

# The major psychoses

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Compared with chromosome anomalies, congenital abnormalities, and inborn errors of metabolism, the schizophrenic and manic depressive psychoses present greater problems both as regards the sense in which they may be considered to be genetic diseases and as regards their incidence in the population. They do not usually become manifest until adult life and are very variable in age at onset, symptomatology, and course. They are sensitive to variation in the postnatal environment. Compared with peptic ulcer, diabetes, and Parkinson's disease, with which there are parallels, the psychoses present much greater problems of diagnosis.

Inheritance is certainly complex. Simple Mendelian ratios are not found. At present it is not known whether schizophrenia and manic depression are essentially monogenic, genetically heterogeneous (like deafness and blindness), or polygenic disorders. Despite these uncertainties, there can be little doubt that genetic factors make an important difference to the risk an individual runs of developing a psychosis and, if so, to its probable type. The evidence comes from the rates of similar psychoses in first degree relatives of cases, in second-degree relatives, and in members of the general population; further, from the psychosis rates in monozygotic compared with dizygotic twins of psychotic probands; and lastly, in the case of schizophrenia, from a few pairs of monozygotic twins reared apart, and interesting recent studies using adoptions (Gottesman and Shields, 1972).

In the case of the depressive psychoses there is some evidence of at least partially different genetic factors in bipolar manic depressive psychosis and unipolar endogenous depression without mania (Angst and Perris, 1972). However, the dictum that one gene can have many effects and that a syndrome can be caused by different genes is particularly true for psychiatry.

In patients with schizophrenia the risk that their sibs and their children will be similarly affected is about 10%. It thus lies in between that in high risk genetic disease (usually 25 to 50%) and low risk genetic disease (where it is usually not more than about 5%). In manic depressive psychosis the morbid risk is usually higher than in schizophrenia, rising to about

20% for affective disorder in the first degree relatives of bipolar cases.

Despite the higher morbid risk for relatives and the increased suicide risk for patients, the affective psychoses are best regarded as being less detrimental than schizophrenia. Schizophrenia generally has an earlier onset and, despite advances in treatment, is still liable to run a chronic course; and there is a greater reduction in fertility. But the illnesses in both groups can vary widely in severity.

## Population frequency

Estimates of the population base rates for schizophrenia and the affective psychoses, against which rates in relatives and any increase with radiation can be compared, vary for a number of reasons. They depend partly on whether they set out to measure the prevalence of cases requiring treatment at a given point of time (point prevalence), the life time prevalence (or all those now alive who have ever been a case), or the incidence of new cases, say, per 100 000 population per year. The same method will give different results depending on the age structure of the population and how this has been dealt with—for example, by including or excluding persons under age 15 or more sophisticated methods of age standardisation. Rates will also depend on whether only hospital statistics are used, or whether field investigations have been carried out, and whether these were cross-sectional (prevalence) surveys or whether they were longitudinal (incidence) surveys of all persons born, say, 50 or 70 years ago. Above all, rates will depend on standards of psychiatric diagnosis and these are liable to vary from country to country and from time to time within the same country. For example, schizophrenia is much more frequently diagnosed in the United States than in this country and manic depressive psychosis much more frequently here. This has been shown to be a feature of diagnostic practice in the two countries rather than of differences in the clinical characteristics of their psychiatric patients (Cooper *et al.*, 1972).

The preferred rate is the morbid risk or life time expectancy. This expresses the chance of developing the disease if one lives long enough. On large samples this risk can be calculated by the actuarial life-table

method, and for samples of the size more usually encountered short-cut methods of estimating morbid risk have been developed by Weinberg and Strömrgren and have been extensively used. (See Slater and Cowie, 1971, for an account of these methods.)

From a number of studies in European countries (e.g. Fremming, 1951; Essen-Möller, 1956) a mean value for the morbid risk of schizophrenia is 0.85% based on a total population of over 262 000. More recently, Slater and Cowie (1971) have calculated a risk of around 1% for England and Wales. As already noted, estimates are greater for the USA, namely about 2.1% for New York State (Deming, 1968) and 6% for certain high risk areas (Yolles and Kramer, 1969). For present purposes a reasonable estimate of the morbid risk for schizophrenia is about 1%. Though environmental factors influence the onset, it is generally assumed that the schizophrenia rate in a country remains fairly stable over time. If that is so, it is one less problem to consider in assessing the possible effect of increased levels of radiation. It is worth noting that admission rates for psychosis are not affected by national disasters such as war.

There is less agreement among European studies about the probable life time expectancy of manic depressive and other affective psychoses. Bipolar manic depressive disorder is rarer than unipolar depression, and it is possible that the old estimate of about 0.4% may not be far off the mark as regards severe bipolar disorders, and that possibly as many as 3% of the population (women more than men) may some time in their life have an endogenous depressive psychosis requiring hospital admission.

With the changing age structure and increasing longevity of our population, the psychoses of later life are becoming more important. Diseases with onset after the reproductive age may include some that are the result of the effects of major genes that have not been exposed to natural selection. Some cases of the rare presenile dementias, such as Pick's disease and Alzheimer's disease, may be the result of dominant genes, and it has even been suggested that most cases of rapidly dementing senile psychosis are the result of a dominant gene with a manifestation rate which increases with age (Larsson *et al.*, 1963). By the age of 80 the morbid risk for senile dementia in Sweden was calculated to be 2.5%. But as with so many of the commoner disorders, the family findings here can perhaps at least as plausibly be interpreted as the result of polygenic inheritance with a threshold effect (Shields, 1975).

### Mutation

The fertility of schizophrenics is about 70% of average. Various estimates have been made of the

fresh mutation rate that would be required to offset this loss of genes, and they have all been too high to be credible. For example, Moran (1965) estimated a mutation rate of 5 per 1000 gametes per generation.

Monogenic theories, therefore, do not rely on a raised mutation rate but posit a hypothetical selective advantage for gene carriers (Huxley *et al.*, 1964), such as increased resistance to infection in early life when mortality is highest. According to Slater's monogenic theory, the necessary gene would be in the polymorphic range with a gene frequency of about 3%.

Those who think schizophrenia may consist of a number of separate disorders, each the result of a different rare gene, plus a residue of sporadic cases, point out that these rare genes (mostly dominant) could each be maintained in the population without invoking an unrealistically high mutation rate or a compensating but so far unproven selective advantage. However, there is as yet no empirical evidence in favour of this theory.

Those who prefer a multifactorial model have not been so concerned with the mutation rate of genes which could contribute to the development of schizophrenia. They will presumably maintain themselves in the population fairly well because in most combinations they will not result in reduced fertility. It is only those few individuals who have unfortunately inherited too many of the predisposing genes who become schizophrenic. Any loss of genes from the population gene pool caused by schizophrenia will be very slight and could well be offset by a slight reduction in fertility sustained by carriers of other, non-schizophrenic genes at the same loci when they and other genes occur in combinations that influence different polygenic disorders with reduced fertility (Edwards, 1972). If many genes are involved the trait will also be insensitive to changes in the mutation rate as well as to the reduced fertility of psychotics. Relatively common, normal polymorphic genes are generally thought to be involved. It could well be that the effect of the mutation of psychosis-protecting alleles into psychosis-predisposing alleles would be offset by mutations in the other direction.

Thus, none of these theories, except possibly one form of the heterogeneity theory, invokes a more than average mutation rate for the genes influencing the major psychoses.

Up to now, attempts to compare the incidence of multifactorial diseases of later onset with congenital abnormalities and simply inherited genetic conditions have run into difficulties. They do not always distinguish between trivial and severely detrimental conditions, and their data are biased in the direction of childhood disorders. In their main analysis Trimble and Doughty (1974) restricted themselves to 30 000 persons all under the age of 21 and mostly

infants or children. The group included only 59 schizophrenics and no manic depressives.

### Conclusions

Schizophrenia and the manic depressive or affective psychoses are the major mental disorders of adult life in which genetic factors have been established as playing an important part. The life time expectancy for someone from the general population developing schizophrenia is probably best taken to be around 1%. Problems of diagnosis and heterogeneity are even greater in the case of the affective psychoses. Bipolar manic depressive psychosis is probably less frequent than schizophrenia and simple unipolar endogenous depression more frequent, but it is difficult to give a firm figure because of the difficulty in drawing a firm line between the endogenous and reactive. The total expectancy for any of these schizophrenic or affective psychoses may be somewhere approaching 5%. To this one should add something like 2.5% for senile dementia, given survival to the age of 80. Among the major psychoses the morbid risk for the children in schizophrenia (about 10%) is lower than that in manic depressive psychosis, but schizophrenia must be regarded as the more detrimental condition.

Most current theories do not rely on new mutations for maintaining disorders like schizophrenia in the population. The genes involved are probably polymorphic, i.e. have a frequency of more than 1% in the gene pool. Instead, selective advantage of heterozygotes is invoked or, alternatively, a compensating minor reduction in fitness of the nonschizophrenic alleles in other polygenic settings. If aetiology is multifactorial the psychoses may be relatively insensitive to changes in mutation rate.

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