GENETIC AND SOCIAL ASPECTS OF THE EPILEPSIES OF CHILDHOOD*

By CHRISTOPHER OUNSTED, D.M., D.C.H.

Introduction

EPILEPSY and other convulsive disorders form, numerically, one of the largest single problems in hospital pædiatrics. Children presenting with fits outnumber the combined total of all those with tuberculosis, asthma and rheumatism: diseases generally regarded as the chief scourges of childhood. (Bridge 1949.)

Estimates of incidence in the general population vary, but there seems to be general agreement that, among men called-up for military service, the incidence of epilepsy is 1 in 200: in the population as a whole the incidence may be 1 per cent. There are then, probably, not less than quarter of a million epileptics in this country and they represent a substantial burden of illnesses and economic loss.

In children, of course, there is a higher incidence of all types of convulsive disorder if one includes infantile convulsions. Precise figures are hard to get. Probably not less than 3 per cent of all children are affected in the healthier provinces of England. Some estimates give higher figures: none that I know of gives a lower.

The Principle of Multiple Aetiology

Any epileptic seizure is the result of multiple ætiological factors (Ounsted 1954). Some of the factors which may converge to generate a single fit or a chronic epilepsy are illustrated in the diagram (Fig. 1).

The list is not exhaustive.

May I illustrate with a single example?

Graham is a little boy who came to us first when he was six months old. He had a single generalized tonic-clonic grand mal seizure whilst suffering a feverish bronchitis: a simple febrile convulsion. His father had had petit mal epilepsy from early childhood.

At this point we had, therefore, to consider fever; age; sex; and a possible genetic factor.

Three months later the boy returned and was admitted to hospital. He had status epilepticus limited mainly to the left side of his body. This attack seems to have been due to thrombosis in his right middle cerebral artery: an acute mechanical insult.

The child was left with a shrunken right hemisphere, a left hemiplegia and some mental retardation associated with aggressive behaviour.

When he was four he began to have frequent minor focal epileptic fits at the rate of five or six a day. His fits and his mental disorder caused a severe and chronic emotional disharmony between the parents. The disharmony itself appeared to increase the child's symptoms—for both the fits and the aggressive outbursts lessened when he stayed with more tranquil relatives; only to relapse when he returned home.

We had now therefore to add in a chronic anatomical lesion, the shrunken hemisphere, which contained an active epileptogenic focus; an emotional and environmental factor, and the factor of retarded mental development; remembering still the influences of sex, age, and genetic endowment. Other factors were soon added, he began to have fits when asleep, a physiological trigger, and, of course, he was given various drugs.

Clearly no one factor could be regarded rationally as the sole cause of his symptoms.

This is perhaps an extreme case but it is generally true of all convulsive disorders that ætiology is multiple. The ictus epilepticus is the resultant of many variables. The seizure-discharge is the final common path, if I may use that analogy, of interacting factors which vary widely from child to

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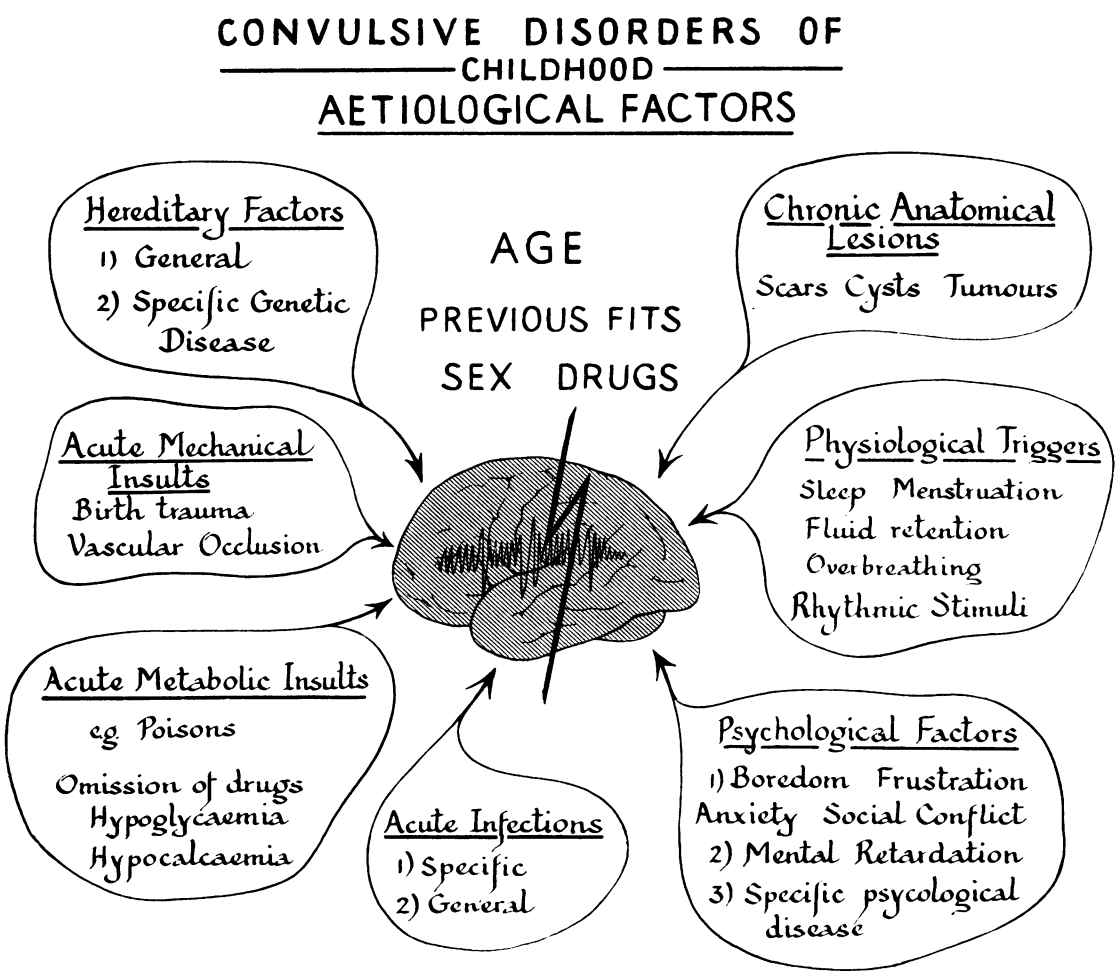

FIG. 1

child; and vary in any child, from time to time.

The Semantic Confusions

Any discussion of epilepsy is confused from the start by the imprecision of terminology, and by the semantic difficulties involved. The terms "epilepsy", and "epileptic fit", although we all know roughly what they mean, have no agreed limits. More serious, perhaps, are the difficulties of classification. At one time convulsive disorders were divided into three groups, namely infantile convulsions, symptomatic epilepsy and idiopathic epilepsy. These terms have now become so loose in their application that their meaning and utility is lost.

Again, all forms of minor epileptic fit were once called "petit mal". These seizures proved heterogeneous and they are now divided into at least six distinct subgroups: only one of which retains the title of "petit mal". This term is now restricted to brief lapses of attentive behaviour associated with the famous 3 c/s generalized, wave-and-spike (the dart and dome) discharge in the electroencephalogram; but it seems probable that this pure petit mal requires still further division by the criteria of different responses to certain drugs, and by variations in the details of the E.E.G. pattern.

The Results of Genetic Surveys

Many genetic and social studies of epilepsy

have been made. If restricted to chronic epilepsy, and confined to adults, they generally agree in giving an *equal* risk of epilepsy to the parents, siblings and children of epileptics; and in giving a risk-value of 2, 3, or 4 per cent to these relatives (Alström 1950; Harvald 1954).

Surveys of this type ignore the richness and variety of man's epileptic experience; and in practice it is found these results cannot safely be used for eugenic or clinical purposes.

Studies made on selected samples give conflicting results.

The influence of heredity is reckoned high by those who study children (Bridge 1949); low by those who study adults (Alström 1950); high by those who use twin material (Lennox 1947: Conrad 1935); low by those attempting general geographical ascertainments (Alström); high by those who use E.E.G. evidence (Lennox, Gibbs & Gibbs) —lower by those relying on clinical evidence.

Conflicting results of this type, together with the great variety in ætiology and manifestation, have persuaded some authorities in America and Scandinavia to abandon genetic analysis as meaningless. But, as Dr. Slater pointed out and demonstrated, the main virtue of genetic analysis is precisely that it clarifies diagnosis and, by establishing distinct diseases, resolves just such confusions as we have here to face. Nor can one, in practice, escape from the genetic issue. One-third of all parents of epileptic children ask me genetic questions: many others centre their anxious ruminations on the genetic theme.

There are strong cultural traditions about eugenics in epilepsy dating from pre-Christian times, and still powerfully linked with the numinous awe which epilepsy evokes. In at least three countries eugenic practice is backed by legal sanctions.

Possible Modes of Genetic Influence on Epilepsy

There are five ways, I think, in which genetic endowment may contribute to convulsive disease.

First, it is plain that, given adequate provocation, all our brains are capable of generating a grand mal seizure. Electroshock treatment produces attacks not, in themselves, different from the spontaneous seizures of epileptics. As Lennox put it "Man is built to convulse". The inherent seizure-mechanism is almost certainly present in all mammals. It is doubtless of genetic determination.

There are some who hold that no other genetic factor is involved: that the varieties of epilepsy are wholly determined by the site and extent of *acquired* cerebral damage and that this damage alone divides epileptics from their fellows. This view is certainly not wholly true. There are a group of rare diseases in which simple single-gene determination is unequivocal, and in which epileptic seizures commonly occur. Phenylketonuria and epiloia are examples. In these diseases the fits are a secondary manifestation of a specific biochemical or anatomical perversion. Diseases of this type segregate. Their distinctive lesions are qualitative. They may be subjected to analysis in terms of mendelian ratios.

An alternative mode of indirect genetic influence is through a defect in a quantitative character of polygenic origin. There is rather a strong suggestion that low intelligence, in general, predisposes to seizures of all types. Here we deal with an essentially non-segregating quantitative variable, polygenetic in origin in the main, and biometrical analysis is the appropriate method of study.

If there are genotypes which predispose directly to epilepsy, they may also be of two main types.

There may be simple single-gene epilepsies, segregating by some distinctive clinical or E.E.G. features (so that factor analysis reveals their characters), breeding-true, and potentially subject to analysis in terms of mendelian ratios.

On the other hand there is the concept of a genetically determined, quantitative seizure-threshold; varying from person to person; potentiating all types of seizure. The concept, in fact, that all men are epileptic but some are more epileptic than others.

There are then these five possibilities. There is an implicit assumption in much

work in this field that only one or two of the possibilities can be true. There is, however, no *a priori* reason why all five modes should not operate. They might even all be at work in a single patient.

The Nature of the Present Series

When we set out six years ago with the aim of studying the natural history of convulsive disease in children we were a good deal baffled, by the many confusions of terminology, by the conflicting results of other workers and by the contrast between the complexity of the problem and our ignorance. So we made no attempt whatever to select our cases in any way, nor to place our patients in distinctive diagnostic categories. We have admitted to study all children who had any sort of fit: those with febrile convulsions and those with epilepsy: those whose fits arose from the gross insults of meningitis or camphor poisoning, and those whose fits were wholly cryptogenic.

The sample now analysed is a consecutive series of such children: all have been studied personally: none was discharged, but 1½ per cent have been lost to observation. The children were studied through the pædiatric departments in three hospitals in our region. (We have, of course, made attempts to get total ascertainment of all cases in specified areas and in control series in order to get an idea of general incidences. But children discovered in this way cannot be subject to the same sustained observation over the years as can those who come to hospital.)

There are approximately 1,000 affected children in this sample from 800 families. More than 80 per cent of the children were admitted to hospital at the time of their first fit or were seen in out-patients within a month of their first fit. The children, and their brothers and sisters and families were then followed up, and studied through the years.

We have, of course, principally been interested in the control and cure of the fits, and in the prophylaxis of established epilepsy. But one cannot study one aspect in isolation and we have tried to record data about the physical, mental and social maturation of these children; for example, the curiously various development of dominant laterality; the emergence and resolution of speech disorders; the unfolding of intelligence and personality; the serial changes in the E.E.G. records.

Genetic questioning can be made reasonably thorough in these families, since one is enabled to pursue inquiries through the grandmothers and one can repeat inquiries at each visit.

Methods of Analysis

No standard agreed method for analysing our particular study is available in the literature.

Most of the standard work on children with epilepsy comes from Johns Hopkins Hospital (Bridge 1949). Here they used a rather individual method of assessing the weight of the genetic factor. An affected child was awarded a score of 1, 2, 3, or 4, depending on how many epileptic relatives he had, and how close in kinship the affected members were to him. An epileptic parent or sibling gave a score of 2; other relatives a score of 1. The total score expressed the weight given to genetic endowment in the propositus (Bridge 1949). It is, perhaps, a rather unusual method, and one which does not seem greatly to attract those of stricter genetic schools.

The results, however, were of interest. Forty per cent of epileptic children had at least one affected relative; 10 per cent scored 4+, the maximum permitted. These are substantially higher figures than those obtainable from any sample of *adult* epileptics. Furthermore the Johns Hopkins workers showed that children with positive family histories of epilepsy had a *better* prognosis than those with a negative history.

In our analysis we have used the standard and generally accepted genetic techniques for computing the risks to kindred of various degrees. But we now divide all those affected, initially, by nine diagnostic labels, which crudely designate the setting and outcome of their diseases.

These groups are, briefly:

(1) Simple remittent febrile convulsions (CvR).
(2) Febrile convulsions which continue until death (CvC).
(3) Febrile convulsions associated with infection of the brain ("B").
(4) Epilepsies which remit (ER).
(5) Epilepsies which resist treatment and persist (EC).
(6) Febrile convulsions which are followed by an epilepsy which then remits (CvER).
(7) Febrile convulsions which are followed by an epilepsy which resists treatment and persists (CvEC).
(8) and (9) Other convulsive diseases—which continue and remit respectively. This is a rag-bag containing camphor convulsions; vitamin deficiencies; anæsthetic seizures and the like (OR:OC).

Remission means freedom from fits for more than half a year at the time of analysis. I think that the nature of these different groups is best explained by dealing with each group in turn. It is relevant at this point to notice that these subgroupings are not based on any presumptions about ætiology nor upon criteria derived from the epiphenomena recorded by electroencephalography. One finds in almost all work on epilepsy that division into special categories is made on *ætiological* assumptions. This leads inevitably to a *petitio principii* as the genetic analysis precedes.

I have taken the risks to siblings as the most reliable measure, and have computed the risks severally for each diagnostic type within each subgroup.

Corrections for age are made from age-of-onset curves obtained from the whole material. Corrections for ascertainment in these particular histograms is based on ascertainment by family.

The Sibling-risk Patterns

(A) *Simple febrile convulsions.*

The histogram for simple remittent febrile convulsions is shown in Fig. 2. These are the commonest of all the seizures of childhood, and they have many names: benign convulsions, infantile convulsions, teething convulsions, and so on.

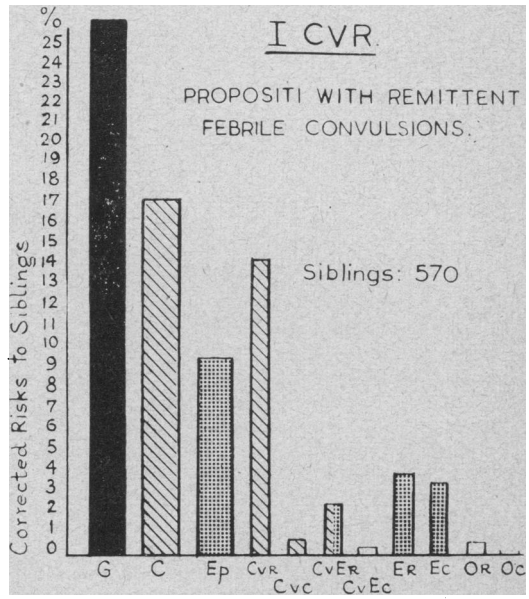

FIG. 2

The pattern of risks for the brothers and sisters* of these children is as follows (Fig. 2):

			%
1.	(*a*)	For any convulsive disorder	25
	(*b*)	For any sort of febrile convulsion ...	17·3
	(*c*)	For any sort of epilepsy	9·7
2.	(*a*)	For simple remittent febrile convulsions	14·5
	(*b*)	For febrile convulsions continuing to death	0·7
	(*c*)	For febrile convulsions which are followed by an epilepsy which then remits	2
	(*d*)	For febrile convulsion, followed by a continuing, resistant, epilepsy ...	0·2
	(*e*)	For remittent epilepsy, ... nearly	4
	(*f*)	For continuing persistent epilepsy ...	3·5
	(*g*)	and (*h*) For the other two types, less than	·5

(B) *Febrile convulsions evoked by infection of the brain.*

Next we may consider the pattern of risks to siblings when the seizures of the propositi were evoked by infection of the brain; by meningitis or encephalitis (Fig. 3).

* In the following Figures the numbers of siblings quoted are the reduced number after age correction to the nearest whole number.

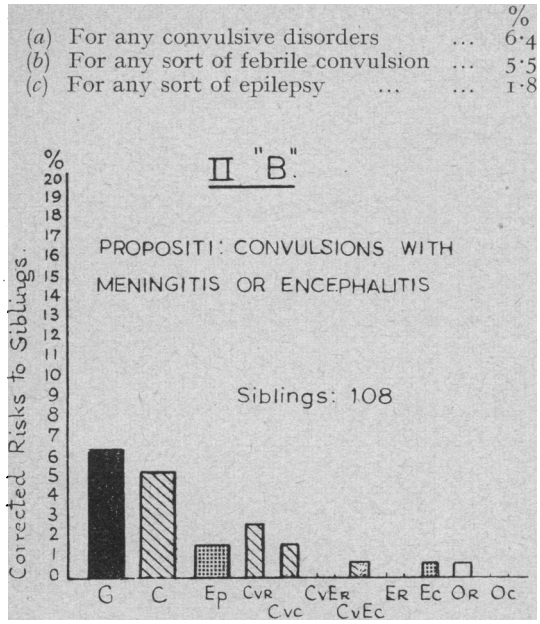

FIG. 3

These are low risk figures for all the sub-groupings; these risks are barely if at all in excess of the general risks. This, of course, is as one would expect.

(C) *Convulsions evoked by other insults.*

The risks to brothers and sisters in the group in which the seizures of the propositi were evoked by camphor poisoning, forced-hydration and so on, are shown in Fig. 4. Again these are like those found in the meningitis group; giving risks close to the general expectation.

Thus it is clear that, by using the sibling-risk pattern as a measure of the ætiological weight of genetic endowment in the propositi, we have shown that, when febrile convulsions are evoked by slight insults genetic endowment seems to play a major ætiological role; but in the two control-series, in which gross insults evoked the seizures, genetic endowment played a negligible part.

We may now consider the more chronic epilepsies:

No division is made at this stage by the type of seizure—petit mal, grand mal and so on—nor by presumptive ætiology. The

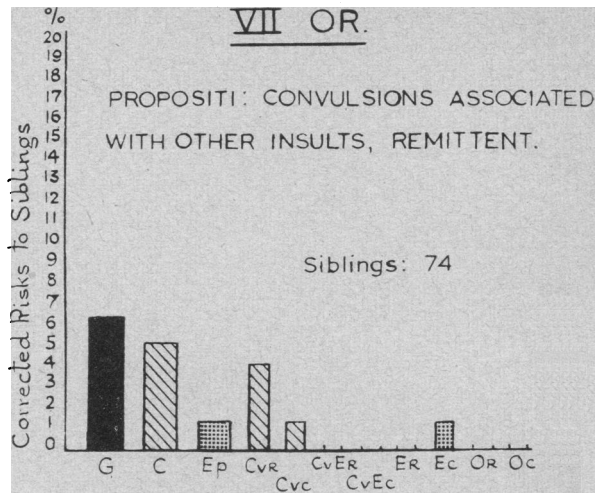

FIG. 4

only division made is whether or not nature, abetted by treatment, has led to a sustained remission of the fits; a quite practical and objective division.

(D) *Remittent epilepsy*

The propositi were children who had simple epilepsies which have gone into a sustained

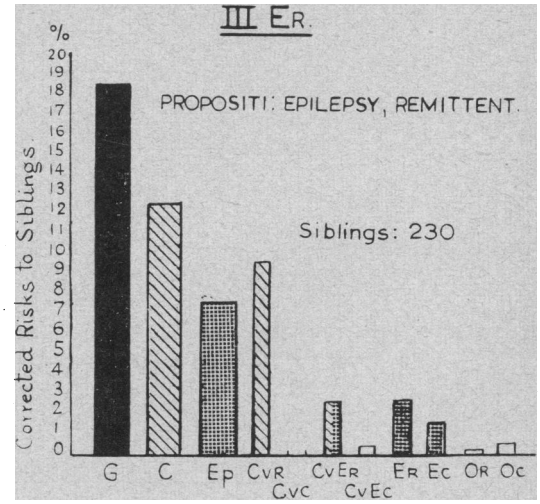

FIG. 5

remission. The risk-pattern for their brothers and sisters is shown in Fig. 5. The main features of the risk-pattern are these:

		%
(*a*)	For any convulsive disorder	17·3
(*b*)	For any sort of epilepsy	7·5
(*c*)	For simple remittent febrile convulsions	9·5
(*d*)	For simple remittent epilepsy (the disease of the propositi)	2·5
(*e*)	For febrile convulsions which proceed to epilepsy, which finally remits ...	2·75

The risks for those epilepsies which resist treatment are rather low.

(E) *Continuing epilepsy.*

We may next compare and contrast the sibling-risk pattern for propositi whose epilepsies have proved resistant to treatment (Fig. 6). The main feature of the pattern of

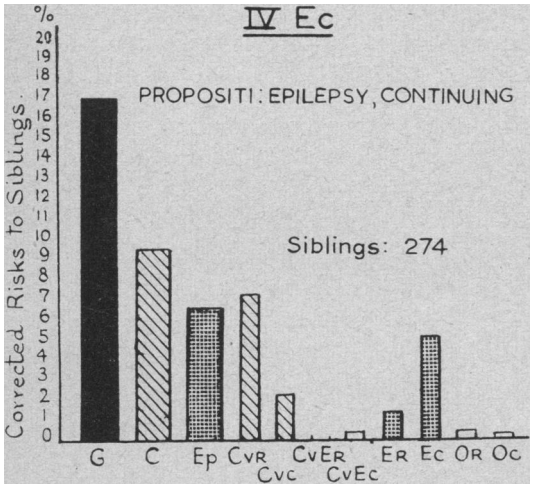

FIG. 6

risks here is the overall similarity to the pattern obtained for the remittent epilepsy group. Again the risk for any sort of convulsive disorder is about 17 per cent; again the benign febrile convulsions (10 per cent) overtop all the epilepsies combined (7 per cent).

In the detailed part of the histogram there are differences. I would just mention one. Most of the epileptic siblings in this group had severe resistant epilepsies: whereas most of the *epileptic* siblings in the previous group had benign remittent epilepsies. There seems at once to be no strict segregation but some " breeding-true " with regard to outcome.

(F) *Febrile convulsions followed by remittent epilepsy.*

Next we have the group in which the propositus had, first, febrile convulsions, then epilepsy and finally went into remission.

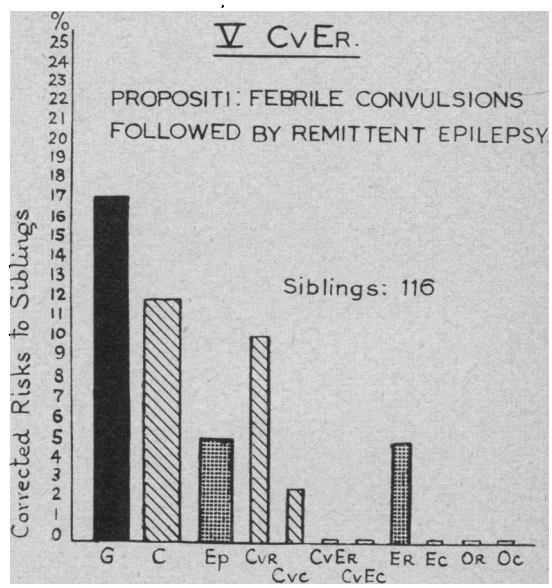

FIG. 7

As might be expected the pattern of the sibling-risks (Fig. 7) lies between that for simple febrile convulsions and that for remittent epilepsy. In fact, in the detailed part of the histogram, these are the only two diseases for which there appears to be any substantial risk: 10½ per cent for benign remittent convulsions; 5½ per cent for remittent epilepsy. The propositi had both convulsions and epilepsy, but these diseases divided in their siblings. This group, in fact, doesn't " breed true ".

(G) *Febrile convulsions followed by continuing epilepsy.*

The group of febrile convulsions proceeding to continuing epilepsy did not seem to present any special features and I had confidently expected that the histogram here would, by analogy with the last one, give a pattern lying between that for simple convulsions and that for continuing resistant epilepsy. The sibling-risk pattern (Fig. 8)

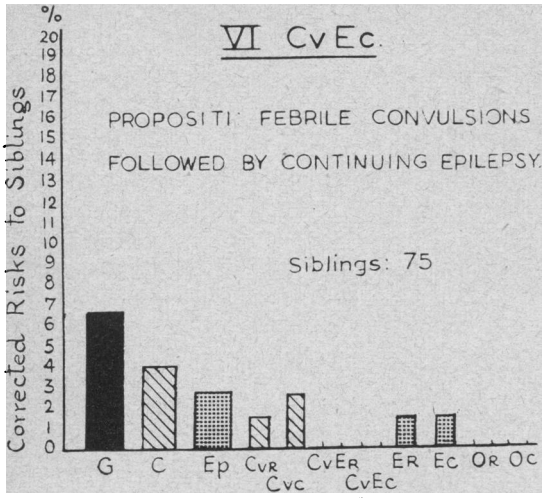

FIG. 8

shows that this assumption was false. The pattern is quite distinctive. It is unlike any for simple convulsions or the epilepsies, but it does not differ much from the pattern obtained for the meningitis group. Indeed I think that this is quite strong evidence that these children were in fact having some acute cerebral damage, an encephalitis it may be, or a cerebral vascular accident at the time of their initial convulsion, and that it was this damage that determined both the initial febrile convulsion and the subsequent seizures, rather than any special genetic endowment. Perhaps these figures serve to show how genetic analysis helps one to pick a way through this complex subject.

(H) *Febrile convulsions continuing to death.*

We now turn to a small but interesting group of children who had febrile convulsions which continued until death or shortly before it.

They are, typically, children aged less than four months who develop a respiratory infection, have fits and die. Nothing very much is found by post-mortem examination.

These children are a rather special group from our *local* point of view, because we go to great pains to prevent, and control, febrile convulsions in small sick children. For example, all small children admitted to our wards with severe feverish illnesses are given prophylactic anti-convulsants on admission, whether they have had a fit or not, and all emergent seizures are treated vigorously at their inception with anti-convulsants by intramuscular injection.

This group are, then, our failures in spite of these measures.

I had regarded them as being children who, by reason of the frailty of their natures, and the severity of their infections, were dying a toxæmic death with the convulsions as merely agonal symptoms. Again the genetic analysis suggests this opinion was ill-grounded.

The sibling-risk pattern is shown in Fig. 9. The overall risks are higher than in any other subgroup: nearly 30 per cent. The risk pattern is distinctive. The risk for epilepsy is substantially higher than the risk for febrile convulsions, and the epilepsies encountered were in the main resistant to treatment: the risk for this severe form of epilepsy is 10 per cent.

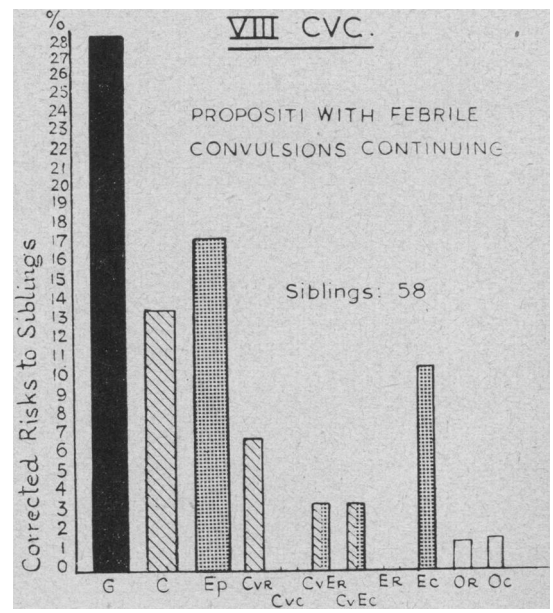

FIG. 9

Thus it seems plausible to suppose that this sort of mortal convulsive disease had in fact a powerful genetic determination. Perhaps we should regard these deaths as the genetic wastage of the severe epilepsies.

1. *Temporal lobe epilepsy.*

In many epileptics there is conclusive evidence that the fits derive from small focal areas of cerebral damage. One cannot, however, assume their epilepsy owes nothing to genetic endowment, although in practice this assumption is rather frequently made.

Temporal lobe epilepsy, the most fashionable of epilepsies just now, is of particular social importance because there is a rather complex association between temporal lobe lesions and certain types of aggressive and psychotic behaviour.

From the present sample I have selected fifty-eight children who had frequent minor lobe seizures and who showed a focal spike discharge in one or other temporal lobe. There were also, of course, many children with other sorts of epilepsy who had temporal lobe discharges in the E.E.G.: but these are, here, excluded, as are also, children whose seizures were, clinically, temporal lobe attacks but whose E.E.G.s are too immature to show the characteristic local discharge.

This group, then, is small but strict.

In no case did we find a relative with temporal lobe epilepsy by the same criteria. But the histogram of sibling-risks shows a pattern

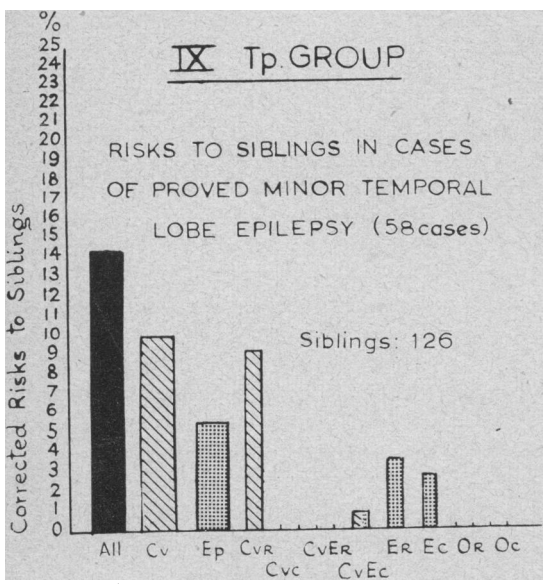

FIG. 10

very like that for other forms of epilepsy (Fig. 10). There is some evidence that genetic endowment plays a part here.

The risk of any convulsive disorder in siblings is 15 per cent, the risk of epilepsy 6½ per cent.

This result has, of course, no direct bearing on the value of surgery for this disease. It is simply a reminder that one cannot get away from multiple ætiology.

TWIN STUDIES

Introduction

Twin studies are of particular interest in epilepsy because much of the most-quoted evidence in favour of genetic determination derives from twin-studies made severally by Conrad (1937), by Rosanoff (1934), and in the E.E.G. field by Lennox (1947) and the Gibbses (1940).

The larger studies agree in showing:

(i) There is a high concordance between monozygous twins—both twins being affected in more than two-thirds of all pairs.

(ii) The concordance of dizygous pairs, although much lower, is in excess of that predicted from the risks to siblings.

This second observation has led to the theory that there is some relationship between twinning and epilepsy. There are in fact two such theories: one proposes that the association is genetic, and the other, more plausibly, suggests that twinning predisposes to epilepsy because twin-birth involves a greater risk of cerebral birth-injury.

Twins in the Present Sample

(A) *The association between twin-birth and epilepsy.*

Among all the children in this sample there were twenty-six pairs of twins. Of these pairs, twenty contained one or more affected child. In six pairs neither partner was affected. Nineteen pairs were proved dizygous; five pairs were proved monozygous; two pairs were doubtful—probably one was dizygous and the other monozygous.

Thus the incidence of the twin-born index cases was just under 3 per cent; among all children, 2 per cent; among all affected 2.4 per cent. These figures do not differ significantly from the incidence of twin-born children in the general population in our region. Our results, therefore, in no way support either theory associating twinning with convulsive disease.

In fact the distribution of diagnostic labels among the affected twin-born in the sample tended to favour the febrile convulsion group as compared with the epilepsies.

(B) *Concordance between dizygous and monozygous twins.*

After eliminating all pairs ascertained through a child whose fits were determined by cerebral infection, and after rejecting those pairs in which the unaffected member died without known fits in early life, twelve dizygous and three monozygous pairs are left. It is, of course, a small group but can be used as a check on the validity of the sibling-risk patterns which I have just described.

There were two pairs wholly concordant for diagnosis, mental development, and nature of seizure—and closely concordant for number of fits, age of onset and age at final fit. Both these pairs were dizygous and oppositely sexed. The diagnosis was simple remittent febrile convulsions in each case.

(C) *Dizygous twins*

Of the twelve children in the six partially or wholly concordant dizygous pairs, eleven had a febrile convulsion as their first fit. Two of these children had those convulsions which continued to death. Our computations of the sibling-risks in these groups gave a higher overall risk to siblings than in any other group, slightly greater than one quarter in all. Moreover febrile convulsions are restricted to a narrow age-range and these seizures require a specific environmental factor, namely an acute infection. Dizygous twins share a common environment at the same age. In siblings the interplay of environment, age and genetic endowment occurs in series; twins, however, are exposed in parallel. This crude 50 per cent concordance of dizygous twins serves rather to support the computations of sibling-risk that have been given.

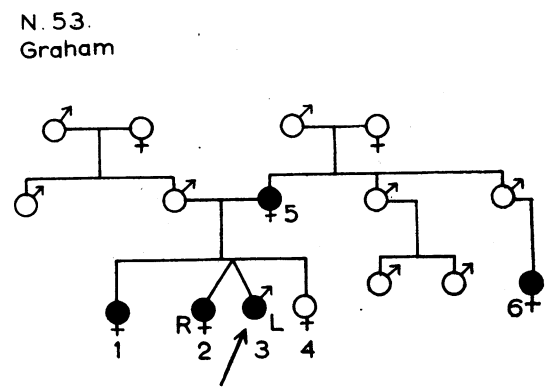

FIG. 11

The pedigree of a partially concordant dizygous pair is shown in Fig. 11. Very briefly all affected members, there are five of them, have had a similar sort of epilepsy. All have had grand mal fits, of frequent occurrence, beginning in the first or second year of life and remitting completely within two years of onset. All five patients had their fits, in the main, between 2—5 a.m. when they were asleep. The variations of interest are these: the first seizure of the twin girl (number 2) was evoked by an acute tonsillitis; it was in fact a febrile convulsion. The boy (number 3) alone in his family had a bout of status epilepticus, he, moreover, is mentally abnormal: he is grossly overactive and aggressive. He has some mild intellectual retardation together with a specific speech defect. He is left-handed although all his relatives are dextrous. He belongs to the group of hyperkinetic epileptics which I will mention later.

It is tempting to regard this pedigree as showing the simple autosomal dominant transmission of a pure remittent epilepsy of rather high penetrance.

There were another pair of oppositely-sexed twins discovered among the siblings who were concordant for febrile convulsions in childhood, but later diverged. The girl had no more fits, but the boy had a remittent

epilepsy and developed aggressive outbursts which have now brought him into the hands of the police.

(D) *Monozygous pairs.*

There were three monozygous pairs in the residual group of twins. One pair was partially concordant, two pairs were wholly discordant.

(*a*) A pair of girls of proven monozygousity have been observed for seven years. The unaffected twin is in all respects normal. The affected twin had a febrile convulsion as her initial seizure and then developed an intractable epilepsy which has proved wholly resistant to treatment. She therefore belongs to that group in which our sibling-risk test (Fig. 8) suggested that genetic endowment plays a negligible role: the convulsions plus resistant epilepsy group. She is mildly psychotic. There is good E.E.G. evidence of focal brain damage.

(*b*) The other discordant monozygous pair are boys. Their family tree is shown in Fig. 12. The points of interest here are that the

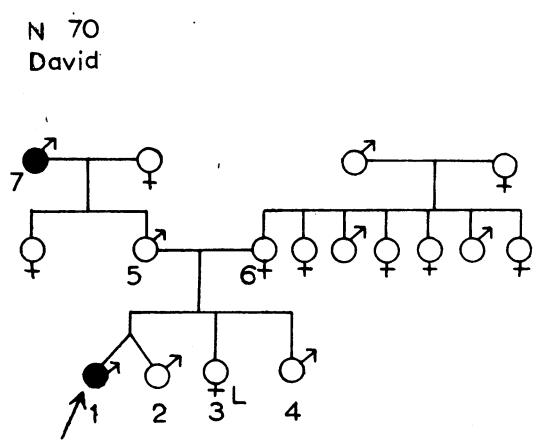

FIG. 12

affected child has had two bouts of severe focal grand mal seizure with fever. He is mentally normal. His paternal grandfather has had grand mal epilepsy virtually all his life—he is 69 and still having fits.

E.E.G. studies have been made on both twins. Both records are alike: both are quite normal. The parents' E.E.G.s are both normal in every way.

(*c*) The partially concordant pair were girls. They were last born in a sibship of eleven. None of their relatives had had any form of convulsive disorder. These twins were alike in personality; intelligence and appearance. One twin (Elsie) is left-handed, the other (Amy) is right-handed.

The twins had their first convulsions together on the third day of mumps just before their fourth birthday. They had convulsions together in the prodromal phase of measles, six months later and again with whooping cough in the same year. Amy had no more fits. Elsie developed a mild epilepsy of grand mal seizures, which occurred just after she roused up in the morning. The attacks were soon controlled and she went into full remission three and a half years ago. She has been off all drugs for a year.

E.E.G.s made shortly after Elsie's last fit gave identical records for both twins. The similarities covered both the normal features and the abnormal feature of paroxysmal, generalized slow-wave outbursts. Whilst both twins have remained in remission we have repeated their E.E.G.s. Amy's record has been maturing well; Elsie's, also maturing, is now, however, discordant and shows a focal spike discharge in her left temporal leads.

Here then there was, first a concordance for febrile convulsions, then a divergence for epilepsy, but a concordance for E.E.G. findings; finally, after a long period of remission and maturation, a divergence in the E.E.G. traces.

The findings here seem to fit quite well for the histogram of sibling-risks for the group to which Elsie belongs, the convulsions plus remittent epilepsy group (Fig. 7) for here we found that there was no breeding-true in siblings. The siblings in this group often had febrile convulsions and often remittent epilepsy, but the double-diagnosis was absent.

This twin material is small indeed but for what it is worth, it does not seem, notably, to conflict with the evidence from the sibling-risk estimates at any point.

Maturity and the Genetic Factor

Those cerebral systems which generate seizures in children are not absolute systems, except at the time of the ictus epilepticus itself.

The stability, or the instability, of the seizure mechanism is affected by many parameters, by variables, that is to say, not themselves inherent in the seizure mechanism.

Paramount among these controlling parameters is the general maturity of the child. Most of the convulsive disorders of childhood die out with advance of maturity. Children, in a word, tend to grow out of their fits. This is evidently true of febrile convulsions. It is also true of epilepsies which spring from gross anatomical cerebral damage.

Salaam epilepsy, the so-called akinetic seizure, is the characteristic epilepsy of young children with gross cerebral damage and mental defect. These attacks die out and disappear before the fourth birthday in the majority of those affected. The anatomical lesions remain; the mental defect remains; the characteristic E.E.G. pattern lingers on, but the fits themselves are inhibited by quite a slight advance in maturity.

Among the more harmful of the assumptions about the genetics of epilepsy is the concept that, if an epilepsy is genetically determined, then the disease must endure throughout life and is not susceptible of cure. (I suppose we all meet this idea in whatever field we work.) In the case of the childhood epilepsies there are sound *a priori* reasons for a contrary assumption. Namely, that a common, non-mortal, genetically-determined disease of early onset is likely to be reduced in severity, before reproductive age, by the action of modifying genes. It is, in fact, true that the majority of the convulsive disorders of childhood remit before the fifteenth birthday.

We must now consider the relationship between immaturity and the direct genetic element in seizures.

The threshold for seizures is low in the first four years of life in all children whatever their genetic endowment (Ounsted 1951). For example, in a personal consecutive series of 150 children with purulent meningitis, which I take as the maximum stress, the incidence of convulsions was 8 per cent in those aged more than four; 45 per cent in those aged less than four years.

The Sibling-risk patterns related to the age of onset in propositi.

After eliminating from the present series all those whose seizures were related to cerebral infection: and after setting aside those children whose first fit occurred after the eighth year, I have arrayed all remaining children in three groups, depending on the age at which they had their first fit. Ætiology and diagnostic labels are, in these propositi, ignored. Age at first fit is the sole criterion. The age-groups are:

(i) The first year.
(ii) The period from 1—3½.
(iii) The period from 3½ to 8.

Next the sibling-risks patterns were computed for each group and now, for each diagnostic category: using the same standard corrections as before and arriving at three of the sibling-risk patterns. Fig. 13 shows the results.

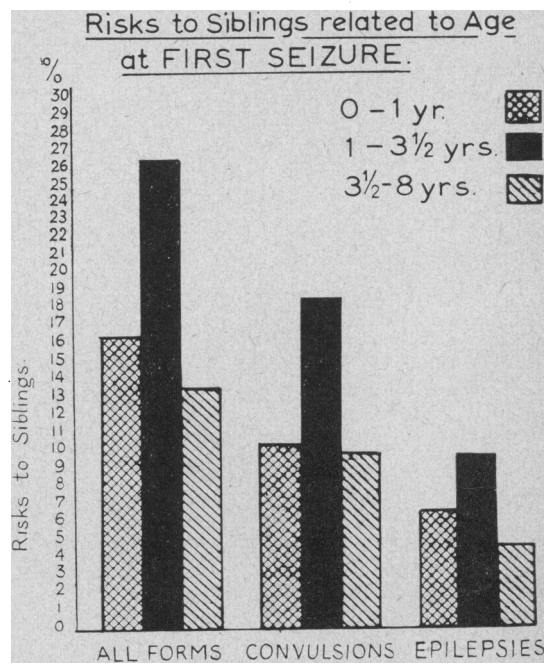

FIG. 13A

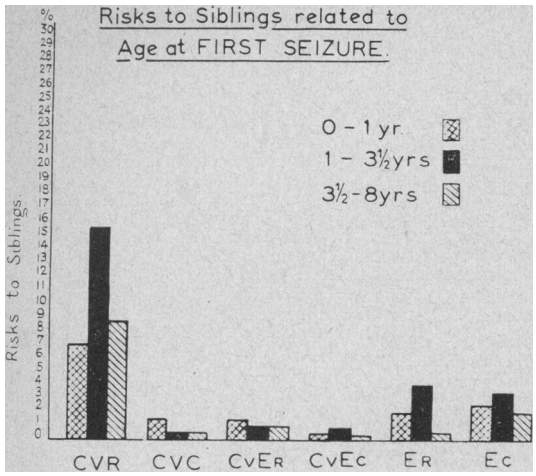

FIG. 13B

The striking feature is that the risks to siblings of children whose first seizure was in the middle-age period (1—3½) are substantially higher than the risks when the first seizure of the propositus occurred either within the first year of life, or when it occurred after the age of 3½. This dominance of the middle-aged group is evident throughout the histogram and holds both for the epilepsies and for the evoked convulsions.

The differences are most unlikely to be due to chance. If we take the sibling-risk patterns to be a measure of the ætiological weight of genetic endowment in the propositus, then it follows that seizures in this crucial age period seem to have a powerful genetic determination and that this genetic determination is to convulsive disorders of all types rather than to some specific epilepsy.

Theoretical implications

The simplest interpretation of these results is that a general, main or non-specific convulsive genotype exists and that the phenotypic expression of this genotype is rather strictly conditional on a specific degree of immaturity. It is indeed a rather useful hypothesis that this genotype itself operates by producing an imbalance, either local or general, in the rate of maturation of the various cerebral systems involved. An imbalance whose expression in seizure is soon overcome by the natural advance of maturity, leaving perhaps a detectable trace in the E.E.G. patterns.

By implication a theory of this kind involves the concept of a quantitative seizure-threshold. But this does not necessarily imply that the main, common, specific convulsive genotype must be polygenetic. On the contrary, a single-gene pair is all that is required; for the phenotypic expression of such a gene will be progressively and quantitatively modified by the operation of those genes which control the natural progress of maturation.

This hypothesis is far from being established, but it is a useful mental tool. It serves to reconcile the conflicting results of other workers, suggesting why genetic factors are prominent in children but much less obvious in adults; it reconciles the discrepancies between the E.E.G. and clinical findings; it offers some sort of coherence to the facts I have put before you tonight. The theory can be subject to critical test by long-term clinical and E.E.G. studies in the maturation of whole sibships.

This, then, perhaps we may find. We may also find specific epilepsies of simple genetic origin with clear-cut E.E.G. and clinical features. I think two or three may already be discernible in the murk. A light-sensitive form of pure petit mal: and, perhaps, a form of grand mal remittent epilepsy.

I should have liked to give some further results. In particular to have discussed the risks to relatives of other degrees, the evidence on modes of transmission, the rather curious finding that aggressive psychopathy was suspiciously common among the fathers of children with severe epilepsy, and so on; but time is running on, so may I now turn very briefly to mention certain social aspects of the problem?

Social Problems

Every epileptic child presents a social problem, for a whole family is involved when a child has fits. The parents have been frightened by the somewhat dramatic nature of the attacks; they fear that their other children may develop the disease; they are

concerned about the future mental development of the affected child. The first point that we have to clarify for them and for the officers involved is that "epilepsy", quite clearly, does not designate a socially homogeneous group. On the contrary, the group of epileptic people covers the whole range of human disabilities and abilities. The fits themselves may be merely a few mild seizures in the privacy of bed: or may be many seizures occurring in public. The children may be physically normal, or they may have some mild or severe neurological lesions. They may be aments, or they may be geniuses—it is traditional to mention Dostoyevsky; perhaps patients are more encouraged by the examples of Julius Caesar and the Pharoah Aknaton, now that these epileptic worthies have become immortal in technicolour.

There used to be an idea that epileptics had a particular sort of personality, but I do not think that this view is now very widely held. In fact one does seem to find certain sorts of personality going with certain types of epilepsy. Dr. Pond, I think, gave a very clear description of the shy turned-in nature of children with petit mal; by contrast there is brash assertive personality of some brain-injured epileptics; or the bland amorality of the psychopath.

Epileptics with normal mentality

In the present sample some three-quarters of the children showed no physical or gross mental abnormalities. Many of these children had had fits at school and had been notified as epileptics, so that the question of special schooling had been raised. Happily the School Medical Service and our clinics for these children have worked in close collaboration, and in no case has it proved necessary to commit a mentally normal epileptic to institutional care. Among mentally normal epileptics there has been no case in our experience in which the fits themselves proved a permanent bar to normal schooling. There *have* been a substantial number who have been excluded from school for a time because of frequent fits, but fortunately we have been able to get sufficient control of the fits in all these children to return them to school within less than six months in every case. For mentally normal epileptics: normal life is the rule.

Epileptics with simple mental retardation

Many epileptics are also mentally abnormal. Simple mental retardation is the commonest deviation found. Here again it seems to us that any form of special isolation is unnecessary and uneconomic. These children do well if they are treated simply in accordance with their I.Q. and the fits are ignored from the point of view of disposal.

Permanent segregation of epileptics with mild mental retardation and poor social backgrounds is, in practice, what happens in some (though by no means all) epileptic colonies. This practice seems to have rather little to recommend it. Inasmuch as these people are retained in segregation until reproductive age the practice is dysgenic, since assortative mating between persons each with two inheritable conditions is encouraged.

Neurotic reactions in epileptic children

Neurotic symptoms are not rare in epileptic children and in their parents: and are to be anticipated when any social rejection occurs. Usually the symptoms are quite superficial. They stem from the ancient myths which still control so much thinking (both lay and medical) about epilepsy.

A simple mechanical explanation of the nature of the seizures goes far in relieving these undesirable reactions.

Fear of an intractable life-long illness is another potent source of neuroticism in these families. This fear, as you will know, is not often founded in fact, but it is, alas, often still encouraged by medical opinion. Adequate management, therefore, involves, whenever possible, the firm assertion that full cure is possible and probable. Too much scientific caution has unhappy consequences.

Psychotic Epileptic Children

There are a group of epileptic children who present an unsolved social problem. These are they who have violent aggressions or an intense sustained overactivity.

From all the children in my series who have had severe mental disturbances I have selected seventy in whom sustained hyperkinesia (overactivity) was the prominent disability. These children showed also the symptoms of distractibility, perseveration, euphoria and aggressiveness which are commonly found in brain-injured children. A detailed clinical account of this group will shortly be published (Ounsted 1955). I wish here just briefly to mention the genetic and social problems presented by these children.

The pattern of sibling-risks for this group is shown in Fig. 14. The pattern of risk is

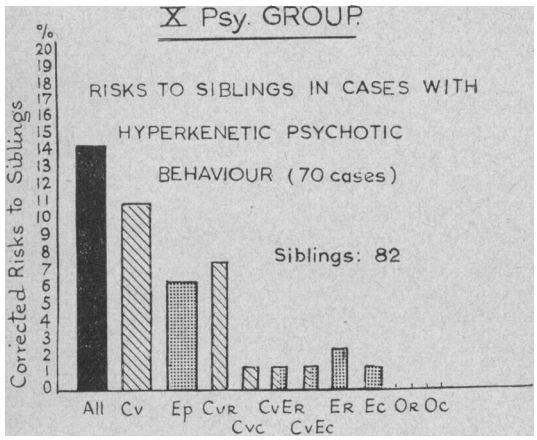

FIG. 14

clearly closely similar to that for the remittent epilepsies (Fig. 5). The pedigree shown in Fig. 11. illustrates that this disorder may occur in only one member of a family although many kinsmen have similar epilepsies. In fact in no case did we find two members of the same family afflicted with this type of mental disorder. It seems, therefore, to be unlikely that eugenic measures will reduce this, the most socially undesirable, group of epileptic children.

Nevertheless the majority of the parents of these children restricted their families when a child developed this psychotic reaction, and this seems natural—for these children occupy the whole attention of their parents. This fact has undesirable social consequences. The devotion of parents is found to be directly proportional to the degree of dementia. The worse the child, the more devoted are the family.

(" Excessive parental devotion " is not a remark that one can safely inscribe in one's clinical notes, for anxious parents are sharpish and apt to read one's notes upside-down as one writes them. So I have been compelled to invent the grim neologism " hyperpædiophilia " to record this parental attitude.)

Now these overactive psychotics when in the atmosphere of their homes, do badly; and they do well if placed in institutional care; so well, surprisingly enough, that a month or so in hospital often induces a remission which endures for several months, only to relapse again. It would seem desirable, therefore, if places were available, and the parents willing, to give these children the advantage of some institutional care.

But their devoted parents resist all attempts to remove these children—even for a few days—if one does not, early in the evolution of the child's illness gain a rather intimate relationship with them.

Here and indeed throughout the epilepsies we are now just beginning to move into the field of prophylaxis, and it is with this aspect of illness that the *Eugenics Society* is especially concerned.

The rôle of eugenics in the prophylaxis of epilepsy

The rôle of the geneticist and the eugenic counsellor is necessarily large in the epilepsies of childhood. This is evident from the fact that genetic ideas enter in any discussion of these diseases.

What answers can we give?

I think the answers can be generally of a positive and cheerful nature. The general risk that the child of an adult epileptic will himself, when adult, be also an epileptic lies between 2 and 4 per cent: a low risk. To impose a general bar on procreation for epileptics seems, therefore, likely to be dysgenic.

In Sweden the marriage of persons with cryptogenic epilepsy, has been illegal for 197 years, since 1757. The incidence of adult epilepsy in 1949, after nearly 200 years

of this law is the same or slightly higher than the incidence of adult epilepsy found in all Western countries; namely 1 to ½ per cent.

On the other hand it seems likely that we shall soon be able to discern some rare but true-breeding epilepsies, in which abstention from child-bearing might recommend itself to some potential parents. Of greater overall importance, I think, is the possibility that genetic considerations will clarify the position about the main convulsive genotype. When this has been achieved it seems probable that, by ascertaining those families in which fits are likely to occur in early childhood, we may by direct medical prophylaxis tide those children through their early years of risk and so, perhaps, effectively reduce the heavy burden of chronic epilepsy.

Summary

1. Epilepsy and other convulsive disorders present numerically one of the largest problems in pædiatrics, and children with these diseases outnumber the combined total of those with rheumatism, asthma and tuberculosis.

2. The ætiology of convulsive disorders is complex; multiple ætiology is the rule.

3. Diagnostic labels give a false impression of homogeneity. Terminology is imprecise; semantic confusions abound.

4. The conflicting results of various surveys complicate the picture. Extrapolation from selected samples is dangerous.

5. One-third of all parents of affected children ask questions of a genetic nature. Treatment and prognosis are often based on genetic considerations. Genetic investigations cannot, therefore, be avoided. Genetic analysis is a valid tool for clarifying the diagnostic confusions.

6. Five possible modes of inheritance are described.

7. A personal sample of 1,000 affected children is described. The limited scope and biased nature of the work are stressed.

8. Some of the results are given in the form of the risk-patterns for varieties of convulsive disorder among the kindred of affected children. This method attempts to give a qualitative and quantitative measure of the genetic element in the various epilepsies.

9. Febrile convulsions and the epilepsies as a whole do not segregate.

10. Some genetic determination is probably to specific, potentially segregating, epileptic diseases.

11. Some genetic determination probably operates through quantitative variations in the seizure threshold.

12. Most genetic determination is conditional for its expressions upon immaturity.

13. Acquired epileptic foci may require an appropriate genetic background for their expression.

14. A small series of twins are presented. There is no association between twinning and epilepsy.

15. Social studies suggest that the term "Epileptic" does not segregate a socially homogeneous group.

16. With modern treatment epilepsy is no bar to normal school and family life for those who are mentally normal.

17. Many children with epilepsy have mental disorders; those children should be treated socially on their mental grading alone. Administrative segregation in terms of the epilepsy is wasteful and valueless.

18. Simple quantitative mental retardation is the commonest deviation and requires measures appropriate to the I.Q.

19. Neurotic symptoms are not rare but are commonly superficial and may be relieved or prevented.

20. Aggressive and overactive behaviour patterns are common and require special methods of management. The hyperkinetic psychosis in epileptic children is briefly mentioned and the genetic background sketched.

21. Parental guilt-feelings are often centred on a genetic idea. Parental devotion increases with severity of the epilepsy and the degree of dementia. A syndrome of excessive parental devotion—hyperpædiophilia—is described together with its social consequences.

22. The possibilities of the eugenic and medical prophylaxis of chronic epilepsy are discussed in the light of the concept of a main common convulsive genotype, whose phenotypic expression is conditioned by a specific immaturity.

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References

Alström, C. H. (1950). *Acta. Psychiat et Neurol.* Sup. 63. Copenhagen.
Bridge, E. M. (1949), *Epilepsy and other Convulsive Disorders in Children.* McGraw-Hill, London.
Conrad, K. (1937), *Stschr. f. d. ges. Neurol. u. Psychiat.* **153,** 271.
Harvald, B. (1954), *Heredity in Epilepsy.* Munksgaard, Copenhagen.
Lennox, W. G. (1947), *Am. J. Psychiat.*, **103,** 457; (1951), *J. Amer. Med. Ass.*, **146,** 529.
Lennox, W. G., Gibbs, F. A. (1940), *Arch. Neurol. Psychiat.*, **44,** 1,155.
Ounsted, C. (1951), *Lancet*, **1,** 1,245; (1954), *Brit. Med. J.*, **1,** 929.
Rosanoff, A. J., Handy, L. M., Rosanoff, I. A. (1934), *Arch. Neurol. Psychiat.*, **31,** 1,165.
Slater, E. T. O. (1953), *Prospects in Psychiatric Research*, pp. 63-67. Ed. Tanner, J. M., Blackwell, Oxford.