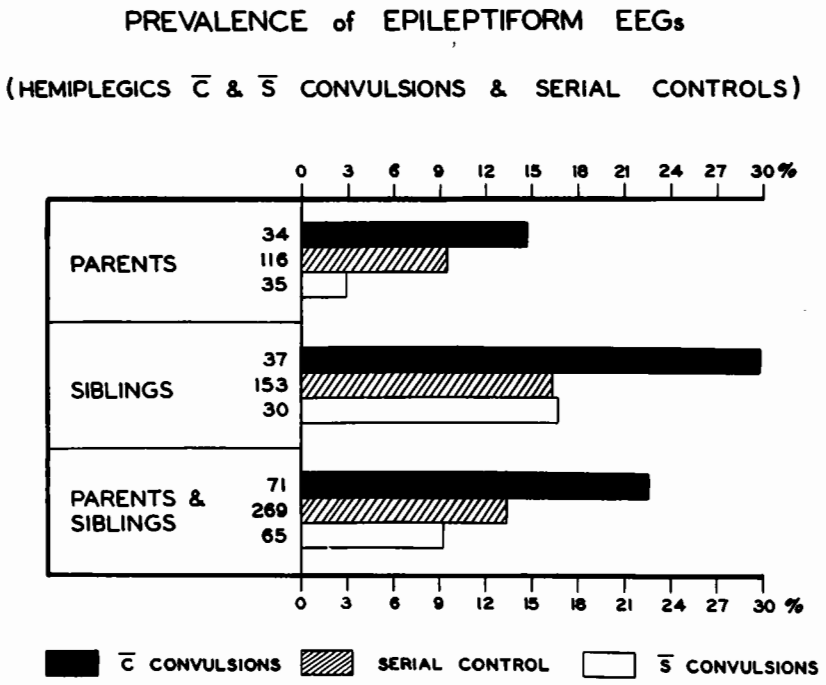
PREVALENCE of EPILEPTIFORM EEGs
(HEMIPLEGICS C̄ & S̄ CONVULSIONS & SERIAL CONTROLS)
0 3 6 9 12 15 18 21 24 27 30 %
PARENTS
34
116
35
SIBLINGS
37
153
30
PARENTS & SIBLINGS
71
269
65
0 3 6 9 12 15 18 21 24 27 30 %
C̄ CONVULSIONS
SERIAL CONTROL
S̄ CONVULSIONS

FIGURE 12

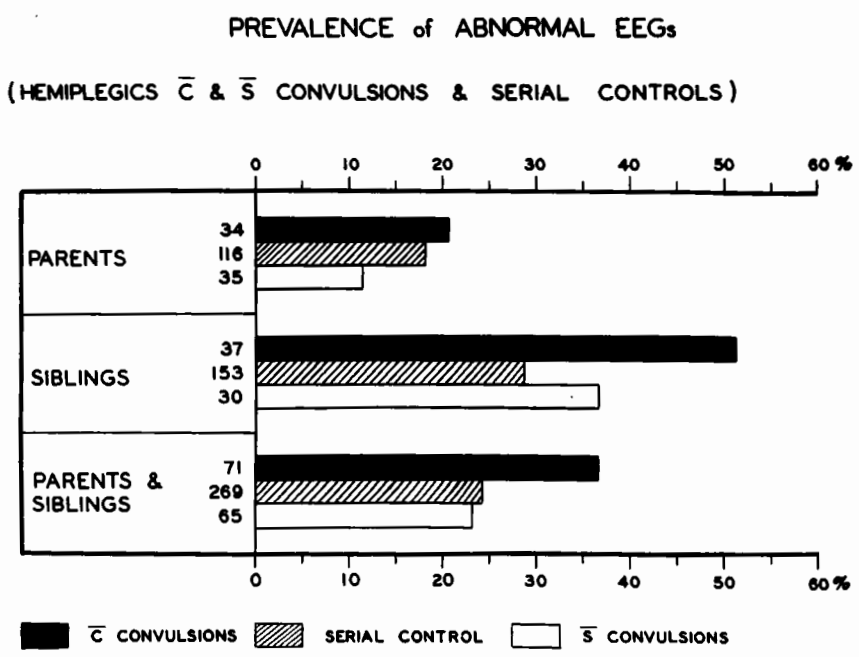
PREVALENCE of ABNORMAL EEGs
(HEMIPLEGICS C̄ & S̄ CONVULSIONS & SERIAL CONTROLS)
0
10
20
30
40
50
60 %
PARENTS
34
116
35
SIBLINGS
37
153
30
PARENTS & SIBLINGS
71
269
65
C̄ CONVULSIONS
SERIAL CONTROL
S̄ CONVULSIONS

FIGURE 13

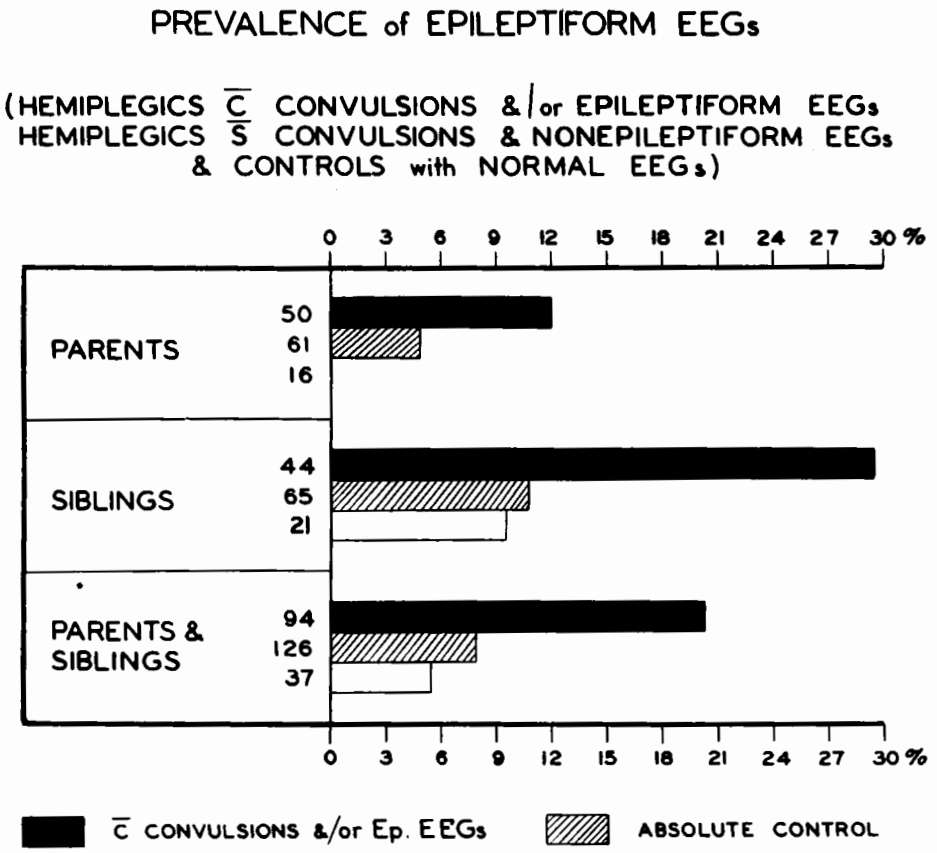
PREVALENCE of EPILEPTIFORM EEGs
(HEMIPLEGICS C̄ CONVULSIONS &/or EPILEPTIFORM EEGs
HEMIPLEGICS S̄ CONVULSIONS & NONEPILEPTIFORM EEGs
& CONTROLS with NORMAL EEGs)
0 3 6 9 12 15 18 21 24 27 30 %
PARENTS
50
61
16
SIBLINGS
44
65
21
PARENTS & SIBLINGS
94
126
37
0 3 6 9 12 15 18 21 24 27 30 %
C̄ CONVULSIONS &/or Ep. EEGs
ABSOLUTE CONTROL

FIGURE 14

siblings combined (37.23 ± 4.98%) of the hemiplegics with convulsions and/or epileptiform EEGs were all significantly higher (P=0.017, 0.001, and 0.001) than the prevalences among the parents (0%), siblings (19.05 ± 8.57%) and parents and siblings combined (10.81 ± 5.10%) of the hemiplegics without convulsions and with non-epileptiform EEGs (Table 41 and Fig. 15).

TABLE 41

The Prevalence of Individuals With Abnormal EEGs Among the Parents and Siblings of: 'Hemiplegics With Convulsions and/or an Epileptiform EEG' and 'Hemiplegics Without Convulsions and a Nonepileptiform EEG'.

Relationship to Proband	Convulsions and/or Epileptiform EEG +/T	% Affected	No Convulsions and a Nonepileptiform EEG +/T	% Affected	P
Parents	11/50	22.00 ± 5.86	0/16	0	0.017**
Siblings	24/44	54.55 ± 7.50	4/21	19.05 ± 8.57	0.001***
Parents and Siblings	35/94	37.23 ± 4.98	4/37	10.81 ± 5.10	0.0001****

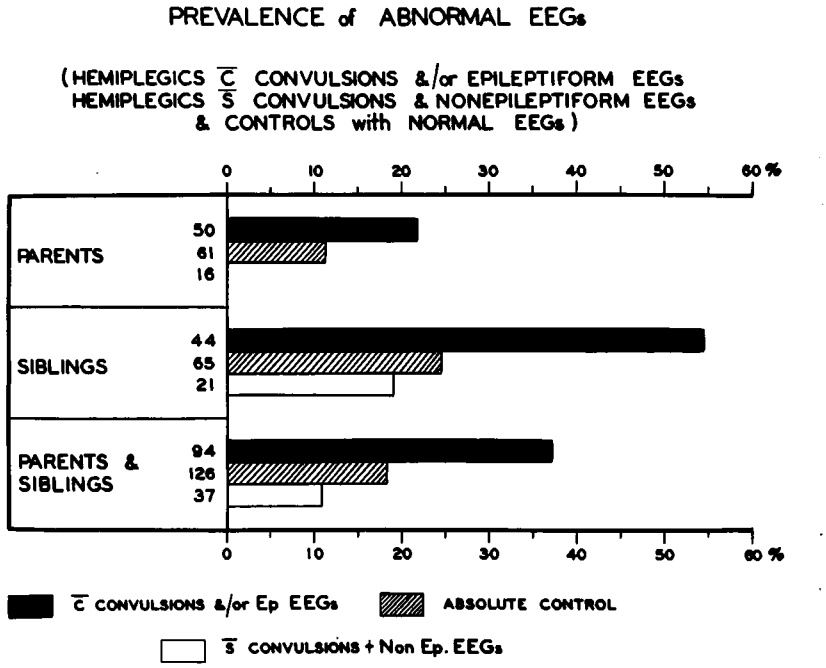
PREVALENCE of ABNORMAL EEGs
(HEMIPLEGICS C̄ CONVULSIONS &/or EPILEPTIFORM EEGs
HEMIPLEGICS S̄ CONVULSIONS & NONEPILEPTIFORM EEGs
& CONTROLS with NORMAL EEGs)
0 10 20 30 40 50 60 %
PARENTS
50
61
16
SIBLINGS
44
65
21
PARENTS & SIBLINGS
94
126
37
0 10 20 30 40 50 60 %
C̄ CONVULSIONS &/or Ep EEGs
ABSOLUTE CONTROL
S̄ CONVULSIONS + Non Ep. EEGs

FIGURE 15

IV. DISUCSSION

A. Convulsive Disorders in Hemiplegia:- Hemiplegia is a condition in which a motor disability of one side of the body arises as a result of lesions within the brain. The motor defect is usually of the spastic type and is the result of neuropathology in the contralateral cerebral cortex (103). This thesis deals with a study of 158 such hemiplegics, of which 98 or 62.0% had experienced one or more convulsions at some time during their lives. In the literature, the proportion of hemiplegics with convulsions ranges from 40% (17, 121, 122) to as high as 68% (162). The prevalence of individuals with a history of seizures in this series seems to be slightly higher than that found by the majority of investigators. This may be due, in part, to the liberal interpretation of the term "Hemiplegic With Convulsions", to include any hemiplegic who has had one or more convulsions due to any cause at any time during his life. Many of the hemiplegics with convulsions have a mild motor disability which may not be noticed until the individual is investigated for his convulsions. Such a patient would then be admitted to the neurology clinic because of his convulsions rather than for his hemiplegia, and would secondarily be included in the hemiplegia series. This procedure would be another factor which would tend to raise the prevalence of convulsors in this sample of hemiplegics.

This factor could not, of course, be measured.

It is generally accepted that 40-50% of hemiplegics have a history of convulsions, and that this is considerably higher than among most forms of cerebral palsy. For example, the prevalence of individuals with convulsions was found to be 25% for all types of cerebral birth injury (35), 35-40% for infantile cerebral palsy (30, 147, 164), 18% for all types of cerebral palsy (17), and 17% for athetoids (119). The prevalence is probably higher among hemiplegics because damage in the cortical motor areas is more likely to involve epileptogenic foci than damage in other areas of the brain which is found in other types of cerebral palsy, e.g., the basal ganglia in athetosis (38, 121).

Of the 98 hemiplegics with convulsions, 64.3% experienced over ten convulsive episodes. All types, focal, generalized and minor were represented (Tables 2 and 3). In 63 of these 98 probands, the convulsions were generalized, even though the motor defect and supposed neuropathology were unilateral. This high prevalence of generalized seizures is compatible with the diagnosis of unilateral encephalopathy since abnormal cortex does, in some instances, exert a noxious influence upon the rest of the brain. This noxious influence can be demonstrated electroencephalographically, since bilateral cerebral dysrhythmias have been found to disappear after the ablation of a focal epileptogenic area of cortex in one hemisphere (114, 115, 156).

Different types of epilepsy tend to occur at different ages. The brain of an infant tends to react to a variety of insults with generalized dysrhythmias, whereas at later ages the response is more apt to be focal (36, 37). Since the majority of the hemiplegic probands of this series acquired their neuropathology perinatally or during infancy, they would be expected to react with generalized dysrhythmias and thus generalized seizures. Furthermore, some of the patients may have had a subclinical bilateral dysrhythmia which was activated by the focal brain damage. Thus the high prevalence of generalized seizures among the hemiplegic probands is compatible with the assumption that they have unilateral neuropathology.

B. Aetiology of the Hemiplegia:- The presumptive aetiology of the neuropathology in this sample of hemiplegics was congenital in 99 or 62.7% and postnatal in 57 or 36.1% (Table 4). Perlstein and Hood (122) found a similar distribution of congenital (66%) and postnatal (34%) causes in their series of hemiplegics. The congenital hemiplegia was thought to be caused by birth trauma in 44%, prematurity in 16% and anoxia in 6% of the cases in this sample. In Perlstein's series the comparable figures are 31%, 12% and 8% respectively.

Among the 57 probands in the author's series, who developed their neuropathology postnatally, the largest number (52.63%) were thought to have vascular lesions, while

in Perlstein's series inflammation was the major factor in 57% of postnatal hemiplegics. This disagreement is probably due to differences in interpretation - e.g., is an inflammatory thrombosis a vascular or an inflammatory lesion? Many of these postnatal hemiplegics are probably examples of Gastaut's (34) H. H. E. syndrome, in which an infant, during the course of an acute febrile illness, develops focal convulsions, an ipsilateral motor deficit, followed at times by chronic epilepsy. Gastaut considers venous thromboses to be the most important cause of such postnatal hemiplegia. Thus birth trauma, perinatal anoxia, prematurity, and postnatal cerebral venous thrombosis appear to be the major factors involved in the aetiology of hemiplegia.

C. Hemiplegic Compared with Control:- A suitable control group should be drawn from the same or a similar population as the test group and be comparable in all factors other than those being studied unless, of course, the variables are associated with the presence or absence of the abnormalities in question. The hemiplegic and control samples were found to be similar with respect to proband's age, maternal and paternal age, parity and the prevalence of livebirths, abortions, stillbirths and multiple births, among the proband's, mother's and father's sibships (Table 17). These findings differ from those of some other authors.

Many authors have considered parity and parental age as important factors in the aetiology of cerebral palsy

(29, 87, 116, 117, 162). This sample provides no evidence that parity or parental age play a role in the aetiology of hemiplegia. The disagreement between the findings of this series and those of others may be due, in part, to the fact that here a comparable control was used, whereas in many of the other authors studies, no such control was employed.

Lilienfeld and Parkhurst (87) have claimed that mothers of children with cerebral palsy have about 35% more foetal and infant loss than among the general population. In the author's data, the prevalence of abortions and stillbirths among the pregnancies of the mothers of the hemiplegic probands was only 5.8% higher than that among the mothers of the control probands, a difference which is not statistically significant. Thus, this data does not indicate that the mothers of the hemiplegics have a significant excess reproductive wastage.

The ratio of boys to girls (75 : 83) among the hemiplegic probands is not significantly different from equality. However, of a random sample of 112 control patients, 73 or 65.2% were male. Although this sex ratio is significantly different from equality, it is similar to that found for the overall population of The Montreal Children's Hospital (98). Thus the control sample seems to be representative of the hospital population, as far as sex ratio is concerned. In this series hemiplegia was found to be equally prevalent among both sexes and thus is not one of the conditions which accounts for the excess of males admitted to The Montreal

Children's Hospital.

Some investigators have claimed that cerebral palsy, and hemiplegia in particular, is more common among boys than girls (17, 96, 121). However, other authors do not agree (50). This sample contained slightly more females than males (Table 17). However, as stated above, this difference is not a statistically significant one.

The control and hemiplegic samples were found to be quite similar in all of the above factors except sex ratio. The hemiplegic sample contained an equal number of boys and girls, while the control group was comparable to the general hospital population consisting of more boys than girls. Since neither parity, parental age nor maternal reproductive wastage differed between the hemiplegic and control groups, it is unlikely that they are important factors in the aetiology of hemiplegia.

D. Associated Characteristics of the Hemiplegic Probands:- Of the 158 hemiplegics in this sample 98 or 62.6% had a history of seizures. The other 60 or 37.4% never experienced a convulsion.

Why do some hemiplegics develop convulsions while others, with presumably similar neuropathology, do not? It is due to sex, severity of the encephalopathy, birth weight, birth order, constitutional seizure threshold or to some yet undefined factors? This is the underlying question of this thesis and in an attempt to unravel this

problem, the two groups of hemiplegic probands, those with and those without a history of convulsions, have been compared in regard to a number of the above-mentioned factors.

a) Uncorrelated Factors:- The two groups of hemiplegics were found to be comparable as to 1) sex ratio (Table 5), 2) laterality of involvement (Table 6), 3) severity of the neuropathology (Table 7), 4) birth weight, prematurity (Table 11), and parity (Table 12), 5) frequency of speech, hearing and visual defects (Table 13) and 6) frequency of congenital malformations (Table 13). These factors were thus considered unimportant in the aetiology of the seizures in the hemiplegic probands. These "negative" factors are summarized briefly below.

1) Sex Ratio:- The presence or absence of convulsions was found to be distributed uniformly among males and females. Of the 98 hemiplegics with convulsions 47 or 48.0% were male as compared to 27 or 45.0% of the 60 hemiplegics without convulsions (Table 5). Perlstein and Hood (121) observed a similar sex distribution in their series of hemiplegics.

2) Laterality of Involvement:- Of the 158 hemiplegic probands, 97 or 61.4% were disabled on the right side of the body and thus had an identifiable or presumptive lesion in the left cerebral hemisphere. This excess of right sided hemiplegia has been found by most other investigators (17, 53, 89, 118, 123). Perlstein and Hood (53, 118)

explain this by saying that 70% of births are in the left occiput anterior position in which case the left side of the foetal skull is more vulnerable to trauma. Another factor which might be important is that a mild weakness of the right hand would be more likely to be noticed by the parents than a left-handed weakness. The child would tend to use its left hand which often disturbs parents, and in seeking medical advice, a mild right-sided hemiplegia may be discovered. On the other hand, in a mild left hemiplegia the possibility of cerebral palsy is often raised only when additional symptoms such as mental retardation or seizures occur (160). Therefore, a mild right hemiplegia would be more apt to be recognized than a mild left hemiplegia.

Phelps (53), although he stated no actual data, claimed that seizures were much less frequent in left hemiplegics and raised the question of the possibility that the dominant hemisphere may have a lower seizure threshold. In Table 6 it can be seen that the prevalence of right motor disability is approximately the same for hemiplegics with convulsions (62.2%) as for those without convulsions (60.0%). Likewise, Perlstein and Hood (121) could find no evidence that right hemiplegics as a group were more prone to convulsions than left hemiplegics. Thus it appears that the probability of developing seizures is not dependent on which of the two cerebral hemispheres is involved.

3) Severity of the Neuropathology:- The severity of the motor disability was used as a rough index of the degree of the neuropathology. The prevalence of individuals with convulsions did not differ significantly among the mild, moderate and severe hemiplegics (Table 7). It was concluded that the data did not demonstrate a relationship between the probability of an individual developing seizures and the severity of the brain lesion. This lack of relationship is emphacized by the fact that 35 hemiplegics with mild motor disorders had a history of convulsions while 29 hemiplegics with moderate or severe motor disorders did not have seizures. Nevertheless, the hemiplegics without convulsions had, on the average, less severe motor disability than those with convulsions. Even if this trend is substantiated by further data, it would appear that the severity of the cerebral pathology cannot be a major factor in the development of convulsions, and cannot be used to predict the chance that a brain injured child has of developing convulsions.

4) Birth Weight, Prematurity and Parity:- The average birth weight of the congenital hemiplegics with convulsions was 6.64 lbs. and not significantly different from the average of the hemiplegics without convulsions (6.56 lbs.) Hood and Perlstein (52) found that the hemiplegics with convulsions were 0.4 lbs. heavier than those without convulsions, a difference which is not statistically significant. The distribution of premature and heavy babies was

similar among the two groups of hemiplegics (Table 11). Similarly the distribution of parity among the two groups of congenital hemiplegics was found to be comparable (Table 12). Thus birth weight, prematurity and parity order do not seem to play a role in the aetiology of seizures in congenital hemiplegia.

5) Speech, Hearing and Visual Defects:- Information concerning speech, hearing and visual defects was obtained from the medical records of the hemiplegic probands. Since they may have had one or more of these problems without it being recorded, the frequencies listed in Table 13 are probably underestimates. The prevalences of speech, hearing and visual defects were found to be comparable among the hemiplegics with convulsions and those without convulsions.

6) Congenital Malformations:- The prevalence of congenital malformations among the hemiplegics with convulsions was 16.3% as compared to 15.0% among the hemiplegics without convulsions. This difference is not statistically significant.

b) Correlated Factors:- Although no differences were found between hemiplegics with and without convulsions for the above six comparisons, differences were found when 1) onset of neuropathology, 2) intelligence and 3) behavior problems were considered.

1) Onset of Neuropathology:- Table 8 shows that a significantly higher proportion of probands who acquired

their lesion postnatally were found among the hemiplegics with convulsions (43.8%) than among those without convulsions (25.0%). Perlstein and Hood (121, 122) observed a similar relationship. This may be due, in part, to the fact that postnatal causes, such as trauma, cerebral vascular accidents, infections of the central nervous system, and poisoning, are often accompanied by an initial convulsive episode. Secondly both convulsions and hemiplegia can be caused by the same aetiological factors, for example, vascular thrombosis (34) and fever (66, 67). Furthermore, seizures themselves may produce enough cerebral pathology to leave a residual hemiplegia (163). Another factor favouring this distribution might be that some mild congenital hemiplegics are not recognized until they experience a convulsion, and the hemiplegia may then be considered to be of postnatal origin. Thus there are a variety of possible explanations for the fact that convulsions are more common among the hemiplegics who acquired their neuropathology postnatally.

2) Intelligence:- Of the158 hemiplegic probands, 148 were tested psychometrically. The mean psychometric score of the hemiplegic probands tested was 73.44. Fifty-two or 35.14% were considered to be mentally retarded, i.e., had a score of 65 or less. The observation that hemiplegics have, on the average, intellectual capacity below normal did not surprise us for there are many reports in the literature demonstrating the lower intelligence of the

cerebral palsy patient (8, 17, 50, 89, 96, 101, 123). Any type of brain damage is likely to produce a deterioration of intellectual function. However, idiopathic epileptics who had no known neuropathology were found to be of average intelligence (20), suggesting that convulsions *per se* do not impair intelligence. Epileptics who have associated brain damage have been consistently found to have intellectual deterioration (19, 58, 74, 79, 85, 132, 142). Thus the neuropathology is responsible for an intellectual deterioration as well as the motor disability.

In Table 9 we can see that a significantly higher proportion of the hemiplegics with convulsions (41.8%) were considered to be mentally retarded than of the hemiplegics without convulsions (24.6%). Using the same criteria for mental retardation, Perlstein and Hood (123) obtained similar results.

The mean psychometric score of the hemiplegics with convulsions was 69.14, significantly lower than the mean of 80.51 for the hemiplegics without convulsions. Perlstein and Hood (123) obtained almost identical results.

When the psychometric scores are plotted on a graph (Table 10, Fig. 5) the highest modal frequency of the hemiplegics without convulsions was found to lie in the normal range (90-109) while that of the hemiplegics with convulsions was in the retarded educable range (50-69). The results of all of the aforementioned analyses are consistent in demonstrating a lower intellectual function among the

hemiplegics with convulsions than among those without convulsions.

The first explanation to come to mind for this observation would be that convulsions per se cause an intellectual deterioration (119, 120). However, Lennox (74) argues that convulsions play a relatively unimportant role in the aetiology of mental retardation, for Collins (20) found that idiopathic epileptics, who are private patients, have, on the average, a normal intelligence.

The severity of the neuropathology does not seem to be the cause of the lowered intelligence since there was an equal distribution of mild, moderate, and severe disabilities among the hemiplegics with and without convulsions. McIntyre (96) claims that lesions of the dominant hemisphere cause more mental deterioration than lesions of the non-dominant hemisphere. However the distribution of the left- and right- sided lesions was comparable among the hemiplegics with and without convulsions, and even if this claim were true it could not explain the lower intelligence in the convulsant group.

Since there are more postnatal hemiplegics among the group with seizures, it may be argued that postnatal lesions cause a greater deterioration of intellect than congenital lesions, and thus lower the mean score of the hemiplegics with convulsions. However, neither in this sample, nor in Perlstein and Hood's sample did the mean psychometric score differ appreciably between the hemiplegics who had their

lesion at birth and those who acquired it postnatally.

Bilateral electroencephalographic abnormalities were found in 40.8% of the hemiplegics with convulsions as compared to 38.3% of the hemiplegics without convulsions (Table 15). Thus the extent of electrical dysrhythmia cannot be considered as a cause of the mental deterioration.

Visuomotor difficulties could cause a lowering of the psychometric score. Such difficulties were found to be more prevalent among the hemiplegics with convulsions (42.7%) than among the hemiplegics without convulsions (25.5%). However, the difference was not significant and the method of collecting these data was not considered absolutely reliable, so that one cannot reach any conclusions about the effect of visuomotor difficulties on the intelligence of the hemiplegics with convulsions.

The difference in intellectual capacity between the hemiplegics with convulsions and those without convulsions is not easily explainable. Possible explanations for this difference are 1) a peculiar type of neuropathology which causes both convulsions and intellectual deterioration; 2) a common inherited predisposition to brain trauma causing both seizures and mental retardation; 3) the convulsions could cause enough distraction in the already retarded child to cause further intellectual deterioration; and 4) the cerebral anoxia occurring with each convulsive episode could cause further brain damage and a gradual deterioration in

intelligence.

3) Behavior Problems:- The prevalence of behavior problems among the hemiplegics with convulsions (36.7%) was found to be significantly higher than the prevalence among the hemiplegics without convulsions (18.3%) (Table 13). Behavior problems in children with convulsive disorders are a well known entity. They have been considered to be due to two main factors 1) Primary - a direct result of the neurophysiological disturbance; and 2) Secondary - the child's reaction to being ill and to the way he is handled by those about him (13). Ounsted (110) found that many hemiplegics with convulsions had the hyperkinetic syndrome which is a behavior disturbance common in epileptic children of all types. Further evidence for a direct relationship between convulsions and behavior disturbances is the disappearance of the convulsions and an improvement in behavior following hemispherectomy in hemiplegics who had seizures and severe behavior disturbances (127). The higher prevalence of behavior problems among the hemiplegics with convulsions is probably due to the same factors which cause behavior disturbances in epileptics of all types.

E. The Electroencephalographic Tracings of the Probands: The records of at least one electroencephalogram were obtained for 141 of the hemiplegic probands. Of these patients 9 or 6.4% had unequivocally normal tracings while 15 or 10.6% did not have anything worse than a borderline

pattern (Table 14). This is not an unusual observation since normal electroencephalograms have been reported in 5-25% of epileptics with and without encephalopathies (1, 2, 40, 42, 55, 74). Electroencephalographic dysrhythmias are fluid traits and can change rapidly, especially in children in whom even epileptiform foci may "migrate" (36, 39). In many of the hemiplegics who had several tracings, some records displayed normal activity, while others showed focal or generalized dysrhythmias. It is quite probable that many of the probands who are listed as normal, electroencephalographically, may be found to have some abnormality if their tests were repeated.

Of the 126 hemiplegics who were found to have some definite electroencephalographic abnormality, 63 displayed an abnormality over one hemisphere alone, while there were bilateral dysrhythmias in the other 63 probands (Table 14). Thus 44.7% of the hemiplegics had bilateral electroencephalographic abnormalities. This is perhaps a little higher than the figures of Perlstein and Hood (122) who observed bilateral dysrhythmias in one-third of their hemiplegics. The presence of bilateral cortical discharge concomitant with unilateral neuropathology is well documented in the literature (10, 18, 104, 105). These contralateral abnormalities (i.e. contralateral to the affected hemisphere) have been seen to disappear after removal of the diseased hemisphere (104) and thus their origin is, most likely, in

the diseased hemisphere.

An unexpected observation was that six of the hemiplegic probands displayed electroencephalographic abnormalities only on the same side as their motor disorder, and thus over the hemisphere opposite to that which was thought to be damaged. In three of them the abnormality was epileptiform (Tables 14 and 15). This paradoxical situation may be explained in the following ways: 1) the EEG abnormalities were unrelated to the hemiplegia; 2) at this particular time no activity was recorded over the damaged hemisphere and all that was observed was the noxious effect on the normal cerebral hemisphere, but in subsequent recordings the abnormality may be seen over the diseased hemisphere; 3) the structural lesion is not evident electroencephalographically, the discharging lesion and the structural lesion are independent, and the discharging lesion can migrate (36); and 4) the patient had bilateral neuropathology even though he only displayed unilateral motor disability.

None of the various types of electroencephalographic abnormalities were confined to one group of hemiplegic probands (Table 15). However, 16.7% of the hemiplegics without convulsions did not have abnormal tracings as compared to only 8.6% of the hemiplegics with convulsions. This agrees with Perlstein and Gibbs' (120) observation that the general character of the electroencephalographic findings in cerebral palsied children with and without convulsions is much the

same, except for a higher incidence of normal tracings among the non-seizure group.

Of 54 hemiplegics without convulsions, 27 or 50.0% were found to have epileptiform disturbances in their electroencephalograms (Table 15). Perlstein, Gibbs and Gibbs (120) found that 50-55% of their hemiplegics without convulsions had seizure discharges. This could mean that these patients are potential epileptics and are likely to develop seizures at any time, that the stress which they experienced was enough to produce a dysrhythmia but not enough to set off a clinical seizure, or that they had a high threshold towards propagation of a dysrhythmia into an actual convulsion. This concept will be developed further later on.

Six of the 98 hemiplegics with convulsions had their first seizure before the onset of their motor disability (Table 15). These patients had both focal and generalized discharges in their electroencephalograms. They may have been idiopathic epileptics or may have experienced a non-specific stress (e.g., fever) prior to the onset of their hemiplegia which was enough to precipitate a seizure in this predisposed individual.

Tracings were obtained for 163 control probands and they were divided into absolute and intermediate control groups on the basis of these records (Table 16). Eighty-four or 51.5% of the control probands were found to have normal tracings and were admitted to the absolute control

group. Thus 79 or 48.5% of the control probands-children who had no evidence of any neuropathology-displayed borderline or abnormal patterns and were admitted into the intermediate control group. It must be remembered that electroencephalographic abnormalities often occur in children who do not give any evidence of neurological disease and who never have had a seizure.

F. Prevalence of Convulsive Disorders in the Near Relatives:- As has been mentioned earlier, the hemiplegics with convulsions did not differ from the hemiplegics without convulsions as to sex, gravidity, birth weight, aetiology, severity of the defect and laterality of the involvement. We can, therefore, exclude these factors as the direct cause of the convulsive disorders in the hemiplegics. Although the mean psychometric score was reduced in the hemiplegics with convulsions, this could not be attributed to an effect of reduced intelligence on seizure susceptability. The prevalence of postnatal onset of neuropathology and of behavior disturbances was increased in the hemiplegics with convulsions, but these were also considered to be unrelated to the seizure susceptability. One of the few possible explanations remaining is that of an inherited seizure threshold. To investigate this possibility, the following question was asked: Is the prevalence of individuals with convulsions and/or cerebral dysrhythmia among the near relatives of hemiplegics with convulsions significantly higher than among

the near relatives of hemiplegics without convulsions? Tables 18, 19 and 20 present the relative data.

Since the person interviewed, in most cases, was the mother of the proband, the realiability of the data is fairly accurate for the parents and siblings of the proband. The reliability of the data fails as one goes from parents to aunts and uncles, to cousins, to grandparents. The least reliable data would probably be that about the grandparents since it would be unlikely for someone to know of an isolated seizure which occurred during his or her parent's or inlaws' childhood.

Another source of bias might be that a parent of a child with convulsions would be more likely to know if any of the relatives had ever had a seizure than a parent of an unaffected child would. However, this type of bias would probably be small when comparing the two groups of hemiplegics, in both of which there is a disabling neurological problem which would tend to make the parents aware of any neurological disorders in the family. This source of bias may be of considerable importance in comparing the hemiplegic families with the control families. It is not expected to apply to the electroencephalographic records of the relatives of the control group.

The prevalence of individuals with a history of convulsions was found to be numerically higher for all classes of relatives of the hemiplegics with convulsions than for

the similar classes of relatives of hemiplegics without convulsions (Table 21, Fig. 6). However, among the individual classes of relatives, Although the only difference that was significant was that for aunts and uncles, when all of the classes of near relatives are grouped together, the prevalence among those of the hemiplegics with convulsions (2.04%) was twice as high as that among the relatives of the hemiplegics without convulsions (1.02%). This difference was highly significant (P=0.001). Thus a familial difference in susceptibility to convulsions has been demonstrated between the relatives of hemiplegics with and hemiplegics without seizures.

The prevalence of individuals with convulsions among most of the classes of near relatives of the control probands was found to lie in between that of the near relatives of the two groups of hemiplegics (Tables 23, 24, and Fig. 7). If the convulsions were due solely to the cerebral damage then the prevalence of affected individuals among the relatives of these three groups of probands should not differ. On the other hand, the results found are consistent with the hypothesis that an inherited seizure threshold was the reason that only some of the hemiplegics developed convulsions. Of the three groups, the hemiplegics with convulsions would be expected to have the lowest threshold (highest susceptibility), followed by the control probands. The hemiplegics without

convulsions would have the highest threshold since they did not convulse even when exposed to cerebral damage. If seizure threshold is genetically influenced, the prevalence of individuals with convulsions should also be highest in the relatives of hemiplegic probands with convulsions and lowest in the relatives of hemiplegics without convulsions.

The control group consistently falls closer to the hemiplegics with convulsions than to those without convulsions in regard to the prevalence of individuals with convulsions among the near relatives (Tables 23 and 24, Fig. 7). When one considers all of the near relatives together, the difference between the control group and the hemiplegics without convulsions is statistically significant (P=0.002). The prevalence of individuals with convulsions is higher among the relatives of the hemiplegics with convulsions than among those of the control probands, but this difference is not statistically significant (P=0.08).

A hypothetical scheme has been designed that would account for the observed relationships between the class of proband and the prevalence of individuals with seizures among their relatives (Fig. 16). If we assume that the degree of genetic predisposition ranges from 0 units (individuals who convulse with only the most intense stimulation) to 100 units (idiopathic epileptics who require little if any, external stimulation to convulse), and that the control group (with some reservations, this is represen-

THE HYPOTHETICAL DISTRIBUTION OF THREE GROUPS OF PROBANDS ACCORDING TO THEIR GENETIC PREDISPOSITION TO CONVULSIONS

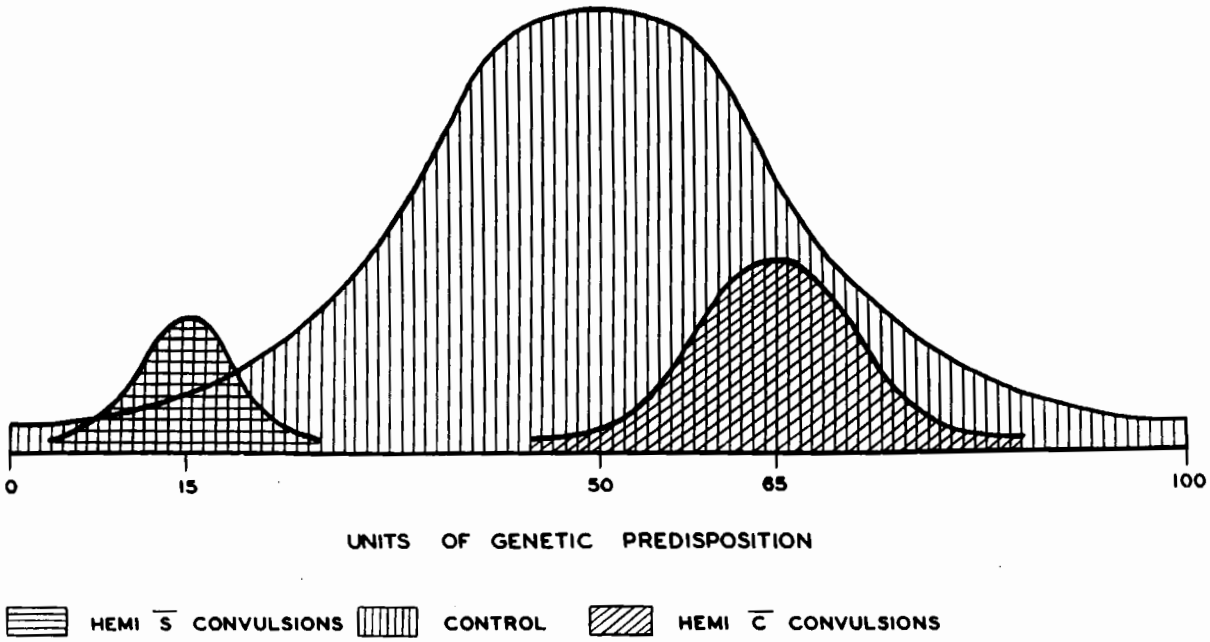

FIGURE 16

tative of the general population) falls in a normal distribution with a mean of about 50 units. Most of the hemiplegics with convulsions convulsed only when they were afflicted with a certain degree of neuropathology. They would, presumably, be slightly more susceptible than the general population, but far less predisposed than the idiopathic epileptics. We may assume that they have a mean predisposition of about 65 units. On the other hand, the hemiplegics without convulsions are a highly selected group in that they did not convulse even with severe brain damage. They might be expected to have a mean predisposition of about 15 units. On the assumption that the hemiplegics without convulsions have a much higher seizure threshold, and the hemiplegics with convulsions have a slightly lower threshold than the general population, and assuming that the threshold is, in part, genetically determined, the prevalence of individuals with convulsions among the near relatives of the control probands would be closer to that of the hemiplegics with convulsions than to that of the hemiplegics without convulsions. This is, in fact, what was found.

This concept may be extended to consider electroencephalographic abnormalities, in that there may be an independently inherited epileptiform dysrhythmia threshold. That is, an individual with a low threshold would display epileptiform dysrhythmias with little, if any, stimulation (centrencephalic epilepsy), whereas an individual with a

high threshold would be found to have an epileptiform EEG disturbance only when exposed to severe environmental stress (high doses of metrazol). If this dysrhythmia threshold is, in part, inherited, the prevalence of individuals with an epileptiform dysrhythmia would be expected to be higher among the relatives of probands with epileptiform EEG abnormalities than among those of probands whose EEGs do not display epileptiform dysrhythmias. Thus, the development of a cerebral dysrhythmia and the propogation of this dysrhythmia into a clinical seizure may be caused by two independent factors.

Support for this concept is obtained by considering the EEGs of the probands. Since the electroencephalographic rhythm is a fluid trait (119, 120) a proband with a history of one or more convulsions may be found, on a single examination, to have a non-epileptiform tracing whereas he does, in fact, have an epileptiform dysrhythmia most of the time. Secondly, individuals without a history of convulsions but who have an epileptiform dysrhythmia are considered by many to be predisposed to convulsions (75, 80, 81, 84, 119, 120). In our series, 27 of the 60 hemiplegics without convulsions had an epileptiform dysrhythmia (Table 15).

An electroencephalographic classification of the hemiplegic probands was devised in which the probands were divided into two groups - hemiplegics with convulsions and/or an epileptiform electroencephalogram and hemiplegics without

convulsions and a non-epileptiform tracing. The prevalence of individuals with a history of convulsions among each class of relative of the former group is consistently higher than that of the latter (Table 25, Fig. 8). When all of the near relatives are grouped together, the prevalence of individuals with convulsions among the relatives of the hemiplegics with convulsions and/or an epileptiform tracing is 1.86%, which is significantly higher (P=0.01) than the prevalence of 1.01% among the relatives of the hemiplegics without convulsions and with a non-epileptiform EEG pattern. If the brain damage alone were the cause of the epileptiform disturbance (pre-convulsive state) then one would not expect to find any such difference among the relatives of the two groups. However, one is dealing with EEG dysrhythmias in the proband, and clinical convulsions in the relatives and there is some question as to whether or not they are just different degrees of the same entity.

The control probands were divided into two groups, absolute controls (normal EEGs) and intermediate controls (borderline or abnormal EEGs). The prevalence of individuals with convulsions among the near relatives of the intermediate control group was higher, but not significantly so, than that of the absolute control group (Table 22). However the intermediate control group is a heterogeneous group in that it contains individuals with EEG abnormalities of all types, rather than just epileptiform disturbances.

This must be kept in mind when trying to assess the relative convulsive threshold of this group.

If one were to assess the relative degree of genetic predisposition to dysrhythmia, as has been done in Fig. 16, the various electroencephalographically classed groups of probands would fall into this order: 1) intermediate control group - these would presumably have the highest predisposition since they have abnormal tracings without any known neuropathology; 2) hemiplegics with convulsions and/or epileptiform dysrhythmias; 3) absolute control group; and 4) hemiplegics without convulsions and non-epileptiform records. Group 4) would have the lowest genetic predisposition since even with brain damage, dysrhythmias failed to develop. The prevalence of individuals with convulsions among the near relatives of these four groups of probands falls in the same order in most of the individual classes of relatives and also when all the relatives are grouped together (Fig. 9). Although these differences are not statistically significant, nevertheless their direction points toward a genetic predisposition to epileptiform dysrhythmias.

From all of the above comparisons between the hemiplegics with convulsions and those without convulsions, it appears that the only difference capable of explaining the development of seizures in some patients and not in others is the predisposition to convulsions that was found

for the near relatives of hemiplegics with convulsions. These findings are compatible with the concept of an inherited seizure threshold by which individuals with a low threshold would convulse with very little stimulation while others with a high threshold would require severe stimulation to precipitate seizures.

G. Prevalence of Electroencephalographic Dysrhythmias Among Parents and Siblings:- Since the reliability of the data concerning the history of seizures among the near relatives is not complete, the electroencephalogram was approached as a means of obtaining objective evidence of seizure susceptibility of the relatives. However, this approach is handicapped by the tendency of some forms of electroencephalographic abnormalities to subside with age (84, 99, 120). A single EEG represents a momentary glimpse at a dynamic entity which changes from day to day. Thus the electroencephalographic patterns can be considered "positive" only if they are abnormal. Unfortunately, the reverse is not true - i.e. a single "negative" tracing does not necessarily identify a normal individual. Many repeat "negative" tracings would be required.

Another difficulty inherent in this method of investigation is that many so-called normal children have been found to have cerebral dysrhythmias. In this series, only 51.5% of the control probands were found to have completely

normal tracings. Since the dysrhythmias tend to disappear with age, many of the parents with normal tracings probably had cerebral dysrhythmias at some earlier time.

Notwithstanding these difficulties, the study of EEG abnormalities in the relatives of hemiplegics supports the hypothesis that the proband's convulsions are a manifestation of an inherited low threshold. The prevalence of individuals with epileptiform dysrhythmias among the parents and siblings of the hemiplegics with convulsions was higher than that of the hemiplegics without convulsions (Table 35, Fig. 10). The individual differences are not statistically significant, but by combining parents and siblings the difference becomes statistically significant. If one considers an epileptiform dysrhythmia as an indication of predisposition to convulsions one again obtains evidence of some type of genetic mechanism operating in the production of seizures in the hemiplegics. One would not expect to find any difference if the convulsions were due solely to the brain damage. The epileptiform dysrhythmia may be considered to be merely a subclinical convulsion, or it may be an independently inherited factor requiring some other threshold mechanism to propagate it into a clinical seizure. If the latter were true, one would still expect to find an increased prevalence of individuals with epileptiform dysrhythmias among the near relatives of hemiplegics with convulsions than among those of the hemiplegics without

convulsions, since an epileptiform dysrhythmia would be a prerequisite, although not the only one, to a seizure. However, one would expect to find a stronger correlation between the EEGs of the probands and the EEGs of their relatives than between the clinical convulsions of the probands and the EEGs of their relatives. This is indeed what was found.

In comparing the prevalence of total electroencephalographic abnormalities among the parents and siblings of the hemiplegics with and without convulsions, the same relationship is observed (Table 36, Fig. 11). However, the differences are not statistically significant. This is probably due to the fact that the results are diluted by non-epileptiform dysrhythmias which are not subclinical seizures and are not related to the presence or absence of seizures in the proband.

The prevalence of epileptiform dysrhythmias and total electroencephalographic abnormalities among the parents and siblings of the intermediate control probands was higher than that of the absolute control probands (Tables 37, 38 and 39). These differences are not statistically significant. It must be remembered that the intermediate control group is a heterogeneous group and contains some individuals with non-epileptiform dysrhythmias. This would tend to bring the two groups closer together with regard to their seizure and/or cerebral dysrhythmia thresholds.

The prevalence of epileptiform dysrhythmias among the parents and siblings of the serial control probands fell in between that of the hemiplegics with and without convulsions. However, the differences are not statistically significant. The numbers are very low and many more tracings would have to be obtained to be able to demonstrate their reality, if so, statistically. The overall indication is that the three groups fall in the order - hemiplegic with convulsions, serial control, hemiplegic without convulsions - as to their genetic threshold. However, it must be pointed out again that there one is dealing with clinical convulsions in the probands and cerebral dysrhythmias in the relatives, and there is some question as to whether or not they are just different degrees of the same entity (See further discussion below).

When one classifies the probands electroencephalographically, one finds that the prevalence of epileptiform dysrhythmias among the parents and siblings of the hemiplegics with convulsions and/or an epileptiform tracing is higher than that of the hemiplegics without convulsions and with a non-epileptiform pattern (Table 40). The difference is significant between the siblings and parents and siblings combined, but not between the parents alone, where the numbers are very low.

The prevalence of individuals with epileptiform type dysrhythmias among the parents and siblings of the absolute

control group falls in between that of the two groups of hemiplegics (Fig. 14). The numbers are too small to assess the relative distances between the three groups but again the results are compatible with the concept of an inherited epileptiform dysrhythmia threshold.

When one considers total electroencephalographic abnormalities, one observes the same relationship between these three groups of probands (Fig. 15). However these results are buffered by non-epileptiform dysrhythmias and do not add any significant information to the problem.

Centrencephalic dysrhythmias were found in the tracings of 18 of the parents and siblings of the hemiplegic probands. Electroencephalographic records were available for 16 of the 18 probands involved here. Fifteen of the 16 probands belonged to the group of hemiplegics with convulsions and/or epileptiform dysrhythmias (Tables 28, 31 and 34). Only one of the probands had a history of no seizures and a non-epileptiform pattern. Although these numbers are too small to be statistically significant, there is a definite indication of a familial factor in epileptiform dysrhythmias. Furthermore, this observation suggests that induced and idiopathic dysrhythmias may be different degrees of the same entity.

Although some authors claim that a cerebral dysrhythmia is merely a subclinical convulsion (75, 80, 81, 84), the two -- dysrhythmia and convulsion -- may not be simply different degrees of the same entity. For example, there may be a

cerebral dysrhythmia threshold plus a threshold factor in transforming this cerebral dysrhythmia into a clinical seizure. The theory that the tendency towards paroxsymal discharges and the tendency for such to pass into clinical seizures may depend on mutually independent hereditary factors has been proposed by several authors (47, 156).

In the various comparisons made throughout this thesis, the relationships between the various hemiplegic and control groups were most consistent when one considered separately a) convulsions in the proband and relatives and b) epileptiform dysrhythmias in the proband and relatives. This observation would tend to support the concept of independent threshold factors for epileptiform dysrhythmias and clinical seizures.

V. CONCLUSIONS

This thesis provides strong evidence in support of a genetic mechanism predisposing an individual with cerebral damage to convulsions. In hemiplegia, as well as other neurological conditions, such as meningitis and tuberose sclerosis, individuals with the same neuropathology differ as to whether they will have convulsions concomitant with their neuropathology. In this study, it has been demonstrated that in hemiplegia it is neither the degree of neuropathology nor any other extraneous factor which determines whether or not an individual will develop a convulsive disorder. The most likely explanation for such individual variation is that of an inherited seizure threshold. An individual with a low threshold would convulse with minimal stimulation, whereas one with a high threshold would require more severe stimulation to develop convulsions. This concept is well substantiated by findings presented in this thesis. Chief among these is the finding that there is a significantly higher prevalence of individuals with convulsions among the near relatives of hemiplegics with convulsions than among the relatives of hemiplegics without convulsions.

The question arises as to whether this inherited seizure threshold differs from the genetic mechanism operating in idiopathic epilepsy. The simplest and most likely concept is that the threshold, which determines an individual's seizure susceptability, is determined by the same neuro-

physiological and genetic mechanisms, no matter what specific epileptogenic agent is involved (6, 11, 84, 86, 130). Idiopathic epileptics would be those individuals whose seizure threshold is so low that minimal stresses and strains of everyday life are sufficient to provoke convulsions.

One can postulate that this inherited seizure threshold is due to a multifactorial gene system and that a seizure is due to the interaction of environmental stimuli and the individual's inborn predisposition. Fig. 17 represents an attempt to illustrate this concept graphically. If the genetic threshold, which is inversely proportional to the genetic predisposition, is plotted along the abscissa, the population would fall along the diagonal line, ranging from those with a low threshold on the left hand side of the graph to those with a high threshold on the right hand side. Environmental stimuli are plotted along the ordinate ranging from the normal stresses and strains of everyday life to such severe stimuli as large doses of metrazol.

Since nature and nurture are never mutually exclusive, practically, one will never meet the end points of this line; that is, there is no circumstance at which there is no environmental stress, nor is there a point where an individual will have such a high threshold that he will be unable to convulse regardless of the amount of stimulation. The minimal stress required to provoke seizures in an individual would depend upon where he falls upon this line. If he falls at

GENETIC INTERPRETATION OF THE CONVULSION-THRESHOLD-CONCEPT

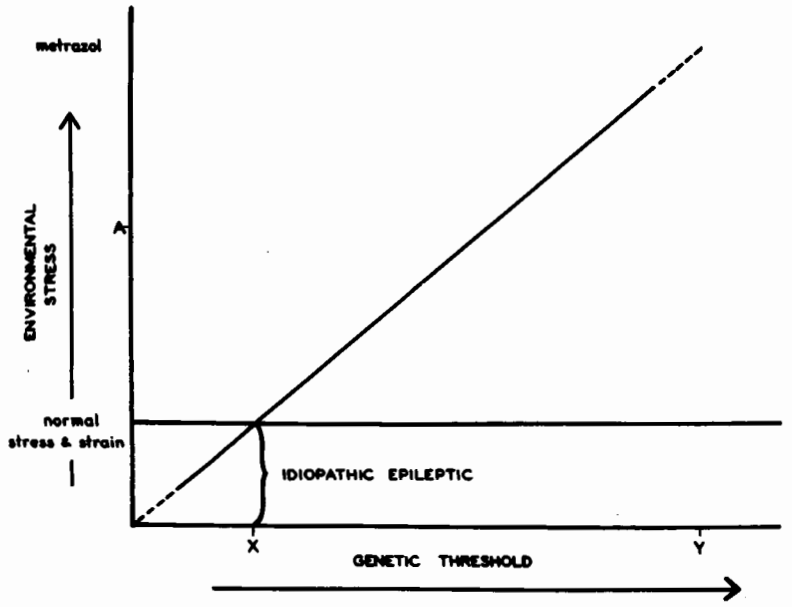

FIGURE 17

point X, then the ordinary stresses and strains of everyday life would be enough to promote a seizure and he would be classed as an idiopathic epileptic. If he falls at point Y then he would only convulse when exposed to such severe stimuli as large doses of metrazol, electroshock, etc.

At any given level of environmental stimulation, all the individuals lying below this point would convulse, and those above it would not. For example, if point A is taken as the average stress produced by the encephalopathy in hemiplegia, the individuals lying below this point would be the hemiplegics with convulsions, while those above the point would be the hemiplegics without convulsions.

According to this concept, idiopathic and acquired epilepsy are due to the interaction of environmental stress and a constitutional predisposition, the difference between them depending upon the relative importance of each. The predisposition would be the major factor in some individuals (idiopathic epileptics) and the minor factor in others (acquired epilepsy).

As to where cerebral dysrhythmias fit in this concept is a matter of conjecture. Some would say that a cerebral dysrhythmia is nothing more than a subclinical seizure (81, 82, 84) and that an individual would require so much stress to produce a cerebral dysrhythmia and just a little more stress to propogate it into a clinical convulsion. Others would say that there is an individual genetic mech-

anism controlling the propagation of such dysrhythmias into clinical seizures (47, 156). Many patients with dysrhythmias never convulse (99, 152). Is it because they were never exposed to a strong enough stimulus or because they lacked the ability to propogate this dysrhythmia into a seizure? It has been stated that dual hereditary factors may operate in the production of a clinical seizure, one producing the dysrhythmia, and the other propagating the dysrhythmia into a convulsion (47, 156). The observation that the relationships of the prevalence of affected individuals among the near relatives of the hemiplegic and control probands in this study are most consistent when one considers electroencephalographic epileptiform dysrhythmias and clinical convulsions separately would tend to support this dual mechanism theory (see IV-G). However, it must be admitted that our knowledge of these matters is far to scanty to permit final acceptance of such a theory.

Individuals do vary as to their seizure thresholds. The results presented in this thesis add further evidence to support the concept of a genetic predisposition to account for this variation. These individual differences are due to variations in the functional stability of the cells of the central nervous system. The degree of stability varies not only between individuals but also in the same individual at different times. At any one time the degree of stability depends on both the convulsive threshold (genotype) and the environmental stimulation to which he is exposed, that is,

an interaction between nature and nurture.

VI. SUMMARY

The underlying question throughout this thesis has been: "Why do some hemiplegics develop convulsions while others, with presumably the same neuropathology, do not?"

In order to answer this question and in order to see if genetic factors are aetiologically linked with "acquired" epilepsy, the near relatives (parents, siblings, uncles, aunts, grandparents and cousins) of 158 hemiplegics and 270 control children were investigated. The hemiplegics were divided into those with a history of having had at least one convulsive episode, irrespective of cause (98), and those who had never had a convulsion (60).

Sex ratio, birth weight, gravidity, prematurity, aetiology of the neuropathology, severity of the encephalopathy, laterality of involvement, onset of the lesion and intelligence were investigated and found to be unimportant as to whether a hemiplegic had convulsions or not.

The prevalence of individuals with convulsions among the near relatives of hemiplegics with convulsions (2.04%) was found to be twice as high as that among the relatives of the hemiplegics without convulsions (1.02%). This difference is highly significant (P=0.001). It is significant too that the prevalence of individuals with convulsions among the near relatives of the serial control probands (1.71%) lies in between.

The prevalence of epileptiform dysrhythmias among the parents and siblings of hemiplegics with convulsions (22.54%) was found to be approximately two and one-half times as

high as that among the parents and siblings of hemiplegics without convulsions (9.23%). This difference is statistically significant (P=0.015). As in the case of convulsions, the prevalence of epileptiform dysrhythmias among the parents and siblings of the serial control probands (13.38%) lies in between.

The hemiplegic and control probands were divided further on the basis of their electroencephalogram and particularly on whether this was epileptiform or not. The prevalence of individuals with convulsions among the near relatives of the hemiplegics with convulsions and/or an epileptiform EEG was 1.86%, which is significantly higher (P=0.01) than the prevalence of 1.01% among the near relatives of the hemiplegics without convulsions and with a nonepileptiform EEG.

The prevalence of individuals with epileptiform dysrhythmias among the parents and siblings of the hemiplegics with convulsions and/or an epileptiform EEG (20.21%) was almost four times as high as that among the parents and siblings of the hemiplegics without convulsions and nonepileptiform EEG (5.41%). This difference was highly significant (P=0.004). The prevalence of individuals with epileptiform EEGs among the parents and siblings of the absolute control probands (i.e. controls with normal EEGs) (7.94%) lies in between.

These findings are compatible with the theory of an inherited seizure threshold determining whether a hemiplegic will or will not have convulsions concomitant with his hemiplegia. Individuals with a low threshold would convulse with very minimal stimulation, while others, with a high threshold, would require severe stimulation to precipitate a convulsion.

The relationships between the various hemiplegic and control groups are most consistent when one considers separately a) convulsions in the proband and relatives and b) epileptiform dysrhythmias in the proband and relatives. This observation tends to support the concept of individual threshold factors for epileptiform dysrhythmias and clinical seizures. It is possible, therefore, that the tendency toward paroxsymal discharges and the tendency of such to be manifested as clinical seizures may rely on independent genetic factors.

VII. ACKNOWLEDGMENTS

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VIII. APPENDIX

EEG Classification

I. EEG PATTERN

1. NORMAL
2. BORDERLINE NORMAL
3. BORDERLINE ABNORMAL
5. CENTRENCEPHALIC
6. NON-SPECIFIC BILATERAL THETA RHYTHMS
5-6 MULTIPLE DIFFUSE DYSRHYTHMIAS (unlocalized)

9	Typical 3/sec. spike and wave
10	Multiple spike and wave
9-10	Paroxysmal 3-6/sec. spike and wave
11	Atypical wave and spike 3-4/sec.
	Irregular or asymmetrical (not slow s-w)
9-11	Paroxysmal
10-11	Paroxysmal with hyperventilation only
12	Organic
9-12	
10-12	
13	Generalized slow
14	Generalized fast
13-14	Generalized mixed
15	Generalized slow spike and wave
13-15	Generalized epileptiform
14-15	Generalized sharp
16	Generalized bil. syn. spike and wave
13-16	
14-16	

-4. ABNORMAL

- 7. FOCAL DYSRHYTHMIAS
  - RIGHT
    - 17 Frontal
    - 18 Temporal
    - 17-18 Central
    - 19 Parietal
    - 17-19 Occipital
    - 18-19 Parasagittal
    - 20
    - 17-20
    - 18-20 Mixed
  - LEFT
    - 21 Frontal
    - 22 Temporal
    - 21-22 Central
    - 23 Parietal
    - 21-23 Occipital
    - 22-23 Parasagittal
    - 24
    - 21-24
    - 22-24 Mixed
- 5-7 HYPSARHYTHMIA
- 6-7 DEPRESSION
- 8 ASYMMETRY, RIGHT
- 5-8 ASYMMETRY, LEFT
- 6-8 POSTERIOR FOSSA

II. EPILEPTIC DISCHARGE	25	None
	26	Sporadic spikes or sharp waves
	25-26	Sharp and slow wave complexes (slow s-w)
	27	Wave and spike rhythm
	25-27	Multiple spike bursts and multiple s-w complexes
	26-27	Paroxysmal rhythmic waves
	28	Spikes
	25-28	
	26-28	
III. PHOTOSENSITIVITY	29	Normal
	30	Abnormal
IV. SLEEP PATTERN	31	Normal
	32	Abnormal
V. HYPERVENTILATION	33	Normal
	34	Abnormal
VI. SEVERITY	35	Minimal
	36	Moderate
	35-36	

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