SCHIZOPHRENIA AS A GENETIC MORPHISM

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IT now appears clear that schizophrenia, at least in the great majority of cases, is based on a single partially dominant gene with low penetrance[1–3]. We wish to put forward the hypothesis that it involves a genetic morphism, a conclusion independently reached by two of us (J. H. and E. M.).

As is now agreed among evolutionary geneticists (for example, Mayr[4a] and Ford[4b]), all genetic characters which exist in a population at a higher frequency than can be maintained by mutation alone involve morphism[5]; the frequency of a morphic gene is the result of a balance between its selectively favourable and unfavourable properties.

(1) In schizophrenia there is abundant evidence of a strong genetic component.

(*a*) In single families, only certain children become schizophrenic.

(*b*) Monozygotic twin-pairs show a concordance rate of 76–91 per cent, dizygotic pairs only 10–17 per cent (for example, Kallmann[6,7], Shields and Slater[8]).

(*c*) An examination of schizophrenics and normal sibs of the same sex and less than 2 years' difference in age, whose mothers were not schizophrenic[9], showed that the future schizophrenics and their sibs manifested marked personality and temperament differences from an early age, and that these could not be associated with environmental influences, including psychological trauma. The future schizophrenics were more dependent and less able to deal with traumatic events: they were *schizoprone*, apparently from birth.

(*d*) The work of Böök[1,2] and Slater[3] on the morbid risk (likelihood of developing schizophrenia) in different relatives of schizophrenics indicates that the usual genetic basis for schizophrenia is a single dominant geno which we will call Sc, with about 25 per cent penetrance, that is, it only induces manifest schizophrenia in about a quarter of the cases where it is present in the genotype. Non-manifestation of the disease in the 75 per cent of Sc-carriers is due to the effect (1) of the genetic environment—minor genes affecting manifestation; (2) of the external environment—familial, social, cultural and physical.

(2) (*a*) Wherever reasonable statistics are available, the incidence of manifest schizophrenia is at least 1 per cent in all racial and ethnic types[10] and probably in all social classes (some authors maintain that there is an increase in the lower strata; but others have been unable to confirm this).

The only considerable exception is the 3 per cent incidence found by Böök[1] in an area north of the Arctic Circle in Sweden. This high figure is doubtless due partly to inbreeding in an isolated but physically dispersed population. Dr. Eliot Slater has further suggested to us that it is correlated with the nature of the environment. We would add that schizophrenics are more likely to be able to lead a normal life in a socially simple and physically harsh environment of this type, and one where they are necessarily withdrawn from much contact with their fellow human beings, and where husbands will not trouble very much about their wives' mental peculiarities, provided they are physically resistant and capable of elementary domestic skills. In addition, it may be suggested that the high incidence may be wholly or partly due to a higher penetrance (manifestation) of the Sc gene in a harsh environment: further investigations of the degree of penetrance in different types of environment would be of great interest.

(*b*) The high frequency of schizophrenia cannot be maintained by mutation alone, and is evidence of a balanced morphism. The fertility (reproductive fitness) of schizophrenics is only about 70 per cent of that found in socio-economically comparable normals[11]*. The incidence of the disease would therefore be rapidly reduced to the level where it is maintained by mutation alone, unless its selective disadvantages of lower viability and fertility were compensated by some selective advantage.

(*c*) There are two possible types of compensatory advantage:

(1) *Physiological.* Overt schizophrenics are extremely resistant to surgical and wound shock (and recover much more rapidly), to visceral perforation, to high doses of histamine (correlated with fewer mast cells in the skin), insulin, thyroxin and other physiologically active substances, to pain, to arthritis, to many allergies, and probably to many infections†[12–16]. One of us (H. O.) has seen a schizophrenic recover successfully from the most appalling burns which would have killed any normal person in hours or minutes‡. We suggest that cryptoschizophrenic Sc-carriers probably enjoy similar selective advantages, though presumably of lower magnitude.

Dr. Slater has suggested to us that in historic times resistance to mass epidemics of diseases like smallpox and

* Many morphic genes are lethal or semi-lethal when homozygous. In view of the drastic physiological effects of the Sc gene (see following) such lethality may well apply to it.

† But not to tuberculosis, where the schizophrenics' reduced ability to produce fibrous tissue reactions is a disadvantage. Further, since the incidence both of schizophrenia and of tuberculosis is positively correlated with Sheldon's ectomorphic (Kretschmer's leptosomic) type of body-build (see Harrison, Weiner, Tanner and Barnicot[17]), schizophrenics are more likely than normals to suffer from tuberculosis.

‡ Clarke[18] mentions some of these advantages of schizophrenia, and discusses the possibility of its being a genetic morphism, but without reaching a firm conclusion.

bubonic plague may have been a contributory factor. If the high frequency of the schizophrenia gene is in any considerable measure due to resistance to infectious diseases, especially of childhood, we may expect its steady decline in the more hygienic modern world.

(2) *Reproductive.* Male schizophrenics are certainly at a high reproductive disadvantage, through earlier onset, higher suicide rate[18], more frequent hospitalization, and failure to marry. Female schizophrenics, however, not infrequently marry, and seem to seek for affectional satisfaction through children: so their fertility may possibly be above average. In hæmophilia, a moderate increase (22 per cent) in female fertility is able to compensate for a high reproductive disadvantage (36 per cent) in males[20]. Nothing is known about the fertility of the cryptoschizophrenic Sc-carriers. This merits intensive investigation, as it could be of great importance for the frequency of Sc.

Presumably both the penetrance and the expressivity of the Sc gene are largely controlled by the residual gene-complex[21].

It will be of importance to be able to identify carriers of the Sc gene, as has been done with a number of other genes[22,23]. The simplest way would be by biochemical tests; but psychological tests would also be useful.

Many workers consider that the perceptual disorder characteristic of schizophrenics is due to a biochemical abnormality which affects the brain's sensory-perceptual integrative system. Much work is in progress on the subject. Symptoms closely resembling those of schizophrenia can be induced both by certain psychomimetic drugs[24], and by hypnotically induced alterations in perception[25,26].

Hoffer and Osmond[24,27] consider that the specific substance involved is adrenolutin, and claim that the urine of schizophrenics in 75 per cent of cases contains a substance giving a mauve reaction when tested by paper chromatography, while Friedhof and Van Winkle[28] claim a similar high frequency for a 'pink spot' chromatographic reaction produced by a closely related substance. If these claims are confirmed, and the methods improved, it might be possible to detect the responsible substance in the urine of non-manifest Sc-carriers.

Hoffer and Osmond (1961) have devised a battery of psychological tests which they claim are diagnostic of schizophrenia as against other psychoses, neuroses and, of course, normality (see also Lidz *et al.*[29]). If it proves possible to identify schizoprones in childhood by such tests, educational and other methods could be devised to prevent or mitigate the manifestation of the disease.

It is clear that schizophrenia constitutes not a purely medical or psychiatric but a biological problem, with opportunities for a combined attack in many fields—genetics, biochemistry, selection theory, psychology, psychiatry, public health, demography, social science, pathology, and general environmental and reproductive physiology.

In particular, we need further investigations: (1) of the selective advantage and disadvantage, both as regards survival (viability) and reproduction (fertility) of overt schizophrenics, non-manifest carriers of the Sc gene, and normals: and also better biochemical and psychological tests identifying the same types, and if possible applicable in childhood; (2) the heritable and environmental contributions to the manifestation of schizophrenia—the major gene (or genes) involved; its (or their) penetrance and expressivity, as influenced by modifiers and by environment; the possible influence of race, physical and cultural environment; and investigations of twins, sibs and other relatives: a comparison of same-sexed and opposite-sexed dizygotic twins would be especially rewarding. (3) Of the psychological and physiological effects of schizophrenia, overt and non-manifest, of psychomimetic drugs, and of induced alterations of perception.

Summary and Conclusions

(1) Schizophrenia probably depends primarily on a major dominant gene, Sc, with about 25 per cent penetrance.

(2) The overt schizophrenia-rate in all countries investigated is at least 1 per cent, much too high to be maintained by mutation alone. The Sc gene must therefore be in morphic balance, and must confer certain selective advantages to compensate for its obvious disadvantages, including a 30 per cent reduction of fertility.

(3) The physiological advantages are high resistance to surgical and wound shock, to otherwise dangerous concentrations of insulin and other hormones, histamine, etc., and to various allergies and infections. Cryptoschizophrenic Sc-carriers (and some overt female schizophrenics) may possibly have a higher than average fertility. Known or presumed Sc-carriers should be tested to ascertain whether they possess any degree of these advantages.

(4) The Sc gene appears to cause an error of metabolism, resulting in the formation of some substance interfering with the normal integration of perception.

(5) The temperamental and personality traits of future schizophrenics in most cases show, from early childhood onwards, distinct differences from those of permanently normal sibs of the same sex and similar age.

(6) Chromatographic tests are beginning to provide evidence of detectable 'mauve' and 'pink' chemical factors in the urine of a large majority of schizophrenics, and suitable psychological tests promise to differentiate schizophrenics from other psychotics, neurotics and normals.

(7) If such tests can be further improved, schizoprones and future schizophrenics might be diagnosed in childhood and appropriate educational and possibly medical measures taken to prevent or ameliorate overt manifestation.

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