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Possible Biological Advantages among Schizophrenics' Relatives

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1. Are genetic factors of importance among the causes of schizophrenia?

There is good evidence that genetic factors are necessary, though by no means sufficient, for the development of schizophrenia. Several studies have compared the incidence of schizophrenia in identical and in fraternal twin pairs: these studies are discussed, for example, in the Medical Research Council Annual Report 1965–66 (pp. 54–61), where Essen-Möller's (1963) cumulative figures are quoted: Identical (MZ) pairs: 69 per cent concordant for schizophrenia (both schizophrenic) (194/280 pairs). Fraternal (DZ) pairs: 13 per cent concordant for schizophrenia (both schizophrenic) (59/448 pairs).

Only the small Scandinavian series of Tienari (1963) conflicts with the rest of the evidence from twin studies; and one possible reason for this may be Tienari's criteria for a diagnosis of schizophrenia.

A recent paper (Pollin *et al.*, 1969) gives a concordance rate for schizophrenia in a large series of identical twins 3·3 times greater than the dizygotic rate.

The incidence of schizophrenia in the relatives of schizophrenics also argues in favour of a genetic influence in the disease.

The excellent work of Heston (1966) makes it very difficult to avoid the conclusion that genetic factors are important; he studied foster-home reared children of schizophrenic mothers separated from their mothers very shortly after birth, and he found that 5 out of 47 became schizophrenic, while none of 50 matched controls similarly reared in foster homes developed schizophrenia. Since these children were not subject to any environmental influences from their mothers, the conclusion that they inherited the liability to develop schizophrenia is difficult to avoid.

The most stringent test favouring genetic rather than environmental influences as being causative in schizophrenia is that comparing the incidence of the disease in monozygotic twin pairs reared together and reared apart: Shields and Slater (1967) collected 16 pairs of monozygotic twins reared apart (Table II of their paper), where at least one twin was schizophrenic; 10 pairs were concordant (i.e. both schizophrenic) and 6 discordant for schizophrenia. This is a concordance rate of 65 per cent—a rate as high as those usually quoted for monozygotic twins reared together. Karllson (1966) in an extensive study of the genetics of schizophrenia in Iceland, found that of 29 biological sibs of schizophrenics reared in foster homes 6 became schizophrenic, while of their 28 foster sibs none became schizophrenic. Karllson also found an incidence of schizophrenia of 29 per cent among biological sibs reared outside the schizophrenic family—a higher figure than the incidence among those sibs brought up within a family with a psychotic parent.

Though few will deny that environmental factors are important in determining which predisposed persons will become schizophrenic, it is clear that genetic factors are also important in the aetiology of schizophrenia.

2. What is the lifetime expectancy of developing schizophrenia?

A survey of the literature establishes that about 0·8–1 per cent of most populations will develop at some time during their lives an illness diagnosed by psychiatrists as schizophrenia. The M.R.C. annual report 1965–6 gives a figure of 'nearly 1 per cent', Gottesman

and Shields (1967) give a figure of 'around 1 per cent', Shields and Slater (1967) give a lifetime expectancy of 0·86 per cent—with reported ranges in various countries between the extremes of 0·4 per cent (Switzerland, 1931) and 2·9 per cent (Böök—Scandinavia, 1953). In England and Wales about 1·1 per cent of the population should develop schizophrenia or have a schizophrenic episode by the age of 55. Incidence is discussed also by Slater and Roth (1969), and these authors agree with this estimate.

Other surveys, not quoted here, are in agreement with this lifetime expectancy.

3. *Why does schizophrenia remain so common?*

There is general agreement that the fertility of schizophrenics is reduced; probably to about 70 per cent of the fertility found in the normal population (M.R.C. Annual Report (1965–6) and Shields (1967) and Gregory (1960)). This reduction in fertility is more marked in schizophrenic males; perhaps because men marry later than women. If, as appears likely, genetic factors are of some importance in the aetiology of schizophrenia, and if the schizophrenics, due to their reduced fertility, contribute fewer descendants than comparable members of the normal population, why does schizophrenia not become a great rarity, instead of remaining so common? The usually accepted mutation rate in man is far too low to maintain schizophrenia at its present high incidence in the face of such relatively strong negative selection pressures.

One possible explanation is that schizophrenia is part of a genetic polymorphism—and that some non-schizophrenic relatives of schizophrenics, in particular those who carry a hidden 'schizophrenic' trait, have certain biological advantages over the normal population. These advantages would increase the number of their offspring reaching reproductive age alive when compared to 'normal' people. This theory was put forward in a paper by Huxley *et al.* (1964) which first drew our attention to the desirability of studying the illnesses and other characteristics of schizophrenics' relatives in our own two general practices.

Erlenmeyer-Kimling (1968) and Kuttner, Lorincz and Swan (1967) suggest that the advantages possessed by some schizophrenics' relatives may be a social one: a genetically determined protection against the stresses and strains of social interaction which gives them a real 'advantage' in coping with anxiety-inducing environments. Erlenmeyer-Kimling and Paradowski (1966) produce some preliminary evidence to show that the reproductive rate of *sisters* of schizophrenics admitted to New York State hospitals in 1954–56 was 140 per cent of that of the general population, though the sisters of schizophrenics admitted in 1934–36 had a birth rate identical with women in the general population. An increased fertility in sibs would, of course, help to maintain schizophrenia at its present frequency.

It is worth mentioning that the hypothesis of Huxley *et al.* is not the only possible one: Shields (1968) has listed several theoretical explanations which would fit the observed facts without the necessity of postulating biological advantage in schizophrenics or their relatives. For example:

1. The fertility of schizophrenics may not have been so reduced in the distant past as it has been recently.

2. Advantages (for example, increased resistance to plague) which have maintained the frequency of schizophrenia in the past may no longer exist, their place being taken by increased fertility of schizophrenics due to modern treatment. (Erlenmeyer-Kimling and Paradowski (1966) have produced evidence of an increase in the fertility of schizophrenics during this century.)

3. The advantage in schizophrenics' relatives could be due to increased resistance to a disease like diphtheria which has only become rare in the very recent past, so that the loss of the advantage has not yet had time to affect the prevalence of schizophrenia.

It is also possible that what we call 'schizophrenia' is in fact a heterogeneous collection of many genotypes which are clinically indistinguishable (Kaplan, 1966) and mutation within the usual range of mutation rates in man could, by occurring at *many* loci, maintain the observed fairly high prevalence of schizophrenia. Erlenmeyer-Kimling and Paradowski (1966)

for example quote Ernst Mayr's calculations that more than six gene loci each capable of predisposing to 'schizophrenia' could have this effect.

The Objects of the Present Study

Other studies had shown some differences in morbidity between schizophrenics and normals—for example a diminished incidence of 'allergies': Erentheil and Marchand (1960), but we were not able to trace any studies in which illnesses in the relatives of schizophrenics had been compared with those of the relatives of a matched group of non-schizophrenics. We therefore planned a pilot study in our own practices to make this comparison. Huxley *et al.* had suggested that increased resistance to diseases which carry, or recently carried, an appreciable mortality, might be found in schizophrenics' relatives. The markedly lowered mortality from falciparum malaria in heterozygotes for the sickle-cell gene is the classical example of this type of mechanism (Allison 1954, 1965).

Method of Investigation

(A) *The two practices*

The Lowestoft practice is in a Suffolk seaport, many of the patients being fishermen or their descendants. The Ibstock practice is larger, and has been fully described by Watts (1966)—it is a rural practice in Leicestershire, including a high proportion of coal-miners. It was hoped that by studying two separate and different practices we would lessen the risk of being led astray by any atypical features of one particular practice.

(B) *Collection of material*

We selected from among the known schizophrenics in both practices, whether in or out of hospital, all the cases of true or typical schizophrenia.

Our criteria for selecting index schizophrenics were that a definite diagnosis of schizophrenia had been made by a psychiatrist, and that the general practitioner concerned, after continued observation of the patient, concurred in the diagnosis. It has been shown that there is agreement on the diagnosis of schizophrenia between different psychiatrists in a given series of individual cases in about 80 to 90 per cent (Hare, 1967), so the likelihood is that most of our index schizophrenics would have been so diagnosed by other psychiatrists.

For each schizophrenic index case we selected a control (the next patient but one of the same sex in the practice files—arranged alphabetically—who was born in the same five-year period as the index schizophrenic). We then traced the records of all the first degree relatives both of the schizophrenics and of the index controls who were in the two practices at the time. Some of the schizophrenics' relatives were themselves probably schizophrenic, and these we allotted by 'forced choice' either to the 'schizophrenic index case' group or to the group of 'normal' relatives. There were 8 schizophrenics among 98 relatives, but the records of only 4 of these 8 were available for analysis.

General Practice records were not available for all those studied—more especially so for schizophrenics in hospital—but for the majority we could analyse the recorded doctor–patient contacts over a ten-year period: 1956–65 inclusive.

At a later stage in the investigation we were advised to double the size of our control group; in order to increase the reliability of our results, and this we did by selecting for each Index Schizophrenic a *second* Index control (the next person but one in the practice files born in the same five-year period, but this time working backwards in the files, not forwards as we did to select the first half of the control group).

We then studied the records of the first-degree relatives of this second half of the control group for a number of illnesses, though not all, during 1956–65. At the same time (the winter of 1968–9) the opportunity was taken to include two further recently diagnosed index schizophrenics together with two index-controls for each, and all their relatives in the practices.

The final totals of patients whose records were analysed are shown in Table I:

TABLE I

	Patients	Patient/years * analyzed
Schizophrenics	31	260¾
Schizophrenics' relatives	77	728¼
Index controls	63	590¼
Controls' relatives ..	144	1273¼

* 1 patient/year = 1 patient observed for 1 year.

In some instances the records did not cover the whole ten-year period—children born after 1956, for example, or persons dying before the end of 1965: this is evident from Table I where the numbers of patient/years shown in the second column are less than ten times the numbers of patients shown in the first column. In all the results quoted below, however, small corrections have been made to allow for this deficit.

RESULTS

1. *Virus infections*

The virus infections studied were influenza, measles, mumps, chickenpox, herpes zoster, rubella, herpes simplex, the common cold, corneal ulcer, infectious warts, and enterovirus infections.

Among schizophrenics' relatives, a total of 77 attacks of a virus infection were observed, whereas from the incidence in the controls' relatives, 125 attacks of virus infection would have been expected. The difference is statistically very highly significant.

A caveat is necessary here, however, since it so happened that the second part of the controls' relatives group contained a larger percentage of those aged under 21 than the first part of the controls' relatives group or the schizophrenics' relatives group (only 20 schizophrenics' relatives observed where 27·8 would have been expected). Further, just over half the observed virus infections in both groups of relatives occurred in those aged 0–20, since several virus infections are commoner in children. A correction was therefore calculated to compensate for this bias, and after it was applied we found 93 attacks of virus infections among schizophrenics' relatives where 125 would have been expected. This difference is still statistically significant ($\chi^2 = 8{\cdot}03$, $p = 0{\cdot}0047$). For individual virus infections numbers were of course smaller, but differences between schizophrenics' relatives and control relatives persisted. Taking four common virus infections where diagnosis is reliable: measles, rubella, chickenpox, and mumps, only 15 attacks were observed among schizophrenics' relatives and 78 in controls' relatives. When the various corrections mentioned have been applied, the number of attacks observed in the schizophrenics' relatives is still only about 40 per cent of the expected incidence.

2. *Bacterial infections*

The diagnoses studied were sore throat (including tonsillitis) otitis media, bacterial skin infections, urinary tract infections, pneumonia, dental abscess and dental sepsis, pertussis, scarlet fever, and conjunctivitis. Among the schizophrenics' relatives, the number of attacks of bacterial infections observed was 136, the expected number being 149; this difference is small and non-significant ($\chi^2 = 1{\cdot}1$: $p = 0{\cdot}3$ approx.).

If the marked deficit of virus infections found among the relatives of schizophrenics had been due to some extraneous factor—for example, their reluctance to consult a doctor, it should also have been marked in the incidence of bacterial infections in the two groups. As it is, bacterial infections are, in a sense, a 'control' for viral infections and help to indicate that at any rate the major part of the deficit of viral infections amongst schizophrenics' relatives may be a genuine phenomenon and not an artifact.

3. *Accidents and injuries*

Among the schizophrenics' relatives, there were 85 recorded accidents and injuries, whereas the number expected, calculated from the incidence in the control group, was 122·2. This deficit of accidents among schizophrenics' relatives is highly significant ($\chi^2 = 8{\cdot}1$, $p = 0{\cdot}0044$). In contrast to virus infections, accidents appeared about equally common in

those aged under 20 and those over 20 (first series only).

It is important to point out, however, that this deficit of accidents and injuries was confined entirely to the schizophrenics' relatives in the Ibstock practice: the smaller number of schizophrenics' relatives in the Lowestoft practice had a slightly higher incidence of accidents and injuries than the control group. The Ibstock results are probably more reliable; since, except for a tiny majority of major accidents, all accidents and injuries for which medical advice was sought had to be seen by the family doctor, this being a rural practice. In Lowestoft, on the other hand, most injuries, particularly towards the end of the ten-year period studied, were seen at the hospital: and thus a slightly greater preference among schizophrenics' relatives for seeing their own doctor rather than the hospital with an injury might account for the results found.

As there is an element of doubt about the incidence of accidents and injuries in the two groups, however, further studies in other practices are desirable.

4. *Allergies*

'Allergy' is difficult to define: we included urticaria, allergic dermatitis (primulas, fishermen's 'weed' dermatitis), drug rashes, hay fever, and asthma with a definite allergic basis.

Since allergy can be a continuing predisposition, calculation of attack rates was not always appropriate, so we calculated 'units of service'—surgery consultations or home visits—instead. Thirteen schizophrenics' relatives had 79 units of service for allergies, the expected figure being 16·6 persons having 175·3 units of service for allergies.

This deficit of attendances for allergies, which occurred in the schizophrenics themselves also, is not inconsistent with the diminished incidence of allergies in schizophrenics found by Erentheil and Marchand (1960).

5. *Other conditions*

No striking findings emerged when the incidences of several other conditions were compared in the schizophrenics' relatives and the controls' relatives (first control group only). For many conditions—rheumatoid arthritis for example—the numbers of cases involved were far too small to demonstrate possible differences in incidence between the two groups. The overall totals of consultations showed a slight *excess* in the schizophrenics' relatives group compared with the control relatives, thus countering the possible argument that the attitudes of schizophrenics' relatives might lead them to consult the doctor less often.

6. *Findings in schizophrenics*

When the schizophrenics were compared with index controls, the smaller numbers in the two groups, together with a tendency which was revealed for some schizophrenics to avoid consultations, combined to make the results less reliable. In general, however, the results in schizophrenics were in line with the findings in their relatives.

TABLE II

Comparison of observed and expected incidences of certain diagnoses in Schizophrenics' relatives

Condition	Observed Incidence	Expected Incidence	Probability (p)
1. Virus infections	77 attacks	125 attacks	Very highly significant
1a. Virus infections (after corrections applied: see text)	93 attacks	125 attacks	P = 0·0047 (highly significant)
2. Bacterial infections	136 attacks	149 attacks	P = 0·3 approx. (non-significant)
3. Accidents and injuries	85	122	P = 0·0044 (highly significant)

7. Relative fertility

In view of the findings mentioned earlier on the fertility of schizophrenics' relatives, the numbers of children born to the adults in our study were of obvious interest. Care was taken to ascertain the numbers of children in the families of all those aged 20 or over in 1966, where there was doubt, the family was asked. The results are shown in Table III.

TABLE III

	Average age	No. of persons aged 20 or over	No. of children	Average no. of children per person
Schizophrenics' Relatives..	45·6*	64	184	2·88
Controls' Relatives..	45·8*	88	186	2·11

* After correction for a slight excess of over 70s among schizophrenics' relatives.

The excess of children in the schizophrenics' relatives group is statistically highly significant ($\chi^2 = 8{\cdot}73$: $p = 0{\cdot}0032$). The 'average' adult schizophrenics' relative had nearly three children, compared with the average of just over two children for a control relative. (It must be remembered that further children may be born to the parents of both groups later.)

Further studies are desirable, with particular reference to the perinatal and childhood mortality found in the children of both groups.

DISCUSSION

(a) *Relative immunity to virus infections in schizophrenics' relatives*

The virus infections in our practices are frequently diseases like measles and influenza which are very infectious; and Dr. D. L. Crombie therefore made the intriguing suggestion that our observation of a diminished incidence of virus infections in schizophrenics' relatives was merely a reflection of their tendency to 'keep themselves to themselves' more than the normal control group, and thus to run less risk of infections, whether viral or bacterial, which were easily transmitted from person to person.

This hypothesis could be tested; and Dr. G. I. Watson, Director of the Epidemic Observation Unit of the Royal College of General Practitioners, kindly divided the list of infections—viral and bacterial—in our study according to their infectivity: 'very infectious' or 'moderately infectious'. This he did 'blind' without knowing our findings.

Using Dr. Watson's gradings, there was very close agreement between the observed and expected incidence of 'very infectious' infections when the schizophrenics' relatives were compared with the control relatives (119 attacks observed: 114·1 expected). The incidence of bacterial and viral infections where the degree of infectivity was very slight was also equal in schizophrenics' and controls' relatives. (In this study, only the first control group was used.)

Thus there was no evidence that, when bacterial and viral infections were considered together, the schizophrenics' relatives were protected against 'very infectious' infections, as had been suggested.

It is evident that the results are more consistent with the hypothesis that schizophrenics' relatives are to some extent protected against virus infections—particularly against severe attacks. These results should be treated with caution until further work has been done, but if this relative protection against virus infections among schizophrenics' relatives is eventually shown to be a genuine phenomenon it could help to explain the continued high incidence of schizophrenia. In a smallpox epidemic, for example, one could suggest that deaths might be relatively rare in those carrying the 'schizophrenic' gene pattern, who could therefore contribute more than their expected share of offspring to the next generation. Similarly, those relatives of schizophrenics who did not die of measles in childhood so often as did 'normal' children in Victorian times—or indeed as they do in parts of Africa even today—would be slightly more likely than the 'normals' to survive to adult life and have children of their own.

(b) *Apparent increased fertility of schizophrenics' relatives*

The findings of increased fertility among the adult relatives of schizophrenics is interesting, and is consistent with the findings of Erlenmeyer-Kimling and Paradowski (1966), that in 1954–56 the reproductive rate of a group of sisters of schizophrenics was 140 per cent of the general population's rate. Our group of schizophrenics' relatives have an average family size just below 140 per cent of that found in the relatives of controls.

Further studies are needed on the fertility of schizophrenics' relatives. If these preliminary findings are confirmed, the increased fertility of the relatives of those affected might well account, wholly or partly, for the preservation of the 'schizophrenia' polymorphism. Erlenmeyer-Kimling and Paradowski found that during this century the reproductive rate of schizophrenics was increasing, while that of their relatives, besides increasing, had surpassed that of the general population. It may well be, therefore, that at the present time the balance of the polymorphism is changing.

(c) *Apparent decreased incidence of accidents in schizophrenics' relatives*

While further studies in other general practices are essential to throw more light on this problem, the lowered consultation rate for accidents and injuries found among the relatives of schizophrenics (if it is a genuine phenomenon) could confer biological advantage upon schizophrenics' relatives. Whatever the cause for their relative freedom from accidents might be, a lowered death rate from accidents would increase the number of offspring that they contributed to the next generation.

(d) *The possible fallacies and errors in this preliminary investigation*

(i) Despite the fact that statistically significant results have been obtained the chief criticism of this survey may well be that the number of persons studied was too small. To meet this objection and others a second and larger survey is in the advanced stages of planning.

(ii) Social class may influence both disease incidence and fertility, and the downward drift in social class that accompanies schizophrenia is well known (Hare, 1967, and others). However, the social class drift may not affect all relatives: Goldberg and Morrison (1963) found that the social class of fathers of schizophrenics did not differ from that expected in the population at large. Many of the relatives of schizophrenics in our series had either completed their families before the disease arose in the index schizophrenic, or were living in a separate household, and so were unlikely to be influenced, either as regards fertility or disease incidence, by the social decline of the schizophrenic.

In summary, although social class will be carefully noted in the next investigation, the authors feel it cannot be the entire explanation of the very striking differences they found between schizophrenics, and controls' relatives.

(iii) In this investigation we studied consultations—contacts between doctor and patient on the initiative of the latter. Many factors influence the decision of a patient to see his doctor, and we found, for example, a lowered consultation rate for many complaints amongst one group of the schizophrenics. In the particular instance of virus infections, however, bacterial infections—in which controls' and schizophrenics' relatives showed about the same incidence—formed a 'control' group of a sort, indicating that the diminished incidence of virus infections among schizophrenics' relatives might be a genuine phenomenon. Also, the fact that the consultation rates for 'all other complaints' were closely similar for the two groups is supporting evidence.

(iv) Even if a diminished incidence of attacks of viral infection among schizophrenics' relatives were fully confirmed by later work, it should be remembered that death from viral infections before the end of reproductive life is what matters where biological advantage is concerned; and deaths from virus infections are very rare in Britain today. At best, therefore, one will still be driven to an extrapolation: 'Because schizophrenics' relatives suffer less often from viral infections than do controls, therefore they are also less likely to die of them than controls.'

(v) It is impossible to study all the first degree relatives of any given index schizophrenic, even if they are all in the same practice: some will have died, and others will be still unborn. It is desirable, however, to study as complete a collection of relatives as possible. The Ibstock practice, being rural, approached this ideal more closely.

(e) *Future possibilities*

As mentioned, further studies have been planned. A number of interesting possibilities may emerge: for example, a general diminution in the death rates from certain virus infections, and increasing fertility among schizophrenics, may exert pressures in opposite directions on the prevalence of schizophrenia; and some light may be thrown on the genetics of this condition.

Summary

There are grounds for supposing that biological advantage among schizophrenics' relatives may be in part responsible for the relatively high incidence of schizophrenia in all parts of the world. Schizophrenics' relatives in two general practices were compared with the relatives of matched controls. There was a significantly diminished incidence of virus infections among schizophrenics' relatives, and, in one practice only, they appeared markedly protected against accidents.

Schizophrenics' relatives may also have increased fertility, and possibly a diminished incidence of allergies.

Further work is required and is being planned.

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