

EDITORIAL

Psychiatric genetics

Genetics and psychiatry make strange bedfellows. Genetical investigations are satisfactory when the material to be studied is precisely defined, when characters segregate and are unequivocally recognizable in different surroundings. In psychiatry such circumstances are very seldom realized unless cases of mental deficiency are included with mental illness under the one heading of mental disorder. Indeed, there are, among the diseases which produce imbecility, a great many with properties which make them suitable for genetical study using statistical pedigree analysis, biochemical tests, or karyotype differentiation. In the miscellaneous collection of diseases which lead to neurosis and psychosis there are very few which have been successfully studied by genetical methods. The outstanding example is Huntington's chorea but, at the present time, the amount of genetical knowledge even of this disease, as compared with that on phenylketonuria in which the biochemistry has been, to a considerable extent, elucidated, is disappointingly small. This brings out another difference between imbecility and psychosis, which is critical for genetical researches—namely, that mental deficiency is evident in childhood, perhaps at birth or earlier, and mental illness, for the most part, is first recognized in adolescence, in adult life, or even in old age.

If the inherent difficulties of the problem are understood, it makes it perhaps easier to tolerate the crude and often equivocal results which have been obtained by those who have been bold, or foolhardy, enough to apply methods of genetical investigation to psychiatric phenomena. When the classical work of Sjögren on amaurotic idiocy is compared with the monumental surveys of Rüdin and his school on psychosis, it is like comparing the movements of a cat with those of a rhinoceros. Nevertheless, some methods, by which pedigree studies can be refined, have been used to obtain information about the genetics of mental illness. In particular, the collection of twin pairs has been favoured, for example, by Kallman, and important general indications of the significance of heredity are obtained from observations on the prevalence of concordant identical pairs. The twin techniques are surrounded by pitfalls, however, because identical pairs are likely, in most cases, to have very similar environments. Consequently, twin study, as opposed to pedigree study, is especially useful, not for genetical researches but in assessing the effects of environmental influences which lead to discordance in identical twin pairs.

In addition to the disadvantages listed earlier, against which the psychiatric geneticist has to contend, is the fact that mental illness cannot be measured quantitatively in any obvious way, like stature or intelligence. Even the meagre satisfaction of being able to make quantitative genetical analysis, as can be done with metrical traits, and to pronounce that the hereditary influences are multifactorial, is denied him. The qualitative approach, in which the disease is recorded as either present or absent and which is the basis of most empirical figures on familial incidence, tells nothing about the severity of the illness and is, thus, unavoidably inaccurate. One quantitative trait, which could contribute but which has not been extensively used for genetical purposes, is age of onset of disease. The fact that age of onset varies between cases with the same diagnosis in different sibships can be used, as Haldane suggested many years ago, as a test to indicate whether the diagnosis represents a single disease or a group of allelic or even quite separate conditions. The age of onset, moreover, is an index of severity from the biological, if not always from the clinical, point of view. It would be possible, for instance, to make a genetical analysis of families, in which psychosis occurred, scoring patients for severity of illness, using the reciprocals of their onset ages in years as the index, with unaffected relatives scoring zero. Consideration of this variable would alter and perhaps strengthen the empirical figures given, traditionally, in genetical counselling because the risk that any given relative may develop a specified condition depends on his age.

The greatest hope of genetically minded psychiatrists has been, for some years, to find inborn metabolic errors correlated with diseases causing insanity, as are the errors, in phenylketonuria or Wilson's disease, which cause mental defect or neurological changes. It is not always realized by biochemical enthusiasts that the metabolic errors to be looked for must be permanent, lifelong, peculiarities. It is of little use to expect the changes, which appear in acute episodes or in long-standing cases whose habits of life are grossly abnormal, to represent simple hereditary characters. The screening of patients for aminoacidurias is probably unlikely to give as significant results in the psychoses as among defectives but, if only the right chemical screen to apply were known, things might look very different.

It seems *prima facie* very improbable that schizophrenia is all one genetical entity. Like epilepsy or, for that matter, mental deficiency, it is a blanket term. What may reasonably be expected is that, eventually, from the conglomeration of those mental illnesses which are predominantly determined by heredity, one by one specific conditions will be separated. A traditional method, which is useful for screening rare recessive traits, is the collection of cases whose parents are consanguineous. This method, which has been used successfully, years ago, in mental deficiency, is less helpful now because cousin marriages are becoming extraordinarily rare in our general population. The use of the method, by Munro and by Slater, led, on the whole, to disappointing results. However, the search for sibships, in which more than one case of the same disease occurs and in which the normal and abnormal sibs can be clearly distinguished, could be used in a preliminary selection of cases for intensive biochemical screening.

Finally, there is the problem of the contribution of abnormal karyotypes to the aetiology of the psychoses. Experience has so far shown that autosomal aberrations tend to produce intellectual defect and physical deformity rather than a tendency to mental illness. Conversely, aberrations which involve the sex chromosomes have been shown to be connected with predispositions to psychotic reactions, accompanied by relatively mild degrees of intellectual weakness. This applies both to male and female patients with too many X-chromosomes, to females who lack one X-chromosome—that is, who have Turner's syndrome—and also to males with two Y-chromosomes. The rule might not unreasonably lead to speculations about the relationship of sex hormones to mental stability. There are, of course, known genes which can cause disturbances of sex differentiation, unconnected with karyotype aberration. Nevertheless, little is established yet concerning genes which affect the biochemistry of sex hormones or other agents which might influence behaviour in subtle ways and could be significant in the development of mental illnesses. It is of interest to note that, more than 50 years ago, Mott expressed the opinion that there was a close correlation between gonadal deterioration and some types of schizophrenia, almost at the same time that Freud's observations were made on the influence of psychosexual disturbances in the aetiology of neuroses.

In the search for genetical factors underlying mental illness, an open mind is a good thing but the experience of human geneticists, who have had successes in other fields, must be the guiding principle when dealing with the genetics of the exceedingly obscure phenomena of the psychoses. Advances, from researches in this field, will surely follow in the near future now that intensive statistical, biochemical, and cytogenetical techniques are all standing ready to be applied in a way which was never before possible.

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