Departement of Biology Western Reserve University
Cleveland 6, Ohio. U.S.A.

THE GENETICS OF EPILEPSY

by
O. P. Kimball, M. D. and *A. H. Hersh. Ph. D.*

Epilepsy is defined as « recurrent convulsive seizures ». This disease has plagued the human race from time immemorial. In the long history (see Temkin, 1945) of fact, error and superstition, there have been three outstanding advances in our knowledge of epilepsy. Hippocrates, with the amazing insight of the genius of his generation, recognized that the seat of convulsive seizures is the brain. The second great step was made by Jackson (1834-1911), who developed the conception of focal seizures of the cerebral cortex. The third and greatest advance in our understanding of epilepsy is, of course, the result of the recent use of electroencephalography.

The advance in our knowledge of the genetics of epilepsy has not been so definite and the literature is still in a rather badly confused state. The defects in the literature are well taken up by Alström (1950).

After 1900, apparently the first extensive study on the genetics of epilepsy, from the Mendelian view, was made by Davenport and Weeks (1911). They point out the defects of the old method by which it was considered sufficient to determine with what frequency epilepsy was known to occur among the immediate ancestors and other near relatives of an epileptic patient. This frequency was then taken as the « index of heredity ». This is still the method which is sometimes used. Lennox (1951) for example finds 3,2% epileptics among the 20.000 near relatives of 4.231 patients. From these data the fraquency is roughly 1 in 30. An earlier value of this index (Lennox, 1945) is about 1 in 40, the figure which is frequently used by genetic counselors for estimating the probability that an epileptic parent will have an epileptic child. Such an index of heredity can be given a quentitative expression by taking into consideration the frequency and closeness of the relatives of any epileptic, who are epileptics. Bridge (1949) has done this to measure the « intensity of hereditary », and has the index vary from 0 to 4 plus. Bridge recognises that such a method in itself may lead to errors from the genetic point of view, but finds that it is of value in the statistical correlation for prognostic prediction.

It is clear to all in the light of modern genetics that this method of studying the inheritance of any trait is defective. If there is any doubt, all one needs to do is to calculate in this way the index of heredity and its intensity for a character such as albinism, a relatively rare autosomal simple recessive trait. However, it seems clear that another main source of confusion regarding heredity in epilepsy, arises from the fact that convulsions

Ricevuto il 21. XII. 1954.

may occur in a wide variety of diseases and condition known to the medical profession. Bridge (1949, p. 242) gives a table which lists some 75 diseases and other conditions in which convulsions are encountered and there is good reason to believe it is not complete since it does not include, e.g., congenital dislocation of the hips and hyperostosis of the frontal bone. Many of these convulsions are clearly caused by environmental factors. In experimental genetics it has been known for a long time that an environmental factor can act in the same direction as an hereditary factor, that is, produce the same or a very similar effect. Indeed Goldschmidt (1935) invented the term « phenocopy » for such effects. They were known long before 1935. Many years ago, Zeleny (1923) had actually shown that in Drosophila a particular gene substitution could bring about the same reduction in eye facet number as an increase in temperature of 10°C. It no doubt will be a long time before an hereditary trait in man can be so definitely related to the variations in the range of an environmental factor.

In consequence of the confusion in the literature on these main points there are those who believe that all epilepsy is symptomatic or acquired, while others incline to the view that all epilepsy is hereditary (see Jasper, 1947).

That epilepsy is hereditary is shown by the high degree of concordance in monozygotic twins, and by the fact that the incidence of epilepsy among the relatives of epileptics decreases as the relationship becomes more distant (see Table 3, Bridge, 1949). Although such data show that epilepsy is hereditary, yet in order to determine the mode of inheritance and the degree of penetrance, it is necessary to gather pedigrees and to make numerical tests of the pooled data. From this point of view there is no adequate substitute for the analysis of pedigrees so that we cannot agree with Kallmann (1947) who writes «the usefulness of this method is bound to be very limited in regard to epilepsy».

In any case the main purpose of the present report is to present the results from an analysis of 520 sibships in which at least one sib is epileptic.

The data

To understand the data and conclusions of this study it is necessary to know how the study was made and the sources of the cases studied. During the school year of 1930-31, a study of all children in the special schools of Cleveland was made to determine more accurately the diagnosis and classification of mental deficiency and delinquency. Many cases of mental and emotional instability were associated with convulsive seizures. Thus began a study of epilepsy which was to include over 4.000 school children of Cleveland and Detroit and extend over a period of 20 years (1930-1951) and also to include adults from private practice. In Detroit, a school clinic was organized in June 1934 and by January 1935, a school was ready for children with seizures. The White Special School of Detroit was the first of its kind in the country and the fact that a public school was open for children with epilepsy made it possible and easy for parents with children suspected of having seizures to come to the special school for diagnosis and schooling if needed.

In attempting to get the family history of an index case, every student of epilepsy has encountered either an ignorance of the family history or an unwillingness to admit any inherited tendency. In such cases only patience and repeated attemps to complete the history, even over a period of several years, will eventually produce an accurate diagnosis and a reliable pedigree. However, in the White Special School there was a marked change in the attitude of the parents as soon as this complex disease was considered a school problem and a special school was ready to accept the child, transport him to and from school, care for him when sick, give him a good lunch, provide adequate educational facilities and medical treatment if this was desired. In the White Special School the parents appeared anxious to bring out all the facts about the child's disease and to give the family history in detail, if it were known.

In the 4.000 and more original index cases, some of the convulsive seizures followed brain injury, or accident of some sort or infection, and for some others no family history was known or was obviously incomplete. The 520 sibships analyzed below represent only those for which the clinical findings and family history are regarded as accurate and reasonably complete. It should be mentioned also that since no difference was observed between Negroes and Whites, or between the families in Cleveland and Detroit, they are combined in the pooled data in Tables 1 and 2. A more extended account of the data especially in regard to the details of the contrast in the expression of epilepsy in different families is given in the paper « On the inheritance of epilepsy » (Kimball, 1954).

The genetic analysis of the data

In their paper mentioned above, Davenport and Weeks reached the conclusion that epilepsy is a simple autosomal recessive, largely because epilepsy was found among the progenysof parents, neither of whom was an epileptic. This is still the rough rule-of-thumb for the identification of a recessive and if the frequency is about the same among males and females, it ordinarily follows that the trait is autosomal.

The view that epilepsy is a simple autosomal recessive prevailed for many years and is still frequently mentioned as such (Penfield and Erickson, 1941 p. 405). After the discovery that in many instances when neither parent of an epileptic was epileptic, yet one showed the cerebral dysrhythmia diagnostic of epilepsy, then it was held by some that epilepsy was a dominant, since one parent could be detected as heterozygous for the hereditary factor responsible for the disease.

In the present series there are 222 sibships with neither parent affected. These effectively conform to the view that epilepsy is a recessive. There are 294 sibships with one parent affected, which so far as the analysis by mere inspection goes, could support either the conception of dominance or recessiveness. The data also include 4 families with both parents affected. If epilepsy is a simple recessive, then when both parents are affected, all the children should be affected.

Since Davenport and Weeks found such cases, they were hence strongly convinced that epilepsy was a recessive. But obviously with the small family system which prevails in human society, a case or two can not be regarded as conclusive. Of the 4 cases men-

Table 1 - One parent affected. Test for 1:1 ratio

Size of Sibship s	Number of Sibships n_s	Total sibs. sn_s	Affected sibs	Corrective factor f	Expected afiected fn_s
1	60	60	60		60
2	69	138	83	1.333	91.98
3	48	144	64	1.715	82.32
4	39	156	58	2.134	83.23
5	25	125	36	2.581	64.53
6	15	90	17	3.047	45.71
7	7	49	15	3.527	24.69
8	13	104	24	4.015	52.20
9	1	9	1	4.509	4.51
10	6	60	11	5.005	30.03
11	5	55	8	5.503	27.52
12	2	24	11	6.001	12.00
13	2	26	8	6.5	13.00
15	2	30	3	7.5	15.00
Totals	294	1070	399		606.72

tioned, one is a family of 16 children, all of whom have epilepsy. If this were the only such family, it would be rather convincing that epilepsy is a recessive, at least in so far as analysis by mere inspection can decide. However, in two other cases with both parents affected, one is a sibship of two, with one affected and the other is a family of 6 children with only 2 affected. Since these two families do not conform to the view that epilepsy is recessive, and since they ostensibly form a relatively small exception in a large body of data, in the past they would usually have been explained away on the assumption or suspicion that the legal parentage and the biological parentage did not coincide. This view could be especially persuasive in the present instance, since feeblemindedness was also involved in the families as well as epilepsy.

To be sure there is nothing logically impossible for the same trait to be recessive in some families and dominant in others. This is the view accepted by Alstrom (1950). Out of a total of 897 he found 11 families for which he ragarded the history as complete in regard to epilepsy. He found 4 in which he concluded the mode of inheritance was recessive and 7 in which the mode of inheritance was dominant.

All such analyses by inspection need to be followed by the analysis of data from accumulated pedigrees. In a numerical test on pooled data, there is, of course, implied the more or less tacit assumption that the trait under investigation is genetically the same in all pedigrees, i.e., the same hereditary factor is involved and if it is a single gene then it occupies the same locus in every case. The data for the 294 sibships with one parent affected and the 222 with neither parent affected are presented in Tables 1 and 2. First of all it is seen that in Table 1 there are 399 sibs affected out of a total of 1070, i.e., 37.3%

Table 2 - Neither parent affected. Test for 1:1 ratio and 3:1 ratio

Size of Sibship s	Number of Sibships n_s	Total Sibs. sn_s	Affected Sibs.	Corrective factor 1:1 f	Expected affected fn_s	Corrective factor 3:1 f	Number Expected fn_s
1	43	43	43		43		43
2	54	108	60	1.333	71.98	1.1428	61.71
3	44	132	51	1.715	75.46	1.2973	57.08
4	24	96	31	2.134	51.22	1.4628	35.11
5	19	95	28	2.581	49.04	1.6389	35.14
6	10	60	12	3.047	30.47	1.8248	18.25
7	13	91	25	3.527	45.85	2.0196	26.25
8	5	40	9	4.015	20.08	2.2225	11.11
9	3	27	4	4.509	13.53	2.4328	7.30
10	2	20	2	5.005	10.01	2.649	5.30
11	2	22	2	5.503	11.01	2.871	5.74
12	2	24	4	6.001	12.00	3.098	6.20
14	1	14	3	7.000	7.00	3.563	3.56
Totals	222	772	274		440.65		311.75

are affected. In Table 2, there are 274 affected sibs out of a total of 772 or 35.5%. Since in Table 2 neither parent is affected and yet the percentage of children affected is essentially the same as in Table 1 with one parent affected, it follows that this result favors the view that epilepsy is more probably a dominant than a recessive and that in Table 2, one of the parents is heterozygous for the factor involved but does not show the trait because of lack of penetrance. The combined results of Tables 1 and 2 show that in genetic epilepsy with one or neither parent affected, the expected affected among the progeny is $36.5 \pm 1.1\%$.

The penetrance calculated for the parents is 57.6% on the assumption that epilepsy is a dominant trait. This follows from the fact that for the entire 520 sibships 302 parents are affected and 524 are expected.

In Table 1 the data from 294 sibships with one parent affected are summarized. Whether epilepsy is a dominant or a recessive trait, the test required is for a 1 to 1 ratio among the progeny. Correction must also be made for small family size. The factors for this as well as the factors for variance are taken from Hogben (1933). From the Table it may be seen that 399 siblings are affected, and after correction for small family size, the number expected affected on the basis of a 1 to 1 ratio is 606.7. The variance, as calculated but not included in the Table, is 204.78. The difference between the observed and expected is 207.7 and the standard deviation is +14.3. There is a wide discrepancy between observed and expected on the basis of a 1 to 1 ratio. On the assumption that this is the result of a lack of penetrance the calculation shows that the penetrance is 65.8%. Estimates of penetrance are, of course, subject to sampling errors. Using the usual formula ($s = \sqrt{pq/n}$) the standard error of this estimate is +1.5%.

https://doi.org/10.1017/S1120962300020758 Published online by Cambridge University Press

It was mentioned above that when one parent is affected, the numerical test on the basis of a 1 to 1 ratio is equally applicable for a dominant or a recessive. When neither parent is affected, and there is a considerable lack of penetrance, the test can be made for 1 to 1 ratio or for a 3 to 1 ratio to cover both the case of a dominant or a recessive, and the degree of penetrance should show a reasonable consistency with the estimate made from pooled data of the sibships with one parent affected.

In Table 2 are assembled the data of 222 sibships with neither parent affected. The number of siblings observed affected is 274 and the number expected affected is 440.7 on the basis of a dominant. The standard deviation is ± 12.0. On the basis of a recessive the number expected is 311.8 and the standard deviation is ± 9.1. In the case of a recessive the result is 87.9% penetrance.

The calculation for a dominant gives 62.2% penetrance and the standard error is $\pm 1.8\%$. This degree of penetrance is very similar to that calculated for the 294 sibships with one parent affected, and obviously favors the conclusion that epilepsy is a dominant rather than a recessive trait. The data on the 4 sibships, with both parents affected are too few for a statistical test, but nevertheless, as mentioned above, they support the view that epilepsy is a dominant trait.

A not entirely exhaustive search of the literature yields very few series of complete pedigrees for comparison with the present data. However, of the 897 probands of Alstrom's study, there were 11 from which he accumulated pedigrees that he regards as reasonably complete and which were published in extenso. These pedigrees yield 15 sibships with 24 observed affected, out of a total of 70 siblings, i.e., 34.3%, which agrees closely with the 36.5% of the present study. After correction for small family size 38 are expected affected on the basis of a 1 to 1 ratio. Consequently the penetrance is 63.1% with a standard error of $\pm$ 5.8%. Although this value of the standard error is high because of the relatively small number (70), yet the result is very close to the estimates of the penetrance mentioned above for the present series, namely 65.8% and 62.2%.

Furthermore, monozygotic twins also can be used to obtain an estimate of the degree of penetrance. Gedda (1951), in his voluminous work on twins, has published a table of data on twins with epilepsy. From several sources, he finds a total of 37 pairs concordant and 29 pairs discordant. In the accumulation of such data there no doubt is sometimes the inclusion of the same individuals more than once. Little and Weaver (1950) studied epilepsy in 5 pairs of twins and then mentioned incidentally in a footnote that the twins would be included in a report by Lennox. Since the table of data, reported by Gedda, included principally the cases of Rosanoff and of Conrad, it seems entirely safe to add the cases accumulated by Lennox (1951) over the years. His data show 42 pairs concordant MZ twins and 27 discordant. When these are added to the totals mentioned above, there are altogether 79 concordant and 56 discordant sets of MZ- twins in regard to epilepsy, or 58% concordance and 42% discordance for the entire 135 sets of twins. In other words, of the 270 individuals with a genetic constitution for epilepsy, 214 showed the trait, i.e., the penetrance is 79.2% and the standard error is $\pm 2.5\%$. This is significantly higher than the average of 64% penetrance for the siblings mentioned above. Howewer, this is what one should naturally expect, since in addition to the causes of lack

of penetrance in MZ– twins, ordinary siblings are subject to the genetic modifiers in which they may differ from one another. Indeed the difference between 64 and 79% may possibly be taken as a measure of these genetic modifiers in producing the lack of penetrance.

The four estimates of penetrance, namely: 65.8% for the siblings with one parent affected, 62.2% for the siblings when neither parent is affected, the 57.6% for the parents in all the sibships and the 79.2% for identical twins give an average of 66.6%. We shall take the round figure of 65% as the estimate of the penetrance, for purposes of further discussion. Incidentally the lower penetrance for the parents reflects again the difficulty of making the clinical findings and family history complete since some of the data for the parents were accepted from patients and relatives without confirmation. « Frequently when parents did not know one or both branches of the family, they would write to some member of the family in Italy, Poland, or Scotland, for example, or to an older member of the family in this country, in order to complete the family history ». Kimball (1954).

It is interesting that the 21% lack of penetrance among MZ– twins does not differ significantly from the 24% of MZ–twins, who develop under dichorial conditions in utero. Price (1950), after a careful study of the pertinent data, found that the figures showed 33 both living MZ-pairs in 10.000 deliveries and a conservative estimate indicates that 8 of these were dichorial MZ-pairs; in other words, 24% of MZ-pairs are dichorial. This is unquestionably the best estimate at present time, although Price himself recognizes that the result needs to be checked for confirmation. And at present it is entirely speculative that the discordance for epilepsy in MZ-twins may be related in whole or in part to the dichorial condition during development.

The data of the present series also in remarkable agreement with the concordance in dizygotic twins. In the Table mentioned above, Gedda listed 24 concordant and 205 discordant DZ-twins. In the Table by Lennox the corresponding figures are respectively 5 and 48, making a total of 29 sets of concordant and 253 sets of discordant DZ-twins, or 10.3+1.8% concordance.

If we combine the data of Tables 1 and 2 of the present series, there are 1326 siblings of the 516 index cases and 157 of those are epileptics, or 11.8%. This is effectively the same as the 10.3% concordance in DZ-twins. Bridge (1941) in his Table 3 gives the incidence among siblings as 3.7%. Since DZ-twins are no more alike genetically than ordinary siblings there has been this unexplained discrepancy for a long time, The most plausible explanation is perhaps the incomplete account in the literature of epilepsy among the siblings of index cases and no doubt also an inclusion of cases of acquired epilepsy. Since the present data remove this discrepancy, they at the same time give confidence in the accuracy and completeness of the history and clinical findings of the present present study.

Although conclusions in human genetics cannot be as decisive as in experimental genetics, yet the very definite conclusion that follows from the previous discussion and analysis is that epilepsy in all probability is a simple autosomal dominant trait with about 65% penetrance.

Gene frequency. General discussion

The view that the normal individual who can be detected as a potential epileptic by the EEG is a heterozygote and so epilepsy is a dominant trait still demands that the patient with recurrent convulsive seizures be homozygous for the hereditary factor involved. This view is entirely different from the conclusions reached in the analysis of the 520 sibships of this paper. As indicated above the data show that epilepsy is an autosomal dominant with offending gene and the potential epileptic who can be detected only because of the cerebral dysrhythmia is also a heterozygote. These are the individuals who account for the 35% decrease from full penetrance. Briefly, on the first view, epilepsy is a recessive, and on the second view, it is a dominant trait. These two distinct views have different consequences regarding the gene frequency to be expected in the population.

It is generally recognized now that the numerical tests on pooled data, which support the hypothesis of the mode of inheritance that results from the analysis of pedigrees by mere inspection should be in reasonable agreement with the gene frequency in the population. It happens that epilepsy is a trait for which the incidence is perhaps better known than for many other human hereditary characteristics. As a result of the deferments of draftees in World War I and World War II because of epilepsy the average incidence for the United States as a whole is usually taken as 1 in 200 or 0.005. This figure needs to be corrected for lack of penetrance. But since the figure of 1 in 200 includes both hereditary and acquired forms of epilepsy and since hereditary epilepsy is approximately 65% of the total (Kimball, 1942) and since the penetrance is also approximately 65%, it is clear that these two factors effectively cancel one another. Consequently 0.005 may be taken as the relative frequency in the population of individuals with a genetic constitution for epilepsy.

With approximately random mating of a population in genetic equilibrium, the frequancy d for the dominant gene for epilepsy and the frequency r for the normal recessive allele are respectively 0.0025 and 0.9975. Consequently $2dr$, the frequency of the heterozygotes, is 0.005. That is, practically all the individuals with a genetic constitution for epilepsy are heterozygotes. The value of d^2, the frequency of the individuals homozygous for the gene is only 1 in about 160,000. And, of course, the frequency of r^2, the homozygous normal, is consequently 0.995. In the remarkable family with both parents affected and 16 children all affected, there is a bare possibility that perhaps one parent may be homozygous for the dominant factor for epilepsy.

Similar calculations for the view that the hereditary factor for epilepsy is recessive show that r, the frequency of the gene, is 0.0707 and the value for the dominant normal allele is 0.9293. Consequently d^2, the frequancy of the normal homozygotes, is 86.4% and the frequency of the heterozygotes $2dr$ is 13.1%.

Although both of these results, namely, the calculation for a dominant and a recessive trait for an incidence in the population of 0.005, are formally and internally consistent, yet the problem involved is which of the two is the more probable in the light of other known facts and conclusions. It seems somehow more reasonable to accept the figure that 99.5% are genetically normal in regard to the factor for epilepsy rather

than the other view that only 86.4% are genetically normal and 13.1% are heterozygous for a recessive factor for epilepsy. The fact that not a single instance of cousin marriage was found among the 520 sibships strongly favors the view that epilepsy is a dominant rather than a recessive trait. Also the best known recessive traits, such as albinism, blue eyes, taste blindness for phenylthio-carbamide, alkaptonuria, phenylketonuria and sickle cell anemia are remarkably uniform in their manifestation and have full penetrance, so far as the data indicate.

In regard to sickle cell disease Neel (1953) points out and discusses the problem of how a gene can maintain a high frequency in the population and at the same time be subjected to a negative selection. A somewhat similar problem exists in regard to epilepsy, but the two are not entirely comparable in all respects. All the necessary data for a solution of the problem are not available. First of all it is not known what the frequency of epilepsy has been in the past, although the statement is sometimes made in the literature that epilepsy was as common in ancient times as at present. Harvald (1951) states that the fertility of epileptic patients is $60.4 \pm 2.1\%$ of the fertility of average urban populations. It is easy to see then that as the generations pass the frequency should decrease and obviously at the present time would be expected to be much less than 1 in 200. The problem is, « what maintains the relatively high frequency? » The chief factors, as Neel points out, could be reproductive overcompensation and high mutation rate. As indicated above the reduced fertility of epileptic patient rules out the factor of greater reproductive fitness. Nothing is known about the mutation rate of epilepsy. However, in the case of epilepsy another factor is present which might well be the full explanation. If the analysis above is correct and epilepsy is an autosomal dominant with approximately 65% penetrance then the individuals who are genetically epileptic, but who are not in fact epileptic, and if they have as high fertility as the general population rather than the reduced fertility of the phenotypic epileptic then it is easy to see that the gene might not merely maintain itself but actually increase in frequency as the generations pass. It is perhaps unnecessary to add that in the present state of knowledge the data are not available to more precisely specify the factors involved.

Another topic needs to be mentioned, if merely for the sake of completeness, since the present data do not allow a decisive answer. The question is, « how does the main gene for epilepsy act to produce its effect? ». The obvious answer seems to involve the growth and development of the central nervous system. The character of the circulation and the oxygen supply are also important. And it is significant that anti-convulsant drugs produce their effect by action on the cerebral circulation. Furthermore the epileptic patient who by the use of anti-convulsant drugs has fairly good control over the seizures, finds frequently that an indulgence in alcoholic beverages again brings on the seizures. It would follow then that the subsidiary genetic factors which contribute to the lack of penetrance perhaps also act to alter the structure and character of the cerebral circulation in a favorable direction.

The physiological balance in which the main factor for epilepsy acts is apparently a fairly sensitive one as shown by the lack of penetrance and the variability in the severity and the type and frequency of the seizures. Threshold effects are involved. Even in expe-

rimental epilepsy in animals where by close inbreeding it is possible to have all the individuals in a population with the same genetic constitution, except for whatever mutations may sporadically occur, yet nevertheless there is a lack of penetrance of the main gene (see review by Hall, 1951).

There is very little known about pleiotropic effects in human genetics, yet such effects are expected to occur, since they are of such widespread occurrence in experimental genetics. It is perhaps significant that the literature on epilepsy is at the same time so much occupied with feeblemindedness, migraine, insanity, chorea and a wide variety of neural symptoms. The suggestion that these may be pleiotropic effects of the main gene for epilepsy is obviuosly merely conjectural in the present state of knowledge. But it is well recognized that a defect in the growth and differentiation of one of the basic tissues has wide spread and diverse secondary effects (see Gruneberg, 1938).

The conclusions from the genetic analysis that may be important for the legal, social and economic aspects of the eugenic problem of epilepsy require a separate paper for their elaboration (see Kimball, 1954), but it may be mentioned briefly for the interest of the genetic counselor that the data show that if one parent is affected or carries the genetic factor for epilepsy then about 36% of the children are expected to be epileptic. And in a sibship with one epileptic the empirical probability, based on the data of Tables 1 and 2, for another child to be epileptic is nearly 0.12, or about 1 in 8.

Summary

Among 520 sibships, in which at least one child was an epileptic and for which the family history and clinical findings were quite complete, there were 294 with one parent affected, 222 with neither parent, and 4 with both parents affected. Numerical tests on the pooled data show quite definitely that epilepsy is inherited as if due to a simple autosomal dominant gene with approximately 65% penetrance. Since about 65% of all epilepsy is genetic and since there is about 65 penetrance in genetic epilepsy, the 2 factors effectively balance one another, so that the incidence of epilepsy in the population, 1 in 200, may be taken as the frequency of individuals with a genetic constitution for epilepsy.

Assuming random mating, the gene frequency for the dominant gene for epilepsy is 0.0025 and for the normal recessive allele the value is 0.9975. It follows that only about 1 in 160,000 is homozygous for the dominant gene for epilepsy and that 99.5% of the population are genetically normal. For the genetic counselor it is of interest that if one parent has a genetic constitution for epilepsy the frequency among the children is about 36%, and if one child in such a family has epilepsy the empirical probability of another child having epilepsy is about in 1 in 8, which having regard to the standard error, agrees with the degree of concordance ($10.3 \pm 1.8\%$) in dizygotic twins, as should be expected.

References

ALSTROM, C. H. 1950. A study of epilepsy in its clinical, social and genetic aspects. *Acta psych. neurol.* Supp. 63.

BRIDGE, E. M. 1949. *Epilepsy and convulsive disorders in children*, pp. 670. McGraw-Hill Book Company, New York.

DARWIN, CHARLES. 1868. *The variation of plants and animals under domestication.* 2. vols. Judd. & Co., New York.

DAVENPORT, C. B. & MEEKS, D. F. 1911. A first study of inheritance of epilepsy. *J. Nerv. Ment. Dis.* 38: 641-670.

GEDDA, LUIGI. 1951. *Studio dei Gemelli*, pp. 1931. Edizioni orizzonte medico, Rome.

GOLDSCHMIDT, RICHARD. 1935. Gen und Ausseneigenschaft. *Zeitsch ind. Abstl.* 69: 38-69.

GRUNEBERG, HANS. 1938. An analysis of the pleiotropic effects of a new lethal mutation in the rat. *Proc. Roy. Soc.* B 125: 123-144.

HALL, CALVIN S. 1951. The genetics of behavior. Chapter 9 in *Handbook of Experimental Psychology.* John Wiley & Sons, New York.

HARVALD, BENT. 1951. On the genetic prognosis of epilepsy. *Acta psych. neur. scand.* 26: 399-352.

HOGBEN, LANCELOT. 1933. *Nature and Nurture.* Norton & Co., New York.

JASPER, HERBERT H. 1947. Electroencephalography in epilepsy. Chapter 14 in *Epilepsy* (edited by Paul H. Hoch and Robert P. Knight) pp. 214. Grune & Stratton, New York.

KALLMANN FRANZ J. 1947. The genetics of epilepsy. Chapter 3 in *Epilepsy* (edited by Paul H. Hoch and Robert P. Knigt) pp. 214. Grune and Stratton, New York.

KIMBALL, O. P. 1942. *A study of epilepsy in the Detroit Schools.* Ohio State Med. J. 38: 435-439.

— 1954. On the inheritance of epilepsy. J. Wis. *State Med. Soc.*, Mary issue pp. 271-276.

LENNOX, W. G. 1945. Marriage and children for epileptics. *Human Fertil.*, 10: 97-106.

— 1951. The heredity of epilepsy as told by relatives and twins. J. A. M. A. 146: 529-536.

LITTLE, S. C. and Weaver, N. K. 1950. Epilepsy in twins (5 pairs). *Am. J. Dis. Child.* 79: 223-232.

NEEL, J. V. 1953. Data pertaining to the population dynamics of sickle cell disease. *Amer. Jour. Human Genetics*, 5: 154-167.

PENFIELD, W. and ERICKSON, T. C. 1941. *Epilepsy and cerebral localization*, pp. 623. Charles C. Thomas, Springfield, I 11.

PRICE, BRONSON. 1950. Primary biases in twin studies. *Amer. J. Human Genetics* 2: 293-352.

TEMKIN, OWSEI. 1945. *The falling sickness, pp.* 380. Johns Hopkins Press, Baltimore, Md.

ZELENY, CHARLES. 1923. The temperature coefficient of a heterozygote with an expression for the value of a germinal difference in terms of an environmental one. *Biol. Bull.* 44: 105-112.

SOMMARIO

Fra 520 fratellanze di cui almeno un bambino era epilettico e per cui la storia famigliare e i reperti clinici erano abbastanza completi, ve ne erano 294 con un genitore affetto, 22 con nessun genitore affetto e 4 con entrambi i genitori affetti. Prove numeriche sui dati conglobati dimostrano abbastanza definitivamente che l'epilessia è ereditata come se dovuta a un semplice gene auto-somatico dominante con circa il 65% di penetranza. Poichè circa il 65% di tutta l'epilessia è genetica e poichè vi è circa una penetranza del 65% nella epilessia genetica, i due fattori si bilanciano effettivamente l'un l'altro in modo che l'incidenza della epilessia nella popolazione, uno su 200 può essere presa come la frequenza degli individui con una costituzione genetica per l'epilessia.

Supponendo accoppiamenti casuali, la frequenza genica per il gene dominante dell'epilessia è 0,0025 e per il normale allele recessivo il valore è 0,9975. Ne consegue che solo circa uno su 160 mila è omozigotico per il gene dominante nell'epilessia e che il 99,5% della popolazione è geneticamente normale. Per il consulente genetico è interessante che se un genitore ha una costituzione genetica per l'epilessia, la frequenza fra i figli è circa il 36% e se un figlio in tale famiglia ha l'epilessia la probalità empirica che anche un altro figlio ne sia colpito è circa uno su 8, il che tenendo presente l'errore medio coincide con il grado di concordanza (10,3 ± 1,8%) nei gemelli dizigotici come è prevedibile.

RESUMÉ

Sur 520 membres issus d'une même généalogie, parmi lesquels au moins un enfant était épileptique et au sujet duquel l'historique familial et les observations cliniques étaient assez completes, 294 comptaient un parent affecté de cette même maladie, 22 n'avaient aucun parent malade, tandis que pour 4 les deux parents étaient atteints de ce mal. Les chiffres pris à un ensemble de données attestent, d'une manière assez définitive, que l'épilepsie est héritée, comme si elle était due à un simple gêne auto-somatique dominant avec environ 65% de pénétration. Or, compte tenu que 65% de toute l'epilepsie est génétique, et qu'on constate une pénétration d'environ 65% dans l'épilepsie génétique, les deux facteurs se balancent effectivement l'un l'autre, de telle sorte que l'incidence de l'épilepsie sur la population — un sur 200 — peut être considérée comme la fréquence des individus dotés d'une constitution génétique pour l'épilepsie.

En supposant des accouplements occasionnels, la fréquence génique pour le gêne dominant de l'épilepsie, est de 0,0025 et pour le normal allèle récessif, la valeur est de 0,9975. Il en résulte qu'environ 1 sur 160.000 est OZ pour le gêne dominant de l'épilepsie, et que 99,5% de la population est génétiquement normal. Pour le généticien, il est intéressant de savoir que si un parent a une constitution génétique pour l'épilepsie, la fréquence parmi les enfants est d'environ 36%. Et encore: si dans cette famille un enfant est atteint d'épilepsie, la probabilité empirique qu'un autre enfant en soit également atteint, est d'environ 1 sur 8. Compte tenu de l'erreur moyenne, ceci coincide avec le degré de concordance (10,3 ± 1,8%) chez les jumeaux DZ, comme il est aisé de le prévoir.

ZUSAMMENFASSUNG

Unter 520 Geschwistergruppen, von denen wenigstens ein Kind epileptisch war, mit ziemlich vollständiger Familiengeschichte und klinischen Befunden, waren bei 294 ein Elternteil, bei 22 keiner der Eltern und bei 4 beide Eltern mit der Krankheit behaftet. Zahlenmässige Proben über die zusammengestellten Angaben beweisen recht eindeutig, dass die Epilepsie erblich ist, als ob sie durch ein einfaches auto-somatisches dominierendes Gen mit ungefähr 65% iger Penetranz bedingt väre. Da ungefähr 65% aller Epilepsieerkrankungen erblich und da bei der erbzlichen Epilepsie eine Penetranz von rund 65% vorhanden ist, gleichen sich die beiden Faktoren in der Tat gegenseitig aus, sodass das Vorkommen der Epilepsie in der Bevölkerung in Verhältnis von 1/200 als Häufigkeitsindex der Individuen mit Erbanlage für Epilepsie angenommen werden kann.

Wenn man Zufallspaarungen annimmt, ist die Genfrequenz für das dominierende Epilepsiegen 0,0025 und für das normale rezessive Allel 0,9975. Daraus folgt, dass nur ungefähr 1/160.000 homozygotisch für das dominierende Epilepsiegen ist, und dass 99,5% der Bevölkerung erblich normal sind. Für den genetischen Berater ist es interessant, dass — wenn ein Elternteil eine Erbanlage für Epilepsie hat — die Häufigkeit unter den Kindern etwa 36% beträgt; und wird ein Kind einer solchen Familie von Epilepsie betroffen, ist die empirische Wahrscheinlichkeit, dass ein anderes Kind in der Familie daran erkrankt, 1:8, was, unter Berücksichtigung eines Durchschnittsfehlers mit dem Konkordanzgrad bei den ZZ (10.3 ± 1,8%) — wie vorauszusehen — übereinstimmt.