Genetic Aspects of Epilepsy

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SUMMARY

Continental, American and South African studies point to a single gene mechanism in epilepsy, carrying with it the hope of chemical cure. Behavioural features should determine the advisability of marriage, rather than genetic considerations, in view of the low penetrance of the gene.

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My delight in the field of genetics, so far from being an amiable foible, springs from what I call the Paradox of Reversibility. This implies that once the origin of a pathological condition or trait can be traced to a single gene mechanism in the field of biochemical genetics, it is susceptible of reversal by chemical, dietetic or pharmacological means. Phenylketonuria exemplifies the former: the recessive genetic defect results in the absence of the enzyme that metabolises phenylalanine, and the formation of the substances including phenylpyruvic acid whose toxic action issues in mental subnormality may be rectified by feeding the infant a diet from which phenylalanine has been excluded. Schizophrenia and manic-depressive psychosis, also based upon single gene mechanisms, may similarly, in principle, be counteracted by drugs specifically directed against the genetically determined enzyme blocks involved, instead of our present agents which operate more peripherally against disturbed chemistry at the phenotypic level. Our current research endeavours at Sterkfontein Hospital and Tara—the H. Moross Centre aim at tracing back metabolic errors in the phenotype of schizophrenics and manic-depressives to their origin in the enzyme blocks determined by their genetic mechanisms. This holds out hope for simple pharmacological attack as near to the gene level as possible.

In contrast to the unequivocal findings regarding specific monohybrid genetic mechanisms in the major psychoses, schizophrenia and manic-depressive psychosis, extensive work in the sphere of epilepsy has not resulted in the same clear-cut conclusions. In fact, the findings of certain substantial studies are in such striking conflict that we are presented with a serious problem as to how they are to be reconciled.

A second problem confronting us in the light of the discrepant findings referred to is whether, and if so on what rational premise, genetic counselling can be given in this field. And finally there is the problem of considerations arising from the advances of neurosurgery and neuropathology encroaching on the preserves of the group of epilepsies hitherto designated idiopathic and cryptogenic, and the refined subtleties of interpretation that have come with the use of electro-encephalography.

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DEFINITION OF HEREDITY AND EPILEPSY

Some definition of the term epilepsy and the meaningful application of the concept of heredity to it, would seem to be essential.

> 'For the practical purpose of genetic investigation, Jackson's interpretation of epilepsy as the tendency to recurring excessive neuronal discharges within the central nervous system still provides an acceptable working basis. His physiological definition remains useful despite many possible variations which may be found not only in the type and localisation of convulsive discharges, but also in the nature of their precipitating agents (Penfield).'[21]

The current concept of heredity is best defined as the transmission of a person's norm of reaction to certain constellations of his life conditions. Irrespective of the kind of stimulating causes required for the provocation of convulsions, epileptic disease should not be expected to be inherited as such. What is genotypically transmitted will merely express itself in a particular type of predisposition which may lead to an abnormal susceptibility to various forms of stimulation.

From a genetic point of view it is advisable, therefore, to distinguish the innate capacity for reacting convulsively to drastically stimulating agents (such as electroconvulsive therapy) from the inherited ability to develop convulsive disease without unusual stimulation and the inheritance of special genes producing specific cerebral lesions (e.g. epiloia and the Sturge-Weber syndrome) which may be incidentally associated with convulsions.

The hereditary origin of the capacity for having any type of convulsion is demonstrated by the fact that this form of motor reaction is universally provided for in the structural organisation of higher vertebrates, from amphibia to man. In man, moreover, it is a universally given pattern of response, achievable by some only as a reaction to such potent stimulation as electroconvulsive therapy, by others only under the influence of something less potent, such as alcohol, and others—our known clinically active epileptics—under the influence of the stimuli of everyday life. The graded quality of this universally-given mode of response led Kallman and Sander[1] to postulate the polygenic character of the underlying genetic mechanism.

BIOLOGICAL AND GENETIC FINDINGS CONCERNING EPILEPSY IN ANIMALS

Despite the universal existence of the epileptic mechanism in the range of animals already indicated, the relative prominence of the clonic *vis-à-vis* the tonic component increases as one ascends the scale from fish and amphibia to primates and man.

Examples of claims for genetic mechanisms in animal epilepsy are those of Atkeson *et al.*[2] for the operation of a dominant autosomal gene in cattle, and those of Nachtsheim[3] of a specific recessive gene which has an expressivity of at least 70% and is allelic to the pigment-determining factor of the Viennese rabbit.

GENETIC STUDIES OF EPILEPSY IN MAN—CONFLICTING EVIDENCE

Radically conflicting evidence in the field of genetics of epilepsy in man comes from Conrad[4] and Lennox *et al.*[5-7] on the one hand, stressing the importance of the hereditary factor, and from Alström[8] on the other, whose figures reduce the role of genetics in this sphere to the barest minimum.

The Points at Issue

What then are the points at issue within the camp of the geneticists in the sphere of epilepsy?[1,2] The work stressing the importance of the genetic factor comes, as has already been indicated, from two groups. In Conrad's[4] comprehensive pioneer study the expectancy figures in consanguineous groups of patients diagnosed as having idiopathic epilepsy were 4,0% for siblings, 4,3% for heterozygous twins, and 86,0% for monozygous twins. The similarity of the figure for siblings and heterozygous twins (categories which may be equated as to hereditary make-up), and the extremely high concordance rate for monozygous twins with identical hereditary make-up, as between co-twins, are eloquent and cogent testimony to the operation of the genetic factor. Lennox *et al.*,[5-7] using dysrhythmia in the electro-encephalogram criterion for epilepsy, record the remarkable finding of 100% concordance in monozygous twins and 25% concordance in those of the heterozygous variety—the ideal figure for a fully penetrant single dominant gene.

In 1950, Alström[8] published findings based on a study of epileptic patients admitted, during the years 1925 - 1940, to the neurological clinic of the Caroline Institute of the Serefimer Hospital, the only university clinic for neurology in Sweden at that time. Alström remarked that the patients came from all over the country, but that the urban population, especially that from the capital, was overrepresented. At the same time he claimed that this sample was otherwise probably a more representative one for patients suffering from convulsive disorders than a sample taken from hospitals for the insane or from institutions for epileptics, with their selection of mentally-affected patients. The investigation of his 897 index cases with their blood relations began in 1945 and ended in 1950. Salient findings of this study were as follows: in the first place the expectancy figures for parents (1,3 ± 0,27%), for siblings (1,5 ± 0,25%), and for children (3,0 ± 0,93%) were not significantly higher than those in the general population. Secondly, families with epilepsy in members other than the index case were lacking in the majority (i.e. 92%) of cases. Thirdly, among the 16 pairs of twins in this study, 2 of which pairs were monozygotic, there was not a single case of concordance as to epilepsy.

Despite Alström's figures, quoted above, which show no genetic factor in epilepsy, the examination of individual pedigrees in his series discloses, according to his own submission, a genetic factor—in fact, a monohybrid mechanism—in approximately 1% (11 index cases belonging to 8 families in his sample of 897 index cases and their families). This is the type of genetic mechanism that Lennox *et al.* postulated as being operative in their series, but present throughout instead of in only 1% of cases.

Meadowlands Clinic Study

With a view to finding further evidence towards settling the dispute, Hurst *et al.*[9] undertook a study at the Meadowlands Clinic in the south-western Black townships of Johannesburg during the period September 1959 to March 1961. The advantage of this clinical material for a genetic study is the large sibship size—average 5,8, range 1 - 16.

The preliminary pilot study produced evidence along the following lines: (*a*) the percentage of families having one or more members with epilepsy in addition to the index case, for comparison with Alström's low figure cited above; and (*b*) the types of genetic mechanism suggested in different pedigrees contained in our material.

With regard to the first point, our material shows an incidence of 13 out of 46 families, i.e. a figure of 28,3% in contrast to Alström's 0,8%. Statistical computation shows this difference to be significant at the 0,1% level. Thus, even at this early stage, our study has afforded evidence on the side of Conrad[4] and Lennox *et al.*[5-7] on the importance of the genetic factor in epilepsy.

With regard to the second point, analysis of the 13 positive pedigrees (of the 46) shows that 3 of these are strongly suggestive of a penetrant single dominant mechanism, 1 of irregular dominance, while the remaining 9 are equally compatible with irregular dominance or recessiveness. A portion at least, therefore, of these results is in line with the thesis of single dominance of Lennox *et al.*,[5-7] appearing also in the 0,8% of Alström's cases where he conceded a genetic mechanism.[8]

Metrakos' Resolution of the Difficulty

In his paper presented at the Second International Conference of Human Genetics, in Rome, J. D. Metrakos[10] resolved the problem in a most ingenious manner. On the basis of the EEGs of the parents and siblings of 211 probands and 112 controls, he claimed that epilepsy of the centrencephalic type may be explained on the basis of a single dominant gene showing a variable penetrance

with age—such that the penetrance is low at birth, rises rapidly to almost complete penetrance at the age of 4 - 16 years, and declines gradually to almost no penetrance at all after the age of 40 years. Alström's[8] work might well be re-examined in the light of this hypothesis to determine whether his low familial incidence of cases may be due to an unusually poor representation of cases in the 4 - 16-year age range.

The reasons why Metrakos' theory would appear to constitute such an advance is its own intrinsic merit, coupled with the untenability of any other hypothesis. If it were to be argued, for instance that the discrepancy between Conrad's findings and those of Alström is to be explained by a greater concentration of the genetic variety of epilepsy in mental hospital cases, this is counteracted by a similar discrepancy between the findings of Lennox *et al.*[5-7] and those of Alström,[8] both of which are based on clinic samples. Apart from Metrakos' findings, therefore, we should have to fall back on the hypothesis of differential geographical distribution of epilepsy with a heavy genetic loading.

CONCLUSIONS AS TO PRACTICAL OUTLOOK IN HEREDITY COUNSELLING

Armed with our modern armamentarium of neurological and neurosurgical knowledge and techniques, including electro-encephalography, we are in a better position than ever before to separate patients into symptomatic and idiopathic groups. It is clear, in the light of contemporary knowledge, that only the latter group of patients are readily susceptible to heredity counselling: and here we are in the fortunate position of offering the inquirer a low empiric risk figure on the basis of which few patients would be deterred from further procreation.

In the light of this, despite any differences we may have with Alström[8] on matters of detail, we are surely in agreement with him in substituting what Aschner and Kallmann[11] characterise as moderate eugenic recommendations for the existing legal restrictions of marriages of Swedish persons afflicted with hereditary epilepsy. 'Following a thorough discussion of the medical, social and genealogical aspects of the disease', he offers 'an emphatic warning against rigid applications of this restrictive law, especially in persons of satisfactory moral and intellectual standards.'

For practical heredity counselling purposes an empiric risk of 1 in 10 can be borne in mind. Most married couples would not be deterred from parenthood by a figure of this low order. In fact, in my own clinical experience, it is not a eugenic factor but the question of the severity of associated behavioural disturbance which would influence me in assessing the suitability of an epileptic for marriage and parenthood. But, the larger hope that comes to us through genetics is the chemical reversal of a condition like idiopathic epilepsy based upon monohybrid inheritance.

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